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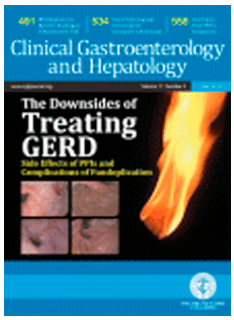

No Association Between Consumption of Sweetened Beverages and Later Risk of Crohn's Disease or Ulcerative Colitis

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Title: No Association Between Consumption of Sweetened Beverages and Later Risk of Crohn's Disease or Ulcerative Colitis

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Hamed Khalili receives consulting fees from Abbvie, Takeda, and Samsung Bioepis. Hamed Khalili also receives grant support from Takeda. Andrew T. Chan receives consulting fees from Janssen, Pfizer Inc., and Bayer Pharma AG. Simon S. Chan has received consulting fees from Abbvie, Takeda and Ferring. Karolinska Institutet has received fees for lectures and consulting performed by Ola Olén for Janssen, Pfizer, Ferring, and Takeda. Ola Olén was supported by grants from the Swedish medical society (Project grants, the fund for research in gastroenterology and the Ihre foundation), Mag-tarmfonden, the Jane and Dan Olsson foundation, and Karolinska Institutet foundations while working on this project. Financial support was also provided through the regional agreement on medical training and clinical research between Stockholm County Council and Karolinska Institutet (ALF). The remaining authors have no conflicts to disclose.

Author Contributions:
Hamed Khalili – Study concept and design, data acquisition, analysis and interpretation of data, drafting manuscript, critically revising manuscript

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Simon S. Chan – Study concept and design, critically revising manuscript
Jonas F. Ludvigsson – Study concept and design, critically revising manuscript
Ola Olen – Study concept and design, data acquisition, critically revising manuscript
Andrew T. Chan – Study concept and design, critically revising manuscript
Andrew R. Hart – Study concept and design, critically revising manuscript
Alicja Wolk - Study concept and design, data acquisition, analysis and interpretation of data, drafting manuscript, critically revising manuscript

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Abstract:
Background & Aims: Consumption of sweetened beverages has been associated with inflammation, based on measurements of C-reactive protein and tumor necrosis factor, as well as immune-mediated disorders including rheumatoid arthritis. We investigated associations with Crohn's disease (CD) or ulcerative colitis (UC).

Methods: We conducted a prospective cohort study of 83,042 participants (44–83 years old) enrolled in the Cohort of Swedish Men or the Swedish Mammography Study. Dietary and lifestyle data were collected using a validated food frequency questionnaire at baseline in 1997. Diagnoses of CD and UC were ascertained from the Swedish Patient Register. We used Cox proportional hazards modeling to calculate hazard ratios (HR) and 95% CIs.

Results: Through December of 2014, we confirmed 143 incident cases of CD (incidence rate = 11 cases/100,000 person-years) and 349 incident cases of UC (incidence rate = 28 cases/100,000 person-years) over 1,264,345 person-years of follow up. Consumption of sweetened beverages was not associated with increased risk of CD (*P*trend = 0.34) or UC (*P*trend = 0.40). Compared to participants who reported no consumption of sweetened beverages, the multivariable-adjusted HRs for 1 or more servings per day were 1.02 for CD (95% CI, 0.60–1.73) and 1.14 for UC (95% CI, 0.83–1.57). The association between consumption of sugar-sweetened beverages and risk of CD or UC were not modified by
age, sex (cohort), body mass index, or smoking (all *P*interaction $\geq$ 0.12).

Conclusion: In analyses of data from 2 large prospective cohort studies from Sweden, we observed no evidence for associations between consumption of sweetened beverages and later risk of CD or UC

KEY WORDS: CoSM, SMC, IBD, BMI; epidemiology

Editor's Notes
Background
Consumption of sweetened beverage has been associated with systemic inflammation and immune-mediated disorders such as rheumatoid arthritis. We analyzed data from 2 large cohorts in Sweden to determine whether consumption was associated with risk of CD or UC.

Findings
We observed no evidence for associations between consumption of sweetened beverages and later risk of CD or UC.

Implications
Consumption of sweetened beverages does not appear to increase risk of CD or UC. Studies are needed to determine the effects on disease progression in patients who already have these diseases.

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INTRODUCTION:

Crohn's disease (CD) and ulcerative colitis (UC), collectively known as inflammatory bowel disease (IBD), are chronic inflammatory bowel disorders of the gastrointestinal tract with rising global incidence, particularly in recently industrialized countries[1, 2]. Westernization of diet has been implicated in the pathogenesis of IBD[3]. Nevertheless, epidemiologic studies of diet have yielded very few promising leads.

Increasing consumption of sweetened beverages has been linked to the growing epidemic of obesity and metabolic-related disorders [4-7]. In parallel, there is mounting evidence for the critical role of obesity in chronic inflammatory disorders of the gastrointestinal tract, particularly CD [8-10]. Additionally, a number of studies have demonstrated a positive association between consumption of sweetened beverages and systemic inflammation as measured by C-reactive protein (CRP) [11, 12]. In turn, we have previously shown that higher prediagnostic levels of circulating CRP are associated with risk of incident CD[13].

A recent study from the European Prospective Investigation into Cancer and Nutrition (EPIC) demonstrated that a dietary pattern consisting of high consumption of sugar and sweetened beverages and low consumption of vegetables is associated with increased risk of UC[14]. Nevertheless, there has been no comprehensive examination of the association between consumption of sweetened beverage and risk of incident CD and UC.

We therefore sought to examine the association between consumption of sweetened-beverages and risk of CD and UC in two large prospective cohort studies in Sweden, the Swedish Mammography Study (SMC) and the Cohort of Swedish Men

(CoSM). With detailed and validated data on dietary information on over 80,000 men and women with linkage to Swedish Patient Register, these cohorts offered us a unique opportunity to examine this relationship while adjusting for other potential lifestyle and dietary factors.

METHODS:

Study population:

SMC is a population-based cohort from the Uppsala county of central Sweden which was established between 1987 and 1990 when 66,651 women returned completed questionnaires on diet, alcohol, weight, height, medications use, and reproductive and menopausal factors. Follow up questionnaires were sent in 1997, 2008, and 2009 and were expanded to include data on smoking, physical activity, medical history, and family history. CoSM is a parallel population-based cohort of 45,906 middle-aged and elderly men established in Central Sweden (Västmanland and Örebro Counties) in the fall of 1997. At baseline, participants provided information on lifestyle factors such as diet, physical activity, smoking, weight, and use of a number of specified medications through a mailed questionnaire similar to that of SMC. Follow up questionnaires were sent to participants in 2008 and 2009. For this study, we included participants who had completed the 1997 questionnaires in both cohorts, which included all participants in CoSM and women in SMC who were still alive in 1997 and returned the dietary questionnaire (n = 38,984, 70% response rate). We excluded men and women who did not provide information on diet or those with diagnosis of IBD at baseline (**Figure 1**). We also excluded participants with implausible total caloric intake defined by intakes not within three standard divisions of the log transformed mean.

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Primary Exposure and Other Covariates:

Dietary information was collected using a 96-item semiquantitative food frequency questionnaire (SFFQ) at baseline in 1997 in both cohorts. SFFQ specifically asked participants to report their usual consumption, during the past year, of a standard glass (200 mL) of sweetened beverages in the form of soft drinks per day or week. Although in the 1997 questionnaire, no distinction was made between sugar-sweetened (Coca Cola, Pepsi, etc.) and artificially sweetened beverages (Diet Coca Cola, Diet Pepsi, etc), according to Swedish national consumption data, artificially-sweetened soft drinks accounted for less than 10% and 20% of all soft drinks among men and women, respectively[15]. Sweetened beverages also did not include fruit juices, syrups, energy and sports drinks, or sweetened coffee, tea, or milk.

Intakes of nutrients were calculated using composition values from the Swedish Food Administration Database and were adjusted for total caloric intake using the residual model. The SFFQ has been validated against fourteen 24-hr diet recall interviews done over one year period in a subset of participants in CoSM (n = 248). The Spearman coefficient correlation ranged between 0.70 to 0.73 for intakes of total carbohydrate, fat, fiber, and sucrose (primary sugar in soft drinks)[16]. In SMC, the SFFQ (version from 1987 similar to that used in CoSM and SMC in 1997) has been validated against four one-week diet records done over one year period in 129 women[17]. The Spearman correlation coefficient between SFFQ and diet records for sweetened beverage was 0.60.

Outcome Ascertainment:

The Swedish National Board of Health and Welfare has collected individual-level data on hospital discharges on a countywide level since 1964 (nationwide since

1987)[18]. Each record, organized according to an individual's personal identity number, includes date of birth, sex, dates of hospital admission, hospital department, and discharge diagnoses (including surgical procedures), coded according to the International Classification of Diseases[19]. Since 2001, this registry was expanded to include specialized outpatient care[18].

Incident cases of CD and UC were identified by linkage of SMC and CoSM participants to the nationwide registry. Incident cases were defined by at least two inpatient or outpatient encounters with a primary or secondary diagnosis (for UC ICD9: '556' or ICD10: 'K51'; for CD ICD9: 555 or ICD10: K50) after the return of the 1997 questionnaires in each cohort. The accuracy of ICD coding for the ascertainment of a number of chronic diseases, including IBD, for the inpatient component of the National Patient Register has been previously validated, with a positive predictive value of 85-95% [20]. Additionally, a recent validation study demonstrated that the positive predictive values using this definition for CD, UC, and IBD cases were 81%, 90%, and 93% respectively[21].

Statistical Analysis:

We examined the possibility that there is a non-linear association between consumption of sweetened-beverages and risk of CD and UC using a previously reported non-parametic cubic spline method,[22] which also permits controlling for covariates and stepwise selection among spline variables. This analysis provides p-values from the likelihood ratio tests for non-linearity, a linear relation, and any relation. Using this method, the likelihood ratio tests comparing models with linear terms with those with spline terms were not statistically significant (All $P_{comparisons} > 0.48$), indicating absence

of non-linear associations between consumption of sweetened-beverages and risk of CD and UC.

Person-time was calculated from January 1, 1998 to date of diagnosis, emigration, death, or end of follow up (January 1, 2015), whichever came first. Categories of sweetened beverage consumption were created according to number of servings, which best approximated quartiles of daily consumption (0, 0.1-0.4, 0.5-0.9, $\geq$ 1 servings/day). We used Cox proportional hazard modeling to estimate the age- and multivariable-adjusted hazard ratio (HR) and 95% confidence interval (CI). Our models were adjusted for age, body mass index (BMI), smoking, total caloric intake, total protein intake, total fiber intake, and non-steroidal anti-inflammatory drugs (NSAIDs) use (number of tablets per week). Additionally, all models were stratified by sex/cohort. Test for trend across categories was done by assigning the median value to each category and modeling this as a continuous variable.

We performed multiple sensitivity and exploratory analyses. First, we restricted our follow up to after January 2002, excluding all IBD cases prior to this date, to allow for a one-year lag between introduction of outpatient data in the National Patient Register and identification of prevalent cases of IBD previously not captured through hospitalizations. In addition, this analysis allowed us to explore the possibility that symptoms related to subclinical or early disease may have altered individual's tendency to consume sweetened beverage. Second, we further adjusted our analysis for total sucrose intake, the primary sugar in sweetened beverages, to further examine the independent association between sweetened beverage and risk of IBD. Lastly, we examined the possibility that the association between sweetened beverage and risk of

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IBD may be modified by age, sex, BMI, and smoking. We tested for the significance of the interaction by entering sweetened beverage consumption and these covariates in our models as multiplicative interaction terms. We also estimated the minimum detectable HR for CD and UC assuming 80% power and an alpha of 0.05 using described methods [23]. We tested for the proportional hazards assumption by examination of the interaction between age in categories and sweetened beverage consumption in quartiles and observed no violations (all $p > 0.65$). We used SAS version 9.4 (Cary, NC) for these analyses. All P-values were 2-sided and < 0.05 was considered statistically significant. The study was approved by the regional ethics committee of Stockholm, Sweden.

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RESULTS:

Through till the end of December 2014, we confirmed 349 incident cases of UC (incidence rate = 28 cases/100,000 person-years) and 143 incident cases of CD (incidence rate = 11 cases/100,000 person-years) among 83,042 participants over 1,264,345 person-years with a mean follow up of 11 years. The age of diagnosis of UC and CD cases ranged from 44 to 92 years. Baseline characteristics of participants are reported in **Table 1.** The median age of participants at baseline was 60 years (range: 44-83 years). Compared to non-consumers of sweetened beverages, participants with one or more serving per day were on average more likely to have used NSAIDs and had a higher caloric intake. However, there were no differences in age, BMI, smoking, total intake of protein, fiber, or fat comparing non-consumers to participants in the highest quartile of sweetened beverage intake.

Higher consumption of sweetened beverage was not associated with increased risk of UC (P_{trend} = 0.13) (**Table 2**). Compared to non-consumer, the age-adjusted HR of UC among participants with ≥ 1 serving per day of sweetened beverage was 1.26 (95% CI, 0.93-1.69). These estimates were not materially altered after adjusting for other covariates (P_{trend} = 0.40). Compared to non-consumers, the MV-adjusted HR of UC among participants with ≥ 1 serving per day of sweetened beverage was 1.14 (95% 0.83-1.57). Similarly, we did not observe an association between higher consumption of sweetened beverage and risk of CD (P_{trend} = 0.11) (**Table 2**). Compared to non-consumers, the age-adjusted HR of CD among participants with ≥ 1 serving per day of sweetened beverage was 1.18 (95% CI, 0.72-1.73). These estimates were not materially altered after adjusting for other potential confounders (P_{trend} = 0.34). Compared to non-

consumers, the MV-adjusted HR of CD among participants with ≥ 1 serving per day of sweetened beverage was 1.02 (95% CI 0.60-1.73). We also repeated our main analyses examining the risk of CD and UC among ever users of sweetened beverage compared to non-users and observed similar results. Compared to non-users, ever users had multivariable-adjusted HRs of 1.20 (95% CI 0.85-1.69) for CD and 1.03 (95% CI 0.83-1.28).

In our sensitivity analyses restricting our follow up to after January 2002, one year after the patient registry was expanded to include outpatient diagnoses, our results remained consistent (All $P_{trend} > 0.69$). Compared to non-users, the MV-adjusted HRs of CD and UC among participants with ≥ 1 serving per day were 0.82 (95% CI 0.43-1.59) and 1.10 (95% CI 0.75-1.61), respectively. We also explored the association between sweetened beverage and risk of CD and UC, independent of its primary sugar component by adjusting our models for total sucrose intake and observed no significant associations. Compared to non-users, the MV-adjusted HRs of CD and UC among participants with ≥ 1 serving per day were 1.13 (95% CI 0.59-2.14, $P_{trend} = 0.21$) and 1.09 (95% CI 0.74-1.61, $P_{trend} = 0.67$), respectively.

We explored whether the association between consumption of sweetened beverages and risk of CD and UC are modified by age, sex (cohort), smoking, or BMI (**Tables 3 and 4**) and observed no evidence for effect modification (All $P_{interaction} > 0.12$). Finally, we explored whether the association between sweetened beverage and risk of UC is limited to participants with low fiber intake as demonstrated in one prior study from the European Prospective Investigation into Cancer and Nutrition[14]. Among participants with lower than median intake of fiber, the MV-adjusted risk of UC with

each daily serving of sweetened beverage was 0.97 (95% CI 0.85-1.11). In addition, there was no evidence of effect modification by fiber intake on the association between sweetened beverage intake and risk of UC ($P_{interaction}$ = 0.93). Finally, in analyses restricting diagnosis to elderly-onset IBD (age ≥ 60 years), we observed no associations between sweetened beverage and risk of CD or UC. Compared to non-users, the MV-adjusted HRs of CD and UC for every one serving increase in sweetened beverage were 0.98 (95% CI 0.85-1.14) and 1.05 (95% CI 0.98-1.13), respectively.

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DISCUSSION:

In two large prospective cohorts in Sweden, we found no association between consumption of sweetened-beverage and risk of CD or UC. The findings were consistent across several sensitivity analyses and among various subgroups.

Consumption of sweetened-beverages has previously been linked to a number of metabolic syndromes including type 2 diabetes and cardiovascular disease[4-6, 12]. Much of these associations have been attributed to the presence of high sucrose, fructose, and corn syrup in sweetened-beverages, which in turn are linked to weight gain and increased insulin resistance. US Preventive Services Task Force has identified higher consumption of sweetened beverage as a dietary factor that at least in part explains the increasing rate of obesity in childhood and adolescence[24, 25]. More recently a number of studies have also demonstrated a link between consumption of sweetened beverages and higher levels of inflammatory markers such as C-reactive protein, IL-6, and TNF receptor 2[11, 12]. Consistent with this observation, an analysis from the Nurses' Health Study demonstrated that sugar-sweetened soda is associated with increased risk of seropositive rheumatoid arthritis[26]. Interestingly in that study the risk was particularly higher in those with later onset disease (age $\geq$ 55 years). Nevertheless, two randomized controlled trials have demonstrated no association between sweetened beverage and measures of inflammatory markers including C-reactive protein and IL-6[27, 28]. Additionally, a recent study by Kuzma and colleagues did not find any changes in measures of inflammation in adipose tissue with intakes of sweetened beverage[27]. These observations are in line with our finding of a lack of an association between sweetened beverage and risk of CD or UC. Nevertheless, as the mean age of IBD

diagnosis in our cohorts was greater than 60 years, future studies examining the role of sweetened beverage in younger-onset CD and UC are needed to examine whether particular subgroups may be at risk.

We acknowledge several limitations. First, at baseline we did not collect information on use of artificial sweeteners. However based on the Swedish national consumption data, these beverages accounted for a small proportion of use in Sweden in 1997. We also did not have updated dietary data over the study period and therefore were not able to account for changes in patterns of use over the follow up time. Nevertheless, volume of sweetened-beverage consumption per capita in Sweden has not changed significantly after 1995[29]. Second, the age of diagnosis of all our participants was above 40 and therefore our findings may not be generalized to earlier onset IBD. Lastly, our study may have not been powered to find a more modest association between sweetened beverage and risk of IBD. Nevertheless, we estimated that our study had over 80% power to detect a minimum HR of 1.6 and 1.4 for CD and UC, respectively, figures that are significantly higher than previously observed associations between sweetened beverage and risk of rheumatoid arthritis in the Nurses' Health Study (HR = 2.64, 95% CI 1.56-4.46 for late-onset RA and HR = 1.63, 95% CI 1.15 – 4.46 for all RA cases) [26]. In addition, specific dietary patterns that include high consumption of sweetened-beverage may be associated with risk of IBD, a possibility that was not explored in the current study.

Our study also had several strengths that are worth noting. First, the prospective nature of our study minimized the possibility of selection and recall biases inherent to case-control and retrospective cohort studies. Second, dietary data including sweetened

beverages from SFFQ have previously been validated against dietary record with good to excellent coefficient correlation. Lastly, in our analyses, we were able to account for other lifestyle and medications that could have potentially confounded the associations.

In two large prospective cohort studies we observed no evidence for strong or clinically meaningful associations between sweetened beverage and risk of CD and UC. Whether sweetened beverages play a role in development of earlier onset IBD (age < 40 years) is unknown and should be the focus of future investigation.

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Table 1: Baseline Characteristics of Participants in the Swedish Mammography Study (SMC) and Cohort of Swedish Men (CoSM) According to Sweetened Beverage Consumption				
	Q1 N = 44,750	Q2 N = 11,577	Q3 N = 16,311	Q4 N = 10,404
Serving size/day, range (median)	0 (0)	0.1 - 0.4 (0.29)	0.5 – 0.9 (0.86)	≥ 1.0 (2.0)
Age (yrs), mean (std)	62 (9)	59 (9)	61 (10)	62 (10)
Body mass index (kg/m^2), mean (std)	25 (4)	25 (3)	26 (4)	26 (4)
Smoking				
Never	44	49	48	42
Past	31	30	30	32
Current	25	21	22	26
Ever use of NSAIDs, %	48	54	48	55
Total Protein intake (g/day)*, mean (std)	89 (21)	86 (20)	87 (20)	83 (20)
Total Fat intake (g/day)*, mean (std)	76 (21)	75 (19)	77 (19)	74 (19)
Total Fiber Intake (g/day)*, mean (std)	27 (9)	26 (8)	26 (8)	24 (8)
Total Caloric Intake (g/day), mean (std)	2052 (759)	2142 (725)	2348 (796)	2718 (886)
Abbreviations: years (yrs), standard deviation (std). * Values are adjusted for total caloric intake.				

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Table 2: Sweetened Beverage Consumption and Risk of Crohn's Disease and Ulcerative Colitis*

	Q1 N = 44,750	Q2 N = 11,577	Q3 N = 16,311	Q4 N = 10,404	
Serving size/day, range (median)	0 (0)	0.1 - 0.4 (0.29)	0.5 – 0.9 (0.86)	≥ 1.0 (2.0)	
					P_{trend}
Person-years of follow up	677,440	185,417	249,435	152,274	
Crohn's disease					
Number of cases	70	14	39	20	
Age-adjusted, HR (95% CI) $^{\Delta}$	1.00	0.96 (0.54-1.71)	1.57 (1.06-2.32)	1.18 (0.72-1.94)	0.11
MV-adjusted, HR (95% CI) $^{\Delta}$	1.00	0.95 (0.53-1.69)	1.46 (0.98-2.18)	1.02 (0.60-1.73)	0.34
Ulcerative colitis					
Number of cases	185	33	74	54	
Age-adjusted, HR (95% CI) $^{\Delta}$	1.00	0.84 (0.58-1.22)	1.12 (0.85-1.46)	1.26 (0.93-1.69)	0.13
MV-adjusted, HR (95% CI) $^{\Delta}$	1.00	0.84 (0.58-1.22)	1.08 (0.82-1.42)	1.14 (0.83-1.57)	0.40

*Abbreviations: Multivariable (MV), hazard ratio (HR), confidence intervals (CI). Δ Models are stratified by cohort (sex) and adjusted for age (years), body mass index, smoking (never, past, and current), total caloric intake, total protein intake, total fiber inake, and NSAIDs use.

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Table 3: Sweetened Beverage Consumption and Risk of Crohn's Disease According to Selected Strata*		
	Risk Per One Daily Serving of Sweetened Beverage	$P_{interaction}$
Cohort = SMC		0.49
Cases	55	
Age-adjusted, HR (95% CI)	1.00 (0.76-1.31)	
MV-adjusted, HR (95% CI) $^{\Delta}$	1.05 (0.79-1.41)	
Cohort = CoSM		
Cases	88	
Age-adjusted, HR (95% CI)	1.00 (0.89-1.12)	
MV-adjusted, HR (95% CI) $^{\Delta}$	0.99 (0.87-1.12)	
Age < 60		0.45
Cases	45	
Age-adjusted, HR (95% CI)	1.14 (1.04-1.25)	
MV-adjusted, HR (95% CI) $^{\Delta}$	1.02 (0.96-1.09)	
Age ≥ 60		
Cases	86	
Age-adjusted, HR (95% CI)	0.88 (0.72-1.08)	
MV-adjusted, HR (95% CI) $^{\Delta}$	0.89 (0.72-1.11)	
BMI < 25 kg/m^2		0.12
Cases	77	
Age-adjusted, HR (95% CI)	1.16 (1.04-1.30)	
MV-adjusted, HR (95% CI) $^{\Delta}$	1.16 (0.98-1.27)	
BMI ≥ 25		
Cases	66	
Age-adjusted, HR (95% CI)	0.98 (0.83-1.15)	
MV-adjusted, HR (95% CI) $^{\Delta}$	0.89 (0.74-1.07)	
Never Smoker		0.33
Cases	78	
Age-adjusted, HR (95% CI)	1.03 (0.87-1.21)	
MV-adjusted, HR (95% CI) $^{\Delta}$	0.98 (0.82-1.18)	
Past/Current Smoker		
Cases	65	
Age-adjusted, HR (95% CI)	1.09 (0.97-1.22)	
MV-adjusted, HR (95% CI) $^{\Delta}$	1.01 (0.88-1.15)	

*Abbreviations: Multivariable (MV), hazard ratio (HR), confidence intervals (CI). Δ Models are adjusted for age (years), cohort, body mass index, smoking (never, past, and current), total caloric intake, total protein intake, total fiber intake, and NSAIDs use.

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Table 4: Sweetened Beverage Consumption and Risk of Ulcerative Colitis According to Selected Strata*		
	Risk Per One Daily Serving of Sweetened Beverage	
	HR (95% CI)	$P_{interaction}$
Cohort = SMC		0.97
Cases	126	
Age-adjusted, HR (95% CI)	0.89 (0.73-1.10)	
MV-adjusted, HR (95% CI) $^{\Delta}$	0.92 (0.74-1.13)	
Cohort = CoSM		
Cases	223	
Age-adjusted, HR (95% CI)	0.99 (0.98-1.01)	
MV-adjusted, HR (95% CI) $^{\Delta}$	1.01 (0.94-1.08)	
Age < 60		0.18
Cases	133	
Age-adjusted, HR (95% CI)	1.10 (1.03-1.18)	
MV-adjusted, HR (95% CI) $^{\Delta}$	1.08 (0.96-1.22)	
Age ≥ 60		
Cases	216	
Age-adjusted, HR (95% CI)	1.03 (0.94-1.12)	
MV-adjusted, HR (95% CI) $^{\Delta}$	0.92 (0.75-1.14)	
BMI < 25 kg/m^2		0.89
Cases	160	
Age-adjusted, HR (95% CI)	1.09 (0.99-1.21)	
MV-adjusted, HR (95% CI) $^{\Delta}$	1.03 (0.92-1.15)	
BMI ≥ 25		
Cases	189	
Age-adjusted, HR (95% CI)	1.07 (1.00-1.15)	
MV-adjusted, HR (95% CI) $^{\Delta}$	1.03 (0.95-1.11)	
Never Smoker		
Cases	144	0.18
Age-adjusted, HR (95% CI)	1.04 (0.92-1.18)	
MV-adjusted, HR (95% CI) $^{\Delta}$	1.01 (0.88-1.15)	
Past/Current Smoker		
Cases	205	
Age-adjusted, HR (95% CI)	1.08 (1.02-1.15)	
MV-adjusted, HR (95% CI) $^{\Delta}$	1.02 (0.95-1.10)	

*Abbreviations: Multivariable (MV), hazard ratio (HR), confidence intervals (CI). Δ Models are adjusted for age (years), cohort, body mass index, smoking (never, past, and current), total caloric intake, total protein intake, total fiber intake, and NSAIDs use.

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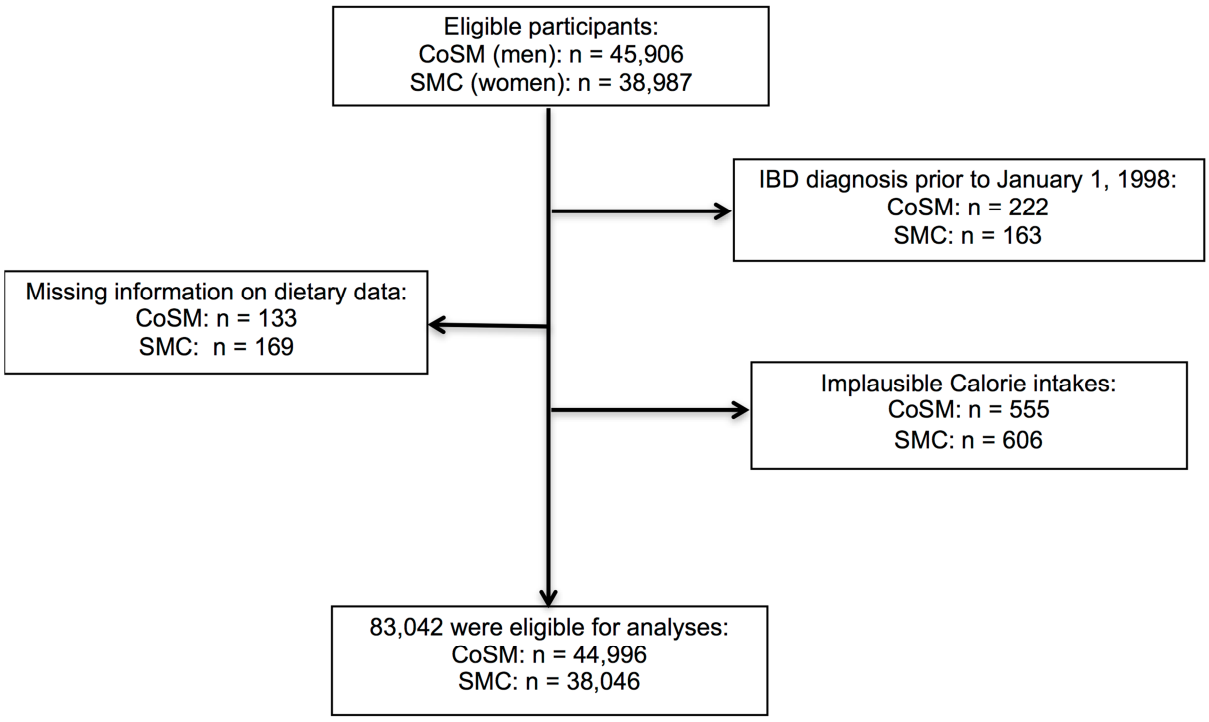
Figure 1: Flow Chart of eligible participants in the study



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