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Dietary sugar/starches intake and Barrett's esophagus - a pooled analysis

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Abstract

Background & Aims: Barrett's esophagus (BE) is the key precursor lesion of esophageal adenocarcinoma, a lethal cancer that has increased rapidly in Westernized countries over the past four decades. Dietary sugar intake has also been increasing over time, and may be associated with these tumors by promoting hyperinsulinemia. The study goal was to examine multiple measures of sugar/starches intake in association with BE.

Methods: This pooled analysis included 472 BE cases and 492 controls from two similarly conducted case-control studies in the United States. Dietary intake data, collected by study-specific food frequency questionnaires, were harmonized across studies by linking with the University of Minnesota Nutrient Database, and pooled based on study-specific quartiles. Logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs), adjusting for age, sex, race, total energy intake, study indicator, body mass index, frequency of gastro-esophageal reflux, and fruit/vegetable intake.

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Results: In both studies, intake of sucrose (cases vs. controls, g/day: 36.07 vs. 33.51; 36.80 vs. 35.06, respectively) and added sugar (46.15 vs. 41.01; 44.18 vs. 40.68, respectively) were higher in cases than controls. BE risk was increased 79% and 71%, respectively, for associations comparing the fourth to the first quartile of intake of sucrose ($OR_{Q4vs.Q1}$=1.79, 95%CI=1.07-3.02, P_{trend}=0.01) and added sugar ($OR_{Q4vs.Q1}$=1.71, 95%CI=1.05-2.80, P_{trend}=0.15). Intake of sweetened desserts/beverages was associated with 71% increase in BE risk ($OR_{Q4vs.Q1}$=1.71, 95%CI=1.07-2.73, P_{trend}=0.04).

Conclusions: Limiting dietary intake of foods and beverages that are high in added sugar, especially refined table sugar, may reduce the risk of developing BE.

Keywords

Barrett's esophagus; added sugar; sweetened desserts/beverages; diet

INTRODUCTION

Incidence of esophageal adenocarcinoma (EA) has increased rapidly in many Westernized countries [1–3]. However, EA prognosis remains poor, with a 5-year survival of less than 20% [4, 5]. Barrett's esophagus (BE) is a key precursor lesion of EA [6]. The increasing incidence and poor prognosis of EA points to the importance of identifying modifiable risk factors that act early during carcinogenesis.

Known modifiable risk factors for BE are gastro-esophageal reflux disease (GERD), obesity, and cigarette smoking [7–9]. However, these risk factors are difficult to modify. GERD usually requires continued medical therapy to control; smoking cessation and weight loss are difficult to achieve or maintain [10–12]. Therefore, additional modifiable risk factors need to be identified.

Caloric sweetener intake has increased dramatically since 1960s [13], corresponding to the increase in BE/EA risk in the last four decades. However, few studies have examined the associations between sugar/starches and BE/EA [14–16]. In addition to the ecological correlations, the link between sugar and cancer risk is biologically plausible. Long-term high intake of dietary sugar/starches may alter levels of insulin-like growth factor compounds, and subsequently promote carcinogenesis [17–19]. Specifically, insulin resistance may hamper the healing of esophageal mucosal injury and decrease cell apoptosis [20]. Thus, exposure to sugar/starches intake may be associated with development of EA and its precursor BE.

To comprehensively examine associations between multiple measures of sugar/starches intake and BE risk, we harmonized, pooled, and analyzed individual-level participant data from two United States (US)-based case-control studies. If sugar/starches intake is found to be associated with BE risk, there is potential to reduce BE risk through limiting sugar/starches intake.

METHODS

This study pooled data from two US community-based case-control studies of Barrett's esophagus, including the western Washington-based Study of Reflux Disease [21] and the northern California-based Epidemiology and Incidence of BE Study [8]. The two parent studies, from the International Barrett's and Esophageal Adenocarcinoma Consortium, were chosen due to their similarities in study design, study population, and data collection methodology (Table 1). This study was approved by the institutional review boards of the participating institutions.

Study Population.

The Study of Reflux Disease was conducted in western Washington state [21]. Eligible cases were between 20-80 years of age, without a previous BE diagnosis, and who underwent an upper endoscopy for GERD symptoms at one of four community gastroenterology clinics during 1997-2000. Cases were those with endoscopic findings of BE and specialized intestinal metaplasia on at least one of the four biopsy specimens taken within the tubular esophagus. Controls were residents of western Washington state identified using a random digit dialing technique during the same period that cases were diagnosed.

The Epidemiology and Incidence of BE Study was conducted within the Kaiser Permanente Northern California (KPNC) population [8]. Cases and controls were 18-79 year-old KPNC members who were continuously enrolled (in KPNC) for at least 2 years, and were able to understand spoken and written English. Cases comprised individuals diagnosed with incident BE (endoscopic findings and biopsies with intestinal metaplasia) during 2002-2005. BE cases were identified using the International Classification of Disease, Ninth Revision code 530.2 and confirmed by review of endoscopy and pathology records. Controls were randomly selected from the eligible KPNC members without a prior diagnosis of BE at the time the cases were diagnosed.

In total, the two studies provided 513 BE cases and 528 controls. We excluded individuals who did not complete a dietary intake assessment, or if their reported energy intake was beyond ±3 standard deviations from study-specific $\log_e$-transformed mean energy intake [22]. After exclusions there remained 472 BE cases and 492 controls for this pooled study.

Dietary Assessment.

Both BE studies collected dietary information using a validated food frequency questionnaire (FFQ), either during a structured interview by trained interviewers [23] or through a self-administered questionnaire [24]. Participants were asked to report their dietary intake for the year before diagnosis (cases) or interview (controls) [23, 24]. The Study of Reflux Disease utilized the 131-item FFQ developed by Fred Hutchison Cancer Research Center [23], and the Epidemiology and Incidence of BE Study utilized the 110-item FFQ (Block 98) [24]. The two FFQs were similar in design and structure, including number of food items and frequency/portion size questions, which enhanced our ability to harmonize the diet data.

Assessment of Sugar/Starches Intake.

Twelve measures were used to assess sugar/starches intake, including: sugar components (free glucose, free fructose, sucrose); added sugar; total sugar; starch; total carbohydrate; glycemic index; glycemic load; servings of sweetened desserts/beverages (servings of sweetened desserts; servings of sweetened beverages, and servings of sweetened desserts/beverages). Added sugar was defined as sugars and syrups added to foods during food preparation or commercial food processing, including white sugar, brown sugar, powdered sugar, honey, pancake syrup, corn syrups, high fructose corn syrups, and molasses [25].

Primary data from the two study-specific FFQs were harmonized and linked with the University of Minnesota Nutrition Coordinating Center Food and Nutrient Database to estimate individual-level intake [25]. For example, sucrose intake was calculated as follows.

$$\text{Sucrose intake / day from an FFQ line item} = \text{amount of food consumed each time (g)} \times \text{frequency(/ day)} \times \text{sucrose / g food}$$

Intake of sucrose per day was calculated by summing up the sucrose intake values across all line items in the FFQ [26]. When a FFQ line item represented multiple foods, the nutrient contents of the line item were weighted according to the estimated relative national distribution of intake for each food [26].

FFQ items categorized as sweetened desserts/beverages were based on previous studies as listed in Supplemental Table S1 [27–29]. Dietary glycemic index and glycemic load were developed to reflect the putative effect of diet on blood glucose [30, 31]. For this pooled study, dietary glycemic index was calculated using the following formula [30–32].

$$\frac{\Sigma\,(\text{amount of food consumed (g / day)} \times \text{carbohydrate contents / g food} \times \text{glycemic index of food})}{\text{total carbohydrate consumed (g / day)}}$$

Similarly, dietary glycemic load was calculated as follows [30–32].

$$\frac{\Sigma\,(\text{amount of food consumed (g / day)} \times \text{carbohydrate contents / g food} \times \text{glycemic index of food})}{100}$$

Covariate Assessment.

Covariate information for non-dietary factors was collected by each parent study during a structured in-person interview [8, 21]. Responses were harmonized in preparation for pooled analyses, as previously described [9, 33, 34]. Potential confounders were identified through the use of directed acyclic graphs (DAGs) [35], and included age (continuous), sex (male/female), race (white/other), fruit/vegetable intake (≤study-specific median/>study-specific median), body mass index (BMI, <25/≥25 kg/m^2), frequency of GERD (≤weekly/>weekly), and total energy intake (kcal/day). We adjusted for study (Study of Reflux Disease/Epidemiology and Incidence of BE) in all models.

Statistical Analysis.

Estimated intake of sugar/starches from each BE study was pooled based on study-specific quartiles, which were determined by the distributions of intake among the controls in each study (Supplemental Table S2) [36].

Logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for associations between sugar/starches intake (categorized in quartiles) and BE risk, with each intake measure modeled separately [37]. Linear trends were tested by modeling the sugar/starches measures as continuous variables. For each exposure measure considered we constructed two different models to adjust for confounding. For Model 1, we used a DAG to identify the adjustment set, which includes age, sex, race, study indicator, BMI, GERD frequency, fruit/vegetable intake, and total energy intake. For Model 2, our aim was to identify a more parsimonious model for each exposure measure to maximize study power. For this second approach, we developed exposure-specific models, using investigator-controlled backward elimination. We started with the DAG-identified adjustment set described above, and for each exposure-specific model, we excluded the covariate if inclusion of that covariate changed the effect estimate on a loge scale by <10% [37]. In the final model 2 for each exposure measure, race, BMI, GERD frequency, and/or fruit/vegetable intake were excluded. Cigarette smoking was considered, but not identified as a confounder by DAG analysis; also, inclusion of this covariate did not change the effect estimates by ≥10%. We evaluated effect measure modification on a multiplicative scale by BMI at interview (<25/≥25 kg/m^2), waist circumference at interview (≤101.6/>101.6 cm for male, ≤89.0/>89.0 cm for female), and frequency of GERD (≤weekly/>weekly) for any significant associations between sugar/starches (categorized at the median) and BE using the likelihood ratio test, by comparing models with and without interaction terms [37].

Multinomial logistic regression was used to calculate ORs and 95%CIs for the associations between sugar/starches intake (categorized at the median) and BE by segment length (defined as short-segment BE (SSBE, <3 cm, n=248) and long-segment BE (LSBE, ≥3 cm, n=165)) [37, 38]. The Wald Test was used to formally evaluate differences by segment length (<3cm/≥3 cm) [39]. BE cases with unknown segment length (n=59) were not included in these models.

We conducted sensitivity analyses by: (1) pooling study-specific ORs using a meta-analytic approach [9, 36] (fixed effect, Supplemental Table S3); (2) excluding GERD and BMI (Supplemental Table S4), or total energy intake from the covariate sets, as they may be on the causal pathway; (3) using nutrient density energy adjustment method where the sugar/starch measure was specified as proportion of kcals in the model [40] (rather than the standard multivariate method, which was used in the main analyses); (4) pooling on identical absolute cut-points determined by the intake distributions among all controls from the two studies [36]; (5) utilizing wider exclusion criteria for plausible total energy intake (±2.5%); (6) comparing effect estimates (ORs and CIs for carbohydrate intake-BE associations) derived using the intake values in the current study (estimated based on University of Minnesota nutrient database) versus the effect estimates derived using the previously calculated carbohydrate values by study-specific nutrient data processing center; and (7) categorizing the sugar/starches intake variables using cut-points other than the median, when

examining effect measure modification. Our results were not substantially altered in any of the sensitivity analyses (data not shown for (2)-(7)).

SAS version 9.3 (SAS Institute, Inc., Cary, NC) was used for all analyses except for meta-analysis, which was analyzed using Stata version 14.0 (StataCorp LP, College Station, TX).

RESULTS

Distributions of demographic factors by study and case-control status are shown in Table 2. Participants in the Epidemiology and Incidence of BE study (based in Northern California) were more likely to be older, male, non-White, with long-segment BE (≥3cm) and higher prevalence of proton pump inhibitors use, consume more servings of fruits/vegetables, and were less likely to report frequent GERD (>weekly), compared to participants in the Study of Reflux Disease (based in western Washington).

In both BE studies, the intake of sucrose, added sugar, and sweetened desserts/beverages, was higher in cases compared to controls (Table 3). In the Study of Reflux Disease, the intake of sucrose (g/day) was 36.07 and 33.51, the intake of added sugar (g/day) was 46.15 and 41.01, and the intake of sweetened desserts/beverages (servings/day) was 3.13 and 2.81, in cases and controls, respectively. In the Epidemiology and Incidence of BE study, the intake of sucrose (g/day) was 36.80 and 35.06, the intake of added sugar (g/day) was 44.18 and 40.68, and the intake of sweetened desserts/beverages (servings/day) was 2.26 and 2.10, in cases and controls, respectively.

After adjustment, BE risk was increased 79% and 71%, respectively, among those in the highest vs. lowest quartiles of sucrose ($OR_{Q4vs.Q1}$=1.79, 95%CI=1.07-3.02, P_{trend}=0.01) and added sugar intake ($OR_{Q4vs.Q1}$=1.71, 95%CI=1.05-2.80, P_{trend}=0.15) (Table 4). Sweetened desserts/beverages were associated with 71% increase in BE risk ($OR_{Q4vs.Q1}$=1.71, 95%CI=1.07-2.73, P_{trend}=0.04). The OR was also elevated for intake of sweetened beverages ($OR_{Q4vs.Q1}$=1.47, 95%CI=0.95-2.26, P_{trend}=0.29), although the 95%CI included the null. There were little or no associations between other measures of sugar/starches intake and BE risk. The association with sweetened desserts/beverages was elevated among those with lower waist circumference (OR=1.63, 95%CI=1.06-2.50), but not among those with higher waist circumference (OR=0.91, 95%CI=0.59-1.41, $P_{interaction}$=0.05). Other statistically significant associations (sucrose intake-BE risk, and added sugar intake-BE risk) were not modified by BMI, waist circumference, or GERD frequency (data not shown).

As shown in Table 5, associations with most sugar/starches intake measures differed significantly by segment length. Risk of SSBE was associated with increased intake of sucrose, total sugar, starch, total carbohydrate, glycemic load, sweetened desserts, or sweetened beverages. In contrast, the risk of LSBE was not associated with sugar/starches intake, except for glycemic load ($OR_{\geq median\ vs.<median}$=0.42, 95%CI=0.24-0.74). These findings did not vary by study site (data not shown).

DISCUSSION

In this pooled US-based study, BE risk was increased by 71%−79% in association with added sugar, sucrose, and sweetened desserts/beverages for intake in the highest compared to the lowest quartile. Risk increased in a dose-dependent manner (P_{trend}<0.05) for both sucrose and sweetened desserts/beverages. Waist circumference appeared to modify the sweetened desserts/beverages-BE association. Thus, altering diet to reduce intake of added sugar or sweetened desserts/beverages (especially among those with lower waist circumference) may be potential risk reduction strategies.

Ours is the first study to investigate the role of added sugar, individual sugar components, and sweetened desserts/beverages in relation to BE risk. Our finding that added sugar was associated with increased risk of BE is consistent with a US-based cohort study that found that added sugar was associated with a 62% increase in EA risk [16]. Thus, from the perspective of the cancer development continuum, added sugar may either play a role during the early (development of BE), or at both early and later (development of EA) stages of carcinogenesis.

One previous BE study from Ireland considered several sugar/starches measures that were also examined in our study, including total sugar, starch, total carbohydrate, glycemic index, and glycemic load [14]. However, none of these other measures were associated with BE in either the Irish study or in our pooled study. It is possible that even though added sugar and naturally occurring sugar are chemically identical. However, their physiological effects may differ. Naturally occurring sugar is an integral part of a cellular structure of whole foods (e.g., fruit), and is usually accompanied with vitamins, minerals, and fiber, which may slow down the absorption of sugar and moderate its impact on blood glucose [41–43]. Moreover, some of these substances can decrease inflammation or oxidative stress, and thus are potentially anti-carcinogenic [42, 44]. In contrast, added sugar is usually present in processed foods that are low in micronutrients and fiber, more energy-dense, and are rapidly digestible. The quick absorption may lead to acute glucose fluctuations, which have been suggested to increase oxidative stress and subsequently to promote carcinogenesis [45, 46]. Thus, our findings of a positive association between added sugar/sweetened desserts/beverages and BE risk, but no association with the other sugar/starches measures we considered, are biologically plausible.

We found a positive association between sucrose and BE. Sucrose was not associated with esophageal cancer in a US cohort study [16]. However, in that study, EA was not differentiated from esophageal squamous cell carcinoma. Because the epidemiology of these two tumor types differs substantially [1, 2], it is unclear whether sucrose may have been associated with EA in the US cohort study. Many fruits/vegetables contain sucrose, but mostly in small amounts [41]. Sucrose is largely found in the form of table sugar that is added in preparation of baked goods, processed foods, and sweetened beverages [25]. Given that naturally occurring sucrose only contributes a small proportion of total sucrose, and the source of natural sucrose (fruits/vegetables) is associated with BE risk reduction [23, 24], it is likely that the association between sucrose and BE we observed was driven by added sucrose. Consequently, our results suggest that public health intervention could target

limiting table sugar intake, by reducing the intake of foods and beverages that are high in table sugar.

Multiple measures of sugar/starches intake were associated with SSBE, but were not associated (or in one instance, inversely associated), with LSBE. Given the small sample size for examining BE length despite our pooling efforts, our results regarding segment length may be spurious, and should be interpreted with caution. In addition, it remains unclear whether LSBE and SSBE have the same pathogenesis and natural history, or whether length of BE segment increases over time [47]. Nonetheless, our findings suggest that it is possible that SSBE may be more susceptible to sugar/starches intake than LSBE. Further studies are needed to explore these associations.

There are several limitations to our study. First, recall bias is possible due to the case-control design. However, the general lack of awareness of the sugar/starches-BE risk association by participants at the time of data collection may reduce the possibility of recall bias. Second, there may be non-differential measurement error (introduced by utilization of FFQ) and non-differential misclassification error (introduced by data harmonization and pooling). Thus, to reduce the impact from these potential non-differential errors, we appropriately pooled and compared intake data based on relative rankings of sugar/starches intake within each study, instead of the absolute values. Third, although the relationship between BMI and BE in the parent studies was inconsistent [8, 21], in our ancillary study reported here, we considered BMI as a potential confounder and/or effect modifier of the sugar/starch associations with BE. However, it is possible that there might be misclassification in BMI category since BMI was measured at interview, after diagnosis. Future studies examining our hypothesis should consider a prospective design. Another limitation of our study is that history of endoscopy may be a potentially unmeasured confounder. However, given that endoscopy is used primarily as a diagnostic tool, rather than as a screening mechanism, the likelihood of confounding is lessened [48]. Nonetheless, we were unable to explore this issue in the study reported here. Finally, because information on diabetes mellitus or insulin resistance was not collected as part of the two parent studies, we were not able to assess the influence of diabetes/insulin resistance on the associations between sugar/starches intake and BE. However, obesity is a strong risk factor for diabetes and insulin resistance [49], yet, we found a stronger association between sweetened desserts/beverages and BE risk only among those with lower waist circumference but not among those with generalized obesity, suggesting that sweetened desserts/beverages intake, in absence of obesity (or potentially diabetes), may be a risk factor for BE. It is possible that abdominal obesity, compared to sweetened desserts/beverages intake, is a metabolically more active risk factor for BE, and therefore the metabolic impact of sweetened desserts/beverages intake on carcinogenesis appeared to be less evident among those with high waist circumference. Further well-powered studies are needed to more formally evaluate the role of diabetes/insulin resistance.

There are several strengths to our study. This is the first US study to comprehensively examine associations between sugar/starches intake and BE. To better capture the complexity of sugar/starches intake, improve understanding of the underlying mechanisms, and provide support for specific evidence-based dietary recommendations, we examined multiple measures, among which added sugar, individual sugar components, and sweetened

desserts/beverages, had not been examined in previous BE studies. Moreover, by pooling individual-level data from two existing studies, we increased our sample size, which yielded more precise estimates of association. Further, harmonization of the exposure variables and covariates, and standardization of the statistical models have minimized potential sources of heterogeneity between studies. Most importantly, food selection is a non-pharmaceutical and potentially sustainable method for disease prevention, and is of interest to patients [50].

In summary, our pooled study examined multiple measures of sugar/starches intake in relation to the risk of developing BE, and we are the first to report that added sugar, sucrose, and sweetened desserts/beverages were associated with a 71%−79% increase in BE risk. Our results suggest that limiting intake of foods and beverages that are high in added sugar (especially table sugar) could potentially reduce the risk of developing BE, a precursor to the lethal tumor EA.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Descriptive summary of two U.S. studies of Barrett's esophagus, which were harmonized and included in our pooled study.

	Study of Reflux Disease	Epidemiology and Incidence of BE
Study Design	Community-based case-control study	Community-based case-control study
Time and Location	Western Washington, 1997-2000	Northern California, 2002-2005
Sample Size	193 BE cases, 211 controls	320 BE cases, 317 controls
FFQ (# items)	FHCRC (131)	Block 98 (110)
Frequency of Consumption	Never or less than once per month, 1 per month, 2–3 per month, 1 per week, 2 per week, 3–4 per week, 5–6 per week, 1 per day	Never or less than once per month, 1 per month, 2–3 per month, 1 per week, 2 per week, 3–4 per week, 5–6 per week, 1 per day
Serving Size	Small, medium, large	1/4 cup, 1/2 cup, 1 cup, 2 cups

FFQ: food frequency questionnaire

FHCRC: Fred Hutchinson Cancer Research Center

Table 2.

Demographic characteristics among 472 cases and 492 controls from two U.S. case-control studies of Barrett's esophagus

	Study of Reflux Disease		Epidemiology and Incidence of BE	
Characteristic	**Controls N=191**	**Cases N=176**	**Controls N=301**	**Cases N=296**
Age, years, mean (SD)	53.37 (12.08)	54.75 (12.77)	62.35 (10.26)	62.28 (10.71)
Sex, n (%)				
Male	119 (62.30)	105 (59.66)	203 (67.44)	217 (73.31)
Female	72 (37.70)	71 (40.34)	98 (32.56)	79 (26.69)
Race, n (%)				
White	175 (91.62)	157 (89.20)	256 (85.05)	256 (86.49)
Other	16 (8.38)	19 (10.80)	45 (14.95)	40 (13.51)
BE Segment Length, n (%)				
<3cm	--	139 (84.76)	--	109 (43.78)
≥3cm	--	25 (15.24)	--	140 (56.22)
Cigarette Smoking, n (%)				
Ever	92 (48.17)	114 (64.77)	170 (56.48)	198 (67.12)
Never	99 (51.83)	62 (35.23)	131 (43.52)	97 (32.88)
Gastro-Esophageal Reflux Disease, n (%)				
Ever	126 (65.97)	160 (90.91)	138 (45.85)	250 (84.46)
Never	65 (34.03)	16 (9.09)	163 (54.15)	46 (15.54)
GERD Frequency, n (%)				
≤Weekly	144 (75.79)	47 (26.70)	259 (86.05)	141 (47.64)
>Weekly	46 (24.21)	129 (73.30)	42 (13.95)	155 (52.36)
Proton Pump Inhibitors use, n (%)				
Ever	12 (6.32)	79 (44.89)	41 (13.71)	201 (68.37)
Never	178 (93.68)	97 (55.11)	258 (86.29)	93 (31.63)
Body Mass Index (kg/m^2)				
<25	62 (33.33)	35 (20.12)	70 (23.25)	59 (19.93)
25-<30	76 (40.86)	73 (41.95)	111 (36.88)	121 (40.88)
≥30	48 (25.81)	66 (37.93)	120 (39.87)	116 (39.19)
Fruit/vegetable Intake, servings/day[a], median (SD)	1.71 (1.49)	1.71 (1.43)	4.40 (2.92)	3.65 (2.54)

[a]Based on study-specific serving sizes and study-specific food frequency questionnaires.

Missing values (N): GERD frequency (1), smoking (1), PPI (5), BMI (7), fruit/vegetable intake (32), BE segment length (59).

Table 3.

Daily mean (SD) intake of sugar/carbohydrate among 472 cases and 492 controls in two U.S. case-control studies of Barrett's esophagus

	Study of Reflux Disease		Epidemiology and Incidence of BE	
Measure	**Controls N=191**	**Cases N=176**	**Controls N=301**	**Cases N=296**
Free glucose (g/day)	16.79 (13.42)	16.80 (11.57)	23.93 (14.48)	22.49 (13.91)
Sucrose (g/day)	33.51 (22.75)	36.07 (23.26)	35.06 (19.38)	36.80 (21.77)
Free fructose (g/day)	18.64 (17.16)	18.82 (14.69)	26.84 (17.89)	24.68 (17.06)
Total Sugar (g/day)	86.30 (54.08)	91.14 (50.95)	100.56 (50.03)	99.38 (49.90)
Added Sugar (g/day)	41.01 (42.96)	46.15 (36.00)	40.68 (32.12)	44.18 (33.23)
Starch (g/day)	75.84 (38.16)	74.97 (36.13)	68.40 (37.53)	66.30 (38.22)
Total Carbohydrate (g/day)	196.95 (92.43)	200.92 (88.68)	215.44 (93.77)	209.17 (95.55)
Glycemic Index	60.62 (4.43)	60.25 (4.68)	60.96 (3.54)	60.62 (4.29)
Glycemic Load	109.23 (55.02)	111.34 (51.57)	116.63 (52.79)	113.28 (53.06)
All Sweetened desserts/beverages[a] (servings/day)	2.81 (2.26)	3.13 (2.18)	2.10 (1.29)	2.26 (1.43)
Sweetened Desserts[a] (servings/day)	1.58 (1.06)	1.76 (1.22)	1.45 (1.08)	1.53 (1.21)
Sweetened Beverages[a] (servings/day)	1.23 (1.84)	1.37 (1.57)	0.64 (0.64)	0.73 (0.74)
Total energy intake (kcal/day)	1672.53 (729.29)	1730.86 (740.65)	1748.54 (778.96)	1714.13 (860.64)

[a]The differences in intakes of all sweetened desserts/beverages, sweetened desserts, and sweetened beverages between the two studies may be attributed to the utilization of study-specific FFQs. Both the serving sizes and the number of FFQ line items that contained sweetened desserts/beverages varied by study. There were 23 FFQ line items that contain sweetened desserts/beverages (15 line items contain sweetened desserts and 8 line items contain sweetened beverages) in Study of Reflux Disease. There were 18 FFQ line items that contain sweetened desserts/beverages (13 line items contain sweetened desserts and 5 line items contain sweetened beverages) in Epidemiology and Incidence of BE.

Table 4.

Multivariable-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for the associations between sugar/carbohydrate intake and risk of developing Barrett's esophagus among 472 cases and 492 controls from two U.S. case-control studies (pooled approach, based on study-specific quartiles)

Measure	Controls (N)/Cases (N)	Model 1 OR (95%CI) (adjusted for covariates identified using DAG [a])	Model 2 OR (95%CI) (adjusted for select covariates)	Model 2 Covariates adjusted for in Model 2
Free glucose (g/day)				
Q1	115/105	Ref.	Ref.	age, sex, study indicator, fruit/vegetable intake, GERD frequency, and total energy intake
Q2	118/134	1.50 (0.97-2.32)	1.44 (0.94-2.21)	
Q3	122/115	1.33 (0.84-2.11)	1.26 (0.80-1.99)	
Q4	121/94	1.39 (0.82-2.34)	1.29 (0.77-2.17)	
P_{trend}		0.96	0.85	
Sucrose (g/day)				
Q1	117/105	Ref.	Ref.	age, sex, race, BMI, study indicator, fruit/vegetable intake, GERD frequency, and total energy intake
Q2	120/108	1.07 (0.69-1.64)	1.07 (0.69-1.64)	
Q3	117/97	1.17 (0.74-1.86)	1.17 (0.74-1.86)	
Q4	122/138	1.79 (1.07-3.02)	1.79 (1.07-3.02)	
P_{trend}		0.01	0.01	
Free fructose (g/day)				
Q1	113/106	Ref.	Ref.	age, sex, study indicator, fruit/vegetable intake, GERD frequency, and total energy intake
Q2	122/131	1.41 (0.91-2.17)	1.35 (0.88-2.07)	
Q3	120/113	1.37 (0.86-2.19)	1.28 (0.81-2.03)	
Q4	121/98	1.34 (0.82-2.21)	1.26 (0.77-2.05)	
P_{trend}		0.78	0.66	
Total Sugar (g/day)				
Q1	116/107	Ref.	Ref.	age, sex, study indicator, fruit/vegetable intake, GERD frequency, and total energy intake
Q2	118/116	1.20 (0.78-1.85)	1.15 (0.75-1.78)	
Q3	121/103	1.15 (0.72-1.83)	1.09 (0.68-1.73)	
Q4	121/122	1.63 (0.94-2.84)	1.54 (0.89-2.67)	
P_{trend}		0.13	0.15	
Added Sugar (g/day)				
Q1	119/97	Ref.	Ref.	age, sex, race, BMI, study indicator, fruit/vegetable intake, GERD frequency, and total energy intake
Q2	118/100	1.12 (0.73-1.72)	1.12 (0.73-1.72)	
Q3	120/112	1.14 (0.73-1.80)	1.14 (0.73-1.80)	
Q4	119/139	1.71 (1.05-2.80)	1.71 (1.05-2.80)	
P_{trend}		0.15	0.15	
Starch (g/day)				
Q1	117/103	Ref.	Ref.	age, sex, race, BMI, study indicator, fruit/vegetable intake, GERD frequency, and total energy intake
Q2	118/109	1.00 (0.65-1.56)	1.00 (0.65-1.56)	
Q3	121/133	1.36 (0.84-2.19)	1.36 (0.84-2.19)	

Measure	Controls (N)/Cases (N)	Model 1 OR (95%CI) (adjusted for covariates identified using DAG [a])	Model 2 OR (95%CI) (adjusted for select covariates)	Model 2 Covariates adjusted for in Model 2
Q4	120/103	1.00 (0.52-1.90)	1.00 (0.52-1.90)	
P_{trend}		0.74	0.74	
Total Carbohydrate (g/day)				
Q1	115/107	Ref.	Ref.	
Q2	119/115	1.16 (0.74-1.82)	1.12 (0.72-1.75)	
Q3	122/127	1.36 (0.81-2.29)	1.29 (0.78-2.16)	age, sex, study indicator, fruit/vegetable intake, GERD frequency, and total energy intake
Q4	120/99	1.39 (0.68-2.86)	1.25 (0.61-2.54)	
P_{trend}		0.25	0.39	
Glycemic Index				
Q1	122/112	Ref.	Ref.	
Q2	122/109	0.84 (0.56-1.28)	0.83 (0.55-1.26)	
Q3	116/112	0.95 (0.63-1.43)	0.93 (0.62-1.41)	age, sex, race, study indicator, fruit/vegetable intake, GERD frequency, and total energy intake
Q4	116/115	0.94 (0.62-1.43)	0.93 (0.62-1.41)	
P_{trend}		0.44	0.39	
Glycemic Load				
Q1	115/108	Ref.	Ref.	
Q2	119/124	1.19 (0.76-1.85)	1.18 (0.76-1.84)	
Q3	123/109	1.13 (0.68-1.88)	1.12 (0.67-1.86)	age, sex, BMI, study indicator, fruit/vegetable intake, GERD frequency, and total energy intake
Q4	119/107	1.40 (0.72-2.74)	1.39 (0.71-2.70)	
P_{trend}		0.32	0.35	
All Sweetened Desserts/Beverages (servings/day)				
Q1	119/88	Ref.	Ref.	
Q2	117/118	1.44 (0.94-2.21)	1.33 (0.88-2.02)	
Q3	120/112	1.29 (0.83-2.00)	1.27 (0.82-1.95)	age, sex, study indicator, GERD frequency, and total energy intake
Q4	120/130	1.80 (1.11-2.94)	1.71 (1.07-2.73)	
P_{trend}		0.03	0.04	
Sweetened Desserts (servings/day)				
Q1	117/112	Ref.	Ref.	
Q2	121/80	0.69 (0.44-1.07)	0.63 (0.41-0.96)	
Q3	119/121	1.20 (0.78-1.86)	1.12 (0.74-1.70)	age, sex, BMI, study indicator, GERD frequency, and total energy intake
Q4	119/135	1.36 (0.85-2.18)	1.26 (0.80-1.99)	
P_{trend}		0.06	0.10	
Sweetened Beverages (servings/day)				
Q1	118/97	Ref.	Ref.	
Q2	118/107	1.11 (0.72-1.69)	1.11 (0.73-1.69)	
Q3	119/106	1.32 (0.86-2.03)	1.29 (0.84-1.98)	age, sex, race, study indicator, fruit/vegetable intake, GERD frequency, and total energy intake
Q4	121/138	1.51 (0.98-2.33)	1.47 (0.95-2.26)	
P_{trend}		0.25	0.29	

[a] Model 1 adjusted for age, sex, race, study indicator, BMI, fruit/vegetable intake, GERD frequency, and total energy intake

Table 5.

Multivariable-adjusted ORs and 95% CIs for the associations between sugar/carbohydrate intake and risk of developing Barrett's esophagus by BE segment length among 413 cases and 492 controls from two U.S. case-control studies (pooled approach, based on study-specific medians)

		Short-segment BE(<3cm)		Long-segment BE (≥3cm)		*P-value*[f]
Measure	**Controls (N)**	**Cases (N)**	**OR (95%CI)**	**Cases (N)**	**OR (95%CI)**	
Free Glucose (g/day)[a]						
<median	236	116	Ref.	96	Ref.	
≥median	245	117	1.23 (0.83-1.83)	65	0.74 (0.47-1.16)	0.04
Sucrose (g/day)[a]						
<median	239	98	Ref.	91	Ref.	
≥median	242	135	1.70 (1.12-2.58)	70	0.82 (0.51-1.31)	<0.01
Free fructose (g/day)[a]						
<median	238	118	Ref.	91	Ref.	
≥median	243	115	1.21 (0.82-1.79)	70	0.92 (0.59-1.43)	0.27
Total Sugar (g/day)[a]						
<median	237	102	Ref.	95	Ref.	
≥median	244	131	1.57 (1.03-2.39)	66	0.72 (0.45-1.17)	<0.01
Added Sugar (g/day)[b]						
<median	237	96	Ref.	78	Ref.	
≥median	239	135	1.50 (0.99-2.26)	83	0.95 (0.60-1.50)	0.07
Starch (g/day)[a]						
<median	237	99	Ref.	91	Ref.	
≥median	244	134	1.65 (1.05-2.58)	70	0.76 (0.45-1.26)	<0.01
Total Carbohydrate (g/day)[a]						
<median	236	102	Ref.	96	Ref.	
≥median	245	131	1.72 (1.07-2.77)	65	0.63 (0.37-1.10)	<0.01
Glycemic Index[c]						
<median	244	108	Ref.	86	Ref.	
≥median	232	123	1.06 (0.75-1.50)	75	0.90 (0.60-1.33)	0.44

		Short-segment BE(<3cm)		Long-segment BE (≥3cm)		P-value[f]
Measure	**Controls (N)**	**Cases (N)**	**OR (95%CI)**	**Cases (N)**	**OR (95%CI)**	
Glycemic Load[a]						
<median	236	99	Ref.	104	Ref.	
≥median	245	134	1.76 (1.10-2.82)	57	0.42 (0.24-0.74)	0.01
All Sweetened Desserts/Beverages (servings/day)[d]						
<median	236	104	Ref.	79	Ref.	
≥median	241	127	1.22 (0.84-1.75)	82	1.04 (0.68-1.57)	0.51
Sweetened Desserts (servings/day)[b]						
<median	238	91	Ref.	81	Ref.	
≥median	238	140	1.81 (1.20-2.71)	80	1.08 (0.69-1.68)	0.04
Sweetened Beverages (servings/day)[e]						
<median	245	104	Ref.	78	Ref.	
≥median	246	144	1.48 (1.05-2.11)	87	1.27 (0.85-1.89)	0.47

[a]Adjusted for age, sex, study indicator, fruit/vegetable intake, GERD frequency, and total energy intake

[b]Adjusted for age, sex, race, study indicator, BMI, fruit/vegetable intake, GERD frequency, and total energy intake

[c]Adjusted for age, sex, study indicator, BMI, fruit/vegetable intake, GERD frequency, and total energy intake

[d]Adjusted for age, sex, study indicator, BMI, fruit/vegetable intake, and total energy intake

[e]Adjusted for age, sex, race, study indicator, fruit/vegetable intake, and total energy intake

[f]*P* value for Wald test of equality of effect across the different outcome types