

# Sugar-sweetened beverage and sugar intake during adolescence and risk of colorectal cancer precursors: a large prospective U.S. cohort study

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H-KJ and KW are the guarantors.

All authors contributed to the interpretation of the results and critical revision of the manuscript for important intellectual content and approved the final version of the manuscript.

The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

**Word count for the text:** 4750

**Word count for the abstract:** 313

**Number of tables:** 4

**Number of figure (black and white):** 1

**Number of supplemental tables:** 13

**Number of supplemental figure:** 1

## **ABSTRACT**

### **OBJECTIVE**

To examine the associations of adolescent sugar-sweetened beverage (SSB) and sugar intake with risk of colorectal cancer (CRC) precursors.

### **DESIGN**

Prospective cohort study.

### **SETTING**

Nurses' Health Study II (1998-2015), United States.

### **PARTICIPANTS**

33106 women who completed a validated high school food frequency questionnaire about adolescent diet in 1998 and underwent lower gastrointestinal endoscopy between 1999 and 2015.

### **MAIN OUTCOME MEASURES**

Incident CRC precursors confirmed by medical record review.

### **RESULTS**

During follow-up, 2909 conventional adenoma, 1082 high-risk adenoma ( $\geq 1$  cm in size, villous, high-grade dysplasia, or number  $\geq 2$ ), and 2355 serrated lesions were identified. Independent of adult intake, adolescent SSB and sugar intake was positively associated with risk of total and high-risk adenoma. Comparing  $\geq 2$  servings/day *v*  $< 1$  serving/week of SSB intake, multivariable odds ratios were 1.21 (95% confidence interval 1.00 to 1.47) for total and 1.21 (0.88 to 1.65) for high-risk adenoma. Per each 5% increment in calorie/day of total fructose intake, odds ratios were 1.17 (1.05 to 1.31) for total and 1.36 (1.14 to 1.62) for high-risk adenoma. By subsite, odds ratios were 1.25 (0.99 to 1.58) for proximal, 1.44 (1.12 to 1.84) for distal, and 1.74 (1.19 to 2.54) for rectal high-risk adenoma. Positive associations were stronger among women with low adolescent fruit, vegetable, or fiber intake. Among women with low fruit intake ( $< 1.3$  servings/day), odds ratios of total adenoma were 1.33 (1.11 to 1.59) for SSBs ( $\geq 1$  serving/day *v*  $< 1$  serving/week) and 1.51 (1.26 to 1.82) for the highest quintile of total fructose ( $P \leq 0.024$  for interaction). Neither SSB nor sugar intake during adolescence was associated with risk of serrated lesions.

### **CONCLUSIONS**

Independent of adult intake, adolescent SSB and sugar intake was positively associated with

colorectal adenoma, especially high-risk rectal adenoma. Our findings suggest that adolescence may be a critical developmental period of enhanced susceptibility to high sugar intake, possibly promoting precancerous lesions of CRC arising through the adenoma-carcinoma sequence.

**Keywords:** adolescence, added sugar, colorectal cancer precursor, colorectal adenoma, fructose, sugar-sweetened beverage, sugar

## **What is already known on this topic**

- Relatively few studies have examined the association between sugar intake and colorectal neoplasia, and most prospective studies have reported null associations.
- Considering the long process of colorectal carcinogenesis and recent upward trends in early-onset colorectal cancer, early-life diet may be etiologically relevant.
- However, data on the relationship between high sugar intake during early-life and risk of colorectal neoplasia are lacking.

## **What this study adds**

- Higher intake of sugar-sweetened beverages (SSBs) and sugars during adolescence was significantly associated with increased risk of total and high-risk adenoma, especially high-risk rectal adenoma, but not serrated lesions.
- Positive associations were stronger among women with low fruit, vegetable, or fiber intake during adolescence.
- Our results suggest that limiting sugar intake and replacing SSBs with healthy alternatives during early-life may help to reduce risk of colorectal cancer precursors.

## INTRODUCTION

The global burden of colorectal cancer (CRC) is expected to increase to over 2.2 million new cases and 1.1 million cancer deaths per annum by 2030.<sup>1</sup> The vast majority of CRC develops from malignant transformation of benign precursors, with the carcinogenesis process generally spanning several decades.<sup>2,3</sup> CRC is among the most preventable cancers,<sup>4</sup> with more than one-half of CRC cases and deaths attributable to modifiable diet and lifestyle factors.<sup>5</sup> In several high-income countries, an emerging trend is the rising incidence of CRC at ages under 50 years, often referred to as early-onset CRC.<sup>3,5,6</sup> In the U.S., incidence of early-onset CRC has been on the rise since the mid-1990s; and among those aged 50–64 years, CRC incidence has also started to increase since 2011 (after declines during the 2000s), reflecting elevated risk in generations born after 1950. This birth cohort effect indicates that shared population-level changes in exposures during early-life may have contributed to the recent increase in early-onset CRC.<sup>5,6</sup>

Sugar-sweetened beverages (SSBs) include carbonated and noncarbonated soft drinks, fruit drinks, and sports drinks, mostly sweetened with high-fructose corn syrup (first marketed in the early 1970s; usually 55% fructose and 45% glucose) or sucrose (table sugar; half fructose and half glucose).<sup>7-9</sup> SSB intake is markedly increasing worldwide, particularly in developing countries,<sup>10</sup> with concomitant increase in fructose and added sugar intake.<sup>9</sup> In 53 low- and middle-income countries, 54% of adolescents aged 12–15 years consumed carbonated soft drinks at least once per day.<sup>11</sup> In the U.S., SSBs were the largest source of added sugar, accounting for nearly a half of all added sugar intake in 2005–2006.<sup>7</sup> One-half of adults and 63% of youths aged 2–19 years consumed at least 1 serving/day of SSBs, with the highest levels in adolescents aged 12–19 years, who consumed about 10% of daily calories from SSBs.<sup>12,13</sup>

SSB and high sugar intake can promote colorectal carcinogenesis by causing insulin resistance, obesity, and type 2 diabetes<sup>14-18</sup>—established risk factors for CRC.<sup>4</sup> Despite the close link between insulin resistance and CRC,<sup>19-22</sup> relatively few studies have examined the association between sugar intake and colorectal neoplasia, and most prospective studies have reported null associations.<sup>4,23,24</sup> However, no previous study examined sugar intake during early-life. Considering the long process of carcinogenesis and recent upward trends in early-onset CRC,<sup>3,6</sup> early-life diet may be etiologically relevant to CRC development.<sup>25,26</sup> Moreover, adolescence is a unique growth period characterized by physiologically decreased insulin



sensitivity and a surge of insulin-like growth factor 1 (IGF1).<sup>27</sup> Thus, adolescence may be a critical developmental period of enhanced susceptibility to the adverse effects of high sugar intake. Our hypothesis was that high sugar intake during adolescence may play a role in early steps of colorectal carcinogenesis. We prospectively investigated the associations of adolescent SSB and sugar intake with risk of CRC precursors in a large cohort of young women.

## **METHODS**

### **Study population**

The Nurses' Health Study II (NHSII) is an ongoing prospective cohort established in 1989 when 116430 U.S. female registered nurses aged 25–42 years returned a mailed questionnaire about various lifestyle factors and medical history.<sup>28</sup> Follow-up questionnaires were mailed biennially to update the information and newly diagnosed diseases. In 1998, 45947 participants completed a high school food frequency questionnaire (HS-FFQ) about diet during adolescence.<sup>29</sup> We included women who had completed the HS-FFQ in 1998 and subsequently underwent at least one lower gastrointestinal endoscopy between 1999 and 2015. We excluded women who had no lower bowel endoscopy during the follow-up because CRC precursors are generally asymptomatic and detected during an endoscopy. We also excluded women with a history of any cancer (other than nonmelanoma skin cancer), CRC precursors, Crohn's disease, or ulcerative colitis prior to the return of the HS-FFQ, and those reporting implausible adolescent caloric intake (<600 or  $\geq$ 5000 kcal/day), leaving a total of 33106 women for the current analyses. Then we additionally excluded individuals with missing values for each exposure variable of interest. The study protocol was approved by the institutional review boards of the Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health, and those of participating registries as required.

### **Dietary assessment**

Adolescent diet was assessed using a 124-item self-administered HS-FFQ, specifically designed to include food items commonly consumed between 1960 and 1982 when participants were 13–18 years.<sup>30</sup> Participants were asked how often, on average, they had consumed a standard portion

size of each food or beverage when they were in high school, with 9 possible responses ranging from “never or less than once per month” to “6 or more times per day.” The reproducibility and validity of the HS-FFQ have been described previously.<sup>29 31</sup> In brief, reproducibility at a 4-year interval was moderate-to-good (correlation for overall nutrients,  $r=0.65$ ; foods,  $r=0.60$ ; total fructose,  $r=0.65$ ; cola,  $r=0.74$ ; orange juice,  $r=0.74$ ).<sup>29</sup> Two independent validation studies reported adequate validity ( $r$  for overall nutrients, 0.40–0.58).<sup>29 31</sup> Since 1991, adult diet was assessed every 4 years using a validated FFQ with approximately 131-food items.<sup>32 33</sup>

SSBs were defined as caffeinated and caffeine-free colas (e.g., Coke, Pepsi) and other carbonated (e.g., 7-Up) and non-carbonated sugary beverages (fruit punches, lemonades, or other fruit drinks). Artificially-sweetened beverages (ASBs) included carbonated and non-carbonated low-calorie or diet beverages. Standard serving sizes for SSBs and ASBs were 1 glass, a bottle, or a can (12 ounces). Fruit juice included orange, apple, grapefruit, and other fruit juices, with 1 small glass (6 ounces) as a serving size. Dairy products included milk, yogurt, cheese, ice cream, sherbet, milkshake, and frappe. Because disaccharide sucrose consists of half fructose and half glucose, total fructose intake was defined as the sum of free fructose and half of sucrose intake, and glucose intake from simple sugars was defined as the sum of free glucose and half of sucrose intake.<sup>9</sup> Added sugar refers to sugar added to foods and beverages during processing or preparation.<sup>34</sup> Total sugar represents the sum of monosaccharides and disaccharides (fructose, glucose, sucrose, and maltose).<sup>34</sup>

The nutrient database was primarily derived from U.S. Department of Agriculture sources,<sup>29 35</sup> supplemented with information from manufacturers. Nutrient intake was adjusted for total energy intake using the residual method reported previously.<sup>36-38</sup> For sugar intake, we also calculated nutrient density (percentage of daily calories contributed by each sugar).<sup>38</sup> To better represent long-term diet during adulthood and reduce measurement error due to within-person variability,<sup>37</sup> cumulative updated intake was calculated for adult diet by averaging the repeated measures from all available FFQs up to 2 years prior to the most recent endoscopy. As an indicator of overall diet during adolescence, we derived prudent and western dietary patterns using principal component analyses as reported previously.<sup>39</sup> A western dietary pattern was characterized by high intake of desserts, sweets, snacks, red and processed meat, and refined grains; while a prudent pattern was characterized by high intake of vegetables, fruits, better-quality grains, fish, and poultry (Supplementary Table 1). For analyses of SSBs, ASBs, and fruit

juice, dietary patterns were derived after excluding each beverage variable to avoid collinearity with the primary exposure.

### **Outcome ascertainment**

On each biennial questionnaire, participants were asked whether they underwent a lower bowel endoscopy and the reasons why (screening, family history of CRC, symptoms), and whether CRC or precursors were diagnosed. Participants who reported a diagnosis of CRC precursors were asked for permission to access medical and pathological records. Physicians blinded to participant exposure information reviewed the records to verify the diagnosis and accrue information on CRC precursor size, number, subtype (conventional adenoma [hereinafter referred to as adenoma], serrated lesion), subsite (proximal, distal, rectal), and histology (tubular, tubulovillous, villous; with or without high-grade dysplasia). We subdivided adenoma into high-risk ( $\geq 1$  cm, any villous histology, high-grade dysplasia, or  $\geq 2$  adenomas) and low-risk ( $< 1$  cm, tubular, and single) adenoma.<sup>40</sup> Serrated lesions included hyperplastic polyps, sessile serrated adenoma/sessile serrated polyp, and traditional serrated adenoma,<sup>41</sup> with subdivision by size ( $< 1$  cm,  $\geq 1$  cm).

### **Statistical analysis**

SSB and other beverage intake was grouped into 4 categories:  $< 1$  serving/week, 1–6 servings/week, 1 serving/day, and  $\geq 2$  servings/day. Sugar intake was categorized into quintiles using either nutrient density or energy-adjusted intake. SSB and sugar intake was also treated as continuous variables. Time-varying covariates were updated to 2 years prior to most recent endoscopy, whenever available. To handle individuals with multiple endoscopies and time-varying covariates efficiently, the Andersen-Gill data structure was used.<sup>42</sup> A new dataset were generated for each questionnaire cycle when participants reported an endoscopy. Thus, participants with multiple endoscopies during follow-up could provide multiple records. Once CRC precursor(s) were diagnosed, the participant was censored.

Odds ratios and 95% confidence intervals of CRC precursors were estimated using logistic regression for clustered data (SAS PROC GENMOD) where each participant represented a cluster. We constructed 3 multivariable models with adjustment for various potential confounders during both adolescence and adulthood.<sup>43</sup> Model 1 included age, time period of

endoscopy, time since most recent endoscopy, number of endoscopies, and reason for endoscopy. Model 2 was additionally adjusted for family history of CRC in first degree of relatives, menopausal status/menopausal hormone use, current aspirin use  $\geq 2$  times/week, history of type 2 diabetes, adult height, body mass index (BMI, at 18 years and current), smoking status (adolescent and current), alcohol consumption (18–22 years and current), and physical activity (adolescent and current). In Model 3, to assess whether associations were independent of other dietary factors and overall unhealthy dietary pattern, we further adjusted for adolescent and adult dietary intake (total calorie, calcium, vitamin D, folate, fiber, fruits, vegetables, and dairy), current total red meat intake, a western dietary pattern score during adolescence, and corresponding adult variables to adolescent exposure variables.

Tests for trend were performed by assigning a median value to each category of exposure variables and modeling this value as a continuous variable, with the Wald test used to assess statistical significance. Stratified analyses were performed to examine whether associations varied across strata of known CRC risk factors during adolescence (e.g., family history of CRC, BMI, physical activity, fruit and vegetable intake).<sup>43</sup> Tests for interaction were performed by including cross-product terms of exposure and stratification variables in the model and utilizing a Wald test. To compare the effects of diet during different life stages, we examined joint associations of adolescent and adult intake with CRC precursor risk. The effects of substituting fruits, fruit juice, or dairy for SSBs were estimated by simultaneously including both SSBs and one of these food items as continuous variables in models; ORs and 95% CIs were calculated from the differences in coefficients and corresponding variances and covariances.<sup>44-46</sup> All tests were two-sided with  $P < 0.05$  considered statistically significant. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

### **Patient and public involvement**

No patients were involved in setting the research question or the outcome measures, nor were they involved in the design and implementation of the study. We plan to disseminate these findings to participants through the study websites ([www.nurseshealthstudy.org](http://www.nurseshealthstudy.org)) and annual newsletter and to the general public in a press release.

## RESULTS

Baseline characteristics of the participants are described in table 1. The mean age of the participants was  $44.1 \pm 4.5$  years when the HS-FFQ was completed. During adolescence, 12.6% of women had consumed  $\geq 1$  serving/day of SSBs ( $\geq 2$  servings/day, 4.8%), while in adulthood, 11.1% consumed  $\geq 1$  serving/day ( $\geq 2$  servings/day, 3.2%). Adolescent SSB intake contributed to 2.6% of daily calories. SSB-source added sugar intake was 18.2 g/day, on average, which was lower than the mean intake (27 g/day) among U.S. youths aged 1–18 years in the national survey in 1971–1974,<sup>47</sup> the median time period when our participants attended high school. Participants with higher adolescent SSB and total fructose intake were more likely to be physically active during adolescence. While women with higher adolescent SSB intake were more likely to have higher red meat intake and lower fruit and vegetable intake, those with higher fructose intake were more likely to have lower red meat and higher fruit and vegetable intake during both adolescence and adulthood. The correlation between SSB and total fructose intake during adolescence was low-to-modest (Spearman correlation,  $r=0.38$ ; supplementary table 2). Adolescent diet was only weakly correlated with adult diet (SSBs, age-corrected partial  $r=0.25$ ; total fructose,  $r=0.27$ ).

During follow-up, 4744 women were diagnosed with at least one CRC precursor, of whom 2909 had at least one adenoma (1548 proximal, 1205 distal, 458 rectal, and 1082 high-risk adenoma), and 2355 at least one serrated lesion. The mean age at diagnoses was  $52.2 \pm 4.3$  years (range, 37–68).

**Table 1 | Baseline characteristics of participants by sugar-sweetened beverage and total fructose intake during adolescence in the Nurses' Health Study II\***

	Sugar-sweetened beverage intake during adolescence (serving)			Total fructose intake during adolescence (% of calorie)		
	<1/wk (n=14398)	1-6/wk (n=14545)	≥1/d (n=4163)	Q1 (<7.9) (n=6598)	Q3 (9.2–10.3) (n=6682)	Q5 (≥11.8) (n=6639)
Age at 1998 questionnaire return (yrs)	44.1 (4.5)	44.3 (4.5)	43.7 (4.5)	44.6 (4.4)	44.2 (4.6)	43.7 (4.5)
Number of endoscopies during the study period (n)	1.2 (0.5)	1.2 (0.5)	1.2 (0.5)	1.2 (0.5)	1.2 (0.5)	1.2 (0.5)
Time since most recent endoscopy (yrs)	1.4 (3.8)	1.4 (3.8)	1.5 (4.0)	1.4 (3.8)	1.4 (3.8)	1.4 (3.8)
Reason for endoscopy, yes†, %	21.5	23.9	25.7	23.4	22.5	24.3
Adult height (inches)	65.0 (2.6)	64.9 (2.6)	64.8 (2.6)	64.8 (2.6)	64.9 (2.6)	64.9 (2.6)
BMI at age 18 y (kg/m <sup>2</sup> )	21.4 (3.2)	20.9 (3.0)	21.0 (3.4)	21.4 (3.3)	21.1 (3.0)	21.0 (3.2)
Current BMI (kg/m <sup>2</sup> )	26.1 (6.1)	26.0 (5.8)	26.9 (6.3)	26.4 (6.0)	26.0 (5.8)	26.3 (6.1)
Smoking before 20 years of age, %	19.7	23.2	30.3	21.9	21.9	24.0
Current smoker, %	4.8	5.8	9.2	6.5	5.6	6.3
Physical activity at grades 9–12 (MET-h/wk)	50.0 (35.6)	52.9 (36.5)	54.7 (37.9)	49.1 (36.1)	51.1 (35.1)	54.5 (37.6)
Current physical activity (MET-h/wk)	20.5 (24.3)	18.4 (22.0)	17.4 (24.4)	17.5 (21.1)	19.0 (22.6)	20.5 (26.0)
Premenopause, %	48.6	48.6	44.4	47.0	48.7	47.5
Family history of colorectal cancer, %	22.6	22.0	23.9	22.4	22.8	22.2
Diabetes, %	4.1	3.9	5.8	4.8	4.3	4.6
Current aspirin use (≥2 d/wk), %	11.8	12.7	13.9	12.6	11.3	13.5
Food and nutrient intake during adolescence‡						
Unprocessed red meat (g/d)	102 (52)	110 (50)	119 (51)	120 (60)	109 (48)	94 (46)
Processed meat (g/d)	20 (18)	24 (19)	26 (21)	24 (22)	23 (18)	20 (17)
Fruits (serving/d)	1.6 (1.1)	1.5 (1.0)	1.3 (1.0)	1.0 (0.6)	1.6 (0.8)	2.1 (1.5)
Vegetables (serving/d)	3.3 (1.9)	3.1 (1.7)	2.9 (1.7)	2.7 (1.6)	3.2 (1.7)	3.4 (2.1)
Total dairy (serving/d)	2.8 (1.5)	2.8 (1.5)	2.7 (1.5)	3.0 (1.6)	2.9 (1.4)	2.3 (1.4)
Calcium (mg/d)	1154 (371)	1065 (320)	925 (274)	1234 (402)	1090 (316)	919 (272)
Vitamin D (IU/d)	377 (211)	341 (174)	277 (163)	410 (212)	347 (178)	283 (175)
Folate (µg/d)	345 (112)	316 (90)	281 (80)	301 (89)	328 (96)	334 (116)
Fiber (g/d)	21.9 (5.8)	20.4 (4.6)	18.7 (4.2)	18.6 (4.6)	21.1 (4.6)	22.3 (6.4)
Glycemic index	54.1 (2.7)	55.1 (2.4)	57 (2.6)	54.6 (2.9)	54.7 (2.5)	55.8 (2.9)

Glycemic load	165 (25)	171 (22)	187 (25)	148 (22)	169 (16)	196 (21)
Alcohol (g/d)	0.2 (1.9)	0.3 (1.7)	0.5 (2.5)	0.3 (2.3)	0.3 (2.0)	0.3 (1.8)
Sugar-sweetened beverage (serving/wk)	0.4 (0.4)	3.2 (1.7)	12.5 (6.7)	1.1 (1.5)	2.4 (2.6)	7.3 (7.6)
Artificially-sweetened beverage (serving/wk)	3.6 (6.5)	1.5 (3.5)	1.5 (4.5)	2.8 (5.8)	2.4 (5.1)	2.1 (5.1)
Fruit juice (serving/wk)	4.9 (4.7)	5.1 (4.6)	4.6 (4.4)	2.7 (2.8)	5.1 (3.9)	6.7 (6.4)
Total fructose (% of calorie)§	9.0 (2.3)	10.1 (2.1)	12.6 (2.7)	6.7 (1.0)	9.7 (0.3)	13.6 (1.8)
Glucose (from simple sugars, % of calorie)§	8.7 (2.1)	9.8 (2.0)	12.5 (2.7)	6.7 (1.0)	9.5 (0.6)	13.2 (1.9)
Added sugar (% of calorie)§	11.7 (3.7)	14.6 (3.6)	20.8 (5.4)	9.5 (2.3)	13.6 (2.6)	19.9 (5.4)
Total sugar (% of calorie)§	22.5 (4.4)	24.3 (4.0)	28.7 (5.1)	18.7 (3.0)	23.7 (2.0)	30.3 (3.7)
Current (adult) food and nutrient intake‡						
Unprocessed red meat (g/d)	51 (33)	58 (33)	64 (35)	58 (35)	56 (33)	53 (33)
Processed red meat (g/d)	7 (7)	8 (7)	9 (8)	8 (7)	8 (7)	7 (7)
Fruits (serving/d)	1.4 (0.8)	1.3 (0.8)	1.1 (0.8)	1.1 (0.7)	1.3 (0.8)	1.4 (1.0)
Vegetables (serving/d)	3.8 (2.0)	3.6 (1.8)	3.5 (1.9)	3.4 (1.8)	3.7 (1.8)	3.8 (2.2)
Total dairy (serving/d)	2.1 (1.1)	2.1 (1.1)	1.9 (1.1)	2.1 (1.1)	2.2 (1.1)	1.9 (1.1)
Calcium (mg/d)	1273 (418)	1189 (397)	1100 (403)	1239 (421)	1228 (406)	1173 (427)
Vitamin D (IU/d)	453 (221)	418 (206)	381 (209)	443 (219)	432 (212)	409 (222)
Folate (µg/d)	599 (215)	562 (200)	525 (200)	562 (208)	573 (204)	577 (214)
Fiber (g/d)	20.9 (5.2)	19.4 (4.6)	18.0 (4.6)	19.2 (4.7)	20.0 (4.8)	20.1 (5.4)
Alcohol (g/d)	4.3 (6.5)	4.3 (6.4)	4.5 (7.3)	4.4 (7.0)	4.4 (6.5)	4.0 (6.3)
Sugar-sweetened beverage (serving/wk)	1.7 (2.8)	3.2 (4.2)	5.4 (7.2)	2.0 (3.4)	2.6 (3.9)	4.1 (6.0)
Artificially-sweetened beverage (serving/wk)	6.1 (7.8)	5.6 (7.1)	8.3 (9.5)	6.3 (7.9)	5.9 (7.4)	6.8 (8.6)
Fruit juice (serving/wk)	4.5 (4.2)	4.8 (4.3)	4.3 (4.2)	3.6 (3.7)	4.7 (4.2)	5.3 (5.0)
Total fructose (% of calorie)§	9.1 (2.5)	9.7 (2.8)	10.2 (3.7)	8.4 (2.6)	9.4 (2.6)	10.6 (3.2)
Glucose (from simple sugars, % of calorie)§	8.8 (2.4)	9.4 (2.6)	10.0 (3.5)	8.2 (2.5)	9.2 (2.4)	10.3 (3.0)
Added sugar (% of calorie)§	9.9 (3.9)	11.5 (4.9)	13.3 (6.8)	9.8 (4.4)	10.9 (4.5)	12.6 (6.0)
Total sugar (% of calorie)§	22.5 (5.4)	23.4 (5.7)	24.0 (7.2)	21.4 (5.6)	23.0 (5.4)	24.8 (6.4)

BMI=body mass index; IU=international units; MET=metabolic equivalent of tasks; Q=quintile

\*Means (SD) are presented for continuous variables; percentages for categorical variables. All variables other than age at 1998 are standardized to the age distribution of the study population.

†Includes bleeding in stool, positive test for occult fecal blood, diarrhea or constipation, and abdominal pain.

‡Nutrients are energy-adjusted values unless otherwise indicated.

§From mono- and disaccharide sugars. Total sugar intake was defined as sum of fructose, glucose, sucrose, and maltose intake.

||Intake from 1999 food frequency questionnaire.

### **SSB and sugar intake and CRC precursor risk**

Independent of adult intake, higher intake of SSBs and total fructose during adolescence was significantly associated with increased risk of total adenoma (tables 2 and 3). For fructose intake, positive associations with adenoma risk were not significant in model 1 and 2. However, additional adjustment for dietary covariables (especially adolescent fruit, fiber, and calcium intake) in model 3 substantially strengthened the associations. In fully adjusted models, the odd ratios of total adenoma were 1.21 (95% confidence interval 1.00 to 1.47;  $P=0.012$  for trend) for SSB intake, comparing  $\geq 2$  servings/day  $\nu$   $< 1$  serving/week, and 1.17 (1.05 to 1.31;  $P=0.006$  for trend) per 5% of calorie/day increase in total fructose intake. By subsite, each serving per day increment in SSBs was associated with higher risk of proximal (odds ratio 1.13, 95% confidence interval 1.02 to 1.26), distal (1.08, 0.95 to 1.21), and rectal (1.28, 1.07 to 1.53) adenoma; a 5% calorie/day increment in total fructose was positively associated with proximal (1.12, 0.96 to 1.30), distal (1.24, 1.05 to 1.48) and rectal (1.43, 1.10 to 1.86) adenoma. Results for glucose (from simple sugars), added sugar, and total sugar were similar to the results for total fructose, but effect sizes were slightly smaller than for total fructose (supplementary table 3). Neither SSB nor sugar intake during adolescence was associated with risk of total and large serrated lesions (all  $P \geq 0.34$  for trend). We found no significant associations between adolescent ASB or fruit juice intake and CRC precursor risk (supplementary table 4). Contrary to adolescent intake, SSB and sugar intake during adulthood was not associated with adenoma risk. For adult SSB intake ( $\geq 2$  servings/day  $\nu$   $< 1$  serving/week), odd ratios were 0.87 (95% confidence interval 0.67 to 1.14) for total and 0.87 (0.47 to 1.61) for rectal adenoma; for adult total fructose intake (highest  $\nu$  lowest quintile), odd ratios were 0.95 (0.82 to 1.09) for total and 0.79 (0.56 to 1.12) for rectal adenoma.



**Table 2 | Odds ratios and 95% confidence intervals of CRC precursor according to sugar-sweetened beverage intake during adolescence in the Nurses' Health Study II, 1998-2015**

	Sugar-sweetened beverage intake during adolescence, servings				P value for trend	Per 1 serving/day increase
	<1/week	1-6/week	1/day	≥2/day		
<b>Total adenoma</b>						
$N_{\text{cases}}/N_{\text{controls}}^*$	1280/21597	1201/22103	267/3834	161/2300		
Model 1†	1	0.91 (0.84 to 0.99)	1.20 (1.04 to 1.37)	1.20 (1.01 to 1.42)	0.007	1.10 (1.03 to 1.17)
Model 2‡	1	0.92 (0.85 to 1.00)	1.18 (1.03 to 1.36)	1.18 (0.99 to 1.40)	0.012	1.09 (1.02 to 1.17)
Model 3§	1	0.92 (0.84 to 1.00)	1.20 (1.03 to 1.39)	1.21 (1.00 to 1.47)	0.012	1.10 (1.02 to 1.19)
<b>Proximal adenoma</b>						
$N_{\text{cases}}/N_{\text{controls}}$	685/21206	630/21732	147/3757	86/2257		
Model 3	1	0.91 (0.81 to 1.03)	1.25 (1.03 to 1.53)	1.27 (0.97 to 1.66)	0.023	1.13 (1.02 to 1.26)
<b>Distal adenoma</b>						
$N_{\text{cases}}/N_{\text{controls}}$	523/21206	508/21732	110/3757	64/2257		
Model 3	1	0.94 (0.82 to 1.07)	1.18 (0.94 to 1.48)	1.13 (0.83 to 1.53)	0.237	1.08 (0.95 to 1.21)
<b>Rectal adenoma</b>						
$N_{\text{cases}}/N_{\text{controls}}$	201/21206	174/21732	50/3757	33/2257		
Model 3	1	0.85 (0.68 to 1.06)	1.45 (1.03 to 2.05)	1.62 (1.03 to 2.53)	0.008	1.28 (1.07 to 1.53)
<b>Total serrated lesion  </b>						
$N_{\text{cases}}/N_{\text{controls}}$	960/21682	1095/21921	179/3881	121/2322		
Model 3	1	1.12 (1.01 to 1.23)	1.01 (0.84 to 1.20)	1.14 (0.91 to 1.43)	0.335	1.04 (0.96 to 1.14)
<b>Small serrated lesion  </b>						
$N_{\text{cases}}/N_{\text{controls}}$	817/21682	940/21921	158/3881	100/2322		
Model 3	1	1.14 (1.03 to 1.26)	1.07 (0.88 to 1.29)	1.14 (0.89 to 1.45)	0.305	1.05 (0.96 to 1.15)
<b>Large serrated lesion  </b>						
$N_{\text{cases}}/N_{\text{controls}}$	86/21682	90/21921	11/3881	9/2322		
Model 3	1	0.99 (0.73 to 1.36)	0.65 (0.34 to 1.26)	0.90 (0.42 to 1.93)	0.528	0.90 (0.66 to 1.24)
<b>Subtype of CRC precursor</b>						
<b>Adenoma only</b>						
$N_{\text{cases}}/N_{\text{controls}}$	1056/20861	985/21224	222/3700	126/2214		
Model 3	1	0.94 (0.85 to 1.03)	1.24 (1.05 to 1.46)	1.18 (0.95 to 1.47)	0.028	1.10 (1.01 to 1.20)
<b>Serrated lesion only</b>						
$N_{\text{cases}}/N_{\text{controls}}$	736/20861	879/21224	134/3700	86/2214		
Model 3	1	1.18 (1.06 to 1.31)	1.02 (0.84 to 1.25)	1.10 (0.86 to 1.43)	0.524	1.03 (0.94 to 1.14)
<b>Both adenoma and serrated lesion</b>						
$N_{\text{cases}}/N_{\text{controls}}$	224/20861	216/21224	45/3700	35/2214		
Model 3	1	0.89 (0.73 to 1.09)	1.03 (0.73 to 1.44)	1.33 (0.88 to 2.01)	0.183	1.12 (0.95 to 1.34)

CRC=colorectal cancer; N=number of endoscopies

\*Due to multiple endoscopies during follow-up per each participant, N is larger than number of participants.

†Adjusted for age, time period of endoscopy, number of endoscopies during the study period (continuous), time since most recent endoscopy (continuous), and reason for current endoscopy (screening/symptoms).

‡Additionally adjusted for family history of colorectal cancer (yes/no), menopausal status/menopausal hormone use (premenopausal, postmenopausal with never, past, or current hormone therapy), current aspirin use  $\geq 2$  times/wk (yes/no), history of type 2 diabetes (yes/no), adult height (continuous), BMI at age 18 y ( $<18.5$ ,  $18.5$ – $<20$ ,  $20$ – $<22.5$ ,  $22.5$ – $<25$ ,  $\geq 25$  kg/m<sup>2</sup>), current BMI ( $<22.5$ ,  $22.5$ – $<25$ ,  $25$ – $<27.5$ ,  $27.5$ – $<30$ ,  $\geq 30$  kg/m<sup>2</sup>), smoking status at 19 y (never,  $0$ – $<2.5$ ,  $>2.5$  pack-years), current smoking status (never smoker, past smoker  $<30$  pack-years, past smoker  $\geq 30$  pack-years, current smoker  $<30$  pack-years, current smoker  $\geq 30$  pack-years), alcohol intake at 18–22 y ( $<0.1$ ,  $0.1$ – $4.9$ ,  $5$ – $14.9$ ,  $\geq 15$  g/d), current alcohol intake (none,  $0.1$ – $4.9$ ,  $5$ – $9.9$ ,  $10$ – $14.9$ ,  $\geq 15$  g/d), physical activity during grades 9–12 (quintile), and current physical activity ( $<21$ ,  $21$ – $<30$ ,  $30$ – $<39$ ,  $39$ – $<54$ ,  $\geq 54$  MET hours/wk).

§Additionally adjusted for adolescent and current (adult) dietary intake (total calorie, total calcium, vitamin D, total folate, total fiber, fruits, vegetables, and dairy; quintile), current total red meat intake (quintile), a western dietary pattern score during adolescence (quintile), and current sugar-sweetened beverage intake ( $<1$  serving/wk,  $1$ – $6$  serving/wk,  $1$  serving/d,  $\geq 2$  serving/d).

||Included hyperplastic polyp, sessile serrated adenoma/polyp, and traditional serrated adenoma; small,  $<1$ cm; large,  $\geq 1$  cm.

**Table 3 | Odds ratios and 95% confidence intervals of CRC precursor according to total fructose intake during adolescence in the Nurses' Health Study II, 1998–2015**

	Total fructose intake during adolescence, % of calorie					P value for trend	Per 5% of calorie/day increase
	Q1 (<7.9)	Q2 (7.9–<9.2)	Q3 (9.2–<10.3)	Q4 (10.3–<11.8)	Q5 (≥11.8)		
<b>Total adenoma</b>							
<i>N</i> <sub>cases</sub> / <i>N</i> <sub>controls</sub> *	573/9976	570/9978	595/9954	591/9958	580/9968		
Model 1†	1	1.00 (0.89 to 1.12)	1.05 (0.93 to 1.18)	1.05 (0.93 to 1.18)	1.03 (0.92 to 1.16)	0.436	1.04 (0.95 to 1.13)
Model 2‡	1	1.00 (0.89 to 1.13)	1.06 (0.94 to 1.20)	1.07 (0.95 to 1.20)	1.06 (0.94 to 1.20)	0.207	1.06 (0.97 to 1.16)
Model 3§	1	1.05 (0.93 to 1.19)	1.14 (1.00 to 1.30)	1.19 (1.04 to 1.36)	1.20 (1.04 to 1.39)	0.006	1.17 (1.05 to 1.31)
<b>Proximal adenoma</b>							
<i>N</i> <sub>cases</sub> / <i>N</i> <sub>controls</sub>	316/9795	306/9807	323/9765	310/9776	293/9809		
Model 3	1	1.03 (0.87 to 1.22)	1.15 (0.96 to 1.36)	1.15 (0.96 to 1.39)	1.13 (0.92 to 1.38)	0.164	1.12 (0.96 to 1.30)
<b>Distal adenoma</b>							
<i>N</i> <sub>cases</sub> / <i>N</i> <sub>controls</sub>	239/9795	221/9807	241/9765	251/9776	253/9809		
Model 3	1	0.97 (0.80 to 1.18)	1.10 (0.90 to 1.35)	1.21 (0.98 to 1.48)	1.25 (1.00 to 1.56)	0.014	1.24 (1.05 to 1.47)
<b>Rectal adenoma</b>							
<i>N</i> <sub>cases</sub> / <i>N</i> <sub>controls</sub>	77/9795	97/9807	84/9765	101/9776	99/9809		
Model 3	1	1.39 (1.01 to 1.89)	1.24 (0.90 to 1.73)	1.61 (1.15 to 2.25)	1.62 (1.14 to 2.31)	0.008	1.43 (1.10 to 1.86)
<b>Total serrated lesion  </b>							
<i>N</i> <sub>cases</sub> / <i>N</i> <sub>controls</sub>	479/9951	442/9993	486/9945	486/9934	462/9983		
Model 3	1	0.93 (0.80 to 1.07)	1.03 (0.89 to 1.20)	1.06 (0.91 to 1.23)	1.01 (0.86 to 1.19)	0.486	1.04 (0.92 to 1.18)
<b>Small serrated lesion  </b>							
<i>N</i> <sub>cases</sub> / <i>N</i> <sub>controls</sub>	405/9951	374/9993	420/9945	430/9934	386/9983		
Model 3	1	0.93 (0.80 to 1.08)	1.06 (0.91 to 1.24)	1.12 (0.96 to 1.32)	1.01 (0.85 to 1.21)	0.408	1.06 (0.93 to 1.21)
<b>Large serrated lesion  </b>							
<i>N</i> <sub>cases</sub> / <i>N</i> <sub>controls</sub>	46/9951	41/9993	40/9945	29/9934	40/9983		
Model 3	1	0.88 (0.57 to 1.37)	0.85 (0.54 to 1.35)	0.60 (0.36 to 1.00)	0.86 (0.54 to 1.37)	0.345	0.83 (0.56 to 1.22)
<b>Subtype of CRC precursor</b>							
<b>Adenoma only</b>							
<i>N</i> <sub>cases</sub> / <i>N</i> <sub>controls</sub>	472/9598	488/9618	482/9581	469/9594	478/9608		
Model 3	1	1.10 (0.96 to 1.26)	1.13 (0.98 to 1.30)	1.15 (0.99 to 1.34)	1.20 (1.03 to 1.41)	0.027	1.15 (1.02 to 1.30)
<b>Serrated lesion only</b>							
<i>N</i> <sub>cases</sub> / <i>N</i> <sub>controls</sub>	378/9598	360/9618	373/9581	364/9594	360/9608		
Model 3	1	0.96 (0.82 to 1.12)	1.00 (0.85 to 1.17)	0.99 (0.84 to 1.17)	0.99 (0.83 to 1.18)	0.998	1.00 (0.87 to 1.15)
<b>Both adenoma and serrated lesion</b>							
<i>N</i> <sub>cases</sub> / <i>N</i> <sub>controls</sub>	101/9598	82/9618	113/9581	122/9594	102/9608		
Model 3	1	0.84 (0.62 to 1.14)	1.20 (0.89 to 1.61)	1.36 (1.01 to 1.85)	1.20 (0.85 to 1.67)	0.061	1.28 (0.99 to 1.65)

CRC=colorectal cancer; N=number of endoscopies; Q=quintile

\*Due to multiple endoscopies during follow-up per each participant, N is larger than number of participants.

†Adjusted for age, time period of endoscopy, number of endoscopies during the study period (continuous), time since most recent endoscopy (continuous), and reason for current endoscopy (screening/symptoms).

‡Additionally adjusted for family history of colorectal cancer, menopausal status/menopausal hormone use, current aspirin use  $\geq 2$  times/wk, history of type 2 diabetes, adult height (continuous), BMI at age 18 y, current BMI, smoking status at 19 y, current smoking status, alcohol intake at 18–22 y, current alcohol intake, physical activity during grades 9–12, and current physical activity.

§Additionally adjusted for adolescent and current dietary intake (total calorie, total calcium, vitamin D, total folate, total fiber, fruits, vegetables, and dairy), current total red meat intake, a western dietary pattern score during adolescence, and current total fructose intake.

||Included hyperplastic polyp, sessile serrated adenoma/polyp, and traditional serrated adenoma; small, <1cm; large,  $\geq 1$  cm.

### **SSB and sugar intake and risk of high-risk adenoma**

Adolescent intake of SSBs and total fructose was positively associated with high-risk adenoma, but not with low-risk adenoma (table 4). The multivariable odds ratios of high-risk adenoma were 1.21 (95% confidence interval 0.88 to 1.65;  $P=0.085$  for trend) for SSB intake, comparing  $\geq 2$  servings/day  $\nu$   $< 1$  serving/week, and 1.36 (1.14 to 1.62;  $P=0.001$  for trend) per each 5% increase in calorie/day of total fructose. By subsite, associations of SSB intake were significant in the rectum (per 1 serving/day, 1.48, 1.16 to 1.88;  $P=0.001$  for trend), but not in the proximal and distal colon ( $P \geq 0.157$  for trend). Per 5% increment in calorie/day, fructose intake was positively associated with high-risk proximal (1.25, 0.99 to 1.58), distal (1.44, 1.12 to 1.84) and rectal (1.74, 1.19 to 2.54) adenoma. Results for glucose (from simple sugars), added sugar, and total sugar were similar (but somewhat weaker) to the results for total fructose (supplementary table 3). Adult sugar intake was not associated with high-risk adenoma with odds ratios of 0.92 (95% confidence interval 0.61 to 1.38) for SSBs ( $\geq 2$  servings/day  $\nu$   $< 1$  serving/week) and 0.93 (0.75 to 1.16) for total fructose (highest  $\nu$  lowest quintile).

**Table 4 | Multivariable odds ratios and 95% confidence intervals of low- and high-risk colorectal adenoma according to sugar-sweetened beverage and total fructose intake during adolescence in the Nurses' Health Study II, 1998-2015**

	Sugar-sweetened beverage intake during adolescence, servings				P value for trend	Per 1 serving/day increase	
	<1/week	1-6/week	1/day	≥2/day			
<b>Low-risk adenoma*</b>							
<i>N</i> <sub>cases</sub> / <i>N</i> <sub>controls</sub> †	607/21206	581/21732	126/3757	70/2257			
Multivariable ‡	1	0.94 (0.83 to 1.07)	1.20 (0.97 to 1.49)	1.14 (0.86 to 1.52)	0.168	1.08 (0.97 to 1.21)	
<b>High-risk adenoma*</b>							
<i>N</i> <sub>cases</sub>	473	439	107	63			
Multivariable	1	0.89 (0.77 to 1.03)	1.25 (0.99 to 1.58)	1.21 (0.88 to 1.65)	0.085	1.11 (0.99 to 1.26)	
<b>Proximal</b>							
<i>N</i> <sub>cases</sub>	283	248	60	36			
Multivariable	1	0.86 (0.72 to 1.04)	1.21 (0.89 to 1.64)	1.22 (0.80 to 1.85)	0.205	1.11 (0.94 to 1.32)	
<b>Distal</b>							
<i>N</i> <sub>cases</sub>	230	229	59	33			
Multivariable	1	0.94 (0.77 to 1.15)	1.36 (1.00 to 1.86)	1.21 (0.79 to 1.88)	0.157	1.13 (0.95 to 1.33)	
<b>Rectal</b>							
<i>N</i> <sub>cases</sub>	97	77	29	20			
Multivariable	1	0.79 (0.57 to 1.09)	1.80 (1.14 to 2.84)	2.19 (1.20 to 4.00)	0.001	1.48 (1.16 to 1.88)	
	Total fructose intake during adolescence, % of calorie					P value for trend	Per 5% of calorie/day increase
	Q1 (<7.9)	Q2 (7.9–<9.2)	Q3 (9.2–<10.3)	Q4 (10.3–<11.8)	Q5 (≥11.8)		
<b>Low-risk adenoma</b>							
<i>N</i> <sub>cases</sub> / <i>N</i> <sub>controls</sub>	301/9795	267/9807	296/9765	249/9776	271/9809		
Multivariable	1	0.92 (0.77 to 1.09)	1.05 (0.87 to 1.26)	0.91 (0.75 to 1.11)	1.02 (0.83 to 1.26)	0.821	1.02 (0.86 to 1.20)
<b>High-risk adenoma</b>							
<i>N</i> <sub>cases</sub>	191	213	214	242	222		
Multivariable	1	1.20 (0.98 to 1.48)	1.27 (1.02 to 1.57)	1.53 (1.23 to 1.92)	1.44 (1.14 to 1.83)	0.001	1.36 (1.14 to 1.62)
<b>Proximal</b>							
<i>N</i> <sub>cases</sub>	129	120	122	138	118		
Multivariable	1	1.02 (0.79 to 1.33)	1.11 (0.84 to 1.46)	1.37 (1.03 to 1.82)	1.23 (0.91 to 1.67)	0.064	1.25 (0.99 to 1.58)
<b>Distal</b>							
<i>N</i> <sub>cases</sub>	94	99	111	121	126		
Multivariable	1	1.12 (0.84 to 1.50)	1.31 (0.97 to 1.77)	1.50 (1.11 to 2.03)	1.54 (1.11 to 2.13)	0.004	1.44 (1.12 to 1.84)
<b>Rectal</b>							
<i>N</i> <sub>cases</sub>	33	49	34	58	49		
Multivariable	1	1.74 (1.09 to 2.77)	1.28 (0.77 to 2.13)	2.45 (1.49 to 4.02)	2.08 (1.23 to 3.53)	0.004	1.74 (1.19 to 2.54)

\*Low-risk: small (<1cm), tubular, and single adenoma, high-risk: large ( $\geq 1$  cm), any villous histology, high-grade dysplasia, or more than 2 adenomas.

†N, number of endoscopies; due to multiple endoscopies during follow-up per each participant, N is larger than number of participants.

‡Adjusted for age, time period of endoscopy, number of endoscopies during the study period (continuous), time since most recent endoscopy (continuous), and reason for current endoscopy, family history of colorectal cancer, menopausal status/menopausal hormone use, current aspirin use  $\geq 2$  times/wk, history of type 2 diabetes, adult height (continuous), BMI at age 18 y, current BMI, smoking status at 19 y, current smoking status, alcohol intake at 18–22 y, current alcohol intake, physical activity during grades 9–12, current physical activity, adolescent and current dietary intake (total calorie, total calcium, vitamin D, total folate, total fiber, fruits, vegetables, and dairy), current total red meat intake, a western dietary pattern score during adolescence, and current sugar-sweetened beverage or total fructose intake.

## **Sensitivity analysis**

Overall, sensitivity analysis results were consistent with the principal findings. In brief, further adjustment for ASB and fruit juice intake or prudent dietary pattern did not materially change the associations of SSB and fructose intake with adenoma risk (supplementary table 5). When energy-adjusted intake of sugars was examined instead of nutrient densities, results were similar (supplementary table 6). An alternative definition of high-risk adenoma ( $\geq 1$  cm, any villous histology, high-grade dysplasia, or  $\geq 3$  adenomas)<sup>48</sup> yielded similar results, especially for high-risk rectal adenoma (supplementary table 7). Results for proximal adenoma were similar when restricting analyses to women who underwent colonoscopy (after excluding those with sigmoidoscopy only; supplementary table 8). After additional adjustment for glycemic index and glycemic load, potential mediators, positive associations were substantially attenuated, especially after adjustment for glycemic load: per 5% increase in calorie/day of total fructose, odd ratios were 1.08 for total and 1.24 for high-risk adenoma (supplementary table 5).

## **Stratified analysis**

Associations of SSB and fructose intake with adenoma risk did not differ appreciably by family history of CRC, adolescent BMI, physical activity, smoking, or alcohol consumption (all  $P \geq 0.15$  for interaction; fig 1, supplementary tables 9 and 10). When stratified by age at diagnosis ( $< 55$  v  $\geq 55$  years), positive associations were similar across strata although the majority of cases were diagnosed at relatively young ages (76.5% before 55 years, 99.6% before 65 years) (supplementary table 11).

Positive associations between sugar intake and adenoma risk were significantly stronger among women with low fruit intake ( $< 1.3$  servings/day) during adolescence compared to those with high intake ( $\geq 1.3$  servings/day). Among women with low fruit intake, odds ratios of total adenoma were 1.33 (95% confidence interval 1.11 to 1.59;  $P = 0.024$  for interaction) for SSBs ( $\geq 1$  serving/day v  $< 1$  serving/week) and 1.51 (1.26 to 1.82;  $P < 0.001$  for interaction) for total fructose (highest v lowest quintile). Similar differential associations were observed after stratification by vegetable and fiber intake, and prudent dietary pattern. In contrast, positive associations with adenoma risk did not differ appreciably by fruit juice intake ( $P \geq 0.75$  for interaction).

Associations were further examined by joint categories of fruit (high/low) and fruit juice (high/low) intake. Positive associations were stronger in the 'low fruit/high fruit juice' subgroup



(odds ratio, 1.61 for SSBs, 1.58 for total fructose) with significant differences across subgroups ( $P \leq 0.016$  for interaction; fig 1). Stratified analysis results for high-risk adenoma were almost identical to those for total adenoma (supplementary table 10).

### **Joint analysis of adolescent and adult diet**

Compared to women with low SSB or fructose intake during both adolescence and adulthood, women with high intake during adolescence had increased risk of total, rectal, and high-risk adenoma (supplementary fig 1, supplementary table 12). Associations did not differ significantly between the ‘high adolescent/high adult intake’ and ‘high adolescent/low adult intake’ groups. However, these results need to be interpreted with caution because of higher added sugar and calorie intake during adolescence and differences in metabolism and nutritional/caloric requirements between adolescents and adults.

### **Substitution analysis**

The 2015–2020 Dietary Guidelines for Americans recommend 2 cup-equivalents of fruits (whole fruits and 100% fruit juice) at the 2000-calorie level and 2–3 cup-equivalents of dairy per day for children and adolescents.<sup>49</sup> Substituting 1 serving/day of fruit juice for 1 serving/day of SSBs during adolescence was not associated with lower risk of adenoma (supplementary table 13). In contrast, replacement with 2 servings/day of fruits for 2 servings/day of SSBs was marginally associated with reduced risk of proximal (odds ratio 0.75, 95% confidence interval 0.54 to 1.05) and rectal (0.62, 0.35 to 1.08) adenoma. Substituting 2 servings/day of dairy products for 2 servings/day of SSBs was associated with lower risk of total (0.82, 0.64 to 1.05) and rectal (0.53, 0.29 to 0.94) adenoma.

## **DISCUSSION**

### **Principal findings**

In this large cohort of young women, independent of adult intake, higher intake of SSBs and sugars during adolescence was significantly associated with increased risk of total and high-risk adenoma, particularly high-risk rectal adenoma. Results were similar, albeit slightly weaker, for

added sugar and total sugar. Neither SSB nor sugar intake was associated with risk of serrated lesions. Thus, high sugar intake during adolescence may be etiologically more important for CRC arising from the conventional adenoma-carcinoma sequence, which accounts for approximately 85% of CRC,<sup>2</sup> rather than those originating from the serrated neoplasia pathway.

### **Comparison with other studies**

Prospective studies on adult SSB or sugar intake in relation to CRC risk have generally found null associations, including 2 comprehensive pooled analyses of prospective studies as well as a recent large cohort study.<sup>18 23 24</sup> We also did not observe significant associations of adult SSB and sugar intake with adenoma risk. In 2018, the World Cancer Research Fund/American Institute for Cancer Research reported that evidence for sugars and foods containing sugars with regard to CRC risk was limited.<sup>4 24</sup> However, this conclusion was based on intake during adulthood, mostly capturing mid-to-late adulthood cases. In contrast, little is known about the influence of early-life diet on colorectal carcinogenesis. Emerging evidence has suggested a potential role for adolescent diet in CRC development. For example, severe energy restriction during adolescence was associated with lower risk of CRC and persistent epigenetic changes involved in colorectal carcinogenesis.<sup>50 51</sup> In the NHSII, we previously reported that a western dietary pattern and physical inactivity during adolescence were associated with higher risk of adenoma, whereas red and processed meat intake, established CRC risk factors in adulthood, was not associated.<sup>52-54</sup>

To our knowledge, no previous study has investigated the association between adolescent sugar intake and colorectal neoplasia. During adolescence, accompanied by accelerated cell proliferation, distinctive hormonal and metabolic changes occur, including physiological (obesity-unrelated) hyperinsulinemia, decreased insulin sensitivity, and elevated IGF1 levels (up to 4-fold higher than in adulthood).<sup>27</sup> Therefore, adolescence might be a critical developmental period of enhanced susceptibility to high sugar intake, further adversely affecting insulin sensitivity. Our joint analysis results indicated that higher risk of adenoma was influenced by sugar intake primarily during adolescence, but not during adulthood.

### **Meaning of the study**

Several biological mechanisms may explain our findings. First, hyperinsulinemia and insulin resistance can play important roles. The high amount of liquid sugar in SSBs can induce rapid

spikes in blood glucose and insulin levels, which over time lead to insulin resistance and elevated free IGF1 levels.<sup>10</sup> The insulin/IGF1 system can promote carcinogenesis by activating intracellular signaling pathways related to altered gene expression, stimulating cell proliferation, differentiation, and angiogenesis, and inhibiting apoptosis.<sup>3 55 56</sup> We found that additional adjustment for dietary glycemic load substantially attenuated positive associations of high sugar intake, supporting this hypothesis.

Second, hyperglycemia may exacerbate chronic inflammation that has been implicated in CRC pathogenesis.<sup>57</sup> Previous studies have reported that SSB intake was significantly associated with increased levels of circulating inflammatory cytokines and biomarkers (e.g., C-reactive protein, interleukin-6, tumor necrosis factor receptors).<sup>17 58</sup>

Third, the distinctive metabolism of fructose, a major ingredient of SSBs, can exert additional adverse effects. Unlike glucose, fructose is metabolized predominantly in the liver after absorption in the small intestine.<sup>10</sup> When fructose intake chronically exceeds the metabolic capacity of the liver, fructose triggers hepatic *de novo* lipogenesis, promoting visceral and ectopic fat accumulation, glucose intolerance, and insulin resistance.<sup>9 59 60</sup> Additionally, a recent experimental animal study found that fructose was metabolized into glucose in murine small intestine as well; and intestinal fructose-to-glucose conversion was not suppressed by insulin, implying a novel unregulated pathway.<sup>61</sup>

Finally, fructose may affect carcinogenesis by directly acting on colorectal cells or interacting with the gut microbiome. Although fructose is readily absorbed in the small intestine, high doses or rapid flux of fructose could saturate small intestine clearance capacity, with excess fructose reaching the colon.<sup>61 62</sup> An 8-week oral administration of high-fructose corn syrup in mice enhanced colorectal tumor cell growth, even at a moderate dose, in the absence of obesity and metabolic syndrome, implying direct effects of fructose on tumor cell metabolism.<sup>63</sup> In addition, sugars may change the gut microbiome composition,<sup>64 65</sup> which could affect CRC development via modulation of gut immune and metabolic responses, and epigenetic alterations.<sup>66 67</sup>

In stratified analyses, positive associations of high sugar intake were significantly stronger among women with low fruit, vegetable, or fiber intake during adolescence than those with high intake. Unlike fruits or vegetables, fruit juice did not appear to offset the adverse effects of high sugar intake. Moreover, positive associations of high sugar intake were stronger

among women consuming low fruits/high fruit juice during adolescence compared to those consuming high fruits/low fruit juice. We found no benefits of substituting fruit juice for SSBs. These results may be explained as follows: although fruits and some vegetables contain naturally occurring sugars,<sup>34</sup> many beneficial micronutrients and potential anti-tumorigenic agents (e.g., fiber, folate, vitamins) may offset or dilute the adverse effects of sugars.<sup>4</sup> Furthermore, one of the key differences between whole fruits and fruit juice may be intestinal fructose release rates.<sup>61</sup> Fructose in whole fruits is slowly digested due to fiber content and the need to disrupt cell structure, facilitating gradual and complete intestinal clearance.<sup>10</sup> In contrast, rapid flux of liquid fructose from fruit juice may exceed small intestine uptake capacity, resulting in fructose overflow to the liver and colon.<sup>10 61 62</sup>

We also found stronger associations among women with unhealthy (low prudent and high western) dietary patterns during adolescence than those with healthy patterns. These results suggest that potential additive and interactive effects of foods consumed together in an overall diet may influence the biological responses of high sugar intake.<sup>68</sup> While excessive sugar intake may elicit unfavorable postprandial glucose and insulin responses, cumulative effects of acute hyperinsulinemia can contribute to colorectal carcinogenesis, particularly when combined with overall unhealthy dietary patterns that affect underlying chronic insulin resistance.<sup>68 69</sup>

### **Strengths and limitations of the study**

This study has several strengths. To our knowledge, this is the first prospective study investigating the role of high sugar intake during adolescence in colorectal neoplasia. The large sample size of 33106 women and 4744 CRC precursor cases enabled investigating various subtypes and subsites and conducting stratified analyses. Diet and lifestyle information was validated and obtained throughout different life stages, enabling us to examine both independent effects and joint associations of adolescent and adult diet. We comprehensively controlled for various known and purported CRC risk factors during both adolescence and adulthood. A majority of CRC precursors were diagnosed at relatively young ages (77% were under 55 years), supporting a plausible link between early-life exposure and early steps of colorectal carcinogenesis. Moreover, in rigorous sensitivity analyses, the principal results were robust.

Potential limitations of this study need to be considered. First, measurement error in dietary assessment can never be excluded when using self-reported questionnaire data. However,

the HS-FFQ showed reasonable reproducibility and validity.<sup>29 31</sup> Also, non-differential misclassification of exposure generally attenuates associations towards the null. Second, residual and unmeasured confounding could exist. High sugar intake could be a marker for a generally unhealthy diet or lifestyle that might track throughout life. However, we controlled for numerous dietary and lifestyle factors as well as overall dietary patterns during both adolescence and adulthood. Finally, the study population consisted of predominantly white female nurses and results may not be generalizable to other populations. However, exposure-CRC associations in our cohorts have been highly consistent with findings in diverse populations,<sup>4 53 70-72</sup> suggesting a common underlying biology.

### **Policy implications**

If confirmed, our findings may have substantial public health implications for the primary prevention of CRC. In many high-income countries, the rising incidence of early-onset CRC has been primarily driven by a disproportional increase in distal and rectal cancers,<sup>3 5</sup> known to arise mainly through the adenoma-carcinoma pathway.<sup>73</sup> The majority of early-onset CRC is sporadic and the causes remain unclear.<sup>3 73</sup> However, the observed birth cohort effect strongly suggests that early-life exposures are involved and causes likely stem from changes in diet and lifestyle factors in youths.<sup>5</sup> In our results, associations of high sugar intake were stronger for distally-located high-risk adenoma, especially high-risk rectal adenoma; and substituting dairy products for SSBs was associated with lower risk of rectal adenoma. In the early 1970s, the national mean intake of SSBs among U.S. adolescents was higher than in our participants,<sup>47</sup> and recent data on global adolescent SSB consumption have indicated a marked increase.<sup>10 11 13</sup> Therefore, if applied to the current general population, the effect size may be even larger than observed in our results. Our findings suggest that adolescence can be a critical developmental period of enhanced susceptibility to high sugar intake, supporting the importance of limiting sugar intake and replacing SSBs with healthy alternatives during early-life in an effort to reduce risk of CRC precursors and possibly CRC.

### **Conclusions**

In conclusion, SSB and sugar intake during adolescence was significantly associated with increased risk of total and high-risk adenoma, especially high-risk rectal adenoma, but not

serrated lesions. Thus, high sugar intake during early-life may promote precancerous lesions in CRC, primarily through the adenoma-carcinoma pathway. Future studies are needed to determine whether high sugar intake during adolescence contributes to CRC risk, particularly the recent upward trend in early-onset CRC.

## **Acknowledgments**

The authors would like to thank the Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School.

The authors would like to thank the participants and staff of the Nurses' Health Study II for their valuable contributions as well as the following state cancer registries for their help: AL, AZ, AR, CA, CO, CT, DE, FL, GA, ID, IL, IN, IA, KY, LA, ME, MD, MA, MI, NE, NH, NJ, NY, NC, ND, OH, OK, OR, PA, RI, SC, TN, TX, VA, WA and WY.

The authors assume full responsibility for analyses and interpretation of these data.

## **Funding**

The Nurses' Health Study II was funded by the National Cancer Institute, National Institutes of Health (U01 CA176726, R01 CA67262, and U01 HL145386) and this project was funded by research grants R03 CA197879 (Wu), R21 CA222940 (Wu), R21 CA230873 (Wu, Ogino), R01 CA151993 (Ogino), R35 CA197735 (Ogino), R01 CA205406 (Ng), K24 DK098311 (Chan), R35 CA253185 (Chan), R37 CA246175 (Cao), K99 CA215314 (Song), R00 CA215314 (Song), and K07 CA188126 (Zhang). This work was also in part supported by an Investigator Initiated Grant from the American Institute for Cancer Research (AICR) to Dr. Wu. In addition, this work was supported by American Cancer Society Research Scholar Grant (RSG130476 to Zhang), the American Cancer Society Research Mentored Research Scholar Grant (MRS-G-17-220-01 to Song), the Stuart and Suzanne Steele MGH Research Scholar Award (Chan), the Raymond P. Laviertes Foundation and the National Comprehensive Cancer Network Young Investigator Awards (Cao), the Bill and Melinda Gates Foundation (Willett), and the Breast Cancer Research Fund (Willett). Dr. Ng is supported in part by Department of Defense CA160344 and the Project P Fund.

## **Role of the funding source**

The funders had no role in the study design; in the collection, analysis, and interpretation of data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. All authors confirm the independence of researchers from funders and have full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

## **Competing interests**

All authors have completed the ICMJE uniform disclosure form and declare: support from the National Institutes of Health for the submitted work.

Dr. Ng has received institutional research funding from Pharmavite, Revolution Medicines, and Evergrande Group, has served on an advisory board for Seattle Genetics and Array Biopharma, and served as a consultant to X-Biotix Therapeutics.

Dr. Meyerhardt has received institutional research funding from Boston Biomedical, has served as an advisor/consultant to Ignyta and COTA Healthcare, and served on a grant review panel for the National Comprehensive Cancer Network funded by Taiho Pharmaceutical.

Dr. Chan has previously served as a consultant to Bayer Pharma AG, Pfizer Inc., and Boehringer Ingelheim for topics unrelated to this manuscript.

Dr. Fuch reports consulting role for Agios, Amylin Pharmaceuticals, Bain Capital, CytomX Therapeutics, Daiichi-Sankyo, Eli Lilly, Entrinsic Health, Evolveimmune Therapeutics, Genentech, Merck, Taiho, and Unum Therapeutics. He also serves as a Director for CytomX Therapeutics and owns unexercised stock options for CytomX and Entrinsic Health. He is a co-Founder of Evolveimmune Therapeutics and has equity in this private company. He had provided expert testimony for Amylin Pharmaceuticals and Eli Lilly.

The remaining authors report no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

## **Ethical approval**

The study protocol was approved by the institutional review boards of the Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health, and those of participating registries as required. Return of the mailed questionnaire was considered to imply informed consent.

## **Transparency statement**

Data described in the manuscript, code book, and analytic code will not be made publicly available. Further information including the procedures for obtaining and accessing data from the Nurses' Health Studies II is described at <https://www.nurseshealthstudy.org/researchers> (email:



[nhsaccess@channing.harvard.edu](mailto:nhsaccess@channing.harvard.edu)).

The lead author (H-KJ) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned have been explained.

**Dissemination declaration:** We have reported whether we plan to disseminate the results to study participants and or patient organisations.

**Data Sharing:** No additional data available.

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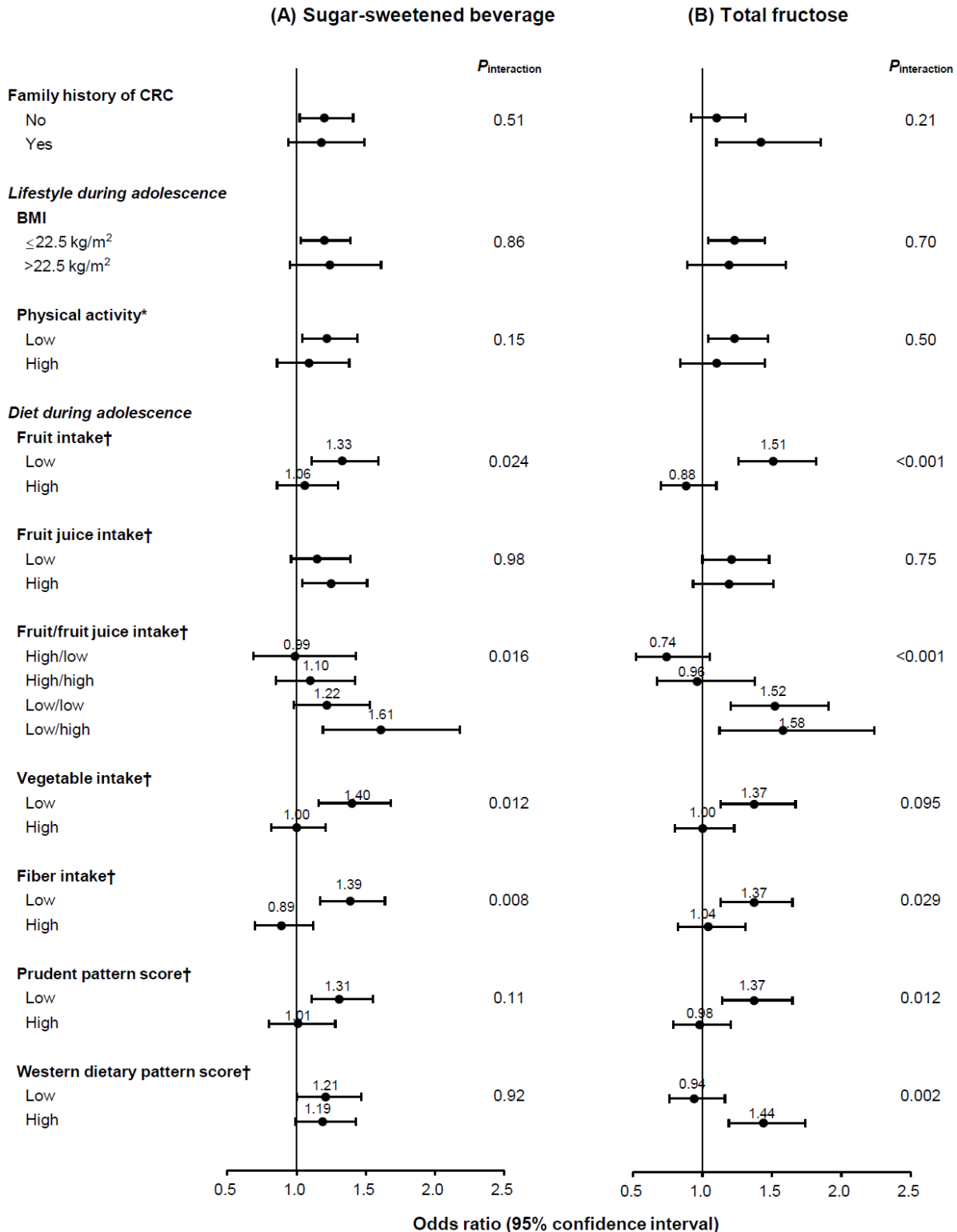
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**Fig 1 | Multivariable odds ratios and 95% confidence intervals of total colorectal adenoma according to (A) sugar-sweetened beverage and (B) total fructose intake during adolescence by family history, lifestyle, and dietary factors in the Nurses' Health Study II, 1998-2015**



CRC, colorectal cancer; BMI, body mass index

Data were adjusted for age, time period of endoscopy, number of endoscopies during the study period (continuous), time since most recent endoscopy (continuous), and reason for current endoscopy, family history of colorectal cancer, menopausal status/menopausal hormone use, current aspirin use  $\geq 2$  times/wk, history of type 2 diabetes, adult height (continuous), BMI at age 18 y, current BMI, smoking status at 19 y, current smoking status, alcohol intake at 18–22 y, current alcohol intake, physical activity during grades 9–12, current physical activity, adolescent and current dietary intake (total calorie, total calcium, vitamin D, total folate, total fiber, fruits, vegetables, and dairy), current total red meat intake, a western dietary pattern score during adolescence, and current sugar-sweetened beverage or total fructose intake except for the stratifying variable of each stratum.

(A) Comparison of sugar-sweetened beverage intake between categories of  $\geq 1$  serving/d vs.  $< 1$  serving/wk (referent).

(B) Comparison of total fructose intake between the highest vs. lowest (referent) quintile.

\*High physical activity was defined as the highest tertile ( $\geq 59$  MET-hr/wk); low physical activity as the 2 lower tertiles ( $< 59$  MET-hr/wk).

†Cut-off values were median intake values (fruits, 1.3 serving/d; fruit juice, 0.4 serving/d; vegetables, 2.8 serving/d).