Cumulative intake of artificially sweetened and sugar-sweetened beverages and risk of incident type 2 diabetes in young adults: the Coronary Artery Risk Development In Young Adults (CARDIA) Study

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Abstract

Background: Epidemiological evidence has demonstrated a positive association between artificially sweetened beverage (ASB) and sugar-sweetened beverage (SSB) consumption and type 2 diabetes (T2D) risk. However, research informing this topic in young adults is limited.

Objective: This study examined the association between ASB, SSB, and total sweetened beverage (TSB; combined ASB and SSB) consumption and T2D risk in young adults.

Methods: A prospective analysis of 4719 Black and White men and women aged 18–30 y at baseline was conducted from the Coronary Artery Risk Development in Young Adults (CARDIA) study. Each participant's beverage intake was assessed using the CARDIA Diet History at baseline and at study Years 7 and 20. Multivariable Cox proportional hazards regression models were used to examine cumulative average ASB, SSB, and TSB intakes and risk of T2D.

Results: During the 30-y follow-up period, 680 participants developed T2D. ASB consumption was associated with a 12% greater risk of T2D per serving/day (HR 1.12, 95% CI 1.04–1.20) in a model adjusted for lifestyle factors, diet quality, and dieting behavior. Further adjustments for baseline BMI (HR 1.07, 95% CI 0.99–1.14) and weight change during follow-up (HR 1.04, 95% CI 0.97–1.12) attenuated the association. SSB and TSB consumption as continuous variables per 1 serving/day of intake were associated with 6% and 5% increased risks of T2D, respectively (HR_{SSB} 1.06, 95% CI 1.01–1.10; HR_{TSB} 1.05, 95% CI 1.01–1.09), in the model accounting for lifestyle factors, dieting behavior, baseline BMI, and weight change. Results were consistent when the exposures were modeled in categories of consumption and quintiles.

Conclusions: In young adults, long-term ASB, SSB, and TSB consumption were associated with increased risks of T2D. However, the estimates for ASB were attenuated when accounting for weight changes. *Am J Clin Nutr* 2019;110:733–741.

Keywords: sugar-sweetened beverage, artificially sweetened beverage, diabetes, diet, Coronary Artery Risk Development in Young Adults, CARDIA

Introduction

For several decades, the rise in obesity and the prevalance of type 2 diabetes (T2D) in the United States closely paralleled the rise in both artificially sweetened beverage (ASB) and sugar-sweetened beverage (SSB) consumption (1). Consequently, lowering SSB intakes has become an important focus of public health nutrition efforts, and recent reports indicate that SSB intake in the United States is declining, while water consumption is rising (2). Consumption of ASBs, often marketed as healthy alternatives to SSBs, has come under scrutiny due to research findings and long-term safety concerns (3). Notably, both ASB and SSB intake trends vary among different age and sociodemographic groups (2–4).

Although the body of evidence supports a positive association between SSB consumption and obesity and T2D risk (5–7), there are methodological limitations of the experimental studies, and a closer examination of observational studies suggests potential publication biases (8, 9). At the same time, despite the promotion of ASBs as healthy, sugar-free, low-calorie alternatives to SSBs (10, 11), their role in weight management remains inconclusive, and evidence on the metabolic and health

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Abbreviations used: ASB, artificially sweetened beverages; CARDIA, Coronary Artery Risk Development in Yong Adults; SSB, sugar-sweetened beverages; TSB, total sweetened beverages; T2D, type 2 diabetes; WC, waist circumference.

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effects of ASB consumption over time is limited (12–14). Furthermore, evidence from prospective, observational studies suggests a positive association between ASB consumption and long-term cardiometabolic risk, but the results have been less consistent than the SSB–T2D relationship, and reverse causation, publication biases, and residual confounding have been suggested as explanatory factors (7, 12, 13). A recent scientific advisory report from the American Heart Association suggested that consuming ASBs may be a useful temporary replacement strategy to reduce SSB intake, but the optimal long-term choice was to avoid both beverages; this implies that both ASB and SSB have similar, negative roles in cardiometabolic health, despite a lack of direct evidence examining the relationship of the combined intake of the beverages with outcomes (3). Additionally, the observational studies on this topic have largely examined middle-aged and older adults, while evidence is lacking for how sweetened beverage consumption habits relate to T2D risks beginning in early adulthood.

To address these gaps, we examined the relationships between ASB, SSB, and total sweetened beverage (TSB; ASB and SSB intake combined) consumption over time and T2D risk in young adult men and women from the Coronary Artery Risk Development In Young Adults (CARDIA) study.

Methods

Study population

The CARDIA study is a prospective, multicenter cohort study designed to investigate the development and determinants of cardiovascular disease and its associated risk factors in young adults. Briefly, 5115 Black and White men and women aged 18–30 years were recruited between 1985–1986 from 4 US cities: Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota; and Oakland, California. Participant enrollment targeted balances among age, race, sex, and educational attainment. The initial examination included standardized measures of known cardiovascular risk factors, as well as psychosocial, dietary, and exercise-related characteristics. Reexamination occurred at 2, 5, 7, 10, 15, 20, 25, and 30 years after baseline, with retention of 91%, 86%, 81%, 79%, 74%, 72%, 72%, and 71% of the surviving cohort, respectively. The CARDIA study was approved by the institutional review board at each field center, and informed consent was obtained from all participants prior to enrollment (15).

Participants with a diagnosis of diabetes at baseline ($n = 34$), missing baseline diabetes status data ($n = 88$), or missing baseline dietary data ($n = 4$) were excluded from this analysis. Additionally, individuals who only participated in the baseline visit and had no follow-up data ($n = 152$) and individuals with extreme energy intakes [<600 kcal/day or >6000 kcal/day for women ($n = 53$) and <800 kcal/day or >8000 kcal/day for men ($n = 64$)] were also excluded. The proportion of missing data for other pertinent covariates was low (<1%); missing values were imputed by sex and race subgroup to the median value for continuous variables (BMI, alcohol intake, physical activity) and to the most frequent categorical value for multichotomous variables (smoking status) (16). The final study sample for this analysis included 4719 Black and White young adult men and women.

Beverage consumption

Dietary intake was assessed at baseline (Year 0) and at Years 7 and 20 using the CARDIA Diet History: an interviewer-administered, validated dietary assessment instrument consisting of a short questionnaire on general dietary practices, followed by a comprehensive questionnaire about typical intake of foods, using the previous 1 month as a reference for recall (17). Briefly, interviewers asked study participants open-ended questions about dietary consumption in the past month within 100 food categories, referencing 1609 separate food items in Years 0 and 7 and several thousand separate food items in Year 20. Follow-up questions for selected foods concerned serving size, frequency of consumption, and common additions to these foods. Provision was made for reporting foods not found in the food frequency list. Diet history data were coded by the University of Minnesota Nutrition Coordinating Center and categorized into 166 food groups. As done in previous CARDIA studies (18, 19), we further collapsed these groups to define SSBs as sugar-sweetened soft drinks and fruit drinks and ASBs as soft drinks and fruit drinks sweetened with non-nutritive (non-caloric) sweeteners, both measured as the total number of 8-ounce servings per day. We also calculated combined TSB intake as the sum of SSB and ASB intake at each time point. The purpose of combining SSB and ASB was to provide an exposure variable that directly tested the most recent scientific statement from the American Heart Association on low-calorie sweetened beverages, which suggested that the hypothesized optimum sweetened beverage intake was essentially no intake (3). Though the potential underlying putative mechanisms between ASB and SSB intakes with cardiometabolic health likely differ, a simple adjustment of the other beverage type may not completely account for the potential confounding of crossover consumption of SSBs to ASBs, or vice versa, that could occur over time.

To examine the relationship between beverage intake over time and T2D risk, we calculated a cumulative, average value of ASB, SSB, and TSB consumption for each participant using dietary data from Years 0, 7, and 20. For participants with follow-up times >0 and ≤7 years, we used beverage intake from Y0 only. For participants with follow-up times >7 and ≤20 years, cumulative, average beverage intakes from Y0 and Y7 data were used. For participants with follow-up time >20 years, the cumulative, average of beverage intakes at Y0, Y7, and Y20 was used. We used this approach to ensure that only beverage consumption prior to incident T2D was included in our analysis. Cumulative averages were calculated based on available data; individuals without repeated measures of diet were assigned their baseline beverage intake level.

Incident type 2 diabetes mellitus

Diabetes status was assessed at examination Years 0, 7, 10, 15, 20, 25, and 30. All blood samples were drawn and processed according to standard procedures, and serum glucose was assayed using the hexokinase method at a central laboratory (15). An incidence of T2D was defined as the use of diabetes medication (all years including 2 and 5), a fasting blood glucose concentration of ≥7 mmol/L (126 mg/dL), 2-hour post-challenge glucose ≥11.1 mmol/L (200 mg/dL), and/or a HbA1c ≥48 mmol/mol (6.5%). The 2-hour glucose test was done at Years 10,

20, and 25, while HbA1c was done at Years 20 and 25. CARDIA did not differentiate between type 1 and type 2 diabetes mellitus; however, it is likely that most incident cases identified during follow-up were T2D, given the age of the cohort and known distributions of types 1 and 2 diabetes.

Covariates

At the CARDIA baseline and follow-up examinations, participants completed self-administered questionnaires to collect information on sociodemographic, psychosocial, and medical backgrounds. Some of these questionnaires were followed up with interviewer-administered questions to obtain more detailed information about illnesses, medications, smoking habits, alcohol use, and life events (15). Physical activity was assessed using the CARDIA physical activity questionnaire: a validated, interviewer-based self-report of duration and intensity of participation in 13 categories of exercise over the past year (20). Physical activity was reported in exercise units (EU), where 300 EU is approximately equal to 150 minutes of moderate-intensity physical activity per week, or 30 minutes of moderate-intensity activity 5 days/week (21). Total energy intake (kcal) was calculated from the CARDIA Diet History. An alternate Mediterranean (aMed) diet score was calculated using methods described in Fung et al. (22). In brief, the aMed score assigns 1 point for intake above the cohort-specific median for fruits, vegetables, legumes, nuts, whole-grain products, fish, and MUFA:SFA fat ratio, and 1 point for intake below the median for red and processed meats. Moderate alcohol intake (5–15 g/day in women and 15–25 g/day in men) also receives 1 point. Individual food group scores are summed for the total aMed score, with a range of 0–9. The aMed diet score was utilized because it does not include ASB or SSB consumption, yet provides an account of overall diet quality, including alcohol intake as a confounder. Cumulative averages were calculated for physical activity, energy intake, and aMed score in the same way as beverage intake, using data from Y0, Y7, and Y20 or until censoring. Body weight was measured with light clothing to the nearest half pound (0.2 kg), and height was measured without shoes to the nearest 0.5 cm. BMI was calculated from these measurements as weight in kg, divided by height in meters squared. Dieting behavior was assessed as part of a weight history questionnaire at baseline and on medical history questionnaires at each follow-up year, except Year 5. Specifically, participants were asked, "have you ever been on a weight reducing diet?" and "if yes: are you on such a diet now?" (yes/no). For this analysis, we included participant reports of being on a weight-loss diet at the time of the dietary history assessment at Year 0, 7, or 20.

Statistical analysis

We examined differences in participants' sociodemographic and clinical characteristics by cumulative, average frequency of intake of ASBs and SSBs, using 2-sided *t* tests and Chi-square tests for continuous and categorical variables, respectively. A survival analysis, using multivariable Cox proportional hazards models, was used to estimate the HRs and corresponding 95% CIs for incident diabetes during follow-up. Separate models were fitted for ASBs, SSBs, and TSBs. Once a participant developed documented diabetes at a CARDIA follow-up examination, they were considered to have had an event and were subsequently censored. Follow-up time was calculated as the time from baseline to the examination visit where diabetes was identified or until the censoring time (i.e., last examination time where diabetes status was ascertained before death, loss to follow-up, or end of cohort surveillance, whichever came first).

For the analysis, we created 5 beverage intake categories that allowed for cut-points with an adequate number of subjects and alignment with common levels of intake. For ASBs, participants were categorized according to frequency of consumption, as 0/never, any to <4 servings/week, 4 to <7 servings/week, 1–2 servings/day, and >2 servings/day. Categories of SSB intake were none to <1 serving/week, 1 to <4 servings/week, 4 to <7 servings/week, 1–2 servings/day, and >2 servings/day. For the TSB analysis, individuals who reported less than 3 servings/week were grouped with non-consumers for statistical stability in comparisons, because of the small number of non-consumers. The remaining TSB categories were 3 to <7 servings/week, 1 to <2 servings/day, 2–3 servings/day, and >3 servings/day. Using this approach, non-consumers served as the reference group for the ASB analysis and non-consumers/infrequent-consumers served as the reference group for the SSB and TSB analyses. In a sensitivity analysis, we also ranked participants into quintiles of beverage intake. Since many participants were ASB non-consumers, we coded non-consumers as 0 and divided consumers into quartiles to ensure variability across 5 levels of consumption. The lowest quintile, or non-consumers, served as the reference group for the analysis.

We first examined the associations between cumulative averages of ASB, SSB, and TSB intake and T2D risks using a crude model without adjustments for covariates. We then used multivariable models that were adjusted for preselected sociodemographic and lifestyle-related confounders to further examine these associations. Model 1 was adjusted for CARDIA field center, education, smoking, dieting behavior, cumulative, average energy intake, and cumulative, average physical activity. Model 2 was adjusted for all Model 1 covariates plus cumulative, average aMed score. Model 3 was adjusted for baseline BMI, and Model 4 further included weight changes from baseline to diabetes diagnosis, censoring, or end of follow-up (whichever came first) as a potential mediator. Education and smoking status were treated as repeated measures in the models. All ASB models were adjusted for cumulative, average SSB intake, and vice versa for SSB models. Beverage consumption was also modeled as a continuous variable, and HRs were calculated per 1 serving/day of beverage intake.

To test the robustness of the results, we also conducted sensitivity analyses comparing the main study findings to results from individuals with baseline data only ($n = 679$), using baseline or most recent dietary data in place of cumulative averages. In our sample, a family history of diabetes was missing for 698 participants (15%); therefore, we repeated the main analysis in the subset of the population who had information on a family history of diabetes ($n = 4021$). In addition, we examined the data for effect modifications by sex, race, and BMI by performing stratified analyses and also including an interaction term for the variable of interest and for ASBs and SSBs separately. Waist circumference (WC) may be a better predictor of T2D than BMI (23), so we repeated the Model 3 analysis for all beverage

TABLE 1 Characteristics of participants

Characteristic[1]	Category of ASB consumption, in servings					P[7]
	None	Any to ≤4/week	4 to ≤7/week	1–2/day	≥2/day	
n	2385	1284	361	378	311	
ASB intake						
Range, servings/day	0.0–0.0	0.01 -0.570	0.573–0.997	1.00–2.00	2.01–13.12	
Mean, servings/day	0.0 (0.0)	0.2 (0.2)	0.8 (0.1)	1.4 (0.3)	3.6 (1.7)	<0.0001
SSB intake, servings/day	1.8 (2.0)	1.0 (1.2)	0.8 (1.0)	0.7 (1.0)	0.7 (1.1)	<0.0001
Baseline age, years	24.5 (3.7)	25.0 (3.6)	25.2 (3.3)	25.4 (3.4)	25.0 (3.4)	<0.0001
Race, % White	34.8	54.7	71.8	80.4	88.8	<0.0001
Sex, % male	52.0	40.1	35.7	35.2	38.9	<0.0001
Cumulative average energy intake, kcal/day	3081.8 (1357.6)	2652.5 (1163.1)	2560.6 (1146.6)	2448.9 (984.9)	2625.8 (1112.6)	<0.0001
Cumulative average aMed score[2]	4.0 (1.5)	4.4 (1.5)	4.4 (1.4)	4.3 (1.4)	4.0 (1.5)	<0.0001
Education, years[3]	13.8 (2.4)	15.1 (2.5)	15.5 (2.5)	15.8 (2.6)	15.7 (2.6)	<0.0001
Baseline smoking status, %						<0.0001
Never	53.9	62.9	62.6	61.4	53.4	
Former	11.6	15.0	16.1	15.1	16.7	
Current	34.6	22.2	21.3	23.5	29.9	
Cumulative average physical activity, EU/week[4]	360.7 (247.9)	385.6 (234.5)	371.8 (215.0)	386.9 (227.5)	402.2 (231.6)	0.003
Baseline alcohol intake, ml/day	12.1 (21.4)	9.6 (15.8)	10.1 (13.9)	12.3 (19.8)	16.0 (24.7)	<0.0001
Baseline BMI, kg/m^2	24.3 (5.1)	24.4 (4.9)	24.6 (4.7)	24.8 (4.4)	25.6 (5.0)	0.0003
Family Hx DM, %[5]	16.7	15.5	13.4	15.4	18.0	0.45
Dieting behavior, %[6]	8.9	20.7	28.8	29.6	28.9	<0.0001

Data are for CARDIA participants, according to Y0, Y7, and Y20 cumulative, average ASB consumption. aMed, alternate Mediterranean diet; ASB, artificially sweetened beverage; CARDIA, Coronary Artery Risk Development in Young Adults; DM, diabetes mellitus; EU, exercise units; Hx, history; SSB, sugar-sweetened beverage; Y, study year.

[1]Unadjusted mean (SD) for all characteristics, unless noted as percentage.

[2]The aMed diet score ranges from 0–9 and assigns 1 point for intake above the cohort-specific median for positively scored components (fruits, vegetables, legumes, nuts, whole grains, fish, and MUFA:SFA ratio) and below the median for negative components (red and processed meat). Moderate alcohol intake (5–15 g/day in women and 15–25 g/day in men) also receives 1 point.

[3]Highest level of education attained through follow-up.

[4]Physical activity score derived from the CARDIA physical activity history, where 300 EU is approximately equal to 150 minutes of moderate-intensity physical activity per week.

[5]Family history data unavailable for 698 subjects.

[6]Dieting behavior (weight-reducing diet Y/N) reported at Y0, Y7, or Y20.

[7]P value is from analysis of variance (age, education, physical activity, alcohol, BMI) or Chi-square t-test (race, gender, smoking, family history, dieting) of association between ASB consumption category and characteristic.

categories, using WC in place of BMI. To avoid any potential misclassification, a sensitivity analysis was performed excluding subjects who developed diabetes before age 30 ($n = 8$). To address potential reverse causation, we repeated the analyses, excluding cases that occurred within the first 7 years of follow-up ($n = 40$). The proportional hazards assumption was tested by including an interaction term with log (base-e)-transformed time for each covariate. There was no evidence that our models violated this assumption. All analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC).

Results

Mean (SD) cumulative averages of Y0, Y7, and Y20 ASB and SSB intakes were 0.46 (1.0) servings/day and 1.38 (1.7) servings/day, respectively. Participant characteristics are presented in **Table 1** and **Table 2**, according to category of ASB and SSB intake, respectively. Participant characteristics by category of TSB intake are shown in **Supplemental Table 1**. Compared with non-consumers, participants who consumed ASBs were older and had a lower cumulative, average estimated energy intake. With higher ASB intake, a greater proportion of participants were White, female, more educated, had a higher physical activity level, had a higher baseline BMI, and consumed more alcohol. With higher SSB intake, a greater proportion of participants were male, Black, a current smoker, less educated, had a higher cumulative, average estimated energy intake, had a lower aMed diet quality score, had a higher baseline BMI, and consumed more alcohol. These individuals were also younger than those reporting less frequent SSB intake. As presented in **Table 3**, repeated measures of SSB and ASB consumption were positively correlated over time ($r_{SSB} = 0.24$ to 0.38, r_{ASB} 0.34 to 0.44). SSB and ASB consumption levels were inversely correlated at all time points ($r = -0.02$ to -0.18).

A total of 680 incident cases of T2D were documented during the follow-up period (mean 25.3, SD 8.3 years). ASB consumption was positively associated with a risk of T2D in Model 2, which adjusted for demographic and lifestyle factors, dieting behavior, and diet quality, as presented in **Table 4**. Participants who reported >2 servings/day of ASB intake had a 71% increased risk for T2D, compared with non-consumers (Model 2 HR 1.71, 95% CI 1.22–2.39; $P = 0.003$). This association was attenuated after adjusting for baseline BMI (Model 3 HR 1.37, 95% CI 0.98–1.92; $P = 0.09$) and weight

TABLE 2 Characteristics of participants

Characteristic [1]	Category of SSB consumption, in servings					P [7]
	None to ≤1/week	1 to ≤4/week	4 to ≤7/week	1–2/day	≥2/day	
n	756	1065	756	1104	1038	
SSB intake						
Range, servings/day	0–0.140	0.143–0.570	0.573–0.997	1.0–2.0	2.01–20.5	
Mean, servings/day	0.04 (00.05)	0.3 (0.1)	0.8 (0.1)	1.4 (0.3)	3.8 (2.2)	<0.0001
ASB intake, servings/day	1.0 (1.5)	0.5 (1.0)	0.4 (1.0)	0.3 (0.8)	0.2 (0.6)	<0.0001
Baseline age, years	25.9 (3.3)	25.2 (3.5)	24.8 (3.5)	24.4 (3.7)	24.1 (3.7)	<0.0001
Race, % White	83.5	61.9	47.6	37.1	29.9	<0.0001
Sex, % male	29.9	38.5	46.0	52.8	55.0	<0.0001
Cumulative average energy intake, kcal/day	2173.2 (853.3)	2419.9 (924.4)	2657.8 (1103.5)	3039.2 (1188.4)	3697.3 (1503.7)	<0.0001
Cumulative average aMed score[2]	4.6 (1.5)	4.5 (1.5)	4.1 (1.4)	4.0 (1.5)	3.8 (1.5)	<0.0001
Education, years[3]	15.7 (2.5)	15.3 (2.5)	14.8 (2.5)	14.1 (2.4)	13.3 (2.1)	<0.0001
Baseline smoking status, %						<0.0001
Never	59.5	60.6	63.5	56.3	50.1	
Former	19.7	18.1	10.7	11.0	8.8	
Current	20.8	21.3	25.8	32.8	41.1	
Cumulative average physical activity, EU/week[4]	396.7 (223.6)	373.4 (224.7)	355.8 (230.3)	373.9 (255.9)	367.7 (252.9)	0.02
Baseline alcohol intake, ml/day	9.7 (14.1)	10.4 (17.2)	10.9 (18.4)	12.2 (19.6)	13.9 (25.5)	<0.0001
Baseline BMI, kg/m^2	23.8 (4.4)	24.2 (4.6)	24.4 (4.5)	24.7 (5.3)	25.0 (5.7)	<0.0001
Family Hx DM, %[5]	15.3	14.6	16.3	17.3	16.8	0.52
Dieting behavior, %[6]	26.7	20.2	17.5	11.9	10.0	<0.0001

Data are for CARDIA participants, according to Y0, Y7, and Y20 cumulative, average SSB consumption. aMed, alternate Mediterranean diet; ASB, artificially sweetened beverage; BMI, body mass index; CARDIA, Coronary Artery Risk Development in Young Adults; DM, diabetes mellitus; EU, exercise units; Hx, history; SSB, sugar-sweetened beverage; Y, study year.

[1]Unadjusted mean (SD) for all characteristics, unless noted as percentage.

[2]The aMed diet score ranges from 0–9 and assigns 1 point for intake above the cohort-specific median for positively scored components (fruits, vegetables, legumes, nuts, whole grains, fish, and MUFA:SFA ratio) and below the median for negative components (red and processed meat). Moderate alcohol intake (5–15 g/day in women and 15–25 g/day in men) also receives 1 point.

[3]Highest level of education attained through follow-up.

[4]Physical activity score derived from the CARDIA physical activity history, where 300 EU is approximately equal to 150 minutes of moderate-intensity physical activity per week.

[5]Family history data unavailable for 698 subjects.

[6]Dieting behavior (weight-reducing diet Y/N) reported at Y0, Y7, or Y20.

[7]P value is from analysis of variance (age, education, physical activity, alcohol, BMI) or Chi-square t-test (race, gender, smoking, family history, dieting) of association between SSB consumption category and characteristic.

change during follow-up (Model 4 HR 1.26, 95% CI 0.90–1.78; $P = 0.30$). An analysis based on per serving/day of ASB intake mirrored these results.

As presented in **Table 5**, higher intake of SSBs was positively associated with the T2D risk (Model 2 HR 1.51, 95% CI 1.11–2.07 for >2 servings/day vs 0 to <1 serving/week). Similar to ASBs, adjustments for BMI (Model 3 HR 1.31, 95% CI 0.95–1.79) and weight change (Model 4 HR 1.27, 95% CI 0.93–1.74) attenuated the association. The analysis modeling cumulative, average SSB intake as a continuous variable per 1 serving/day showed a positive association between higher SSB intake and T2D risk, adjusting for baseline BMI and weight change (Model 4 $HR_{serving/day}$ 1.06, 95% CI 1.01–1.10; $P = 0.009$).

A higher quantity of TSB intake was associated with an increased risk for T2D in the most comprehensively adjusted model (Model 4), which included adjustments for dieting behavior, overall diet quality, energy intake, baseline BMI, and weight change (**Table 6**). Individuals who reported an intake of >3 servings/day of TSB had a 73% increased risk of T2D during follow-up, compared with those who reported a TSB intake <3 servings/week (Model 4 HR 1.73, 95% CI 1.29–2.34). Modeling the cumulative, average TSB intake as a continuous variable, higher intake was associated with a 5% increased risk of T2D per 1 serving/day of intake in Model 4 (HR 1.05, CI 1.01–1.09; $P = 0.008$). In our secondary analysis using quintiles of ASB, SSB, and TSB intakes, the findings were similar to the main results, as presented in **Supplemental Table 2**.

TABLE 3 Pearson's correlation coefficients among sweetened beverage consumption[1]

	SSB Year 0	SSB Year 7	SSB Year 20	ASB Year 0	ASB Year 7	ASB Year20
SSB Year 0	1.00	0.38	0.24	−0.18	−0.03	−0.02
SSB Year 7	0.38	1.00	0.28	−0.10	−0.15	−0.04
SSB Year 20	0.24	0.28	1.00	−0.08	−0.09	−0.12
ASB Year 0	−0.18	−0.10	−0.08	1.00	0.36	0.34
ASB Year 7	−0.03	−0.15	−0.09	0.36	1.00	0.44
ASB Year 20	−0.02	−0.04	−0.12	0.34	0.44	1.00

[1]ASB, artificially sweetened beverage; SSB, sugar-sweetened beverage. $P < 0.0001$ for all correlations.

TABLE 4 Association between cumulative, average artificially sweetened beverage intake and diabetes risk in young adult men and women

	Category of ASB consumption, in servings						
	None	Any to ≤4/week	4 to ≤7/week	1–2/day	≥2/day	Per serving/day[5]	*P*
n diabetes/person-years	364/54,660	174/33,583	52/9277	45/9614	45/7589		
Crude model (95% CI)	1.0 (ref)	0.74 (0.62–0.89)	0.81 (0.61–1.09)	0.67 (0.49–0.92)	0.87 (0.64–1.18)	0.96 (0.88–1.04)	0.28
Model 1[1] HR (95% CI)	1.0 (ref)	1.00 (0.83–1.21)	1.32 (0.97–1.79)	1.21 (0.87–1.69)	1.71 (1.22–2.40)	1.12 (1.04–1.20)	0.003
Model 2[2] HR (95% CI)	1.0 (ref)	1.01 (0.83–1.22)	1.32 (0.98–1.80)	1.21 (0.87–1.69)	1.71 (1.22–2.39)	1.12 (1.04–1.20)	0.003
Model 3[3] HR (95% CI)	1.0 (ref)	0.94 (0.78–1.14)	1.22 (0.90–1.65)	1.11 (0.79–1.54)	1.37 (0.98–1.92)	1.07 (0.99–1.14)	0.09
Model 4[4] HR (95% CI)	1.0 (ref)	0.92 (0.76–1.12)	1.12 (0.82–1.52)	1.04 (0.75–1.44)	1.26 (0.90–1.78)	1.04 (0.97–1.12)	0.30

Data are from Y0, Y7, and Y20 from the CARDIA study, 1985–2016. ASB, artificially sweetened beverage; CARDIA, Coronary Artery Risk Development in Young Adults; SSB, sugar-sweetened beverage; Y, study year.

[1]Cox Proportional Hazards multivariable model adjusted for age, race, sex, CARDIA center, time-updated measures of education and of smoking status, cumulative, average physical activity, SSB intake and energy intake (Y0, 7, and 20), and dieting behavior (weight-reducing diet Y/N).

[2]Model 2 adjusted for Model 1 covariates plus cumulative, average Mediterranean diet score.

[3]Model 3 adjusted for Model 2 covariates plus baseline BMI.

[4]Model 4 adjusted for Model 3 covariates plus weight change from baseline to type 2 diabetes diagnosis, censoring, or end of follow-up, whichever occurred first.

[5]HR (95% CI) calculated per 1 serving/day of ASB intake.

Stratified analyses, as well as formal tests, for interactions between the frequency of ASB intake and cumulative, average BMI, race, and sex provided no evidence of effect modifications by these factors (**Supplemental Table 3**). Results of these analyses for SSB consumption suggested a potential effect modification by race (P interaction = 0.014). In an analysis of SSB intake as a continuous variable (servings/day), stratified by race, SSB intake was positively associated with T2D risk in both groups, but the association was slightly stronger in Whites than Blacks (Supplemental Table 3). Our sensitivity analyses provided no evidence for effect modifications of the association between SSB intake and T2D risk by BMI or sex. The substitution of WC for BMI in Model 3 did not alter the direction or magnitude of the results (data not shown). The main study findings were not impacted by sensitivity analyses that excluded the 8 participants who developed diabetes before age 30 or the 40 cases of T2D diagnosed within the first 7 years of follow-up. Results were also consistent in the subset of the population with data on a family history of diabetes.

Discussion

In this long-term study of sweetened beverage intakes and T2D risks in young adults from the CARDIA cohort, we observed a positive association between higher ASB, SSB, and TSB intakes and risks for T2D over 30 years. The nature and magnitude of the ASB–T2D and SSB–T2D relationships appeared similar. Accounting for a potential mediator in weight change over time attenuated the associations, but both were still positively associated, albeit with varying precision. When ASB and SSB intakes were combined, higher intake was positively associated with T2D risk, even after adjustment for the baseline BMI and weight change. The purpose of this analysis was to test the recent scientific advisory statement by the American Heart Association, suggesting that the hypothesized optimum sweetened beverage intake is essentially no intake (3).

Previous studies have found that overweight and obese individuals report higher consumption of ASBs than leaner individuals (10, 24), and those who consume ASBs often do so in an attempt to lose weight or because of poor health

TABLE 5 Association between cumulative, average sugar-sweetened beverage intake and diabetes risk in young adult men and women

	Category of SSB consumption, in servings						
	None to ≤1/week	1 to ≤4/week	4 to ≤7/week	1–2/day	≥2/day	Per serving/day[5]	*P*
n diabetes/person-years	74/18,531	130/27,334	105/18,927	168/26,691	203/23,240		
Crude model (95% CI)	1.0 (ref)	1.19 (0.89–1.58)	1.40 (1.04–1.89)	1.62 (1.23–2.13)	2.32 (1.78–3.03)	1.12 (1.09–1.16)	<0.0001
Model 1[1] HR (95% CI)	1.0 (ref)	1.06 (0.79–1.41)	1.08 (0.79–1.48)	1.14 (0.85–1.55)	1.51 (1.11–2.07)	1.12 (1.04–1.20)	0.003
Model 2[2] HR (95% CI)	1.0 (ref)	1.05 (0.79–1.41)	1.08 (0.79–1.48)	1.14 (0.85–1.55)	1.51 (1.11–2.07)	1.12 (1.04–1.20)	0.003
Model 3[3] HR (95% CI)	1.0 (ref)	0.99 (0.74–1.33)	1.05 (0.77–1.43)	1.02 (0.75–1.37)	1.31 (0.95–1.79)	1.05 (1.01–1.10)	0.01
Model 4[4] HR (95% CI)	1.0 (ref)	0.98 (0.73–1.31)	0.97 (0.71–1.32)	0.96 (0.71–1.29)	1.27 (0.93–1.74)	1.06 (1.01–1.10)	0.009

Data are from Y0, Y7, and Y20 from the CARDIA study, 1985–2016. ASB, artificially sweetened beverage; CARDIA, Coronary Artery Risk Development in Young Adults; ref, reference group; SSB, sugar-sweetened beverage; Y, study year.

[1]Cox Proportional Hazards multivariable model adjusted for age, race, sex, CARDIA center, time-updated measures of education and of smoking status, cumulative, average physical activity, ASB intake and energy intake (Y0, 7, and 20), and dieting behavior (weight-reducing diet Y/N).

[2]Model 2 adjusted for Model 1 covariates plus cumulative, average Mediterranean diet score.

[3]Model 3 adjusted for Model 2 covariates plus baseline BMI.

[4]Model 4 adjusted for Model 3 covariates plus weight change from baseline to type 2 diabetes diagnosis, censoring, or end of follow-up, whichever occurred first.

[5]HR (95% CI) calculated per 1 serving/day of SSB intake.

TABLE 6 Association between cumulative, average total sweetened beverage intake and diabetes risk in young adult men and women

	Category of TSB consumption (servings)						
	None to ≤3/week	3 to ≤7/week	1 to ≤2/day	2–3/day	≥3/day	Per serving/day[5]	*P*
n diabetes/person-years	72/17,882	136/27,574	194/34,253	107/16,664	171/18,350		
Crude model (95% CI)	1.0 (ref)	1.22 (0.92–1.63)	1.42 (1.08–1.86)	1.64 (1.21–2.20)	2.44 (1.86–3.22)	1.11 (1.07–1.14)	<0.0001
Model 1[1] HR (95% CI)	1.0 (ref)	1.14 (0.86–1.52)	1.24 (0.94–1.63)	1.40 (1.03–1.90)	2.12 (1.58–2.85)	1.12 (1.04–1.20)	0.003
Model 2[2] HR (95% CI)	1.0 (ref)	1.14 (0.86–1.52)	1.24 (0.94–1.64)	1.40 (1.03–1.91)	2.12 (1.58–2.87)	1.12 (1.04–1.20)	0.003
Model 3[3] HR (95% CI)	1.0 (ref)	1.12 (0.84–1.49)	1.13 (0.86–1.49)	1.19 (0.87–1.62)	1.78 (1.32–2.41)	1.06 (1.02–1.10)	0.005
Model 4[4] HR (95% CI)	1.0 (ref)	1.09 (0.82–1.46)	1.07 (0.81–1.41)	1.12 (0.82–1.52)	1.73 (1.29–2.34)	1.05 (1.01–1.09)	0.008

Data are from Y0, Y7, and Y20 from the CARDIA study, 1985–2016. CARDIA, Coronary Artery Risk Development in Young Adults; ref, reference group; TSB, total sweetened beverage; Y, study year.

[1]Cox Proportional Hazards multivariable model adjusted for age, race, sex, CARDIA center, time-updated measures of education and of smoking status, cumulative, average physical activity, energy intake (Y0, 7, and 20), and dieting behavior (weight-reducing diet Y/N).

[2]Model 2 adjusted for Model 1 covariates plus cumulative, average Mediterranean diet score.

[3]Model 3 adjusted for Model 2 covariates plus baseline BMI.

[4]Model 4 adjusted for Model 3 covariates plus weight change from baseline to type 2 diabetes diagnosis, censoring, or end of follow-up, whichever occurred first.

[5]HR (95% CI) calculated per 1 serving/day of TSB intake.

(25). In CARDIA, an adjustment for BMI partially attenuated the association between ASB intake and T2D risk. While consumption of ASBs was associated with an increased risk of metabolic syndrome and T2D in the Multi-Ethnic Study of Atherosclerosis (26), Atherosclerosis Risk in Communities (27), and Framingham Offspring (28) prospective cohort studies after an adjustment for BMI, our findings align with those of more recent studies by de Koning et al. (29) and the InterAct Consortium et al. (30). In the Health Professionals Follow-Up Study, de Koning et al. (29) observed that the association between ASB consumption and T2D risk was attenuated but still positive after adjustments for BMI and measures of previous weight change, dieting, and total energy intake (HR 1.09, 95% CI 0.98–1.21 for the top vs bottom quartiles of intake; $P = 0.13$). In the European Prospective Investigation into Cancer and Nutrition study, the association between one 12-ounce daily increment in ASB consumption and the increased T2D risk was similar after adjustments for energy intake and BMI (HR 1.11, 95% CI 0.95–1.31) (30).

Few intervention studies have directly examined the effects of ASB consumption on cardiometabolic parameters in humans, and the randomized, controlled trials investigating the effect of ASBs on weight management have, thus far, provided inconsistent results (12, 13). Some large prospective observational studies have found positive associations between ASB intake and BMI, as well as risk of obesity, hypertension, metabolic syndrome, T2D, stroke, and cardiovascular events (13), while others observed a null or even subtle inverse association with weight gain in a population without obesity or chronic disease (31). Several factors may contribute to these discrepancies, including the specific types of artificial sweeteners, study duration, and baseline cardiometabolic risks of the populations under study (32, 33). Further, a potential publication bias has been implicated in studies of artificial sweeteners and T2D risk and, thus, the interpretation of the current evidence base should account for these considerations (13).

Several mechanisms have been proposed to explain the potential role of artificial sweeteners in metabolic dysregulation (34, 35), including alterations of the composition and function of gut microbiota (36) and the glycemic response (37). It has also been suggested that the consumption of artificial sweeteners in foods and beverages over time may alter taste preferences and diet quality by increasing preferences for sweet-tasting foods, increasing appetites, and altering gut hormone secretion, leading to excess energy intake (1, 12, 38). The lack of consistent evidence to support the use of artificial sweeteners for weight loss and preventing metabolic abnormalities, coupled with observational evidence suggesting a positive association between routine ASB intake and cardiometabolic risks, highlights the need for more research to assess the effects of long-term consumption.

The results from the SSB analysis are consistent with previous research demonstrating a positive association between SSB consumption and T2D risk after adjustments for confounders such as diet quality and total energy intake. The attenuation of the association with adjustments for baseline BMI and weight change suggests that the SSB–T2D association may be explained, to some extent, by relative weight status and weight change. Of note, an adjustment for weight change may be an over-adjustment, as weight gain attributed to excess energy intake from SSB consumption is hypothesized as a plausible mechanism linking SSBs and T2D (9, 39). Speculatively, these results suggest that SSB consumption impacts etiological factors beyond weight, as the results for both SSB (as a continuous variable) and TSB intake were only partially attenuated by adjustments for baseline BMI and weight change. SSB consumption has frequently been linked to weight gain and T2D risk in observational studies (6–9), and several long-term intervention studies have demonstrated that SSB consumption is associated with a positive energy balance (40–43). However, the results of short-term intervention studies on this topic have provided inconsistent results (44), and evidence for whether or not decreased consumption would impact the obesity prevalence and T2D risk remains inconclusive (45).

This analysis of sweetened beverage intake and T2D risk in the CARDIA cohort adds to the evidence base by examining a younger population with repeated measurements of diet and potential confounding variables, an assessment of dieting behaviors, and the clinical adjudication of diabetes. The current study thus addresses some of the hypothesized issues related

to reverse causality, confounding, and misclassification that are inherent in previous studies of sweetened beverages and T2D risk in older populations. In particular, this study addresses these concerns since few cases occurred early in follow up, the early follow-up rate was high, and diabetes statuses were clinically adjudicated.

We note several limitations to this study. Although we accounted for many confounders in our models, residual confounding is likely to occur in all diet–disease observational studies. As noted in several recent systematic reviews (7), reverse causality due to the higher consumption of ASBs by overweight and obese individuals or residual confounding from a clustering of lifestyle factors associated with consumption, such as diet quality, may bias the ASB–cardiometabolic risk. The use of self-reported dietary data is also subject to recall and other biases that may alter estimates. The validity and reliability of the CARDIA Diet History has been demonstrated; however, nutrient and energy estimates were found to have larger variability among Blacks than Whites (17, 46). This may, in part, explain the stronger positive association observed between SSB intake and T2D risk in Whites versus Blacks. Sample size limitations prevented us from investigating these stratified group associations by category of SSB intake and, thus, limit the interpretation of whether the relationship truly differs between groups. In addition, a dietary assessment reflecting the previous 1 month of beverage intake may not adequately capture seasonal differences (47). While we were adequately powered to detect an association between beverage intake and T2D, a larger sample size could improve the precision of the estimates, given the limitations of self-reported dietary data, particularly for the sensitivity analysis of beverage intake patterns over time and the effect modification analyses.

In conclusion, the results from the CARDIA cohort mirror previous studies and suggest that higher, frequent ASB and SSB intake is positively associated with T2D risk in young adults, and baseline BMI and weight change over time explain some level of this association. Furthermore, the TSB–T2D results from this study inform and support evolving scientific advisory reports (3) suggesting that cutting or avoiding any sweetened beverage intake may be the optimum choice for cardiometabolic health (3). The continued triangulation of observational, experimental, and mechanistic research related to sweetened beverage intakes will enhance the evidence base and better inform the public.

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