Artificially Sweetened Beverages and Stroke, Coronary Heart Disease, and All-Cause Mortality in the Women's Health Initiative

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Background and Purpose—We examine the association between self-reported consumption of artificially sweetened beverages (ASB) and stroke and its subtypes, coronary heart disease, and all-cause mortality in a cohort of postmenopausal US women.

Methods—The analytic cohort included 81 714 women from the Women's Health Initiative Observational Study, a multicenter longitudinal study of the health of 93 676 postmenopausal women of ages 50 to 79 years at baseline who enrolled in 1993 to 1998. This prospective study had a mean follow-up time of 11.9 years (SD of 5.3 years.) Participants who completed a follow-up visit 3 years after baseline were included in the study.

Results—Most participants (64.1%) were infrequent consumers (never or <1/week) of ASB, with only 5.1% consuming ≥2 ASBs/day. In multivariate analyses, those consuming the highest level of ASB compared to never or rarely (<1/wk) had significantly greater likelihood of all end points (except hemorrhagic stroke), after controlling for multiple covariates. Adjusted models indicated that hazard ratios and 95% confidence intervals were 1.23 (1.02–1.47) for all stroke; 1.31 (1.06–1.63) for ischemic stroke; 1.29 (1.11–1.51) for coronary heart disease; and 1.16 (1.07–1.26) for all-cause mortality. In women with no prior history of cardiovascular disease or diabetes mellitus, high consumption of ASB was associated with more than a 2-fold increased risk of small artery occlusion ischemic stroke hazard ratio =2.44 (95% confidence interval, 1.47–4.04.) High consumption of ASBs was associated with significantly increased risk of ischemic stroke in women with body mass index ≥30; hazard ratio =2.03 (95% confidence interval, 1.38–2.98).

Conclusions—Higher intake of ASB was associated with increased risk of stroke, particularly small artery occlusion subtype, coronary heart disease, and all-cause mortality. Although requiring replication, these new findings add to the potentially harmful association of consuming high quantities of ASB with these health outcomes. **(*Stroke*. 2019;50:555-562. DOI: 10.1161/STROKEAHA.118.023100.)**

Key Words: brain ischemia ■ coronary heart disease ■ death ■ diabetes mellitus ■ sweetening agents ■ stroke

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Although the role of sugar-sweetened beverages in cardiovascular disease (CVD) risk has been described,[1–3] previous research on artificially sweetened beverages (ASB) has been limited. In a previous Women's Health Initiative (WHI) study, consumption of ≥2 servings of ASB a day was associated with a 30% increase in composite CVD events and all-cause mortality and a 50% increase in CVD mortality after controlling for CVD risk factors.[4] Data regarding ASB consumption and CVD events from other studies are inconsistent. In the Framingham Offspring cohort, ASB consumption, but not consumption of sugar-sweetened beverages, was associated with an increased risk for both stroke and dementia.[5,6] In the Nurses' Health Study, an association was observed between sweetened beverages, but not ASB, and coronary heart disease (CHD).[3] Data from the Northern Manhattan Study indicated an association of ASB consumption with increased risk of cardiovascular events (stroke, myocardial infarction [MI], and vascular deaths).[7]

The WHI Observational Study (WHI-OS) cohort affords an excellent opportunity to examine the association of ASB with stroke, CHD, and all-cause mortality in older women with an extended duration of follow-up. The WHI-OS is a multicenter

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*A list of all WHI study participants is given in the Appendix.

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longitudinal study of the health of nearly 100 000 postmenopausal women enrolled in 1993 to 1998 and with continuing follow-up. Here we investigated the association of ASB with both ischemic and hemorrhagic stroke separately. We also evaluated the association of ASB with subtypes of ischemic stroke, which previous studies have not explored. We hypothesized that ASBs were associated with all types of ischemic stroke.

Methods

Data used in this study are publicly available at the NHLBI BioLINCC and can be accessed at https://biolincc.nhlbi.nih.gov/home/. The WHI consists of a set of overlapping clinical trials (hormone therapy, dietary modification, and calcium/Vitamin D supplementation) and a separate observational study (WHI-OS), which is the cohort used in this study. Women of ages 50 to 79 years were recruited into the WHI-OS during 1993 to 1998 in 40 clinical sites in the United States through mass mailings using voter registration, motor vehicle registration, and commercial lists. Women who did not wish to join or were not eligible for the WHI clinical trials of hormone therapy or dietary modification were also invited to enroll in WHI-OS. A detailed description of WHI is published elsewhere.[8,9] WHI-OS participants (N=93 676) had a clinic visit at enrollment (referred to henceforth as a screening visit) during which they completed questionnaires and had a physical examination and blood draw. They were also asked to bring in all their pill bottles. The label data from the pill bottles were transcribed into the Medications Database and matched to the corresponding item in a pharmacy database (Master Drug Database [MDDB]; Medi-Span, Indianapolis, IN) that included brand and generic drug names, national drug codes, and a therapeutic class code provided by the American Hospital Formulary Service. The computer system was updated approximately every quarter with a new pharmacy database to ensure completeness of the list of available products. Participants were asked to return for another clinic visit 3 years after enrollment (year 3 visit), at which point these procedures were repeated (N=82 563). It was at the year 3 visit that participants were asked to estimate their consumption of ASB. Participants with missing responses to the question (n=849) were excluded from the analyses. Therefore, our analytic cohort consisted of 81 714 women. Follow-up time after year 3 was for a mean of 11.9 years (SD=5.3 years.) The overall WHI protocol was approved by institutional review committees of participating institutions, and participating women provided written informed consent for their overall study activities.

Ascertainment of Stroke, CHD Outcomes, and Mortality

Outcomes studied were overall stroke, which includes fatal and nonfatal stroke; ischemic stroke; hemorrhagic stroke, ischemic stroke subtypes as determined by the TOAST (Trial of ORG 10172 Acute Stroke Trial) classification[10]; CHD, which includes nonfatal MI and CHD death; and death from all causes, occurring after the year 3 visit, at which time our exposure variable, ASB, was assessed. These outcomes were first identified through self-report at annual contacts or third-party report, and potential cases were thoroughly investigated by obtaining medical records from hospitals, physicians, and laboratories where appropriate.[11] Data linkage with the National Death Index was performed to assure completeness of survival data. Adjudication of outcomes was performed by uniformly trained physicians first at the Clinical Centers, then centrally, under the auspices of the Clinical Coordinating Center. The adjudicating physicians were blinded to any participant information that could potentially result in bias.[4]

Assessment of the Exposure Variable: Artificially Sweetened Beverages

Data regarding ASB were available from the year 3 annual follow-up questionnaire, which asked: "During the past 3 months, how often did you drink these beverages?" (Beverages refer to diet drinks such as Diet Coke or diet fruit drinks, with a 12 fl oz can as a reference size.) Frequency was described in 9 categories: never or less than once per month (reference), 1 to 3 per month, 1 per week, 2 to 4 per week, 5 to 6 per week, 1 per day, 2 to 3 per day, 4 to 5 per day, ≥6 per day. These categories were collapsed for analysis to 4 categories: never or less than once per week, 1 to 4 times a week, 5 to 7 times a week, and ≥2 times a day.

Measurement of Covariates

Age and ethnicity, characterized by 1990 US Census options, were ascertained at the WHI screening visit, while lifestyle and risk factor variables were obtained from year 3 visit questionnaires. Body mass index (BMI) was calculated by dividing weight in kilograms by square of height in meters. Women were classified as hypertensive if they were either taking antihypertensive medications (as determined from the medications inventory) or had a systolic blood pressure ≥140 mmHg or a diastolic blood pressure ≥90 mmHg at the year 3 visit. Use of cholesterol-lowering medications was obtained from the computer medication inventory. Diabetes mellitus was defined as any self-report of a doctor diagnosis of diabetes mellitus before the year 3 visit. History of stroke or MI was defined as either a self-report of the condition at the WHI screening visit or as having a stroke or MI event between the screening visit and year 3 visit. History of CVD, which consisted of MI, stroke, transient ischemic attack, angina, or revascularization, was considered positive if participant reported such history at the screening visit or if any of the events occurred between the screening visit and year 3. Recreational physical activity was assessed using information about frequency, duration, and intensity of activity and organized into categories of activity as described elsewhere.[9] Diet quality was assessed using the Healthy Eating Index score (2005), which is a measure of diet quality that assesses conformance to US Dietary Guidelines 2005. The year 2005 was chosen because it is closest to ascertainment of the exposure variables. The standards were created using a density approach, that is, they are expressed as a percent of calories or per 1000 calories. The score ranges from 0 to 100, with higher score indicating healthier diet. It is the sum of 10 individual food components including whole fruits, total fruit including 100% fruit juice, total vegetables, dark green and orange vegetables including legumes, total grains, whole grains, milk, meat and beans, saturated fats, sodium, calories from solid fats, alcoholic beverages, and added sugars.[12] Data regarding regular soda consumption and other nutrients were assessed at the WHI screening visit and at year 3 follow-up visit using the WHI Food Frequency Questionnaire, described in detail elsewhere.[13] The Food Frequency Questionnaire database was derived from the University of Minnesota Nutrition Coordinating Center Nutrient Data for Scientific Research database. For assessment of regular soda consumption, serving sizes were specified as small (6 fl oz,) medium (12 fl oz), or large (18 fl oz); frequency of consumption ranged from never to 6 times per day. Information on calories and other nutrients was derived solely from the Food Frequency Questionnaire administered at year 3 visit to align with the year 3 annual follow-up questionnaire that included the diet drink question. Consumption of ASB was not assessed by the Food Frequency Questionnaire.

Statistical Analysis

Demographic, behavioral, and comorbid conditions variables were compared across ASB categories by χ^2. Cox regression analyses were done to investigate the relationship between level of ASB consumption and the outcomes of interest, controlling for multiple covariates.

Cox models are presented controlling for age, race/ethnicity, and education (Model 2), additionally for health risk variables assessed at year 3: history of diabetes mellitus, history of CVD, hypertension, taking cholesterol-lowering medications, and BMI as a continuous variable (Model 3), and lastly, additionally controlling for health behaviors: smoking, alcohol, physical activity (using MET), and a diet quality variable, the Healthy Eating Index 2005 (HEI-2005; Model 4). Because of a priori interest in BMI (because consumption of ASB may be related to BMI) and a priori interest in race/ethnicity (because black women have higher rates of stroke than white women), we stratified results by BMI category and by

Table 1. Characteristics of Participants by Frequency of Artificially Sweetened Beverage Consumption—No Exclusions*

Participant Characteristics	Frequency of Artificially Sweetened Beverage Consumption				*P* Value†
	Never or <1/wk	1–4 /wk	5–7/wk	≥2/day	
Total sample (81 714)‡	52 317	15 819	9382	4196	
Variable, N	64.1%	19.4%	11.5%	5.1%	
Age at screening, yr					<0.0001
50–59 (25 821)	28.3	33.1	40.0	48.8	
60–69 (36 455)	44.7	46.1	43.5	39.5	
70–79+ (19 438)§	27.0	20.8	16.5	11.7	
Race/ethnicity (screening)					0.181
White (69 641)	89.1	89.7	89.9	89.5	
Black (5687)	7.4	7.0	7.1	7.1	
Hispanic (2625)	3.4	3.4	3.0	3.3	
Education (screening)					
0–8 y (1011)	1.3	1.1	1.3	1.2	<0.0001
Some high school/high school diploma (15 453)	18.4	20.2	20.3	20.7	
Some college/college graduate or postgraduate (64 618)	80.3	78.7	78.4	78.2	
Income (screening)					
<$20 000 (11 151)	14.8	13.1	12.9	14.2	<0.0001
$20 000–$49 999 (33 079)	42.6	42.3	40.7	41.3	
≥$50 000 (31 805)	39.6	41.7	43.9	41.7	
Do not know (2247)	2.9	2.9	2.6	2.8	
Smoking history					<0.0001
Yes (3758)	4.7	3.6	4.7	7.6	
Alcohol intake					<0.0001
Yes (56 692)	70.2	71.0	68.1	60.4	
Weight status, BMI, kg/m^2					<0.0001
<25 (29 782)	45.4	32.4	27.9	21.7	
25.0–29.9 (26 051)	33.6	37.4	36.5	33.7	
≥30.0 (19 264)	21.0	30.2	35.7	44.6	
Hypertensive (self-reported treatment or BP≥140/90 mmHg) (38 242)	47.9	50.6	51.9	52.5	<0.0001
History of diabetes mellitus, %	4.1	8.1	10.3	14.6	<0.0001
History of myocardial infarction, %	2.6	2.9	3.0	3.5	0.0023
History of stroke, %	1.4	1.1	1.5	1.5	0.0519
History of cardiovascular disease, %	10.5	10.6	11.6	11.8	0.0019
Sugar sweetened drinks					
None or <1 /mo (53 939)	65.61	63.27	72.85	79.14	<0.0001
<Once a day (24 023)	30.99	35.20	21.02	12.18	
≥Once a day (2926)	3.39	1.54	6.13	8.68	
Age at screening, yr, mean (SD)	64.3 (7.3)	63.1 (7.1)	62.0 (7.1)	60.5 (6.9)	<0.0001
BMI, kg/m^2, mean (SD)	26.6 (5.4)	28.1 (5.7)	28.9 (6.1)	30.3 (6.7)	<0.0001
Total METs/wk, mean (SD)	14.0 (14.8)	13.4 (14.0)	12.8 (14.0)	11.4 (13.9)	<0.0001

(*Continued*)

Table 1. Continued

Participant Characteristics	Frequency of Artificially Sweetened Beverage Consumption				*P* Value†
	Never or <1/wk	1–4 /wk	5–7/wk	≥2/day	
Healthy eating index (2005) Total HEI score, mean (SD)	69.8 (10.7)	69.8 (9.9)	68.3 (10.3)	65.3 (11.4)	<0.0001
Systolic blood pressure, mmHg mean (SD)	126.1 (17.6)	126.2 (17.1)	125.9 (17.0)	125.7 (17.0)	0.34
Diastolic blood pressure, mmHg mean (SD)	73.1 (9.3)	73.4 (9.1)	73.6 (9.2)	73.8 (9.3)	<0.0001
Waist hip ratio, mean (SD)	0.8 (0.1)	0.8 (0.1)	0.82 (0.1)	0.8 (0.1)	<0.0001
Energy intake, kcal, mean (SD)	1453.1 (605.9)	1490.4 (611.4)	1513.9 (642.2)	1617.2 (812.1)	<0.0001

BMI indicates body mass index; BP, blood pressure; HEI, Healthy Eating Index; and MET, metabolic equivalent of task.

*At year 3 visit—unless indicated as screening visit.

†*P* Value were obtained from χ^2 tests or analyses of variance across the various categories of each covariate. % only include non-missing values.

‡The numbers in the various categories may not add up to the total in our analytic cohort of 81 714 because of some missing data.

§All were 70-79 years of age at screening except 1 participant who was 80 years old, and 2 who were 81 years of age.

race/ethnicity. We did 5 tests of interaction with BMI and race/ethnicity for each of primary outcomes.

We did sensitivity analyses excluding participants with history of diabetes mellitus or CVD before year 3 (ie, those who reported such history at WHI screening visit or who had incident diabetes mellitus or CVD between baseline and year 3). Statistical analyses were performed using SAS software (SAS Institute Inc, Cary, NC). Study procedures were approved by the institutional review boards of all the sites and the coordinating center.

Results

The sociodemographic composition of the cohort was as follows: 31.6% of participants were between 50 to 59 years of age, 44.6% were between 60 and 69 years of age, and 23.8% were 70 years or older; 85.2% were white, 7.0% were black, 3.2% were Hispanic. The majority of the 81 714 participants (64.1%) were infrequent consumers (never or less 1/wk) of

Table 2. Hazard Ratio and 95% CI: Artificially Sweetened Beverage Consumption and Outcomes—No Exclusions

Outcomes	N	No. of Events	Artificially Sweetened Beverage Consumption				*P* Trend
			Never of <1/wk	1–4/wk	5–7/wk	≥2/day	
All stroke (fatal and nonfatal)							
Model 1	81 072	2838	Reference	0.86 (0.77–0.94)*¶	0.87 (0.77–0.98)†¶	1.06 (0.90–1.24)	0.091
Model 2	80 230	2801	Reference	0.97 (0.88–1.08)	1.10 (0.97–1.24)	1.59 (1.35–1.87)‡¶	<0.001
Model 3	72 502	2528	Reference	0.93 (0.84–1.04)	1.01 (0.89–1.16)	1.29 (1.08–1.55)*¶	0.146
Model 4	71 592	2492	Reference	0.93 (0.84–1.04)	1.00 (0.87–1.14)	1.23 (1.02–1.47)†¶	0.304
Ischemic stroke							
Model 4	70 773	1673	Reference	0.98 (0.86–1.11)	0.99 (0.84–1.16)	1.31 (1.06–1.63)†¶	0.166
Hemorrhagic stroke							
Model 4	69 428	328	Reference	0.96 (0.72–1.3)	0.93 (0.63–1.38)	1.14 (0.65–1.97)	0.982
CHD (fatal and nonfatal)							
Model 1	80 968	3618	Reference	0.96 (0.88–1.04)	1.01 (0.91–1.12)	1.27 (1.11–1.46)§¶	0.037
Model 2	80 128	3579	Reference	1.08 (0.99–1.18)	1.29 (1.16–1.43)‡¶	1.94 (1.69–2.22)‡¶	<0.0001
Model 3	72 394	3203	Reference	0.99 (0.90–1.08)	1.05 (0.94–1.18)	1.38 (1.19–1.60)‡¶	0.003
Model 4	71 488	3161	Reference	1.01 (0.91–1.10)	1.05 (0.93–1.17)	1.29 (1.11–1.51)‖¶	0.011
All-cause mortality							
Model 1	81 491	15 005	Reference	0.89 (0.85–0.92)‡¶	0.88 (0.83–0.93)‖¶	0.99 (0.89–1.03)	<0.0001
Model 2	80 642	14 842	Reference	1.01 (0.96–1.05)	1.17 (1.11–1.23)‡¶	1.53 (1.42–1.65)‡¶	<0.0001
Model 3	72 840	13 143	Reference	0.95 (0.91–1.00)†¶	1.06 (1.10–1.12)	1.26 (1.16–1.37)‡¶	0.0114
Model 4	71 926	12 978	Reference	0.96 (0.92–1.01)	1.05 (0.98–1.11)	1.16 (1.07–1.26)‖¶	0.007

Model 1 is unadjusted; Model 2 is adjusted for age, race, education; Model 3 is Model 2 + health risk variables (diabetes mellitus, CVD, high cholesterol requiring pills, hypertension [defined as blood pressure ≥140/90 mmHg], BMI); Model 4: Model 3 + behaviors (smoking, alcohol, MET, HEI). CHD indicates coronary heart disease, CI, confidence interval; CVD, cardiovascular disease; HEI, Healthy Eating Index; and MET, metabolic equivalent of task.

**P*<0.01, †*P*<0.05, ‡*P*<0.0001, §*P*<0.0004, ‖*P*<0.001.

¶Significant findings.

ASBs, with only 5.1% consuming ≥2 ASBs a day. Table 1 indicates that participants who consumed a high level of ASBs (≥2 ASBs/day) compared to women with a lower level of ASB consumption were younger (50–59 years at WHI screening) were more likely to be obese, had lower levels of exercise, had higher energy intake and lower diet quality as judged by HEI-2005, were more likely to be a current smoker, less likely to be a drinker, and were more likely to have a history of diabetes mellitus, MI, or cardiovascular disease. The majority (79.1%) of participants who consumed ≥2 servings of ASBs daily never or rarely consumed regular soda, with only a small proportion (8.7%) consuming ≥1 serving of regular soda per day. The Spearman correlation between regular soft drink consumption and ASBs, although statistically significant because of the large sample size, was extremely small with $R^2 = 0.0003$.

Incidence of Outcomes

In our analytic cohort of WHI-OS participants (n=81 714), there was a total of 2838 fatal and nonfatal strokes, 2227 ischemic strokes, 422 hemorrhagic strokes, 3618 CHD events, and 15 005 deaths occurring during follow-up after year 3. The cumulative incidence rates of all stroke (fatal and nonfatal), ischemic stroke, and CHD were highest for those who consumed the most ASBs (Table I in the online-only Data Supplement). Hemorrhagic stroke incidence was not statistically significantly different across different levels of ASB consumption.

ASBs and Risk of Stroke, CHD, and All-Cause Mortality

In multivariate analyses (Table 2), participants consuming the highest levels of ASBs had significantly greater likelihood of all end points (except hemorrhagic stroke), even after controlling for demographic, risk factors, comorbidities, and behavioral variables. For fatal and nonfatal stroke, the hazard ratio (HR) was 1.23 (95% confidence interval [CI], 1.02–1.47); for ischemic stroke, the HR was 1.31 (95% CI, 1.06–1.63); for CHD, the HR was 1.29 (95% CI, 1.11–1.51); and for all-cause mortality, the HR was 1.16 (95% CI, 1.07–1.26). Sensitivity analyses (excluding participants with CVD or diabetes mellitus before year 3), shown in Table 3, for the fully adjusted model, yielded similar results.

BMI, Race/Ethnicity, ASB, and Risks of Outcomes

Although we found no significant interaction between BMI treated as a continuous variable and diet drinks on the outcomes we studied (except for the category of 5–7 ASB per week and all-cause mortality), we nevertheless looked at these relationships within the BMI strata because of a priori interest in BMI (Table II in the online-only Data Supplement). Although there is no clear pattern of association across the BMI strata, high consumption of ASBs shows increased risk of ischemic stroke only among those with BMI≥30 (HR, 2.03; 95% CI, 1.38–2.98), with *P* for trend =0.002, and increased risk of all-cause mortality only in those with BMI<30. It is important to note that where *P* for trend is not significant but the highest category of ASB is significantly different from the lowest, we may be observing an association that has a threshold or other nonlinear relationship.

Because of a priori interest in ethnicity/race, we also looked at relationships with outcomes within the ethnicity/race strata. Higher ASB consumption was significantly associated with higher ischemic stroke risk among blacks (HR, 3.93; 95% CI, 1.87–8.26) but not among whites or other race/ethnic groups (Table 4). We saw a significant interaction between black race and all stroke and ischemic stroke *P*=0.0006 and *P*=0.002, respectively. There was no significant interaction with age. One hundred fourteen of 2838 (4%) of all strokes occurred among black women.

Subtypes of Ischemic Stroke

Cox proportional hazards models were run for the predominant TOAST classes: large artery artherosclerosis, cardioembolism, and small artery occlusion (SAO). We compared each subtype with a reference group of no stroke. Even though the sample sizes for TOAST subtypes were relatively small, higher intake of ASBs was associated with a higher risk of SAO in models both with and without exclusions for participants with diabetes mellitus or CVD at year 3 (Table 5; Table III in the online-only Data Supplement). In fully adjusted models, participants with ≥2 ASBs per day had HR (95% CI) for SAO of 1.81 (1.18–2.80); in sensitivity analyses, where participants

Table 3. Hazard Ratio and 95% CI for Artificially Sweetened Beverage Consumption and Outcomes With Exclusions

Outcomes (N/No. of Events)	Artificially Sweetened Beverage Consumption				*P* Trend
	Never or <1/wk	1–4/wk	5–7 /wk	≥2/day	
Ischemic `stroke (60 380/1190)	Reference	0.99 (0.85–1.15)	0.96 (0.78–1.17)	1.38 (1.05–1.81)*§	0.273
Hemorrhagic stroke (59 449/259)	Reference	0.88 (0.63–1.23)	0.77 (0.48–1.24)	1.17 (0.63–2.17)	0.557
All stroke (fatal and nonfatal) (60 998/1808)	Reference	0.95 (0.84–1.08)	0.99 (0.84–1.17)	1.26 (1.00–1.58)†	0.340
CHD (fatal and nonfatal) (61 178/2084)	Reference	0.98 (0.87–1.10)	0.98 (0.84–1.14)	1.35 (1.10–1.65)‡§	0.154
All-cause mortality (61 204/9769)	Reference	0.97 (0.92–1.03)	1.04 (0.97–1.11)	1.19 (1.07–1.32)‡§	0.023

Excluding participants with diabetes mellitus or cardiovascular disease at year 3 before artificially sweetened beverage assessment based on: Model 4 = Model 3 + behaviors: smoking, alcohol, MET, HEI. CHD indicates coronary heart disease; HEI, Healthy Eating Index; and MET, metabolic equivalent of task.

*$P<0.05$, †$P=0.054$, ‡$P<0.01$.

§Significant findings.

Table 4. Hazard Ratio and 95% CI for Artificially Sweetened Beverage Consumption and Outcomes by Race/Ethnicity With Exclusions

Outcomes by Race/Ethnicity (N/No. of Events)	Artificially Sweetened Beverage Consumption			
	Never or <1/wk	1–4/wk	5–7/wk	≥2/day
All stroke				
White (53 042/1602)	Reference group	0.92 (0.81–1.06)	0.10 (0.84–1.19)	1.12 (0.86–1.44)
Black (3531/114)	Reference group	1.31 (0.82–2.10)	0.77 (0.35–1.69)	3.27 (1.69–6.33)*
P interaction with black race/ethnicity		0.124	0.639	0.0006‡
other (4425/92)	Reference group	1.10 (0.63–1.94)	1.26 (0.60–2.63)	2.03 (0.72–5.70)
P interaction with other race/ethnicity		0.445	0.510	0.234
Ischemic stroke				
White (52 483/1043)	Reference group	0.95 (0.80–1.11)	0.96 (0.77–1.19)	1.19 (0.88–1.61)
Black (3500/83)	Reference group	1.47 (0.85–2.53)	0.80 (0.32–2.02)	3.93 (1.87–8.26)*‡
P interaction with black race/ethnicity		0.112	0.741	0.002‡
other (4397/64)	Reference group	1.28 (0.67–2.43)	1.13 (0.44–2.87)	2.34 (0.71–7.76)
P interaction with other race/ethnicity		0.296	0.730	0.303
Hemorrhagic stroke				
White (51 672/232)	Reference group	0.87 (0.61–1.24)	0.76 (0.46–1.25)	1.04 (0.52–2.05)
Black (3430/13)	Reference group	0.88 (0.19–4.04)	0.000	2.72 (0.33–22.55)
P interaction with black race/ethnicity		0.945	0.963	0.409
other (4347/14)	Reference group	1.17 (0.25–5.49)	2.56 (0.54–12.22)	3.68 (0.44–30.60)
P interaction with other race/ethnicity		0.725	0.162	0.237
Coronary heart disease				
White (53 194/1868)	Reference group	0.96 (0.85–1.09)	0.10 (0.85–1.17)	1.31 (1.06–1.63)†‡
Black (3546/117)	Reference group	1.21 (0.74–1.97)	1.10 (0.58–2.09)	1.60 (0.73–3.55)
P interaction with black race/ethnicity		0.467	0.603	0.305
other (4438/99)	Reference group	1.17 (0.70–1.98)	0.51 (0.19–1.40)	1.74 (0.68–4.41)
P interaction with other race/ethnicity		0.353	0.265	0.254
All-cause mortality				
White (53 194/8976)	Reference group	0.97 (0.92–1.03)	1.04 (0.97–1.12)	1.22 (1.10–1.36)*
Black (3566/400)	Reference group	1.07 (0.82–1.39)	1.06 (0.75–1.50)	0.74 (0.41–1.34)
P interaction with black race/ethnicity		0.353	0.498	0.282
Other (444/393)	Reference group	0.96 (0.73–1.27)	0.99 (0.67–1.47)	1.03 (0.54–1.96)
P interaction with other race/ethnicity		0.785	0.881	0.867

Excluding participants with diabetes mellitus or cardiovascular disease at year 3 before artificially sweetened beverage assessment based on Model 4: Model 3 + behaviors: smoking, alcohol, MET, HEI. White race is reference for *P* interaction with race/ethnicity. CI indicates confidence interval; HEI, Healthy Eating Index; and MET, metabolic equivalent of task.

*$P<0.001$, †$P<0.05$.

‡Significant findings.

with diabetes mellitus or CVD were excluded, ASB consumption was associated with even higher risk, HR=2.44 (95% CI, 1.47–4.04); *P* for trend =0.001. Additionally, in analyses stratifying participants given in Table 5 by hypertension at year 3, the results remained the same: for participants with ≥2 ASBs/day, HRs were 2.45 (95% CI, 1.09–5.50; *P*=0.030) and 2.38 (1.25–4.55; *P*=0.009) for nonhypertensives and hypertensives, respectively. Therefore, the increased risks of stroke and especially SAO are not likely to be mediated by diabetes mellitus or hypertension.

Discussion

The finding in this largest US cohort study of postmenopausal women of a positive association between higher intake of ASB (twice or more daily) and the incidence of ischemic stroke, in particular SAO subtype, CHD, and all-cause mortality, but not hemorrhagic stroke even after accounting for confounding factors, suggests that there may be a pathway leading to vascular injury related to SAO, which may be different from the pathway leading to vascular injury related to hemorrhagic stroke. Insofar as ASB consumption is concerned, the reason

Table 5. Hazard Ratio and 95% CI for Artificially Sweetened Beverage Consumption and TOAST Classification (Ischemic Stroke)

Outcomes (N/No. of Events)	Artificially Sweetened Beverage Consumption				*P* trend
	Never or <1/wk	1–4/wk	5–7/wk	≥2/day	
Large artery artherosclerosis (59 265/75)	Reference	1.33 (0.77–2.29)	1.24 (0.60–2.55)	0.36 (0.05–2.62)	0.970
Cardioembolism (59 534/344)	Reference	0.94 (0.71–1.24)	0.67 (0.43–1.03)	1.23 (0.72–2.09)	0.422
Small vessel occlusion (59 424/234)	Reference	1.09 (0.77–1.54)	1.41 (0.94–2.13)	2.44 (1.47–4.04)*†	0.001†

Excluding participants with diabetes mellitus or cardiovascular disease at year 3 before artificially sweetened beverage assessment; based on Model 4: Model 3 + behaviors: smoking, alcohol, MET, HEI. CI indicates confidence interval; HEI, Healthy Eating Index; MET, metabolic equivalent of task; and TOAST, Trial of ORG 10172 Acute Stroke Trial.

*P<0.001.

†Significant findings.

for a lack of a relationship with hemorrhagic stroke is unclear. The finding that in women with BMI ≥30, high consumption of diet drinks was associated with an increased risk of all end points except hemorrhagic stroke in women is notable.

We investigated whether these associations with ASB consumption and ischemic stroke subtypes existed because women with underlying diabetes mellitus or CVD or hypertension at year 3 were switching to ASBs. A sensitivity analysis excluding participants who had diabetes mellitus or CVD at year 3 baseline stratified by hypertension did not materially change the association with risk even in the fully adjusted models. However, it is possible that if a participant's weight, blood pressure, and glucose levels were slowly increasing (even if not yet diagnosed with diabetes mellitus or CVD), it could lead high-risk women to change to ASB to attain weight loss as suggested by their physician.

The finding that risks associated with both all stroke and ischemic stroke were significantly associated with being black as opposed to other races merits further investigation. Although too early to comment on the public health implications, the following questions and knowledge gaps need to be addressed by future research: Is there something about high ASB consumption, mix of foods not accounted for by the diet quality measure, or other lifestyle measure (sleep, stress, environment) among black postmenopausal women that creates a toxic mixture that is associated with higher risk of ischemic stroke? Are there genetic differences that need to be accounted for? Are there protective factors among non-black postmenopausal women that mitigate this affect? On the other hand, high ASB consumption was associated with increased risk of CHD in white postmenopausal women as opposed to their black counterparts.

It is also notable that in the Framingham Study[5] where participants were primarily white men and women, ASBs were associated with stroke risk, whereas in our cohort of postmenopausal women of diverse backgrounds, these associations were noted among black postmenopausal women. It is not clear whether sex or ethnicity is associated with these stroke risks because the results from the Framingham study were not stratified by sex.

Although these findings require replication, potential mechanisms explaining these findings are manifold. On the one hand, residual confounding of traditional risk factors such as hypertension and (undetected) diabetes mellitus, as well as reverse causality, may contribute to this association; on the other hand, it is known that noncaloric artificial sweeteners display unfavorable metabolic effects[14] which may put consumers at additional risk. Intake of saccharin, acesulfame-potassium, or stevia and saccharin have been linked to weight gain and increased adiposity.[15] Additionally, saccharin and aspartame have been also associated with impaired glucose homeostasis and hyperinsulinemia.[16] These data are underscored by recent experimental studies demonstrating that artificial sweeteners can cause glucose intolerance in mice by altering gut microbiota and cause dysbiosis and glucose intolerance in humans.[17] There may also be residual confounding because of imprecision of covariates. The diet quality variable (HEI-2005) and physical activity measurements are based on self-report and may not precisely capture the quality of the diet or physical activity. In a prior WHI study, low potassium intake was also associated with higher risk of SAO, indicating that diet is a potentially modifiable strategy to reduce the risk of this stroke subtype.[18]

A limitation of this study is that it was observational, rather than a clinical trial, and therefore results must be interpreted with caution. ASB was self-reported, and this information could not be validated as it was not captured on other diet assessment instruments. Our estimates of ASB covered a 3-month period, and consumption patterns may have changed over time before the outcomes occurred. However, particularly in weight-stable older women, the likelihood of changes in dietary patterns is likely low. In the Nurse's Health Study, the diet quality score was relatively stable within an individual for as long as 24 years.[19] We were unable to determine which ASB might be accounting for these associations. Because the ASB was framed as Diet drinks, such as Diet Coke or diet fruit drinks (12 ounce cans), it is not clear whether participants considered other ASBs such as tea or coffee with artificial sweeteners when answering this question. Additionally, women with high intakes of ASB of all types may have differed systematically in many ways from women with little or no intake, most especially since they were more likely to be obese and have a higher energy intake.

Conclusions

In this study of well-characterized postmenopausal women in the United States, self-reported consumption of ASBs was associated with increased risk of ischemic stroke, CHD, and all-cause mortality. A novel finding of this study is that higher

risk was associated with ischemic stroke subtype of SAO. Because of the observational nature of the study, however, the possibility of residual confounding cannot be excluded. Future studies are needed to replicate the findings and to examine specific ASBs in relation to stroke and other outcomes to guide clinical recommendations.

Appendix

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For a list of all the investigators who have contributed to WHI science, please visit: https://www.whi.org/researchers/Documents%20%20Write%20a%20Paper/WHI%20Investigator%20Long%20List.pdf

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