Association of Sweetened Beverage Intake with Incident Hypertension

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BACKGROUND: Consumption of sugar-sweetened beverages (SSBs) is associated with an increased risk of hypertension in cross-sectional studies. However, prospective data are limited.

OBJECTIVE: To examine the associations between SSBs and artificially sweetened beverages (ASBs) with incident hypertension.

DESIGN AND SETTING: Prospective analysis using Cox proportional hazards regression to examine the association between SSBs and ASBs with incident hypertension in three large, prospective cohorts, the Nurses' Health Studies I (n=88,540 women) and II (n=97,991 women) and the Health Professionals' Follow-Up Study (n=37,360 men).

MEASUREMENTS: Adjusted hazard ratios for incident clinically diagnosed hypertension.

RESULTS: Higher SSB and ASB intake was associated with an increased risk of developing hypertension in all three cohorts. In a pooled analysis, participants who consumed at least one SSB daily had an adjusted HR for incident hypertension of 1.13 (95 % CI, 1.09–1.17) compared with those who did not consume SSBs; for persons who drank at least one ASB daily, the adjusted HR was 1.14 (95 % CI, 1.09–1.18). The association between sweetened beverage intake and hypertension was stronger for carbonated beverages versus non-carbonated beverages, and for cola-containing versus non-cola beverages in the NHS I and NHS II cohorts only. Higher fructose intake from SSBs as a percentage of daily calories was associated with increased hypertension risk in NHS I and NHS II (p-trend=0.001 in both groups), while higher fructose intake from sources other than SSBs was associated with a decrease in hypertension risk in NHS II participants (p-trend=0.006).

LIMITATIONS: Residual confounding factors may interfere with the interpretation of results.

CONCLUSIONS: SSBs and ASBs are independently associated with an increased risk of incident hypertension after controlling for multiple potential confounders. These associations may be mediated by factors common to both SSBs and ASBs (e.g., carbonation or cola), but are unlikely to be due to fructose.

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INTRODUCTION

Sugary sodas and the agent used to sweeten them, high-fructose corn syrup (HCFS), have been implicated in the development of a variety of conditions, including dyslipidemia, insulin resistance, diabetes, non-alcoholic liver disease, and gout.[1–4] Cross-sectional studies have reported positive associations between sugar-sweetened beverage intake and hypertension prevalence.[5,6] However, prospective data are lacking. Although they do not contain fructose, artificially sweetened beverages (ASBs) may also be associated with the development of adverse metabolic consequences such as obesity and chronic kidney disease, through unclear mechanisms.[7,8] We performed a prospective investigation of the association between intake of SSBs and ASBs and incident hypertension in three large cohort studies: The Nurses' Health Study I (NHS I), the Nurses' Health Study II (NHS II), and the Health Professionals' Follow Up Study (HPFS).

METHODS

Design Overview

Cox proportional hazard regression models were used to calculate the hazard ratios of developing new-onset hypertension in persons consuming different amounts of SSBs and ASBs. Sweetened drink consumption was subdivided according to various beverage components (caffeine, carbonation), and the hazard ratios for incident hypertension according to intake of drink subtype was determined. Lastly, hypertension risk was assessed in relation to fructose consumption from SSBs versus fructose from other sources (e.g. fruits and vegetables).

Setting and Participants

We examined cohorts of older (NHS I) and younger (NHS II) female women, along with a cohort of males (HPFS).

The NHS I cohort was assembled in 1976, when 121,700 female nurses aged 30 to 55 years returned an initial questionnaire. The NHS II cohort was assembled in 1989, when 116,430 nurses aged 25–42 years completed and returned a mailed questionnaire. The HPFS cohort was assembled in 1986 after 51,529 male health professionals aged 40–75 years returned a similar questionnaire. Approximately every four years, information on dietary intake, including information on beverage consumption, has been collected via a semi-quantitative food frequency questionnaire (FFQ).[9,10] Since FFQ data was first available in the NHS I cohort in 1980 and NHS II and HPFS participants first returned FFQs in 1991 and 1986, we defined the baseline year as 1980 for NHS I, 1991 for NHS II, and 1986 for HPFS. Follow-up for incident hypertension in this study was 38 years for NHS I, 16 years from NHS II, and 22 years for HPFS. The institutional review board at Brigham and Women's Hospital reviewed and approved this study, including that participants provided implied consent by virtue of voluntarily returning their questionnaires.

SSB and ASB intake were queried on the FFQs by asking participants how frequently they consumed a serving of sugar-sweetened cola, sugar-sweetened caffeine-free cola, sugar-sweetened non-cola, and fruit punch or other sugar-sweetened fruit drink. A serving was defined as a "bottle, glass, or can". Please see Appendix 1 for details on how fructose intake from SSB and non-SSB sources was calculated. Our assessment of beverage intake and fructose-rich food consumption has been validated compared with two to four one-week diet records.[9,10] In a validation study of the FFQ used in our analyses, the de-attenuated correlation coefficients comparing the intakes of fructose sources as measured by our FFQs with intakes of these foods measured by diet records were 0.84 for sugar-sweetened cola, 0.55 for other sugar-sweetened soft drinks, and 0.74 for artificially-sweetened soft drinks.[11] Beverage and fructose intake were calculated initially at baseline for each participant, and then these values were updated when participants returned subsequent FFQs. In sensitivity analyses, we used time-weighted averages of SSB and ASB intake, as well as fructose intake, rather than replacing older intake values with newer values derived from the most recent FFQs.

We controlled for multiple other dietary factors that could confound the association of SSBs and ASBs with hypertension, including diet quality (a dietary score modeled after the diet followed in the Dietary Approaches to Stop Hypertension, or DASH, trial),[12] alcoholic beverage intake, and intakes of calcium, magnesium, vitamin D, trans fat intake, and cereal fiber. Age, BMI (calculated as weight in kilograms divided by height in meters squared), smoking status (never, former, or current), oral contraceptive use (never, former, or current in NHS I and NHS II), non-narcotic analgesic use, and categories of physical activity were also ascertained from questionnaires and updated at each time point that SSB and ASB intake were updated. Weight change in the follow-up period between questionnaires was ascertained by subtracting the prior weight from the later weight. Questionnaire-derived information about these covariates has been previously validated.[10,13,14] Race and family history of hypertension were queried in 1992 for NHS I, 1989 for NHS II, and 1990 for HPFS.

We used self-reporting to determine the development of new-onset high blood pressure. The baseline and follow-up biennial questionnaires asked participants to report whether a clinician had made a new diagnosis of hypertension during the preceding two years. Self-reported hypertension has been shown to be highly reliable in the HPFS and NHS I[15]: in a subset of HPFS participants who reported hypertension, medical record review confirmed a documented systolic and diastolic BP>140 and 90 mmHg, respectively, in 100 %; among the NHS I women, 100 % of a subset who reported hypertension also had the diagnosis confirmed by medical record review.[15,16] Participants who reported hypertension on any questionnaire up to and including the 1980 (NHS I), 1991 (NHS II), or 1986 (HPFS) questionnaires were excluded. Cases included individuals who first reported hypertension on subsequent questionnaires and whose year of diagnosis postdated the return of the 1980, 1991, or 1986 questionnaire.

Statistical Analysis

Cox proportional regression models were used to determine the hazard ratios for developing hypertension in participants who consumed SSBs or ASBs. Beverage intake was divided into four categories: less than one serving per month, 1–4 servings monthly, 2–6 servings weekly, or one or more servings per day. Multivariable models were adjusted for the potential confounders listed above. In another sensitivity analysis of the association between ASB intake and hypertension, we further adjusted for total sugar intake (fructose, maltose, lactose, and other sugars).

Next, beverage intake was subdivided by components into cola and non-cola drinks, caffeine-containing and caffeine-free drinks, and carbonated and non-carbonated drinks (fruit punch-type beverages). Multivariate regression models were utilized to calculate hazard ratios for incident hypertension in different types of beverages. Finally, we sought to assess the relation between fructose consumption as a percentage of a person's daily caloric intake and the risk of developing hypertension. Fructose consumption was separated into categories of fructose derived from SSBs, and fructose from other sources (e.g. fruit). These groups were further subdivided by percentage of caloric intake from fructose into five categories (>5 %, 5–7 %, 8–10 %, 11–14 %, and ≥15 %). Multivariate-adjusted regression models were used to calculate the hazard ratio of hypertension given percentage of calories derived from fructose.

RESULTS

Cohort Characteristics

Baseline characteristics of the NHS I (in 1980), NHS II (in 1991), and HPFS (1986) cohorts, stratified by category of SSB intake, are displayed in Table 1. With increasing intake of SSBs at baseline in all three cohorts, age, physical activity, and alcohol intake were all lower, while total daily caloric intake was higher. As expected, total fructose intake was higher among those who consumed higher amounts of SSBs, and diet quality (as assessed by DASH score) was poorer. In all three cohorts, the proportion of black participants increased as intake category increased, although they were a relatively small percentage of the cohort populations overall.

SSB and ASB Intake and Risk of Hypertension

Higher consumption of SSBs was associated with a small but significantly increased risk for incident hypertension in the two female cohorts, and a trend toward an increased risk in the male cohort (Table 2). Compared with participants who consumed less than one SSB per month, the fully adjusted HR for the development of hypertension among participants who drank one or more SSB per day was 1.12 (95 % CI 1.08–1.17) in NHS I, 1.17 (95 % CI 1.11–1.23) in NHS II, and 1.06 (95 % CI 0.99–1.14) in HPFS. In a pooled analysis of all three cohorts, the adjusted HR for new-onset hypertension was 1.01 (95 % CI, 0.99–1.03) for participants who consumed 1–4 sugary drinks monthly, 1.06 (95 % CI, 1.03–1.08) for those drinking 2–6 SSBs weekly, and 1.13 (95 % CI, 1.09–1.17) for those drinking at least one SSB daily, compared with those who consumed fewer than one SSB per month.

Consumption of ASBs showed similar associations with hypertension (Table 2). In NHS I, consumption of ≥ 1 ASB daily was associated with a fully adjusted HR of 1.11 (95 % CI 1.08–1.14). NHS II and HPFS results were comparable. Pooled analyses of all three cohorts yielded an adjusted HR of 1.04 (95 % CI, 1.01–1.07) for 1–4 diet drinks a month, 1.07 (95 % CI, 1.05–1.09) for 2–6 ASBs weekly, and 1.14 (95 % CI, 1.09–1.18) for at least one ASB daily. In secondary analyses, adjustment for adherence to a low-calorie diet and for total sugar intake produced no change in results.

We then performed a number of secondary analyses to explore whether there were certain characteristics of both SSBs and ASBs that were uniquely associated with hypertension. In general, the direct relation between sweetened beverage intake (whether sugar- or artificially-sweetened) and hypertension was stronger with intake of cola-containing as compared with non-cola-containing beverages (Table 3); however, the difference in the magnitude of the associations was significant only in the NHS I and HPFS cohorts (p-interaction < 0.001 and 0.04, respectively). The association between sweetened beverage intake and hypertension incidence was markedly stronger for carbonated as compared with non-carbonated beverages in all three cohorts (Table 3; p-interactions were <0.001 in NHS I, 0.03 in NHS II, and 0.009 in HPFS). There was no significant difference in hypertension risk and intake of caffeinated versus non-caffeinated beverages.

The fructose content of SSBs has been implicated as a possible mechanism for their relation with hypertension in cross-sectional studies.[5,6] To explore further whether fructose intake is associated with hypertension risk, we analyzed fructose intake from SSBs and fructose intake from other food sources as separate nutrients (Table 4). The association between fructose intake derived from SSBs and risk of hypertension was significant in NHS I and NHS II, but not in HPFS. In contrast, a higher intake of fructose derived from other food sources was inversely associated with hypertension risk in NHS II (p-trend 0.006), and a tendency toward an inverse association was observed in both NHS I (p-trend=0.08) and HPFS (p-trend=0.09).

DISCUSSION

This study is the first prospective analysis of the association between SSB and ASB consumption and the risk of incident hypertension. Previous cross-sectional studies have reported an association between SSB consumption and incident hypertension: Nguyen et al. found a relation between intake of sodas sweetened with HFCS and hypertension in a population of adolescents,[5] and an analysis of NHANES data found an increased prevalence of hypertension among individuals consuming higher than average amounts of fructose (≥ 74 g/d) derived mostly from SSBs.[6] Because SSBs contain fructose, which in animal studies has been shown to cause renal damage, increased gastrointestinal sodium uptake, and endothelial dysfunction,[17–19] it was hypothesized that the HFCS in sugary beverages was responsible for the increased risk of incident hypertension. In a prospective study, however, Forman et al. found no association between total fructose intake (regardless of source) and hypertension risk.[20] Another study measuring inflammatory markers and reactive oxygen species (ROS) after sugar intake showed no increase in inflammation or ROS after ingesting orange juice or a fructose-containing solution.[21] Our data indicate that higher intake of both SSBs and ASBs is independently associated with an increased risk of developing hypertension, and call into question the assumption that fructose in sweetened beverages is central to their association with elevated blood pressure.

It is tempting to hypothesize that an ingredient common to both sugary and diet beverages could be responsible for the increased risk of new-onset hypertension seen in

Table 1. Baseline Characteristics of the Three Cohorts According to Category of Sugar-Sweetened Beverage Intake

Variable	SSB Intake Category < 1 serving/month	1-4 servs/mo	2-6 servs/wk	≥1 serv/d
NHS I				
N=88,540				
Age, yrs	47 (41–53)	46 (40–52)	44 (39–50)	43 (38–49)
Race (%)				
Caucasian	95.3	94.7	94.4	93.0
Black	0.7	1.0	1.4	2.3
Hispanic	0.1	0.1	0.1	0.1
Asian	0.3	0.9	0.7	0.8
Other	3.6	3.3	3.4	3.7
FHx HTN (%)	38.3	40.4	40.1	39.5
Smoking (%)				
Former Current	32.429.8	26.3	23.8	20.8
		26.4	27.9	34.9
BMI, kg/m^2	23.0 (21.3–25.7)	23.0 (21.1–25.6)	23.0 (21.1–25.7)	23.0 (21.0–26.1)
Physical Activity, METs/wk	9.0 (3.1–20.9)	7.7 (2.9–18.2)	7.1 (2.5–16.9)	5.8 (2.2–15.9)
Total Fructose, g/d	16.4 (11.1–22.7)	16.2 (11.7–21.7)	20.5 (15.9–26.0)	33.5 (26.3–44.2)
Total calories/d				
Alcohol intake, g/d	1393 (1112–1718)	1481 (1188–1803)	1602 (1304–1930)	1772 (1441–2160)
		1.8 (0–7.2)	1.8 (0–6.7)	
DASH score	2.5 (0–11.0)			1.0 (0–5.7)
		24 (21–27)	22 (19–25)	
Diet soda intake, s/d	26 (23–29)			21 (18–24)
		0 (0–0.4)	0 (0–0.4)	
	0.03 (0–1.0)			0 (0–0.4)
NHS II				
N=97,991				
Age, yrs	37 (33–40)	36 (33–40)	36 (32–39)	35 (31–39)
Race (%)				
Caucasian	94.5	94.0	92.0	90.5
Black	0.6	0.9	1.6	2.4
Hispanic	1.0	0.9	1.0	1.2
Asian	0.9	1.2	2.0	2.0
Other	1.8	1.6	1.8	2.1
Family Hx HTN (%)	50.9	50.2	49.3	49.9
Smoking status (%)				
Former	26.8	22.5	19.5	16.4
Current	11.2	11.0	11.9	17.4
BMI, kg/m^2	23.3 (21.3–26.6)	23.0 (21.1–26.3)	22.7 (20.8–25.8)	22.7 (20.6–26.0)
Physical Activity, METs/wk	14.9 (5.9–30.4)	13.0 (5.4–26.8)	11.5 (4.7–24.7)	10.4 (3.9–23.4)
Total Fructose, g/d	17.8 (13.2–23.4)	18.4 (14.2–23.8)	22.2 (17.7–27.6)	32.3 (25.7–41.8)
Total calories/d	1559 (1254–1915)	1675 (1362–2040)	1819 (1485–2201)	2076 (1717–2497)
Alcohol intake, g/d	1.0 (0–4.0)	0.9 (0–3.7)	0.9 (0–3.4)	0 (0–2.7)
DASH score	25 (21–29)	24 (21–28)	23 (19–27)	21 (18–25)
Diet soda intake, s/d	1.0 (0.2–2.5)	0.6 (0.1–1.4)	0.1 (0–0.9)	0 (0–0.4)
HPFS				
N=37,360				
Age, yrs	55 (47–63)	53 (45–61)	50 (43–58)	47 (42–55)
Race (%)				
Caucasian	91.3	92.1	91.3	
Black	0.5	0.7	0.9	89.9
Asian	1.0	1.3	1.9	1.4
Other	1.8	1.3	1.5	2.2
				1.5
FHx HTN (%)	31.5	30.2	32.0	33.8
Smoking status (%)				
Former	45.7	40.2	36.6	
Current	8.4	8.9	10.0	32.9
				13.4
BMI, kg/m^2	24.7 (23.0–26.6)	24.8 (23.2–26.5)	24.8 (23.1–26.6)	24.8 (23.0–26.6)
DASH score	26 (22–29)	24 (20–28)	22 (19–26)	21 (17–24)
Alcohol intake, g/d	6.1 (0.9–15.8)	5.8 (1.0–14.6)	5.5 (1.0–14.0)	3.1 (0–12.4)
Physical Activity, METs/wk	14.8 (4.6–32.1)	12.7 (4.4–28.8)	11.5 (3.8–27.9)	10.1 (3.1–26.5)
Total Fructose, g/d	20.9 (15.1–27.9)	21.4 (16.1–27.7)	24.8 (19.9–30.8)	35.0 (28.4–44.2)
Total calories/d	1730 (1396–2120)	1847 (1495–2260)	2059 (1685–2475)	2384 (1950–2890)
Diet soda Intake, s/d	0.1 (0–0.9)	0.1 (0–0.5)	0.1 (0–0.4)	0 (0–0.1)

Median and interquartile range (IQR) values are shown for all variables. S, servings

consumers of soft drinks. Our study found that consumption of carbonated beverages carried a significantly higher risk of incident high blood pressure than intake of non-carbonated drinks. The potential mechanisms are unclear. One possibility is that the average serving size of a carbonated beverage could be higher than the average

Table 2. Intake of Sugar-Sweetened and Artificially-Sweetened Beverages (SSBs and ASBs) and Hazard Ratio for Incident Hypertension

Beverage Consumption (servings)	<1/month (reference)	1–4/month	2–6/week	≥1/day
SSBs				
NHS I				
Person-years	556,939	402,891	276,384	129,827
# Cases	17,989	11,849	8186	3998
Age-Adjusted Hazard Ratio	1.0	1.03 (1.00–1.05)	1.09 (1.06–1.12)	1.22 (1.18–1.27)
MV-Adjusted Hazard Ratio	1.0	1.00 (0.98–1.03)	1.02 (0.99–1.05)	1.11 (1.07–1.15)
MV and Weight-Adjusted HR	1.0	1.02 (0.99–1.04)	1.04 (1.01–1.07)	1.12 (1.08–1.17)
NHS II				
Person-years	456,363	307,057	303,437	176,141
# Cases	8394	5137	5027	3315
Age-Adjusted Hazard Ratio	1.0	1.02 (0.98–1.05)	1.14 (1.10–1.18)	1.39 (1.34–1.46)
MV-Adjusted Hazard Ratio	1.0	0.97 (0.94–1.01)	1.02 (0.98–1.06)	1.12 (1.06–1.17)
MV and Weight-Adjusted HR	1.0	1.00 (0.96–1.04)	1.07 (1.03–1.11)	1.17 (1.11–1.23)
HPFS				
Person-years	172,999	118,553	142,434	49,658
# Cases	5038	3198	3872	1331
Age-Adjusted Hazard Ratio	1.0	0.97 (0.92–1.01)	1.05 (1.00–1.09)	1.09 (1.02–1.16)
MV-Adjusted Hazard Ratio	1.0	0.96 (0.92–1.01)	1.02 (0.98–1.07)	1.04 (0.97–1.12)
MV and Weight-Adjusted HR	1.0	0.97 (0.93–1.02)	1.04 (1.00–1.10)	1.06 (0.99–1.14)
ASBs				
NHS I				
Person-years	594,401	205,768	223,434	392,345
# Cases	16,893	7411	9337	8429
Age-Adjusted Hazard Ratio	1.0	1.13 (1.10–1.16)	1.24 (1.21–1.27)	1.38 (1.34–1.41)
MV-Adjusted Hazard Ratio	1.0	1.12 (1.09–1.15)	1.21 (1.18–1.24)	1.32 (1.28–1.35)
MV and Weight-Adjusted HR	1.0	1.03 (1.00–1.06)	1.07 (1.04–1.10)	1.11 (1.08–1.14)
NHS II				
Person-years	109,966	54,192	57,645	98,884
# Cases	6504	3378	4037	7954
Age-Adjusted Hazard Ratio	1.0	1.14 (1.09–1.19)	1.29 (1.24–1.34)	1.56 (1.50–1.61)
MV-Adjusted Hazard Ratio	1.0	1.15 (1.10–1.20)	1.25 (1.20–1.31)	1.42 (1.37–1.47)
MV and Weight-Adjusted HR	1.0	1.01 (0.97–1.06)	1.06 (1.01–1.10)	1.12 (1.08–1.16)
HPFS				
Person-years	225,263	68,929	112,024	72,749
# Cases	5706	1972	3255	2506
Age-Adjusted Hazard Ratio	1.0	1.13 (1.07–1.19)	1.20 (1.15–1.25)	1.43 (1.36–1.50)
MV-Adjusted Hazard Ratio	1.0	1.13 (1.07–1.19)	1.18 (1.13–1.24)	1.36 (1.30–1.43)
MV and Weight-Adjusted HR	1.0	1.08 (1.02–1.13)	1.09 (1.04–1.14)	1.20 (1.14–1.26)

One serving is defined as 12 oz. MV models were adjusted for age, race, family history of HTN, physical activity, calcium, magnesium, and vitamin D intake, cereal fiber and trans fat intake, carbohydrate consumption, DASH-style diet, total fructose consumption, daily calories, alcohol, whether or not they were trying to lose weight, smoking status, oral contraceptive use (in the female cohorts), and non-narcotic analgesic use. Models were mutually controlled for SSB and ASB intake. MV and weight adjusted models were adjusted for the above variables as well as BMI, BMI^2 and weight change between surveys.

serving of a non-carbonated beverage. It would appear, however, that increased acidity from dissolved carbon dioxide is unlikely to play a role: despite the low pH of carbonated beverages (most fall between 2.5 and 3.5)[22] they present a modest acid load in the context of everyday acid consumption.[23] We also found larger associations with cola compared with non-cola beverage intake; however, this was only significant in NHS I and HPFS. One could postulate that either the cola itself, the caramel coloring used to darken cola drinks, or the increased phosphate load, could mediate this observation, although no mechanisms for such effects have been proposed.

Another potential explanation for the similar relations of SSBs and ASBs with hypertension risk is that both are associated with the development of metabolic derangements that in turn might lead to elevated blood pressure. In the Framingham cohort, consumption of at least one SSB daily was associated with impaired fasting glucose, onset of the metabolic syndrome, and elevated LDL cholesterol.[1] A significant association between artificially sweetened sodas and the metabolic syndrome was also shown, which persisted when elevated blood pressure > 135/80 mmHg was analyzed separately. Previous studies in the NHS I and NHS II cohorts have shown an increased relative risk of developing Type 2 diabetes in those drinking at least one sugary beverage daily.[24] In the Multi-Ethnic Study of Atherosclerosis (MESA), Nettleton et al. reported an increased risk of Type 2 diabetes with consumption of diet soft drinks,[25] and Lutsey et al. showed that in the Atherosclerosis Risk in Communities (ARIC) study, intake of diet soda in the highest tertile conferred a similar risk of developing the metabolic syndrome as did the highest tertile of sugary soda consumption.[26] These observations raise the possibility that a common element in sugar-sweetened and diet soft drinks is at least in part responsible for the abnormalities associated with the metabolic syndrome, and in particular blood pressure.

At least two other possibilities should be considered. It is plausible that there are separate ingredients that individually confer risk. As an example, perhaps the sugar content in

Table 3. Hazard Ratio for Hypertension stratified by Cola and Carbonated Beverage Intake

Beverage Type Frequency of Consumption (servings)	Multivariable-Adjusted Risk Ratio NHS I	NHS II	HPFS
Sugar-Sweetened or Artificially-Sweetened Cola Consumption			
<1/month (reference)	1.0	1.0	1.0
1–4/month	1.04 (1.01–1.07)	1.02 (0.97–1.08)	1.06 (1.01–1.12)
2–6/week	1.09 (1.06–1.13)	1.10 (1.05–1.15)	1.11 (1.05–1.16)
≥1/day	1.14 (1.11–1.18)	1.16(1.10–1.22)	1.17 (1.10–1.24)
Sugar-Sweetened or Artificially-Sweetened Non-Cola Consumption			
<1/month (reference)	1.0	1.0	1.0
1–4/month	1.02 (0.99–1.04)	1.02 (0.99–1.06)	1.03 (0.98–1.07)
2–6/week	1.00 (0.97–1.03)	1.06 (1.02–1.11)	1.08 (1.03–1.14)
≥1/day	1.08 (1.03–1.13)	1.08 (1.02–1.14)	1.10 (1.02–1.18)
P-interaction between cola and non-cola beverages	<0.001	0.11	0.04
Carbonated Beverage Consumption			
<1/month (reference)	1.0	1.0	1.0
1–4/month	1.04 (1.01–1.08)	1.01 (0.95–1.07)	1.07 (1.01–1.14)
2–6/week	1.08 (1.05–1.11)	1.08 (1.02–1.14)	1.14 (1.08–1.20)
≥1/day	1.14 (1.11–1.18)	1.18 (1.12–1.24)	1.23 (1.16–1.30)
Non-Carbonated Beverage Consumption			
<1/month (reference)	1.0	1.0	1.0
1–4/month	1.01 (0.98–1.03)	1.01 (0.98–1.04)	0.99 (0.95–1.04)
2–6/week	1.03 (0.99–1.07)	1.05 (1.00–1.10)	1.05 (0.98–1.13)
≥1/day	1.03 (0.94–1.13)	1.10 (1.00–1.21)	1.08 (0.89–1.31)
P-interaction between carbonated and non-carbonated beverages	<0.001	0.03	0.009

One serving is defined as 12 oz. All models were adjusted for age, BMI, BMI^2, weight change between surveys, race, family history of HTN, physical activity, calcium/magnesium/vitamin D intake, cereal fiber and trans fat intake, carbohydrate consumption, DASH-style diet, total fructose consumption, daily calories, alcohol intake, smoking status, oral contraceptive use (in the female cohorts), and non-narcotic analgesic use. Models were mutually controlled for intake of both beverage categories (either for both cola and non-cola beverages or for both carbonated and non-carbonated beverages).

SSBs mediates the association between these beverages and hypertension, while aspartame and saccharine (the most common sweeteners in ASBs) are responsible for the associations between ASBs and hypertension. Second, it is also possible that our findings of modest associations of SSBs and ASBs with incident hypertension are the result of residual confounding. Although we were as careful as possible to account for confounding factors, error in the ascertainment of these covariates could have resulted in spurious associations for SSBs, ASBs, or both. It is important to note that intake of sodium, which was a component of our DASH score, is not as well measured by our FFQs as other nutrients, and thus an association between beverage intake and sodium intake could partly explain our findings.

Our study makes important progress in elucidating the relation between fructose intake and hypertension risk. We demonstrate an inverse association between fructose from other sources and hypertension risk in NHS II, and the trend toward an inverse association in the other two cohorts. As the molecular structure of fructose is identical whether it is

Table 4. Percentage of Caloric Intake from Fructose Sources and Hazard Ratio for Incident Hypertension

Multivariable-Adjusted Risk Ratio (95 % CI)	NHS I #Cases	HR (95 % CI)	NHS II #Cases	HR (95 % CI)	HPFS #Cases	HR (95 % CI)
Fructose Intake from SSBs						
<5 % (reference)	39,159	1.0	18,809	1.0	12,686	1.0
≥5 % and <8 %	1573	1.05 (0.99–1.11)	1148	1.07 (1.01–1.14)	451	1.02 (0.91–1.14)
≥8 % and <11 %	800	1.04 (0.96–1.12)	774	1.12 (1.03–1.21)	200	1.00 (0.84–1.19)
≥11 % and <15 %	269	1.09 (0.96–1.23)	293	1.21 (1.06–1.36)	42	1.01 (0.72–1.42)
≥15 %	268	1.20 (1.05–1.35)	227	1.05 (0.91–1.21)	47	1.12 (0.74–1.69)
p-trend		0.001		0.001		0.14
Fructose Intake from Sources Other Than SSBs						
<5 % (reference)	3196	1.0	2843	1.0	1398	1.0
≥5 % and <8 %	13,570	0.96 (0.92–1.00)	9808	0.96 (0.92–1.00)	5140	0.95 (0.89–1.02)
≥8 % and <11 %	19,734	0.93 (0.89–0.97)	7586	0.93 (0.89–0.98)	5587	0.91 (0.85–0.98)
11 % and <15 %	4358	0.94 (0.89–1.00)	853	0.93 (0.85–1.01)	1014	0.93 (0.84–1.03)
≥15 %	1211	0.95 (0.88–1.03)	161	0.86 (0.72–1.01)	267	0.93 (0.80–1.09)
p-trend		0.08		0.006		0.09

All models were adjusted for age, BMI, BMI^2, weight change between surveys, race, family history of HTN, physical activity, calcium/magnesium/vitamin D intake, cereal fiber and trans fat intake, carbohydrate consumption, DASH-style diet, daily calories, alcohol intake, smoking status, oral contraceptive use (in the female cohorts), and non-narcotic analgesic use. Model adjusted mutually for the two specified sources of fructose.
A 12 oz. serving of cola contains 17.5 g fructose, which contribute 70 kcals of energy. A person who consumes 2000 kcal per day and obtains 5 % of her calories from cola would drink approximately 1.4 servings of cola each day. If she obtained 15 % of her total daily calories from cola, she would be drinking 4.3 colas per day.

found in SSBs or other foods, the most obvious explanation for the contrasting associations is that fructose, per se, is not associated with developing hypertension, and that some other factor mediates the relation observed with SSBs.

There are several limitations to our study. As discussed in detail above, the foremost potential limitation is that our findings might be due to residual confounding. However, we carefully controlled for numerous dietary and lifestyle factors, the ascertainment of each of which has been validated. There is also the potential for misclassification of beverage intake by our participants, since accuracy is dependent on a person's memory and reporting. However, this type of misclassification is likely to be random, and therefore would produce an underestimate of the true associations. In addition, beverage intake was reported before the diagnosis of hypertension, making recall bias unlikely. Serving size may vary between participants or change over time, as packaging of sweetened beverages changes, and these variations in serving size may have affected our calculation of fructose intake from SSBs. However, our study dieticians track these trends and account for them in calculations of fructose intake. Hypertension was self-reported, and we did not directly measure our participant's blood pressure. However, all of the participants are trained health professionals, and we have previously shown that self-reporting of hypertension is accurate in these cohort. Lastly, all three cohorts are comprised of healthcare professionals, the majority of whom (>90 %) are Caucasian. Thus, our results may not be generalizable to the overall population.

CONCLUSION

Consumption of sweetened beverages is associated with an increased risk of incident hypertension, regardless of whether drinks are sweetened with sugar or artificial agents. Factors common to both SSBs and ASBs, such as cola or carbonation, may underlie these associations, while fructose, per se, is unlikely to be responsible. These findings warrant corroboration in future studies.

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Conflict of Interest: *The authors declare that they do not have a conflict of interest.*

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APPENDIX 1

We ascertained fructose intake from sugar-sweetened beverages by multiplying the frequency of consumption of a particular SSB by the sugar content (in grams) per beverage serving, derived from US Department of Agriculture Research Service nutritional data (http://www.ars.usda.gov/SP2UserFiles/Place/12354500/Data/SR23/reports/sr23fg14.pdf). The fructose derived from each type of SSB was then computed as 55 % of the sugar total obtained from that beverage, since the high-fructose corn syrup used to sweeten all sugary beverages contains 55 % fructose. The fructose intakes from each individual type of SSB were then summed to determine the fructose intake from all SSBs for each participant (in grams). Next, fructose intake obtained from sugar-sweetened beverages was subtracted from their total fructose intake to obtain the fructose intake from other sources (such as apples, bananas, raisins, etc.). Grams of fructose from SSBs and fructose from other sources were then multiplied by 4 calories/gram to obtain energy derived from that source of fructose, and divided by the participant's total daily energy intake to obtain the following variables: percent of total daily calories from fructose from SSBs; and percent of total daily calories from fructose from other sources. In the NHS I at baseline, SSBs contributed 16 % of all fructose consumed by the cohort. In NHS II at baseline, SSBs accounted for 20 % of fructose intake. In HPFS at baseline, SSBs made up approximately 17 % all fructose consumed.