

JOURNAL OF THE AMERICAN HEART ASSOCIATION

Reducing Consumption of Sugar-Sweetened Beverages Is Associated With Reduced Blood Pressure: A Prospective Study Among United States Adults Liwei Chen, Benjamin Caballero, Diane C. Mitchell, Catherine Loria, Pao-Hwa Lin, Catherine M. Champagne, Patricia J. Elmer, Jamy D. Ard, Bryan C. Batch, Cheryl A.M. Anderson and Lawrence J. Appel

Circulation 2010;121;2398-2406; originally published online May 24, 2010; DOI: 10.1161/CIRCULATIONAHA.109.911164

Circulation is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514

Copyright © 2010 American Heart Association. All rights reserved. Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at: http://circ.ahajournals.org/cgi/content/full/121/22/2398

An erratum has been published regarding this article. Please see the attached page or: http://circ.ahajournals.org/cgi/content/full/circulationaha;122/4/e408

Subscriptions: Information about subscribing to Circulation is online at http://circ.ahajournals.org/subscriptions/

Permissions: Permissions & Rights Desk, Lippincott Williams & Wilkins, a division of Wolters Kluwer Health, 351 West Camden Street, Baltimore, MD 21202-2436. Phone: 410-528-4050. Fax: 410-528-8550. E-mail:

journalpermissions@lww.com

Reprints: Information about reprints can be found online at

http://www.lww.com/reprints

Reducing Consumption of Sugar-Sweetened Beverages Is Associated With Reduced Blood Pressure

A Prospective Study Among United States Adults

Liwei Chen, MD, PhD; Benjamin Caballero, MD, PhD; Diane C. Mitchell, MS, RD; Catherine Loria, PhD; Pao-Hwa Lin, PhD; Catherine M. Champagne, PhD, RD; Patricia J. Elmer, PhD; Jamy D. Ard, MD; Bryan C. Batch, MD; Cheryl A.M. Anderson, PhD, MPH, MS; Lawrence J. Appel, MD, MPH

Background—Increased consumption of sugar-sweetened beverages (SSBs) has been associated with an elevated risk of obesity, metabolic syndrome, and type II diabetes mellitus. However, the effects of SSB consumption on blood pressure (BP) are uncertain. The objective of this study was to determine the relationship between changes in SSB consumption and changes in BP among adults.

Methods and Results—This was a prospective analysis of 810 adults who participated in the PREMIER Study (an 18-month behavioral intervention trial). BP and dietary intake (by two 24-hour recalls) were measured at baseline and at 6 and 18 months. Mixed-effects models were applied to estimate the changes in BP in responding to changes in SSB consumption. At baseline, mean SSB intake was 0.9±1.0 servings per day (10.5±11.9 fl oz/d), and mean systolic BP/diastolic BP was 134.9±9.6/84.8±4.2 mm Hg. After potential confounders were controlled for, a reduction in SSB of 1 serving per day was associated with a 1.8-mm Hg (95% confidence interval, 1.2 to 2.4) reduction in systolic BP and 1.1-mm Hg (95% confidence interval, 0.7 to 1.4) reduction in diastolic BP over 18 months. After additional adjustment for weight change over the same period, a reduction in SSB intake was still significantly associated with reductions in systolic and diastolic BPs (P<0.05). Reduced intake of sugars was also significantly associated with reduced BP. No association was found for diet beverage consumption or caffeine intake and BP. These findings suggest that sugars may be the nutrients that contribute to the observed association between SSB and BP.

Conclusions—Reduced consumption of SSB and sugars was significantly associated with reduced BP. Reducing SSB and sugar consumption may be an important dietary strategy to lower BP.

Clinical Trial Registration—URL: http://clinicaltrials.gov. Unique identifier: NCT00000616. (*Circulation*. 2010;121:2398-2406.)

Key Words: blood pressure ■ diet ■ follow-up studies ■ hypertension

Elevated blood pressure (BP) continues to be one of the most common and important health problems in the United States. In 2004, 72 million US adults (35%) had hypertension (defined as systolic BP [SBP] \geq 140 mm Hg and/or diastolic BP [DBP] \geq 90 mm Hg or use of antihypertensive medication), and another 59 million (29%) had prehypertension (defined as SBP from 120 to 140 mm Hg or DBP from 80 mm Hg to 90 mm Hg).\(^1\) Elevated BP is an established risk factor for cardiovascular disease, stroke,

kidney disease, all-cause mortality, and shortened life expectancy.²

Clinical Perspective on p 2406

Sugar-sweetened beverages (SSBs) are the most commonly consumed caloric beverage and the leading source of added sugars in the United States.³ Mean SSB consumption was 28 ± 1 oz/d (2.3 servings per day) for US adults (>20 years of age) as reported by the National Health and Nutri-

Received September 22, 2009; accepted March 19, 2010.

From the Program of Epidemiology, School of Public Health, Louisiana State University Health Science Center, New Orleans (L.C.); Center for Human Nutrition, Johns Hopkins Bloomberg School of Public Health, Baltimore, Md (B.C., C.A.M.A.); Diet Assessment Center, Department of Nutritional Sciences, Pennsylvania State University, University Park (D.C.M.); Division of Prevention and Population Sciences, National Heart, Lung, and Blood Institute, Bethesda, Md (C.L.); Department of Medicine, Duke University Medical Center, Durham, NC (P.-H.L.); Pennington Biomedical Research Center, Baton Rouge, La (C.M.C.); Kaiser Permanente Center for Health Research, Portland, Ore (P.J.E.); Division of Clinical Nutrition & Dietetics, University of Alabama at Birmingham (J.D.A.); Duke Hypertension Center, Duke University, Durham, NC (B.C.B); Welch Center for Prevention, Epidemiology and Clinical Research, Johns Hopkins Medical Institutions, Baltimore, Md (C.A.M.A., L.J.A.).

Correspondence to Liwei Chen, Program of Epidemiology, School of Public Health, Louisiana State University Health Science Center, 1615 Poydras St, Ste 1400, New Orleans, LA 70112. E-mail Ichen@Isuhsc.edu

© 2010 American Heart Association, Inc.

Circulation is available at http://circ.ahajournals.org

DOI: 10.1161/CIRCULATIONAHA.109.911164

tional Examination Survey (NHANES) 1999 to 2004.4 An emerging body of evidence from prospective studies documented that increased SSB consumption is associated with a higher risk of obesity,5-7 type II diabetes mellitus,7-9 and coronary heart disease. 10 Experimental studies 11-14 found that high consumption of sugary drinks can induce hypertension in animal models. Whether long-term consumption of SSB has a direct effect on BP in humans has not been well investigated. To date, 3 human studies have provided limited data that suggest a positive association between habitual SSB consumption and BP.15-17 However, these studies are crosssectional,16 did not have a direct measure of BP,17 or failed to show that the association was statistically significant.¹⁵ In addition, it is not clear whether high consumption of both SSBs and diet beverages (sweetened by artificial sweeter, no calories) may increase the risk of high BP.

A relationship between consumption of SSB or diet beverages and BP could have substantial public health implications, given the high prevalence of elevated BP and widespread consumption of these beverages. Therefore, the primary objective of this study is to prospectively examine the relationship between changes in SSB consumption and BP among US adults. Additionally, we evaluate whether a change in consumption of diet beverages is associated with BP.

Methods

Study Population

Study participants are from the PREMIER study. PREMIER is a completed, 18-month multicenter randomized trial designed to test the BP-lowering effects of 2 multicomponent behavioral interventions in adults with SBP of 120 to 159 mm Hg and DBP of 80 to 95 mm Hg. The study consisted of 810 men and women 25 to 79 years of age recruited from 4 study centers in the United States (Baltimore, Md; Baton Rouge, La; Durham, NC; and Portland, Ore). Information on study design, participant recruitment, and data collection has previously been published. 19

Eligible participants were randomly assigned to 1 of 3 groups: an "advice only" comparison group that received information but no behavioral counseling on weight loss, physical activity, sodium intake, or the Dietary Approaches to Stop Hypertension (DASH) dietary pattern; a behavioral intervention group called "established" that received counseling on how to lose weight, increase physical activity, and reduce sodium intake; or a behavioral intervention group, "established plus DASH," that received counseling on the same lifestyle goals as the established group plus counseling on the DASH dietary pattern. The weight loss approaches in the established group focused on increased physical activity and reduced energy intake. In contrast, the weight loss approach in established plus DASH group focused on increased physical activity, reduced energy intake, and substitution of high-fat, high-calorie foods with fruits and vegetables. All 810 study participants enrolled at baseline were included in this analysis.

Measurement of BP

BP was measured manually by trained, certified observers at baseline, 3, 6, 12, and 18 months using a standard protocol. After participants sat quietly for 5 minutes, the observer measured BP in the right arm with an appropriately sized cuff. For this analysis, the values of SBP and DBP were calculated by taking the mean of all available measurements at baseline (4 visits), 6 months (3 visits), or 18 months (3 visits). At each visit, a set of 2 BP measurements was obtained. BPs taken in participants who reported using antihypertensive medication within the preceding month were censored; along with missing values, these cases received imputed values by using the BP measured at the preceding visit (last observation carried

forward method) or using BP values from similar participants in the advice group (single-imputation Hot-Deck procedure). Overall, 9% of the BP at 6 months (5% because of the use of antihypertensive medication and 4% because of loss to follow-up; 3% were imputed using last observation carried forward method) and 17% at 18 months (13% because of the use of antihypertensive medication and 4% because of loss to follow-up; 5% were imputed using last observation carried forward method) were imputed. Hypertension was defined as an average SBP \geq 140 mm Hg, a DBP \geq 90 mm Hg, or use of antihypertensive medication.

Measurement of Dietary and Beverage Intake

Dietary intake was measured by unannounced 24-hour dietary recalls conducted by telephone interviews. Two recalls (1 on a weekday and 1 on a weekend) per participant were obtained at baseline, 6 months, and 18 months. A multiple-pass technique and portion-size estimation aids (2 Dimensions Food Portion Visual, Nutrition Consulting Enterprises, Framingham, Mass) were used during the phone interview. Intakes of total energy, nutrients (eg, sugar and caffeine), and food groups (eg, dairy foods and fruits and vegetables) were calculated with the Nutrition Data System for Research (version NDS-R 1998, University of Minnesota, Minneapolis). For this analysis, participants' daily nutrient, energy, and beverage intake was calculated by taking the average from two 24-hour dietary recalls. SSB was defined as carbonated or uncarbonated drinks that were sweetened with sugars (sucrose or high-fructose corn syrup). These included regular soft drinks, fruit drinks, lemonade, fruit punch, and other sweetened beverages but excluded diet drinks. Diet beverages were defined as carbonated or uncarbonated drinks that were sweetened with artificial sweeteners (noncaloric sweeteners).

Measurement of Covariates

Weight and height were measured with subjects wearing light clothing and no shoes using a calibrated scale and a wall-mounted stadiometer. Fitness was assessed with a 2-stage 10-minute submaximal treadmill stress test and defined as the heart rate (bpm) at a fixed workload (stage 2). Physical activity and estimated energy expenditure (kcal[middot]kg⁻¹[middot]d⁻¹) were assessed with a 7-day recall questionnaire.20 Urinary excretion of sodium and potassium was obtained from 24-hour urinary collection at baseline, 6 months, and 18 months. Participants' characteristics such as age, sex, race/ethnicity, income, education, employment and marriage status, and smoking habits were collected at baseline. Because the DASH diet includes several dietary components, we used a single index, the DASH Index, to measure overall adherence to the DASH diet. The DASH Index is an average of 3 subindexes measuring daily intake of dairy products, fruit and vegetable servings, and percentage of calories from saturated fat. A score of 0 to 1 indicates that the intake is in the target range of the DASH diet, whereas scores <0 indicate worse than target and scores >1 indicate better than target. The computational details of the DASH Index have been described previously.21

Statistical Analysis

Descriptive data on SSB consumption and BP at each visit are expressed as mean \pm SD if not mentioned otherwise. The Student ttest and χ^2 test were applied to compare continuous variables and categorical variables, respectively. For the primary analysis, we applied mixed-effects models to account for the correlation between repeated measurements and to incorporate between-individual variability to estimate the overall effect. The main exposure was the change in SSB consumption from baseline to follow-up visits (continuous: δ =follow-up-baseline). In this way, the regression coefficient of change in SSB consumption represents the longitudinal association between SSB and BP (the average change in BP on the concurrent average change in SSB consumption). Potential confounding factors that were adjusted for included gender, race, baseline age, alcohol intake, randomization assignment, study sites, baseline physical activity and change in physical activity, baseline fitness and change in fitness, baseline SSB consumption, baseline

Table 1. Baseline Characteristics of PREMIER Study Participants by Quartile of SSB Consumption

		SSB Consu				
Variables	1	2	3	4	P for Trend	All Participants
SSB intake, fl oz/d						
Mean (SD)	0	6.3 (2.3)	12.0 (1.8)	27.0 (10.7)		10.5 (11.9)
Median (range)	0 (0-0)	6.3 (0.2-8.5)	12.4 (8.6–16.4)	25.0 (16.5–75.4)		8.5 (0-75.4)
Age, y	52.2 (8.4)	50.3 (9.3)	49.4 (8.9)	47.1 (8.5)	< 0.001	50.0 (8.9)
Female, %	63.3	72.0	64.5	50.5	0.01	61.5
Black, %	19.0	34.0	44.7	46.5	< 0.001	34.0
Education (college degree or above), %	59.4	65.0	57.4	50.0	0.06	57.2
Annual household income (>\$45 000/y), %	76.4	65.0	65.5	67.0	0.01	70.0
Marriage status (married), %	69.2	65.0	62.9	65.0	0.50	66.1
Current smoking (yes), %	4.4	3.0	4.1	7.1	0.50	4.8
Current alcohol intake (yes), %	58.4	56.0	42.1	34.5	< 0.001	48.1
Physical activity (time spent on moderate or hard activity), \min/wk^*	210	180	145	175	0.19	173.5
Fitness, mean (SD), bpm	129.0 (13.6)	130.3 (14.6)	130.0 (14.4)	133.2 (15.7)	0.009	130.5 (14.5)
Anthropometric measurements, mean (SD)						
Weight, Ib	204.3 (40.1)	193.9 (40.0)	211.3 (39.4)	224.7 (42.7)	< 0.001	209.8 (41.5)
BMI, kg/m ²	32.4 (5.7)	31.2 (5.2)	33.5 (5.8)	34.5 (5.9)	< 0.001	33.1 (5.8)
Waist circumference, cm	106.7 (14.8)	102.5 (14.6)	107.9 (15.2)	111.3 (15.5)	< 0.001	107.6 (15.2)
Dietary intake, mean (SD)						
Total energy, kcal/d	1785.8 (567.2)	1755.2 (509.8)	1988.4 (611.3)	2180.0 (683.5)	< 0.001	1904.5 (625.2)
Total protein, % of TEI	17.3 (4.5)	16.0 (3.6)	15.2 (3.4)	14.4 (3.1)	< 0.001	15.9 (4.0)
Total fat, % of TEI	33.9 (8.5)	32.1 (7.7)	32.8 (7.0)	32.7 (6.7)	0.13	33.1 (7.6)
Saturated fat, % of TEI	11.2 (3.5)	10.9 (3.0)	10.7 (3.0)	10.7 (2.8)	0.35	10.9 (3.2)
Monounsaturated fat, % of TEI	13.4 (4.1)	12.6 (3.5)	12.8 (3.3)	12.9 (3.2)	0.17	13.2 (3.6)
Polyunsaturated fat, % of TEI	7.2 (2.8)	6.5 (2.5)	7.1 (2.4)	7.0 (2.4)	0.75	7.0 (2.6)
Trans fat, % of TEI	2.3 (1.2)	2.3 (1.1)	2.4 (1.1)	2.3 (1.2)	0.96	2.3 (1.2)
Total carbohydrate, % of TEI	48.6 (10.3)	52.1 (8.9)	52.4 (9.2)	53.7 (8.3)	< 0.001	51.3 (9.6)
Glucose, g/d	18.3 (10.2)	24.0 (11.0)	29.2 (11.7)	42.1 (17.4)	< 0.001	27.5 (15.8)
Fructose, g/d	16.0 (10.8)	20.1 (9.0)	28.1 (11.6)	42.1 (17.6)	< 0.001	25.9 (16.5)
Sucrose, g/d	42.6 (28.1)	44.5 (23.1)	49.8 (29.1)	59.0 (31.9)	< 0.001	48.7 (29.5)
Total sugar, g/d	92.3 (42.7)	104.6 (41.2)	122.1 (44.3)	156.8 (52.2)	< 0.001	116.9 (52.4)
Dairy foods, serving/d*	1.5	1.5	1.4	1.3	0.01	1.4
Fruits and vegetables, serving/d	4.7 (2.3)	4.5 (2.3)	4.5 (2.3)	4.2 (2.4)	0.003	4.5 (2.3)
Dietary fiber, g/d	18.0 (7.7)	16.4 (7.8)	16.3 (7.5)	16.0 (7.7)	0.001	16.9 (7.7)
Caffeine, mg/d*	157.8	110.9	79.1	101.4	< 0.001	111.2
Calcium, mg/d*	711.4	633.5	666.2	651.1	0.049	672.5
Magnesium, mg/day	287.2 (98.1)	261.7 (102.7)	265.9 (105.5)	261.2 (114.6)	0.001	272.0 (105.3)
Folate, μ g/d	346.2 (157.2)	333.1 (148.0)	332.5 (165.2)	332.2 (162.8)	0.70	337.6 (158.4)
DASH Index	-3.2(2.3)	-3.3(2.2)	-3.2(2.1)	-3.4(1.9)	0.68	-3.3(2.1)
Urinary excretion, mean (SD)						
Sodium, mmol/24 h	174.7 (72.4)	155.7 (55.9)	169.4 (71.2)	189.1 (80.4)	0.21	174.5 (72.7)
Potassium, g/24 h	70.1 (25.0)	65.7 (23.9)	63.8 (24.8)	65.2 (29.6)	0.002	66.6 (26.0)
BP, mean (SD)						
SBP, mm Hg	135.2 (9.5)	135.7 (10.0)	135.6 (9.7)	133.2 (9.6)	0.57	134.9 (9.6)
DBP, mm Hg	84.2 (3.8)	84.9 (4.0)	85.4 (4.6)	85.0 (4.2)	0.01	84.8 (4.2)
Prevalence of hypertension, %	35.4	41.0	41.2	34.0	0.31	37.5

TEI indictes total energy intake. P for trend by Wilcoxon rank-sum test.

^{*}Median is given instead of mean because of the highly skewed distribution of that variable.

Table 2. Associations of BP With Change in SSB Consumption Among PREMIER Participants: Results From Mixed-Effects Models

	SBP			DBP		
	β	95% CI	Р	β	95% CI	Р
All participants						
Age-adjusted model	1.99	1.46-2.52	< 0.001	1.12	0.78-1.45	< 0.001
Multivariate model 1	1.76	1.17-2.35	< 0.001	1.08	0.69-1.47	< 0.001
Multivariate model 2	0.70	0.15-1.25	0.01	0.38	0.02-0.75	0.04
Hypertensive status at baseline						
Hypertensive						
Age-adjusted model	2.26	1.32-3.21	< 0.001	1.33	0.75-1.90	< 0.001
Multivariate model 1	1.94	0.82-3.06	0.001	1.42	0.71-2.14	< 0.001
Multivariate model 2	0.76	-0.30 - 1.82	0.16	0.62	-0.05– 1.29	0.07
Nonhypertensive						
Age-adjusted model	1.61	1.05-2.17	< 0.001	0.91	0.53-1.31	< 0.001
Multivariate model 1	1.60	0.94-2.20	< 0.001	0.88	0.43-1.33	< 0.001
Multivariate model 2	0.58	-0.02 - 1.17	0.06	0.19	-0.24 - 0.61	0.34
Race						
White						
Age-adjusted model	2.29	1.62-2.95	< 0.001	1.29	0.87-1.70	< 0.001
Multivariate model 1	1.76	1.17-2.35	< 0.001	1.08	0.69-1.47	< 0.001
Multivariate model 2	0.70	0.15-1.25	0.01	0.38	0.02-0.75	0.04
Black						
Age-adjusted model	1.38	0.48-2.29	0.003	0.72	0.14-1.31	0.016
Multivariate model 1	1.54	0.52-2.56	0.003	0.92	0.23-1.62	0.009
Multivariate model 2	0.60	-0.42 - 1.63	0.25	0.15	0.53-0.83	0.67
Gender						
Male						
Age-adjusted model	2.01	1.33-2.68	< 0.001	1.29	0.84-1.74	< 0.001
Multivariate model 1	1.75	0.98-1.52	< 0.001	1.14	0.60-1.67	< 0.001
Multivariate model 2	0.78	0.09-1.47	0.03	0.50	0.01-1.00	0.05
Female						
Age-adjusted model	1.84	1.01-2.68	< 0.001	0.96	0.46-1.62	< 0.001
Multivariate model 1	1.84	0.93-1.75	< 0.001	1.04	0.46-1.61	< 0.001
Multivariate model 2	0.61	-0.27 - 1.48	0.01	0.21	-0.34 - 0.76	0.45

 β Indicates change in mm Hg per change in servings per day. Multivariate model 1: adjusted for gender, race, family history of hypertension, randomization assignment, site, baseline age, alcohol drinking, BMI, baseline SSB intake, baseline fitness and change in fitness, baseline physical activity and change in physical activity, baseline urinary sodium excretion and change in urinary sodium excretion, and baseline DASH Index and change in DASH Index. Multivariate model 2: model 1 plus change in body weight.

dietary intakes of selected foods and nutrients and their changes during follow-up, and baseline body mass index (BMI) and change in weight. The primary analyses were conducted by combining all participants and adding intervention assignment as a covariate in all models. Stratified analyses were performed to evaluate whether the associations of SSB and BP were modified by race (white versus black), gender (male versus female), and hypertension status (hypertensive versus nonhypertensive). All statistical analyses were performed with STATA version 9.0 (Stata Corp, College Station, Texas). Statistical significance was set at $P \le 0.05$ (2 tailed).

Results

Baseline Characteristics and SSB Consumption

At baseline, mean SSB intake in PREMIER participants was 0.9 ± 1.0 servings per day (equal to 10.5 ± 11.9 fl oz/d), and

mean diet beverage intake was 0.9 ± 1.2 servings per day $(11.2\pm14.0 \text{ fl oz/d})$. The mean SBP/DBP was $134.9\pm9.6/84.8\pm4.2 \text{ mm Hg}$. Table 1 displays the sociodemographic characteristics, anthropometric measurements, physical activity, fitness levels, dietary intakes of selected foods and nutrients, adherence to DASH Index, and urinary sodium and potassium excretions across the baseline SSB consumption quartiles and in the entire study population. Compared with persons in the lowest (first) quartile, individuals in the higher quartiles on average were younger, were less fit, had lower annual household incomes, and drank less alcohol. Blacks drank more SSBs than whites (difference, 4.3 fl oz/d; P < 0.0001), and men drank more than women (difference, 3.7 fl oz/d; P < 0.0001). Participants in the higher quartiles of

Table 3. Baseline Characteristics and Changes in Selected Variables From Baseline to 18 Months According to the Tertiles of Change in SSB Intake at 18 Months

	Tertiles of Change in SSB Intake at 18 mo				
	1	2	3	P for Trend	
Baseline characteristics					
Age, y	49.3 (8.6)	51.4 (8.8)	49.8 (9.0)	0.5	
Female, %	59.6	63.5	58.7	8.0	
Black, %	33.8	28.9	37.2	0.3	
Education, (have college degree or above), %	57.6	58.3	58.3	0.8	
Annual household income (>\$45 000/y), %	66.7	75.1	66.1	8.0	
Marriage status (married), %	62.1	69.1	66.5	0.4	
Change (18 mo-baseline)					
SSB intake, fl oz/d	9.5 (7.4)	-0.9 (1.6)	-15.3(9.9)	< 0.001	
Total energy intake, kcal/d	-81.2 (534.1)	-199.8 (563.0)	-350.6 (615.4)	< 0.001	
DASH Index	1.1 (2.6)	1.2 (2.6)	1.4 (2.7)	0.3	
Glucose intake, g/d	7.4 (13.9)	0.9 (13.6)	-7.5 (18.7)	< 0.001	
Fructose intake, g/d	9.3 (15.9)	1.4 (13.5)	-8.2 (19.6)	< 0.001	
Sucrose intake, g/d	-1.6 (33.4)	-6.1 (30.9)	-9.5 (34.2)	0.001	
Combined sugars intake, g/d	14.4 (50.0)	-3.3(49.7)	-23.4 (55.9)	< 0.001	
Urinary excretion of sodium, mmol/24 h	-10.1 (80.4)	-17.4 (76.8)	-18.2 (101.1)	0.2	
Urinary excretion of potassium, g/24 h	2.1 (28.6)	0.5 (28.7)	4.7 (31.7)	0.3	
Physical activity (time spent on moderate or hard activity), min/wk*	0	0	-10.0	0.2	
Body weight, Ib	-3.9(9.2)	-6.4(12.7)	-10.9 (16.4)	< 0.001	

Data are shown in mean (SD) if not mentioned otherwise.

SSB consumption also had greater body weights, BMIs, and waist circumferences compared with those in the first quartile (P<0.0001 for trend). For dietary intake, there was a trend of higher consumption of total calories, total carbohydrates, glucose, fructose, sucrose, and combined sugar (sum of monosaccharide and disaccharide) and lower consumption of protein, dairy foods, fruit and vegetables, dietary fiber, caffeine, calcium, and magnesium with higher SSB intake. Across quartiles of SSB consumption, a slightly significant increase was observed in DBP but not in SBP or prevalence of hypertension.

At 18 months, 94% of study participants had at least 1 BP measurement, and 90% had at least 1 dietary recall. For all participants, mean SBP declined 9.8 ± 9.4 mm Hg at 6 months and 8.2 ± 9.9 mm Hg at 18 months, each net of baseline. For DBP, corresponding declines were 5.4 ± 6.5 and 5.6 ± 6.8 mm Hg, respectively. Compared with baseline, the mean reduction in SSB consumption was 0.5 ± 1.1 servings per day $(6.0\pm13.0 \text{ fl oz/d})$ at 6 months and 0.2 ± 1.0 servings per day $(2.8\pm12.0 \text{ fl oz/d})$ at 18 months. The consumption of diet beverages was reduced by 0.2 ± 1.1 servings per day $(2.3\pm13.6 \text{ fl oz/d})$ at 6 months but increased by 0.1 ± 1.2 servings per day $(1.5\pm14.0 \text{ fl oz/d})$ at 18 months.

Association Between Change in SSB Consumption and Change in BP

Change in SSB consumption was strongly and positively associated with SBP and DBP in both age-adjusted and

multivariate-adjusted models (Table 2). In a multivariateadjusted model that did not include weight change (model 1), a reduction of 1 serving per d (12 fl oz) in SSB consumption was associated with reduced SBP (β =1.8; 95% confidence interval [CI], 1.2 to 2.4) and DBP (β =1.1; 95% CI, 0.7 to 1.5). With additional adjustment for concurrent change in weight (model 2), the associations between SSB intake and BPs were attenuated but still statistically significant, with a reduction of 1 serving per day in SSB consumption being associated with a decrease of 0.7 mm Hg in SBP (95% CI, 0.12 to 1.25) and 0.4 mm Hg (95% CI, 0.02 to 0.75) in DBP. Results were similar in sensitivity analyses that adjusted for change in total energy instead of change in weight (data not shown). These results suggest that change in SSB consumption is positively associated with BP independently of weight change and other risk factors for BP. In a sensitivity analysis using nonimputed BP, the results were virtually unchanged, even slightly stronger: A reduction of 1 serving per day in SSB consumption was associated with a reduction in SBP of 2.0 mm Hg (95% CI, 1.4 to 2.6) and in DBP of 1.2 mm Hg (95% CI, 0.9 to 1.6) in model 2.

A similar pattern was evident in subgroups (Table 2) defined by baseline hypertension status (hypertensive/nonhypertensive), race (black/white), and gender (female/male). Although the pattern of subgroup analyses was similar to that of the overall analyses, not all results were statistically significant, likely because of reduced sample size. A test for interactions showed that the association between BP and change in SSB consumption

^{*}Median is given instead of mean because of the highly skewed distribution of that variable.

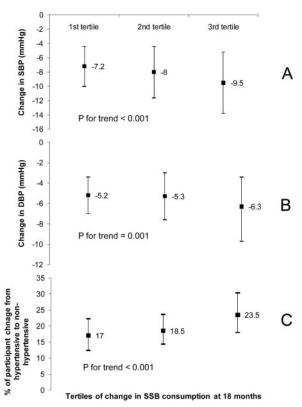


Figure. Model-adjusted mean BP changes (A, SBP; B, DBP) and proportion (%) of participants who moved from hypertensive at baseline to nonhypertensive at 18 months (C) by tertiles of change in SSB consumption (fl oz/d) from baseline to 18 months (18 months minus baseline). The mean change in SSB consumption across the tertiles was 9.5 ± 7.4 , -0.9 ± 1.6 , and -15.3 ± 9.9 fl oz/d (persons in the third tertile had the greatest reduction in SSB). Covariates in the model included gender, race, family history of hypertension, randomization assignment, site, baseline age, alcohol drinking, BMI, baseline SSB intake, baseline fitness and change in fitness, baseline physical activity and change in physical activity, baseline urinary sodium excretion and change in urinary sodium excretion, baseline DASH Index and change in DASH Index, and change in body weight from baseline to 18 months.

was not modified by baseline hypertension status, race, or gender (each P for interaction >0.05).

To examine the dose-response relationship, we divided participants into tertiles based on their 18-month change in SSB consumption. Table 3 shows the baseline sociodemographic characteristics and changes in selected variables across the tertiles of 18-month change in SSB consumption. There is a linear trend in weight loss and reductions in intakes of total energy, glucose, fructose, sucrose, and combined sugars across the tertiles.

We calculated the model-adjusted mean changes in SBP and DBP and the proportion of participants who moved from hypertensive at baseline to nonhypertensive at 18 months by tertile of 18-month change in SSB consumption (the Figure). The mean changes in SSB consumption across the tertiles were 9.5 ± 7.4 , -0.9 ± 1.6 , and -15.3 ± 9.9 fl oz/d (persons in the third tertile had the greatest reduction in SSB consumption). Adjustment variables were the same as those in model 2 in Table 2. At 18 months, participants in the third tertile had a significantly greater reduction in SBP compared with individuals in the first

Table 4. Associations of BP With Change in Diet Beverages Among PREMIER Participants: Results From Mixed-Effects Models

All		SBP		DBP			
All Participants	β	95% CI	Р	β	95% CI	Р	
Age-adjusted model	0.14	-0.35-0.64	0.57	-0.18	-0.49-0.14	0.09	
Multivariate model 1	-0.20	-0.41-0.89	0.73	-0.34	-0.69-0.01	0.08	
Multivariate model 2	0.25	-0.24-0.74	0.99	-0.05	-0.38-0.27	0.75	

 β Indicates change in mm Hg per change in servings per day. Multivariate model 1: adjusted for gender, race, family history of hypertension, randomization assignment, site, baseline age, alcohol drinking, BMI, baseline SSB intake, baseline fitness and change in fitness, baseline physical activity and change in physical activity, baseline urinary sodium excretion and change in urinary sodium excretion, and baseline DASH Index and change in DASH Index. Multivariate model 2: model 1 plus change in body weight.

and second tertiles; the mean reduction in SBP across the tertiles was 7.2 ± 4.3 , 8.0 ± 4.3 , and 9.5 ± 4.3 mm Hg, respectively (P for trend <0.001). There was also a statistically significant decline in DBP across tertiles (-5.2 ± 1.8 , -5.3 ± 2.3 , and -6.3 ± 2.9 mm Hg, respectively; P for trend=0.001). A trend of increase in the proportion of individuals who moved from hypertensive at baseline to nonhypertensive at 18 months across tertiles was also observed (17.0%, 18.5%, and 23.5%, respectively; P for trend <0.001).

Association Between Change in Diet Beverage Consumption and Change in BP

We also examine the relationship between consumption of diet beverages and BP. Change in consumption of diet beverages was not associated with either SBP or DBP in both age-adjusted and multivariate-adjusted models (Table 4).

Association Between Changes in Sugar or Caffeine Consumption and Change in BP

To investigate which specific nutrients might be responsible for the observed association between SSB and BP, we examined the associations of change in consumption of sugars (glucose, fructose, sucrose, or combined sugar from all foods and beverages) or caffeine (from all foods and beverages) with change in BP (Table 5). In model 1, without weight change as a covariate, change in BP was significantly and positively associated with changes in glucose, fructose, sucrose, and combined sugars. A 10-g/d reduction in glucose, fructose, sucrose, or combined sugar was associated with reductions in SBP of 0.6 mm Hg (95% CI, 0.2 to 1.0), 0.5 mm Hg (95% CI, 0.1 to 0.8), 0.4 mm Hg (95% CI, 0.2 to 0.6), and 0.3 mm Hg (95% CI, 0.1 to 0.5). Corresponding data for DBP were 0.5 mm Hg (95% CI, 0.3 to 0.8), 0.4 mm Hg (95% CI, 0.2 to 0.6), 0.3 mm Hg (95% CI, 0.2 to 0.5), and 0.3 mm Hg (95% CI, 0.2 to 0.3), respectively. Further adjustment for weight loss attenuated these associations; however, in most instances, they were still statistically significant (Table 5). There was no significant relationship between change in caffeine consumption and change in BP.

Table 5. Associations of BP With Change in Sugars or Caffeine Among PREMIER Participants: Results From Mixed-Effects Models

	SBP			DBP			
	β	95% CI	Р	β	95% CI	Р	
Sugars							
Glucose (per 10 g/d)							
Multivariate model 1	0.62	0.24-1.00	0.001	0.54	0.29-0.78	< 0.001	
Multivariate model 2	0.32	-0.02 - 0.67	0.07	0.33	0.10-0.56	0.005	
Fructose (per 10 g/d)							
Multivariate model 1	0.46	0.01-0.83	0.01	0.40	0.16-0.64	0.001	
Multivariate model 2	0.15	-0.19 - 0.48	0.39	0.18	-0.04– 0.40	0.11	
Sucrose (per 10 g/d)							
Multivariate model 1	0.43	0.23-0.62	< 0.001	0.32	0.19-0.45	< 0.001	
Multivariate model 2	0.29	0.11-0.47	0.002	0.22	0.11-0.34	< 0.001	
Combined sugars (per 10 g/d)							
Multivariate model 1	0.30	0.17-0.42	< 0.001	0.24	0.16-0.32	< 0.001	
Multivariate model 2	0.17	0.06-0.28	0.003	0.15	0.08-0.23	< 0.001	
Caffeine (per 100 mg/d)							
Multivariate model 1	0.35	-0.09– 0.80	0.12	0.06	-0.23- 0.34	0.70	
Multivariate model 2	0.36	-0.04– 0.76	0.08	0.08	-0.18 - 0.34	0.56	

 β indicates mm Hg per unit of exposure. Multivariate model 1: adjusted for gender, race, family history of hypertension, randomization assignment, site, baseline age, alcohol drinking, BMI, baseline SSB intake, baseline fitness and change in fitness, baseline physical activity and change in physical activity, baseline urinary sodium excretion and change in urinary sodium excretion, and baseline DASH Index and change in DASH Index. Multivariate model 2: model 1 plus change in body weight.

Discussion

In this prospective study of 810 men and women with prehypertension and stage I hypertension, there was a positive association between change in SSB consumption and change in BP. After potential confounders were controlled for, an average reduction in SSB intake by 1 serving per day (12 fl oz) was associated with a 1.8-mm Hg (95% CI, 1.2 to 2.4) reduction in SBP and 1.1-mm Hg (95% CI, 0.7 to 1.5) reduction in DBP over 18 months. This association was partially mediated through weight change. Specifically, after weight change over the same period was controlled for, the association between SSB intake and BP was attenuated by ≈61% (0.7 mm Hg per serving for SBP and 0.4 mm Hg per serving for DBP) but was still statistically significant (P < 0.05 for each), suggesting that reducing SSB intake has a BP-lowering effect that is independent of weight loss. We also observed significant, positive associations of BP with change in consumption of sugars (glucose, fructose, sucrose, and combined sugar) but not with change in consumption of caffeine. No association was found for diet beverage consumption and BP. These data suggest that sugars may be the nutrients in SSB that contribute to the observed association between SSB and BP.

Our results are supported by data from 2 large prospective studies and 1 cross-sectional study suggesting a positive association between SSB consumption and the risk of hypertension. Data from the Nurses' Health Study¹⁷ showed a strong positive association between cola beverage intake and hypertension risk (P for trend <0.001). Additionally, an analysis of data from the Framingham Offspring Study¹⁵ found that consumption of soft drinks (regular and diet soda combined) was

associated with an increased, although not statistically significant, risk of high BP. In addition, cross-sectional findings from NHANES (1999 to 2004) data among adolescents (12 to 18 years of age) indicated a positive association between SSB consumption and directly measured BP.¹⁶

Our results provide additional evidence supporting a relationship between higher SSB consumption and elevated BP. First, the data show that SSB affects BP in part via mechanisms that are independent of weight change. Second, the relationship is evident in both nonhypertension and hypertension, suggesting that reduced SSB should have a role in both preventing and treating hypertension. In contrast with the above-mentioned 2 studies, which observed an increased hypertension risk associated with both SSB and diet soft drinks, 15,17 we found no association between diet beverages and BP in the present study (Table 4).

The mechanism by which a higher intake of SSB may increase BP is uncertain. It is well documented that ingestion of caffeine has a short-term pressor effect.^{22,23} However, tolerance to the caffeine-induced pressor effect develops within days.²³ We found no association between 18-month change in caffeine intake and BP in the present study. Studies in a variety of animal models, including rats, dogs, and primates,^{11–14} have shown that diets high in glucose, fructose, or sucrose can induce hypertension. There are few similar studies in humans, and 1 study has reported that a diet high in sucrose consumed for 6 weeks causes a significant elevation in BP.²⁴

A possible mechanism for the pressor effect of sugars may be enhanced sympathetic nervous system activity. A short-term increase in catecholamine secretion has been shown after ingestion of sugar during euglycemic clamp studies.²⁵ Another mechanism may be a reduction in sodium excretion, as documented in animal and human studies.²⁶ Recent evidence suggests that fructose consumption might increase BP by raising serum uric acid,^{16,27} which can decrease endothelial nitric oxide and/or activate the renin-angiotensin system.²⁸

Our study has several strengths. First, both diet and BP were measured frequently by trained, certified staff. Second, our study had precise, objective measurements of potential confounders, including weight, urinary sodium excretion, physical activity, fitness, and other covariates. Third, the follow-up rate was high, and missing data were uncommon. Furthermore, the BP status of our study population is comparable to the BP of two thirds of the US population. Our study is limited in that it included few Hispanics and Asians. Additionally, given the observational nature of our study, it cannot prove causality or completely rule out residual confounding. Randomized controlled trials are needed to confirm the observation and to determine whether interventions that target SSB or sugar consumption can lower BP among adults.

Our study has important public health implications. In view of the direct, progressive relationship of BP with cardiovascular disease, even small reductions in BP are projected to have substantial health benefits. For example, it has been estimated that a 3-mm Hg reduction in SBP should reduce stroke mortality by 8% and coronary heart disease mortality by 5%.²⁹ Such reductions in SBP would be anticipated by reducing SSB consumption by an average of 2 servings per day. Currently, the average intake of SSB is 2.3 servings per day for US adults. In our study, one third of participants reduced SSB consumption on average of 1.3 servings per day over the 18 months and had an average of 1.5 mm Hg more reduction in SBP compared with participants who did not change their SSB consumption, suggesting that such reduction in SSB consumption should be achievable and could be beneficial.

Conclusion

Findings from this prospective study suggest a positive association between SSB consumption and BP. These findings warrant future studies, particularly randomized controlled trials, to establish the causal relationship.

Acknowledgment

We thank the PREMIER participants and staff for their contributions to this study.

Sources of Funding

The PREMIER Trial was supported by the National Heart, Lung, and Blood Institute, National Institutes of Health grants UO1 HL60570, UO1 HL60571, UO1 HL60573, UO1 HL60574, and UO1 HL62828. The present study is supported in part by the School of Public Health, Louisiana State University Health Science Center and by the Center for Human Nutrition, Johns Hopkins Bloomberg School of Public Health.

Disclosures

None.

References

- Rosamond W, Flegal K, Friday G, Furie K, Go A, Greenlund K, Haase N, Ho M, Howard V, Kissela B, Kittner S, Lloyd-Jones D, McDermott M, Meigs J, Moy C, Nichol G, O'Donnell CJ, Roger V, Rumsfeld J, Sorlie P, Steinberger J, Thom T, Wasserthiel-Smoller S, Hong Y. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2007 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation. 2007;115:e69-e171.
- Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. *Lancet*. 2005; 365:217–223.
- Bray GA, Nielsen SJ, Popkin BM. Consumption of high-fructose corn syrup in beverages may play a role in the epidemic of obesity. Am J Clin Nutr. 2004;79:537–543.
- 4. Bleich SN, Wang YC, Wang Y, Gortmaker SL. Increasing consumption of sugar-sweetened beverages among US adults: 1988–1994 to 1999–2004. *Am J Clin Nutr.* 2009;89:372–381.
- Berkey CS, Rockett HR, Field AE, Gillman MW, Colditz GA. Sugar-added beverages and adolescent weight change. *Obes Res.* 2004; 12:778–788.
- Ludwig DS, Peterson KE, Gortmaker SL. Relation between consumption of sugar-sweetened drinks and childhood obesity: a prospective, observational analysis. *Lancet*. 2001;357:505–508.
- Schulze MB, Manson JE, Ludwig DS, Colditz GA, Stampfer MJ, Willett WC, Hu FB. Sugar-sweetened beverages, weight gain, and incidence of type 2 diabetes in young and middle-aged women. *JAMA*. 2004;292: 927–934.
- Montonen J, Jarvinen R, Knekt P, Heliovaara M, Reunanen A. Consumption of sweetened beverages and intakes of fructose and glucose predict type 2 diabetes occurrence. *J Nutr.* 2007;137:1447–1454.
- Palmer JR, Boggs DA, Krishnan S, Hu FB, Singer M, Rosenberg L. Sugar-sweetened beverages and incidence of type 2 diabetes mellitus in African American women. Arch Intern Med. 2008;168:1487–1492.
- Fung TT, Malik V, Rexrode KM, Manson JE, Willett WC, Hu FB. Sweetened beverage consumption and risk of coronary heart disease in women. Am J Clin Nutr. 2009;89:1037–1042.
- Hwang IS, Ho H, Hoffman BB, Reaven GM. Fructose-induced insulin resistance and hypertension in rats. *Hypertension*. 1987;10:512–516.
- Preuss HG, Zein M, MacArthy P, Dipette D, Sabnis S, Knapka J. Sugarinduced blood pressure elevations over the lifespan of three substrains of Wistar rats. J Am Coll Nutr. 1998;17:36–47.
- 13. Reaven GM, Ho H. Sugar-induced hypertension in Sprague-Dawley rats. *Am J Hypertens*. 1991;4:610–614.
- Sanchez-Lozada LG, Tapia E, Jimenez A, Bautista P, Cristobal M, Nepomuceno T, Soto V, Avila-Casado C, Nakagawa T, Johnson RJ, Herrera-Acosta J, Franco M. Fructose-induced metabolic syndrome is associated with glomerular hypertension and renal microvascular damage in rats.
 Am J Physiol Renal Physiol. 2007;292:F423–F429.
- Dhingra R, Sullivan L, Jacques PF, Wang TJ, Fox CS, Meigs JB, D'Agostino RB, Gaziano JM, Vasan RS. Soft drink consumption and risk of developing cardiometabolic risk factors and the metabolic syndrome in middle-aged adults in the community. *Circulation*. 2007;116:480–488.
- Nguyen S, Choi HK, Lustig RH, Hsu CY. Sugar-sweetened beverages, serum uric acid, and blood pressure in adolescents. *J Pediatr*. 2009;154: 807–813.
- Winkelmayer WC, Stampfer MJ, Willett WC, Curhan GC. Habitual caffeine intake and the risk of hypertension in women. *JAMA*. 2005;294: 2330–2335.
- Appel LJ, Champagne CM, Harsha DW, Cooper LS, Obarzanek E, Elmer PJ, Stevens VJ, Vollmer WM, Lin PH, Svetkey LP, Stedman SW, Young DR, for the Writing Group of the PREMIER Collaborative Research Group. Effects of comprehensive lifestyle modification on blood pressure control: main results of the PREMIER clinical trial. *JAMA*. 2003;289: 2083–2093.
- Svetkey LP, Harsha DW, Vollmer WM, Stevens VJ, Obarzanek E, Elmer PJ, Lin PH, Champagne C, Simons-Morton DG, Aickin M, Proschan MA, Appel LJ. PREMIER: a clinical trial of comprehensive lifestyle modification for blood pressure control: rationale, design and baseline characteristics. *Ann Epidemiol*. 2003;13:462–471.
- Blair SN, Haskell WL, Ho P, Paffenbarger RS Jr, Vranizan KM, Farquhar JW, Wood PD. Assessment of habitual physical activity by a seven-day recall in a community survey and controlled experiments. Am J Epidemiol. 1985;122:794–804.

- Obarzanek E, Vollmer WM, Lin PH, Cooper LS, Young DR, Ard JD, Stevens VJ, Simons-Morton DG, Svetkey LP, Harsha DW, Elmer PJ, Appel LJ. Effects of individual components of multiple behavior changes: the PREMIER trial. Am J Health Behav. 2007;31:545–560.
- Casiglia E, Bongiovi S, Paleari CD, Petucco S, Boni M, Colangeli G, Penzo M, Pessina AC. Haemodynamic effects of coffee and caffeine in normal volunteers: a placebo-controlled clinical study. *J Intern Med*. 1991;229:501–504.
- Robertson D, Frolich JC, Carr RK, Watson JT, Hollifield JW, Shand DG, Oates JA. Effects of caffeine on plasma renin activity, catecholamines and blood pressure. N Engl J Med. 1978;298:181–186.
- Israel KD, Michaelis OE, Reiser S, Keeney M. Serum uric acid, inorganic phosphorus, and glutamic-oxalacetic transaminase and blood pressure in carbohydrate-sensitive adults consuming three different levels of sucrose. *Ann Nutr Metab.* 1983;27:425–435.
- Rowe JW, Young JB, Minaker KL, Stevens AL, Pallotta J, Landsberg L. Effect of insulin and glucose infusions on sympathetic nervous system activity in normal man. *Diabetes*. 1981;30:219–225.
- Rebello T, Hodges RE, Smith JL. Short-term effects of various sugars on antinatriuresis and blood pressure changes in normotensive young men. Am J Clin Nutr. 1983;38:84–94.
- 27. Johnson RJ, Segal MS, Sautin Y, Nakagawa T, Feig DI, Kang DH, Gersch MS, Benner S, Sanchez-Lozada LG. Potential role of sugar (fructose) in the epidemic of hypertension, obesity and the metabolic syndrome, diabetes, kidney disease, and cardiovascular disease. Am J Clin Nutr. 2007;86:899–906.
- Feig DI, Kang DH, Nakagawa T, Mazzali M, Johnson RJ. Uric acid and hypertension. Curr Hypertens Rep. 2006;8:111–115.
- Stamler R. Implications of the INTERSALT study. Hypertension. 1991;17(suppl):I-16–I-20.

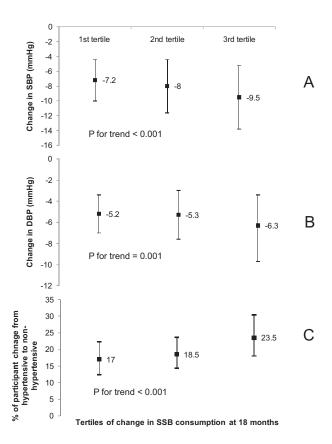
CLINICAL PERSPECTIVE

Consumption of sugar-sweetened beverages (SSBs) has increased dramatically in the United States. Although high SSB consumption has been linked to excess calorie intake and overweight/obesity, SSBs may have other adverse effects. In a prospective study of 810 US adults with prehypertension and stage I hypertension, we found that reducing SSB consumption was associated with significant reductions in blood pressures (BP). On average, a reduction in SSB intake of 1 serving a day (12 oz/d) was associated with a 1.8-mm Hg reduction in systolic BP and 1.1-mm Hg reduction in diastolic BP over 18 months. A positive association was also found for dietary sugar intake and BP. No association was found for diet beverage consumption or caffeine intake and BP. These findings have important clinical and public health implications. It has been estimated that a 3-mm Hg reduction in systolic BP should reduce stroke mortality by 8% and coronary heart disease mortality by 5%. Such reductions in systolic BP would be anticipated by reducing SSB consumption by an average of 2 servings per day. Currently, the average intake of SSBs is 2.3 servings per day for US adults. Nationwide, 72 million US adults (35%) have hypertension, and another 59 million (29%) have prehypertension. Given the high prevalence of both SSB consumption and hypertension in the United States and throughout much of the world, even small reductions in SSB consumption may be an important dietary strategy to lower BP.

Correction

In the article by Chen et al, "Reducing Consumption of Sugar-Sweetened Beverages Is Associated With Reduced Blood Pressure: A Prospective Study Among United States Adults," which appeared in the June 8, 2010 issue of the journal (*Circulation*. 2010;121:2398–2406), there were two errors in Figure 1. In the graph, the letters "A, "B," and C," are supposed to designate the figure; only A appears. As well, "SPB" appears on the Y-axis label instead of "DBP."

The corrected version of Figure 1 appears below.



The correction has been made to the current online version of the manuscript. The authors regret the error.

DOI: 10.1161/CIR.0b013e3181ec4670