Increased Fructose Associates with Elevated Blood Pressure

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ABSTRACT

The recent increase in fructose consumption in industrialized nations mirrors the rise in the prevalence of hypertension, but epidemiologic studies have inconsistently linked these observations. We investigated whether increased fructose intake from added sugars associates with an increased risk for higher BP levels in US adults without a history of hypertension. We conducted a cross-sectional analysis using the data collected from the National Health and Nutrition Examination Survey (NHANES 2003 to 2006) involving 4528 adults without a history of hypertension. Median fructose intake was 74 g/d, corresponding to 2.5 sugary soft drinks each day. After adjustment for demographics; comorbidities; physical activity; total kilocalorie intake; and dietary confounders such as total carbohydrate, alcohol, salt, and vitamin C intake, an increased fructose intake of $\geq$74 g/d independently and significantly associated with higher odds of elevated BP levels: It led to a 26, 30, and 77% higher risk for BP cutoffs of $\geq$135/85, $\geq$140/90, and $\geq$160/100 mmHg, respectively. These results suggest that high fructose intake, in the form of added sugar, independently associates with higher BP levels among US adults without a history of hypertension.

Hypertension is the most common chronic disease in developed countries.[1] Studies have documented a progressive increase in the prevalence of hypertension in the United States, from a frequency of approximately 5 to 10% of the adult population at the turn of the 20th century to approximately 31% of the adult population today.[2] In addition to an alarming increase in the prevalence of hypertension in the adult population, essential hypertension is becoming increasingly common in adolescents.[3] This has grave implications considering that it is a major risk factor for coronary artery disease, congestive heart failure, stroke,[4] and chronic kidney disease[5] and that it is estimated to account for 7.1 million deaths per year worldwide.[6] Despite the presence of effective antihypertensive agents, two thirds of these patients remain either untreated or treated ineffectively[7]; therefore, it is important to identify potentially modifiable factors that contribute to the increased number of cases of hypertension in the United States and worldwide.

The rise in the incidence and prevalence of hypertension has been linked to adaptation of Western diets and culture. In particular, fructose consumption has increased dramatically in industrialized nations including the United States since the 1900s.[8,9] Fructose is a simple sugar that is a key component in table sugar (sucrose) and high-fructose corn syrup. Although fructose also occurs naturally in fruits, the noted increase in fructose consumption in the United States is mainly due to an increase in the intake of added sugars in processed drinks and foods such as sugary

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Table 1. Clinical characteristics of participants by SBP categories ($n = 4528$)

Characteristic	SBP Category[a]				P for Trend
	Normal SBP (<120 mmHg; $n = 2774$)	Prehypertension (120 to 139 mmHg; $n = 1369$)	Stage 1 (140 to 159 mmHg; $n = 261$)	Stage 2 (≥160 mmHg; $n = 94$)	
Fructose intake (g/d; mean ± SD)	71 ± 93	76 ± 96	86 ± 81	98 ± 85	0.05
Age (years; mean ± SD)	37 ± 13	44 ± 16	58 ± 15	66 ± 12	<0.0001
Gender (%)					<0.0001
male	38	40	47	68	
female	62	60	53	32	
Ethnicity					<0.07
non-Hispanic white	52	52	56	48	
non-Hispanic black	18	21	20	27	
Mexican American	26	23	20	21	
other	4	4	4	5	
Smoking status (%)					<0.0001
never	53	49	47	59	
former	18	23	28	27	
current	23	25	24	14	
unknown	5	3	1	0	
Diabetes (%)	2	5	9	8	<0.0001
Average daily METs exercise (mean ± SD)	210 ± 356	198 ± 256	175 ± 229	152 ± 199	0.02
Waist circumference (in; mean ± SD)	37 ± 6	39 ± 6	39 ± 5	38 ± 5	<0.0001
BMI (kg/m²; mean ± SD)	27 ± 6	29 ± 6	29 ± 6	28 ± 5	<0.0001
Serum glucose levels (mg/dl; mean ± SD)	90 ± 23	97 ± 31	101 ± 27	102 ± 30	<0.0001
Uric acid (mg/dl; mean ± SD)	5.0 ± 1.3	5.4 ± 1.3	5.3 ± 1.3	5.3 ± 1.1	<0.0001
Total cholesterol (mg/dl; mean ± SD)	199 ± 44	204 ± 42	214 ± 49	218 ± 32	<0.0001
LDL (mg/dl; mean ± SD)	129 ± 43	138 ± 45	147 ± 52	144 ± 36	<0.0001
HDL (mg/dl; mean ± SD)	57 ± 17	53 ± 17	55 ± 15	60 ± 14	<0.0001
Triglycerides (mg/dl; mean ± SD)	128 ± 100	154 ± 132	168 ± 180	143 ± 88	<0.0001
eGFR (ml/min per 1.73 m²; mean ± SD)	103 ± 26	95 ± 23	88 ± 20	81 ± 18	<0.0001
Dietary recall (mean ± SD)					
kilocalories	2187 ± 868	2300 ± 901	2052 ± 750	1849 ± 679	0.21
carbohydrate intake (g/d)	274 ± 117	281 ± 120	252 ± 93	240 ± 106	0.03
sodium (mg/d)	3466 ± 1529	3557 ± 1580	3248 ± 1338	2863 ± 991	<0.05
potassium (mg/d)	2688 ± 1134	2776 ± 1103	2671 ± 954	2399 ± 730	0.83
alcohol intake (g/d)	7 ± 17	12 ± 27	8 ± 19	5 ± 12	0.0002
vitamin C (mg/d)	98 ± 92	94 ± 88	95 ± 70	90 ± 57	0.15

[a]In accordance with the JNC 7 classification of hypertension.

soft drinks and grain (bakery) products.[10] Studies in rats suggested that fructose can raise BP.[11] Few epidemiologic studies have examined the association between fructose intake and BP levels, the results of which have been conflicting.[12–14] This conflicting evidence is underlined by a recent statement by the American Heart Association that highlights the controversy over whether increased intake of fructose in the form of added sugar causes hypertension.[9]

The National Health and Nutrition Examination Survey (NHANES 2003 to 2006) involved a large cross-sectional evaluation of healthy adults from whom direct BP measurements were obtained and for whom fructose intake could be calculated from a self-administered diet questionnaire. Using this population, we determined the median intake of fructose from foods high in added sugar in a nationally representative population, and we examined the hypothesis that excessive fructose intake from added sugars is associated with higher BP levels in participants with no history of hypertension.

RESULTS

Clinical Characteristics of Participants by Systolic BP Categories

Of the 4528 eligible individuals, 2774 had normal systolic BP (SBP) readings defined as an SBP <120 mmHg. Of the remaining individuals, 1369 had BP levels consistent with prehypertension and 355 had stage 1 ($n = 261$) and stage 2 ($n = 94$) hypertension according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) guidelines,[15] in which stage 1 hypertension is defined as SBP 140 to 159 mmHg or diastolic BP (DBP) 90 to 99 mmHg and stage 2 hypertension is defined as SBP ≥160 mmHg or DBP ≥100 mmHg. Table 1 describes the distribution of the cohort's baseline characteristics by SBP category. There was a trend toward greater fructose intake with the higher BP levels that achieved borderline statistical significance. Individuals with prehypertension and hy-

pertension were older and more likely to be male. In addition, the individuals with higher BP levels had a larger prevalence of diabetes, greater waist circumferences, and higher serum glucose and uric acid levels.

Factors Independently Associated with Fructose Intake

Factors that were associated with high fructose intake are shown in Table 2. Non-Hispanic black race and total carbohydrate and vitamin C intake were independently and directly correlated with high fructose intake. In contrast, dietary sodium, potassium, and alcohol intake were independently and inversely associated with high fructose intake. Total kilocalorie intake and serum uric acid levels were not associated with high fructose intake in this multivariate analysis.

Cross-sectional Relationship Between High Fructose Intake and BP Levels

A total of 2253 participants included in the analysis were noted to have high fructose intake defined as ≥74 g/d. Figure 1 shows that a fructose intake of ≥74 g/d is associated, in unadjusted analysis, with higher odds of elevated BP levels. After adjustment for age; gender; race/ethnicity; smoking; diabetes, average daily metabolic equivalents (METs); waist circumference; body mass index (BMI); glucose; uric acid; total cholesterol; HDL cholesterol; triglycerides; LDL cholesterol; estimated GFR (eGFR) by the Modification of Diet in Renal Disease (MDRD) formula; and dietary recalls of total kilocalories, total carbohydrate, sodium, potassium, alcohol, and vitamin C, high fructose intake ≥74 g/d is associated with an increased risk for elevated BP levels. Specifically, increased fructose intake led to a 26, 30, and 77% higher risk for the following clinically relevant BP cutoffs: ≥135/85, ≥140/90, and ≥160/100 mmHg, respectively, in multivariate analysis. Almost identical results were obtained for logistic regression analysis in which fructose intake was entered as a continuous measure (data not shown).

To characterize further the relationship between high fructose intake from added sugars and BP levels, we applied the same multivariate logistic regression model to SBP and DBP categories individually. In Figure 2, we show that increased fructose intake from added sugars is independently associated with SBP. This risk increases with higher SBP: It is 36% greater (multiple adjusted

Figure 1. Cross-sectional association between high fructose intake and clinically relevant BP categories in individuals with no history of hypertension (*n* = 4528). Data are odds ratios (ORs) and 95% CIs. Adjusted analysis included the following covariates: Age, gender, race/ethnicity, smoking, diabetes, average daily METs, waist circumference, BMI, serum glucose levels, serum uric acid levels, total cholesterol, HDL cholesterol, triglycerides, LDL cholesterol, and eGFR, in addition to 24-hour dietary recalls of kilocalories and total carbohydrate, sodium, potassium, alcohol, and vitamin C intake.

odds ratio 1.36; 95% confidence interval [CI] 1.01 to 1.85) for participants with an SBP of 140 to 159 mmHg and more than double (multiple adjusted odds ratio 2.10; 95% CI 1.20 to 3.61) for participants with an SBP of ≥160 mmHg. We found no association between high fructose intake from added sugars and DBP on unadjusted or adjusted analysis (Figure 3).

When we examined the association between fructose intake and SBP and DBP levels all modeled as continuous variables, we found that fructose intake from added sugars directly correlated with SBP (adjusted correlation coefficient 1.70; 95% CI 0.72 to 2.68; *P* = 0.0007). We found no correlation between fructose intake and DBP.

DISCUSSION

We report an independent association between high fructose intake from added sugars and higher BP levels of the participating individuals in a large sample representative of the US adult population independent of demographics; comorbidities; physical activity; total kilocalorie intake; and dietary confounders such as total carbohydrate, alcohol, salt, and potassium intake. Fructose intake, based on the US Department of Agriculture (USDA) fructose content of various foods, was calculated and applied to the NHANES dietary questionnaire, and the analysis excluded individuals without a history of hypertension. We show that the median fructose intake

Table 2. Factors associated with high fructose intake in multivariate linear regression analysis

Covariate	Coefficient	95% CI	*P*
Male gender	−13.1	−20.7 to −5.5	0.0009
Non-Hispanic black ethnicity	19.1	11.1 to 27.1	<0.0001
Dietary kilocalories	0.02	0.01 to 0.03	0.07
Dietary carbohydrates	0.10	0.04 to 0.16	<0.0001
Dietary sodium	−0.005	−0.009 to −0.001	0.0005
Dietary potassium	−0.009	−0.010 to −0.005	<0.0001
Dietary alcohol	−8.3	−13.0 to −3.6	0.0006
Dietary vitamin C	0.0400	0.0008 to 0.0800	0.03

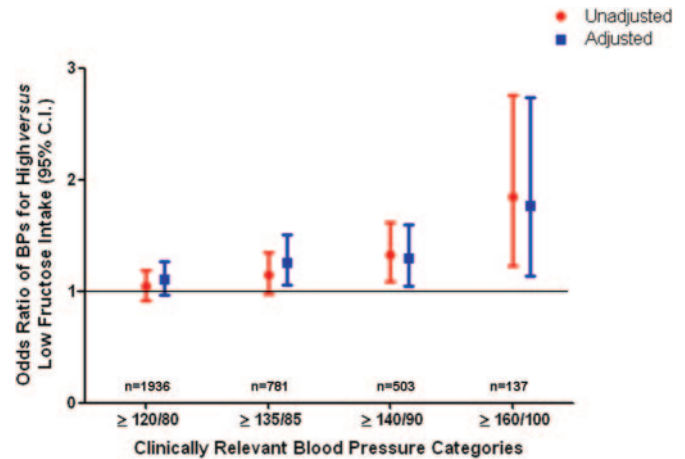Positive coefficients indicate a direct relationship between the variable and high fructose intake ≥74 g/d.
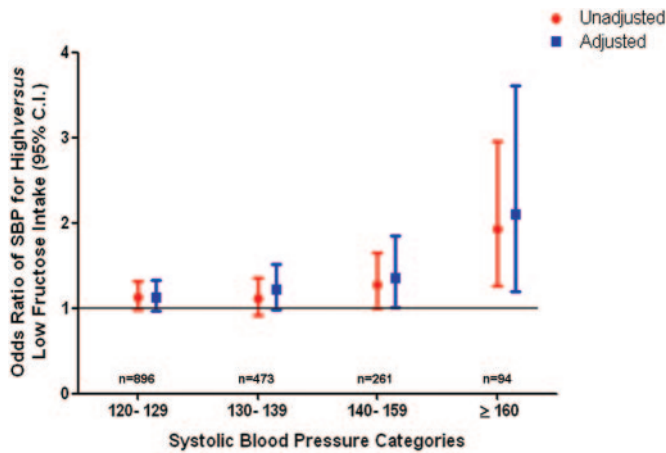
Figure 2. Cross-sectional association between high fructose intake and SBP in individuals with no history of hypertension (*n* = 4528). Data are ORs and 95% CIs. Adjusted analysis included the following covariates: Age, gender, race/ethnicity, smoking, diabetes, average daily METs, waist circumference, BMI, serum glucose levels, serum uric acid levels, total cholesterol, HDL cholesterol, triglycerides, LDL cholesterol, and eGFR, in addition to 24-hour dietary recalls of kilocalories and total carbohydrate, sodium, potassium, alcohol, and vitamin C intake.

from added sugars for the NHANES population is 74 g/d (the equivalent of 2.5 soft drinks per day). The large amount of fructose ingested from added sugar by this population could potentially explain why our study has identified an association between fructose intake and elevated BP levels whereas other studies have not.[12,13]

Dhingra *et al.*[13] explored the relationship between soft drink consumption and metabolic syndrome in the Framingham
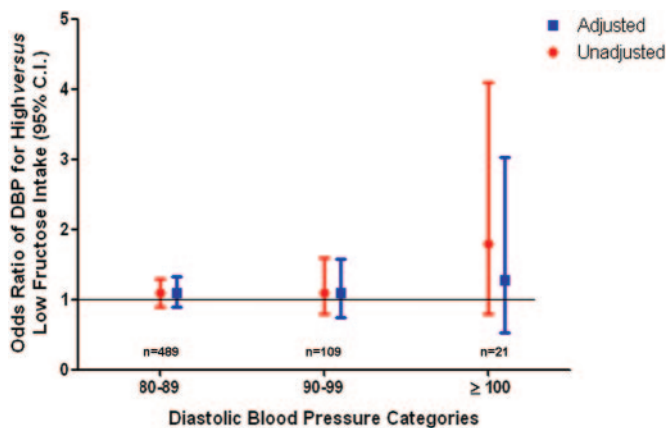

Figure 3. Cross-sectional association between high fructose intake and DBP in individuals with no history of hypertension (*n* = 4528). Data are ORs and 95% CIs. Adjusted analysis included the following covariates: Age, gender, race/ethnicity, smoking, diabetes, average daily METs, waist circumference, BMI, serum glucose levels, serum uric acid levels, total cholesterol, HDL cholesterol, triglycerides, LDL cholesterol, and eGFR, in addition to 24-hour dietary recalls of kilocalories and total carbohydrate, sodium, potassium, alcohol, and vitamin C intake.

Heart Study population. In their study, individuals who consumed ≥1 soft drink per day had a 25 to 32% higher adjusted risk for incidence of each individual metabolic trait (obesity, increased waist circumference, increased fasting glucose, high triglycerides, and lower HDL cholesterol), except for hypertension. According to the USDA, only approximately one third of ingested added sugars come from soft drinks; the rest comes from bakery products, fruit drinks, dairy desserts, and candies, and analyses exclusive to soft drinks likely underestimate the actual sugar intake of the participating individuals.[16] Forman *et al.*[12] studied the association between fructose and hypertension prospectively in three large cohort studies: The Nurses Health Study I (NHSI), The Nurses Health Study II (NHSII), and the Health Professionals Follow up Study (HPFS). The investigators found no association between fructose intake and hypertension; however, all of the participants in those cohorts were health care professionals and had a high intake of fruits that were included in the fructose intake scale (*e.g.*, 23.6% of total fructose intake in NHSI was from fruits). This pattern of dietary intake does not mirror that of the general US population, in which the majority of the fructose ingested comes from added sugars rather than from fruits.[16]

Recently, Nguyen *et al.*[14] showed an association among sugar-sweetened beverages, serum uric acid levels, and SBP in a cross-sectional analysis of 4867 adolescents who were between the ages of 12 and 18 years and had participated in the NHANES (1999 to 2004). Studies in animals suggested that fructose may raise BP *via* several mechanisms, including stimulation of uric acid,[17–19] inhibition of endothelial nitric oxide synthase system,[20,21] and stimulation of the sympathetic nervous system,[22] or by directly increasing sodium absorption in the gut.[23] Although uric acid has been shown to mediate fructose-induced hypertension in rats, we could not demonstrate a relationship between high fructose intake and serum uric acid levels in this study. In our study, serum uric acid levels were not associated with increased fructose intake; neither were triglycerides, BMI, waste circumference, or diabetes. One potential explanation is that the individuals with these characteristics of the metabolic syndrome ingested smaller amounts of fructose-rich foods in an attempt to control their weight or their blood glucose levels. Alternatively, other mechanisms, such as discussed already, may underlie our findings.

Our study has several limitations. First, this is was cross-sectional analysis, the results of which cannot be used to deduce a cause-and-effect relationship. Second, the exact intake of fructose was not measured in the participants; by definition, we relied on self-reporting. That may have led to misclassification of individuals into either category of fructose intake. Third, we calculated fructose intake from sources that are rich in added sugars and include fructose and glucose in almost equal amounts. Although we did adjust for total carbohydrate intake in an attempt to control for glucose intake, we cannot exclude the possibility that the high glucose content of the included foods might have contributed to our findings.

Despite these limitations, our study has several strengths.

First, it includes a large nationally representative population of adults in the United States. Second, we took advantage of the availability of actual BP measurements for the participating individuals. Third, although we were unable to take into account all of the possible confounding dietary factors for which 24-hour dietary recall was unavailable (*e.g.*, animal protein), we did account for a large number for potentially confounding variables, including the most important risk factors for elevated BP: Sodium intake and body weight. In addition, our reported results are independent of total kilocalorie and total carbohydrate intake.

In conclusion, our findings suggest that a high intake of fructose of ≥74 g/d (corresponding to 2.5 sugary soft drinks per day), in the form of table sugar or high-fructose corn syrup, is independently associated with a greater risk for elevated SBP levels in the adult US population with no history of hypertension. These findings support the hypothesis that increased intake of fructose may result in hypertension through a variety of mechanisms. Limiting fructose intake is readily feasible, and, in light of our results, prospective studies are needed to assess whether decreased intake of fructose from added sugars will reduce the incidence of hypertension and the burden of cardiovascular disease in the US adult population.

CONCISE METHODS

Study Population and Sample

Data for this analysis were obtained from the NHANES (2003 to 2006), a cross-sectional survey conducted by the National Center for Health Statistics of the Centers for Disease Control and Prevention. A stratified, multistage sampling design was used, with oversampling of non-Hispanic black individuals, Mexican-American individuals, and individuals aged ≥60 years. Data collection consisted of a home interview, during which the medical history of the participants was obtained *via* a standardized questionnaire administered by the interviewer, and of a detailed physical examination. In addition, the home visit included the collection of blood specimens at a mobile examination center or at the participant's home.[24–26]

The analysis was restricted to adult participants who were aged ≥18 years and had complete dietary data (*n* = 6653) and no history of hypertension. Participants who had been told by a physician that they have high BP or were taking antihypertensive medications were excluded from this analysis (*n* = 1824). Participants who did not have hypertension or BP data (*n* = 301) were also excluded from the analysis. Thus, the final sample size used in this analysis was 4528 participants.

Primary Predictor and Outcome

The independent variable used in this analysis was fructose intake from added sugars, and it was calculated from the NHANES (2003 to 2006) dietary questionnaire that was self-administered to the participating individuals and was based on their intake during the previous month to the home interview.[27] Food frequency questionnaire assessments are a valid and reproducible method for assessing average dietary consumption.[28,29] Briefly, each food item was assigned grams of

fructose per portion size on the basis of the documented USDA fructose content of various foods, supplemented with information from manufacturers. Only foods with high fructose content from added sugars were included, such as fruit juices and punch; sugar-sweetened soft drinks and beverages; and bakery products such as pies, cakes, strudels, doughnuts, and cookies, in addition to dairy dessert, chocolate, candy, and dried fruits. Natural fruits were excluded from the calculation, because although they do contain fructose, they also have a high content of potassium, ascorbate, and other antioxidants. These nutrients have been shown to counter the effects of fructose in animal models, and controlling for these factors can be difficult.[30,31] Contrary to natural fruits, because dried fruits are deprived of their natural content of vitamins and antioxidants and yet maintain a high fructose content when processed, they were included in the analysis. For each questionnaire, the total intake of grams of fructose per day was determined. We found the median fructose intake for the included participants was 74 g/d (interquartile range 40 to 133 g/d). An intake of 74 g/d fructose is the equivalent of 2.5 soft drinks per day. Previous reports of the NHANES have associated the consumption of two or more soft drinks with an increased risk for adverse events, namely albuminuria.[32] Hence, we decided to dichotomize the exposure variable on the basis of the median fructose intake; therefore, participants with an average daily fructose intake of ≥74 g were labeled as having high fructose intake, and participants with a daily intake of <74 g were considered to have low fructose intake.

The dependent variables of interest were BP levels. For the purpose of this analysis, results are presented according to clinically relevant BP categories: ≥120/80, ≥135/85, ≥140/90, and ≥160/100 mmHg. In addition, we examined the association between high fructose intake from added sugars and SBP and DBP categories. SBP was stratified as follows: 120 to 129, 130 to 139, 140 to 159, and ≥160 mmHg. DBP was similarly stratified: <80, 80 to 89, 90 to 99, and ≥100 mmHg. BP was measured at the mobile examination centers by physicians with mercury sphygmomanometers using a standard protocol. Up to three measurements were collected from each participant while in the sitting position; when more than two measurements were collected, the last two were averaged. SBP was defined as the point at which the first Korotkoff sound was heard; the DBP was the level of mercury 2 mm below where the last sound was heard.

Other Measurements

Potential confounding factors were chosen on the basis of previous studies or of their biologic plausibility. The following covariates were included in the analysis: Age, gender, race/ethnicity, smoking, diabetes, physical activity (average daily METs), waist circumference, BMI, glucose, uric acid, total cholesterol, HDL cholesterol, triglycerides, LDL cholesterol, and eGFR. In addition, we adjusted for the intake of multiple dietary factors that have been reported to influence BP, such as total kilocalories and total carbohydrate, sodium, potassium, alcohol, and vitamin C intake. Adjustment for potentially confounding dietary factors was based on a 24-hour dietary recall questionnaire rather than on the 1-month NHANES dietary questionnaire that was used to calculate fructose intake.

Age was modeled as a continuous variable. Race/ethnicity was classified into four categories: Non-Hispanic white, non-Hispanic

black, Mexican American, and other. Smoking status was classified as never, former, and current. Participants were considered to have diabetes when they had been told by a physician that they have diabetes, were taking hypoglycemic medications, or had a fasting glucose concentration of ≥126 mg/dl. Physical activity was measured as average METs exercised per day and was based on the average duration of the activity reported by the participant and the known MET score per activity. (METs are a simplified system for classifying physical activities: 1 MET is equal to the resting oxygen consumption, which is approximately 3.5 ml/kg per min oxygen). BMI was calculated as weight in kilograms divided by the square of height in meters. Average METs and BMI both were modeled as continuous variables.

Serum uric acid levels were measured by oxidization with the specific enzyme uricase to form allantoin and H_2O_2 (Hitachi model 737 Multichannel Analyzer; Boehringer Mannheim Diagnostics, Indianapolis, IN). Fasting levels of HDL cholesterol and triglycerides were measured enzymatically with a Hitachi 704 analyzer (Boehringer Mannheim Diagnostics). LDL cholesterol concentration was calculated using the Friedewald equation (LDL cholesterol = total cholesterol − HDL cholesterol − triglycerides/5), except for those with triglycerides of >400 mg/dl.[33] GFR was estimated from the abbreviated MDRD study formula[34] as follows: eGFR = 186.3 × (serum creatinine mg/dl)$^{-1.154}$ × age$^{-0.203}$ × 0.742 (if female) × 1.21 (if black). As recommended by NHANES analytic guidelines,[27] NHANES serum creatinine values in 2005 through 2006 were adjusted to ensure comparability with standard creatinine using the following formula: Standard creatinine (mg/dl) = −0.016 + 0.978 × (NHANES 2005 through 2006 uncalibrated serum creatinine [mg/dl]). No adjustment was needed for serum creatinine levels measured in 2003 through 2004.[35] Total kilocalorie consumption and total carbohydrate, sodium, potassium, alcohol, and vitamin C intake were based on the self-reported values from the 24-hour dietary recall.

Statistical Analysis

Univariate modeling was first performed to determine whether a directional trend existed between variables and ordered stages of hypertension in accordance with JNC 7 classification. Categorical variables were examined with a Cochran-Armitage trend test, and continuous variables were examined with one-way ANOVA. The independent relationship of high fructose intake on BP levels, stratified into clinically relevant BP categories (≥120/80, ≥135/85, ≥140/90, and ≥160/100 mmHg), was investigated using logistic regression models, adjusting simultaneously for several potential confounders. The listed clinically relevant BP categories each were referenced to the group <120/80 mmHg. Logistic regression analysis was also used to examine the relationship of fructose intake to SBP categories (120 to 129, 130 to 139, 140 to 159, and ≥160 mmHg) and to DBP categories (80 to 89, 90 to 99, and ≥100 mmHg). The listed categories each were referenced to <120 and <80 mmHg for the SBP and DBP categories, respectively.

In our analysis, fructose intake was modeled as a categorical variable derived from the median value of grams per day of fructose intake reported by participants during the previous month to the home interview (<74 *versus* ≥74 g/d) or as a continuous variable. Because of skewness of the distribution, fructose intake was logarithmically

transformed for statistical analyses. In all regression models, observations were weighted to reflect the general US population as of early 2000s, using weights calculated for that purpose by the National Center for Health Statistics. Analyses were conducted using SAS 9.1.3 (Research Triangle Institute, Research Triangle Park, NC). $P < 0.05$ was considered statistically significant.

DISCLOSURES

R.J.J. is listed as an inventor on several patent applications on lowering uric acid as it relates to BP and metabolic syndrome; in addition, he is author of *The Sugar Fix* (2008, Rodale Inc.; 2009, Simon and Schuster).

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