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Serum Carbon Isotope Values Change in Adults in Response to Changes in Sugar-Sweetened Beverage Intake[1,2]

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Abstract

Serum carbon isotope values [^{13}C-to-^{12}C serum carbon isotope ratio (δ^{13}C)], which reflect consumption of corn- and cane-based foods, differ between persons consuming high and low amounts of sugar-sweetened beverages (SSBs). In this study, we determined whether serum δ^{13}C changes in response to change in SSB intake during an 18-mo behavioral intervention trial. Data were from a subset of 144 participants from the PREMIER trial, a completed behavioral intervention (Maryland, 1998–2004). SSB intake was assessed using 2 24-h dietary recall interviews. Blinded serum samples were assayed for δ^{13}C by natural abundance stable isotope mass spectroscopy. Multiple linear regression models with generalized estimating equations and robust variance estimation were used. At baseline, mean SSB intake was 13.8 ± 14.2 fl oz/d, and mean δ^{13}C serum value was −19.3 ± 0.6 units per mil (designated ‰). A reduction of 12 oz (355 mL)/d SSB (equivalent to 1 can of soda per day) was associated with 0.17‰ (95% CI: 0.08‰, 0.25‰; $P < 0.0001$) reduction in serum δ^{13}C values over 18 mo (equivalent to a 1% reduction in δ^{13}C from baseline). After adjusting for potential confounders, a reduction of 12 oz/d SSB (equivalent to 1 can of soda per day), over an 18-mo period, was associated with 0.12‰ (95% CI: 0.01‰, 0.22‰; $P = 0.025$) reduction in serum δ^{13}C. These findings suggest that serum δ^{13}C can be used as a measure of dietary changes in SSB intake.   J. Nutr. doi: 10.3945/jn.113.186213.

Introduction

Epidemiologic investigations of the association between diet and chronic disease outcomes are limited by measurement error resulting from self-reported data (1–9), which underscores the need for biomarkers that reflect dietary intake. The ratio of ^{13}C-to-^{12}C (measured as δ^{13}C)[9] in human serum has been proposed as a novel biomarker of sugar-sweetened beverage (SSB) intake because carbon stable isotope values in blood have been shown to differ between persons consuming high and low amounts of SSBs (10,11). It has been hypothesized that, because *Zea mays* (corn) and *Saccharum* (cane) are C4 plants and because C4 plants are naturally enriched in carbon ^{13}C compared with other plants, a measure of δ^{13}C in human serum can be used as a surrogate for assessing the intake of foods sweetened with corn syrup and cane sugar (10).

Previous studies showed an association between the δ^{13}C value of human blood and sugar intake (11–13); however, these studies were cross-sectional and could not provide data on whether serum δ^{13}C values change in response to changes in sugar intake. In this study, we evaluated whether serum δ^{13}C values change in response to changes in SSB intake during an 18-mo behavioral intervention trial. We use data from the PREMIER trial, a study in which participants changed their SSB intake over the course of the intervention (14).

Participants and Methods

Study population. Study participants were from the Baltimore, Maryland center of the PREMIER trial. Information on PREMIER study design, recruitment, and data collection was published previously (15). Briefly, PREMIER is a completed, 18-mo, multicenter, randomized trial designed to determine the blood pressure–lowering effects of 2 behavioral interventions in adults with a high-normal blood pressure or stage 1 hypertension (15). Participants consisted of 810 men and women, aged 25–79 y, recruited from 4 study centers in the United States (Baltimore, Maryland; Baton Rouge, Louisiana; Durham, North Carolina; and Portland, Oregon) from 1998 to 2004. The protocol of the trial was approved by institutional review boards at each center and an external protocol review committee. Written consent was obtained for each participant. Participants were randomly assigned to 1 of 3 groups: 1) an "advice-only" control group that received information but no behavioral counseling; 2) an "established" behavioral intervention group that received counseling on weight loss, physical activity, and dietary sodium

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intake; or *3)* an "established plus DASH" behavioral intervention group that received counseling similar to the established group plus counseling on the DASH (Dietary Approaches to Stop Hypertension) diet plan. Participants were advised to reduce intake of foods or beverages that were the highest contributors to their total caloric intake.

Measurement of $\delta^{13}C$ in serum. In the PREMIER study, blood was drawn after an 8-h fast, and samples were stored at 70°C after collection. For the purpose of this analysis, serum samples obtained at baseline, 6 mo, and 18 mo were thawed to measure $\delta^{13}C$ value. Information on laboratory methods used to measure $\delta^{13}C$ were published previously (10). Briefly, samples were quantitatively combusted to carbon monoxide in a EuroVector elemental analyzer (EA3000; EuroVector) configured with a continuous-flow stable isotope ratio mass spectrometer (Isoprime; Micromass). Conventionally, natural abundance isotope ratios are expressed relative to an international standard, expressed using the δ notation as units per mil (‰). The equation defining isotope ratios was published previously (13). The ‰ unit is approximately equivalent to 10 times the percentage difference of the ^{13}C-to-^{12}C ratio of a sample from the ^{13}C-to-^{12}C ratio of a standard reference. Because serum samples from this study have lower ^{13}C-to-^{12}C than VPDB (Vienna Pee Dee Belemnite), sample $\delta^{13}C$ values are <0.

Organic standards were introduced every 5 samples, and blanks were introduced every 50 samples. Each sample was analyzed in triplicate, and the mean value was used in statistical analysis. Total variability across the 3 measurements never exceeded 0.02‰. An analytical uncertainty of <0.05‰ is associated with each sample measurement. All samples were analyzed, with blinding to sample source, in the Jahren laboratory at the University of Hawaii. Two internal laboratory standards referenced to VPDB were used, for a 2-point calibration that encompassed the range of $\delta^{13}C$ values present in our samples of −20.9‰ to −17.7‰.

Measurement of SSB intake and dietary factors. Details on dietary data collection were published previously (15,16). Briefly, dietary intake was measured by 2 unannounced 24-h dietary recalls conducted by telephone interviews. Dietary recalls (1 on a weekday and 1 on a weekend day) per participant were obtained at baseline, 6 mo, and 18 mo. Analysis of energy and macronutrient content was completed using Nutrition Data System for Research (version NDS-R 1998, University of Minnesota). Participants' daily nutrient, energy, and beverage intake were calculated by taking the mean from 2 24-h dietary recalls. SSB was defined as carbonated or noncarbonated drinks that were sweetened with added sugars (sucrose or high-fructose corn syrup). SSBs included regular soft drinks, fruit drinks, lemonade, fruit punch, and other sweetened beverages but excluded diet drinks.

Statistical methods. Descriptive data on SSB consumption and $\delta^{13}C$ at each visit are expressed as means ± SEMs. Differences across quartiles in

Table 1 were tested using the χ^2 test for categorical variables and using 1-factor ANOVA for continuous variables. Linear trend tests across quartiles of SSB intake were tested by using the median concentrations for each quartile as an ordinal variable. For the primary analysis, a multiple linear regression model with generalized estimating equations, with an independence working correlation model and robust variance estimation was used to account for correlations within the repeated measures in the outcome ($\delta^{13}C$). The exposure of interest is SSB consumption. Regression coefficients are interpreted as the mean change in $\delta^{13}C$ values with every 12-oz increase in SSB consumption across the population, taking into account the correlation of repeated measurements. In model 1, we adjusted for total caloric intake to assess the association between SSB and serum $\delta^{13}C$ values independent of the total amount of foods and beverages consumed. Additionally, because serum $\delta^{13}C$ values are not specific to corn- and cane-based sweeteners but are also associated with other foods, such as meats and corn, we adjusted for animal protein intake using the ^{15}N-to-^{14}N nitrogen isotope ratio ($\delta^{15}N$) as a biomarker of intake and for corn consumption, which was based on data from the dietary recall. In model 2, we further adjusted for potential confounding by age, sex, and race. All models adjusted for the PREMIER study visit. All statistical analyses were performed with STATA version 11.0 (StataCorp). Statistical significance was set at $P = 0.05$ (2 tailed).

Results

Baseline characteristics and SSB consumption. At baseline, SSB intake in PREMIER $\delta^{13}C$ participants was 13.8 ± 14.2 fl oz/d, and mean $\delta^{13}C$ value was −19.3 ± 0.6‰. Table 1 displays demographic, dietary, and clinical characteristics by baseline SSB consumption and for the entire PREMIER $\delta^{13}C$ population. There was a statistically significant difference in age, sex, and race across quartiles of SSB intake. Compared with participants in the lowest quartile, participants in the higher quartiles of SSB intake had higher body weight, BMI, and waist circumferences. There was also a trend of higher consumption of total calories but not for $\delta^{15}N$, a biomarker for protein intake. Mean values of $\delta^{13}C$ were greater in the higher quartiles of SSB intake compared with the first quartile ($P = 0.011$).

The trends in SSB consumption over the 18-mo period and in $\delta^{13}C$ values at each visit are shown in **Figure 1**. Compared with baseline, the mean reduction in $\delta^{13}C$ was 0.15 ± 0.04‰ at 6 mo ($P < 0.0001$). $\delta^{13}C$ values increased from 6 to 18 mo by 0.09 ± 0.04‰ ($P = 0.041$). The mean reduction in SSB consumption was 6.4 ± 1.3 fl oz/d at 6 mo ($P < 0.0001$) and 4.6 ± 1.1 fl oz/d at 18 mo ($P < 0.001$) compared with baseline.

TABLE 1 Baseline characteristics of PREMIER $\delta^{13}C$ study participants by quartile of SSB consumption[1]

		SSB consumption quartiles				
Variables	All participants (*n* = 144)	1 (0–0 fl oz/d; *n* = 60)	2 (4.3–12.9 fl oz/d; *n* = 12)	3 (13.0–24.5 fl oz/d; *n* = 36)	4 (25.0–56.9 fl oz/d; *n* = 36)	P^2
$\delta^{13}C$, ‰	−19.3 [2.5]	−19.5 [2.2]	−19.2 [1.6]	−19.1 [2.4]	−19.2 [2.3]	0.011
Age, *y*	50.7 ± 8.5	52.9 ± 8.3	46.2 ± 7.8	49.6 ± 8.0	49.6 ± 9.0	0.037
Sex, female, *n* (%)	95 (66.0)	41 (68.3)	10 (83.3)	28 (77.8)	16 (44.4)	0.010
Race, black, *n* (%)	81 (56.3)	22 (36.7)	10 (83.3)	27 (75.0)	22 (61.1)	<0.0001
Weight, *kg*	96.4 ± 19.6	90.8 ± 18.8	94.1 ± 15.1	98.3 ± 18.1	104.6 ± 21.2	0.007
BMI, *kg/m²*	33.6 ± 6.0	31.8 ± 5.6	33.5 ± 5.7	35.7 ± 6.0	34.6 ± 6.1	0.011
Waist circumference, *cm*	109.1 ± 14.9	105.5 ± 14.8	103.9 ± 10.5	113.0 ± 15.1	112.9 ± 14.4	0.018
Total energy, *kcal/d*	1830 ± 624	1670 ± 593	1480 ± 522	2050 ± 700	2010 ± 512	0.002
Corn consumption, *n* (%)	49 (34.0)	22 (36.7)	4 (33.3)	13 (36.1)	10 (27.8)	0.73
$\delta^{15}N$, ‰	9.1 [1.7]	9.2 [1.7]	9.1 [1.1]	9.1 [1.3]	9.0 [1.3]	0.65

[1] Values are means ± SDs or medians [ranges] unless noted otherwise. SSB, sugar-sweetened beverage; $\delta^{13}C$, ^{13}C-to-^{12}C serum carbon isotope ratio; $\delta^{15}N$, ^{15}N-to-^{14}N nitrogen stable isotope ratio.
[2] Differences across quartiles were tested using χ^2 test for categorical variables and using 1-factor ANOVA for continuous variables.
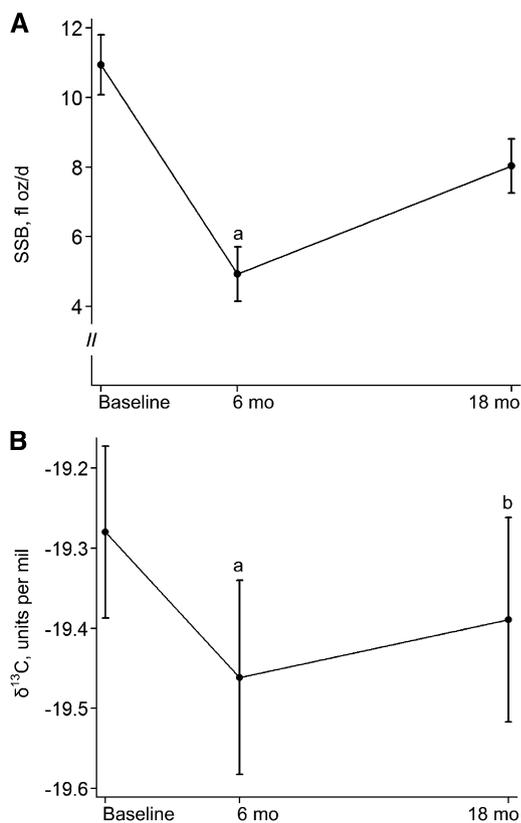
FIGURE 1 SSB intake (*A*) and serum $\delta^{13}C$ values (*B*) at baseline, 6 mo, and 18 mo of a behavioral intervention in adults (PREMIER $\delta^{13}C$ study). Values are means and 95% CIs, *n* = 144. [a]Different from baseline, *P* < 0.05. [b]Different from 6 mo, *P* < 0.05. SSB, sugar-sweetened beverage; $\delta^{13}C$, ^{13}C-to-^{12}C serum carbon isotope ratio.

Relation between change in SSB consumption and change in serum $\delta^{13}C$ values. Change in SSB consumption was associated with mean serum $\delta^{13}C$ values after adjusting for total calories, corn consumption, $\delta^{15}N$ values, age, sex, race, and visit (**Table 2**). In model 1, a reduction of 1 serving per day (12 fl oz) in SSB consumption was associated with a 0.17‰ (95% CI: 0.08, 0.25; *P* < 0.0001) decrease in serum $\delta^{13}C$ values. The association between SSB intake and $\delta^{13}C$ value was unchanged after adjusting for concurrent change in total energy (kilocalories per day), corn consumption, and $\delta^{15}N$ values (model 1: 0.20; 95%

CI: 0.08, 0.31; *P* = 0.001) (Table 2). With additional adjustment for age, race, and sex (model 2), the association between SSB intake and $\delta^{13}C$ was attenuated but remained statistically significant, with a reduction of 1 serving per day (12 fl oz/d) in SSB consumption being associated with a decrease in $\delta^{13}C$ of 0.12‰ (95% CI: 0.01, 0.22; *P* = 0.025). Adjusting for intervention arm had no effect on the estimate (data not shown).

Discussion

In this study, we showed that a mean reduction in SSB intake by 1 serving per day (12 fl oz/d) was associated with a reduction in serum $\delta^{13}C$ over 18 mo. Although this reduction is small compared with the magnitude of variability in $\delta^{13}C$ within sweetened foods (17), it is more than twice the analytical uncertainty of the measurement. To our knowledge, this is the first study to evaluate the change in serum $\delta^{13}C$ values that are associated with change in SSB intake. These results are consistent with recent findings by Nash et al. (11), who showed that self-reported intake of corn and cane sugar–based market foods were associated with high $\delta^{13}C$ values relative to other foods. We also reported previously, in cross-sectional analyses, that $\delta^{13}C$ values increased by 0.20‰ for every additional serving per day of SSBs (*P* < 0.01) (10). The results of this study provide additional evidence for a strong association between SSB consumption and $\delta^{13}C$ values. Importantly, our analyses demonstrate that serum $\delta^{13}C$ values are dynamic, can reflect changes in SSB consumption over time, and are sensitive to relatively minor, but sustained, changes in dietary patterns.

Consumption of SSBs is associated with excess weight gain and obesity (18–20), increased risk of diabetes (19,21,22), elevated plasma TG concentrations (23,24), increased blood pressure (14,25–27), and increased risk of cardiovascular diseases (27,28). Small reductions in SSB consumption can positively influence health (14). However, our ability to accurately and objectively measure small changes in SSB consumption is compromised by measurement error in self-reported dietary assessment methods (e.g., reliance on only 1 24-h recall measurement and FFQs to measure SSB intake) and systematic bias due to underreporting of SSB intake among certain subgroups (3,4,21,29,30). These issues in SSB intake assessment can be resolved by using a biomarker that can objectively measure caloric sweeteners consumption and can accurately quantify and evaluate intervention-associated changes.

TABLE 2 Association of $\delta^{13}C$ with SSB consumption in the PREMIER $\delta^{13}C$ study population[1]

Predictors	Crude		Model 1[2]		Model 2[3]	
	Coefficients (95% CI)	*P*	Coefficients (95% CI)	*P*	Coefficients (95% CI)	*P*
SSB[4] per 12 fl oz/d	0.17 (0.08, 0.25)	<0.0001	0.20 (0.08, 0.31)	0.001	0.12 (0.01, 0.22)	0.025
Total calories per 1000 kcal			−0.15 (−0.32, 0.03)	0.11	−0.14 (−0.32, 0.03)	0.11
Corn consumption			0.07 (−0.08, 0.23)	0.36	0.06 (−0.09, 0.21)	0.43
$\delta^{15}N$ (‰)			0.45 (0.15, 0.74)	0.003	0.45 (0.19, 0.70)	0.001
Age (y)					−0.01 (−0.02, 0.00)	0.021
Sex					−0.11 (−0.33, 0.10)	0.30
Race					−0.45 (−0.65, −0.25)	<0.0001

[1] *n* = 140. All models were adjusted for visit (baseline, 6 mo, and 18 mo). SSB, sugar-sweetened beverage; $\delta^{13}C$, ^{13}C-to-^{12}C serum carbon isotope ratio; $\delta^{15}N$, ^{15}N-to-^{14}N nitrogen stable isotope ratio.
[2] Analyses were adjusted for total energy calories, corn consumption, and $\delta^{15}N$ values.
[3] Analyses were additionally adjusted for age, sex, and race.
[4] The regression coefficient for SSB is interpreted as the mean change in $\delta^{13}C$ values with every 12-oz increase in SSB consumption across the population, taking into account the correlation of repeated measurements.

Given the previously detected relation between animal protein and $\delta^{13}C$, we treat animal protein as a potential confounder in our examination of the relation between SSBs and $\delta^{13}C$. We are limited in our ability to determine causation, but our results remained unchanged after adjustment for this important confounder.

A limitation of our study is that the PREMIER study was not designed or powered for repeated-measure analysis of $\delta^{13}C$ value. However, dietary intake of SSBs was well characterized in the PREMIER study, which was essential for our evaluation of the time course of change of serum $\delta^{13}C$ value. A limitation of serum $\delta^{13}C$ as a biomarker of caloric sweeteners consumption is that it can only capture consumption of corn and sugar-based sweeteners but no other forms of sugar, such as beet sugar (beet is a C3 plant).

In conclusion, we show that a measurable change in serum carbon isotope value can be detected months after dietary change in SSBs occurs. This study does not allow us to understand what timeframe of dietary intake influences $\delta^{13}C$ values. Using serum $\delta^{13}C$ as a surrogate for caloric sweeteners consumption is promising; however, future better-powered studies with more granular time-course analyses are needed to ascertain the specificity of $\delta^{13}C$ values to intake of caloric sweeteners. If our results are validated, the use of this biomarker will prove to be an invaluable tool in objectively quantifying caloric sweeteners consumption and in evaluating intervention-associated changes in SSB intake.

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