


ORIGINAL RESEARCH

# Effects of Sugar-Sweetened, Artificially Sweetened, and Unsweetened Beverages on Cardiometabolic Risk Factors, Body Composition, and Sweet Taste Preference: A Randomized Controlled Trial

Cara B. Ebbeling , PhD; Henry A. Feldman, PhD; Sarah K. Steltz, MPH; Nicolle L. Quinn, MS, RD; Lisa M. Robinson, MPH, RD; David S. Ludwig, MD, PhD

**BACKGROUND:** A 2018 American Heart Association science advisory indicated that, pending further research, artificially sweetened beverages (ASBs) may be an appropriate initial replacement for sugar-sweetened beverages (SSBs) during transition to unsweetened beverages (USBs).

**METHODS AND RESULTS:** We randomly assigned 203 adults (121 males, 82 females; 91.6% retention), who habitually consumed SSBs, to 3 groups and delivered free SSBs, ASBs, or USBs to their homes for 12 months. Outcomes included serum triglyceride to high-density lipoprotein cholesterol ratio (primary), body weight, and sweet taste preference (experimental assessment, 0%–18% sucrose solutions). Change in serum triglyceride to high-density lipoprotein cholesterol ratio was not different between groups. Although overall change in weight also was not different between groups, we found effect modification ( $P=0.006$ ) by central adiposity. Among participants in the highest tertile of baseline trunk fat but not other tertiles, weight gain was greater ( $P=0.002$ ) for the SSB ( $4.4\pm 1.0$  kg, estimate $\pm$ SE) compared with ASB ( $0.5\pm 0.9$  kg) or USB ( $-0.2\pm 0.9$  kg) group. Both sweetness threshold ( $-1.0\pm 0.2\%$  m/v;  $P=0.005$ ) and favorite concentration ( $-2.3\pm 0.4\%$  m/v;  $P<0.0001$ ) decreased in the USB group; neither changed in the SSB group. In the ASB group, sweetness threshold did not change, and favorite concentration decreased ( $-1.1\pm 0.5\%$  m/v;  $P=0.02$ ). Pairwise comparison between the ASB and USB groups indicated a difference in sweetness threshold ( $P=0.015$ ).

**CONCLUSIONS:** Replacing SSBs with noncaloric beverages for 12 months did not affect serum triglyceride to high-density lipoprotein cholesterol ratio. Among individuals with central adiposity, replacing SSBs with either ASBs or USBs lowered body weight. However, USBs may have the most favorable effect on sweet taste preference.

**REGISTRATION:** URL: <https://www.clinicaltrials.gov>; unique identifier: NCT01295671.

**Key Words:** beverages ■ body weight ■ diet ■ dyslipidemia ■ sweet taste preference

**W**ith increasing awareness of the adverse health outcomes of consuming added sugars,<sup>1,2</sup> particularly sugar-sweetened beverages (SSBs),<sup>3</sup> much attention has been directed toward the effects of replacing SSBs with noncaloric options. The *Dietary*

*Guidelines for Americans 2015–2020* emphasizes the importance of drinking unsweetened beverages (USBs), most notably plain water.<sup>4</sup> Pending further research, a science advisory from the American Heart Association indicated that artificially sweetened beverages (ASBs)

Correspondence to: Cara B. Ebbeling, PhD, 300 Longwood Avenue, BCH 3179, Boston, MA 02115. E-mail: [cara.ebbeling@childrens.harvard.edu](mailto:cara.ebbeling@childrens.harvard.edu)

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## CLINICAL PERSPECTIVE

### What Is New?

- In this 12-month intervention study, replacing sugar-sweetened beverages (SSBs) with artificially sweetened beverages (ASBs) or unsweetened beverages (USBs) had no effect on cardiometabolic risk factors.
- In a subgroup analysis, individuals with fat around the midsection lost more weight with replacement of SSBs by either ASBs or USBs, and sweet taste preference decreased more when SSBs were replaced with USBs compared with ASBs.
- The null findings for cardiometabolic risk factors may relate to compensatory changes in other dietary sources of refined carbohydrate; in comparison with randomized controlled trials, the positive associations in observational studies typically include statistical control for carbohydrate source and other measures of dietary quality.

### What Are the Clinical Implications?

- Overall dietary quality should be considered in interventions involving SSBs to reduce risk for cardiometabolic disease.
- Consistent with American Heart Association recommendations, substitution of SSBs with ASBs or USBs may help to control body weight in susceptible individuals (eg, those with central adiposity).
- As replacements for SSBs, USBs decrease sweet taste preference more compared with ASBs, an effect that may have implications for promoting adherence to low-sugar diets.

## Nonstandard Abbreviations and Acronyms

<b>ASB</b>	artificially sweetened beverage
<b>HDL-C</b>	high-density lipoprotein cholesterol
<b>RCT</b>	randomized controlled trial
<b>SSB</b>	sugar-sweetened beverage
<b>TG</b>	triglyceride
<b>USB</b>	unsweetened beverage

may be an appropriate initial replacement for SSBs in adults who are habitual consumers, have a strong sweet taste preference, and consider USBs an undesirable alternative.<sup>5</sup>

Data are limited regarding the effects of consuming ASBs compared with USBs as replacements for SSBs. Randomized controlled trials (RCTs) of beverage interventions have compared consumption of

SSBs versus a combination of ASBs and USBs,<sup>6,7</sup> only ASBs,<sup>8–10</sup> and either ASBs or USBs in just 1 study,<sup>11,12</sup> with results showing a beneficial effect of various noncaloric beverages on body weight. Prospective observational studies of ASB consumption have yielded mixed results, with some indicating negative associations with weight gain,<sup>13–15</sup> consistent with the cited RCTs,<sup>6–10,12</sup> and others indicating positive associations with weight gain,<sup>16,17</sup> dyslipidemia,<sup>18,19</sup> metabolic syndrome,<sup>18,20,21</sup> type 2 diabetes mellitus,<sup>22–25</sup> and cardiovascular disease.<sup>26–29</sup> These positive associations, if causal, may relate to the metabolic effects of the synthetic sweeteners in ASBs (eg, acesulfame potassium, aspartame, and sucralose) that potentially activate chemoreceptors for sweet taste at very low concentrations.<sup>30</sup> Of special concern is the possibility that the high-intensity sweetness of ASBs may increase the preference for sweet foods, in a manner similar to SSBs, with implications for long-term food choices and dietary quality.<sup>31–33</sup>

The aim of this RCT was to compare effects of consuming SSBs, ASBs, and USBs in adults who habitually consumed SSBs. We hypothesized that, as replacements for SSBs, USBs versus ASBs would produce greater reductions in cardiometabolic risk factors, body weight and adiposity, and sweet taste preference. We also explored whether replacing SSBs with ASBs or USBs would be especially beneficial for individuals with high trunk fat mass, in view of the relationship between central adiposity and insulin secretion.<sup>34</sup>

## METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

### Study Design

We randomly assigned participants to 3 groups (SSB, ASB, USB) for 12 months. The randomization was stratified by sex, ethnicity/race (non-Hispanic white versus other), and baseline body mass index (normal weight, 18.5–24.9; overweight, 25–29.9; obese, ≥30). Following randomization, participants received a 12-month intervention to promote consumption of beverages consistent with group assignment. Study outcomes were assessed at baseline and 12 months. The institutional review board at Boston Children's Hospital approved the study protocol. Participants provided written informed consent. The study was conducted at Boston Children's Hospital between February 2011 and November 2015. The protocol history, documented in institutional review board

amendments, with no change in the primary outcome, is presented in Table S1.

### Participants

We screened adults aged 18 to 40 years who reported consuming at least 1 serving (12 fl oz) per day of SSBs and had a body mass index ranging from 18.5 to 40.0 kg/m<sup>2</sup>. Exclusion criteria included fasting blood glucose ≥110 mg/dL, physician diagnosis of a major medical or psychiatric illness, chronic use of any medication that could affect ≥1 study outcomes, and heavy smoking (>10 cigarettes/d). Additional exclusion criteria for females included: pregnancy (preceding 12 months) or plans to become pregnant during the study period, lactation (preceding 3 months), and change in hormonal contraceptives (preceding 3 months). Before baseline assessments, we obtained medical clearance from a primary care provider. Demographic information based on participant self-report included: sex, date of birth, ethnicity (Hispanic or non-Hispanic), race (white, black, Asian, multiple, or other), and total annual household income. We provided monetary incentive upon completion of assessments at baseline (\$25) and 12 months (\$275).

### Interventions

The interventions comprised home deliveries of free beverages, specific messages pertaining to beverage consumption, and check-in telephone calls. We asked each participant to select a desired beverage combination, consistent with group assignment, from a menu of options and ordered the desired combination from an online delivery service affiliated with a supermarket chain (Peapod, Stop & Shop, Quincy, MA). Unsweetened beverages included spring water, purified water, and sparkling water (with or without flavoring). Beverages were ordered at a frequency to ensure continuous availability, such that delivered beverages could be replacements for the SSBs consumed at baseline, as determined using a beverage frequency questionnaire adapted from a validated instrument.<sup>35</sup> The intervention messages presented in Table 1 were

conveyed to study participants in writing and during biweekly check-in telephone calls. Core messages regarding consumption of delivered beverages were consistent across groups. Group-specific messages provided instructions on which beverages to avoid. During the check-in telephone calls, we reviewed beverage consumption, reiterated intervention messages, and encouraged compliance with intervention protocols. Discussions focused exclusively on beverage consumption, with no attention to other dietary behaviors. The target duration of each call was 10 minutes.

### Intervention Fidelity

Procedures to maintain intervention fidelity included group-specific scripts for reiterating intervention messages, obtaining beverage orders, and negotiating delivery times; systems for cross-checking beverage orders with supermarket receipts; guides to provide structure for check-in calls, with adequate flexibility for addressing situations unique to each participant; protocols for documenting each check-in call; and regular study team meetings to discuss strategies for promoting adherence without compromising differentiation among groups. We also digitally recorded check-in calls for periodic review.

### Process Evaluation

Implementation of the beverage interventions was evaluated based on numbers of completed beverage deliveries and check-in calls. Three unannounced telephone interviews (2 weekdays, 1 weekend day) were conducted at baseline and again at 12 months to assess dietary intake and physical activity for the day preceding each call. The interviewer was masked to group assignment. Dietary data were collected using the Nutrition Data System for Research software versions 2010–2014, and final data were generated with version 2015 (Nutrition Coordinating Center, University of Minnesota, Minneapolis). Healthy Eating Index 2015 scores (total and subcomponent) were calculated according to a standardized protocol<sup>36</sup> using Nutrition Data System for Research

**Table 1. Intervention Messages**

Core Messages (For All Groups)	Group-Specific Messages
<ul style="list-style-type: none"> <li>• Drink the beverages delivered to your home.</li> <li>• The delivered beverages are a <i>replacement</i> for the sugar-sweetened beverages that you usually drink. Please drink these beverages in place of the ones that you would have purchased prior to enrolling in the research study.*</li> <li>• Drink the delivered beverages at the same rate (number of servings per day) that you were consuming sugar-sweetened beverages prior to enrolling in the research study.</li> <li>• Do not share the delivered beverages.</li> </ul>	SSB Group
	ASB Group
	USB Group

ASB indicates artificially sweetened beverage; SSB, sugar-sweetened beverage; and USB, unsweetened beverage.

\*To establish an individualized point of reference for the target number of delivered beverages to be consumed daily, we assessed baseline intake of SSBs using a beverage frequency questionnaire adapted from a validated instrument.<sup>35</sup>

output and code from the Nutrition Coordinating Center. Physical activity data were collected, and daily metabolic equivalent was calculated as previously described.<sup>34</sup>

## Outcomes

Study outcomes were measured during 2 visits at each time point (baseline, 12 months), following a 12-hour overnight fast. Personnel who assessed study outcomes were masked to group assignment. A secure web-based application (Research Electronic Data Capture),<sup>37</sup> hosted at Boston Children's Hospital, was used for data management.

The prespecified primary outcome was ratio of serum triglyceride (TG) to high-density lipoprotein cholesterol (HDL-C) concentration (TG:HDL-C). Reducing refined sources of dietary carbohydrate, including sugar, has been shown to decrease TG and increase HDL-C,<sup>34,38,39</sup> possibly mediated by attenuated postprandial insulinemia.<sup>40</sup> A lipid profile characterized by hypertriglyceridemia and low HDL-C correlates with insulin resistance<sup>41</sup> and is a component of the metabolic syndrome.<sup>42</sup> Previous studies indicate that the TG:HDL-C is an independent predictor of coronary atherosclerosis,<sup>43</sup> risk of myocardial infarction,<sup>44</sup> and cardiovascular events and all-cause mortality.<sup>45</sup> Other prespecified outcomes included blood levels of low-density lipoprotein cholesterol (direct determination by enzymatic spectrophotometric assay), high-sensitivity C-reactive protein, fibrinogen, uric acid, alanine aminotransferase, glucose, and insulin. Insulin sensitivity and  $\beta$ -cell function, expressed as percentages of values for a normal reference population, were evaluated by homeostasis model assessment using glucose and insulin data.<sup>46</sup> All biochemical analyses were done in facilities certified by the Clinical Laboratory Improvement Amendments. Resting blood pressure was measured by auscultation.<sup>47</sup>

Body weight and height were measured using an electronic scale and a wall-mounted stadiometer. Whole-body fat mass (henceforth referred to as *fat mass*) and trunk fat mass (henceforth referred to as *trunk fat*) were assessed by dual-energy X-ray absorptiometry (Discovery A, Hologic, Inc., Bedford, MA). According to our original proposal, insulin secretion was specified as an effect modifier; however, because of scheduling challenges and the need to streamline study visits, we did not measure insulin secretion. In a previous study,<sup>34</sup> we measured insulin concentration 30 minutes after a 75-g dose of oral glucose (insulin-30), as a proxy measure of insulin secretion, and noted a significant association between trunk fat and log insulin-30 (C.B. Ebbeling, H.A. Feldman, and D.S. Ludwig, unpublished data, 2007: N=97; Pearson

$r=0.46$ ;  $P<0.0001$ ).<sup>48</sup> Based on this relationship, we conducted exploratory analyses to evaluate effect modification by trunk fat when comparing effects of consuming SSBs, ASBs, or USBs on body weight and fat mass. These analyses are consistent with the American Heart Association science advisory, which notes that replacing SSBs with noncaloric options may be particularly beneficial for weight control among individuals with central adiposity due to high levels of visceral fat.<sup>5</sup>

We evaluated sweet taste preference using 10 samples of solutions ranging in sucrose concentration (%m/v) from 0% to 18%. The samples were made using distilled water, flavored with lemon juice, and served at 4°C. On the morning of the taste testing protocol, personnel in the clinical research center at Boston Children's Hospital prepared and served a standard breakfast (Table S2). Ninety minutes after breakfast, we instructed participants to sip, taste, swallow, and rate the sweetness of each sample in order of increasing sucrose concentration. Sweetness ratings were obtained using a 10-cm visual analog scale, with verbal anchors at 0 (not at all sweet) and 10 (extremely sweet). Participants consumed a small cracker and sip of water after rating each solution. At the end of the protocol, participants tasted all of the samples again and selected 1 as an overall favorite concentration.

## Adverse Events

An adverse event was defined as any symptom or safety concern requiring medical attention, as reported by a participant.

## Statistical Analysis

Baseline characteristics and process data were compared across the three study groups by 1-way ANOVA for continuous measures and Fisher's exact test for discrete variables. Longitudinal analysis of anthropometric, dietary, and biochemical measures was conducted by repeated-measures ANOVA. The independent variables were study group and visit (baseline or 12 months), with an interaction term to test for differential change across groups. All models were adjusted for sex, ethnicity, race, and baseline age. A compound-symmetric covariance structure was employed for the repeated-measures model, chosen over alternatives that either failed to account for within-participant correlation (independence), were equivalent to compound symmetry in this 2-point design (autoregressive, Toeplitz, spatial power), or required additional parameters unjustified by evidence of nonuniform variance (heterogeneous, unstructured). From parameters of the fitted model, we calculated covariate-adjusted mean changes



for each group, with standard error. The mean changes were compared within group to 0 by t test (mean $\pm$ standard error), and across groups by the F-test for interaction.

Variables displaying a sharply skewed distribution were log-transformed for analysis. For descriptive purposes, in place of the unadjusted mean and standard deviation, we retransformed the mean and quartile boundaries of the log-transformed distribution and reported them as median and interquartile range. The covariate-adjusted mean changes and standard errors from analysis of log-transformed variables ( $\Delta\pm$ SE) were retransformed for reporting as percentages ( $100\%\times\exp(\Delta)\pm 100\%\times\exp(\Delta)\times(\exp(\text{SE})-1)$ ).

To investigate effect modification, we employed analysis of variance with 12-month change as the dependent variable. The independent variables were study group and the value of the effect modifier at baseline, expressed as tertiles (irrespective of study group), with an interaction term to test whether the group differences varied by tertile. The model was adjusted for sex, ethnicity, race, and baseline age.

To characterize sweet taste preference at each time point, we used nonlinear regression analysis to fit a sigmoid curve to each participant's ratings of the 10 sucrose solutions, and calculated sweetness threshold as the concentration corresponding to 5 cm on the 10-cm visual analog scale (Figure S1). We calculated each participant's 12-month change for this parameter and the designated favorite concentration, and then compared the mean changes across study groups. To minimize the influence of extreme values, we applied robust (outlier-resistant) regression,<sup>39</sup> an iterative procedure by which data points with greater deviation from the fitted mean are given lower weight on subsequent iterations. Among the available variants of this procedure, we employed M-estimation, most suitable for a discrete independent variable; the quasi-triangular bisquare weighting function; and a modified Wald test for comparing study groups. We repeated the analysis with adjustment for sex, ethnicity, race, and baseline age, and corroborated the results with the nonparametric Kruskal–Wallis test.

We used SAS software (version 9.4, SAS Institute, Cary, NC) for all computations and specified  $P<0.05$  as indicating statistical significance. In cases where the hypothesis of 3 equal groups was rejected, the principle of closed testing allowed us to conduct pairwise comparisons between groups using  $P<0.05$  as critical value while preserving the family-wise type I error rate of 5% per outcome variable.<sup>49</sup> We applied the 5% family-wise type I error rate to each study outcome independently, without adjustment for multiple comparisons, following the rationale of Glantz and Slinker.<sup>50</sup> When designing the RCT, we specified a sample size of 270 participants to detect, with 80%

power, a mean difference for change in TG:HDL-C between groups as small as 24%, based on associations observed in the Framingham Heart Study (and a magnitude of effect deemed to have clear clinical implications).<sup>18</sup>

Drs Ebbeling, Feldman, and Ludwig had full access to all the data and take responsibility for its integrity and data analysis.

## RESULTS

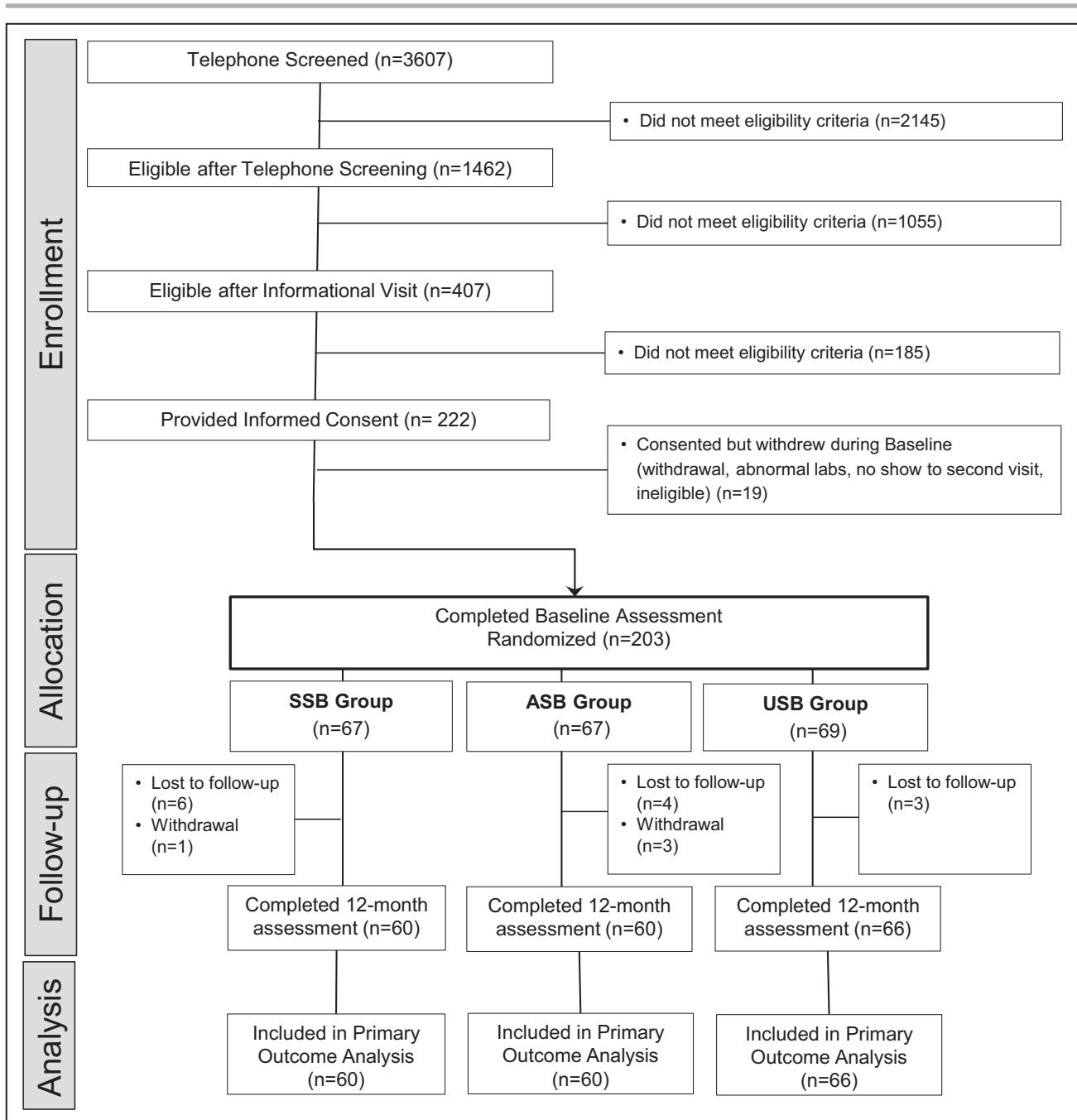
### Participants

We randomly assigned 203 participants (121 males and 82 females) to an intervention group (Figure 1). The overall retention rate at 12 months was 91.6%. The 17 dropouts were uniformly distributed among study groups (7/67 SSB group, 7/67 ASB group, 3/69 USB group;  $P=0.32$ ). Dropouts did not differ significantly from the 186 completers with respect to the baseline characteristics shown in Table 2, with minor exceptions. Compared with completers, dropouts more often declined to report household income (11/17 versus 39/186;  $P<0.001$ ) or education (9/17 versus 7/186;  $P<0.001$ ), but these discrepancies did not vary significantly across study groups. Dropouts were on average slightly younger than completers (24.2 $\pm$ 4.7 versus 27.1 $\pm$ 5.7 years, mean $\pm$ SD;  $P=0.04$ ), but this difference likewise did not vary significantly across study groups. All parametric analyses were adjusted for age, further obviating any selection bias from this source.

### Process Data

Intervention intensity did not differ among groups (Table S3). Participants retained in the study ( $N=186$ ) received 7.4 $\pm$ 4.1 beverage deliveries and completed 19.2 $\pm$ 4.5 of 24 planned check-in calls (mean $\pm$ SD).

Changes in dietary intake are presented in Table 3. Daily consumption of SSBs increased by 1 serving in the SSB group ( $P<0.001$ ) and declined to almost 0 in the ASB and USB groups ( $P<0.001$ ). Reflecting these changes, consumption of added sugars and energy from SSBs increased in the SSB group ( $P=0.002$  for added sugars;  $P<0.001$  for energy from SSB) and declined in the ASB and USB groups ( $P<0.001$ ). Consumption of ASBs increased by 1.5 servings (12 fl oz/serving) in the ASB group ( $P<0.001$ ) and did not change in the SSB and USB groups. At 12 months, participants in the ASB group consumed (mean $\pm$ SD) 185.2 $\pm$ 202.1 mg/day of aspartame, 268.35 $\pm$ 559.89 mg/day of sucralose, and negligible amounts of other artificial sweeteners (including acesulfame potassium and saccharine). Consumption of USBs increased for the USB group ( $P<0.001$ ) and remained constant for the SSB and ASB groups.



**Figure 1. Participant flow.**

ASB indicates artificially sweetened beverage; SSB, sugar-sweetened beverage; and USB, unsweetened beverage.

Changes in Healthy Eating Index total score and subcomponent scores are presented in Table S4. Change in Healthy Eating Index total score did not differ between groups ( $P=0.14$ ) but improved in the USB group ( $P=0.03$ ) on the basis of exploratory within-group analyses. Changes in the added sugars score differed between groups ( $P<0.001$ ), consistent with data presented in Table 3. The between-group effect for the refined grains score was of borderline significance ( $P=0.06$ ), attributable to decreased consumption in the

SSB group ( $P=0.05$ ) and no change in the ASB and USB groups.

### Study Outcomes

Blood lipids, homeostasis model assessment variables, and body weight and fat mass are presented in Table 4. Change in TG:HDL-C from baseline to 12 months, the prespecified primary outcome, was not significantly different between groups ( $P=0.65$ ). Likewise, changes in homeostasis model assessment

**Table 2. Baseline Characteristics of Study Participants by Beverage Group**

	Beverage Group		
	SSB	ASB	USB
N	67	67	69
Categorical variables*	N (%)		
Sex			
Male	40 (59.7)	40 (59.7)	41 (59.4)
Female	27 (40.3)	27 (40.3)	28 (40.6)
Ethnicity†			
Hispanic	10 (14.9)	7 (10.4)	8 (11.6)
Race†			
White	38 (56.7)	33 (49.3)	32 (46.4)
Black	14 (20.9)	15 (22.4)	11 (15.9)
Asian	6 (9.0)	6 (9.0)	14 (20.3)
Multiple/unknown/other	9 (13.4)	13 (19.4)	12 (17.4)
Annual household income			
<\$30 000	13 (19.4)	19 (28.4)	20 (29.0)
\$30 000–\$59 999	18 (26.9)	16 (23.9)	12 (17.4)
\$60 000–\$89 999	8 (11.9)	9 (13.4)	7 (10.1)
≥\$90 000	10 (14.9)	5 (7.5)	16 (23.2)
Not reported/unknown	18 (26.9)	18 (26.9)	14 (20.3)
Education			
Some high school	1 (1.5)	0 (0.0)	3 (4.4)
High school or GED	5 (7.5)	5 (7.5)	4 (5.8)
Some college or vocational school	17 (25.4)	20 (29.9)	14 (20.3)
Associate's degree	4 (6.0)	4 (6.0)	3 (4.4)
Bachelor's degree	19 (28.4)	19 (28.4)	20 (29.0)
Some graduate school or degree	16 (23.9)	14 (20.9)	19 (27.5)
Not reported/unknown	5 (7.5)	5 (7.5)	6 (8.7)
Continuous variables	Mean±SD		
Age, y	25.9±5.1	26.7±5.7	27.9±6.0
Weight, kg	75.5±15.6	76.8±16.7	77.5±16.1
Height, cm	170.8±9.2	171.3±9.6	170.3±10.5
Body mass index, kg/m <sup>2</sup>	25.8±4.7	26.1±5.2	26.6±4.6

ASB indicates artificially sweetened beverage; GED, General Educational Development; SSB, sugar-sweetened beverage; and USB, unsweetened beverage.

\*Percentages may not sum to 100 because of rounding.

†Ethnicity and race reported by participants.

variables (insulin sensitivity,  $P=0.38$ ;  $\beta$ -cell function,  $P=0.49$ ), body weight ( $P=0.66$ ), fat mass ( $P=0.27$ ), and other outcomes (Table S5) did not differ significantly between groups. We observed mean ( $\pm$ SE) differences for change in TG:HDL-C of  $-5.4\%\pm 7.5$  for the ASB versus SSB group and  $-6.2\%\pm 7.2$  for the USB versus SSB group. We had only 8% power to detect a group effect of this magnitude with the attained sample size, which was smaller than proposed because of recruitment challenges. Nevertheless, enrollment of

additional participants to attain the proposed sample size would not have substantially enhanced power to detect such small differences.

To explore individual differences in response according to central adiposity, we divided the cohort into tertiles of baseline trunk fat. As shown in Figure 2 (and Table S6), trunk fat was a significant effect modifier (group $\times$ time $\times$ trunk fat tertile) for change in body weight ( $P=0.006$ ) and fat mass ( $P=0.004$ ). Among participants with the most trunk fat (tertile 3), body weight and fat mass increased significantly more in the SSB group compared with the other 2 groups ( $P=0.002$ ). There were no discernible group effects for these outcomes among participants in the lower tertiles of trunk fat.

Changes in sweet taste preference are shown in Figure 3. Comparison across the 3 beverage groups by robust regression analysis showed a significant difference in the mean change for both sweetness threshold ( $P=0.008$ ) and favorite concentration ( $P=0.006$ ). Sweetness threshold did not change discernibly in the SSB or ASB group but decreased significantly in the USB group ( $P=0.001$ ), with pairwise comparison indicating a significant difference between the ASB and USB groups ( $P=0.015$ ). Similarly, favorite concentration did not change discernibly in the SSB group but decreased significantly in the USB group ( $P<0.0001$ ) and ASB group ( $P=0.02$ ), with the difference between the ASB and USB groups of borderline statistical significance ( $P=0.06$ ). Adjustment for covariates left the between-group difference significant for both measures ( $P=0.01$  and  $P=0.003$ , respectively). The nonparametric Kruskal–Wallis test confirmed the group differences in distribution ( $P=0.03$  for sweetness threshold;  $P=0.009$  for favorite concentration; Table S7).

## Adverse Events

Three adverse events were documented during the study (hospitalization for body aches; hospitalization for asthma; headache and mood swings attributable to a toothache). Each of these events was deemed unrelated to participation in the RCT.

## DISCUSSION

Our study aimed to address a major controversy of relevance to dietary guidelines for the public: Are artificially sweetened beverages equivalent to unsweetened beverages as replacements for sugar-sweetened beverages? To address this controversy, we conducted an RCT of well-differentiated interventions, controlling for intervention intensity. We found no overall group differences for changes in TG:HDL-C and other prespecified cardiometabolic risk factors.

**Table 3. Self-Reported Dietary Intake and Physical Activity**

Variable	Study Group	Unadjusted Data				Adjusted Data*		
		Baseline		12 mo		Mean Change±SE	P Within Group	P Between Groups
		N	Mean±SD	N†	Mean±SD			
Beverages (12 fl oz/serving)								
SSBs, servings/d	SSB	67	1.4±1.1	60	2.5±1.8	1.0±0.2	<0.001	<0.001
	ASB	67	1.5±1.4	60	0.1±0.3	-1.4±0.2	<0.001	
	USB	69	1.8±1.3	65	0.2±0.5	-1.6±0.2	<0.001	
ASBs, servings/d	SSB	67	0.2±0.4	60	0.1±0.2	-0.2±0.1	0.17	<0.001
	ASB	67	0.1±0.3	60	1.6±1.4	1.5±0.1	<0.001	
	USB	69	0.2±0.7	65	0.0±0.3	-0.2±0.1	0.14	
USBs, servings/d	SSB	67	1.6±1.5	60	1.6±1.5	-0.0±0.3	0.92	<0.001
	ASB	67	1.8±1.6	60	1.9±1.9	0.1±0.3	0.70	
	USB	69	2.1±1.6	65	4.3±2.1	2.2±0.3	<0.001	
Sugar								
Total, g/d	SSB	67	115.8±50.7	60	139.0±64.2	23.7±7.4	0.002	<0.001
	ASB	67	122.4±57.9	60	63.6±37.0	-57.6±7.4	<0.001	
	USB	69	123.2±57.0	65	62.8±34.6	-60.3±7.1	<0.001	
Added, g/d	SSB	67	75.7±44.0	60	98.5±61.7	23.2±7.4	0.002	<0.001
	ASB	67	80.9±51.5	60	34.1±28.4	-46.6±7.4	<0.001	
	USB	69	86.2±47.3	65	30.0±23.1	-56.1±7.2	<0.001	
Energy								
Total, kcal/d	SSB	67	2053±638	60	2207±577	130±79	0.10	<0.001
	ASB	67	2225±676	60	1894±576	-312±79	<0.001	
	USB	69	2113±689	65	1874±591	-247±76	0.002	
From SSBs, kcal/d	SSB	67	202±167	60	338±256	138±25	<0.001	<0.001
	ASB	67	207±190	60	21±43	-186±25	<0.001	
	USB	69	242±164	65	9±31	-232±24	<0.001	
Physical activity								
Total physical activity (MET)	SSB	67	1.58±0.19	60	1.59±0.21	0.01±0.03	0.68	0.90
	ASB	67	1.64±0.21	60	1.65±0.26	0.01±0.03	0.80	
	USB	69	1.56±0.19	65	1.58±0.24	0.03±0.03	0.37	

ASB indicates artificially sweetened beverage; MET, metabolic equivalent; SSB, sugar-sweetened beverage; and USB, unsweetened beverage.

\*Data analyzed using repeated measures analysis of variance, adjusted for covariates (sex, ethnicity, race, age).

†Dietary recall data missing for one participant in USB group, who could not be reached for telephone interviews at 12 months.

Although body weight and fat mass also did not differ among groups, baseline trunk fat was a significant effect modifier for these outcomes. As such, among individuals with central adiposity, replacing SSBs with either ASBs or USBs had a favorable effect on body weight and fat mass. Overall, USBs were a better replacement than ASBs for decreasing sweet taste preference. Length of the intervention period, level of beverage exposure, and individual susceptibility warrant careful consideration when comparing results to data from prospective observational studies<sup>25,29,51,52</sup> and previous RCTs.<sup>6,7,11,12,34,53-55</sup>

The benefits of replacing consumption of SSBs with ASBs or USBs on cardiometabolic risk factors may require longer periods of study for the general population. In prospective observational

studies, significant associations between SSB or ASB consumption and mortality have been observed in several cohorts over long-term follow-up periods.<sup>25,29,51,52</sup> For example, SSB consumption was positively associated with all-cause and cardiovascular disease mortality in the Health Professionals' Follow-up Study (28 years of follow-up) and Nurses' Health Study (34 years of follow-up), with mortality increasing by 10% with each additional daily serving of SSB.<sup>51</sup> In addition, ASB consumption was associated with all-cause and cardiovascular disease mortality in the Nurses' Health study among women who were consuming at least 4 servings per day.<sup>51</sup> Statistical models of beverage substitutions in the Women's Health Initiative (mean follow-up of 8.4 years)<sup>25</sup> and European Prospective Investigation into Cancer and



**Table 4. Blood Lipids, Homeostasis Model Assessment Variables, and Body Weight and Fat Mass**

Variable*	Study Group	Unadjusted Data				Adjusted Data <sup>§</sup>		
		Baseline		12 mo		Mean Change±SE	P Within Group	P Between Groups
		N <sup>†</sup>	Mean±SD Median (IQR) <sup>‡</sup>	N <sup>†</sup>	Mean±SD or Median (IQR) <sup>‡</sup>			
Blood lipids								
TG:HDL-C (primary outcome)*	SSB	67	1.37 (0.87–2.16)	60	1.46 (0.98–2.19)	3.2±5.7	0.56	0.65
	ASB	67	1.30 (0.78–1.98)	60	1.19 (0.86–1.87)	−2.4±5.4	0.65	
	USB	69	1.51 (1.08–2.51)	66	1.45 (0.99–2.31)	−3.2±5.1	0.52	
LDL-C, mg/dL	SSB	67	99.6±26.8	60	102.5±30.5	1.2±2.6	0.65	0.67
	ASB	67	101.5±28.0	60	104.0±30.2	1.7±2.6	0.51	
	USB	69	109.9±33.3	66	109.1±29.4	−1.3±2.5	0.61	
Homeostasis Model Assessment								
Insulin sensitivity, %*	SSB	67	89.1 (69.9–161.5)	60	84.3 (59.3–143.0)	−7.5±6.1	0.22	0.38
	ASB	66	81.8 (58.7–125.0)	60	87.5 (60.4–148.8)	4.9±6.9	0.46	
	USB	69	85.2 (55.8–122.9)	65	87.4 (57.5–126.5)	−0.6±6.3	0.93	
β-cell function, %*	SSB	67	120.6 (89.7–141.9)	60	127.6 (88.4–153.8)	0.7±4.2	0.86	0.49
	ASB	66	126.3 (98.6–155.8)	60	122.1 (90.9–147.5)	−5.7±4.0	0.15	
	USB	69	122.3 (99.2–163.9)	65	117.7 (96.4–154.1)	−4.3±3.9	0.27	
Body weight and fat mass								
Weight, kg	SSB	67	75.5±15.6	60	78.0±17.4	1.2±0.6	0.03	0.66
	ASB	67	76.8±16.7	60	77.0±17.1	0.6±0.6	0.32	
	USB	69	77.5±16.1	66	78.3±17.1	0.7±0.5	0.22	
Whole-body fat mass, kg	SSB	64	22.0±9.6	44	24.2±11.1	1.0±0.5	0.03	0.27
	ASB	65	22.5±9.8	44	22.8±10.2	0.1±0.5	0.81	
	USB	66	24.0±8.8	52	23.5±8.2	0.1±0.4	0.81	

ASB indicates artificially sweetened beverage; LDL-C, low-density lipoprotein cholesterol; SSB, sugar-sweetened beverage; TG:HDL-C, triglyceride to high-density lipoprotein cholesterol ratio; and USB, unsweetened beverage.

\*TG:HDL-C and homeostasis model assessment log-transformed for analysis, results retransformed for reporting as described below.

<sup>†</sup>Missing data: Homeostasis model assessment missing for 1 participant in ASB group at baseline (missing glucose) and 1 participant in USB group at 12 months (missing insulin); dual-energy x-ray absorptiometry whole body fat mass missing for 8 participants at baseline (including 1 dropout in SSB group) and 44 participants at 12 months (scanned on a replacement scanner that was not adequately calibrated with the original scanner); 2 additional participants did not complete the dual-energy x-ray absorptiometry scan at 12 months (1 in SSB group, 1 in USB group).

<sup>‡</sup>Unadjusted mean±standard deviation; in the case of variables log-transformed for analysis, median and interquartile range (25th, 75th percentiles).

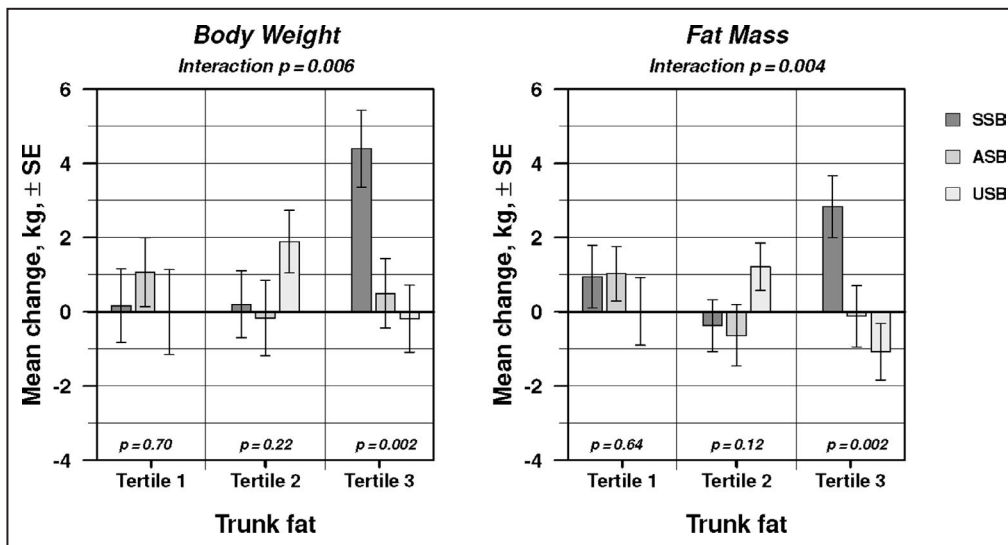
<sup>§</sup>Mean change±standard error and *P*-values, from repeated-measures analysis of variance, adjusted for prespecified covariates (sex, ethnicity, race, age). For variables log-transformed for analysis, adjusted change in mean log value and its standard error ( $\Delta$ ±SE) expressed as percentages:  $100\% \times \exp(\Delta) \pm 100\% \times \exp(\Delta) \times (\exp(SE) - 1)$ .

Nutrition (mean follow-up of 10.8 years)<sup>52</sup> indicate reductions in risk for type 2 diabetes mellitus when replacing SSBs with USBs but no benefit when replacing SSBs with ASBs.

The intervention messages in the present RCT focused on replacing SSBs consumed at baseline with provided beverages. While relevant from a public health perspective, these messages may have resulted in more variability in consumption and thus less consistent exposure compared with interventions specifying an absolute daily intake. In a Danish RCT of healthy adults, participants were instructed to consume provided beverages at a rate of 1 L (≈36 fl oz) per day.<sup>11,12,55</sup> At this level of daily consumption for just 6 months, regular cola compared with aspartame-sweetened cola or water caused greater increases in triglycerides, total cholesterol, and uric

acid, but not HDL-cholesterol and insulin sensitivity. On average, participants in the present RCT did not consume the daily volumes specified in the Danish RCT, even with the unintended increase in consumption of SSBs (in the SSB group) leading to a total volume of ≈30 fl oz per day on average (≈2.5 servings, rather than ≈1.5 servings reflecting baseline consumption).

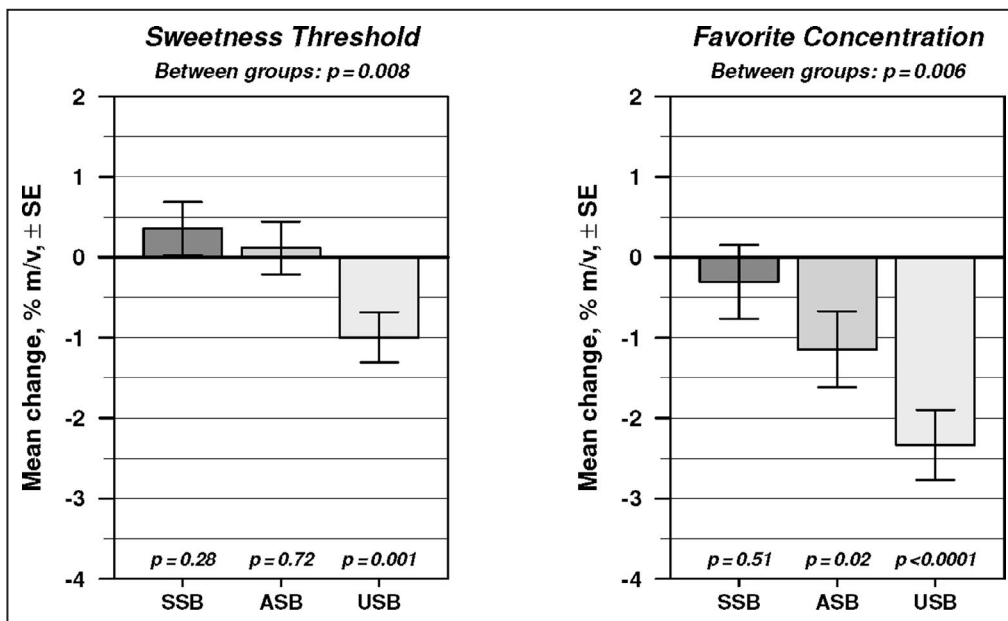
Certain individuals may be particularly susceptible to the adverse effects of dietary carbohydrate on deposition of fat tissue and weight gain and thus more likely to benefit from replacing consumption of SSBs with noncaloric options.<sup>6,7,34,53,54</sup> The present RCT indicates that consumption of SSBs had an adverse effect on body weight and fat mass among individuals with high baseline trunk fat, likely attributable in part to increased consumption in the SSB



**Figure 2. Effect modification by baseline trunk fat for changes in body weight and fat mass.** Each bar indicates 12-month mean change±standard error, from repeated-measures analysis of variance, adjusted for prespecified covariates (sex, ethnicity, race, age). Within each tertile of trunk fat, *P* (bottom) tests for difference in mean change across beverage groups. Interaction *P* (top) tests for difference in beverage effect across tertiles. ASB indicates artificially sweetened beverage; SSB, sugar-sweetened beverage; and USB, unsweetened beverage.

group. Insulin secretion may be one key component of complex mechanisms underlying susceptibility in that individuals with higher central adiposity are more likely to have high initial insulin secretion in response to sugar consumption.<sup>48</sup> As summarized previously,<sup>56</sup> consumption of high-glycemic-load sources

of carbohydrate, such as SSBs, may promote weight gain by raising the postprandial ratio of serum insulin to glucagon, resulting in increased hunger and decreased energy expenditure. Dietary changes to reduce glycemic load may have the most pronounced effect among individuals with high trunk fat, in whom



**Figure 3. Changes in sweet taste preference.** Robust (outlier-resistant) regression analysis provided 12-month mean change±standard error and *P* values testing for difference in mean change between groups (top) and within groups (bottom). ASB indicates artificially sweetened beverage; SSB, sugar-sweetened beverage; and USB, unsweetened beverage.

the postprandial insulin response to oral glucose may be greatest.<sup>34,56</sup> In the present RCT, similar changes in body weight among participants with high trunk fat who consumed ASBs or USBs are consistent with studies indicating that mixed meals containing sucralose or aspartame do not raise postprandial blood glucose or insulin levels to the same extent as those containing sucrose.<sup>57,58</sup>

The observed decrease in sweetness threshold among participants who consumed USBs is consistent with the findings of Wise et al.<sup>59</sup> In their RCT, a dietary intervention to reduce consumption of sugar for 3 months altered perceived sweet taste intensity, such that puddings and beverages containing specified sucrose concentrations were perceived as more sweet in the intervention compared with control group. In the present RCT, favorite concentration also decreased with USBs, and to a lesser extent ASBs. Change in sweet taste preference, achieved by replacing SSBs with USBs, may provide a mechanism for promoting adherence to prescribed low-sugar diets in the context of comprehensive behavioral intervention programs.<sup>60</sup> Improved Healthy Eating Index total score for the USB group is consistent with the change in overall dietary quality observed by Hedrick et al<sup>61</sup> with an intervention aimed solely at reducing consumption of SSBs.

Group effects must be interpreted in the context of the unintended mean increase in consumption of SSBs. With delivery of free SSBs to their homes, participants in the SSB group exhibited propensity to increase, rather than maintain, baseline levels of consumption. Neither sweetness threshold nor favorite concentration changed for the SSB group, suggesting that increased exposure to SSBs did not have an effect on sweet taste preference. While contributing to differentiation in beverage intake among groups (and thus confidence in the null outcomes), increased intake in the SSB group arguably would not threaten external validity for the positive outcomes, as consumption remained within the prevailing range for 60% of adults aged 20 to 39 years who consume SSBs in the United States.<sup>62</sup>

In light of the effects of dietary carbohydrate on TG and HDL-C observed in previous studies,<sup>34,39</sup> the spontaneous decrease in consumption of refined grains for the SSB group may have contributed to the null finding. In a recent epidemiologic study,<sup>19</sup> consumption of SSBs was directly associated with adverse changes in TG and HDL-C in analyses adjusted for dietary quality. To detect the potential effects of beverage consumption on these variables in RCTs, more attention may be needed toward behavioral strategies for controlling intake of other foods (most notably, sources of refined carbohydrate) that could attenuate the independent effects of beverage consumption in intervention studies.

Strengths of this RCT include an intervention targeting a single dietary behavior (beverage consumption), home delivery of beverages to promote differentiation in consumption across study groups, examination of several biomarkers of cardiometabolic risk, evaluation of effect modification by baseline central adiposity, a novel protocol for assessing sweet taste preference, a diverse sample (~50% nonwhite), and high retention rates across groups. Limitations include limited power to observe small effects because of study design (single site rather than multisite study) and recruitment challenges, inability to mask participants to study group assignments, lack of biomarkers of compliance, and reliance on self-report to assess dietary intake and physical activity (with high likelihood of inaccurate reporting and possibly differential misreporting among intervention groups related to factors such as social desirability bias). To speculate, participants with a strong desire to be viewed favorably by others (high social desirability bias) may have demonstrated more underreporting of actual energy intake in response to interventions focusing on consumption of non-caloric beverages (ASBs and USBs) compared with SSBs.<sup>63</sup> Also, the study was not designed to compare the effects of different artificial sweeteners on study outcomes. Emerging data indicate that, while some metabolic effects are consistent, others vary depending on choice of artificial sweetener.<sup>30</sup>

In conclusion, replacing consumption of SSBs with either ASBs or USBs for 12 months had no effect on cardiometabolic risk factors. Among individuals with central adiposity, replacing SSBs with either ASBs or USBs had a favorable effect on body weight and adiposity, consistent with prior findings.<sup>6-10</sup> As stated in the American Heart Association science advisory, replacing SSBs with ASBs may be an appropriate initial recommendation for susceptible adults who habitually consume SSBs and consider USBs an undesirable alternative because of a strong sweet taste preference.<sup>5</sup> However, USBs were a better replacement than ASBs for decreasing sweet taste preference, particularly sweetness threshold, a finding with plausible implications for promoting adherence to prescribed low-sugar diets. In light of epidemiologic data,<sup>25,51,52</sup> the benefits of eliminating consumption of SSBs and the differential effects of ASBs and USBs on cardiometabolic risk factors may require longer periods of study for the general population.

## ARTICLE INFORMATION

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### Affiliations

From the New Balance Foundation Obesity Prevention Center (C.B.E., S.K.S., D.S.L.), and Institutional Centers for Clinical and Translational Research (H.A.F., N.L.Q.), Boston Children's Hospital, Boston, MA; and Shape Up Somerville, City of Somerville, MA (L.M.R.).

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Dr Ludwig received royalties for books on obesity and nutrition that recommend a low-glycemic-load diet. The remaining authors have no disclosures to report.

## Supplementary Materials

Tables S1–S7

Figure S1

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## **Supplemental Material**

**Table S1. Protocol History (with dates of approval by the Boston Children’s Hospital Institutional Review Board).**

<b>Approval Date</b>	<b>Summary</b>
06/28/2010	Full protocol (initial approval)
01/25/2011	<p><u>Eligibility</u></p> <ul style="list-style-type: none"> <li>• Added an inclusion criterion specifying body weight <math>\leq 275</math> pounds (corresponding to the weight limit of DXA instrumentation)</li> <li>• Revised the exclusion criterion for diabetes risk to focus exclusively on impaired fasting glucose (IFG, fasting blood glucose <math>\geq 100</math> mg/dL), rather than both IFG and impaired glucose tolerance (IGT)</li> <li>• Added female-specific exclusion criteria: Pregnant in the past 12 months or planning to become pregnant during the study period; lactating in the preceding 3 months; change in birth control medication in previous 3 months or plans to change during the study period</li> <li>• Replaced 7-day beverage diary with a beverage consumption questionnaire (based on a validated food frequency questionnaire), to assess the inclusion criterion pertaining to consumption of SSBs</li> </ul> <p><u>Assessment</u></p> <ul style="list-style-type: none"> <li>• Replaced the oral glucose tolerance test with homeostatic model assessment (HOMA) of insulin sensitivity and <math>\beta</math>-cell function</li> <li>• Eliminated 24-hour urine collection for assessment of oxidative stress status</li> </ul>
02/14/2011	<i>Posting on ClinicalTrials.gov</i>
03/01/2011	<i>First screening/ informational visit</i>
04/01/2011	<p><u>Assessment</u></p> <ul style="list-style-type: none"> <li>• Specified details for assessing sweet taste preference</li> <li>• Eliminated consideration of menstrual cycle when scheduling assessments (document time of last menstrual period)</li> </ul>
04/12/2011	<i>First fasting blood draw (for later assessment of primary outcome); First DXA scan</i>
05/05/2011	<i>First assessment of sweet taste preference</i>
05/09/2011	<i>First beverage delivery</i>
05/17/2011	<p><u>Eligibility</u></p> <ul style="list-style-type: none"> <li>• Revised exclusion criterion for IFG, increasing the upper limit from <math>\geq 100</math> mg/dL to <math>\geq 110</math> mg/dL</li> </ul> <p><u>Intervention</u></p> <ul style="list-style-type: none"> <li>• Increased the number of beverage units in each delivery from <math>\sim 100</math> to <math>\sim 160</math></li> </ul>
05/26/2011	<p><u>Assessment</u></p> <ul style="list-style-type: none"> <li>• Added 8-hour overnight urine collection for assessment of oxidative stress status (<math>F_{2\alpha}</math>-isoprostanes)</li> </ul> <p><u>Remuneration</u></p> <ul style="list-style-type: none"> <li>• Adjusted remuneration: Increase from \$200 (\$80 at 6 months, \$120 at 12 months) to \$300 (\$50 for completing each 3-month quarter of the study, additional \$100 for completing the fourth quarter and 12-month data collection)</li> </ul>
08/04/2011	<p><u>Eligibility</u></p> <ul style="list-style-type: none"> <li>• Revised smoking exclusion criterion from “Current smoking (1 cigarette in the past week)” to “Current moderate or heavy smoker (<math>&gt;10</math> cigarettes per day)”</li> </ul>
04/03/2012	<p><u>Remuneration</u></p> <ul style="list-style-type: none"> <li>• Adjusted remuneration schedule: \$300 (\$25 after baseline assessments, \$75 at 6 months, \$200 at 12 months)</li> </ul>

*Continued on Next Page*

**Table S1. Continued**

Approval Date	Summary
04/20/2012	<u>Eligibility</u> <ul style="list-style-type: none"><li>• Revised upper limit for age inclusion criterion from 35 to 40 years</li></ul>
01/22/2013	<u>Eligibility</u> <ul style="list-style-type: none"><li>• Added an inclusion criterion pertaining to required proficiency in speaking and understanding English</li></ul>
05/13/2013	<u>Eligibility</u> <ul style="list-style-type: none"><li>• Removed exclusion criterion pertaining to residence in a college or university dormitory</li></ul> <u>Assessment</u> <ul style="list-style-type: none"><li>• Eliminated measurement of circumferences</li></ul>
08/05/2013	<u>Remuneration</u> <ul style="list-style-type: none"><li>• Adjusted remuneration schedule: \$300 (\$25 after baseline assessments, \$275 at 12 months)</li></ul>

**Table S2. Standard Breakfast Prior to Assessment of Sweet Taste Preference (per 430 kcal).**

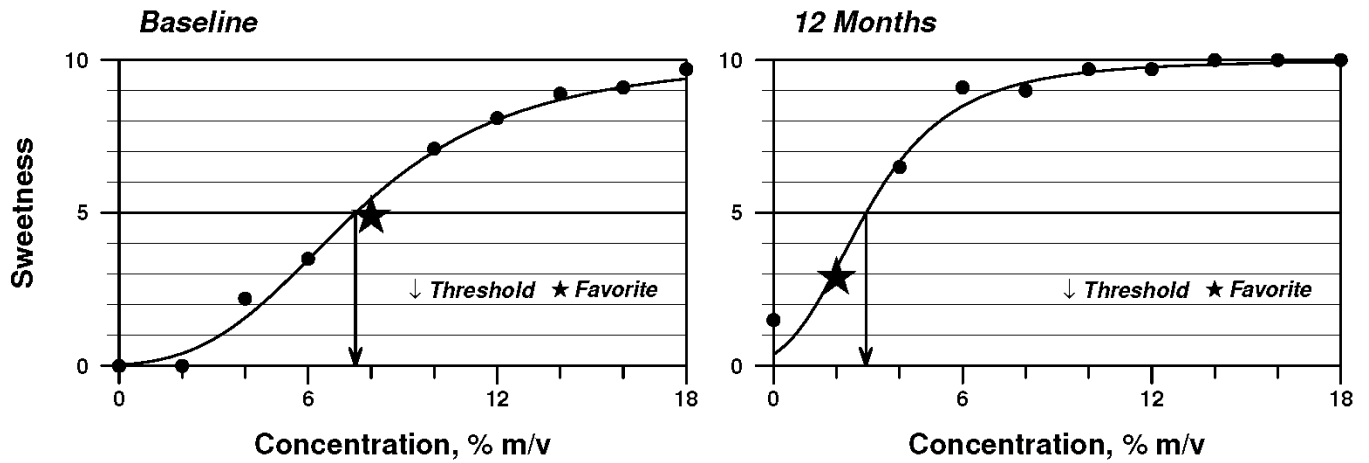
Ingredient	Weight (g)	Macronutrients		
		Carbohydrate (g)	Fat (g)	Protein (g)
Egg Beaters, original ®	165	2.7	0.0	16.2
Oil, vegetable (for cooking eggs)	11	0.0	11.0	0.0
Bread, 100% whole wheat, toasted	50	20.9	2.3	5.8
Butter, unsalted (spread on toast)	5	0.0	4.1	0.0
Apple Slices	200	24.9	0.3	0.5

We estimated daily energy needs for each participant as the arithmetic product of resting requirements, estimated using the Harris-Benedict equation, and a physical activity factor of 1.5. This standard breakfast was scaled to meet 17.5% of estimated needs.

We instructed each participant to finish breakfast within 15-20 minutes. Assessment of sweet taste preference commenced 90 minutes from the time of the first bite of breakfast. This lag time was determined based on the anticipated blood glucose response curve, recognizing that postprandial glucose usually reaches peak at approximately 1 hour.

If a participant had an aversion or allergy to any foods in the standard breakfast, we provided an alternative breakfast that met macronutrient targets (40-45% of energy from carbohydrate, 20-25% protein, and 35% fat). We provided the exact same breakfast at baseline and 12 months for each respective participant.

Figure S1. Assessment of Sweet Taste Preference (Example, Participant #2239).



A logistic curve was fitted to each participant's ratings at baseline (left) and 12 months (right). Sweetness threshold was defined as the concentration corresponding to 5 cm on the scale ( $\downarrow$ ). The overall favorite concentration ( $\star$ ) was assessed after data were collected for determining sweetness threshold. Participant #2239 was in Group 3 and received unsweetened beverages during the intervention period.



**Table S3. Beverage Deliveries and Check-in Calls Completed.**

Variable	Study Group	N*	Mean $\pm$ SD	<i>P</i> †	Median (IQR)	<i>P</i> ‡
<b>Number of Beverage Deliveries</b>				0.84		0.33
	SSB	60	7.1 $\pm$ 4.4		6 (4, 9)	
	ASB	60	7.5 $\pm$ 4.0		7 (5, 8)	
	USB	66	7.6 $\pm$ 4.0		6 (5, 9)	
<b>Number of Check-in Calls Completed</b>				0.71		0.50
	SSB	60	19.3 $\pm$ 3.7		20.0 (17.5, 22.0)	
	ASB	60	18.3 $\pm$ 4.6		19.5 (16.5, 23.0)	
	USB	66	19.4 $\pm$ 5.0		21.0 (18.0, 23.0)	

\* Study completers.

† Testing for equal mean across groups by one-way analysis of variance.

‡ Testing for equal distribution across groups by Kruskal-Wallis test.

ASB denotes artificially sweetened beverage; SSB, sugar-sweetened beverage; and USB, unsweetened beverage.

**Table S4. Self-Reported Dietary Quality (adjusted for energy intake).**

Healthy Eating Index Variable (possible score)	Study Group	Unadjusted Data				Adjusted Data		
		Baseline		12 Months		Change * Mean ± SE	P within group	P between groups
		N	Mean ± SD	N†	Mean ± SD			
<b>Total Score (0-100)</b>	SSB	67	46.35 ± 10.79	60	45.41 ± 8.64	-0.89 ± 1.48	0.55	0.14
	ASB	67	46.82 ± 10.21	60	47.81 ± 11.37	1.02 ± 1.48	0.49	
	USB	69	46.68 ± 10.82	65	50.14 ± 11.69	3.19 ± 1.43	0.03	
<b>Adequacy‡</b>								
<b>Total Fruits (0-5)</b>	SSB	67	1.31 ± 1.44	60	1.07 ± 1.12	-0.25 ± 0.21	0.24	0.38
	ASB	67	1.66 ± 1.58	60	1.26 ± 1.41	-0.39 ± 0.21	0.07	
	USB	69	1.59 ± 1.53	65	1.62 ± 1.56	0.02 ± 0.21	0.93	
<b>Whole Fruits (0-5)</b>	SSB	67	1.19 ± 1.42	60	0.88 ± 1.19	-0.31 ± 0.22	0.16	0.34
	ASB	67	1.21 ± 1.51	60	1.25 ± 1.57	0.04 ± 0.22	0.86	
	USB	69	1.37 ± 1.61	65	1.51 ± 1.56	0.11 ± 0.21	0.59	
<b>Total Vegetables (0-5)</b>	SSB	67	2.53 ± 1.18	60	2.50 ± 1.06	-0.06 ± 0.16	0.70	0.06
	ASB	67	2.51 ± 1.15	60	3.00 ± 1.18	0.47 ± 0.16	0.004	
	USB	69	2.57 ± 1.14	65	2.78 ± 1.20	0.18 ± 0.15	0.24	
<b>Greens and Beans (0-5)</b>	SSB	67	1.50 ± 1.35	60	1.37 ± 1.31	-0.12 ± 0.21	0.56	0.52
	ASB	67	1.45 ± 1.31	60	1.71 ± 1.56	0.21 ± 0.21	0.30	
	USB	69	1.72 ± 1.57	65	1.81 ± 1.52	0.09 ± 0.20	0.67	
<b>Whole Grains (0-10)</b>	SSB	67	2.80 ± 2.78	60	2.71 ± 2.59	-0.08 ± 0.40	0.84	0.29
	ASB	67	2.98 ± 2.77	60	3.24 ± 2.90	0.26 ± 0.40	0.52	
	USB	69	2.82 ± 2.56	65	3.64 ± 2.86	0.80 ± 0.39	0.04	
<b>Dairy (0-10)</b>	SSB	67	6.02 ± 2.40	60	5.07 ± 2.51	-0.93 ± 0.35	0.008	0.02
	ASB	67	5.05 ± 2.24	60	4.69 ± 2.38	-0.36 ± 0.35	0.30	
	USB	69	4.66 ± 2.50	65	5.05 ± 2.62	0.42 ± 0.34	0.22	
<b>Total Protein Foods (0-5)</b>	SSB	67	3.95 ± 0.95	60	4.13 ± 1.00	0.18 ± 0.14	0.20	0.80
	ASB	67	4.00 ± 0.92	60	4.15 ± 0.95	0.12 ± 0.14	0.39	
	USB	69	4.08 ± 1.02	65	4.34 ± 1.03	0.25 ± 0.13	0.07	
<b>Seafood and Plant Proteins (0-5)</b>	SSB	67	1.69 ± 1.43	60	1.85 ± 1.61	0.15 ± 0.23	0.53	0.94
	ASB	67	1.77 ± 1.42	60	1.89 ± 1.49	0.08 ± 0.23	0.72	
	USB	69	1.49 ± 1.51	65	1.71 ± 1.60	0.20 ± 0.23	0.38	
<b>Fatty Acids (0-10)</b>	SSB	67	3.53 ± 2.40	60	4.09 ± 2.26	0.57 ± 0.38	0.13	0.45
	ASB	67	3.77 ± 2.47	60	4.00 ± 2.55	0.25 ± 0.38	0.51	
	USB	69	3.93 ± 2.26	65	3.86 ± 2.48	-0.10 ± 0.37	0.79	

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**Table S4. Continued**

<b>Moderation§</b>								
<b>Refined Grains (0-10)</b>	SSB	67	5.23 ± 2.57	60	6.02 ± 2.57	0.80 ± 0.40	0.05	0.06
	ASB	67	5.40 ± 2.62	60	5.09 ± 2.37	-0.33 ± 0.40	0.41	
	USB	69	6.20 ± 2.41	65	5.78 ± 2.43	-0.44 ± 0.39	0.26	
<b>Sodium (0-10)</b>	SSB	67	4.20 ± 2.27	60	4.35 ± 2.49	0.14 ± 0.43	0.74	0.008
	ASB	67	5.11 ± 2.66	60	3.36 ± 2.46	-1.75 ± 0.43	<0.001	
	USB	69	4.52 ± 2.20	65	3.92 ± 2.62	-0.59 ± 0.41	0.16	
<b>Added Sugars (0-10)</b>	SSB	67	5.92 ± 2.72	60	4.82 ± 2.88	-1.17 ± 0.40	0.004	<0.001
	ASB	67	5.90 ± 2.74	60	8.64 ± 2.05	2.75 ± 0.40	<0.001	
	USB	69	5.20 ± 2.62	65	9.00 ± 1.13	3.79 ± 0.38	<0.001	
<b>Saturated Fats (0-10)</b>	SSB	67	6.48 ± 2.25	60	6.55 ± 2.39	0.13 ± 0.37	0.73	0.009
	ASB	67	5.99 ± 2.13	60	5.53 ± 2.34	-0.44 ± 0.37	0.24	
	USB	69	6.55 ± 2.35	65	5.12 ± 2.66	-1.46 ± 0.36	<0.001	

\* Data analyzed using repeated measures analysis of variance, adjusted for covariates (sex, ethnicity, race, age).

† Dietary recall data missing for one participant in USB group, who could not be reached for telephone interviews at 12 months.

‡ Higher score indicates higher consumption.

§ Higher score indicates lower consumption.

ASB denotes artificially sweetened beverage; SSB, sugar-sweetened beverage; and USB, unsweetened beverage.

**Table S5. Biochemical Measures and Blood Pressure.**

Variable *	Study Group	Unadjusted Data				Adjusted Data §		
		Baseline		12 Months		Change Mean ± SE	P within group	P between groups
		N †	Mean ± SD Median (IQR) ‡	N †	Mean ± SD or Median (IQR) ‡			
<b>Biochemical measures</b>								
<b>Triglycerides (mg/dL) *</b>	SSB	67	73 (50, 100)	60	74 (54,101)	-1.0 ± 4.3	0.81	0.83
	ASB	67	70 (49, 95)	60	70 (48, 96)	-2.0 ± 4.3	0.65	
	USB	69	78 (62, 123)	66	78 (60, 113)	-4.4 ± 4.0	0.28	
<b>HDLC (mg/dL)</b>	SSB	67	54.1 ± 14.9	60	51.3 ± 14.3	-2.3 ± 1.2	0.06	0.26
	ASB	67	55.2 ± 13.8	60	56.2 ± 14.5	0.5 ± 1.2	0.68	
	USB	69	53.8 ± 14.2	66	53.7 ± 14.0	-0.5 ± 1.1	0.64	
<b>hsCRP (mg/L) *</b>	SSB	67	0.62 (0.32, 1.84)	60	0.86 (0.38, 1.79)	19.2 ± 16.8	0.18	0.21
	ASB	67	0.77 (0.34, 2.30)	60	0.63 (0.38, 1.79)	-10.6 ± 12.6	0.39	
	USB	69	0.73 (0.43, 1.38)	66	0.85 (0.39, 1.76)	-10.0 ± 12.1	0.41	
<b>Fibrinogen (mg/dL)</b>	SSB	66	245 ± 57	60	244 ± 49	-0 ± 6	0.95	0.44
	ASB	65	249 ± 60	60	248 ± 62	-2 ± 6	0.70	
	USB	68	254 ± 64	64	244 ± 59	-11 ± 6	0.08	
<b>Uric acid (mg/dL)</b>	SSB	67	5.3 ± 1.3	60	5.2 ± 1.3	-0.1 ± 0.1	0.45	0.56
	ASB	67	5.2 ± 1.4	60	5.1 ± 1.4	-0.1 ± 0.1	0.66	
	USB	69	5.3 ± 1.5	66	5.4 ± 1.5	0.1 ± 0.1	0.49	
<b>ALT (U/L) *</b>	SSB	67	14 (12, 21)	60	16 (12, 21)	6.3 ± 5.6	0.24	0.15
	ASB	67	18 (13, 27)	60	16 (13, 23)	-7.6 ± 4.9	0.12	
	USB	69	16 (13, 22)	66	17 (11, 26)	1.2 ± 5.1	0.81	
<b>Glucose (mg/dL)</b>	SSB	67	82.8 ± 5.9	60	84.8 ± 6.9	1.8 ± 0.8	0.02	0.63
	ASB	66	83.4 ± 7.0	60	84.3 ± 6.4	0.9 ± 0.8	0.24	
	USB	69	83.5 ± 7.0	66	85.4 ± 7.9	1.8 ± 0.7	0.01	
<b>Insulin (μIU/L) *</b>	SSB	67	7.5 (4.2, 10.0)	60	8.0 (4.8, 11.5)	7.5 ± 7.1	0.26	0.37
	ASB	67	8.3 (5.4, 11.8)	60	7.7 (4.7, 11.4)	-5.4 ± 6.3	0.39	
	USB	69	8.1 (5.6, 12.4)	65	7.7 (5.4, 11.9)	-0.0 ± 6.4	0.99	

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**Table S5. Continued**

<b>Blood pressure</b>								
<b>Systolic (mmHg)</b>	SSB	67	108.0 ± 8.8	60	108.8 ± 10.4	0.5 ± 1.3	0.67	0.31
	ASB	67	109.1 ± 13.5	60	106.9 ± 11.2	-1.9 ± 1.3	0.14	
	USB	69	105.7 ± 9.7	66	106.0 ± 9.2	0.5 ± 1.2	0.71	
<b>Diastolic (mmHg)</b>	SSB	67	66.6 ± 7.6	60	68.3 ± 8.7	1.6 ± 1.1	0.13	0.31
	ASB	67	66.6 ± 8.1	60	66.7 ± 7.7	0.1 ± 1.1	0.90	
	USB	69	67.7 ± 7.4	66	67.1 ± 7.8	-0.7 ± 1.0	0.53	

\* Triglycerides, hsCRP, ALT, and insulin were log-transformed for analysis, results retransformed for reporting as described below.

† Missing data: fibrinogen was missing for 4 participants (1 in SSB group, 2 in ASB group, 1 in USB group) at baseline and 2 participants in USB group at 12-months; glucose was missing for 1 participant in ASB group at baseline; insulin was missing for 1 participant in USB group at 12 months.

‡ Unadjusted mean ± standard deviation; in the case of variables log-transformed for analysis, median and interquartile range (25th, 75th percentiles).

§ Change in mean value ± standard error and *p*-values, from repeated-measures analysis of variance, adjusted for pre-specified covariates (sex, ethnicity, race, age). In the case of variables log-transformed for analysis, adjusted change in mean log value and its standard error ( $\Delta \pm SE$ ) are expressed as percentages:  $100\% \times \exp(\Delta) \pm 100\% \times \exp(\Delta) \times (\exp(SE) - 1)$ .

ALT denotes alanine aminotransferase; ASB, artificially sweetened beverage; HDLC, HDL-cholesterol; hsCRP, high-sensitivity C-reactive protein; SSB, sugar-sweetened beverage; and USB, unsweetened beverage.



**Table S6. Effect Modification by Baseline Trunk Fat for Changes in Body Weight and Whole-Body Fat Mass.**

Variable Tertile – Baseline Trunk Fat *	Study Group	N †	Adjusted Data ‡			
			Change Mean ± SE	P within group	P within tertile	P Effect modification
<b>Body Weight (kg)</b>						
Tertile 1– Baseline Trunk Fat	SSB	19	0.2 ± 1.0	0.87	0.70	
	ASB	21	1.1 ± 0.9	0.25		
	USB	14	-0.0 ± 1.1	0.99		
Tertile 2 – Baseline Trunk Fat	SSB	22	0.2 ± 0.9	0.82	0.22	0.006
	ASB	17	-0.2 ± 1.0	0.87		
	USB	26	1.9 ± 0.8	0.03		
Tertile 3 – Baseline Trunk Fat	SSB	17	4.4 ± 1.0	<0.001	0.002	
	ASB	20	0.5 ± 0.9	0.60		
	USB	23	-0.2 ± 0.9	0.84		
<b>Whole-Body Fat Mass (kg)</b>						
Tertile 1– Baseline Trunk Fat	SSB	13	0.9 ± 0.8	0.26	0.64	
	ASB	17	1.0 ± 0.7	0.17		
	USB	11	0.0 ± 0.9	0.99		
Tertile 2 – Baseline Trunk Fat	SSB	18	-0.4 ± 0.7	0.60	0.12	0.004
	ASB	13	-0.6 ± 0.8	0.44		
	USB	24	1.2 ± 0.6	0.06		
Tertile 3 – Baseline Trunk Fat	SSB	13	2.8 ± 0.8	0.001	0.002	
	ASB	14	-0.1 ± 0.8	0.88		
	USB	17	-1.1 ± 0.8	0.16		

\* DXA trunk fat missing for 7 participants at baseline (scanned on a replacement scanner that was not adequately calibrated with the original scanner).

† Missing data: DXA whole body fat mass missing for 7 participants at baseline and an additional 37 participants at 12 months (scanned on a replacement scanner); 2 additional participants did not complete the DXA scan at 12 months (1 in SSB group, 1 in USB group).

N=179 for body weight analysis (186–7)

N=140 for whole-body fat mass analysis (186–44–2)

‡ Change in mean value ± standard error and P-values, from repeated-measures analysis of variance, adjusted for pre-specified covariates (sex, ethnicity, race, age) and tertile of baseline trunk fat.

ASB denotes artificially sweetened beverage; SSB, sugar-sweetened beverage; and USB, unsweetened beverage.

**Table S7. Sweet Taste Preference.**

Variable*	Study Group	Baseline		12 Months		Change		
		N †	Median (IQR) ‡	N	Median (IQR)	Median (IQR) §	P within group	P between groups ¶
<b>Sweet Taste Preference</b>								
<b>Sweetness Threshold</b>	SSB	66	7.0 (2.5)	58	7.5 (3.5)	0.23 (3.5)	0.40	0.03
	ASB	67	7.4 (3.1)	59	7.2 (3.5)	-0.18 (3.9)	0.76	
	USB	69	7.2 (2.8)	65	6.7 (4.1)	-1.04 (2.7)	0.005	
<b>Favorite concentration</b>	SSB	67	10 (4)	59	10 (4)	0 (4)	0.36	0.009
	ASB	67	10 (6)	60	10 (5)	-2 (6)	0.004	
	USB	69	12 (4)	66	8 (4)	-2 (6)	<0.0001	

\* Concentration ranged from 0 to 18% m/v.

† Missing data: sweetness threshold missing for 1 participant (SSB group) at baseline and 12 months and another participant (ASB group) only at 12 months for whom we could not fit a sigmoid curve; 1 participant (USB group) did not follow instructions in filling out the VAS at 12 months; 1 participant (SSB group) did not complete sweet taste preference testing at 12 months (missing sweetness threshold and favorite concentration).

‡ Median value (interquartile range).

§ Median of 12-month change (interquartile range).

|| Testing for zero median change within group by signed-rank test.

¶ Testing for equal distribution of change across groups by Kruskal-Wallis test.

ASB denotes artificially sweetened beverage; SSB, sugar-sweetened beverage; and USB, unsweetened beverage.