ORIGINAL ARTICLE

A Trial of Sugar-free or Sugar-Sweetened Beverages and Body Weight in Children

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ABSTRACT

BACKGROUND

The consumption of beverages that contain sugar is associated with overweight, possibly because liquid sugars do not lead to a sense of satiety, so the consumption of other foods is not reduced. However, data are lacking to show that the replacement of sugar-containing beverages with noncaloric beverages diminishes weight gain.

METHODS

We conducted an 18-month trial involving 641 primarily normal-weight children from 4 years 10 months to 11 years 11 months of age. Participants were randomly assigned to receive 250 ml (8 oz) per day of a sugar-free, artificially sweetened beverage (sugar-free group) or a similar sugar-containing beverage that provided 104 kcal (sugar group). Beverages were distributed through schools. At 18 months, 26% of the children had stopped consuming the beverages; the data from children who did not complete the study were imputed.

RESULTS

The z score for the body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) increased on average by 0.02 SD units in the sugar-free group and by 0.15 SD units in the sugar group; the 95% confidence interval (CI) of the difference was −0.21 to −0.05. Weight increased by 6.35 kg in the sugar-free group as compared with 7.37 kg in the sugar group (95% CI for the difference, −1.54 to −0.48). The skinfold-thickness measurements, waist-to-height ratio, and fat mass also increased significantly less in the sugar-free group. Adverse events were minor. When we combined measurements at 18 months in 136 children who had discontinued the study with those in 477 children who completed the study, the BMI z score increased by 0.06 SD units in the sugar-free group and by 0.12 SD units in the sugar group (P=0.06).

CONCLUSIONS

Masked replacement of sugar-containing beverages with noncaloric beverages reduced weight gain and fat accumulation in normal-weight children. (Funded by the Netherlands Organization for Health Research and Development and others; DRINK ClinicalTrials.gov number, NCT00893529.)

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The increased prevalence of obesity in children, a major health problem,[1,2] has coincided with a large increase in the consumption of sugar-sweetened beverages.[3] These beverages are considered to be more fattening than solid foods because they do not lead to a sense of satiety.[4] Thus, children who increase their consumption of sugar-sweetened beverages may not reduce their intake of calories from other foods and beverages, with a resultant increase in total energy intake and weight gain.

Consumption of sugar-sweetened beverages has been associated with weight gain in most observational studies,[5-8] though not all such studies.[9,10] However, children who drink more sugar-sweetened beverages also tend to eat more fast food and to watch more television.[11] Most studies adjust statistically for such confounders, but residual and unmeasured confounding cannot be ruled out.[12,13]

Results of available trials are inconclusive,[14-19] possibly owing to small samples, a lack of adequate placebos, a short duration of the study, lack of individual randomization, or a combination of these factors. In addition, effectively blinded trials are important, because when investigators and participants know which treatment should cause weight loss, results may be biased.[20]

We conducted the Double-blind, Randomized Intervention Study in Kids (DRINK)[20] to examine the effect on weight gain of masked replacement of sugar-sweetened beverages with noncaloric, artificially sweetened beverages. The double-blind design permitted the study of physiological mechanisms that were independent of behavioral cues and voluntary changes in consumption.

METHODS

DESIGN AND STUDY POPULATION

The study was an 18-month, double-blind, randomized, controlled trial involving schoolchildren living in the community who were 4 years 10 months to 11 years 11 months of age. The design of the study has been described previously.[20] The study started on November 14, 2009, and ended on July 22, 2011. We recruited children at eight elementary schools in an urban area near Amsterdam. Baseline characteristics, including usual beverage consumption, were determined with the use of a questionnaire. Children were eligible only if they commonly drank sugar-sweetened beverages, because we considered it unethical to provide sugary beverages to children who did not habitually consume such beverages. We excluded children with various medical conditions (see Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). We enrolled and individually randomly assigned 641 children, stratified according to school, sex, age, and initial body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) (Fig. 1).[20] Children in the same household received the same type of beverage, but they were unaware of this assignment.

For each child enrolled in the study, written informed consent was provided by a parent or guardian who had obtained assent from the child. The study protocol was approved by the medical ethics committee of VU University Medical Center Amsterdam and is available at NEJM.org. Refresco Benelux, the manufacturer of the beverages, had no role in the design of the study, the accrual or analysis of the data, or the preparation of the manuscript. All authors vouch for the accuracy of the data and the fidelity of the study to the protocol.

INTERVENTION

We provided children with 1 can per day of a noncaloric, artificially sweetened, noncarbonated beverage or a sugar-containing noncarbonated beverage. We developed custom drinks for this study to ensure that the sugar-free and sugar-containing drinks tasted and looked essentially the same.[20] We hired Refresco Benelux to produce these beverages. The identical-looking 250-ml (8-oz) cans provided either 0 or 26 g of sucrose (0 or 104 kcal per day). The sugar-free beverages contained 34 mg of sucralose and 12 mg of acesulfame potassium per can.[21]

Participating children received a box at school each week labeled with their name and containing 8 cans, 1 for each day of the week plus 1 extra to be used as a spare in case a can was misplaced. The teachers checked to see whether the children consumed their beverage during the morning break in class and reminded them to take cans home for the weekend and any holidays.

We measured body weight, height, skinfold thickness (of the biceps, triceps, and subscapular and suprailiac regions), waist circumference, and arm-to-leg electrical impedance, and we collected urine samples at 0, 6, 12, and 18 months.[20] For children who stopped drinking the beverages before the study was completed, measurements were obtained if the parent or guardian consent-

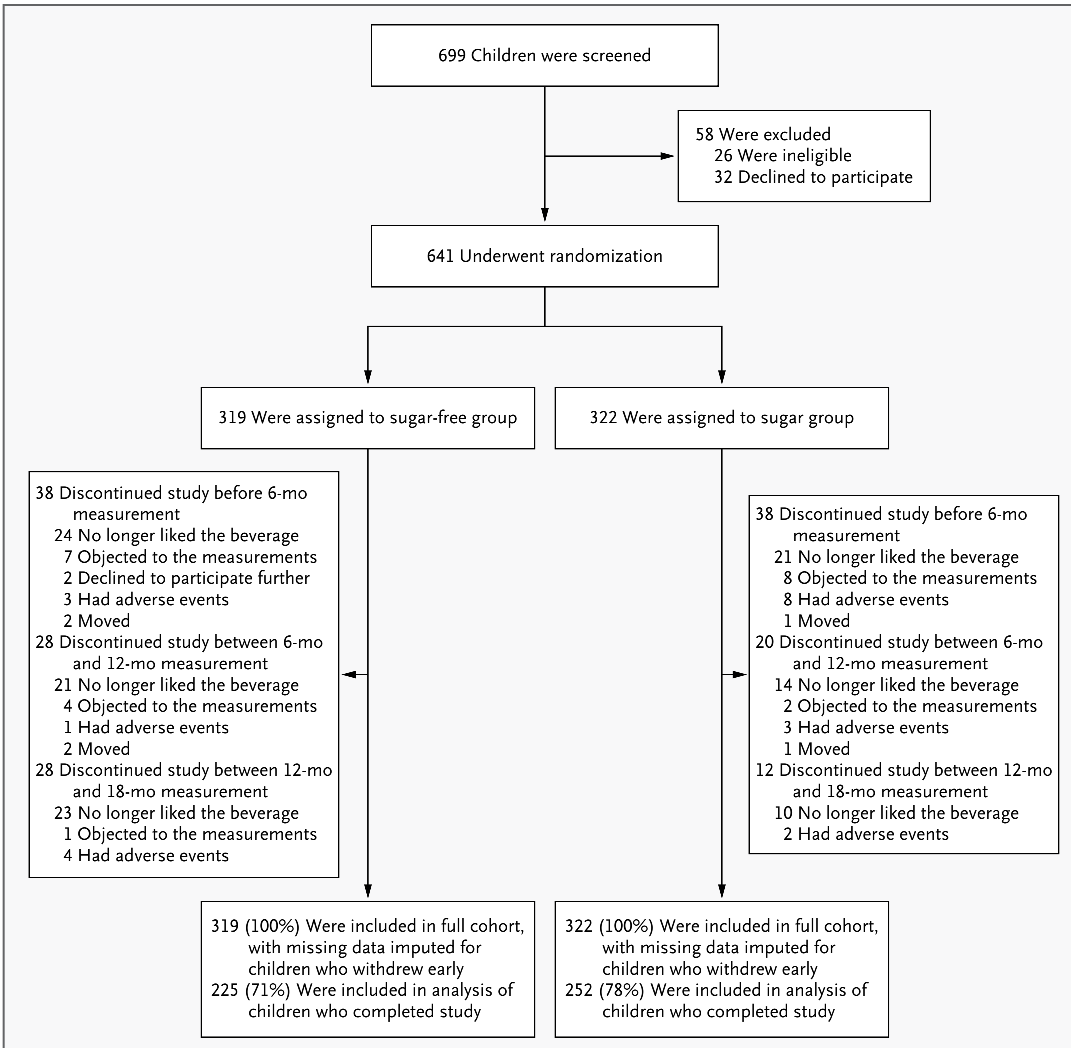

Figure 1. Screening, Randomization, and Follow-up of the Study Participants.

A total of 164 children stopped consuming the study beverages. Measurements in 136 of these children (79 children in the sugar-free group and 57 in the sugar group) were available at 18 months. Thus, measurements in 28 children who did not complete the study (15 children in the sugar-free group and 13 in the sugar group) were not available at 18 months. We randomly assigned 641 children, not 642, as previously reported,[20] since after unblinding, one child whom we believed to have undergone randomization[20] had not undergone randomization.

ed and the child assented. Data were available at 18 months for 136 children who did not complete the study and for 477 children who did complete the study. Each child was evaluated by the same investigator throughout the study. Two specially trained researchers measured the waist circumference and the thickness of four skinfolds.

ADHERENCE

We provided frequent incentives for schools, teachers, parents, and children, including tournaments, newsletters, birthday cards, and small gifts to encourage adherence. We requested that parents report adverse events by contacting us through the e-mail address or telephone number printed on each beverage can.[20] We visited the schools at least once a month to ensure that the study beverages were delivered correctly to the classrooms. We calculated the adherence rate per child during school days from the number of cans returned empty, half-filled, or full during one randomly selected week each month (Table S2 in the Supplementary Appendix). We measured the sucralose concentration in urine as an additional compliance marker.[22]

STATISTICAL ANALYSIS

Our predefined primary analysis involved the 477 children who completed the study (i.e., the children who consumed the study beverages throughout the study).[20] We also used multiple imputation to impute the outcome values for the 164 children who did not complete the study at 18 months. We created 30 multiple imputed-data sets with five iterations, using the multivariate imputation by chained-equations algorithm in R software, version 2.13. Variables included in the imputation model were age at baseline, race or ethnic group, parents' level of education, sex, compliance, study group, and baseline and 18-month measurements — when available — of the outcome being predicted.

The primary outcome[20] was the BMI z score (expressed as the number of standard deviations by which the BMI differed from the mean for a child's age and sex in the Netherlands).[23] Prespecified secondary outcomes were the waist-to-height ratio, the sum of the four skinfold-thickness measurements, and fat mass determined by means of electrical impedance.[20] Additional outcomes were weight, height, z score for height,[23] waist circumference, and weight change adjusted for height change. Responses of the two study groups to the beverages were compared with two-sided t-tests. We performed adjusted analyses with linear regression, using SPSS software. Prespecified adjustments for interdependency of outcomes in siblings, degree of adherence, and baseline values[20] had negligible effects on outcomes (Tables S3, S4, and S5 in the Supplementary Appendix).

RESULTS

PARTICIPANTS

Baseline characteristics were similar in the two study groups, except for a difference in the parents' level of education (Table 1). The mean BMI z score was 0.03, which corresponded with the 51st percentile of Dutch children.[23] The SD of 1.02 confirmed that our sample was representative of Dutch children, for whom the SD equals 1.00 by definition. At baseline, the participants consumed a mean (±SD) of 1.02±0.20 sugar-sweetened beverages in the classroom during the 10 a.m. break, Monday through Friday, and 1.50±1.40 sugar-sweetened beverages per day during weekends.

The net duration of the study was a mean of 541±8 days.[20] The percentage of participants who consumed the study beverages decreased from 100% at the beginning of the study to 88% at 6 months, 81% at 12 months, and 74% at 18 months (Fig. 1). The major reasons for discontinuing the study were dislike of the beverage (accounting for 69% of the children who discontinued the study) and minor adverse events (13%); weight gain accounted for 4% of children who discontinued the study (four in the sugar group and two in the sugar-free group) (Fig. 1, and Table S6 in the Supplementary Appendix).

ADHERENCE AND BLINDING

A total of 26% of the participants stopped consuming the beverages. These children had a slightly higher BMI at baseline, and their parents had completed fewer years of school (Table S7 in the Supplementary Appendix). This difference in educational levels theoretically might have influenced the effect of the beverages on weight loss. During the first 6 months of the study, however, weight loss was the same among children who ultimately completed the study as among children who discontinued the study after 6 months or more (Fig. S1E in the Supplementary Appendix). The proportion of children who were aware of the type of beverage they were consuming was similar among children who did and those who did not complete the study (Table S8 in the Supplementary Appendix). Also, most children who did not complete the study were lean, and few children dropped out because of concern about weight (Tables S6 and S7 in the Supplementary Appendix). Most children who stopped drinking the study beverages did so because they no longer liked the beverages. Analyses in which missing values were imputed (Table 2) also suggested that results for the full cohort would have been similar to those for the children who completed the study.

The 477 children who completed the study consumed 5.8 cans, or 83% of the assigned 7 cans per week, with no difference according to the type of beverage consumed and no changes over time (Table S2 in the Supplementary Appendix). The mean level of urinary sucralose was 6.7±4.7 mg per liter in the sugar-free group and 0.1±0.3 mg per liter in the sugar group (Fig. 2), indicating adherence in the group of children who drank the artificially sweetened beverages.

At 18 months, 609 children were asked which type of beverage they thought they had received (Table S8 in the Supplementary Appendix). Among 474 children who completed the study, 48% in

Table 1. Baseline Characteristics of the Study Participants.*

Characteristic	Sugar-free Group (N=319)	Sugar Group (N=322)
Female sex (%)	46	47
Age (yr)	8.2±1.8	8.2±1.8
Ancestry (%)†		
Dutch	80	76
Non-Western	19	22
Highest level of education attained by parent or guardian (%)‡		
Elementary, vocational, or technical school	17	10
High-school diploma	33	28
College or university degree	49	61
Weight (kg)	30.04±8.93	30.33±8.82
Height		
Measured (cm)	132.1±12.5	133.0±12.7
z score (SD units above or below mean in the Netherlands)§	−0.09±1.00	0.03±0.99
BMI		
Calculated BMI	16.9±2.6	16.8±2.6
BMI z score (SD units above or below mean in the Netherlands)§	0.06±1.00	0.01±1.04
Low (%)¶	1	1
Normal (%)	80	81
Overweight (%)	16	15
Obese (%)	3	3
Sum of thicknesses of four skinfolds (mm)‖	36.4±17.7	35.6±17.9
Waist-to-height ratio (%)	44.6±4.0	44.2±4.0
Fat mass on electrical impedance		
Measured (kg)**	5.8±3.8	5.7±3.7
As % of body weight	18	18

* Plus–minus values are means ±SD. There were no significant between-group differences at baseline except for the educational level of the parent or guardian (P=0.02). P values were based on chi-square tests and t-tests.
† Data were available for 633 children; eight households did not provide this information. A child was classified as Dutch if both parents were born in the Netherlands and as non-Western if one or both parents were born in Suriname, Dutch Antilles, Turkey, Morocco, Russia, Egypt, or Vietnam.
‡ Data were available for 632 children; nine households did not provide this information. We based the educational level on that of the parent or guardian who had the higher level of education.
§ The z scores for BMI and height were calculated with the use of the data described by Schönbeck et al.[23]
¶ We used international cutoff points for low and normal BMI[24] and for overweight and obesity.[25]
‖ Data were available for 640 children; 1 child declined to be measured.
** Data were available for 637 children; 4 children declined to be measured.

the sugar-free group and 50% in the sugar group answered that they did not know, 36% in the sugar-free group and 27% in the sugar group answered "artificially sweetened," and the remainder said "sugar-sweetened." The proportion of participants who correctly responded "artificially sweetened" was 21% (95% confidence interval [CI], 12 to 30) higher (47 more children) than expected by chance, as estimated with the "blinding index" described by Bang et al.[27] In the sugar group, the proportion of children who were aware of the type of beverage they had consumed was 3% (95% CI, −12 to 6) lower (7 fewer children) than expected. Among 135 children who did not complete the study, the beverage was correctly identified by 12% more, or 9 more children, than expected, in the sugar-free group, and by 1 less child than expected in the sugar group.

Table 2. Primary and Secondary Outcomes in the Full Cohort, with Imputed Data for Children Who Did Not Complete the Study, and in the Cohort of Children Who Completed the Study.*

Outcome	Sugar-free Group (N=319)			Sugar Group (N=322)			Difference in Change from Baseline (95% CI)	P Value for Difference†
	0 Mo	18 Mo	Change	0 Mo	18 Mo	Change		
Full cohort, with imputed data								
Primary end point: BMI z score‡	0.06±1.00	0.08±0.99	0.02±0.41	0.01±1.04	0.15±1.06	0.15±0.42	−0.13 (−0.21 to −0.05)	0.001
Secondary end points								
Sum of thicknesses of four skinfolds (mm)	36.4±17.7	39.6±20.4	3.2±8.8	35.6±17.9	41.1±21.1	5.5±10.2	−2.2 (−4.0 to −0.4)	0.02
Waist-to-height ratio (%)	44.6±4.0	43.7±4.0	−0.9±2.0	44.2±4.0	43.7±4.0	−0.5±2.0	−0.4 (−1.0 to −0.0)	0.05
Fat mass on electrical impedance (kg)§	5.76±3.85	6.77±4.71	1.01±2.62	5.70±3.68	7.28±4.89	1.58±2.47	−0.57 (−1.02 to −0.12)	0.02
Fat mass on electrical impedance (% of body weight)§	17.91±7.01	17.22±8.44	−0.70±5.31	17.67±6.92	18.05±8.25	0.38±4.86	−1.07 (−1.99 to −0.15)	0.02
Other end points								
Weight (kg)	30.04±8.93	36.39±10.41	6.35±3.07	30.33±8.82	37.69±11.05	7.37±3.35	−1.01 (−1.54 to −0.48)	<0.001
Height (cm)	132.06±12.55	142.34±12.48	10.28±1.91	133.02±12.71	143.67±13.05	10.65±1.97	−0.37 (−0.72 to −0.02)	0.04
Height z score‡	−0.09±1.00	−0.07±0.99	0.03±0.27	0.03±0.99	0.09±0.99	0.06±0.27	−0.04 (−0.10 to 0.02)	0.17
Waist circumference (cm)	58.85±7.44	62.22±7.97	3.37±2.97	58.69±7.05	62.72±7.92	4.03±3.12	−0.66 (−1.23 to −0.09)	0.02
Children who completed study¶								
Primary end point: BMI z score‡	0.05±0.99	0.07±0.98	0.02±0.40	−0.02±1.00	0.14±1.06	0.15±0.42	−0.13 (−0.20 to −0.06)	0.001
Secondary end points								
Sum of thicknesses of four skinfolds (mm)	36.0±16.9	39.1±20.2	3.2±8.1	34.4±15.8	40.1±20.4	5.7±10.0	−2.5 (−4.2 to −0.8)	0.003
Waist-to-height ratio (%)	44.6±3.7	43.7±3.8	−0.9±1.9	44.1±3.7	43.7±4.1	−0.5±2.1	−0.4 (−0.8 to −0.1)	0.02
Fat mass on electrical impedance (kg)§	5.61±3.44	6.65±4.29	1.02±1.68	5.45±3.21	7.02±4.40	1.57±2.05	−0.55 (−0.89 to −0.21)	0.001
Fat mass on electrical impedance (% of body weight)	17.69±6.63	17.11±7.22	−0.61±3.71	17.35±6.39	17.85±7.36	0.45±3.81	−1.05 (−1.73 to −0.37)	0.003
Other end points								
Weight (kg)	29.76±8.44	36.09±10.19	6.33±2.71	29.75±8.20	37.06±10.66	7.30±3.39	−0.97 (−1.52 to −0.42)	0.001
Height (cm)	131.72±12.44	141.92±12.23	10.21±1.85	132.40±12.57	142.98±12.89	10.57±1.93	−0.36 (−0.71 to −0.02)	0.04
Height z score‡	−0.12±0.92	−0.12±0.95	−0.001±0.38	−0.002±1.01	0.06±0.99	0.06±0.44	−0.07 (−0.14 to 0.01)	0.08
Waist circumference (cm)	58.63±6.90	61.99±7.79	3.36±2.69	58.30±6.43	62.35±7.55	4.05±3.10	−0.69 (−1.22 to −0.17)	0.01

* Values are means (±SD) or means with 95% confidence intervals. Children were considered to have completed the study if they consumed the beverages for the full 18 months. Mean changes for the children who completed the study may differ slightly from the difference between means at 18 and 0 months because measurements were not available from a few participants at either time point. We used R software, version 2.1, to impute end points for the 164 participants who discontinued the study and SPSS software, version 17.0, for all other analyses.

† Differences in changes from baseline between the sugar-free group and the sugar group were analyzed with the use of an independent-sample t-test; P≤0.05 was considered to indicate significance.

‡ The z scores for body-mass index and height were calculated with the use of the data described by Schönbeck et al.[23]

§ Impedance measurements were calculated with the use of the method described by Rush et al.[26]

¶ A total of 225 children in the sugar-free group and 252 children in the sugar group completed the study.

BMI Z SCORE AND OTHER END POINTS

In the full cohort of 641 children, the mean BMI z score increased by 0.02±0.41 SD units in the sugar-free group and by 0.15±0.42 SD units in the sugar group (Table 2) when missing values were imputed. The mean difference of 0.13 SD units was significant. The sugar-free group gained significantly less body fat, as evidenced by skinfold thickness, waist-to-height ratio, and electrical impedance. The mean weight increased by 6.35±3.07 kg in the sugar-free group and by 7.37±3.35 kg in the sugar group. The mean difference of 1.01 kg (2.2 lb) was significant. The mean difference in weight gain decreased to 0.82 kg (P=0.002) when adjusted for height change. The BMI adjusted for age[28] increased 0.36 less in the sugar-free group than in the sugar group (P=0.001). An alternative method for handling missing data — namely, complete case analysis with covariate adjustment[29] — yielded very similar results and levels of significance (Table S9 in the Supplementary Appendix).

Similar results were also seen in the 477 children who consumed the study beverages for the full 18 months (74% of the children enrolled) (Table 2 and Fig. 3). Children in the sugar-free group who completed the study gained 35% less body fat than those in the sugar group, according to impedance measurements,[26] and 19% less when fat mass was calculated from the sum of the thicknesses of four skinfolds. According to the changes in skinfold thickness, the sugar-free group gained 1.47 kg of body fat and the sugar group gained 1.82 kg.[30] Most of the effect on BMI z score and weight was achieved in the first 6 months (Fig. 3B, and Fig. S2B in the Supplementary Appendix). The mean height increased by 10.21±1.85 cm in the sugar-free group and by 10.57±1.93 cm in the sugar group. The mean difference of 0.36 cm (0.14 in) was significant (P=0.04), but the difference in z score for height was not significant (Table 2).

We obtained measurements at 18 months in 136 of the 164 children who did not complete the study. When we combined their measurements with those in the 477 children who completed the study, the mean BMI z score increased by 0.06±0.44 SD units in the sugar-free group and by 0.12±0.44 SD units in the sugar group. The mean difference of 0.07 SD units was not significant (95% CI, −0.134 to 0.002; P=0.06).

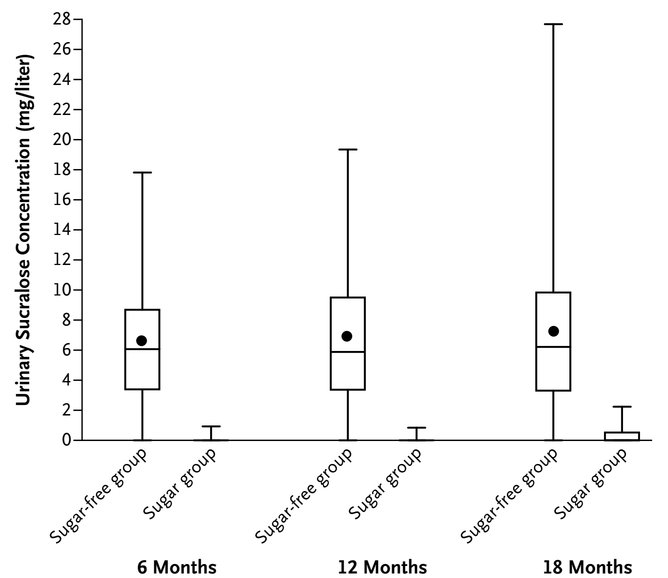

Figure 2. **Urinary Sucralose Concentrations.**

The sucralose concentration was determined in spot urine samples by means of liquid chromatography with mass spectrometry.[21] Samples were obtained from randomly selected children who completed the study. We assigned a value of 0.01 to samples below the detection limit of 0.02 mg per liter. The upper and lower ends of the boxes indicate the 25th and 75th quartiles, the black dots means, the horizontal lines within the boxes medians, the upper whisker the maximum value, and the lower whisker the minimum value. Values for the sugar-free group are based on samples obtained from 116 children at 6 months and from 117 children at 12 and 18 months. Mean (±SD) urinary sucralose concentrations were 6.3±3.7 mg per liter at 6 months, 6.6±4.5 mg per liter at 12 months, and 7.0±5.6 mg per liter at 18 months; sucralose was undetectable in 3% of samples at 6 months, 8% of samples at 12 months, and 10% of samples at 18 months. Values for the sugar group are based on samples obtained from 54 children at 6 months and 36 children at 12 and 18 months. Mean values were 0.04±0.13 mg per liter at 6 months, 0.03±0.14 mg per liter at 12 months, and 0.31±0.56 mg per liter at 18 months; sucralose was undetectable in 93% of samples at 6 months, 97% of samples at 12 months, and 67% of samples at 18 months. We also pooled 543 samples from participants at baseline to produce 20 pools. The mean sucralose concentration in these samples was 0.06±0.07 mg per liter.

DISCUSSION

We found that masked replacement of a sugar-containing beverage with a sugar-free beverage significantly reduced weight gain and body fat gain in healthy children. Our study had several strengths. The double-blind design eliminated the effects of psychological cues and socially desirable behavior and allowed testing of biologic mechanisms alone. Although blinding was im-

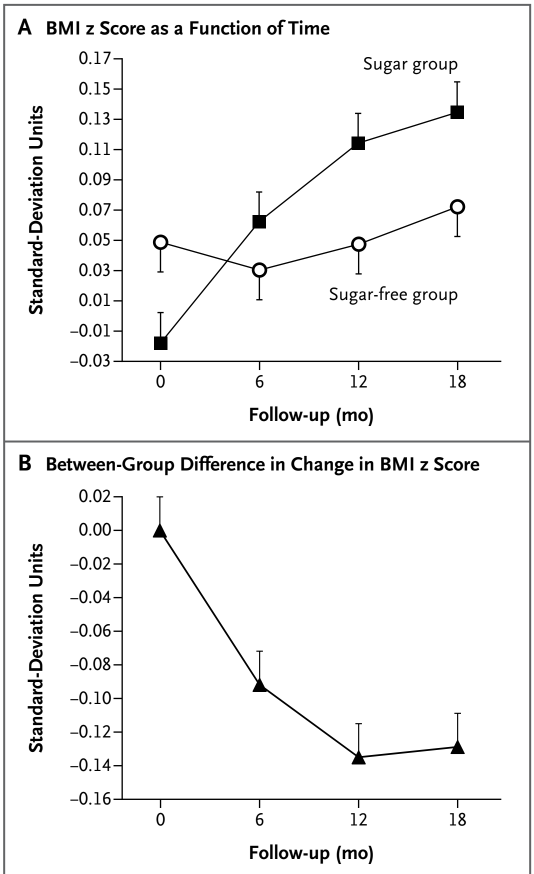

Figure 3. Body-Mass Index (BMI) z Score in the 477 Children Who Drank the Study Beverages for the Full 18 Months.

The z score for BMI is the BMI expressed as the number of standard deviations by which a child differed from the mean in the Netherlands for his or her age and sex. Panel A shows mean z scores for the two study groups over the 18-month study period. Panel B shows the between-group difference in the mean change from baseline (the mean change in the BMI z score in the sugar-free group minus the mean change in the sugar group), as a function of time. T bars in both panels indicate standard errors.

perfect, it was more successful than in most randomized, double-blind trials.[31,32] Measurements of urinary sucralose levels suggested a high rate of adherence. Previous trials may have yielded inconsistent results because of small samples, short duration, poor adherence, or lack of individual randomization.[14-19] Our sample size was adequate to allow precise outcomes, and the 18-month study duration ensured that the observed effect was not transient. The large sample and stratified randomization produced well-balanced study groups at baseline. We assume that the mean changes in other factors that affect weight were also similar between the groups. Thus, the observed differences in body fat and BMI z score can be ascribed primarily to the assigned beverage.

Our study had certain limitations. A total of 26% of the participants did not complete the study. However, as long as they were participating in the study, their changes in weight and body fat paralleled those in children who ultimately completed the study. We therefore suggest that the study beverage was not inherently inefficacious in these children. Data on weight and height at the end of the study were available for most of the children. When we pooled those measurements with the measurements for the children who completed the study, the effect of the study beverage became smaller and nonsignificant. This finding was expected; the children who did not complete the study probably went back to drinking sugary beverages, which attenuated the effect of any sugar-free beverages that they consumed before discontinuation.

Approximately 0.5 kg of the difference in weight gain between the two study groups was due to fat mass. We speculate that another 0.3 kg may have been due to the changes in lean mass that accompany changes in body fat.[33-35] Thus, about 0.8 kg of the difference in weight gain was probably due to body fat and associated muscle and other tissues.[33] Another 0.2 kg can be ascribed to the difference in height gain.[23] Therefore, the increases in body weight as predicted from increases in fat mass and height differed by about 1 kg between the study groups. This estimate is consistent with the actual measured difference in body-weight change.

Although the difference in height gain was minute, it warrants scrutiny. Some studies suggest that obese prepubertal children are indeed taller than normal-weight children.[36] However, obesity is associated with an earlier onset of puberty,[37-39] which predicts shorter stature in adults.[40] The increase in BMI in Dutch children in the past decades has not led to an increase in final height.[23] We speculate that a modest reduction of liquid calories in children will have little effect on adult height.

A plausible explanation for the observed reduction in body fat is that the removal of liquid sugar was not sensed by satiating mechanisms and was incompletely compensated for by the increased consumption of other foods.[41] We speculate that reduced ingestion of liquid sugars might also reduce the insulin spike and thus diminish hunger.[42] We find it less likely that our results were caused by the artificial sweeteners in the sugar-free beverages, because sweeteners do not suppress caloric intake.[43,44] Therefore, we assume that water or other noncaloric beverages would be as effective.

In observational studies, the consumption of artificially sweetened beverages is associated with weight gain rather than weight loss.[45,46] This finding has led to the hypothesis that artificial sweeteners induce weight gain (e.g., by activating sweet-taste receptors in the gut).[47] Our findings do not support this hypothesis. Alternatively, people who are at risk for gaining weight may turn to artificial sweeteners in an attempt to reduce caloric intake.[45,46] Consumers may also believe that the use of such sweeteners permits them to eat more of other foods, but this may lead to a net increase in total caloric intake.[46] Whatever the explanation, the epidemiologic association of the use of artificial sweeteners with obesity does show that switching to artificially sweetened beverages by itself is insufficient to combat weight gain.

The participants in our study were healthy Dutch children, most of whom were white and of normal weight. Thus, we do not know whether the results would be similar in other ethnic groups, obese children, or adults, though we speculate that the same biologic mechanisms are operative. The findings of Ebbeling et al.,[48] reported elsewhere in this issue of the *Journal*, would support such speculation. The findings of Qi et al.,[49] reported elsewhere in this issue of the *Journal*, suggest that persons with a genetic predisposition to obesity are especially susceptible to the effects of sugar-sweetened beverages on BMI.

Children in the United States consume on average almost three times as many calories from sugar-sweetened beverages as the amount provided in our trial.[50] We speculate that decreased consumption of such beverages might reduce the high prevalence of overweight in these children.

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REFERENCES

1. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of obesity and trends in body mass index among US children and adolescents, 1999-2010. JAMA 2012;307:483-90.
2. Olds T, Maher C, Zumin S, et al. Evidence that the prevalence of childhood overweight is plateauing: data from nine countries. Int J Pediatr Obes 2011;6:342-60.
3. Duffey KJ, Popkin BM. Shifts in patterns and consumption of beverages between 1965 and 2002. Obesity (Silver Spring) 2007;15:2739-47.
4. Mattes R. Fluid calories and energy balance: the good, the bad, and the uncertain. Physiol Behav 2006;89:66-70.
5. Dhingra R, Sullivan L, Jacques PF, et al. Soft drink consumption and risk of developing cardiometabolic risk factors and the metabolic syndrome in middle-aged adults in the community. Circulation 2007;116:480-8. [Erratum, Circulation 2007;116(23):e557.]
6. Dubois L, Farmer A, Girard M, Peterson K. Regular sugar-sweetened beverage consumption between meals increases risk of overweight among preschool-aged children. J Am Diet Assoc 2007;107:924-34.
7. Ludwig DS, Peterson KE, Gortmaker SL. Relation between consumption of sugar-sweetened drinks and childhood obesity: a prospective, observational analysis. Lancet 2001;357:505-8.
8. Schulze MB, Manson JE, Ludwig DS, et al. Sugar-sweetened beverages, weight gain, and incidence of type 2 diabetes in young and middle-aged women. JAMA 2004;292:927-34.
9. Newby PK, Peterson KE, Berkey CS, Leppert J, Willett WC, Colditz GA. Beverage consumption is not associated with changes in weight and body mass index among low-income preschool children in North Dakota. J Am Diet Assoc 2004;104:1086-94.
10. O'Connor TM, Yang SJ, Nicklas TA. Beverage intake among preschool children and its effect on weight status. Pediatrics 2006;118(4):e1010-e1018.
11. Park S, Blanck HM, Sherry B, Brener N, O'Toole T. Factors associated with sugar-sweetened beverage intake among United States high school students. J Nutr 2012;142:306-12.
12. Fewell Z, Davey Smith G, Sterne JAC. The impact of residual and unmeasured confounding in epidemiologic studies: a simulation study. Am J Epidemiol 2007;166:646-55.
13. Vandenbroucke JP. Observational research, randomised trials, and two views of medical science. PLoS Med 2008;5(3):e67.
14. Raben A, Vasilaras TH, Møller AC, Astrup A. Sucrose compared with artificial sweeteners: different effects on ad libitum food intake and body weight after 10 wk of supplementation in overweight subjects. Am J Clin Nutr 2002;76:721-9.
15. Tordoff MG, Alleva AM. Effect of drinking soda sweetened with aspartame or high-fructose corn syrup on food intake and body weight. Am J Clin Nutr 1990;51:963-9.
16. Raben A, Møller BK, Flint A, et al. Increased postprandial glycaemia, insulinemia, and lipidemia after 10 weeks' sucrose-rich diet compared to an artificially sweetened diet: a randomised controlled trial. Food Nutr Res 2011;55:5961-74.
17. Ebbeling CB, Feldman HA, Osganian SK, Chomitz VR, Ellenbogen SJ, Ludwig DS. Effects of decreasing sugar-sweetened beverage consumption on body weight in adolescents: a randomized, controlled pilot study. Pediatrics 2006;117:673-80.

18. James J, Thomas P, Cavan D, Kerr D. Preventing childhood obesity by reducing consumption of carbonated drinks: cluster randomised controlled trial. BMJ 2004; 328:1237-43. [Erratum, BMJ 2004;328: 1236.]

19. Tate DF, Turner-McGrievy G, Lyons E, et al. Replacing caloric beverages with water or diet beverages for weight loss in adults: main results of the Choose Healthy Options Consciously Everyday (CHOICE) randomized clinical trial. Am J Clin Nutr 2012;95:555-63.

20. de Ruyter JC, Olthof MR, Kuijper LD, Katan MB. Effect of sugar-sweetened beverages on body weight in children: design and baseline characteristics of the Double-blind, Randomized INtervention study in Kids. Contemp Clin Trials 2012;33:247-57.

21. Yang DJ, Chen B. Simultaneous determination of nonnutritive sweeteners in foods by HPLC/ESI-MS. J Agric Food Chem 2009;57:3022-7.

22. Roberts A, Renwick AG, Sims J, Snodin DJ. Sucralose metabolism and pharmacokinetics in man. Food Chem Toxicol 2000; 38:Suppl 2:S31-S41.

23. Schönbeck Y, Talma H, van Dommelen P, et al. Increase in prevalence of overweight in Dutch children and adolescents: a comparison of nationwide growth studies in 1980, 1997 and 2009. PLoS One 2011;6(11):e27608.

24. Cole TJ, Flegal KM, Nicholls D, Jackson AA. Body mass index cut offs to define thinness in children and adolescents: international survey. BMJ 2007;225:194.

25. Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. BMJ 2000; 3220:1240-3.

26. Rush EC, Puniani K, Valencia ME, Davies PS, Plank LD. Estimation of body fatness from body mass index and bioelectrical impedance: comparison of New Zealand European, Maori and Pacific Island children. Eur J Clin Nutr 2003;57:1394-401.

27. Bang H, Ni L, Davis CE. Assessment of blinding in clinical trials. Control Clin Trials 2004;25:143-6.

28. Berkey CS, Colditz GA. Adiposity in adolescents: change in actual BMI works better than change in BMI z score for longitudinal studies. Ann Epidemiol 2007; 17:44-50.

29. Groenwold RH, Donders AR, Roes KC, Harrell FE Jr, Moons KG. Dealing with missing outcome data in randomized trials and observational studies. Am J Epidemiol 2012;175:210-7.

30. Deurenberg P, Pieters JJ, Hautvast JG. The assessment of the body fat percentage by skinfold thickness measurements in childhood and young adolescence. Br J Nutr 1990;63:293-303.

31. Fergusson D, Glass KC, Waring D, Shapiro S. Turning a blind eye: the success of blinding reported in a random sample of randomised, placebo controlled trials. BMJ 2004;328:432-4.

32. Hróbjartsson A, Forfang E, Haahr MT, Als-Nielsen B, Brorson S. Blinded trials taken to the test: an analysis of randomized clinical trials that report tests for the success of blinding. Int J Epidemiol 2007;36:654-63.

33. Ducher G, Bass SL, Naughton GA, Eser P, Telford RD, Daly RM. Overweight children have a greater proportion of fat mass relative to muscle mass in the upper limbs than in the lower limbs: implications for bone strength at the distal forearm. Am J Clin Nutr 2009;90:1104-11.

34. Tremblay A, Després JP, Thériault G, Fournier G, Bouchard C. Overfeeding and energy expenditure in humans. Am J Clin Nutr 1992;56:857-62.

35. Treuth MS, Butte NF, Sorkin JD. Predictors of body fat gain in nonobese girls with a familial predisposition to obesity. Am J Clin Nutr 2003;78:1212-8.

36. Ajala O, Frémeaux AE, Hosking J, et al. The relationship of height and body fat to gender-assortative weight gain in children: a longitudinal cohort study (EarlyBird 44). Int J Pediatr Obes 2011;6:223-8.

37. Buyken AE, Karaolis-Danckert N, Remer T. Association of prepubertal body composition in healthy girls and boys with the timing of early and late pubertal markers. Am J Clin Nutr 2009;89:221-30.

38. Mumby HS, Elks CE, Li S, et al. Mendelian randomisation study of childhood BMI and early menarche. J Obes 2011; 2011:180729.

39. Ong KK, Emmett P, Northstone K, et al. Infancy weight gain predicts childhood body fat and age at menarche in girls. J Clin Endocrinol Metab 2009;94: 1527-32.

40. McIntyre MH. Adult stature, body proportions and age at menarche in the United States National Health and Nutrition Survey (NHANES) III. Ann Hum Biol 2011;38:716-20. [Erratum, Ann Hum Biol 2012;39:264.]

41. Cassady BA, Considine RV, Mattes RD. Beverage consumption, appetite, and energy intake: what did you expect? Am J Clin Nutr 2012;95:587-93.

42. Ludwig DS. The glycemic index: physiological mechanisms relating to obesity, diabetes, and cardiovascular disease. JAMA 2002;287:2414-23.

43. Blundell JE, Green SM. Effect of sucrose and sweeteners on appetite and energy intake. Int J Obes Relat Metab Disord 1996;20:Suppl 2:S12-S17.

44. Renwick AG, Molinary SV. Sweet-taste receptors, low-energy sweeteners, glucose absorption and insulin release. Br J Nutr 2010;104:1415-20.

45. Foreyt J, Kleinman R, Brown R, Lindstrom R. The use of low-calorie sweeteners by children: implications for weight management. J Nutr 2012;142:1155S-1162S.

46. Fowler SP, Williams K, Resendez RG, Hunt KJ, Hazuda HP, Stern MP. Fueling the obesity epidemic? Artificially sweetened beverage use and long-term weight gain. Obesity (Silver Spring) 2008;16:1894-900.

47. Pepino MY, Bourne C. Non-nutritive sweeteners, energy balance, and glucose homeostasis. Curr Opin Clin Nutr Metab Care 2011;14:391-5.

48. Ebbeling CB, Feldman HA, Chomitz VR, et al. A randomized trial of sugar-sweetened beverages and adolescent body weight. N Engl J Med 2012. DOI: 10.1056/NEJMoa1203388.

49. Qi Q, Chu AY, Kang JH, et al. Sugar-sweetened beverages and genetic risk of obesity. N Engl J Med 2012. DOI: 10.1056/NEJMoa1203039.

50. Wang YC, Bleich SN, Gortmaker SL. Increasing caloric contribution from sugar-sweetened beverages and 100% fruit juices among US children and adolescents, 1988-2004. Pediatrics 2008;121(6):e1604-e1614.