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Fueling the Obesity Epidemic? Artificially Sweetened Beverage Use and Long-term Weight Gain

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We have examined the relationship between artificially sweetened beverage (ASB) consumption and long-term weight gain in the San Antonio Heart Study. From 1979 to 1988, height, weight, and ASB consumption were measured among 5,158 adult residents of San Antonio, Texas. Seven to eight years later, 3,682 participants (74% of survivors) were re-examined. Outcome measures were incidence of overweight/obesity (OW/OB_{inc}) and obesity (OB_{inc}) (BMI ≥ 25 and ≥ 30 kg/m^2, respectively), and BMI change by follow-up (ΔBMI, kg/m^2). A significant positive dose–response relationship emerged between baseline ASB consumption and all outcome measures, adjusted for baseline BMI and demographic/behavioral characteristics. Consuming >21 ASBs/week (vs. none) was associated with almost-doubled risk of OW/OB (odds ratio (OR) = 1.93, P = 0.007) among 1,250 baseline normal-weight (NW) individuals, and doubled risk of obesity (OR = 2.03, P = 0.0005) among 2,571 individuals with baseline BMIs <30 kg/m^2. Compared with nonusers (+1.01 kg/m^2), ΔBMIs were significantly higher for ASB quartiles 2–4: +1.46 (P = 0.003), +1.50 (P = 0.002), and +1.78 kg/m^2 (P < 0.0001), respectively. Overall, adjusted ΔBMIs were 47% greater among artificial sweetner (AS) users than nonusers (+1.48 kg/m^2 vs. +1.01 kg/m^2, respectively, P < 0.0001). In separate analyses—stratified by gender; ethnicity; baseline weight category, dieting, or diabetes status; or exercise-change category—ΔBMIs were consistently greater among AS users. These differences, though not significant among exercise increasers, or those with baseline diabetes or BMI >30 kg/m^2 (P = 0.069), were significant in all 13 remaining strata. These findings raise the question whether AS use might be fueling—rather than fighting—our escalating obesity epidemic.

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INTRODUCTION

In the face of an expanding epidemic of overweight and obesity, individuals have increasingly turned to artificially sweetened (AS) foods and beverages during the past three decades, in an attempt to lose weight, or control it. Implicit and explicit messages of manufacturers—and conventional wisdom—have suggested that use of AS products would enhance weight loss—or, at the least, help prevent further gain. To test this assumption, we have assessed long-term weight change among participants in the San Antonio Heart Study who reported using these products, compared with those who did not.

METHODS AND PROCEDURES

The San Antonio Heart Study is a prospective study of 3,301 Mexican Americans and 1,857 non-Hispanic whites, aged 25–64 years old, residing in households randomly chosen from San Antonio neighborhoods. At baseline, 5,158 individuals were enrolled: cohort 1, from 1979 to 1982, and cohort 2, from 1984 to 1988. The sampling strategy has been previously described (1). Of 4,998 surviving participants, 3,682 (74%) had follow-up examinations 7–8 years later. The study protocol was approved by the Institutional Review Board of the University of Texas Health Science Center at San Antonio; all participants gave written informed consent to participate.

Dietary and exercise measures

At baseline, cohort 1 participants were asked, "How many bottles or cans of soft drinks do you drink per week?" Cups of coffee and cups/glasses of tea were similarly assessed. Cohort 2 participants were asked how often they drank these beverages, and how many beverages they drank per occasion; weekly doses were calculated accordingly.

Participants reporting soft drink use were asked whether they usually drank sugar-free sodas, regular sodas, or similar amounts of each; their AS soda dose was calculated accordingly. For abstainers, AS soda dose was set equal to zero. "Usual" sweeteners for coffee and tea were ascertained, and AS dosage calculated accordingly (or set equal to zero for abstainers). Participants were also asked whether they "usually" used sugar or sugar substitutes.

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We summed AS soda, coffee, and tea intakes to estimate AS beverage (ASB) consumption, and—among consumers—identified ASB consumption quartiles. Participants using AS sweeteners and/or cereals—but not ASBs—were included in ASB consumption quartile 1. Participants reporting no AS use were categorized "nonusers."

Dieting status and exercise frequency (2) were recorded at baseline and follow-up. In cohort 1 only, baseline 24-h dietary recalls were performed (2). In cohort 2 only, follow-up AS use (present or absent) was ascertained.

Physical measurements and demographic data

Standard anthropometric measurements were performed (2). A BMI <25 kg/m^2 was categorized normal weight (NW); ≥ 25 and <30 kg/m^2, overweight (OW); and ≥ 30 kg/m^2, obese (OB). The latter categories were combined as OW/OB (BMI ≥ 25 kg/m^2). Baseline education and occupation were recorded, and occupation-based Duncan socioeconomic index scores (range: 0–96) assigned. Of 3,682 follow-up participants, 3371 (91.6%) had complete data for all variables reported.

Statistical analyses

Incidence of OW/OB (OW/OB$_{inc}$) was defined as the percent of baseline NW participants who had become OW/OB by follow-up. Incidence of obesity (OB$_{inc}$) was defined as the percent of baseline NW-or-OW participants (BMI < 30 kg/m^2) who had become OB by follow-up. Change in BMI (ΔBMI) was calculated as BMI at follow-up minus BMI at baseline. Change in exercise frequency (Δexercise) was calculated as the number of exercise sessions per week at follow-up minus the number of sessions per week at baseline. Participants with Δexercise ≥1/week were categorized as "exercising more"; those ≤−1/week, as "exercising less"; and all others, as "exercising same." Excess BMI gains in AS users ("users") were calculated as ΔBMI among users minus ΔBMI among nonusers, divided by ΔBMI among nonusers.

Means of continuous variables and percentages of categorical variables are presented by baseline AS consumption status. We used logistic regression to adjust odds ratios (ORs) for baseline BMI, as well as gender and ethnicity; baseline age, education, socioeconomic index, exercise frequency, and smoking status; interim change in exercise level; and interim smoking cessation ("demographic/behavioral covariates"), with ordinal categories of AS doses/day as a predictor variable. Analysis of covariance was used to assess associations between ASB consumption category and ΔBMI. In logistic regression and analysis of covariance models, linear trend was assessed by models using the ordinal category of ASB doses/day as a continuous measure. All statistical calculations were performed using SAS version 9.1 (SAS Institute, Cary, NC).

Analyses of ΔBMI—with adjustment for baseline BMI and demographic/behavioral covariates—were performed for the entire sample. Within cohort 2, they were repeated separately by baseline AS use status (present or absent), with additional adjustment for follow-up AS status. Within cohort 2, these analyses were also repeated among participants whose AS use status (present or absent) remained unchanged at follow-up.

RESULTS

Table 1 presents baseline characteristics for 3,371 participants whose baseline ASB dose, baseline and follow-up BMI, and all covariate data were available. Age, education, socioeconomic index, exercise, and dieting were greater in AS users, who were more likely to be female and OW/OB, and less likely to be Hispanic or smokers (vs. non-AS-users, all $P < 0.0001$). Total calories, calories from carbohydrates and sucrose, and alcohol consumption were lower among AS users ($P < 0.0001$), whose sugar-sweetened beverage (SSB) consumption was one-fourth that of nonusers. Milk consumption was also lower among AS users ($P = 0.018$), but calcium intake was similar in the two

Table 1 Baseline characteristics by self-reported AS use: means (s.d.) and percentages

	Self-reported artificial sweetener use		
Characteristics	No AS use	Any AS use	*P* for difference
n	1,767	1,604	—
Female (%)	53.0%	63.2%	<0.0001
Age (years)	43.5 (11.0)	44.7 (10.7)	0.0012
Mexican American (%)	70.5%	56.6%	<0.0001
Education (years)	11.2 (4.3)	12.8 (3.7)	<0.0001
Socioeconomic index	46.8 (22.8)	56.1 (20.4)	<0.0001
BMI (kg/m^2)	26.9 (5.3)	27.9 (5.6)	<0.0001
Currently dieting (%)	12.1%	33.4%	<0.0001
Currently exercising (%)	19.7%	35.6%	<0.0001
Exercise frequency/week	1.4 (2.6)	2.1 (2.8)	<0.0001
Currently smoking	31.6%	21.5%	<0.0001
Overweight or obese (%)	60.2%	67.6%	<0.0001
Obese (%)	23.1%	27.8%	0.0019
Diet sodas/day	0.0 (0.0)	0.7 (1.4)	—
Regular sodas/day	1.0 (2.6)	0.3(0.8)	<0.0001
Total sodas/day	0.95 (2.6)	1.03 (1.6)	0.285
Cups of coffee/day	2.1 (2.7)	2.2 (2.3)	0.344
Cups/glasses of tea/day	1.3 (2.4)	1.4 (2.0)	0.028
Sugar-sweetened drinks[a]/day	3.2 (4.2)	0.9 (1.7)	<0.0001
Artificially sweetened drinks/day	0.0 (0.0)	2.3 (2.9)	—
Alcoholic beverages/day	0.76	0.50	<0.0001
Glasses of milk/day	0.8 (1.3)	0.7 (1.0)	0.018
Total beverage servings[b]/day	5.8 (4.9)	5.8 (3.8)	0.8702
AS beverages (% of total[b])	0	40.1%	—
24-h dietary data (cohort 1 only)			
n	827	668	—
Total kilocalories/day	2,080.3 (903.9)	1,857.4 (827.8)	<0.0001
Fat (% of calories)	37.5 (9.7)	40.4 (10.3)	<0.0001
Saturated fat (% of calories)	13.1 (4.3)	14.3 (4.7)	<0.0001
Protein (% of calories)	15.7 (4.7)	17.2 (5.5)	<0.0001
Carbohydrates (% of calories)	43.7 (10.8)	39.9 (10.9)	<0.0001
Sucrose (% of calories)	10.8 (7.8)	8.5 (6.6)	<0.0001
Fiber (g/day)	7.8 (7.6)	7.6 (6.9)	0.608
Calcium (mg/day)	613.1	596.1	0.512

AS, artificial sweetner.
[a]Sugar-sweetened coffee, tea, and soft drinks. [b]Coffee + tea + soft drinks + milk + alcohol.

groups. Percent of calories from protein, total fat, and saturated fat were significantly higher in AS users ($P < 0.0001$).

Follow-up participants and nonreturnees had comparable baseline BMIs (27.16 vs. 27.25 kg/m^2, $P = 0.58$). Dieting rates were also similar (22.4% vs. 20.6%, respectively, $P = 0.16$). Returnees were older (44.6 vs. 42.1 years, < 0.001) and more likely to exercise (26.8% vs. 24.2%, $P = 0.054$) and use AS (47.1% vs. 44.0%, $P = 0.040$) at baseline, than nonreturnees. Among returnees, baseline AS users were more likely than nonusers to have decreased exercise frequency: −0.161 vs. +0.17 times/week, respectively ($P = 0.005$).

ORs for OW/OB$_{inc}$ (**Figure 1a**) and OB$_{inc}$ (**Figure 1b**) for 3,371 participants for whom all covariate data are available are displayed by baseline ASB consumption quartile (vs. nonusers). These ORs have been adjusted for baseline BMI, age, ethnicity, gender, education, socioeconomic index, baseline and interim change in exercise frequency, baseline smoking status, and interim smoking cessation.

Overall, among 1,250 participants who had been NW at baseline, 428 (34.0%) had BMIs ≥25 kg/m^2 by follow-up; among 2,571 with BMI <30 kg/m^2 at baseline, 390 (15.2%) had BMIs ≥30 kg/m^2 by follow-up. Both OW/OB$_{inc}$ and OB$_{inc}$ showed significant dose–response relationships with ASB consumption. Among users, in ASB quartiles 1–4, ORs for OW/OB$_{inc}$ (with 95% confidence intervals) were 1.56 (1.02, 2.40, $P = 0.041$), 1.74 (1.10, 2.77, $P = 0.018$), 1.75 (1.09, 2.82, $P = 0.021$), and 1.93 (1.20, 3.11, $P = 0.007$), respectively. ORs for OB$_{inc}$ for ASB consumption quartiles 1–4 were 1.34 (0.86, 2.08), 1.46 (0.96, 2.22, $P = 0.075$), 1.73 (1.13, 2.63, $P = 0.011$), and 2.03 (1.36, 3.03, $P = 0.0005$). Risk increased most between nonuse and quartile 1, but continued rising (trend: $P < 0.001$ for OW/OB$_{inc}$, $P < 0.0001$ for OB$_{inc}$) toward a doubling with peak dosage.

A positive dose–response relationship was observed between ASB use and ΔBMI (**Figure 2a**, $P < 0.0001$ for trend): mean ΔBMIs were 1.01 (0.88, 1.14), 1.11 (0.85, 1.38), 1.46 (1.20, 1.73, $P = 0.003$), 1.50 (1.23, 1.78, $P = 0.002$), and 1.78 (1.51, 2.06, $P < 0.0001$) kg/m^2 for nonusers and ASB quartiles 1–4, respectively. Thus, participants in ASB quartile 4 experienced 78% greater ΔBMIs than nonusers. Similar results emerged from cohort 2 sub-analyses excluding interim AS adopters and discontinuers (**Figure 2b**): in this subset, ASB quartiles 3 and 4 experienced 74% ($P = 0.013$) and 83% ($P = 0.003$)

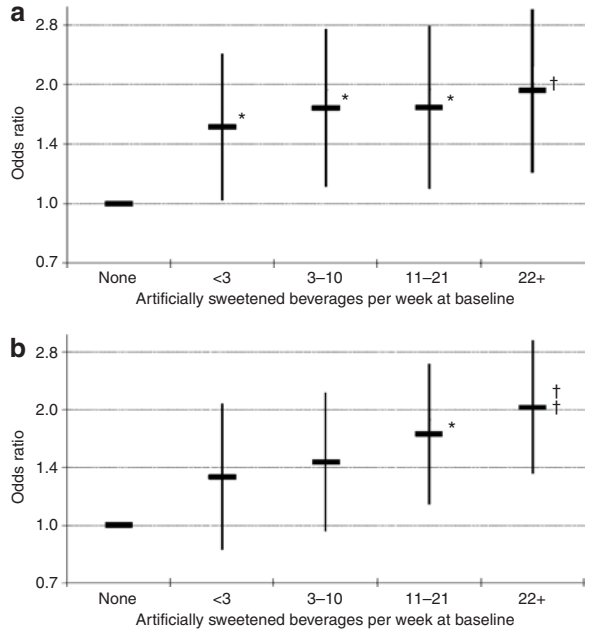

Figure 1 Odds ratios (ORs) and 95% confidence intervals for OW/OB$_{inc}$ by 7- to 8-year follow-up. (**a**) ORs for becoming overweight/obese by 7- to 8-year follow-up, according to artificially sweetened beverage consumption quartile at baseline. (**b**) ORs for becoming obese by 7- to 8-year follow-up, according to artificially sweetened beverage consumption quartile at baseline. Panel **a** shows ORs for the incidence of BMI ≥25 kg/m^2 at follow-up: 428 incident cases among 1,250 with BMI <25 kg/m^2 at baseline. Overall $P = 0.008$; trend $P < 0.001$. Panel **b** shows ORs for the incidence of BMI ≥30 kg/m^2: 390 incident cases among 2,571 with BMI <30 kg/m^2 at baseline. Overall $P = 0.005$; trend $P < 0.0001$. Adjusted for gender and ethnicity; baseline age, education, socioeconomic index, BMI, exercise frequency, and smoking status; and interim change in exercise level and smoking cessation. *vs. none: $P < 0.05$; †vs. none: $P < 0.01$; ‡vs. none: $P < 0.001$. OB$_{inc}$, incidence of obesity; OW/ OB$_{inc}$, incidence of overweight/obesity.

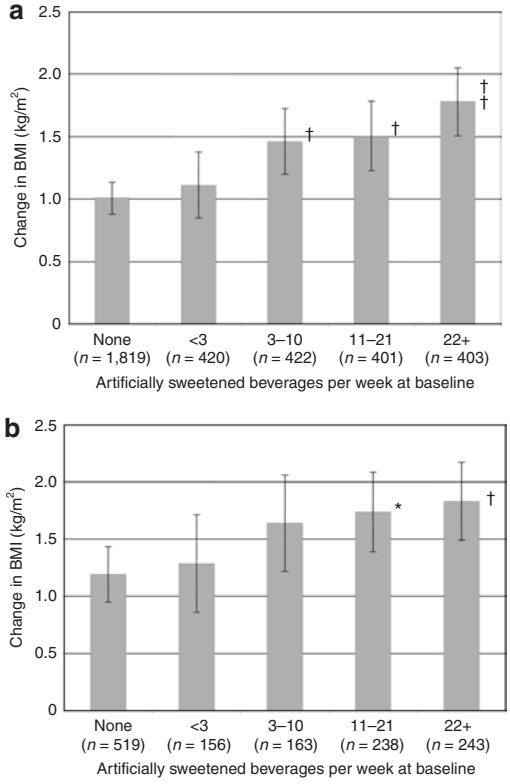

Figure 2 Change in BMI in kg/m^2, by 7-to 8-year follow-up. (**a**) Change in BMI, in kg/m^2, by 7- to 8-year follow-up, in both cohorts, according to artificially sweetened beverage consumption quartile at baseline. $P < 0.0001$ for trend. (**b**) Change in BMI, in kg/m^2, by 7- to 8-year follow-up, among cohort 2 participants, with interim artificial sweetener adopters and discontinuers excluded. $P < 0.0006$ for trend. Adjusted for gender and ethnicity; baseline age, education, socioeconomic index, BMI, exercise frequency, and smoking status; and interim change in exercise level and smoking cessation. *vs. none: $P < 0.05$; †vs. none: $P < 0.01$; ‡vs. none: $P < 0.001$.

Table 2 Change in BMI[a] (mean ± s.e., kg/m²), by 7- to 8-year follow-up, by AS consumption

Stratum	ΔBMI among nonusers	*n*	ΔBMI among AS users	*n*	Difference[b] (95% CI)	Excess gains[c] among AS users (%)	*P* for difference
Overall	1.01 ± 0.07	1,767	1.48 ± 0.07	1,604	0.47 (0.26, 0.66)	+47	<0.0001
Men	0.67 ± 0.09	830	1.08 ± 0.11	591	0.40 (0.11, 0.69)	+59	0.0071
Women	1.26 ± 0.10	937	1.78 ± 0.09	1,013	0.51 (0.24, 0.79)	+41	0.0003
Mexican American	1.04 ± 0.08	1,245	1.43 ± 0.10	9,080	0.39 (0.13, 0.65)	+37	0.0038
Non-Hispanic white	0.95 ± 0.12	522	1.56 ± 0.10	696	0.61 (0.30, 0.93)	+65	<0.0001
BMI <25	1.45 ± 0.09	703	2.00 ± 0.10	519	0.55 (0.28, 0.83)	+38	<0.0001
25 ≤BMI <30	1.01 ± 0.10	655	1.35 ± 0.10	639	0.35 (0.06, 0.63)	+34	0.0181
BMI ≥30	0.43 ± 0.19	409	0.94 ± 0.18	446	0.51 (–0.04, 1.05)	+116	0.0687
Diabetic	–0.76 ± 0.26	133	–0.37 ± 0.22	179	0.39 (–0.31, 1.08)	51% smaller loss	0.2740
Nondiabetic	1.20 ± 0.07	1,616	1.69 ± 0.08	1,412	0.49 (0.29, 0.70)	+41	<0.0001
Dieting	1.23 ± 0.22	213	2.00 ± 0.14	534	0.77 (0.26, 1.28)	+62	0.0033
Not dieting	0.97 ± 0.07	1,548	1.24 ± 0.08	1,065	0.26 (0.04, 0.48)	+27	0.0191
Exercise less	1.42 ± 0.14	405	2.03 ± 0.13	498	0.61 (0.23, 0.99)	+43	0.0016
Exercise same	1.01 ± 0.10	910	1.49 ± 0.11	671	0.48 (0.17, 0.78)	+47	0.0021
Exercise more	0.60 ± 0.13	452	0.92 ± 0.13	435	0.32 (–0.05, 0.69)	+53	0.0920
Cohort 1	0.94 ± 0.10	858	1.34 ± 0.11	689	0.40 (0.10, 0.71)	+43	0.0104
Cohort 2	1.10 ± 0.09	909	1.58 ± 0.09	915	0.48 (0.22, 0.75)	+44	0.0004

ΔBMI, change in BMI; CI, confidence interval.
[a]Mean ± s.e., stratified by baseline characteristics, and adjusted for remaining characteristics: gender and ethnicity; baseline age, education, socioeconomic index, BMI, exercise frequency, and smoking status; and interim change in exercise level, and smoking cessation. [b]ΔBMI in artificial sweetner (AS) users minus ΔBMI in nonusers, in kg/m². [c]Difference divided by ΔBMI in nonusers.

greater ΔBMIs, respectively, compared with nonusers (P = 0.0006 for trend).

In separate cohort 2 analyses examining baseline non-AS-users (n = 915), interim AS adopters and nonadopters experienced similar ΔBMIs: 1.08 and 1.20 kg/m², respectively (P = 0.488). Baseline AS users (n = 920) who discontinued use by follow-up experienced 59% lower ΔBMIs than continuers (1.03 kg/m² vs. 1.62 kg/m², respectively, P = 0.038). Thus, AS adoption conferred no significant advantage, but discontinuation was associated with significantly lower ΔBMI.

No positive relationship emerged between SSB consumption and ΔBMI in our data. Overall, ΔBMIs were, in fact, lower among SSB users: 1.48 (1.30, 1.66) kg/m² among SSB nonusers, compared with 1.18 (0.90, 1.45), 1.17 (0.93, 1.41; P = 0.04), 1.05 (0.83, 1.26; P = 0.003), and 1.15 (0.95, 1.34; P = 0.02) kg/m² for SSB quartiles 1–4 (P = 0.009 for trend). In cohort 2 subanalyses excluding AS adopters and discontinuers, however, no significant relationship was found between SSB consumption and ΔBMIs, which were 1.59 (1.34, 1.84) kg/m² for nonusers, vs. 1.64 (1.20, 2.09), 1.40 (0.99, 1.82), 1.06 (0.71, 1.42; P = 0.02), and 1.54 (1.23, 1.85) kg/m² for SSB quartiles 1–4 (P = 0.26 for trend).

Overall (Table 2, n = 3,371), ΔBMIs were 47% higher in AS users than nonusers (+1.48 vs. +1.01 kg/m², respectively, P < 0.0001). Within-stratum analyses were performed for seven key variables: gender; ethnicity; weight category, diabetes and dieting status at baseline; Δexercise category; and cohort. Point estimates for all subgroups suggested greater BMI gains (or smaller losses) for AS users vs. nonusers; these differences were significant for all but three strata: those with increasing exercise frequency, and those with either diabetes or BMI ≥30 kg/m² at baseline (P = 0.069 for the latter).

Dieting was strongly associated with AS consumption: 72% of dieters—vs. 41% of nondieters—used ASs. Overall, baseline dieters gained more weight by follow-up than nondieters (P < 0.001). Within each group, however, AS users experienced significantly higher ΔBMIs. Among dieters, mean ΔBMI was 2.00 kg/m² for AS users, 1.23 kg/m² for nonusers (P = 0.003). Thus, a 5′ 3″dieter might have gained 11 lbs with AS use, 7 lbs without; a 6′ 2″dieter might have gained 15 lbs with AS use, 10 lbs without.

Excess gains associated with AS use were marked among dieters (62%), men (59%), and non-Hispanic whites (65%). Within each Δexercise category, point estimates for ΔBMI were over 40% higher for AS users.

Soft drinks, tea, and coffee comprised 31.3, 39.4, and 29.3%, respectively, of AS beverage consumption. For each beverage, AS users experienced significantly higher ΔBMIs (Table 3).

DISCUSSION

Limitations

Sweetener-specific ORs cannot be calculated because AS type was not recorded. Our beverage-dose estimates also represent minima. Fruit-flavored juices/drinks/mixes—usually less

Table 3 Change in BMI[a] (mean ± s.e., kg/m²), by AS beverage type consumed at baseline

AS beverage type	ΔBMI with no use of specified beverage	*n*	ΔBMI with any use of specified beverage (kg/m²)	*n*	Difference[b] (95% CI)	*P*
Diet soft drinks	1.10 ± 0.06	2,301	1.52 ± 0.09	1,070	0.42 (0.21, 0.63)	<0.0001
AS tea	1.14 ± 0.06	2,527	1.54 ± 0.10	844	0.40 (0.18, 0.63)	<0.0001
AS coffee	1.19 ± 0.05	2,894	1.52 ± 0.13	477	0.32 (0.05, 0.60)	<0.0001

AS, artificial sweetner; ΔBMI, change in BMI; CI, confidence interval.
[a]BMI, adjusted for gender and ethnicity; baseline age, education, socioeconomic index, BMI, exercise frequency, and smoking status; and interim change in exercise level and smoking cessation. [b]ΔBMI in users minus ΔBMI in nonusers.

costly than sodas—were not included. Dose underestimation was therefore probably greater among the poor, who also experience greater obesity. Thus, risks may be underestimated for both SSB and ASB.

In addition, beverage-only AS dose calculations significantly underestimate total exposure, because over 6,000 products—including foods, beverages, cosmetics, and pharmaceuticals—contain aspartame alone (3). Users' AS doses from "lite" foods were probably substantial; "nonusers" almost certainly consumed AS, knowingly or otherwise, to varying degrees.

Results from previous studies

Results from interventional studies have varied significantly. Several studies have described increased appetite (4,5), hunger (6), and food consumption (7–10) following AS exposure. The majority, however, as reviewed by Rolls (11) and Malik (12), have reported either no increases, or actual decreases, in hunger, consumption, and/or weight following AS exposure. De la Hunty, summarizing a meta analysis of weight-change data from nine randomized clinical trials (13), reported significantly greater weight loss among aspartame users vs. nonusers ($P = 0.04$ for the most conservative comparison, which excluded follow-up periods and studies with weight gains among enforced-intake comparison groups), and concluded a beneficial role for aspartame use in weight control.

Each of the nine interventions included in the meta analysis incorporated one or more design features, however, which would limit replicability in long-term, population-based observational studies such as our own: short duration (7 days to 16 weeks); gender, ethnicity, and age exclusions; blinding to sweetener type; and, perhaps most significant, aggressive ancillary interventions, including caloric restriction; dietary record-keeping; frequent clinic visits; physical activity programs; and weekly behavior-modification sessions. Not surprisingly, therefore, community-based observational studies have typically failed to replicate the findings of weight-loss benefits from AS use reported from such interventions.

Several prospective studies have found no strong relationship between AS use and weight change. Striegel-Moore reported increased caloric intake and 10-year weight gain among diet-soda consumers in a pediatric study, but the latter were not significant (14). Parker (15) reported increased weight gain among adult New England saccharin users, but this relationship was not significant after adjustment for total caloric intake. It should be noted, however, that if AS use somehow leads to increased caloric consumption, this would represent overadjustment.

More often, however, long-term observational studies have reported results congruent with our own. Stellman, reporting results from an American Cancer Society study, found modestly higher 1-year weight gain among middle-aged AS users (vs. nonusers) (16). Colditz reported a weak positive association between saccharin use and subsequent weight gain in 1976–1984 Nurses' Health Study data (17). Blum reported higher baseline diet-soda intake, and greater interim increases, among NW elementary-school children who became OW (vs. not) by 2-year follow-up (18). Berkey reported increased 1-year ΔBMI with increased diet-soda consumption among sons of Nurses' Health Study II participants; daughters exhibited a similar—though nonsignificant—trend (19). Lutsey reported 34% higher 9-year incidence of metabolic syndrome within the highest (vs. lowest) tertile of diet-soda consumption in the Atherosclerosis Risk in Communities study (20), and Dhingra reported 53% higher 4-year incidence of metabolic syndrome among daily (vs. <1/week) diet-soda users, among Framingham Heart Study participants [21]. Because baseline BMI was not included as a covariate in these latter two analyses, this leaves open the possibility that these associations were at least partially confounded by higher diet-soda intake among heavier participants at baseline. But clearly no significant *benefit* from diet-soda consumption was observed in these studies.

In a notable exception, Schulze reported significantly lower 4-year weight gain among a subset of Nurses' Health Study II participants who had increased—vs. decreased—their diet-soda consumption from 1991 to 1995 (22). Interestingly, though, 8-year follow-up data for the total study sample (1991–1999) showed "slight [21%], nonsignificant increased diabetes risk" among daily diet-soda users (23).

Thus, though AS-associated weight gains from observational studies have been modest, these studies, as a rule, have failed to demonstrate weight loss. On the contrary, increased incidence of metabolic syndrome has been observed among AS users in two major observational studies, and nonsignificantly increased incidence of diabetes has been reported in a third.

Possible explanations for our findings

There may be no causal relationship between AS use and weight gain. Individuals seeking to lose weight often switch to ASs in order to reduce their caloric intake. AS use might therefore

simply be a marker for individuals already on weight-gain trajectories, which continued despite their switching to ASs. This is the most obvious possible explanation of our findings. Increased fast food consumption among soda users might further confound apparent associations (24).

The emergence, however, of a significant, positive, dose–response relationship between AS consumption and all three measures of weight gain in our analyses raises the question whether AS use—either directly or indirectly—might in fact have contributed to long-term weight gain in our study population.

We have summarized below several possible putative mechanisms for this apparent relationship.

AS use may be indirectly related to weight gain. Sugar consumption induces a sense of satiety (25). In its absence, fat and protein intake typically increase (5,26–30), and disadvantageous compensation—and/or inadvertent overcompensation—may occur. Percent of calories from total and saturated fat did, in fact, rise with ASB dosage in our data: fat represented 37.5% of calories in nonusers, but 39.6, 40.0, 41.7, and 40.9% for ASB quartiles 1–4, respectively ($P < 0.0001$ for trend). Low-fat diets have been successfully prescribed for weight loss (31,32), and higher fat intake may increase weight gain among genetically susceptible individuals (33). But whether caloric fat increases overall obesity risk is unclear (34,35).

Do consumers of "lite" products overestimate caloric savings achieved through AS use, and unintentionally overcompensate elsewhere in their diets? Several studies support this possibility (36–38), although our AS users reported lower baseline caloric intake. Whether dietary vigilance subsequently waned is unknown, however, because caloric intake at follow-up was not measured in our study.

Alternatively, AS use may successfully support short-term caloric deficit, thereby lowering resting metabolic rate, and increasing long-term weight gain. Because sucrose partially counteracts decreased resting metabolic rate in low-calorie dieters(39), sugar avoiders might face metabolic-rate disadvantages. This might explain the apparently paradoxical findings of increased ΔBMI among AS users, despite lower baseline caloric intake, as in our own study, and/or apparently healthier food choices, as reported in the American Cancer Society study (16). It might also explain the discrepancies between results of short-term interventions and long-term observational studies.

Finally, aspartame, acesulfame potassium, saccharin, sucralose, and neotame are 180, 200, 300, 600, and 7,000–13,000 times sweeter than sugar, respectively. Has their adoption led to taste distortion, and increased appetite for intensely sweet, highly caloric foods?

ASs might directly increase risk of weight gain in some individuals. Some studies have reported that AS use—or sweet taste itself—may increase hunger, cravings, or food intake (10,40–42), though most studies have reported no such increases (43,44). A few studies have reported elevated insulin and/or falling glucose levels (45–47).

Of particular concern are results from rodent studies. Elevated levels of aspartate—which constitutes 40% of aspartame—are toxic to neurons in the arcuate nucleus of the hypothalamus(48,49), a key forebrain site for leptin signaling to reduce food intake (50,51). The earlier the exposure, the more profound the damage (52). *In utero* exposure of rat pups produced OB offspring with elevated intra-abdominal fat levels (49); neonatal exposure by injection produced "an almost total absence of neurons in the arcuate nucleus" (49). Could aspartame exposure at high-normal levels cause neurotoxicity, with increased leptin resistance and obesity, in humans?

Conclusions

We observed a classic, positive dose–response relationship between AS beverage consumption and long-term weight gain. Such an association does not, by itself, establish causality. But it raises a troubling question, which can be answered only by further research: are ASs fueling—rather than fighting—the very epidemic they were designed to block?

These results, together with findings of increased lymphoma and leukemia in young rodents exposed to aspartame (53), should be carefully considered when policy recommendations to deter the development of obesity in children and adolescents are being formulated—particularly those recommending increased AS consumption. Further research is needed to evaluate the possible impact of AS use on the risk of obesity—and its metabolic sequelae—in the next generation, as well as our own.

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DISCLOSURE

The authors declared no conflict of interest.

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