Sugar-Sweetened and Artificially-Sweetened Beverages in Relation to Obesity Risk

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ABSTRACT

The goal of this review was to critically evaluate the scientific evidence in humans on the potential effect of sweetened beverages on weight gain and risk of obesity in youth and adults. Two categories of these beverages were reviewed. Sugar-sweetened beverages (SSBs) include soft drinks, colas, other sweetened carbonated beverages, and fruit drinks with added sugar. Artificially sweetened beverages (ASBs), also referred to as non-nutritive sweetened beverages, are marketed and used as a replacement for SSBs for those who want to reduce sugar and caloric intake. The totality of evidence to date demonstrates a pattern across observational and experimental studies of an increased risk of weight gain and obesity with higher intake of SSBs. However, it remains difficult to establish the strength of the association and the independence from other potentially confounding factors. The primary reason for unclear conclusions regarding the robustness of any effect of SSBs is due to the heterogeneity and methodologic limitations of both observational and experimental studies on this topic. Although some observational studies have suggested that ASBs may cause increased risk of obesity and cardiometabolic diseases, there is no clear mechanism for this pathway, and the epidemiologic studies are highly inconsistent. An important issue with the observational studies on ASBs and obesity or disease risk is reverse causality bias, with higher-quality studies demonstrating this possibility. The field needs higher-quality experimental studies in humans, with relevant direct comparisons between sweetened beverages and their sweetened solid-food alternatives. Adv Nutr 2014;5:797–808.

Introduction

The intake of beverages has changed dramatically over the past few decades, coinciding with an increased prevalence of obesity. Intakes of soft drinks, colas, other sweetened carbonated beverages, and fruit drinks with added sugar have increased dramatically, especially among youth, whereas the intake of milk has declined (1–3). Collectively, these beverages are referred to in this article as sugar-sweetened beverages (SSBs), but it is important to note that the type of sugar and many other physical and chemical characteristics vary considerably across these beverages. Whether any effects on appetite, obesity, or health can be explained by specific sugar content or other characteristics remains unanswered. Ecological correlations between the secular increases in body weight and changes in beverage consumption have raised questions about the role of SSBs in the etiology of obesity (4). Because nutritional epidemiology has its roots in nutrients rather than in whole foods and beverages, it was only recently, in 2001, that the first prospective cohort study on the topic of soft drinks and obesity risk was published (5). Since that time, myriad observational studies on this topic have emerged, as well as several randomized trials and comprehensive review papers or meta-analyses. As pointed out by Allison and Mattes (6), there is wide variation among the scientific community in the interpretation of the scientific literature on SSBs and body weight regulation. Although there have been at least 5 comprehensive reviews of the literature on this topic since 2006 (4,7–10), the authors of these reviews have come to a number of different conclusions regarding the nature and strength of the

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2 An introduction to this series of articles is being published concurrently in The American Journal of Clinical Nutrition and the journal Obesity.

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Evidence. In nutritional epidemiology, whether observational cohort studies or randomized controlled trials, there are many important potential biases that must be carefully considered when evaluating each relevant study. To simply use 3 levels of quality to classify studies (11), such as randomized trials > observational prospective studies > cross-sectional studies, is far from sufficient. Within each of these study design classifications, as we will see in the critical review below, there is a great deal of heterogeneity in study quality. Therefore, the primary goal of this article was to identify the important methodologic nuances across the growing literature on this topic in an attempt to bring more clarity toward the state of the science and to address what research needs remain.

A second goal of this article is to critically review the literature on the possible association between artificially sweetened beverages (ASBs) and obesity risk in humans. ASBs, often also referred to as non-nutritive sweetened beverages, or in the lay press as “diet” drinks or beverages, are marketed and used as a replacement for SSBs for those who want to reduce sugar and caloric intake. Indeed, those trying to lose weight report higher ASB consumption than those not attempting weight loss (12–15). The sweeteners used in ASBs are potent stimulators of sweetness on the palate, ≥100 times the sweetness of sucrose. Six artificial sweeteners have been deemed safe for human consumption by the U.S. FDA on the basis of the available evidence from animal and human studies, including acesulfame potassium, aspartame, saccharin, sucralose, neotame, and stevia (rebaudioside A or rebiana). The percentage of the U.S. population reporting intake of ASBs is considerably lower than those reporting intake of SSBs (16,17). Furthermore, it appears that the prevalence of ASB consumers may have reached a plateau at ~10% since approximately 1990 (18).

The main components of this review include a summary of the hypothesized mechanisms through which these different beverages may influence body weight regulation, the evidence in humans from prospective observational and experimental studies, and recommendations for further research. In the interest of space and relevance, animal studies are not reviewed here because of their limited generalizability and the wealth of data now available on humans. Ecological and cross-sectional studies are not included because they are considerably more prone to bias compared with prospective study designs and experimental studies, which have been abundantly published on this topic. It is not possible to establish temporality with cross-sectional studies because exposure and outcome are measured simultaneously, and as such, there can be no estimate of weight change or obesity incidence.

Mechanisms

SSBs. The primary hypothesized mechanism through which SSBs may increase weight gain is via a relatively blunted effect on satiation and/or satiety relative to solid foods. If an increase in calories from beverages does not stimulate passive habitual compensation that would downregulate intake from solid foods, one would expect an increase in weight gain over time for high- vs. low-beverage diets. The experimental evidence in support of this mechanism is not conclusive, but it is accumulating (7,19–21). SSBs are typically sweetened with high-fructose corn syrup or sucrose, which are composed of ~55% and 50% fructose, respectively, with the balance being glucose. On the basis of animal and human experiments, fructose consumed in relatively high quantities, ≥20% of total energy intake, appears to have unique metabolic effects with respect to liver metabolism, leading to insulin resistance, visceral fat accumulation, and dyslipidemia (22–26). However, a recent meta-analysis suggested that fructose does not promote weight gain in humans unless consumed in high doses in hypercaloric diets (27). Other characteristics of SSBs that are consistent with the possibility of body weight dysregulation include the typically large portion sizes (28) and effects on postprandial glycemia and insulinemia through glycemic index or load (7,29,30). Energy density is not a plausible hypothesis for consumption of SSBs and obesity risk because most liquids, including SSBs, are not high in energy density.

ASBs. The mechanism through which ASBs may increase weight gain is through a dysregulation of appetite control due to the mismatch between the intense taste of sweetness during consumption and the lack of energy that is consumed. Thus, ASBs may stimulate appetite and lead to weight gain (31), but the evidence is not consistent (30,32,33). Short-term mechanistic trials in animals and humans provided some etiologic insights as a basis for further study of the possible effects of ASBs on appetite dysregulation and weight gain (31).

Critical Appraisal of the Literature

To identify the pertinent literature, the Medline database was searched from 1946 through March 2012 for articles in the English language that were original scientific research papers in humans and that included the key text words “soft drink,” “soda,” “cola,” “beverage,” “sugar-sweetened beverage,” “artificial sweetener,” “non-nutritive sweetener,” “low-calorie beverage,” or “diet beverage.” The articles identified were then restricted to those that were prospective cohort studies or randomized controlled trials that included body weight or body fat as an outcome. Observational studies were excluded if they were particularly short in duration (<6 mo). If a study did not attempt to quantitatively estimate the independent association (or effect) of SSBs or ASBs and the outcomes of interest, it was not included. Studies that combined SSBs and ASBs into 1 exposure variable were excluded—for example, the study by Dhingra et al. (34), which has been included in past reviews on this topic. The reference lists of the identified articles, as well as those of the prior published reviews on this topic, were also carefully searched in an attempt to find relevant articles that may have been missed in the main literature search.
TABLE 1  Prospective cohort studies of SSBs and body weight in youth

<table>
<thead>
<tr>
<th>First author (ref)</th>
<th>Sample (baseline)</th>
<th>Duration</th>
<th>Diet assessment</th>
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<tbody>
<tr>
<td>Ludwig (5)</td>
<td>n = 548</td>
<td>19 mo</td>
<td>FFQ</td>
<td>Objective BMI percentile Δ</td>
<td>Missing dietary confounders</td>
<td>+0.24 kg/m² per SSB serving/d +60% obesity odds per SSB serving/d</td>
</tr>
<tr>
<td>Phillips (35)</td>
<td>n = 96</td>
<td>7 y</td>
<td>FFQ</td>
<td>Objective BMI Z, body fat</td>
<td>Adequate</td>
<td>Positive linear association for BMI Z No association with body fat</td>
</tr>
<tr>
<td>Berkey (36)</td>
<td>n = 16,771</td>
<td>2 y</td>
<td>FFQ</td>
<td>Self-report of height and weight</td>
<td>Adequate</td>
<td>+0.14 kg/m² for boys, +0.10 kg/m² for girls per 2 SSB servings/d No association after adjustment for energy intake</td>
</tr>
<tr>
<td>Blum (41)</td>
<td>n = 164</td>
<td>2 y</td>
<td>Single 24-h recall</td>
<td>Objective BMI Z</td>
<td>Missing many diet and lifestyle confounders</td>
<td>No association</td>
</tr>
<tr>
<td>Newby (42)</td>
<td>n = 1345</td>
<td>6–12 mo</td>
<td>FFQ by mother</td>
<td>Objective BMI Z</td>
<td>Missing dietary and physical activity</td>
<td>No association</td>
</tr>
<tr>
<td>Welsh (37)</td>
<td>n = 10,904</td>
<td>1 y</td>
<td>FFQ by mother</td>
<td>Objective BMI percentile</td>
<td>Missing dietary and physical activity</td>
<td>+100% obesity odds for &gt;1 vs. &lt;1 serving/d No dose-response, no association between normal or underweight at baseline</td>
</tr>
<tr>
<td>Striegel-Moore (38)</td>
<td>n = 2371</td>
<td>9 y</td>
<td>3-d food record</td>
<td>Objective BMI</td>
<td>Missing physical activity and other dietary factors</td>
<td>+0.01 kg/m² per 100 g SSBs/d</td>
</tr>
<tr>
<td>Viner (39)</td>
<td>n = 4900</td>
<td>14 y</td>
<td>Brief dietary habits questionnaire</td>
<td>Objective BMI Z at baseline; self-reported height and weight at follow-up</td>
<td>Missing many beverage, dietary, and other lifestyle factors</td>
<td>+0.13 BMI Z per ≥2 SSBs/d at age 16</td>
</tr>
<tr>
<td>Mundt (43)</td>
<td>n = 108</td>
<td>7 y</td>
<td>2–3 24-h recalls/y</td>
<td>Body fat directly by DXA</td>
<td>Missing other dietary factors</td>
<td>No association</td>
</tr>
<tr>
<td>Libuda (44)</td>
<td>n = 244</td>
<td>5 y</td>
<td>3-d food record</td>
<td>Objective BMI</td>
<td>Missing physical activity and other dietary factors</td>
<td>No association</td>
</tr>
<tr>
<td>Nissinen (40)</td>
<td>n = 2280</td>
<td>21 y</td>
<td>Dietary questionnaire (by parental proxy in young children)</td>
<td>Objective height and weight</td>
<td>Missing other beverages and dietary factors</td>
<td>+0.45-kg weight change in females per 2.5-serving/wk change in SBB intake from childhood to adulthood No association in males</td>
</tr>
<tr>
<td>Vanselow (13)</td>
<td>n = 2294</td>
<td>5 y</td>
<td>FFQ</td>
<td>Self-report of height and weight</td>
<td>Adequate</td>
<td>No association</td>
</tr>
</tbody>
</table>

1 ref, reference; SSB, sugar-sweetened beverage; Z, Z-score; Δ, change.
Prospective cohort studies of SSBs and body weight. Table 1 includes the salient features of 12 prospective cohort studies of SSBs and body weight or body fat in children and adolescents. Sample sizes ranged from 108 to 16,771, and study durations ranged from 6 mo to 14 y. Most studies used FFQs to assess dietary intake, and most studies assessed height and weight directly for the outcome measure of BMI, standardized to age and sex. Only 3 of the 12 studies appeared to have adequate statistical adjustment for many potential confounding factors, including a variety of other dietary components, other beverage consumption, and physical activity measurements (13,35,36). Seven studies reported evidence of a positive prospective association between SSB intake and relative body weight (BMI) or body fat (5,35–40). However, for 3 of these studies, the findings were restricted to subgroups of the population (37,40) or were not replicated for body fat measures (35). Five studies reported no association or associations that were not statistically significant (13,41–44). The largest study, a national cohort of 16,771 adolescents, observed a positive association that was no longer significant after adjustment for energy intake (36). However, Ludwig et al. (5) reported that the positive association identified in the Plant Health cohort was independent of energy intake. Of course, energy intake is expected to be on the causal pathway, but it is measured with a great deal of error with FFQs, and findings are thus quite inconsistent across studies. Two studies were conducted in toddlers, aged 2–5 y, with dietary assessment by maternal proxy; 1 of these studies reported a positive association between SSBs and BMI (37), and the other found no association (42).

In summary, among prospective cohort studies in youth, the findings overall provide weak evidence for a positive association of SSBs and weight gain or obesity risk. The magnitude of the positive associations is modest, and there is significant potential for residual confounding and other biases. Indeed, most studies did not appropriately adjust for potentially confounding dietary and other factors. On the other hand, most studies are likely biased by nondifferential misclassification due to dietary measurement error, which is a possible explanation for null or weak findings.

Eleven prospective cohort studies, and their findings, on SSBs and body weight in adults are described in Table 2. The studies were generally large in size and duration, with all but 2 having >2500 participants and 6 studies having >7000 participants. Durations ranged from 12 mo to 20 y. Most studies used FFQs to measure dietary intake. In contrast to the studies in youth, most (9 of 11) studies reported thorough adjustment for potentially confounding dietary and lifestyle variables. However, the study by Duffey et al. (45) adjusted for total solid food intake rather than for specific dietary food groups. Such an approach may increase the likelihood of residual confounding because energy intake is not a valid proxy for dietary quality (e.g., equating the potential confounding effects of fresh fish intake with fast-food fried chicken). As with the studies in youth described above, the estimated effect sizes for weight gain or waist circumference increase were modest. The 3 cohort studies reported by Mozaffarian et al. (14) derived adjusted estimates for weight gain over 4-y follow-up periods ranging from 0.88 to 1.16 pounds of weight per 1.0-serving/d increase in SSBs. The study by Duffey et al. (45) observed a 9% increase in the odds (OR = 1.09) of elevated waist circumference over a 20-y period per each estimated baseline difference of SSB intake of 100 kcal/d. Overall, the prospective cohort studies of SSBs and body weight or waist circumference in adults are of high quality in terms of size, duration, and statistical methods. The findings demonstrate more consistency for a possible positive association than was observed in youth, but the effect sizes in terms of weight gain continue to be modest. The differences or changes in SSBs that are used to estimate associations with weight or weight change are typically ≥1 servings/d, and yet the estimated effect size for body weight on the basis of this SSB difference appears to be 1 or 2 pounds of body weight over many months or years. As indicated earlier, it is likely that these estimates are biased toward the null due to measurement error, and thus the true estimates may indeed be larger. However, again, it is also possible that there is residual confounding, also due to measurement error, which may bias the results away from the null.

Prospective cohort studies of ASBs and body weight. As shown in Table 3, there are few studies on ASBs and body weight in youth compared with the number of studies on SSBs and body weight in youth. This is undoubtedly due to the relative lack of ASB use in young children. Each of these 5 cohort studies was also described earlier for the summary of findings on SSBs and body weight in youth (5,13,36,38,41). Here, the results for ASBs and body weight or obesity risk overall suggest no clear association. One study reported a strong inverse (protective) association, 1 study reported a possible positive association that was apparent more so in boys than in girls, and 3 studies reported no association after full adjustment. The study by Ludwig et al. (5) estimated that the odds of becoming obese over 19 mo was reduced by 56% (OR: 0.44; P = 0.03) for each serving per day increase in ASBs. The opposite finding was observed in the cohort study by Blum et al. (41), in which ASBs were the only beverage associated positively with BMI at the 2-y follow-up assessment in their cohort of youth. It is quite possible, due to the observation described earlier of those trying to lose weight being more likely to consume ASBs than those not attempting weight loss (46–49), that a positive association between ASB intake and weight gain may be explained by bias due to “reverse causality.” Reverse causality is a term for bias resulting from the outcome—in this case, weight gain or obesity risk—having an effect on the exposure—in this case, the behavior or ASB consumption. Indeed, the study by Vanselow et al. (13)
TABLE 2  Prospective cohort studies of SSBs and body weight among adults

<table>
<thead>
<tr>
<th>First author</th>
<th>Sample (baseline)</th>
<th>Duration</th>
<th>Diet assessment</th>
<th>Outcome measure</th>
<th>Statistical adjustments</th>
<th>Results for associations between SSBs and outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mozaffarian² (14)</td>
<td>n = 50,422 Age: 52.2 ± 7.2 y Sex: F</td>
<td>20 y</td>
<td>FFQ</td>
<td>Self-report of height and weight</td>
<td>Adequate</td>
<td>+0.95-lb weight change over 4 y per SSB increase of 1.0 serving/d</td>
</tr>
<tr>
<td>Mozaffarian² (14)</td>
<td>n = 47,898 Age: 37.5 ± 4.1 y Sex: F</td>
<td>12 y</td>
<td>FFQ</td>
<td>Self-report of height and weight</td>
<td>Adequate</td>
<td>+1.16-lb weight change over 4 y per SSB increase of 1.0 serving/d</td>
</tr>
<tr>
<td>Mozaffarian² (14)</td>
<td>n = 22,557 Age: 50.8 ± 7.5 y Sex: M</td>
<td>20 y</td>
<td>FFQ</td>
<td>Self-report of height and weight</td>
<td>Adequate</td>
<td>+0.88-lb weight change over 4 y per SSB increase of 1.0 serving/d</td>
</tr>
<tr>
<td>Odegaard (62)</td>
<td>n = 43,580 Age: 45–74 y Sex: F, M</td>
<td>5.7 y</td>
<td>FFQ</td>
<td>Self-report of height and weight</td>
<td>Adequate</td>
<td>+1.1-lb weight change over 5.7 y per baseline SSB difference of ≥2.0 servings/wk</td>
</tr>
<tr>
<td>Chen (63)</td>
<td>n = 810 Age: 25–79 y Sex: F, M</td>
<td>18 mo</td>
<td>24-h recalls</td>
<td>Directly measured height and weight</td>
<td>Adequate</td>
<td>+1.10-lb weight change at 6 mo and +1.65-lb weight change at 18 mo per increase in SSBs of 1 serving/d</td>
</tr>
<tr>
<td>Duffey (45)</td>
<td>n = 2774 Age: 18–35 y Sex: F, M</td>
<td>20 y</td>
<td>Diet history interview</td>
<td>Directly measured waist circumference</td>
<td>Adequate</td>
<td>+9% increase in incidence of elevated waist circumference per quartile difference (~100 kcal/d) in distribution of baseline SSB intake</td>
</tr>
<tr>
<td>Palmer (64)</td>
<td>n = 43,960 Age: 21–69 y Sex: F</td>
<td>6 y</td>
<td>FFQ</td>
<td>Self-report</td>
<td>Adequate</td>
<td>+6.8-lb change over 6 y for SSB increase of ≥1 serving/d (n = 880) +4.1-lb change over 6 y for SSB decrease of ≥1 serving/d (n = 1472)</td>
</tr>
<tr>
<td>Bes-Rastrollo (65)</td>
<td>n = 7194 Age: 41 ± 12 y Sex: F, M</td>
<td>29 mo (median)</td>
<td>FFQ</td>
<td>Self-report of height and weight</td>
<td>Adequate</td>
<td>+1.55 odds of excess weight gain for those in highest vs. lowest quintile of baseline SSB intake; association only observed among those with a history of weight gain</td>
</tr>
<tr>
<td>Fowler (12)</td>
<td>n = 3682 Age: 25–64 y Sex: F, M</td>
<td>8 y</td>
<td>FFQ</td>
<td>Directly measured height and weight</td>
<td>No adjustment for other dietary factors</td>
<td>No association observed after adjustment for ASB intake</td>
</tr>
<tr>
<td>Kvaavik (66)</td>
<td>n = 422 Age: 23–27 y Sex: F, M</td>
<td>8 y</td>
<td>FFQ</td>
<td>Self-report of height and weight</td>
<td>No adjustment for other dietary factors other than energy intake</td>
<td>No association</td>
</tr>
<tr>
<td>French (67)</td>
<td>n = 3552 Age: 38 ± 10 y Sex: F, M</td>
<td>2 y</td>
<td>FFQ</td>
<td>Directly measured height and weight</td>
<td>Adequate</td>
<td>No association</td>
</tr>
</tbody>
</table>

¹ ASB, artificially sweetened beverage; lb, pound; ref, reference; SSB, sugar-sweetened beverage. To convert lb to kg, divide lb by 2.2.
² Three cohort studies were reported in the same publication. Another earlier article by Schulze et al. (68) also reported similar findings for the Nurses’ Health Study II.
observed a positive association between ASB intake and weight gain over 5 y in the Project EAT cohort study in Minneapolis/St. Paul, MN, schoolchildren, only to demonstrate that this association was considerably attenuated and no longer significant after adjusting for dieting behaviors and weight-loss concerns (13). It is therefore likely that ASBs may only be positively associated with obesity risk in some studies, because those trying to control their weight use ASBs as 1 of their strategies but their overall approach to weight control is typically unsuccessful.

The findings of 6 prospective cohort studies of ASBs and body weight among youth are summarized in Table 4. Four of the studies reported an inverse association, with 1 study being of borderline significance likely due to the modest sample size. The other 2 studies reported positive associations between ASBs and obesity risk (12,49). The study by Nettleton et al. (50) did not consider reverse causality by dieting behavior. Data from the San Antonio Heart Study supported graded, positive associations between ASBs and weight gain or obesity among adults, and this association appeared to be consistent for those who were or were not dieting at baseline (12). However, this study has a number of important limitations, including lack of repeated assessments of diet intake or dieting behavior and lack of adjustment for other dietary beverages or dietary components (12). Thus, questions still remain about confounding, reverse causality, and other possible biases. Overall, the studies in youth and adults suggest an inverse association between ASBs and body weight change or obesity risk, but the evidence is not entirely consistent and a variety of possible biases cannot be ruled out.

**Randomized controlled trials of SSBs and of ASBs on body weight.** On issues of diet and health, randomized controlled trials are critical to understanding mechanisms of causality. At least 5 randomized trials of SSBs, ASBs, and body weight were conducted in youth, as summarized in Table 5 (51–55). Two of these trials were group-randomized, school-based educational interventions for 1 y (51,52), whereas the other 3 were individual-randomized trials based primarily either at school or through the home (53–55). All 5 studies had no overall effect on change in BMI between groups. However, the school-based, group-randomized trial by James et al. (52) reported a large effect on the percentage of children who were overweight at the end of the study, with a higher rate in the control compared with the intervention group. However, others have pointed out a variety of important limitations with this study, including low response rate (~50%) for completing the beverage diaries, lack of information on changes in other beverages, and failure to explain why the control classrooms had such large increases in obesity rates (56). Interestingly, the trials by Sichieri et al. (51) and by Ebbeling et al. (53) both observed an intervention effect for a subset of the sample who was overweight or obese, providing a suggestion for a plausible interaction between the intervention and susceptibility to weight gain among certain individuals. Ebbeling et al. (54) followed up their earlier study with a larger sample size of obese adolescents (n = 224) and a longer duration of 1 y active intervention and 2 y follow-up. Cohort retention was excellent (97% at 1 y and 93% at 2 y). They found a modest effect on BMI for the intervention arm at the 1-y interim analysis (replacing SSBs with water or ASBs; intervention minus control: −0.57 kg/m²; P = 0.05), but no effect for the primary endpoint, change in BMI at 2 y (−0.3 kg/m²; P = 0.46). It was also noted that the intervention effect was only significant for the smaller group of Hispanic

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**TABLE 3** Prospective cohort studies of ASBs and body weight among youth

<table>
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<tr>
<th>First author (ref)</th>
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<td>−56% odds of becoming obese per 1 daily serving increase in ASBs +0.12 kg/m² per 2 ASBs/d in boys +0.05 kg/m² per 2 ASBs/d in girls (P = 0.16)</td>
</tr>
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<td>Objective BMI Z</td>
<td>Missing many diet and lifestyle confounders</td>
<td>No association</td>
</tr>
<tr>
<td>Stiegel-Moore (38)</td>
<td>n = 2371</td>
<td>9 y</td>
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<td>5 y</td>
<td>FFQ</td>
<td>Self-report of height and weight</td>
<td>Adequate</td>
<td>No association after adjustment for dieting/weight-control practices</td>
</tr>
</tbody>
</table>

1 ASB, artificially sweetened beverage; ref, reference; Z, Z-score; Δ, change.
children (n = 42), with no effect in the larger group of non-Hispanic children (n = 158). Results were also null for percentage of body fat. The recent 18-mo trial in 641 normal-weight children ages 4 to 12 y examined the effect of 1 serving/d of either SSBs (104 kcal) or ASBs (55). Twenty-six percent of the children stopped consuming the beverages by 18 mo. The analysis conducted only on those children who completed the intervention demonstrated a significant intervention effect on BMI Z-score (difference = −0.13, P = 0.001), body weight (−1.0 kg; P < 0.001), and other measures of body fat. Not surprisingly, the intention-to-treat analysis including data on 136 of the children who did not adhere to the intervention revealed a much weaker and no longer significant effect on BMI Z-score (−0.06; P = 0.06).

Table 6 includes a description of 5 randomized controlled trials of SSBs or ASBs and body weight in adults (35,57–60). The studies were relatively small and short term, with the exception of the recent trial by Tate et al. (61), which included 318 adults over 6 mo. Although only 1 study failed to observe an effect on energy intake (59), only 2 studies observed a significant effect on body weight (33,58), favoring modestly higher weight gain for the SSB group relative to the active intervention group who replaced SSBs with ASBs, milk, or water. The trial by Maersk et al. (59) is unique in that it included detailed, direct measures of specific body fat depots across 4 randomized, although small, groups over 6 mo. Although BMI, total body fat, and subcutaneous fat did not change differentially across groups, there appeared to be a unique effect of SSBs on increasing fat in the visceral region, compared with milk, and in the liver compared with milk, ASBs, and water. These findings are provocative and are consistent with the accumulating metabolic evidence on high intakes of fructose, whether it be ingested via sucrose or high-fructose corn syrup (22–26,61).

Summary
Of the totality of scientific evidence to date, there is a pattern across studies of an increased risk of weight gain and obesity with higher intakes of SSBs. However, it remains difficult to establish the strength of the association and the independence from other potentially confounding factors. The primary reason for such tentative conclusions regarding the strength of this association is the limited number and scope of controlled trials on this topic, and the unimpressive findings of those that have been conducted. Last, another recent development has been a focus on the possible role of ASBs in preventing obesity when compared with SSBs.

Proposed Future Research Agenda
To provide further scientific insight and clarity into questions about the role of beverages in the regulation of body

<table>
<thead>
<tr>
<th>First author (ref)</th>
<th>Sample (baseline)</th>
<th>Duration</th>
<th>Diet assessment</th>
<th>Outcome measure</th>
<th>Statistical adjustments</th>
<th>Results for associations between ASBs and outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mozaffarian² (14)</td>
<td>n = 50,422</td>
<td>20 y</td>
<td>FFQ</td>
<td>Self-report of height and weight</td>
<td>Adequate</td>
<td>Inverse association</td>
</tr>
<tr>
<td>Mozaffarian² (14)</td>
<td>n = 47,898</td>
<td>12 mo</td>
<td>FFQ</td>
<td>Self-report of height and weight</td>
<td>Adequate</td>
<td>Inverse association</td>
</tr>
<tr>
<td>Mozaffarian² (14)</td>
<td>n = 22,557</td>
<td>20 y</td>
<td>FFQ</td>
<td>Self-report of height and weight</td>
<td>Adequate</td>
<td>Inverse association</td>
</tr>
<tr>
<td>Chen (63)</td>
<td>n = 810</td>
<td>18 mo</td>
<td>24-h recalls</td>
<td>Directly measured height and weight</td>
<td>Adequate</td>
<td>Inverse association</td>
</tr>
<tr>
<td>Nettleton (50)</td>
<td>n = 2428</td>
<td>5 y</td>
<td>FFQ</td>
<td>Directly measured waist circumference</td>
<td>Adequate</td>
<td>+59% risk of developing high waist circumference for ≥1 serving ASBs/d compared with none</td>
</tr>
<tr>
<td>Fowler (12)</td>
<td>n = 3682</td>
<td>8 y</td>
<td>FFQ</td>
<td>Directly measures height and weight</td>
<td>No adjustment for other dietary factors</td>
<td>+100% increased risk for ≥1 serving SSBs/d compared with none; dose-response observed +0.42-kg/m² BMI increase for SSB users vs. nonusers; dose-response observed</td>
</tr>
</tbody>
</table>

1 ASB, artificially sweetened beverage; ref, reference
2 Three cohort studies were reported in the same publication. Another earlier article by Schulze et al. (68) also reported similar findings for the Nurses’ Health Study II.
<table>
<thead>
<tr>
<th>First author (ref)</th>
<th>Sample</th>
<th>Design</th>
<th>Duration</th>
<th>Intervention</th>
<th>Dietary intake</th>
<th>Body weight</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sichieri (51)</td>
<td>n = 1140</td>
<td>47 classrooms randomized to intervention or control</td>
<td>1 y</td>
<td>Education to promote replacing SSBs with water through 10 1-h sessions</td>
<td>SSBs decreased for intervention vs. control: −56 mL/d</td>
<td>No overall effect on BMI change or percentage of overweight or obese</td>
<td>Despite a 4-fold decrease in SSBs for intervention vs. control, both groups had increased BMI over time</td>
</tr>
<tr>
<td>James (52)</td>
<td>n = 644</td>
<td>29 classrooms randomized to intervention or control</td>
<td>1 y; a 3-y follow-up on 424 students was also conducted (69)</td>
<td>Four 1-h education sessions over 1 y, or control</td>
<td>Carbonated beverages decreased for intervention (0.6 servings/3 d), no difference in SSBs</td>
<td>No effect on BMI change Percentage of overweight less for intervention vs. control No difference in overweight at 3-y follow-up</td>
<td>Low overall intakes of SSBs as well as a number of important methodologic limitations (56)</td>
</tr>
<tr>
<td>Ebbeling (53)</td>
<td>n = 103</td>
<td>Two-group parallel</td>
<td>6 mo</td>
<td>Water or ASBs delivered to homes, or control condition</td>
<td>82% reduction in SSB intake for intervention, no change in control (P &lt; 0.0001)</td>
<td>No effect on BMI change; significant intervention effect on weight loss for those in the highest third of BMI</td>
<td>It is biologically plausible that the intervention would be most efficacious in those with the highest baseline BMI, perhaps due to gene X environment interactions</td>
</tr>
<tr>
<td>Ebbeling (54)</td>
<td>n = 224</td>
<td>Two-group parallel</td>
<td>2 y</td>
<td>Water or ASBs delivered to homes, or control condition</td>
<td>Reduction in SSB intake for intervention vs. control = 0.4 servings/d (P &lt; 0.01)</td>
<td>No effect on BMI change between groups at 2 y Significant effect on BMI in the interim 1-y analysis only for Hispanic children</td>
<td>No effect on percentage body fat; the effect in Hispanic adolescents was also observed in a post hoc analysis of the earlier study by this group (53)</td>
</tr>
<tr>
<td>de Ruyter (55)</td>
<td>n = 641</td>
<td>Two-group parallel</td>
<td>18 mo</td>
<td>Water or ASBs delivered to schools, or control condition</td>
<td>Urinary sucralose evidence for adherence to the ASB intervention; 477 children who completed the study consumed 83% of the assigned beverages</td>
<td>No effect on BMI change in the total sample; effect only seen after excluding those who did not adhere</td>
<td>The children were normal weight and younger than in the other studies</td>
</tr>
</tbody>
</table>

1 ASB, artificially sweetened beverage; ref, reference; SSB, sugar-sweetened beverage.
<table>
<thead>
<tr>
<th>First author (ref)</th>
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<th>Design</th>
<th>Duration</th>
<th>Intervention</th>
<th>Dietary intake</th>
<th>Body weight or fat</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tordoff (33)</td>
<td>n = 30</td>
<td>Two-treatment crossover with washout</td>
<td>3 wk</td>
<td>SSBs (530 kcal/d) vs. ASBs</td>
<td>Energy intake greater for SSBs</td>
<td>Greater for SSBs</td>
<td>Artificial sweetener caused some reduction in overall energy intake and weight loss. Partial dietary compensation during SSB intake resulting in less weight loss than predicted.</td>
</tr>
<tr>
<td>DiMeglio (57)</td>
<td>n = 15</td>
<td>Two-treatment crossover with washout</td>
<td>4 wk</td>
<td>Jelly beans vs. SSBs, isocaloric (450 kcal)</td>
<td>Energy intake greater for SSBs</td>
<td>No differences between groups</td>
<td>Discrepant findings between energy intake and body weight.</td>
</tr>
<tr>
<td>Raben (58)</td>
<td>n = 41</td>
<td>Two-group parallel</td>
<td>10 wk</td>
<td>Sucrose (150 g/d, 600 kcal) mostly as SSBs vs. ASBs+ASFs</td>
<td>Energy intake greater for sucrose</td>
<td>Greater for sucrose</td>
<td>Weight gain during SSB intake, 1.6 kg, was much less than predicted by diet records.</td>
</tr>
<tr>
<td>Maersk (59)</td>
<td>n = 47</td>
<td>Four-group parallel</td>
<td>6 mo</td>
<td>1 L/d of either SSBs, ASBs, semi-skim milk, or water</td>
<td>No differences in energy intake</td>
<td>No differences in body weight, BMI, total fat mass, subcutaneous fat, or skeletal muscle fat. Visceral fat higher for SSBs than for milk. Hepatic fat higher for SSBs than for the other 3 groups; similar but weaker effects for intramuscular fat. Visceral fat higher for SSBs than for milk.</td>
<td>Sample size was small, with 60 randomized and 13 dropouts, leaving only 10–13 per group. Adherence was not reported.</td>
</tr>
<tr>
<td>Tate (60)</td>
<td>n = 318</td>
<td>Three-arm parallel</td>
<td>6 mo</td>
<td>Replace 2 servings/d of caloric beverages with either water, ASBs, or control</td>
<td>Energy intake from beverages decreased in water and ASB groups compared with control groups</td>
<td>No difference between groups over time. Water and ASB groups twice as likely to lose ≥5% body weight than the control group.</td>
<td>Energy intake estimates are unlikely to be accurate, given a reported decrease in energy intake of ~600 kcal/d across all groups, which would have resulted in substantially more weight loss than the observed ~2.5% in all groups.</td>
</tr>
</tbody>
</table>

1 ASB, artificially sweetened beverage; ref, reference; SSB, sugar-sweetened beverage.
weight and risk of obesity, it is unlikely that additional observational studies will be helpful because of problems in measuring diet accurately and in handling many problematic biases including residual confounding and, in the case of ASBs, reverse causality. Well-designed, well-powered randomized controlled trials will be needed to answer the lingering and important scientific and public health questions on beverage intake and obesity risk. These experiments will need to include studies of mechanisms of action, include detailed assessment of behaviors on both sides of the energy balance equation, and address both efficacy and effectiveness. The overall background habitual diet of the study participants must be measured well in observational or experimental studies, as well as physical activity and other potentially confounding or modifying factors. As described above, the trials that have been conducted to date have a variety of limitations, especially with respect to design, sample selection, and statistical power. Future studies should include diversity across age groups, sexes, ethnicities, and other socioeconomic factors.

The fundamental questions remain: Do ingested calories in liquid form have a greater impact on weight gain than calories in solid form, and do certain forms of liquid calories have a greater impact on weight gain than other types of beverages? Studies in several hundred or more overweight subjects followed closely for over a year, with adherence checks, monitoring with 24-h recalls, biomarkers, and direct measures of body composition as well as satiety and other possible mechanistic pathways, are economically and operationally realistic and scientifically appropriate. The alternative to such investment is our continued reliance on bias-prone observational studies and poorly designed, underpowered, underfunded experimental studies that leave us open to debate and confusion. Progress in this area is unlikely without better science.

Acknowledgments
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References
28. Rolls BJ. The supersizing of america: portion size and the obesity epi-
29. Pawlak DB, Ebbeling CB, Ludwig DS. Should obese patients be coun-
32. Renwick AG, Molinvy SV. Sweet-taste receptors, low-energy sweet-
33. Tordoff MG, Alleva AM. Effect of drinking soda sweetened with aspar-
36. Berkey CS, Rockett HR, Field AE, Gillman MW, Colditz GA. Sugar-
40. Niissinen K, Mikkila V, Mannisto S, Lahti-Koski M, Rasanen L, Viikari J, Raitakari OT. Sweets and sugar-sweetened soft drink intake in child-
42. 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 Da-
44. Libuda L, Alexy U, Sichert-Hellert W, Stehle P, Karaolis-Danckert N, Buyken AE, Kersting M. Pattern of beverage consumption and long-
term association with body-weight status in German adolescents—
49. Stice E, Presnell K, Shaw H, Rohde P. Psychological and behavioral risk factors for obesity onset in adolescent girls: a prospective study. J Con-
50. Nettleton JA, Lutes NY, Wang Y, Lima JA, Michos ED, Jacobs DR. Diet soda intake and risk of incident metabolic syndrome and type 2 dia-
52. James J, Thomas P, Cavan D, Kerr D. Preventing childhood obesity by reducing consumption of carbonated drinks: cluster randomised con-
53. Ebbeling CB, Feldman HA, Osganian SK, Chomitz VR, Ellenbogen SJ, Ludwig DS. Effects of decreasing sugar-sweetened beverage consump-
54. Ebbeling CB, Feldman HA, Chomitz VR, Antonelli TA, Gortmaker SL, Osganian SK, Ludwig DS. A randomized trial of sugar-sweetened bev-
61. Odegaard AO, Choc AH, Czerwinska SA, Towne B, Denerath EW. Sugar-sweetened and diet beverages in relation to visceral adipose tis-
62. Odegaard AO, Koh WP, Arakawa K, Yu MC, Pereira MA. Soft drink and juice consumption and risk of physician-diagnosed incident type 2 di-