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Sugar-Sweetened Beverages, Obesity, Type 2 Diabetes Mellitus, and Cardiovascular Disease Risk

Vasanti S. Malik, MSc; Barry M. Popkin, PhD; George A. Bray, MD;
Jean-Pierre Després, PhD; Frank B. Hu, MD, PhD

Obesity has recently emerged as a major global health problem. According to World Health Organization estimates, ≈ 1.6 billion adults worldwide were overweight (body mass index [BMI] ≥ 25 kg/m²) and at least 400 million were obese (BMI ≥ 30 kg/m²) in 2005, numbers that are expected to reach 2.3 billion and 700 million, respectively, by 2015. In the United States, the percentage of overweight and obese adults increased markedly from 47% and 15% in 1976 to 1980 to $>66\%$ and 33% in 2005 to 2006, with the greatest proportion of increase seen among non-Hispanic black and Mexican American women.^{1,2} The implications of excess body weight are far-reaching. Epidemiological studies indicate that overweight and obesity are important risk factors for type 2 diabetes mellitus (T2DM), cardiovascular disease, cancer, and premature death.³ In the United States, healthcare expenditures attributable to overweight and obesity are estimated to be \$147 billion or 9.1% of total healthcare costs per year.⁴ Such excess costs could have serious repercussions for resource-poor countries, which must manage the dual burdens of chronic and infectious disease.

In the setting of a pandemic of obesity and related chronic diseases, the American Heart Association recently released a scientific statement recommending reductions in added-sugar intake to no more than 100 to 150 kcal/d for most Americans.⁵ The statement identified sugar-sweetened beverages (SSBs) as the primary source of added sugars in the American diet.⁶ Although it has long been suspected that SSBs contribute at least in part to the obesity epidemic, only in recent years have large epidemiological studies been able to substantiate the relationship between SSB consumption and long-term weight gain, T2DM, and cardiovascular risk. It is thought that SSBs contribute to weight gain because of their high added-sugar content, low satiety, and potential incomplete compensation for total energy, leading to increased energy intake.^{7,8} In addition, because of their high amounts of rapidly absorbable carbohydrates such as various forms of sugar and high-fructose corn syrup (HFCS) and the large quantities consumed, SSBs may increase T2DM and cardiovascular risk independently of obesity as a contributor to a

high dietary glycemic load (GL), leading to inflammation, insulin resistance, and impaired β -cell function.⁹ Fructose from any sugar or HFCS may also increase blood pressure and promote the accumulation of visceral adiposity, dyslipidemia, and ectopic fat deposition because of increased hepatic de novo lipogenesis.¹⁰ Here, we review temporal patterns in SSB consumption and clinically relevant effects on obesity, T2DM, and cardiovascular disease risk, emphasizing potential underlying biological mechanisms, clinical implications, and consideration of methodological issues inherent in the literature.

SSB Global Pattern

Although carbonated beverages trace their history back to the 1760s when carbonation techniques were developed to reproduce naturally occurring carbonated mineral waters believed to be healthy, these beverages did not add sugar.¹¹ A century later, one of the most pivotal events in soft drink history occurred when Atlanta pharmacist J.S. Pemberton combined kola, a caffeinated nut from Africa, with coca, a stimulant from South America, to create Coca-Cola, which, like most other sweetened beverages developed in the 1800s, was marketed as a tonic.¹² In about 1904, Asa Candler purchased legal rights to the formula from Pemberton and soon developed the first mass factory.¹³ During World War II, Coca-Cola worked closely with the US Department of War to provide free Cokes to army soldiers. As a result of a lobbying campaign, they were allowed to break sugar ration rules and to create Coke plants in European countries with the support of the government, ultimately becoming synonymous globally with SSBs.¹³

During the past 30 years, there has been a marked increase in the consumption of SSBs across the globe. For instance, in the United States, intake of these beverages, which includes the full range of soft drinks, fruit drinks, energy drinks, and vitamin water drinks, increased from 3.9% of calories in the late 1970s to 9.2% in 2001, representing a 3-fold increase in intake.¹⁴ In other countries, there have been varying levels of increase in SSBs, with some countries such as Mexico reaching such magnitudes that serious government interven-

From the Departments of Nutrition and Epidemiology, Harvard School of Public Health (V.S.M., F.B.H.), and Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School (F.B.H.), Boston, Mass; Centre de Recherche de l'Institut Universitaire de Cardiologie et de Pneumologie de Québec, Québec City, Québec, Canada (J.P.D.); Dietary Obesity Laboratory, Pennington Biomedical Research Center, Baton Rouge, La (G.A.B.); and Department of Nutrition, Gillings School of Global Public Health, University of North Carolina, Chapel Hill (B.M.P.).

Correspondence to Frank B. Hu, Department of Nutrition, Harvard School of Public Health, 665 Huntington Ave, Boston, MA 02115. E-mail frank.hu@channing.harvard.edu

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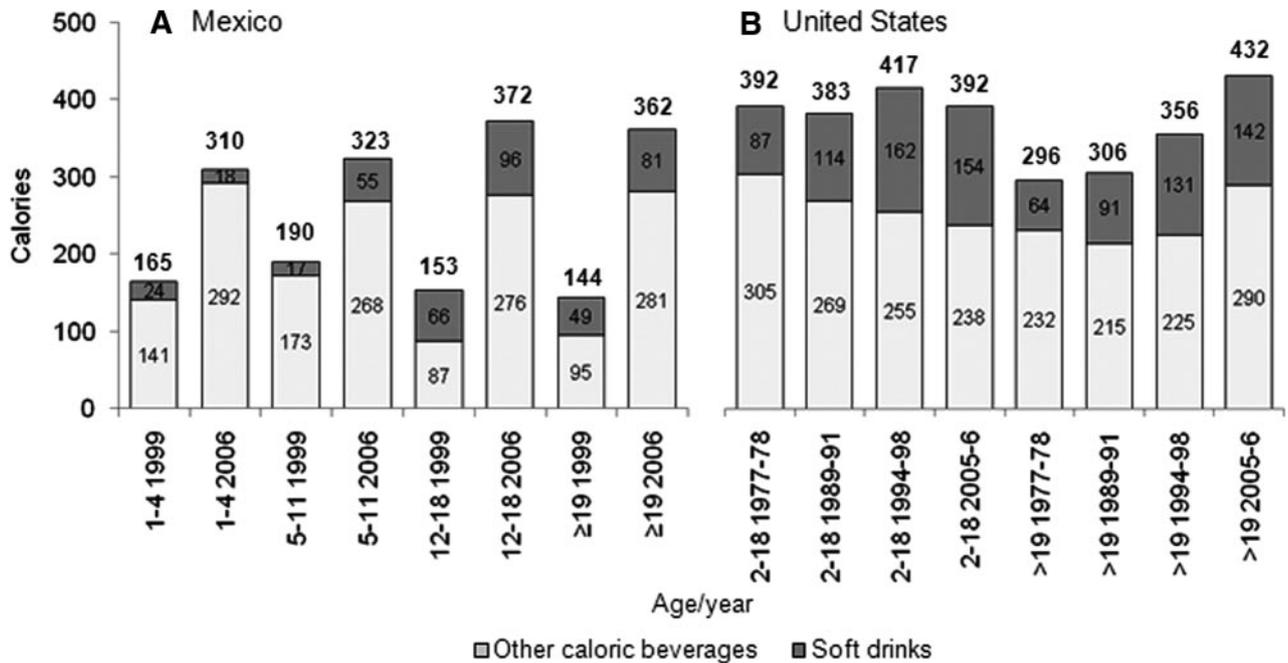


Figure 1. Trends in consumption of calories from soft drinks and all caloric beverages in Mexico and the United States (weighted to be nationally representative) by age groups (1 to 4, 5 to 11, 12 to 18, and ≥19 years) in 1999 and 2006. Soft drinks include carbonated, noncarbonated beverages with sugar added, and commercially processed, bottled/formula fountain soft drinks and fruit drinks but exclude agua frescas, Mexican hand-prepared added-sugar fruit juices, and fruit drinks.

tion to reduce intake is being undertaken.¹⁵ Nation-level food disappearance data from China, India, Vietnam, Thailand, and other South Asian countries also show rapid trajectories of an increase in SSB intake, as well as large per capita consumption across the Americas, Germany, Australia, Spain, and Great Britain.¹⁶ The most rigorous sources of nationally representative patterns in SSB intake come from the United States and Mexico, where large-scale dietary intake surveys have been repeated in the last decade.^{15,17} According to these data, all age groups in Mexico consume ≈10% of their total energy intake from SSBs. As shown in Figure 1A, SSB intake has increased considerably among those ≥5 years of age in Mexico. Figure 1B presents the same data for the United States. As seen in both children 2 to 18 years of age and adults >19 years of age, substantial increases across each decade have continued.

SSB and Childhood Obesity

Childhood obesity is known to increase risk of obesity in adulthood and can lead to serious consequences for T2DM and cardiovascular disease risk later in life. In fact, recent evidence suggests consideration of lipid screening for children with BMI beginning at the 80th percentile rather than ≥85th percentile, the point at which a child is considered overweight.¹⁸

Given the preponderance of SSB consumption among children and adolescents, several epidemiological studies have examined the relationship between SSB and weight gain or obesity in this group. Recently, we conducted a meta-analysis evaluating change in BMI per increase in 1 serving of SSB per day and found a significant positive association between SSB intake and weight gain (0.08; 95% confidence interval [CI], 0.03 to 0.13 kg)¹⁹ among studies that did not adjust for total energy intake.²⁰⁻²⁴ Because the association

between SSB intake and weight gain is partially mediated by total energy intake, adjusting for energy is expected to attenuate this effect. In these data, the effect was also strongest in larger studies with longer durations of follow-up that used robust dietary assessment methods such as food frequency questionnaires rather than a single 24-hour diet recall, which is not able to capture patterns in dietary intake.^{20,21} These results are supported by previous systematic reviews and meta-analyses,²⁵⁻²⁷ as well as more recent studies. For example, Dubois and colleagues²⁸ found that in >2000 children 2.5 years of age followed up for 3 years, regular consumers of SSBs between meals had a 2.4-fold greater odds of being overweight compared with nonconsumers ($P < 0.05$). Another study conducted among 5-year-old subjects in the UK with 4 years of follow-up did not find an association between SSB intake and fatness, possibly because intake levels were too low.²⁹ Recent studies have also shown that greater SSB consumption in childhood or adolescence predicted weight gain into adulthood.^{30,31}

Findings from intervention studies, which are few in number, generally support those from well-powered prospective cohort studies and show positive associations between SSB intake and weight gain either in the overall study²² or in subgroup analyses among participants overweight at baseline.^{24,32} A follow-up analysis of a school-based intervention that showed that reducing SSB intake decreased overweight and obesity²² did not see an effect 2 years after the intervention had been discontinued, which supports an effect of SSB consumption on weight gain.³³

SSB Consumption and Weight Gain in Adults

To date, a large number of studies have evaluated the relationship between SSB consumption and weight gain or

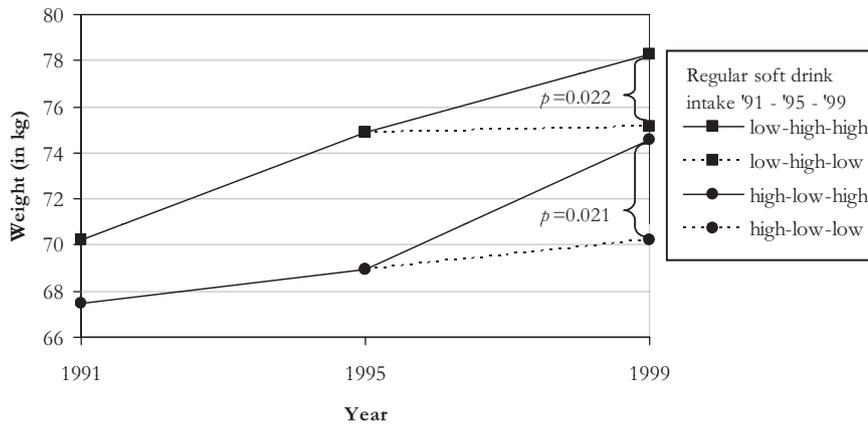


Figure 2. Low and high intakes were defined as ≤ 1 /week and ≥ 1 /day. The numbers of subjects were as follows: low-high-high=323, low-high-low=461, high-low-high=110, and high-low-low=746. Groups with similar intake in 1991 and 1995 were combined for estimates for these time points. Means were adjusted for age, alcohol intake, physical activity, smoking, postmenopausal hormone use, oral contraceptive use, cereal fiber intake, and total fat intake at each time point. Adapted with permission from Schulze et al.³⁴

risk of overweight and obesity among adults. However, differences in study design, methodologies, and data quality have made it difficult to observe a consistent effect. Cross-sectional studies are not optimal because of the high potential for intractable confounding and reverse causation. Experimental studies are not well suited to capture long-term patterns because compliance tends to wane with increasing duration, but they do provide important insight into potential underlying biological mechanisms. Prospective cohort studies tend to provide the most robust evidence despite a large degree of diversity between studies in terms of outcome measurements, size, and duration of follow-up. Therefore, greater emphasis should be placed on larger studies of longer duration that are better powered to detect an effect. In this literature, the longest and largest studies^{34,35} show stronger and more consistent associations compared with smaller and shorter studies.^{36,37} For example, in the study by Schulze et al³⁴ of >50 000 nurses followed up for two 4-year periods (1991 to 1995 and 1995 to 1999), a higher consumption of SSBs was associated with a greater magnitude of weight gain. After adjustment for potential confounders, women who increased their SSB consumption from 1991 to 1995 and maintained a high level of intake gained on average 8.0 kg during the 2 periods, whereas women who decreased their SSB intake between 1991 and 1995 and maintained a low level of intake gained on average 2.8 kg during the 2 periods (Figure 2). Similar results were reported by Palmer and colleagues³⁵ in >40 000 black women followed up for 6 years. Those whose SSB intake increased from ≤ 1 serving per week to ≥ 1 serving per day gained the most weight, whereas those who decreased their intake gained the least weight (6.8 and 4.1 kg, respectively) after adjustment for potential confounders. A smaller study from Spain³⁸ with >7000 participants followed up for ≈ 2 years found that a higher consumption of SSB was associated with significant weight gain among subjects who gained ≥ 3 kg in the 5 years before baseline. These participants had a higher absolute intake of SSB at baseline compared with participants with no previous weight gain, consistent with a positive association between SSB intake and weight gain. It is possible that the study was not long enough to evaluate weight gain in relation to SSB intake in subjects with no previous weight gain. In a large cohort from Germany (n=17 369) with a similar duration of follow-up, SSB intake was associated with weight

gain in men but not women.³⁹ In the Framingham Offspring Study⁴⁰ with an average duration of 4 years and >4000 participants, compared with infrequent consumers, participants who consumed ≥ 1 soft drinks per day had a 37% higher risk of obesity.⁴⁰ Because this analysis included both diet and regular soft drinks, it is difficult to disentangle the independent effect of SSBs because consumers of diet soft drinks may be weight conscious or trying to lose weight. In an observational analysis of the Clinical Trial of Comprehensive Lifestyle Modification for Blood Pressure Control (PREMIER) study (n=810), Chen et al⁴¹ found that a reduction in SSB intake of 1 serving per day was associated with a weight loss of 0.49 kg (95% CI, 0.11 to 0.82; $P=0.006$) at 6 months and of 0.65 kg (95% CI, 0.22 to 1.09; $P=0.003$) at 18 months. However, participants in this study were part of a trial to lower blood pressure and had higher baseline BMI than other cohorts and stage 1 hypertension, which could partly explain why such a strong effect was seen with relatively little power. At the same time, because this study adjusted for total energy, the effect of SSBs on weight gain may have been underestimated.

SSB Consumption and T2DM and the Metabolic Syndrome

Similar to the weight-gain literature, prospective cohort studies evaluating the effect of SSBs on risk of T2DM and the metabolic syndrome (MetSyn) have found the strongest and most consistent associations in large studies with long durations of follow-up. These aspects of study design are particularly important when assessing diet in relation to chronic disease origin because sufficient time is required for causal action and disease initiation and detection to occur. In >50 000 women followed up for 8 years, after adjustment for potential confounders, those consuming ≥ 1 SSBs per day had an 83% greater risk of developing T2DM compared with those consuming < 1 SSB per month (relative risk [RR], 1.83; 95% CI, 1.42 to 2.36; $P<0.001$ for trend; Figure 3).³⁴ The RR comparing extreme categories further controlling for BMI was 1.41 (95% CI, 1.09 to 1.83; $P<0.001$ for trend). This finding suggests that BMI accounts for about half of the excess risk. Similarly, in the Black Women's Health Study,³⁵ with >40 000 women followed up for 10 years, those who consumed ≥ 2 SSBs per day had a 24% greater risk of

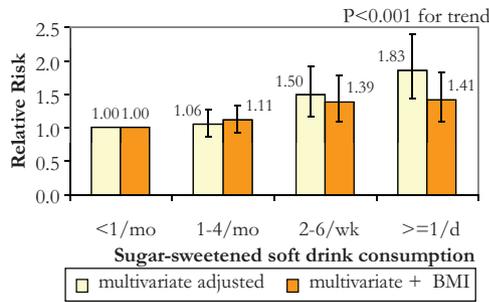


Figure 3. Multivariate RRs were adjusted for age, alcohol (0, 0.1 to 4.9, 5.0 to 9.9, ≥ 10 g/d), physical activity (quintiles), family history of diabetes mellitus, smoking (never, past, current), postmenopausal hormone use (never, ever), oral contraceptive use (never, past, current), intake (quintiles) of cereal fiber, magnesium, *trans* fat, polyunsaturated:saturated fat, and consumption of sugar-sweetened soft drinks, diet soft drinks, fruit juice, and fruit punch (other than the main exposure, depending on model). These data are based on data from Schulze et al.³⁴

developing T2DM compared with those who consumed <1 SSB per month (RR, 1.24; 95% CI, 1.06 to 1.45; $P=0.002$ for trend). After additional adjustment for BMI, the RR was no longer statistically significant, suggesting that in this population the majority of effect was mediated by BMI. Findings from these studies were replicated in a large cohort of >70 000 women followed up for 18 years that showed that women who consumed 2 to 3 SSBs per day had a 31% greater risk of developing T2DM than women who consumed <1 SSB per month (RR, 1.31; 95% CI, 0.99 to 1.74; $P<0.01$ for trend).⁴² Because this study adjusted for BMI and total energy intake, both potential mediators of effect, the association between SSB intake and T2DM risk may actually be underestimated. In contrast to these studies, findings from the Atherosclerosis Risk in Communities Study ($n=12\ 204$) did not show a consistent association between SSB intake and incidence of T2DM after 9 years of follow-up (men: RR, 1.09; 95% CI, 0.89 to 1.33; women: RR, 1.17; 95% CI, 0.94 to 1.46).⁴³ Compared with the study by Schulze et al,³⁴ participants in this study were older (53.6 versus 36.1 years of age) and heavier (27.2 versus 24.6 kg/m²) at baseline. Because the effect of SSB on T2DM is mediated in part by BMI, once BMI is increased, it is possible that the additional effect of continued SSB intake is diminished; however, further research is needed to confirm this hypothesis.

Few studies have examined the effect of SSBs on the development of MetSyn, but they are in line with findings from studies evaluating T2DM. For example, findings from the Framingham Offspring Study ($n=6154$) showed that compared with nonconsumers, individuals who consumed ≥ 1 soft drinks per day had a 39% greater risk of developing MetSyn during the course of 4 years.⁴⁰ Although this analysis combined diet and regular soft drinks, it can be assumed that the majority of this effect was due to regular soft drink consumption. Other studies of MetSyn have found marginal effects of SSBs, but because they adjusted for total energy intake, the results may have been underestimated.^{44,45}

SSB Consumption and Cardiovascular Risk

The evidence relating SSB intake to cardiovascular risk is limited, although data are starting to accumulate that suggest

that greater SSB consumption may have a role in the development of hypertension, adverse lipid parameters, inflammation, and clinical coronary heart disease (CHD). The Framingham Offspring Study, which also looked at SSB intake in the context of MetSyn components in 6154 adults followed up for 4 years, found that individuals who consumed ≥ 1 soft drink per day had a 22% higher incidence of hypertension ($\geq 135/85$ mm Hg or on treatment) compared with nonconsumers (RR, 1.22; 95% CI, 1.05 to 1.41).⁴⁰ Similarly, in the Nurses' Health Studies I and II, women who consumed ≥ 4 SSBs per day had a 44% and 28% higher risk of incident hypertension, respectively, compared with infrequent consumers (RR, 1.44; 95% CI, 0.98 to 2.11; and RR, 1.28; 95% CI, 1.01 to 1.62, respectively).⁴⁶ Regarding lipids, daily soft drink consumers in the Framingham Offspring Study were found to have a 22% higher incidence of hypertriglyceridemia (≥ 1.7 mmol/L or on treatment) and low high-density lipoprotein cholesterol (<1.03 mmol/L for men or <1.3 mmol/L for women or on treatment) compared with nonconsumers (RR, 1.22; 95% CI, 1.07 to 1.41; and RR, 1.22; 95% CI, 1.04 to 1.44, respectively).⁴⁰ Results from the Multi-Ethnic Study of Atherosclerosis (MESA) study, which had fewer participants ($n=3878$), showed a significant effect of SSBs on hypertriglyceridemia (≥ 1.7 mmol/L or on treatment) and trends toward an effect on hypertension ($\geq 130/85$ mm Hg or on treatment) and low high-density lipoprotein cholesterol (<1.03 mmol/L for men or <1.3 mmol/L for women or on treatment) in daily SSB consumers compared with nonconsumers (RR, 1.28; 95% CI, 1.02 to 1.60; RR, 1.14; 95% CI, 0.91 to 1.43; and RR, 1.28; 95% CI, 0.99 to 1.64, respectively).⁴⁵ These findings are supported by a recent cross-sectional analysis of National Health and Nutrition Examination Survey data that found a positive association between SSB intake and blood pressure in adolescents.⁴⁷ A 10-week intervention study comparing the effects of sucrose- and artificially sweetened foods/beverages on markers of inflammation found that serum levels of haptoglobin, transferrin, and C-reactive protein increased in the sucrose group and decreased in the sweetener group (between-group differences: $P=0.006$, $P=0.01$, and $P=0.1$, respectively).⁴⁸ Indirect evidence for an effect of SSBs on inflammation also stems from observational studies that have found positive associations between dietary patterns that are high in SSBs with markers of inflammation such as C-reactive protein and tumor necrosis factor receptor 2⁴⁹ and dietary GL, to which SSB intake is a large contributor with C-reactive protein.⁵⁰ In addition, higher consumption of soft drinks has been associated with hyperuricemia⁵¹ and incidence of developing gout,⁵² a condition commonly associated with insulin resistance and MetSyn.

Recently, in the Nurses Health Study, a positive association between SSB intake and risk of CHD (nonfatal myocardial infarction or fatal CHD) was observed even after accounting for other unhealthy factors.⁵³ In >88 000 women followed up for 24 years, those who consumed ≥ 2 SSBs per day had a 35% greater risk of developing CHD compared with those who consumed <1 SSB per month (RR, 1.35; 95% CI, 1.1 to 1.7; $P<0.001$ for trend). Additional adjustment for BMI, energy intake, and incident T2DM attenuated the

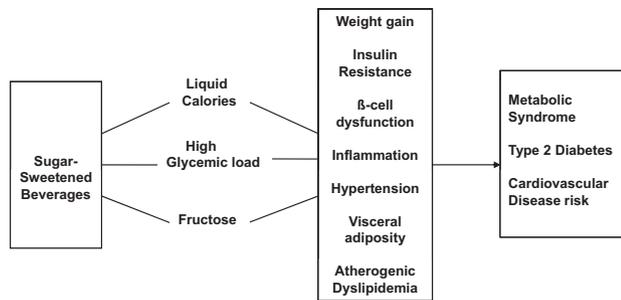


Figure 4. SSBs may lead to weight gain as a result of incomplete compensation for liquid calories at subsequent meals, resulting in positive energy balance. Independently of weight gain, SSBs may increase the risk of MetSyn, T2DM, and cardiovascular disease because of their large contribution to a high dietary GL and large fructose fraction, leading to the development of insulin resistance, β -cell dysfunction, inflammation, hypertension, visceral adiposity, and atherogenic dyslipidemia.

associations, but they remained statistically significant, suggesting that the effect of SSBs on CHD is not entirely mediated by these factors.

Potential Mechanisms

The prevailing mechanisms linking SSB intake to weight gain are decreased satiety and incomplete compensatory reduction in energy intake at subsequent meals after consumption of liquid calories (Figure 4).^{7,8} On average, SSBs contain 140 to 150 calories and 35 to 37.5 g sugar per 12-oz serving. If normal dietary intake does not decrease by an equivalent amount of calories per serving, then weight gain is expected.^{25,54} This has been illustrated in short-term feeding trials showing greater energy intake and weight gain after consumption of calorically sweetened beverages (sugar, sucrose, HFCS) compared with noncaloric artificially sweetened beverages.^{55,56} In addition, a number of studies have shown greater energy intake and weight gain after isocaloric consumption of beverages as opposed to solid food.⁷ These studies argue that sugar or HFCS in liquid beverages may not suppress intake of solid foods to the level needed to maintain energy balance; however, the mechanism responsible for that weaker compensatory response to fluids is unknown.⁵⁷

SSBs may contribute to T2DM and cardiovascular risk in part by their ability to induce weight gain, but an independent effect may also stem from the high amounts of rapidly absorbable carbohydrates such as any form of sugar or HFCS, the primary sweeteners used in SSBs (Figure 4). Consumption of SSBs has been shown to result in rapid and dramatic increases in blood glucose and insulin concentrations,⁵⁸ which, in conjunction with the large quantities that are often consumed, contribute to a high dietary GL. High-GL diets are thought to stimulate appetite and to promote weight gain and have been shown to induce glucose intolerance and insulin resistance.⁵⁹ An increase in GL has also been shown to exacerbate levels of inflammatory biomarkers such as C-reactive protein linked to T2DM and cardiovascular disease risk.⁵⁰ Inflammation is known to influence atherosclerosis, plaque stability, and thrombosis; therefore, SSB consumption may affect CHD risk within just a few years.⁵³ High dietary GL has also been associated with greater risk of

CHD.⁶⁰ In addition, the caramel coloring used in cola-type soft drinks is high in advanced glycation end products, which may further increase insulin resistance and inflammation.⁶¹ For instance, an 8-oz serving of cola delivers 16.3 μ mol advanced glycation end products.⁶²

Recent evidence also suggests that consuming fructose, which is found in similar amounts in sucrose and HFCS, may have particularly adverse effects on selective deposition of visceral and ectopic fat, lipid metabolism, de novo lipogenesis, blood pressure, and insulin sensitivity compared with glucose¹⁰ (Figure 4). The different pathways for the metabolism of fructose and glucose are clearly important potential mechanisms. Fructose alone is poorly absorbed but is enhanced by glucose in the gut, thus accounting for the rapid and complete absorption of both fructose and glucose when ingested as sucrose or HFCS. Studies in humans and animals have shown that fructose is preferentially metabolized to lipid in the liver, leading to increased triglyceride levels, which have been associated with the development of insulin resistance and cardiovascular disease.^{63–66} A recent study in overweight adults compared the effects of consuming glucose- or fructose-sweetened beverages providing 25% of energy requirements.¹⁰ After 10 weeks, both groups showed similar weight gain; however, only the fructose group showed a significant increase in visceral adiposity, which has also been observed in a number of recent studies.^{67–69} Although fasting plasma triglyceride levels increased only in the glucose group, hepatic de novo lipogenesis, postprandial triglycerides, and markers of altered lipid metabolism and lipoprotein remodeling such as fasting apolipoprotein B and small low-density lipoprotein particles significantly increased in the fructose group. In addition, fasting plasma glucose and insulin levels increased and insulin sensitivity decreased in the fructose group. Of interest, Ghanim and colleagues⁷⁰ did not find evidence of oxidative or inflammatory stress after intake of 300 kcal fructose or orange juice, whereas reactive oxygen species generation and nuclear factor- κ B binding were significantly increased after intake of glucose. However, the quantities of fructose contained in SSBs are far greater than those contained in these preloads.⁷⁰ Fructose can also increase blood uric acid concentrations.⁷¹ The production of uric acid in the liver by xanthine oxidase may reduce endothelial nitric oxide,⁷² which could partly mediate the association between SSBs and risk of CHD. Increases in blood pressure have also been observed when fructose is administered acutely, an effect not seen with glucose.⁷³ In addition, an increase in blood pressure spanning 10 weeks was found when individuals drank SSBs but not aspartame-sweetened beverages.⁵⁵ Fructose intake may also lead to weight gain by decreasing the production of insulin and leptin in peripheral tissues, thereby initiating the hunger cascade in the central nervous system⁶⁴; this area warrants further investigation because others have found greater satiety and lower total energy intake after fructose preloads compared with glucose preloads.⁷⁴

Clinical Implications

Controlling the intake of SSBs represents an important component of lifestyle management for weight control and

maintenance. Limiting SSBs may also confer favorable benefits on T2DM and cardiovascular risk such as improving lipid profiles and insulin sensitivity and reducing blood pressure, inflammation, and accumulation of visceral adiposity. The excess risk imparted by SSBs may have particular relevance for certain individuals or populations who are more susceptible to developing T2DM.⁷⁵ Limiting SSB intake among children and adolescents is imperative because overweight and obesity are rampant in this population, which can have serious downstream effects on cardiovascular health. Public policy approaches such as taxation have been proposed to reduce SSB consumption in the general population.⁷⁶

When SSBs are replaced with other beverages, it is important to select alternatives that are healthy and do not promote weight gain. The average individual needs at least 1 mL fluid for every calorie burned, which is approximately eight 8-oz glasses per day for a 2000-kcal diet.⁷⁷ Adequate hydration is essential for maintaining blood volume and kidney function and preventing constipation.⁷⁸ Water has no calories or additives and is widely available, inexpensive, and generally safe. Findings from epidemiological studies show that energy intake is significantly lower ($\approx 9\%$, or 194 kcal/d) in water drinkers compared with non-water drinkers,⁷⁹ which was supported by a recent randomized controlled trial in German schoolchildren.⁸⁰ This study found that 1 year of water intake was linked with a 31% reduction in the risk of being overweight.⁸⁰ Unlike SSBs, water does not contain liquid calories to be compensated for at subsequent meals. As shown in secondary analysis of a clinical weight loss trial, replacing SSBs with water was associated with lower total energy intake (predicted mean decrease of 200 kcal/d spanning 12 months).⁸¹ In addition, some evidence indicates that consuming water before or with a meal reduces feelings of hunger and increases satiety,^{79,82} in contrast to both diet and regular soft drinks, which are thought to stimulate appetite by their intense sweet flavor.^{83,84} Coffee and tea are also reasonable alternatives provided that caloric sweeteners and whitening agents are used sparingly. A number of studies have shown that regular consumption of coffee and tea can have favorable benefits on T2DM and cardiovascular disease risk, possibly by virtue of their polyphenol content.^{85,86} In recent decades, consumption of milk has decreased markedly in the United States. Displacement by SSBs in the pediatric population is of great concern because it can lead to lower intakes of protein, calcium, magnesium, zinc, vitamin A, and vitamin D and increase the risk for osteoporosis and bone fracture.^{14,87} Because of the excess calories and saturated fat content of whole milk, low-fat milk is recommended but should be consumed in moderation because one 8-oz serving of nonfat milk still provides 85 kcal. Some evidence suggests that low-fat dairy products may also be beneficial for weight loss and the prevention of hypertension, T2DM, and CHD.^{88,89}

Diet soda is a reasonable alternative to SSBs in that they have few to no calories, but they provide no nutritional value, and little is known about the health consequences of consuming artificial sweeteners during a lifetime.⁹⁰ In addition, some evidence suggests that the intense sweetness of artificial sweeteners could lead to conditioning for a greater preference for sweets and thus may actually enhance appetite, but this

area remains controversial.⁹¹ Several epidemiological studies have suggested a positive association between diet soda consumption and weight gain and risk of MetSyn.^{40,44,45} However, these observations may be due to reverse causation or residual confounding because, for example, diet soda consumption is higher among individuals with diabetes mellitus than those without diabetes mellitus.⁹² Studies with longer durations of follow-up and repeated measures, which are less prone to reverse causation, showed only marginal nonsignificant associations with diet soda.^{34,35,53} Some evidence suggests that a subset of diet soda consumers use diet soda as rationale for consuming other higher-calorie foods.⁹⁰

There is also growing concern about excessive fruit juice intake, but the evidence is limited. In a large cohort of women, high intake of fruit juices was positively associated with incidence of T2DM, whereas intake of whole fruits and green leafy vegetables was inversely associated.⁴² Although Schulze and colleagues did not find an association between fruit juice and risk of T2DM, they did find a positive association with weight gain.³⁴ Fruit juice has also been linked with increased weight among Australian children.⁹³ However, Ghanim and colleagues observed significantly lower reactive oxygen species generation and nuclear factor- κ B binding after consumption of orange juice compared with a glucose drink, possibly resulting from its flavonoid content.⁷⁰ Although fruit juice can provide some vitamins and nutrients, they often contain high amounts of sugar and calories and should therefore be consumed in moderation.

Methodological Issues

Although more studies are warranted to better understand the underlying biological mechanisms mediating the effect of SSBs on weight gain, T2DM, and cardiovascular risk, evidence from observational studies shows clear positive associations. Clinical trials, on which policies and recommendations are often based, are not well suited to this modality because they are greatly affected by intervention intensity and are limited by compliance, which tends to wane with increasing study length. To effectively evaluate the risk of chronic disease, sufficient follow-up time is needed for causal action and disease initiation and detection to occur, which would be difficult to emulate in the setting of a clinical trial. Thus, in the midst of an obesity epidemic that is fueling an epidemic of T2DM and cardiovascular risk, ample evidence exists from the observational studies at hand for nutrition recommendations and policy to discourage consumption of SSBs. However, certain limitations inherent in these studies are important to consider when interpreting the evidence.

Most studies discussed here adjusted their analyses for potential confounding by various lifestyle factors, and for the majority, a positive association persisted, suggesting an independent effect of SSBs. However, residual confounding by unmeasured or imperfectly measured factors cannot be ruled out. Higher SSB intake could be a marker of a globally undesirable diet because it tends to cluster with other unhealthy dietary and lifestyle habits such as higher intakes of saturated and *trans* fats^{44,94} and higher GL.³⁴ Therefore, incomplete adjustment for various lifestyle factors could lead

to an overestimation of the strength of the positive associations. However, the consistency of results from different cohorts reduces the likelihood that residual confounding is responsible for the findings. Because total energy intake partially mediates the effect of SSBs on weight gain, T2DM, and cardiovascular risk, whether a study has adjusted for total energy intake can seriously affect its results. For example, in our recent meta-analysis evaluating SSB intake and BMI in children,¹⁹ when energy-adjusted estimates were excluded, the summary effect estimate increased from a nonsignificant inverse trend (-0.03 ; 95% CI, -0.11 to 0.04) to a significant positive association (0.08 ; 95% CI, 0.03 to 0.13). Even after adjustment for total energy and other mediating factors such as BMI, some studies have still shown positive associations, supporting an effect of SSBs that is not mediated through energy intake or adiposity.^{53,95,96} Measurement error in dietary assessment is inevitable. However, in the setting of prospective cohort studies, misclassification of SSB intake does not likely differ by case status. Such nondifferential misclassification of exposure may actually attenuate the associations. Awareness of weight status, however, could result in systematic underreporting of SSB intake (as of body weight), which could weaken the association of SSBs with weight gain.

Longitudinal studies evaluating diet and weight change may also be prone to reverse causation (ie, people change their diet because of their weight, which could result in spurious associations). Ascertainment of repeated measures of diet and weight or stable intake patterns during long periods of follow-up may reduce the likelihood of this. Although most studies have been conducted among white populations from the West, the underlying biological process should be generalizable to other populations, although it is possible that some ethnic groups may be more prone to the deleterious effects of SSBs on cardiovascular risk. Further work in this area is clearly warranted.

Conclusions

SSB intake has increased considerably across the globe in recent decades, tracking positively with rising rates of obesity. Given the large number of comorbidities, reduced quality of life, and high healthcare expenditures, large-scale obesity prevention efforts are now a priority for many countries around the world. SSB intake is a significant contributor to weight gain and can lead to increased risk of T2DM and cardiovascular disease. In general, longer studies with greater numbers of participants that do not adjust for potential mediators of effect such as energy intake report stronger and more consistent results. SSBs are the greatest contributor to added-sugar intake in the United States and are thought to promote weight gain in part because of incomplete compensation for liquid calories at subsequent meals. SSBs may also increase T2DM and cardiovascular risk independently of obesity as a potential contributor to a high dietary GL and increased fructose metabolism, leading to inflammation, insulin resistance, impaired β -cell function, and high blood pressure, as well as accumulation of visceral adiposity/ectopic fat and atherogenic dyslipidemia. For these reasons and because they have little nutritional value, intake of SSBs

should be limited, and SSBs should be replaced by healthy alternatives such as water.

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KEY WORDS: diabetes mellitus ■ epidemiology ■ meta-analysis ■ nutrition ■ prevention