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Sugar Sweetened Beverages, Obesity, Type 2 Diabetes and Cardiovascular Disease risk

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Obesity has recently emerged as a major global health problem. According to World Health Organization (WHO) estimates, approximately 1.6 billion adults worldwide were overweight (BMI ≥ 25 kg/m^2) and at least 400 million were obese (BMI ≥ 30 kg/m^2) in 2005, numbers which 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 1976-1980 to over 66% and 33% in 2005-2006, 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. Epidemiologic studies indicate that overweight and obesity are important risk factors for of type 2 diabetes (T2DM), cardiovascular disease (CVD), cancer and premature death [3]. In the US, health care expenditures attributable to overweight and obesity are estimated to be $147 billion or 9.1% of total health care costs per year[4]. Such excess costs could have serious repercussions for resource-poor countries, which must manage 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

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intake to no more than 100-150 kcal per day for most Americans[5]. The statement identified sugar sweetened beverages (SSB) as the primary source of added sugars in the American diet[6]. While it has long been suspected that SSBs contribute at least in part to the obesity epidemic, only in recent years have large epidemiologic studies been able to substantiate the relationship between SSB consumption and long-term weight gain, T2DM and cardiovascular risk. It is thought that SSB's contribute to weight gain due to 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 large quantities consumed, SSB's may increase T2DM and cardiovascular risk, independent of obesity as a contributor to a high dietary glycemic load (GL) leading to inflammation, insulin resistance, and impaired ß-cell function [9]. Fructose from any sugar or HFCS may also increase blood pressure, and promote accumulation of visceral adiposity, dyslipidemia and ectopic fat deposition due to 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

While carbonated beverages trace their history back to the 1760's 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 an 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 1800's 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 U.S. War Department to provide free Cokes to army GIs. 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 and ultimately to become synonymous globally with SSB's [13]

Over the past 30 years, there has been a marked increase in consumption of SSBs across the globe. For instance in the US, intake of these beverages which includes the full range of soft drinks, fruit drinks, energy and vitamin water drinks increased from 3.9 % of calories in the late 1970's to 9.2% in 2001, representing a 3-fold increase in intake.[14] In other countries there have been varying levels of increase in SSB's with some, such as Mexico, reaching such magnitudes that serious government intervention to reduce intake is being undertaken[15]. National-level food disappearance data from China, India, Vietnam, Thailand and other South Asian countries also show rapid trajectories of increase in SSB intake, as well as large per capita consumption across the Americas, Germany, Australia, Spain and Great Britain[16]. Currently, the most rigorous sources of nationally representative patterns in SSB intake come from the US and Mexico where large-scale dietary intake surveys have been repeated over the last decade [15, 17]. According to these data, all age groups in Mexico consume about 10% of their total energy intake from SSBs. As shown in Figure 1 **Panel A**, SSB intake has increased considerably among those aged 5 y and older in Mexico. Figure 1 **Panel B** presents the same data for the US. As is seen in both children aged 2-18 y and adults aged 19 y and older, there have continued to be substantial increases across each decade.

SSB and childhood obesity

Childhood obesity is known to increase risk of obesity in adulthood and can lead to serious consequences for T2DM and CVD risk later in life. In fact recent evidence suggests consideration of lipid screening for children with BMI beginning at the 80th percentile, rather than BMI ≥ 85th percentile, which is the point at which a child is considered overweight[18]. Given the preponderance of SSB consumption among children and adolescents, several epidemiologic 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 one serving of SSB per day and found a significant positive association between SSB intake and weight-gain (0.08; 95% CI: 0.03, 0.13 kg)[19] among studies that did not adjust for total energy intake [20-24]. Since 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 colleagues found that in over 2000 children aged 2.5 y followed for 3 y, regular consumers of SSB between meals had a 2.4-fold greater odds of being overweight compared to non-consumers ($p<0.05$)[28]. Another study conducted among 5-year olds in the UK with 4 y 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 study[22] or in sub-group analyses among participants overweight at baseline [24, 32]. A follow-up analysis of a school based intervention which showed that reducing SSB intake decreased overweight and obesity[22], did not see an effect two 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 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 since 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 which are better powered to detect an effect. In this literature, the longest and largest studies [34, 35]show stronger and more consistent associations compared to smaller and shorter studies [36, 37]. For example, in the study by Schulze et al.,[34] with over 50,000 nurses followed for 2 four-year periods (1991-1995 and 1995-1999), 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 over the two periods while women who decreased SSB intake between 1991 and 1995 and maintained a low level of intake gained on average 2.8 kg over the two periods (Figure 2). Similar results

were reported by Palmer and colleagues[35] in over 40,000 African American women followed for 6 years. Those who increased SSB intake from ≤ 1 serv/wk to ≥ 1 serv/d gained the most weight whereas those who decreased their intake gained the least weight (6.8 kg and 4.1 kg respectively) after adjusting for potential confounders. A smaller study from Spain[38] with over 7000 participants followed for ~ 2 years, found that a higher consumption of SSB was associated with significant weight- gain among subjects who gained 3 or more kg in the five years before baseline. These participants had a higher absolute intake of SSB at baseline compared to participants with no previous weight-gain, consistent with a positive association between SSB intake and weight-gain. It is possible that the duration of the study was not sufficient 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 study [40] with an average duration of 4 y and over 4000 participants, compared with infrequent consumers, participants who consumed ≥ 1 soft drinks per day had a 37% higher risk of obesity[40]. Since this analysis included both diet and regular soft drinks it is difficult to disentangle the independent effect of SSBs, as consumers of diet soft drinks may be weight-conscious or trying to lose weight. In an observational analysis of the PREMIER study (N=810), Chen et al[41] found that a reduction in SSB intake of 1 serv/d was associated with a weight loss of 0.49 kg (95% CI: 0.11, 0.82; P = 0.006) at 6 months and of 0.65 kg (95% CI: 0.22, 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, MetSyn

Similar to the weight-gain literature, prospective cohort studies evaluating the effect of SSBs on risk of T2DM and 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 etiology as sufficient time is required for causal action and disease initiation and detection to occur. In over 50,000 women followed for 8 years, after adjustment for potential confounders, those consuming ≥ 1 SSB per day had an 83% greater risk of developing T2DM compared to those consuming <1 SSB per month RR= 1.83 (95% CI, 1.42-2.36; p<.001 for trend) (figure 3)[34]. The RR comparing extreme categories further controlling for BMI was 1.41 (95% CI: 1.09-1.83; *P* for trend<0.001). This finding suggests that BMI accounts for about half of the excess risk. Similarly, in the Black Women's Health study [35] with over 40,000 women followed for 10 years, those who consumed ≥2 SSB per day had a 24% greater risk of developing T2DM compared to those who consumed < 1 SSB per month RR=1.24 (95% CI, 1.06-1.45; 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 over 70,000 women followed for 18 years which showed that women who consumed 2-3 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, 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, 1.33), Women RR= 1.17 (95% CI 0.94, 1.46)[43]. Compared to the study by Schulze[34], participants in this study were older (53.6 y vs. 36.1 y) and heavier (27.2 kg/m^2 vs. 24.6 kg/m^2) at baseline. Since 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 development of MetSyn but they are in line with findings from studies evaluating T2DM. For example, findings from the Framingham Offspring study (N= 6154) show that compared to non-consumers, individuals who consumed ≥1 soft drink per day had a 39% greater risk of developing Met Syn over 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 since 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 is starting to accumulate which suggests that greater SSB consumption may have a role in the development of hypertension, adverse lipid parameters, inflammation and clinical CHD. The Framingham offspring study which also looked at SSB intake in the context of MetSyn components in 6154 adults followed for 4 years found that individuals who consumed ≥ 1 soft drink per day had a 22% higher incidence of hypertension (≥ 135/85 mm hg or on treatment) compared to non-consumers RR= 1.22 (95% CI 1.05, 1.41)[40]. Similarly, in the Nurses' Health Studies I and II, women who consumed ≥ 4 SSB's per day had a 44 % and 28 % higher risk of incident hypertension respectively, compared to infrequent consumers (RR= 1.44 (95% CI 0.98, 2.11); RR=1.28 (95% CI 1.01, 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 HDL-cholesterol (<1.03 mmol/L for men or <1.3 mmol/L for women or on treatment), compared to non-consumers: RR= 1.22 (95% CI 1.07, 1.41) and RR=1.22 (95% CI 1.04, 1.44) respectively[40]. Results from the 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 towards an effect on hypertension (≥ 130/85 mm hg or on treatment), and low HDL-cholesterol (<1.03 mmol/L for men or <1.3 mmol/L for women or on treatment), in daily SSB consumers compared to non-consumers: RR = 1.28 (95% CI 1.02, 1.60); RR=1.14 (95% CI 0.91, 1.43); RR=1.28 (95% CI 0.99, 1.64), respectively[45]. These findings are supported by a recent cross-sectional analysis of NHANES data which 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 (CRP) 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 CRP and TNFR2[49] and dietary glycemic load, to which SSB intake is a large contributor with CRP[50]. In addition, higher consumption of soft drinks has been associated with hyperuricemia[51] and incidence of developing gout[52], a condition that is 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 over 88,000 women followed for 24 years, those who consumed ≥ 2 SSB per day had a 35% greater risk of developing CHD compared to those who consumed <1 SSB per month: RR=1.35 (95% CI 1.1, 1.7; p<0.001 for trend). Additional adjustment for BMI, energy intake and incident T2DM attenuated the 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 mechanism linking SSB intake to weight gain is decreased satiety and incomplete compensatory reduction in energy intake at subsequent meals following consumption of liquid calories (Figure 4)[7, 8]. On average, SSBs contain 140-150 calories and 35-37.5 g of 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 following consumption of calorically sweetened beverages (sugar, sucrose, HFCS) compared to non-caloric artificially sweetened beverages[55, 56]. In addition, a number of studies have shown greater energy intake and weight gain following 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 large quantities that are often consumed, contribute to a high dietary glycemic load (GL). High GL diets are thought to stimulate appetite and 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 impact 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 (AGEs), which may further increase insulin resistance and inflammation [61]. For instance an 8-oz serving of cola delivers 16.3 kU of AGEs.[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 to glucose [10](figure 4). The different pathways for metabolism of fructose and glucose are clearly important potential mechanisms. Fructose alone is poorly absorbed, but 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 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 only increased in the glucose group, hepatic *de novo* lipogenesis, postprandial triglyceride, and markers of altered lipid metabolism and lipoprotein remodeling, such as fasting apoB, and small LDL 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 colleagues did not find evidence of oxidative or inflammatory stress following

intake of 300 kcal of fructose or orange juice while ROS generation and NF-kB binding was significantly increased after intake of glucose[70]. However, 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 SSB's and risk of CHD. Increases in blood pressure have also been observed when fructose is administered acutely, an effect not seen with glucose[73]. As well, an increase in blood pressure over 10 weeks was found when individuals drank SSB's but not with aspartame-sweetened beverages.[55] Fructose intake may also lead to weight gain by decreasing production of insulin and leptin in peripheral tissues, thereby initiating the hunger cascade in the central nervous system, [64] although this area warrants further investigation since others have found greater satiety and lower total energy intake following fructose preloads compared to glucose preloads[74].

Clinical implications

Controlling 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 as overweight and obesity is 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 replacing consumption of SSBs with other beverages, it is important to select alternatives that are healthy and do not promote weight gain. The average individual needs at least a milliliter of 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, kidney function, and preventing constipation[78]. Water has no calories or additives, is widely available, inexpensive and generally safe. Findings from epidemiological studies show that energy intake is significantly lower (~9%, or 194 kcal/d) in water drinkers compared to non-water drinkers[79] which was supported by a recent randomized controlled trial in German school-children[80]. This study found that one 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 over 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 whereby it is thought that the intense sweet flavor may stimulate appetite[83, 84]. Coffee and tea are also reasonable alternatives provided that caloric sweeteners and whiteners are used sparingly. A number of studies have shown that regular consumption of coffee and tea can have favorable benefits on T2DM and CVD risk, possibly by virtue of their polyphenol content[85, 86]. In recent decades, consumption of milk has decreased markedly in the US. Displacement by SSBs in the pediatric population is of great concern as this can lead to lower intakes of protein, calcium, magnesium, zinc, vitamin A, and vitamin D and increase risk for osteoporosis and bone fracture[14, 87]. Due to excess calories and saturated fat content of whole milk, low-fat milk is recommended but should be consumed in moderation as one eight-oz serving of non-fat milk still provides 85 kcal. Some evidence suggests that low-fat dairy products may also be beneficial for weight-loss and 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 over a life-time[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 epidemiologic 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 since for example, diet soda consumption is higher among individuals with diabetes than those without diabetes.[92] Studies with longer durations of follow-up and repeated measures, which are less prone to reverse causation, showed only marginal non-significant associations with diet soda [34, 35, 53] Some evidence suggests that a subset of diet soda consumers use the 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]. While Schulze and colleagues did not find as 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 (ROS) generation and NF-κB binding following consumption of orange juice compared to glucose drink, possibly due to 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

While more studies are warranted to better understand the underlying biologic mechanisms mediating the effect of SSBs on weight gain, T2DM and cardiovascular risk, evidence from observational studies show clear positive associations. Clinical trials, which policy and recommendations are often based, are not well-suited to this modality as they are greatly affected by intervention intensity and limited by compliance which tends to wane with increasing study length. To effectively evaluate 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 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 we discussed 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 as it tends to cluster with other unhealthy dietary and lifestyle habits such as higher intakes of saturated and trans fat [44, 94], and higher glycemic load[34]. Therefore incomplete adjustment for various lifestyle factors could lead to an overestimation in strength of the positive associations. However, consistency of results from different cohorts reduces the likelihood that residual confounding is responsible for the findings. Since 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 impact 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 non-significant inverse trend (−0.03; 95% CI:

−0.11, 0.04) to a significant positive association (0.08; 95% CI: 0.03, 0.13). Even after adjusting for total energy and other mediating factors such as BMI, some studies have still shown positive associations, supporting an effect of SSBs that are 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 i.e. persons 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 over long periods of follow-up may reduce the likelihood of this. Although most studies have been conducted among white populations from the West, 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 health care 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 US and are thought to promote weight gain in part due to incomplete compensation for liquid calories at subsequent meals. SSBs may also increase T2DM and cardiovascular risk independent of obesity, as a potential contributor to a high dietary GL and increased fructose metabolism leading to inflammation, insulin resistance, impaired beta-cell function, and high blood pressure as well as accumulation of visceral adiposity/ectopic fat, and atherogenic dyslipidemia. For these reasons and the fact that they have little nutritional value, intake of SSBs should be limited and replaced by healthy alternatives such as water.

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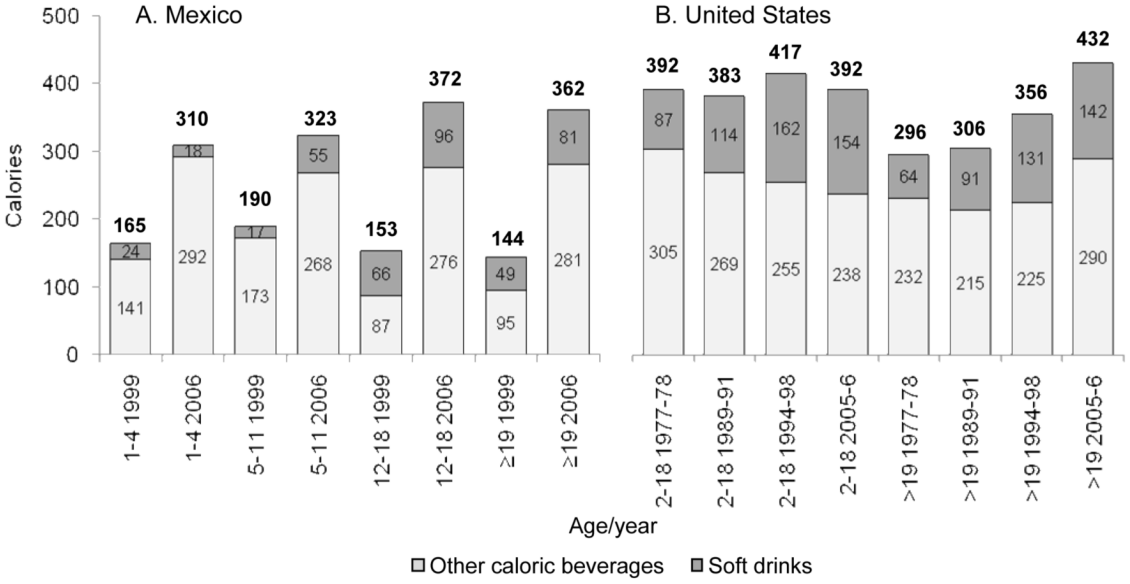

Figure 1. Trends in Soft drinks and total calories from beverages in Mexico and the United States

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: 1-4 years; 5-11 years; 12-18 years and ≥ 19 y in 1999 and 2006. Definition: soft drinks include carbonated, noncarbonated beverages with sugar added and commercially processed, bottled/formula fountain soft drinks and fruit drinks but exclude agua frescas, the Mexican hand-prepared added sugar fruit juices and fruit drinks.

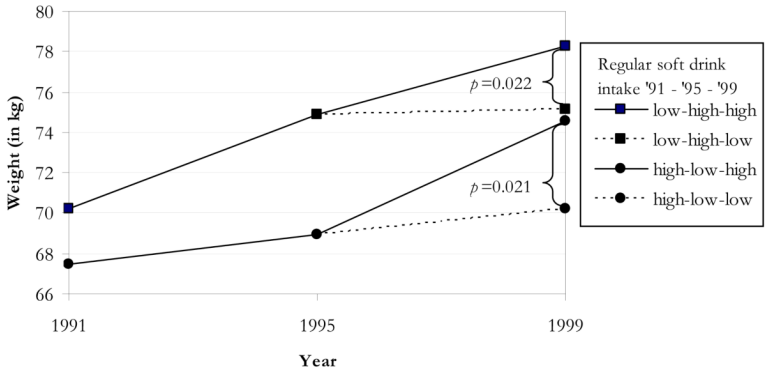

Figure 2. Mean weight in 1991, 1995, and 1999 according to trends in sugar-sweetened soft drink consumption in 1,969 women who changed consumption between 1991 and1995 and either changed or maintained level of consumption until 1999

Low and high intakes were defined as ≤1/week and ≥1/day. The number of subjects were: 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 MB et al. [34]

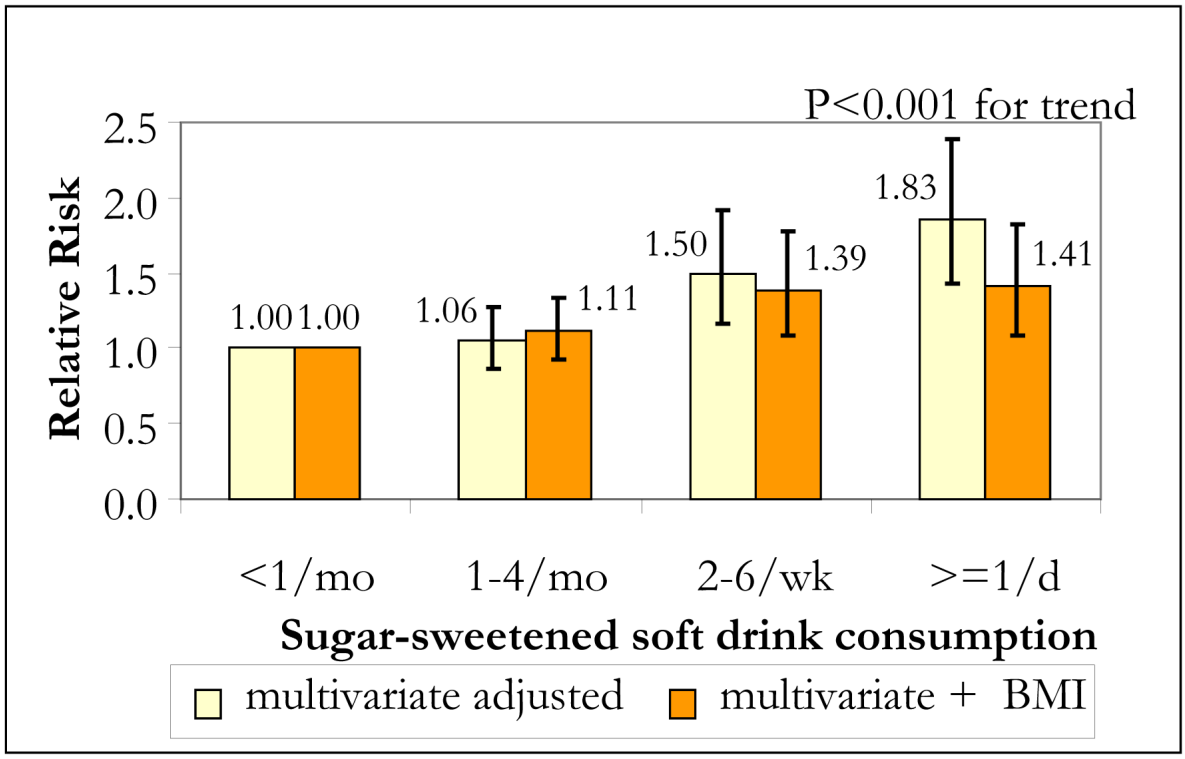

Figure 3. Multivariate relative risks (RRs) of type 2 diabetes according to sugar-sweetened soft drink consumption in the Nurses' Health Study II 1991-1999

Multivariate RRs were adjusted for age, alcohol (0, 0.1-4.9, 5.0-9.9, 10+ g/d), physical activity (quintiles), family history of diabetes, 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 Schulze MB et al.[34]

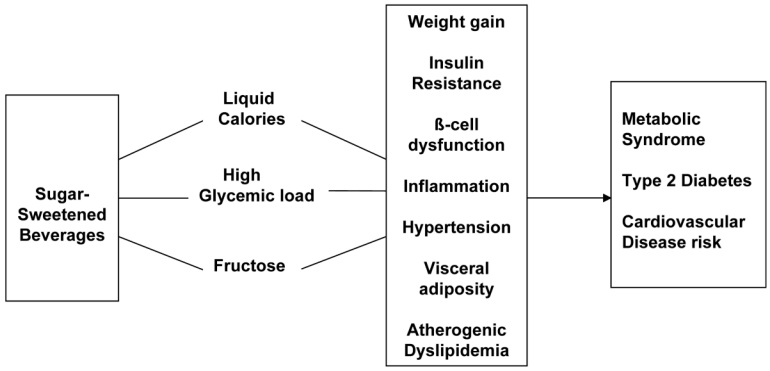

Figure 4. Potential biological mechanisms underlying the effect of SSBs on weight gain and risk of Metabolic Syndrome, Type 2 Diabetes and Cardiovascular Disease Risk

SSBs may lead to weight gain due to incomplete compensation for liquid calories at subsequent meals resulting in positive energy balance. Independent of weight gain, SSB's may increase risk of MetSyn, T2DM and CVD due to their large contribution to a high dietary GL, and large fructose fraction, leading to development ofinsulin resistance, beta cell dysfunction, inflammation, hypertension, visceral adiposity and atherogenic dyslipidemia