Sugar-Sweetened Beverages and Cardiovascular Disease

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Abstract During the past several decades, consumption of sugar-sweetened beverages (SSBs) has increased dramatically worldwide, contributing to the significant rise in consumption of total energy and added sugars. The health impact of current high consumption of SSBs has attracted scientific and public concerns. We have reviewed the studies published in 2010 and 2011 examining the relationship between consumption of SSBs and risk of cardiovascular disease. This review focuses on human studies, including cross-sectional studies, prospective cohorts, and randomized controlled trials, of relatively long duration (>3 weeks). The purpose of this review is to provide insights for future research and public health recommendations.

Keywords Sugar-sweetened beverages · Obesity · Type 2 diabetes · Hypertension · Cardiovascular disease · Coronary heart disease · Stroke · Metabolic syndrome · Blood pressure · Soft drinks · Fruit drinks

Introduction

Sugar-sweetened beverages (SSBs) are generally defined as carbonated or noncarbonated beverages that were sweetened with sugars (sucrose, high-fructose corn syrup, or other calorically sweeteners). These included regular soft drinks, fruit drinks, lemonades, fruit punch, and other sweetened beverages. These beverages have relatively high calorie and sugar

contents but no or very small amounts of other nutrients. On average, SSBs contain 140–150 kcal and 35–40 g of sugar per 12-fl oz serving [1]. According to a national survey, SSBs are the most commonly consumed caloric beverage [2], with a mean daily SSB consumption of 28 ± 1 fl oz (2.3 servings) for adults (>20 years of age) in the United States [3]. Because of the current high consumption levels, SSB intake has attracted both scientific and public interest in the past decade. In 2009, the American Heart Association (AHA) released a scientific statement that recommended reductions in added sugar intake to less than 100–150 kcal/d (6–9 teaspoons) for heart health, and identified SSBs as the primary source of added sugars (33 %) in the American diet [4].

The first prospective study that linked SSB consumption to the risk of childhood obesity was published in 2001 by *The Lancet* [5]. Since then, emerging data from cross-sectional studies, prospective cohorts, and randomized controlled trials (RCTs) in different populations and regions have examined the association of SSB consumption with cardiovascular disease (CVD) risk factors (ie, obesity, type II diabetes [T2D], metabolic syndrome [MetS]) and CVD events (ie, hypertension, coronary heart disease [CHD], and stroke). Most of the published studies found positive associations between SSB consumption and CVD risk factors/events.

The prevailing mechanisms linking SSB intake to weight gain or obesity risk might be the low satiety of liquid calories and incomplete compensatory reduction in energy intake at subsequent meals as compared with solid calories, leading to an increase in total calorie intake [6]. Another possible link between SSBs and obesity is related to the high fructose content of these beverages. Long-term consumption of a large amount of fructose can promote fat storage and excessive food intake through an increase in de novo lipogenesis and changes in postprandial hormonal patterns [7]. Independent of obesity, consuming large amounts of SSBs

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could also increase the risk of MetS, T2D, and CVD by increasing dietary glycemic load, impairing pancreatic β -cell function, and promoting chronic inflammation [8•].

In a review paper published in 2010 by *Circulation*, Malik et al. [9••] provided a comprehensive overview on the available studies in the area of SSB consumption and obesity, T2D, and CVD. This review also discussed the potential underlying biological mechanisms. Therefore, the purpose of the current review is to summarize the new studies published between 2010 (those that were not included in the Malik et al. [9••] review) and 2011, and to provide an updated review to guide future research and public health recommendations.

Sugar-Sweetened Beverages and Cardiovascular Disease Risk Factors

Obesity

Recent epidemiologic data linking SSB consumption to obesity comprise cross-sectional studies, prospective cohorts, and interventional trials. The most important publication during the past year was a study published by the *New England Journal of Medicine* [10•]. This study was conducted by investigators from Harvard University and included data from three separate prospective cohorts (The Nurses' Health Study [NHS], The Nurses' Health Study II [NHS II], and The Health Professionals Follow-up Study [HPFS]). In total, 120,877 US men and women who were nonobese and free of major chronic diseases at baseline were observed for up to 20 years. Weight changes, physical activity, and food consumption were evaluated at 4-year intervals. On average, increased daily SSB intake of one serving was associated with a 1.0-pound weight gain (95 % CI, 0.83–1.17) in a 4-year interval after controlling for potential confounders. Such an effect was similar in men and women and in participants from each cohort. Results from such large studies with long-term follow-up time and high follow-up rate provide relatively robust evidence to support a positive association between SSB consumption and body weight in adults. However, given its observational nature, residual confounding by unmeasured factors or imprecise measured variables is inevitable. In addition to this prospective study, two recent cross-sectional analyses contributed to the literature by examining different measures of adiposity or investigating different populations. One cross-sectional study examined the consumption of SSB in relation to visceral adipose tissue (VAT, measured by MRI) among 791 non-Hispanic US men and women (18–70 years of age) [11]. In their findings, consumption of SSBs was positively associated with proportion of visceral to subcutaneous abdominal adipose tissue ($\%VAT = 100 \times VAT / [VAT + \text{subcutaneous abdominal adipose tissue}]$). On average, VAT% increased from

30.0 % in individuals without SSB intake to 32.8 % in those with more than 1 serving/d (P for trend=0.03). This finding held for men and women and for participants in all age groups. Greater VAT proportion is correlated with greater insulin resistance and inflammation. Therefore, this finding indicates that SSB consumption is not only associated with the risk of overall obesity or weight gain but may also lead to a more adverse adiposity tissue deposit pattern, which in turn is linked to increased cardiometabolic risks. Because the majority of participants in the above two studies were Caucasian, it is interesting to ask whether the data from other racial/ethnic groups also suggested the same association. Another cross-sectional study used data from a mixed group of US young adults ($n=947$; 20–39 years of age; 45 % non-Hispanic whites, 23 % non-Hispanic blacks, and 32 % Mexican Americans) in the US National Health and Examination Survey (NHANES) 1999–2000 [12]. In this study, individuals with a greater intake of SSBs had a higher risk of total and abdominal obesity after controlling for potential confounders. The ORs across the SSB consumption quartile (0.02, 1.3, 2.8, 6.4 servings/d) were 1.0 (reference), 1.0, 1.6, and 2.3 (P for trend=0.007) for total obesity (defined as body mass index [BMI] ≥ 30 kg/m²) and 1.0 (reference), 1.6, 2.0, and 2.2 (P for trend=0.01) for abdominal obesity (defined as waist circumference [WC] >102 cm for men and >88 cm for women). BMI and WC were directly measured by trained examiners in the NHANES. Similarly, there is no effect modification by sex and age. Interestingly, the authors did not mention whether they conducted stratified analyses by race or tested the interaction of SSB consumption and race. Given that African Americans, particularly young adults (<40 years of age), consumed a significantly higher level of SSBs compared with non-Hispanic whites, it would be interesting to show the association in different racial/ethnicity groups.

Although findings from well-designed, prospective studies have provided strong and consistent data to support a positive association between consumption of SSBs and risk of obesity, evidence from RCTs is still needed to establish the causality. In the literature, only a few RCTs have been published to date, probably due to the difficulty of conducting a powerful trial over a long term and with a proper control group [9••]. In 2011, a group of scientists in The Netherlands published a paper on study design and baseline information for a double-blind RCT [13]. The objective of this trial was to examine the effect on body weight of replacing SSBs with sugar-free beverages in children (5–11 years of age) over 18 months. Children were eligible if their habitual SSB consumption was greater than 250 mL/d. Children in this trial received a 250-mL can of containing a beverage daily (containing either 10 % [25 g] of sugar or sugar free [0 g]) for 18 months. Body weight was measured at baseline and at 6, 12, and 18 months. The primary outcome was z-score of BMI for age. The predicted difference of change in z-score was 0.18, and the

adequate sample size was 212 children in each group (power=0.80). The researchers carefully designed and tested the beverages to ensure that the SSBs and sugar-free beverages looked and tasted the same. The beverages were packed and delivered to schools by study staff. Each child received a box of 8 cans/wk, with 5 for school days, 2 for weekends, and 1 as a spare can. Schoolteachers and parents were asked to help monitor SSB intake. Compliance was measured by counting the returned cans and by analyzing the sucralose (the artificial sweetener in the sugar-free beverages) in urine. While the overall study design was of high quality, the lack of measured dietary intake was a major limitation. Without collecting children's dietary intake data, it was not possible to assess whether children also drank beverages from other sources (eg, home, restaurants, parties, movie theaters) and whether children in the sugar-free beverage group compensated for the reduced sugars and/or calories by consuming other foods/beverages. The study recruitment started in August 2009, and intervention ended in July 2011. We anticipate that the results will be published in the near future.

Type 2 Diabetes and Metabolic Syndrome

A large number of prospective studies have linked higher consumption of SSBs to an elevated risk of T2D among middle-aged or older adults [9•], and to gestational diabetes in pregnant women [14]. In addition, several cohorts reported a positive association between SSB consumption and risk of MetS [9•]. In 2010, a group of Harvard scientists published a meta-analysis on SSBs and risk of T2D and MetS based on 11 prospective studies (8 for T2D, 3 for MetS) [8•]. For T2D, the pooled relative risk (RR) for comparing the highest quintile of intake (1–2 servings/d) with the lowest quintile (none or <1 serving/mo) was 1.26 (95 % CI, 1.12–1.41) from a total of 310,819 participants and 15,043 cases. For MetS, the pooled RR was 1.20 (95 % CI, 1.02–1.42) from a total of 19,431 participants and 5,803 cases. One study (HPFS; $n=40,389$) included in this meta-analysis was actually published in 2011 by the *American Journal of Clinical Nutrition* [15]. After this meta-analysis, results from the Coronary Artery Risk Development in Young Adults (CARDIA) study also consistently reported that higher intake of SSBs was significantly associated with an elevated risk of the components of MetS (ie, high WC, high triglycerides, high low-density lipoprotein [LDL] cholesterol, and high blood pressure) [16]. This study included 2,774 adults aged 18–30 years at baseline (1985–1986) and observed for 20 years. Higher SSB consumption (comparing the higher quartile to the next lower quartile) was associated with higher risk of high WC (defined as WC >102 for men and >88 for women; adjusted RR, 1.09 [95 % CI, 1.04–1.14]; P for trend<0.001), high LDL cholesterol (defined as LDL >4.1 mmol/L or use of cholesterol-lowering medications;

RR=1.18 [95 % CI, 1.02–1.35]; P for trend=0.018), high triglycerides (defined as triglycerides >1.7 mmol/L or use of cholesterol-lowering medications; RR=1.06 [95 % CI, 1.01–1.13]; P for trend=0.033), and high blood pressure (defined as systolic blood pressure [SBP] ≥ 130 mm Hg or diastolic blood pressure [DBP] >85 mm Hg; RR=1.06 [95 % CI, 1.01–1.12]; P for trend=0.023). It is interesting to note that although consumption of SSBs was significantly associated with several components of the MetS, it was not associated with the MetS itself in this study. The authors also acknowledged this observation but could not provide any explanations.

Similar to the literature of obesity, RCTs evaluating the effect of SSB consumption on the risk of T2D are lacking. One, a small interventional study ($n=29$) among healthy young men, was published in 2011 by the *American Journal of Clinical Nutrition* [17]. The study was designed to analyze the effect of SSB consumption on changes in metabolic biomarkers for 3 weeks. It was a crossover study in design, with five treatment periods and one control period (each for 3 weeks). While the control was to receive dietary advice to consume low amounts of fructose, the treatments were 600 mL of SSBs per day containing 1) 40 g fructose (MF), 2) 80 g fructose (HF), 3) 40 g glucose (MG), 4) 80 g glucose, or 5) 80 g sucrose (HS, contains both fructose and glucose in a 1:1 ratio). Compared with control, the fasting glucose and high-sensitivity C-reactive protein (hs-CRP) increased significantly (by 4–9 % and 60–109 %, respectively; $P<0.05$). In addition, a more atherogenic LDL subtype profile was observed when fructose-containing SSBs were consumed (MF, HF, and HS). Although small in sample size, this study provided a new insight that SSB intake at the level of 1–2 servings/d may increase CVD risk factors such as LDL particles, fasting glucose, and hs-CRP within 3 weeks. These findings warrant future studies with larger samples and of longer duration to establish the casual relationship.

Sugar-Sweetened Beverages and Cardiovascular Disease Events

Hypertension

Hypertension is one of the most common CVDs and one of the most important risk factors for stroke. It has been estimated that a 3-mm Hg reduction in SBP should reduce stroke mortality by 8 % and CHD mortality by 5 % [18]. Data on SSB consumption and hypertension risk are starting to accumulate from both cross-sectional and prospective studies. In 2010, we published (in *Circulation*) a prospective analysis of an 18-month lifestyle intervention ($n=810$), the PREMIER study [19•]. Findings from this study provided strong evidence to support consumption of SSBs as positively associated with blood pressure and risk of hypertension. In

this study, a reduction of SSB consumption by 1 serving/d was associated with a decreased SBP of 1.8 mm Hg and DBP of 1.1 mm Hg after controlling for potential confounders. With additional control for weight loss during the trial, a reduction in SSB consumption was still associated with a significant reduction in blood pressure (0.7 mm Hg in SBP, 0.4 mm Hg in DBP), indicating that reducing consumption of SSBs may lower blood pressure independently of its effect on body weight. These effects occurred in men and women, Caucasians and African Americans, obese and nonobese individuals, and nonhypertensive and hypertensive individuals. In addition, we observed a trend of increase in the proportion of individuals who moved from hypertensive at baseline to nonhypertensive at 18 months across tertiles of SSB consumption (17.0 %, 18.5 %, and 23.5 %, respectively; P for trend < 0.001) (Fig. 1). Taken together, these findings suggested that reducing consumption of SSBs might be a potential dietary approach to lower blood pressure for the general population. These results were supported by another cross-sectional study published in 2011 in *Hypertension* [20]. This study analyzed data from the International Study of Macro/Micronutrients on Blood Pressure (INTERMAP), which included 2,696 participants from 10 population samples in the United States and United Kingdom. Additional intake of 1 serving/d of SSBs was associated with higher SBP (by 1.6 mm Hg) and DBP (by 1.1 mm Hg), which is consistent with the longitudinal estimates from the PREMIER study. In addition, both studies also found a positive association of blood pressure with sugars (ie, fructose and glucose), suggesting sugars may be the nutrients that contribute to the observed association between SSBs and blood pressure.

To our knowledge, no RCTs or interventional studies have been published examining the effect of SSB intake on blood pressure. The related evidence is from animal studies that have repeatedly shown that high consumption of SSBs or sugars can induce hypertension [19]. The literature is expected to be filled by future studies.

Coronary Heart Disease and Stroke

To date, very few published studies have examined the direct association of SSB consumption with CHD and stroke. In 2009, a prospective analysis using data from the NHS reported a positive association between consumption of SSBs and risk of CHD (nonfatal and fatal myocardial infarctions) [20, 21]. Among 88,520 women who were observed for up to 24 years, the RRs (95 % CI) for cross-habitual SSB consumption at less than 1 serving/mo, 1–4 servings/mo, 2–4 servings/wk, 1 serving/d, and 2 or more servings/d were 1.0, 0.96 (0.87–1.06), 1.04 (0.95–1.14), 1.23 (1.06–1.43), and 1.35 (1.07–1.69), respectively (P for trend=0.001). To date, we are not aware of any published studies that have investigated the direct association between consumption and risk of stroke.

Fig. 1 Model adjusted mean blood pressure changes (**a**, systolic blood pressure [SBP]; **b**, diastolic blood pressure [DBP]) and proportion of participants (%) who moved from hypertensive at baseline to nonhypertensive at 18 months (**c**) by tertiles of change in sugar-sweetened beverage (SSB) consumption (fl oz/d) from baseline to 18 months (18-months–baseline). The mean change in SSB consumption across the tertiles was 9.5 ± 7.4 , -0.9 ± 1.6 , and -15.3 ± 9.9 fl oz/d (persons in the 3rd tertile had the greatest reduction in SSB). Covariates in the model included gender, race, family history of hypertension, randomization assignment, site, baseline age, alcohol drinking, body mass index [BMI], baseline SSB intake, baseline fitness and change in fitness, baseline physical activity and change in physical activity, baseline urinary sodium excretion and change in urinary sodium excretion, baseline DASH Index and change in DASH Index, and change in body weight from baseline to 18 months. (From Chen L, Caballero B, Mitchell DC et al. Reducing consumption of sugar-sweetened beverages is associated with reduced blood pressure: a prospective study among United States adults. *Circulation* 2010;121(22):2398–406. Copyright 2010, Wolters Kluwer Health; with permission)

Conclusions

Consumption of SSBs has increased dramatically in developed and some developing countries, which contributes to the significant increase in intake of added sugars and liquid calories. Such a trend has attracted a great deal of attention in both scientific and public realms. During the past decade,

a large number of studies with different designs and in different populations have investigated the health impact of high SSB consumption. Many health outcomes, including oral health, bone health, chronic diseases, and cancer, have been examined. Regarding SSB consumption and CVD risk/risk factors, the strongest evidence was found in the association with obesity and T2D. In particular, results from well-designed prospective cohorts (eg, NHS, NHS II, HPFS, Atherosclerosis Risk in Communities Study [ARIC], Framingham Offspring Study, Black Women's Health Study [BWHS], Multi-Ethnic Study of Atherosclerosis [MESA], Singapore Chinese Health Study, Finnish Mobile Clinic Health Examination) with large sample sizes and long-term follow-up have provided consistent and compelling evidence that higher intake of SSBs is associated with elevated risk of obesity and T2D. Emerging evidence also suggested a positive association between SSB intake and MetS, hypertension, inflammation, and dyslipidemia. As all these conditions and diseases are established key risk factors for CVD, it is reasonable to speculate that a reduction in SSB consumption might be beneficial in lowering the risk of development of CVD. However, studies directly linking consumption of SSBs to CVD event is limited. Also, only a few long-term human RCTs have provided limited data to support the causal relationship and to estimate the attributable benefits for reductions in SSB consumption on CVD prevention and management. Methodologic issues, such as inaccurate measures of SSB consumption and/or health outcomes, inadequate controlling for important confounders, and over-controlling for mediating factors, have been found in many studies. More studies are warranted to fill the research gaps. Nevertheless, SSBs have high calorie and sugar content but very little nutritional value. Intake of SSBs should be limited given current high intake levels of calories and added sugars.

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- Of major importance

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