Frequent Sugar-Sweetened Beverage Consumption and the Onset of Cardiometabolic Diseases: Cause for Concern?

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The incidence of noncommunicable diseases is on the rise and poses a major threat to global public health. This is in parallel to a steady increase in worldwide intake of sugar-sweetened beverages (SSBs) among all age groups. As several studies demonstrated a controversial relationship between SSB consumption and the metabolic syndrome (MetS), this mini-review focuses on links between its intake and (1) MetS, (2) prediabetes/type 2 diabetes mellitus (T2DM), and (3) hypertension. A detailed search for clinical and observational studies published during the past 10 years was conducted using key terms that link SSBs to the MetS, T2DM, and hypertension. Here we excluded all meta-analyses and also literature that solely focused on obesity. The analysis revealed that most epidemiological studies strongly show that frequent SSB intake contributes to the onset of the MetS in the longer term. Some of the findings also show that regular SSB intake can alter glucose handling and insulin sensitivity, thereby contributing to the development of the MetS and T2DM. There is also evidence that frequent SSB intake (and particularly fructose) is linked to hypertension and well-known cardiovascular disease risk factors. However, some studies report on the lack of negative effects as a result of SSB consumption. Because of this discrepancy, we propose that well-designed long-term clinical studies should further enhance our understanding regarding the links between SSB consumption and the onset of cardiometabolic diseases.

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During 2011, the United Nations announced for the first time that noncommunicable diseases pose a greater health risk than infectious diseases in both developed and developing countries [1]. The World Health Organization estimates that noncommunicable diseases result in 38 million deaths annually, with cardiometabolic diseases accounting for ~19 million fatalities [2]. The umbrella term cardiometabolic diseases describes both cardiovascular diseases (CVDs) and conditions such as the metabolic syndrome (MetS) and type 2 diabetes mellitus (T2DM). Furthermore, obesity, MetS, and T2DM are all risk factors for the onset of CVD, the current leading cause of global mortality [3]. Beside such risk factors, sugar-sweetened beverage (SSB) intake can also drive CVD onset by promoting hypertension, inflammation, and dyslipidemia [4].

The increased prevalence of cardiometabolic disorders is strongly linked to greater urbanization and the adoption of detrimental lifestyle choices that include sedentary behavior, smoking, and poor dietary preferences. For example, excess sugar consumption has surfaced...
as one of the most prominent global dietary changes during the past few decades and is considered a primary driver of cardiometabolic disease onset [5]. In support, a 5-year South African Adult Prospective Urban and Rural Epidemiology cohort study showed an association between higher consumption of added sugars and sucrose-sweetened beverages with increased noncommunicable disease risk factors [6]. It was also recently established that 74% of the 85,451 different edible products (mainly cereals, energy bars, and beverages) on the US market contained added sugars [7]. Here SSBs emerge as a strong culprit with estimates showing that it provides ~46% of added sugars [8]. Nevertheless, there is controversy regarding findings from various studies investigating the relationship between SSBs and the onset of cardiometabolic diseases [9–13]. In light of this, the current mini-review explores the links between SSB intake and the risks for cardiometabolic disease development, focusing on three main aspects: MetS, T2DM, and hypertension.

1. Methods

For the present review, three searches for clinical (including all clinical trial phases, clinical studies, controlled clinical trials, randomized controlled trials) and observational studies were performed. Meta-analyses and systematic reviews were not considered for this review process. The term sugar is often being used to represent a range of different molecules, and for the purposes of the current review article, it includes sucrose, glucose, fructose, high-fructose corn syrup, and artificial sweeteners. The first search was performed on the link between SSBs and the MetS where we used two keyword combinations: sugar-sweetened beverages and metabolic syndrome and sugar-sweetened beverages and cardiometabolic risk. The search was performed in PubMed (https://www.ncbi.nlm.nih.gov/pubmed/) and only human studies (written in English) and published within the past decade were selected. This search yielded a total of 12 results.

For the second search, we aimed to establish the link between SSBs and the risk for T2DM. Using the same parameters mentioned previously, the search phrases included sugar-sweetened beverages and type 2 diabetes and sugar-sweetened beverages and prediabetes. This search yielded a total of 16 results. The third search focused on SSBs and hypertension using the same parameters described previously. Here search terms included sugar-sweetened beverages and hypertension and sugar-sweetened beverages and blood pressure. The search yielded a total of eight results.

The searches are the latest as of September 2017. The extra literature included in this review was identified separately (not using our systematic review criteria) to demonstrate additional aspects within this field. Although obesity forms a component of MetS, it will not be reviewed in detail as it falls beyond the scope of the current mini-review. During such searches, we observed that there was an overlap with some of the articles as would be predicted because the MetS includes impaired glucose metabolism and increased blood pressure.

2. Results

We have structured our results in the same way as the search criteria stipulated in the Methods section of this article.

A. SSBs and the MetS/Cardiometabolic Risk

The literature revealed, at times, contradictory observations in terms of the relationship between SSBs and the MetS. High SSB consumption is considered a risk factor for the onset of the MetS [4], which refers to a cluster of complications that manifest concurrently and serves as a prognostic tool for the future development of T2DM and CVD. Limited clinical and observational trials assess the contribution of SSBs to the MetS. Here some studies do show a
direct correlation [14], whereas in other cases, there is a lack of sufficient evidence to link SSBs to all the comorbidities associated with the MetS [15, 16].

Despite such contradictory findings, most studies thus far completed support a link between SSB intake and the MetS. Here all but one of the studies showed that SSBs promote the risk of developing some or all the components of the MetS [14–24]. In support, Dhingra et al. [17] found that the odds of developing the MetS (the mean follow-up period was 4 years) is significantly higher in individuals who consume one or more SSB servings daily (odds ratio, 1.44; 95% confidence interval (CI), 1.20 to 1.74). The Prevención con Dieta Mediterránea prospective study also found that the frequent intake of SSBs (>5 servings/wk), artificially sweetened beverages, and natural and bottled fruit juices was associated with an increased risk for the MetS and some of its components [25]. SSB effects are also related to ethnicity; for example, African Americans (28 to 40 years old) who consumed relatively higher SSB amounts (>2 per day), but not moderate dosages, displayed kidney damage as indicated by increased levels of microalbuminuria [26].

De Ruyter et al. [27] conducted a small study to establish whether SSB consumption induced weight gain. Here children (4 to 11 years old) of normal weight were assigned to either experimental or control groups in a double-blinded manner and were expected to consume 250 mL SSB or 250 mL artificially sweetened beverage, respectively, on a daily basis. The authors found that body weight, body mass index (BMI), waist circumference, waist-to-hip ratio, and body fat percentage increased significantly in the SSB group compared with the artificially sweetened group after the 18-month intervention period. A substantial increase in body weight and BMI was observed only in the group consuming glucose-sweetened beverages, whereas sucrose- and fructose-sweetened drinks induced changes in the waist circumference and waist-to-hip ratio. Of note, others found a decrease in body weight and BMI in fructose-consuming participants [28], whereas another study also did not support the link between SSB consumption and weight gain [29]. This could possibly be explained by the shorter intervention period (6 months), although the intervention itself was more intense (1 L sucrose-sweetened beverage/d compared with 250 mL/d).

SSB consumption may also trigger effects that occur independently of body weight and energy balance changes. For example, some reported increased low-density lipoprotein cholesterol levels that were induced by the intake of fructose-sweetened beverages [30]. Here metabolites such as triglycerides, fasting blood glucose, and uric acid levels also increased in a dose-dependent manner with SSB intake. Bruun et al. [31] reported similar findings (i.e., the daily intake of regular cola for 6 months enhanced circulating uric acid levels in overweight and obese participants). Other cross-sectional studies in adolescents also showed that SSB increased serum uric acid in association with hypertension [32] and pediatric insulin resistance [33]. By contrast, some established that moderate SSB intake did not affect fasting or postprandial cholesterol and triglyceride levels or hepatic insulin clearance [34]. The lack of any effects might be attributed to the short duration of the study (only done over a 2-week period), thus providing a likely explanation why no discernable effects were observed at this relatively early time point.

In addition to ethnicity, sex is also a factor that may account for the different observations discussed. In support, a recent prospective study by Kang and Kim [35] showed increased MetS parameters were associated with frequent consumers of soft drinks (>4 servings/wk), but only in females and not in men. Together, the bulk of epidemiological data strongly indicates that frequent SSB intake is linked to the MetS, with potentially serious long-term effects on overall health and well-being (Table 1).

B. SSBs and Prediabetes/T2DM

Epidemiological studies reported that regular SSB consumption, in some cases as little as two SSB servings per week, is linked to a greater risk for the development of T2DM [36, 37]. The negative effects of SSB consumption may also further exacerbate the already impaired glucose metabolism underlying T2DM [38]. As most studies used specific intervals of SSB
consumption (lowest: <1 SSB per month; highest: ≥1 SSB per day), Fagherazzi *et al.* [5] designed a model to describe the continuous correlation between SSB consumption and T2DM development. These findings revealed that the consumption of SSB (0 to 1000 mL/wk) is directly related to a greater T2DM risk (relative risk, 1.3; 95% CI, 1.03 to 1.66) [39]. Moreover, the 14-year prospective Framingham study showed an association between increased insulin resistance and a higher risk of developing prediabetes with regular SSB intake but not for

| Author                  | Cohort/Location                  | Participants                          | Age (Mean/Range), y | Sex | Average Follow-up Period |
|-------------------------|----------------------------------|---------------------------------------|--------------------|-----|----------------------------|
| Barrio-Lopez *et al.* (14) | SUN Project; Spain            | 8157                                  | 36                 | M and F | 6 y                     |
| Khosravi-Boroujeni *et al.* (15) | Iran                      | 1752                                  | 39.4 ± 14.2 (F); 41.6 ± 16.7 (M) | M and F | Cross-sectional study     |
| Chan *et al.* (16)       | Taiwan                          | 2727                                  | 12–16              | M and F | Cross-sectional study     |
| Wang *et al.* (18)       | QUALITY study, Canada            | 633                                   | 8–10               | M and F | 8 y                      |
| Hernandez-Cordero *et al.* (19) | Mexico                    | 240                                   | 18–45              | F    | 9 mo                     |
| Mattei *et al.* (20)     | Costa Rica                      | 1872                                  | 49–70.3            | M and F | Cross-sectional study     |
| Denova-Gutierrez *et al.* (21) | Mexico                  | 8307                                  | 20–70              | M and F | Cross-sectional study     |
| Loh *et al.* (22)        | Malaysia                        | 873                                   | 13                 | M and F | Cross-sectional study     |
| Dhingra *et al.* (17)    | Framingham Offspring study; United States | 6039                      | 46–66              | M and F | Cross-sectional study     |
| Duffey *et al.* (23)     | CARDIA study; United States     | 2774                                  | 25 ± 3.6 (at start)| M and F | 20 y                     |
| Ambrosini *et al.* (24)  | Raine study; Australia          | 1433                                  | 14 (at start)      | M and F | 14 y                     |
| Ferreira- Pêgo *et al.* (25) | PREDIMED; Spain               | 1868                                  | M: 55–80 F: 60–80 (at start) | M and F |                           |
| Kang and Kim (35)        | KoGES                           | 5797                                  | 40–69              |                   | 10 y                     |
Table 1. Continued

| Range of SSB Intake/d | Elevated Risk Factors of MetS | P Value for Trends | Confounder Adjustment |
|-----------------------|-------------------------------|--------------------|-----------------------|
| 0–2.4 servings        | BP, WC, TAG                   | BP (P < 0.001); WC (P < 0.001);TAG (P = 0.016) | Yes                   |
| <1/wk to >3/wk        | DBP in females                | P < 0.05           | Yes                   |
| 0/d; 1–500 mL/d and >500 mL/d | WC, TGs; SBP in males | Metabolic risk cluster (P-trend < 0.038); SBP males (P = 0.043) | Yes                   |
| Median SSB intake 146 mL/d | HOMA-IR; SBP; WC | In overweight children, HOMA-IR (increase) (P = 0.009); SBP (P = 0.001); in children with impaired glucose tolerance, SBP higher by (>1.4 mm Hg); WC (P < 0.001) | Yes                   |
| 418 ± 11 mL/d         | No elevated risk factors observed | NA | No                   |
| None to ≥1 serving/d | WC, TGs; higher odds of MetS | WC (P ≤ 0.001); TGs (P ≤ 0.001); MetS (P = 0.009) | Yes                   |
| None to >2 servings/d | Prevalence of MetS higher in obese subjects; increased TGs; reduced HDL | 26.65 obese people had MetS; 0.49-mmol/L increase in TGs/additional SSB consumption; 0.39-mmol/l decrease in HDL/additional SSB consumption | Yes                   |
| 110–190 mL/d          | Elevated TGs; FBG; insulin; insulin resistance; low HDL-C | None were statistically significant | Yes                   |
| <1 to ≥2 servings/d   | Increased prevalence of MetS; obesity; WC; fasting glucose; blood pressure; TGs; HDL | Increased MetS (OR, 1.48; 95% CI, 1.30–1.69); Obesity (OR, 1.31; 95% CI, 1.02–1.68); WC (OR, 1.30; 95% CI, 1.09–1.56); fasting glucose (OR, 1.25; 95% CI, 1.05–1.48); BP (OR, 1.18; 95% CI, 0.96–1.44); TGs (OR, 1.25; 95% CI, 1.04–1.51); HDL (OR, 1.32; 95% CI, 1.06–1.64) | Yes                   |
| Average intake over 7 y | WC; TG; LDL; hypertension | WC (P < 0.001); TGs (P = 0.033); LDL (P = 0.018); hypertension (P = 0.023) | Yes                   |
| None to >1.3 servings/d | BMI; obesity risk; TGs; HDL | Girls consuming >1.3 servings/d had increased BMI and obesity risk (P-trend ≈ 0.001); girls and boys consuming >1.3 servings/d show increased TGs (P-trend ≈ 0.03); boys show reduced HDL (P-trend < 0.04) | Yes                   |
| <1 to >5/wk           | BMI; fasting glucose; blood pressure; TGs; HDL | Females consuming >4 servings/wk showed increased BMI (P = 0.0095); systolic blood pressure (P = 0.0086); fasting glucose (P = 0.0150) | Yes                   |

Abbreviations: BP, blood pressure; CARDIA, coronary artery risk development in young adults; CI, confidence interval; DBP, diastolic blood pressure; F, female; FBG, fasting blood glucose; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment–insulin resistance; KoGES, Korean Genome and Epidemiology Study; LDL, low-density lipoprotein; M, male; NA, not applicable; OR, odds ratio; QUALITY, Quebec Adipose and Lifestyle Investigation in Youth; SBP, systolic blood pressure; SUN, Seguimiento Universidad de Navarra; TAG, triacylglycerol; TG, triglyceride; WC, waist circumference.
diet-type beverages [40]. In addition, ethnicity, sex, and age may influence the interplay between SSB intake and the onset of T2DM [41] (Table 2).

Daily SSB intake for 6 months also increased ectopic fat accumulation (liver, skeletal muscle, visceral depots) [29], whereas another study reported that replacement of SSBs with artificially sweetened beverages decreased intrahepatic fat over a 12-week period [45]. As ectopic fat accumulation is linked to insulin resistance and T2DM, this may represent early signs of longer-term damaging effects elicited by regular SSB intake. A 4-week observational study in which healthy participants received SSB supplementation showed a metabolic adaptation with a shift toward carbohydrates, increasing glycolytic and lipogenic gene expression that is likely the cause of altered glucose metabolism [46]. Similarly, a cross-sectional observational study showed altered glucose homeostasis following consumption of SSB vs consumption of dairy products [43]. A prediction-type study found that a 10% to 12% reduction in SSB consumption would lower new cases of diabetes, coronary heart disease, and myocardial infarctions [9]. Of note, this reduction is projected to have the most impact on African Americans, especially those who fall within the lower-income bracket [9]. Despite some contradictory studies, the collective data at present provide robust evidence that SSB intake plays a central role in the onset of T2DM.

C. SSBs and Hypertension/Blood Pressure

Obesity, MetS, and T2DM are all risk factors for the onset of CVD, the leading cause of global mortality [3]. Besides such risk factors, SSB intake can also drive the onset of CVD by promoting hypertension, inflammation, and dyslipidemia [4]. For example, Kim et al. [47] found that daily SSB consumption (≥1 to <3 servings) is linked to an increased risk for developing hypertension (odds ratio, 1.43; 95% CI, 0.93 to 2.20) (refer to Table 3). Some studies show that SSB intake specifically elevates systolic blood pressure [32, 48], whereas others found that it raised diastolic blood pressure [53]. However, one such study [32] was criticized as the published adult norms were directly applied to an adolescent cohort [54]. A pooled

| Author | Cohort/Location | Participants | Average Follow-up Period |
|--------|----------------|-------------|-------------------------|
| De Koning et al. (42) | HPFS; United States | 40,389 (2680 developed diabetes) | 40–75 M and F, 20 y |
| Fagherazzi et al. (5) | E3N study; France | 66,118 | 52.6 ± 6.6 F, 14 y |
| The InterAct Consortium (37) | EPIC database; 8 European countries | 11,684 | 41–62 M and F, 16 y |
| Lofvenborg et al. (10) | ESTRID study; Sweden | 2864 | 45.2–71.8 M and F, 5 y |
| Maki et al. (43) | Black Women’s Health Study, United States | 43 (n = 21 for SSB) | 53.8 ± 2.1 M and F, 14 wk |
| Palmer et al. (39) | | 43,960 | 29–49 F, 10 y |
| Sakurai et al. (41) | Japan | 2037 | 35–55 M, 7 y |
| Teshima et al. (44) | Mihama Diabetes Prevention Study; Japan | 93 | 40–69 M and F, 3.6 ± 0.2 y |
| Odegaard et al. (36) | Singapore | 43,580 | 45–74 M and F, 5.7 y |
an analysis of three prospective cohorts (Nurses’ Health Studies I and II and the Health Professionals Follow-up Study; total N > 220,000) supports the notion that there is a higher incidence of hypertension among those consuming $\geq 1$ SSB serving/d compared with nonconsumers (RR, 1.13; 95% CI, 1.09 to 1.17) [50]. Interestingly, the association between carbonated drinks and hypertension was also significantly stronger compared with noncarbonated ones for all three cohorts, whereas the consumption of cola-containing SSBs also indicated a robust link to hypertension compared with noncola ones (Nurses’ Health Study I; Health Professionals Follow-up Study). Other prospective studies provide additional evidence for an association between regular SSB intake and the development of hypertension [24], whereas some demonstrated that blood pressure can be successfully lowered by decreasing SSB consumption [49]. In support, others found a significantly higher risk for hypertension with increasing SSB intake (especially in females); that is, hazard ratios for new-onset hypertension were 1.01 (95% CI, 0.99 to 1.03; 1 to 4 SSB/mo), 1.06 (95% CI, 1.03 to 1.08; 2 to 6 SSB/wk), and 1.13 (95% CI, 1.09 to 1.17; $\geq 1$ SSB/d) vs those who consumed $\leq 1$ SSB/mo [50]. Furthermore, Sayon-Orea et al. [51] identified 1308

### Table 2. Continued

| Mean SSB Intake/d | Risk of T2DM | $P$ Value for Trend | Confounder Adjustment |
|------------------|--------------|---------------------|----------------------|
| 887 mL/d         | HR, 1.25 (95% CI, 1.11–1.39) vs nonconsumers | <0.01 | Yes |
| 328.3 mL/d      | HR, 1.34 (95% CI, 1.05–1.71) vs nonconsumers | 0.0002 | Yes |
| <1 glass/mo to $\geq 1$ glass/d | HR, 1.22 (95% CI, 1.09–1.38) increase with one serving of SSB | 0.86 | Yes |
| None to $>2$ servings/d | OR increased to 2.39 (95% CI, 1.39–4.09); 20% increase with each additional serving | Not available | Yes |
| 2160 ± 91.7 kcal/d | SSB consumption is associated with less favorable values for T2DM risk | Not available | Yes |
| <1 to $\geq 2$/d | Incident rate ratio was 1.51 (95% CI, 1.31–1.75) vs fruit juice | 0.002 | Yes |
| 0 to $\geq 1$ serving/d | HR, 1.34 (0.72–2.36), $\geq 1$ serving/d vs rare/never | 0.424 | Yes |
| No intake to daily intake | OR, 3.26 (95% CI, 1.17–9.06) vs no SSB intake | 0.001 | No |
| None to 2–3 servings/wk | RR, 1.42 (95% CI, 1.25–1.62) vs no SSB intake | $P$-trend < 0.0001 | Yes |

**Abbreviations:** CI, confidence interval; ESTRID, Epidemiological Study of Risk Factors for LADA and Type 2 Diabetes; E3N, Étude Épidémiologique auprès des femmes de la Mutuelle Générale de l’Education Nationale; F, female; HPFS, Health Professionals Follow-up Study; HR, hazard ratio; M, male; OR, odds ratio; RR, relative risk.
new hypertension cases in their 6-year follow-up Seguimiento Universidad de Navarra Study and established that increased SSB consumption was associated with 26% higher odds of developing hypertension—this association was especially strong in women.

One study compared blood pressures in adolescents from 20 public schools in Brazil [52], and after adjusting for confounding factors, they found higher systolic blood pressure and diastolic blood pressure values for youngsters consuming SSBs. Others investigated the effects of the monosaccharides glucose, fructose, and sucrose on blood pressure. Here they showed that fructose and glucose triggered opposite effects, with fructose resulting in increased blood pressure due to increased total peripheral resistance, unlike glucose [56]. The impact of varying SSB doses within this context is best demonstrated by focusing on studies aiming to lower consumption. For example, a reduction of 1 SSB serving/d resulted in a decrease of 2 and 1.2 mm Hg in systolic and diastolic blood pressures, respectively [49].

### 3. Discussion

Long-term epidemiological studies provide sufficient evidence to prove a positive association between SSB and weight gain and the eventual risk for developing MetS [4]. However, it is important to also consider studies (limited number) that report negative or neutral results with SSB intake. Here the lack of standardization of measurements used to assess obesity can make it difficult to interpret and compare the results of various published studies [57]. For example, although some only measured weight gain, others determined BMI, waist-to-hip ratio, and skinfold thickness (all markers of obesity).

SSBs are energy dense, and their consumption is associated with excessive caloric intake and subsequent weight gain [58], and such changes can induce cardiometabolic perturbations. For example, SSB drinkers—especially young African Americans—are more likely to consume salty and sweet snacks [59]. In a study on the Australian population, SSBs contributed

### Table 3. SSB Consumption and Risk of Hypertension

| Author            | Cohort/Location                        | Participants | Age (Mean/Range), y | Sex   | Average Follow-up Period |
|-------------------|----------------------------------------|--------------|---------------------|-------|-------------------------|
| Brown et al. [48] | INTERMAP; United States, United Kingdom| 2696         | 48.8–50.8           | M and F | 3 y                     |
| Chen et al. [49]  | PREMIER; United States                 | 810          | 25–79               | M and F | 18 mo                   |
| Cohen et al. [50] | NHS I, NHS II and HPFS; United States  | 223,891      | 39–52 (NHS I); 31–40 (NHS II); 42–63 (HPFS) | F (NHS I); F (NHS II); M and F (HPFS) | 38 y (NHS I); 16 y (NHS II); 22 y (HPFS) |
| Green et al. [11] | Cohort used from Framingham; United States | 5107        | 40.8–53.9 (combined) | M and F |                         |
| Sayon-Orea et al. [51] | SUN; Spain                        | 1308/13,843  | 36.4               | M and F | 8.1 y                   |
| Souza et al. [52] | Brazil                                | 559          | 9–16                | M and F | Once off study          |
| Kim et al. [47]   | NHANES; South Korea                   | 3044         | ≥19                 | M and F | Cross-sectional study   |
| Nguyen et al. [32] | NHANES; United States                | 4867         | 12–18               | M and F | Cross-sectional study   |

**Note:** NHANES = National Health and Nutrition Examination Survey; HPFS = Health Professionals Follow-up Study; INTERMAP = International MONitoring Project; PREMIER = Preventing Risk of End-Stage Renal Disease in Minority Elderly and Racially and Ethnically Diverse Elderly; SUN = Seguimiento Universidad de Navarra.
to the highest added sugar intake, causing more than half of the total population to exceed the free sugar intake norms set by the World Health Organization [60]. Alarmingly, this effect was predominantly observed in children and adolescents. Epidemiological studies are not sufficient to establish causality between SSB consumption and the development of cardiometabolic diseases. For this reason, there is a great need for clinical intervention studies to support existing findings. Clinical studies may also help reveal plausible molecular mechanisms—a necessary step in establishing causality between SSB consumption and cardiometabolic pathophysiology [61]. These findings may provide some insights into the mechanisms at play and may help explain why some failed to detect changes in body weight. Unfortunately, there are limited clinical findings available regarding SSB intake and the onset of cardiometabolic diseases, and most of the available studies have some drawbacks as reviewed before [62].

An assessment of the metabolic health of 5107 individuals from the Framingham Heart Study Offspring and third-generation cohorts showed that, irrespective of weight, SSB consumers were at a higher risk for the onset of metabolic abnormalities such as hypertension, insulin resistance, high fasting glucose and triglycerides, and lower high-density lipoprotein cholesterol levels [11]. Aerberli et al. [63] explained that higher glucose consumption stimulates an intensified insulin response to promote the deposition of subcutaneous fat, thereby increasing the BMI. By contrast, fructose (and sucrose to some extent) possesses a lower glycemic load and does not trigger the release of insulin to the same degree as glucose. Thus, the activity of lipoprotein lipase is reduced and the deposition of visceral fat is favored, resulting in an increase in waist circumference and waist-to-hip ratio (also concluded by Stanhope et al. [30]). Waist circumference and waist-to-hip ratio are markers of

| Maximum SSB Intake | Mean Systolic Pressure (mm Hg) After High SSB Intake | Mean Diastolic Pressure (mm Hg) After High SSB Intake | P Value for Trend | Confounder Adjustment |
|--------------------|------------------------------------------------------|------------------------------------------------------|------------------|-----------------------|
| 306 mL/d (United States) | 122.5 mm Hg | 75.5 mm Hg | <0.001 | Yes |
| 66 mL/d (United Kingdom) | 133.2 mm Hg | 85.0 mm Hg | 0.57 (SBP); 0.01 (DBP) | Yes |
| 310.5 ± 351.9 mL/d | >140 mm Hg (HPFS) | >90 mm Hg (HPFS); HR, 1.13 (95% CI, 1.09–1.17) ≥1 serving/d vs <1/mo | Not stated | Yes |
| 354.8 mL/d (7 servings/wk) | 54.6% increase in SBP vs normal weight | 59.7% increase in DBP vs normal weight | <0.001 | Yes |
| ≥354.8 mL/d (≥ 7 servings/wk) | HR, 1.33 (95% CI, 1.08–1.68) vs no SSB consumption | 0.007 | Yes |
| +709.6 mL/d (+2 servings/d) | 102.6 mm Hg | 58.8 mm Hg | 0.01 (SBP); 0.04 (DBP) | Yes |
| None to 6 times/d | SSBs 3 times/d associated with 1.74 times higher prevalence of hypertension (95% CI, 1.60–3.01) | 0.05 | Yes |
| 0 to >36 oz/d | Data not shown | Data not shown | 0.03 (SBP); 0.09 (DBP) | Yes |

Abbreviations: CI, confidence interval; DBP, diastolic blood pressure; F, female; HPFS, Health Professionals Follow-up Study; HR, hazard ratio; M, male; NHANES, National Health and Nutritional Examination Survey; NHS, Nurses’ Health Study; PREMIER, a randomized trial to determine the effects of multi-component lifestyle interventions on blood pressure; SBP, systolic blood pressure.
abdominal obesity—a key feature of the MetS—indicating that SSB consumption can elicit detrimental consequences even if it does not always reflect in overall body weight.

Some studies also provide insight into the effects on glucose handling; for example, some found that SSB intake attenuated insulin sensitivity [43]. Moreover, participants consuming glucose- or fructose-sweetened drinks display elevated fasting blood glucose levels [30, 63]. This is a noteworthy result considering that such beverage intake elicited no effects on fasting insulin levels. Here glucose consumption resulted in a spike in insulin levels [30], whereas it decreased in response to fructose intake. Indeed, individuals consuming either glucose- or fructose-sweetened beverages for 10 weeks displayed a ~17% decrease in insulin sensitivity with fructose consumption, explaining the rise in fasting blood glucose levels associated with fructose intake [30]. Of note, the adverse effects of SSBs are mainly attributed to the fructose component as it has been suggested to upregulate lipid production, leading to increases in liver fat content [30, 64]. The lack of negative effects observed with diet-type beverages in some of the studies may possibly result due to its effect on gut hormones (e.g., glucagon-like peptide 1) that promote insulin secretion [65].

After careful examination of the available clinical studies, it is clear that SSB consumption does trigger metabolic perturbations together with the development of obesity. Here some of the findings show that frequent SSB consumption can alter hepatic insulin sensitivity and fat accumulation, thereby contributing to the development of the MetS and T2DM. SSB intake is also linked to dyslipidemia, higher uric acid levels, and inflammation (known CVD risk factors) [4]. Although none of the clinical studies support a link between SSB consumption and the onset of hypertension, there is some support for a link between SSB intake and inflammation. For example, some observed higher C-reactive protein levels of young men consuming SSB for a 3-week period [28, 63].

SSB consumption has been widely studied in different ethnic groups as well as varying age groups. The consumption of SSB is closely linked to socioeconomic class, with poorer communities displaying relatively higher intakes compared with their more affluent counterparts. For example, the Native American Indian population exhibits a relatively high prevalence of obesity and T2DM, and here it was reported that a significant percentage of Navajo girls and boys consumed SSBs (86% and 93%, respectively) [66]. Together these studies show that SSB intake not only is detrimental to the adult population but extends to adolescents as well and that its effects may vary depending on ethnicity.

4. Conclusion

Recent data show that SSB consumption has increased globally, thus putting many at risk for the onset of weight gain, T2DM, hypertension, CVD, and other chronic illnesses. The mechanisms whereby such diseases progress are closely linked to insulin resistance, pancreatic β-cell dysfunction, visceral adiposity, dyslipidemia, and inflammation. The current mini-review evaluated recent literature (past decade) and shows that SSB consumption worsens the risk for MetS, T2DM, and CVD onset. However, there are limitations; for example, many do not take the sex and/or ethnicity of participants into account, although it is evident that such factors may contribute to the complexity of the results. The short-term nature of numerous studies is also a problem as long-term effects can therefore only be projected or predicted. Together these data highlight the need for (1) well-designed basic and clinical studies to obtain a clearer picture, (2) further research into the molecular mechanisms underlying the development of such debilitating conditions, and (3) increased roll-out of educational programs to inform the general public of the harmful effects of high SSB intake.

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References and Notes
1. Lustig RH, Schmidt LA, Brindis CD. Public health: The toxic truth about sugar. Nature. 2012;482(7383):27–29.
2. World Health Organization. Non communicable diseases fact sheet 355. 2015. Available at: http://www.who.int/mediacentre/factsheets/noncommunicable-diseases/en/. Accessed 31 October 2017.
3. World Health Organisation (WHO). Cardiovascular diseases fact sheet. 2016. Available at: http://www.who.int/mediacentre/factsheets/fs317/en/. Accessed 31 October 2017.
4. Malik VS, Popkin BM, Bray GA, Després J-P, Hu FB. Sugar-sweetened beverages, obesity, type 2 diabetes mellitus, and cardiovascular disease risk. Circulation. 2010;121(11):1356–1364.
5. Fagherazzi G, Vilier A, Saes Sartorelli D, Lajous M, Balkau B, Clavel-Chapelon F. Consumption of artificially and sugar-sweetened beverages and incident type 2 diabetes in the Etude Epidemiologique auprès des femmes de la Mutuelle Generale de l’Education Nationale-European Prospective Investigation into Cancer and Nutrition cohort. Am J Clin Nutr. 2013;97(3):517–523.
6. Vorster HH, Kruger A, Wentzel-Viljoen E, Kruger HS, Margetts BM. Added sugar intake in South Africa: findings from the Adult Prospective Urban and Rural Epidemiology cohort study. Am J Clin Nutr. 2014;99(6):1479–1486.
7. Ng SW, Slining MM, Popkin BM. Use of caloric and noncaloric sweeteners in US consumer packaged foods, 2005–2009. J Acad Nutr Diet. 2012;112(11):1828–1834.e6.
8. McGuire SUS. Department of Agriculture and U.S. Department of Health and Human Services, Dietary Guidelines for Americans, 2010. 7th Edition, Washington, DC: U.S. Government Printing Office, January 2011. Adv Nutr. 2011;2(3):293–294.
9. Mekonnen TA, Odden MC, Coxson PG, Guzman D, Lightwood J, Wang YC, Bibbins-Domingo K. Health benefits of reducing sugar-sweetened beverage intake in high risk populations of California: results from the cardiovascular disease (CVD) policy model. PLoS One. 2013;8(12):e81723.
10. Løvenborg JF, Andersson T, Carlsson P-O, Dorkhan M, Groop L, Martinell M, Tuomi T, Wolk A, Carlsson S. Sweetened beverage intake and risk of latent autoimmune diabetes in adults (LADA) and type 2 diabetes. Eur J Endocrinol. 2016;175(6):605–614.
11. Green AK, Jacques PF, Rogers G, Fox CS, Meigs JB, McKeown NM. Sugar-sweetened beverages and prevalence of the metabolically abnormal phenotype in the Framingham Heart Study. Obesity (Silver Spring). 2014;22(5):E157–E163.
12. Kuzma JN, Cromer G, Hagman DK, Breymeyer KL, Roth CL, Foster-Schubert KE, Holte SE, Weigle DS, Kratz M. No differential effect of beverages sweetened with fructose, high-fructose corn syrup, or glucose on systemic or adipose tissue inflammation in normal-weight to obese adults: a randomized controlled trial. Am J Clin Nutr. 2016;104(2):306–314.
13. Angelopoulos TJ, Lowndes J, Sinnett S, Rippe JM. Fructose containing sugars at normal levels of consumption do not effect adversely components of the metabolic syndrome and risk factors for cardiovascular disease. Nutrients. 2016;8(4):179.
14. Barrio-Lopez MT, Martinez-Gonzalez MA, Fernandez-Montero A, Beunza JJ, Zazpe I, Bes-Rastrollo M. Prospective study of changes in sugar-sweetened beverage consumption and the incidence of the metabolic syndrome and its components: the SUN cohort. Br J Nutr. 2013;110(9):1722–1731.
15. Khosravi-Boroujeni H, Sarrafzadegan N, Mohammadifard N, Alikhasi H, Sajjadi F, Asgari S, Esmaillzadeh A. Consumption of sugar-sweetened beverages in relation to the metabolic syndrome among Iranian adults. Obes Facts. 2012;5(4):527–537.
16. Chan T-F, Lin W-T, Huang H-L, Lee C-Y, Wu P-W, Chiu Y-W, Huang CC, Tsai S, Lin CL, Lee CH. Consumption of sugar-sweetened beverages is associated with components of the metabolic syndrome in adolescents. Nutrients. 2014;6(5):2088–2103.
17. Dhingra R, Sullivan L, Jacques PF, Wang TJ, Fox CS, Meigs JB, D’Agostino RB, Gaziano JM, Vasan RS. Soft drink consumption and risk of developing cardiometabolic risk factors and the metabolic syndrome in middle-aged adults in the community. Circulation. 2007;116(5):480–488.
18. Wang JW, Mark S, Henderson M, O’Loughlin J, Tremblay A, Wortman J, Paradis G, Gray-Donald K. Adiposity and glucose intolerance exacerbate components of metabolic syndrome in children consuming sugar-sweetened beverages: QUALITY cohort study. Pediatr Obes. 2012;8(4):284–293.
19. Hernández-Cordero S, Barquera S, Rodriguez-Ramírez S, Villanueva-Borbolla MA, González de Cossio T, Dommarco JR, Popkin B. Substituting water for sugar-sweetened beverages reduces circulating triglycerides and the prevalence of metabolic syndrome in obese but not in overweight Mexican women in a randomized controlled trial. *J Nutr*. 2014;144(11):1742–1752.

20. Mattei J, Malik V, Hu FB, Campos H. Substituting homemade fruit juice for sugar-sweetened beverages is associated with lower odds of metabolic syndrome among Hispanic adults. *J Nutr*. 2012;142(6):1081–1087.

21. Denova-Gutiérrez E, Talavera JO, Huitrón-Bravo G, Méndez-Hernández P, Salmerón J. Sweetened beverage consumption and increased risk of metabolic syndrome in Mexican adults. *Public Health Nutr*. 2010;13(6):835–842.

22. Loh DA, Moy FM, Zaharan NL, Jalaludin MY, Mohamed Z. Sugar-sweetened beverage intake and its associations with cardiometabolic risks among adolescents. *Pediatr Obes*. 2016;12(1):1–5.

23. Duffy KJ, Gordon-Larsen P, Steffen LM, Jacobs DR, Jr, Popkin BM. Drinking caloric beverages increases the risk of adverse cardiometabolic outcomes in the Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Am J Clin Nutr*. 2010;92(4):954–959.

24. Ambrosini GL, Oddi WH, Huang RC, Mori TA, Beilin LJ, Jebb SA. Prospective associations between sugar-sweetened beverage intakes and cardiometabolic risk factors in adolescents. *Am J Clin Nutr*. 2013;98(2):327–334.

25. Ferreira-Pégo C, Babio N, Bes-Rastrollo M, Corella D, Estruch R, Ros E, Fitó M, Serra-Majem L, Arós F, Fiol M, Santos-Lozano JM, Muñoz-Bravo C, Pinto X, Ruiz-Canela M, Salas-Salvadó J; PREDIMED Investigators. Frequent consumption of sugar- and artificially sweetened beverages and natural and bottled fruit juices is associated with an increased risk of metabolic syndrome in a Mediterranean population at high cardiovascular disease risk. *J Nutr*. 2016;146(8):1528–1536.

26. Chang A, Van Horn L, Jacobs DR Jr, Liu K, Muntner P, Newsome B, Shoham DA, Durazo-Arvizu R, Bibbins-Domingo K, Kramer H. Lifestyle-related factors, obesity, and incident microalbuminuria: the CARDIA (Coronary Artery Risk Development in Young Adults) study. *Am J Kidney Dis*. 2013;62(2):267–275.

27. de Ruyter JC, Olthof MR, Seidell JC, Katan MB. A trial of sugar-free or sugar-sweetened beverages and body weight in children. *N Engl J Med*. 2012;367(15):1397–1406.

28. Stanhope KL, Medici V, Bremer AA, Lee V, Lam HD, Nunez MV, Chen GX, Keim NL, Havel PJ. A dose-response study of consuming high-fructose corn syrup-sweetened beverages on lipid/lipoprotein risk factors for cardiovascular disease in young adults. *Am J Clin Nutr*. 2015;101(6):1144–1154.

29. Maersk M, Belza A, Stedkilde-Jørgensen H, Ringgaard S, Chabanova E, Thomsen H, Pedersen SB, Astrup A, Richelsen B. Sucrose-sweetened beverages increase fat storage in the liver, muscle, and visceral fat depot: a 6-mo randomized intervention study. *Am J Clin Nutr*. 2011;95(2):283–289.

30. Stanhope KL, Griffen SC, Bremer AA, Vink RG, Schaefer EJ, Nakajima K, Schwarz JM, Beysen C, Berglund L, Keim NL, Havel PJ. Metabolic responses to prolonged consumption of glucose- and fructose-sweetened beverages are not associated with postprandial or 24-h glucose and insulin excursions. *Am J Clin Nutr*. 2011;94(1):112–119.

31. Bruun JM, Maersk M, Belza A, Astrup A, Richelsen B. Consumption of sucrose-sweetened soft drinks increases plasma levels of uric acid in overweight and obese subjects: a 6-month randomised controlled trial. *Eur J Clin Nutr*. 2015;69(9):949–953.

32. Nguyen S, Choi HK, Lustig RH, Hsu CY. Sugar-sweetened beverages, serum uric acid, and blood pressure in adolescents. *J Pediatr*. 2009;154(6):807–813.

33. Lin WT, Chan TF, Huang HL, Lee CY, Tsai S, Wu PW, Yang YC, Wang TN, Lee CH. Fructose-rich beverage intake and central adiposity, uric acid, and pediatric insulin resistance. *J Pediatr*. 2016;171:90–96e1.

34. Heden TD, Liu Y, Park YM, Nyhoff LM, Winn NC, Kanaley JA. Moderate amounts of fructose- or glucose-sweetened beverages do not differentially alter metabolic health in male and female adolescents. *Am J Clin Nutr*. 2014;100(3):796–805.

35. Kang Y, Kim J. Soft drink consumption is associated with increased incidence of the metabolic syndrome only in women. *Br J Nutr*. 2017;117(2):315–324.

36. Odegaard AO, Koh W-P, Arakawa K, Yu MC, Pereira MA. Soft drink and juice consumption and risk of physician-diagnosed incident type 2 diabetes: the Singapore Chinese Health Study. *Am J Epidemiol*. 2010;171(6):701–708.

37. Romaguera D, Norat T, Wark PA, Vergnaud AC, Schulze MB, van Woudenbergh GJ, Drogan D, Amiano P, Molina-Montes E, Sánchez MJ, Baikou B, Barricarte A, Beulens JW, Clavel-Chapelon F, Crispim SP, Fagherazzi G, Franks PW, Grote VA, Huybrechts I, Kaaks R, Key TJ, Khaw KT, Nilsson P, Overvad K, Palli D, Panico S, Quirós JR, Rolandsson O, Sacerdote C, Sieri S, Slimani N, Spijkerman AM, doi: 10.1210/jc.2017-00262 | Journal of the Endocrine Society | 1383
46. Sartor F, Jackson MJ, Squillace C, Shepherd A, Moore JP, Ayer DE, Kubis HP. Adaptive metabolic
response to 4 weeks of sugar-sweetened beverage consumption in healthy, lightly active individuals and
intrahepatic fat: a randomized controlled trial. *Eur J Nutr*. 2015;54(1):251–258.
47. Kim YH, Abris GP, Sung M-K, Lee JE. Sugar-sweetened beverage but not diet soda consumption is positively associated with progression of insulin resistance and prediabetes. *J Nutr*. 2016;146(12):2544–2550.
48. Campos V, Despland C, Brandejsky V, Kreis R, Schneiter P, Chiolero A, Boesch C, Tappy L. Sugar- and fructose? *Br J Nutr*. 2013;109(3):85–93.
49. Brown IJ, Stamler J, Van Horn L, Robertson CE, Chan Q. Sugar-sweetened beverage, sugar intake of individuals, and their blood pressure: international study of macro/micronutrients and blood pressure. *Hypertension*. 2011;57(4):695–701.
50. Chen L, Caballero B, Mitchell DC, Loria C, Lin P-H, Champagne CM, Elmer PJ, Ard JD, Batch BC, Anderson CA, Appel LJ. Reducing consumption of sugar-sweetened beverages is associated with reduced blood pressure: a prospective study among United States adults. *Circulation*. 2010;121(22):2398–2406.
51. Cohen L, Curhan G, Forman J. Association of sweetened beverage intake with incident hypertension. *J Gen Intern Med*. 2012;27(9):1127–1134.
52. Sayon-Orea C, Martinez-Gonzalez MA, Gea A, Alonso A, Pimenta AM, Bes-Rastrollo M. Baseline consumption and changes in sugar-sweetened beverage consumption and the incidence of hypertension: the SUN project. *Clin Nutr*. 2015;34(6):1133–1140.
53. Souza B da SN, Cunha DB, Pereira RA, Sichieri R. Soft drink consumption, mainly diet ones, is associated with increased blood pressure in adolescents. *J Hypertens*. 2016;34(2):221–225.
54. Tayel DI, El-Sayed NA, El-Sayed NA. Dietary pattern and blood pressure levels of adolescents in Sohag, Egypt. *J Egypt Public Health Assoc*. 2013;88(2):97–103.
55. White JS. Sugar-sweetened beverage effect on cardiovascular risk factors lacks significance. *J Pediatr*. 2010;156(5):860–861.
56. Flint N, Hamburg NM, Holbrook M, Dorsey PG, LeLeiko RM, Berger A, de Cock P, Bosscher D, Vita JA. Effects of erythritol on endothelial function in patients with type 2 diabetes mellitus: a pilot study. *Acta Diabetol*. 2014;51(3):513–516.
57. Grasser EK, Dullao A, Montani J-P. Cardiovascular responses to the ingestion of sugary drinks using a randomised cross-over study design: does glucose attenuate the blood pressure-elevating effect of fructose? *Br J Nutr*. 2014;112(2):183–192.
57. Poppitt SD. Beverage consumption: are alcoholic and sugary drinks tipping the balance towards overweight and obesity? *Nutrients*. 2015;7(8):6700–6718.

58. Miller PE, McKinnon RA, Krebs-Smith SM, Subar AF, Chriqui J, Kahle L, Reedy J. Sugar-sweetened beverage consumption in the U.S.: novel assessment methodology. *Am J Prev Med*. 2013;45(4):416–421.

59. Bleich SN, Wolfsön JAUS. U.S. adults and child snacking patterns among sugar-sweetened beverage drinkers and non-drinkers. *Prev Med*. 2015;72:8–14.

60. Lei L, Rangan A, Flood VM, Louie JCY. Dietary intake and food sources of added sugar in the Australian population. *Br J Nutr*. 2016;115(5):868–877.

61. Stanhope KL. Sugar consumption, metabolic disease and obesity: the state of the controversy. *Crit Rev Clin Lab Sci*. 2015;53(1):52–67.

62. Macdonald IA. A review of recent evidence relating to sugars, insulin resistance and diabetes. *Eur J Nutr*. 2016;55(Suppl 2):17–23.

63. Aeberli I, Gerber PA, Hochuli M, Kohler S, Haile SR, Gouni-Berthold I, Berthold HK, Spinas GA, Berneis K. Low to moderate sugar-sweetened beverage consumption impairs glucose and lipid metabolism and promotes inflammation in healthy young men: a randomized controlled trial. *Am J Clin Nutr*. 2011;94(2):479–485.

64. Matikainen N, Söderlund S, Björnson E, Bogl LH, Pietiläinen KH, Hakkarainen A, Lundbom N, Eliasson B, Räisänen SM, Rivellese A, Patti L, Prinster A, Riccardi G, Després JP, Alméras N, Holst JJ, Deacon CF, Borén J, Taskinen MR. Fructose intervention for 12 weeks does not impair glycemic control or incretin hormone responses during oral glucose or mixed meal tests in obese men. *Nutr Metab Cardiovasc Dis*. 2017;27(6):534–542.

65. Brown RJ, Walter M, Rother CI. Effects of diet soda on gut hormones in youths with diabetes. *Diabetes Care*. 2012;35(5):959–964.

66. Yracheta JM, Lanaspa MA, Le MT, Abdelmalak MF, Alfonso J, Sánchez-Lozada LG, Johnson RJ. Diabetes and kidney disease in American Indians: potential role of sugar-sweetened beverages. *Mayo Clin Proc*. 2015;90(6):813–823.