

# Sugar-Sweetened Beverages and Risk of Metabolic Syndrome and Type 2 Diabetes

## A meta-analysis

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**OBJECTIVE**— Consumption of sugar-sweetened beverages (SSBs), which include soft drinks, fruit drinks, iced tea, and energy and vitamin water drinks has risen across the globe. Regular consumption of SSBs has been associated with weight gain and risk of overweight and obesity, but the role of SSBs in the development of related chronic metabolic diseases, such as metabolic syndrome and type 2 diabetes, has not been quantitatively reviewed.

**RESEARCH DESIGN AND METHODS**— We searched the MEDLINE database up to May 2010 for prospective cohort studies of SSB intake and risk of metabolic syndrome and type 2 diabetes. We identified 11 studies (three for metabolic syndrome and eight for type 2 diabetes) for inclusion in a random-effects meta-analysis comparing SSB intake in the highest to lowest quantiles in relation to risk of metabolic syndrome and type 2 diabetes.

**RESULTS**— Based on data from these studies, including 310,819 participants and 15,043 cases of type 2 diabetes, individuals in the highest quantile of SSB intake (most often 1–2 servings/day) had a 26% greater risk of developing type 2 diabetes than those in the lowest quantile (none or <1 serving/month) (relative risk [RR] 1.26 [95% CI 1.12–1.41]). Among studies evaluating metabolic syndrome, including 19,431 participants and 5,803 cases, the pooled RR was 1.20 [1.02–1.42].

**CONCLUSIONS**— In addition to weight gain, higher consumption of SSBs is associated with development of metabolic syndrome and type 2 diabetes. These data provide empirical evidence that intake of SSBs should be limited to reduce obesity-related risk of chronic metabolic diseases.

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In recent decades, consumption of sugar-sweetened beverages (SSBs), which include the full spectrum of soft drinks (soda), fruit drinks, and energy and vitamin water drinks has been steadily increasing to various degrees across the globe. For example, in the U.S. between the late 1970s and 2006 the per capita consumption of SSBs increased from 64.4 to 141.7 kcal/day, representing more than a twofold increase (1). Similar temporal

patterns have been shown for Mexico, where currently >12% of total energy intake is contributed by these beverages (2). Of particular concern is the rapid trajectory of increase evident in many developing countries where access to SSBs has grown concomitantly with rising rates of urbanization. Sales figures from Coca Cola's 2007 annual report show that during 2007, India and China experienced growths of 14 and 18%, respectively, in

the volume of beverages sold, indicative of substantial increases in sales at the population level (3).

SSBs, which are now the primary source of added sugars in the U.S. diet, are composed of energy-containing sweeteners such as sucrose, high-fructose corn syrup, or fruit juice concentrates, all of which have essentially similar metabolic effects (4). In contrast, a beverage that is 100% fruit juice and not blended with added sweeteners is not considered an SSB. Increasingly, groups of scholars and organizations such as the American Heart Association are calling for major reductions in consumption of SSBs (5,6). Findings from well-powered prospective epidemiological studies have shown consistent positive associations between SSB intake and weight gain and obesity in both children and adults (7). Emerging evidence also suggests that habitual SSB consumption is associated with increased risk of metabolic syndrome and type 2 diabetes (8). SSBs are thought to lead to weight gain by virtue of their high sugar content and incomplete compensation for total energy at subsequent meals after intake of liquid calories (7). Because of the high content of rapidly absorbable carbohydrates such as sucrose (50% glucose and 50% fructose) and high-fructose corn syrup (most often 45% glucose and 55% fructose), in conjunction with the large volumes consumed, SSBs may increase the risk of metabolic syndrome and type 2 diabetes not only through obesity but also by increasing dietary glycemic load, leading to insulin resistance,  $\beta$ -cell dysfunction, and inflammation (9). Additional metabolic effects of these beverages may also lead to hypertension and promote accumulation of visceral adipose tissue and of ectopic fat due to elevated hepatic de novo lipogenesis (10), resulting in the development of high triglycerides and low HDL cholesterol and small, dense LDL, although the specific metabolic effects of fructose versus glucose remain to be further examined. To summarize the available literature, we conducted a meta-analysis of prospective cohort studies to examine the relationship between SSB

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Table 1—SSB intake and risk of type 2 diabetes and metabolic syndrome

Ref.	Population (cases)	Age range (years)	Duration (years)	Dietary assessment method	Outcome	Results	Adjustment for potential confounders
Montonen et al., 2007 (14)	2,360 adults, Finnish Mobile Clinic Health Examination, Finland (177)	40–69	12	Diet history	Type 2 diabetes*	RR (95% CI) between extreme quartiles of median SSB intake (0 vs. 143 g/day): 1.67 (0.98–2.87); $P_{\text{trend}} = 0.01$	Age, sex, BMI, energy intake, smoking, geographic area, physical activity, family history of diabetes, prudent dietary score, and conservative pattern score
Paynter et al., 2006 (15)	12,204 adults ARIC study, U.S. (718 men, 719 women)	45–64	9	FFQ	Type 2 diabetes†	Men: RR (95% CI) between extreme quartiles of SSB intake (<1 8-oz serving/day vs. $\geq 2$ 8-oz servings/day): 1.09 (0.89–1.33); $P_{\text{trend}} = 0.68$ . Women: RR (95% CI) between extreme quintiles of SSB intake: 1.17 (0.94–1.46); $P_{\text{trend}} = 0.05$	Race, age
Schulze et al., 2004 (16)	91,249 women NHS II, U.S. (741)	24–44	8	133-item FFQ	Type 2 diabetes‡	RR (95% CI) between extreme quartiles of SSB intake (<1 serving/month vs. $\geq 1$ serving/day): 1.83 (1.42, 2.36); $P_{\text{trend}} = <0.001$	Age, alcohol intake, physical activity, family history of diabetes, smoking, postmenopausal hormone use, oral contraceptive use, cereal fiber, magnesium, trans fat, ratio of polyunsaturated to saturated fat, diet soft drinks, fruit juice, fruit punch
Palmer et al., 2008 (17)	43,960 women BWHS, U.S. (2,713)	21–69	10	68-item FFQ	Type 2 diabetes§	RR (95% CI) between extreme quintiles of SSB intake (<1 12-oz serving/month vs. $\geq 2$ 12-oz servings/day): 1.24 (1.06–1.45); $P_{\text{trend}} = 0.002$	Age, family history of diabetes, physical activity, smoking, education, fruit drinks, orange and grapefruit juice, fortified fruit drinks, Kool-Aid, other fruit juices, red meat, processed meat, cereal fiber, coffee and glycemic index
Bazzano et al., 2008 (18); author correspondence	71,346 women NHS, U.S. (4,529)	38–63	18	FFQ	Type 2 diabetes‡	RR (95% CI) between extreme quintiles of SSB intake: (<1 12-oz serving/month vs. 2–3 12-oz servings/day): 1.31 (0.99–1.74); $P_{\text{trend}} = <0.001$	BMI, physical activity, family history of diabetes, postmenopausal hormone use, alcohol use, smoking, and total energy intake
Odegaard et al., 2010 (19)	43,580 adults, Singapore Chinese Health study (2,273)	45–74	5.7	FFQ	Type 2 diabetes‡	RR (95% CI) between extreme quintiles of SSB intake: (none vs. $\geq 2$ 8-oz servings/week): 1.42 (1.25–1.62); $P_{\text{trend}} = <0.0001$	Age, sex, dialect, year of interview, educational level, smoking, alcohol, physical activity, saturated fat, dietary fiber, dairy, juice, coffee
De Koning, 2010, personal communication	41,109 male health professionals, U.S. (2,760)	40–75	20	FFQ	Type 2 diabetes†	RR (95% CI) between extreme quartiles of median SSB intake (0 vs. 0.79 serving/day): 1.14 (1.03–1.28); $P_{\text{trend}} = 0.0024$	Age, smoking, physical activity, alcohol, coffee, family history of type 2 diabetes

(continued)

Table 1—Continued

Ref.	Population (cases)	Age range (years)	Duration (years)	Dietary assessment method	Outcome	Results	Adjustment for potential confounders
Nettleton et al., 2009 (11); author correspondence	5,011 adults, MESA, U.S. (413)	45–84	5	FFQ	Type 2 diabetes $\parallel$	RR (95% CI) between extreme quartiles of SSB intake (0 vs. $\geq 1$ serving/day): 0.86 (0.62–1.17); $P_{\text{trend}} = 0.09$	Study site, age, sex, race, energy intake, education, physical activity, smoking, at least weekly supplement use, waist circumference
Nettleton et al., 2009 (11); author correspondence	3,878 adults, MESA, U.S. (871)	45–84	5	FFQ	Metabolic syndrome $\S$	RR (95% CI) between extreme quartiles of SSB intake (0 vs. $\geq 1$ serving/day): 1.15 (0.92–1.42); $P_{\text{trend}} = 0.65$	Study site, age, sex, race, energy intake, education, physical activity, smoking, at least weekly supplement use, waist circumference
Dhingra et al., 2007 (13)	6,039 adults, Framingham Offspring Study, U.S.A. (1,150)	52.9	4	FFQ	Metabolic syndrome $\#$	RR (95% CI) between extreme quartiles of soft drink intake (0 vs. $\geq 1$ 12-oz serving/day): 1.39 (1.21–1.59)**	Age and sex
Lutsey et al., 2008 (12)	9,514 adults ARIC, U.S. (3,782)	45–64	9	66-item FFQ	Metabolic syndrome $\S$	RR (95% CI) between extreme tertiles of SSB intake (0 vs. 1 median serving/day): 1.09 (0.99–1.19); $P_{\text{trend}} = 0.07$	Age, sex, race, education, center, total calories, smoking, physical activity, intake of meat, dairy, fruits and vegetables, whole grains, and refined grains

ARIC, Atherosclerosis Risk in Communities Study; BWHS, Black Women's Health Study; MESA, Multi-Ethnic Study of Atherosclerosis; NHS, Nurses' Health Study. \*National register confirmed by medical record. †Presence of one of the following: 1) fasting glucose  $\geq 126$  mg/dl, 2) nonfasting glucose  $\geq 200$  mg/dl, 3) current use of hypoglycemic medication, and 4) self-report physician diagnosis. ‡Self-report of physician diagnosis and supplemental questionnaire. §Confirmed self-report of physician diagnosis. ¶Presence of one of the following: 1) fasting glucose  $\geq 126$  mg/dl, 2) current use of hypoglycemic medications; and 3) self-report physician diagnosis. ¶Metabolic syndrome diagnosed according to the modified National Cholesterol Education Program Adult Treatment Panel III criteria/American Heart Association guidelines as the presence of three or more of the following: 1) waist circumference  $\geq 102$  (men) or  $\geq 88$  cm (women), 2) triglycerides  $\geq 150$  mg/dl, 3) HDL cholesterol  $\leq 40$  (men) or  $\leq 50$  mg/dl (women), 4) blood pressure  $\geq 130/85$  mmHg or antihypertensive treatment, and 5) fasting glucose  $\geq 100$  mg/dl or antihyperglycemic treatment/insulin. #Metabolic syndrome diagnosed according to the modified National Cholesterol Education Program Adult Treatment Panel III definition/American Heart Association guidelines as the presence of three or more of the following: 1) waist circumference  $\geq 102$  (men) or  $\geq 88$  cm (women), 2) triglycerides  $\geq 150$  mg/dl, 3) HDL cholesterol  $\leq 40$  (men) or  $\leq 50$  mg/dl (women), 4) blood pressure  $\geq 135/85$  mmHg or antihypertensive treatment, and 5) fasting glucose  $\geq 100$  mg/dl or antihyperglycemic treatment/insulin. \*\*Includes diet and nondiet soft drinks.

consumption and risk of developing metabolic syndrome and type 2 diabetes.

## RESEARCH DESIGN AND METHODS

### Literature search

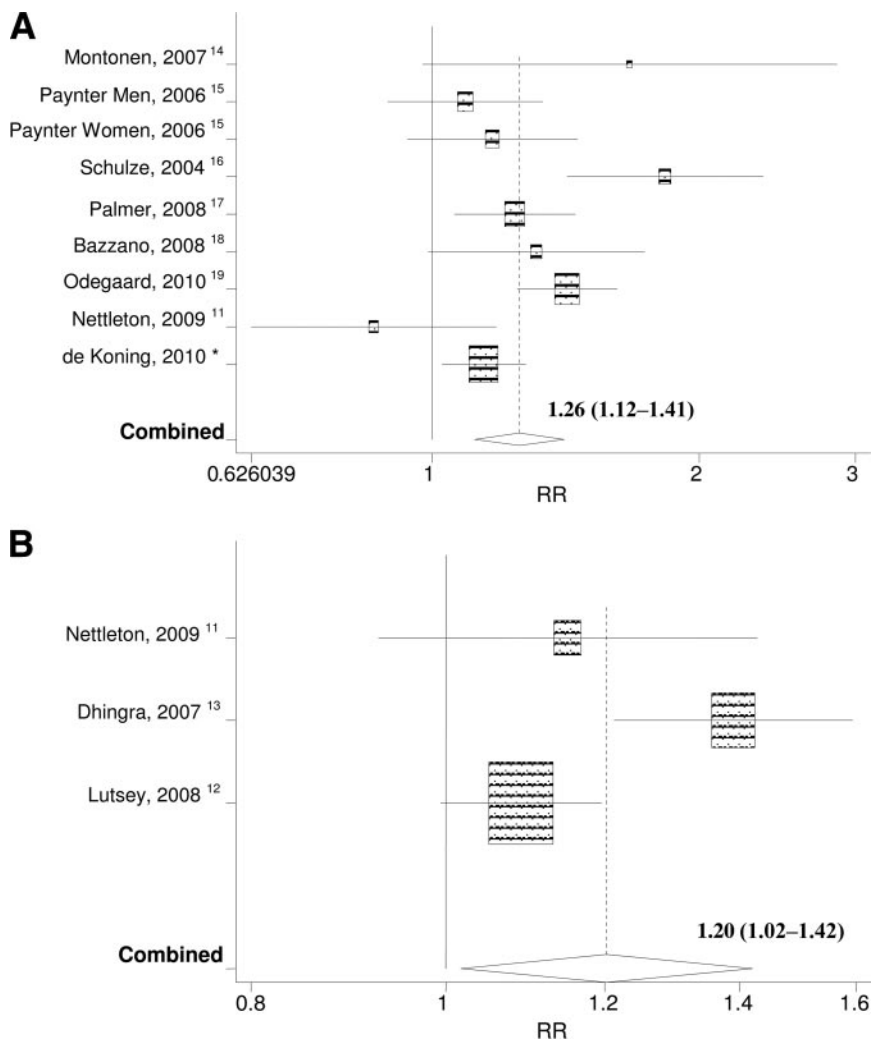
Relevant English-language articles were identified by searching the MEDLINE database (National Library of Medicine, Bethesda, MD) from 1966 to May 2010 for prospective cohort studies of intake of SSBs (soft drinks, carbonated soft drinks, fruitades, fruit drinks, sports drinks, energy and vitamin water drinks, sweetened iced tea, punch, cordials, squashes, and lemonade) and risk of metabolic syndrome and type 2 diabetes in adults. Key words such as “soda,” “soda-pop,” and “sugar-sweetened beverage” combined with “diabetes,” “type 2 diabetes,” and “metabolic syndrome” were used in the

primary search strategy and in a subsequent medical subheading (MESH) terms search. Because of the high potential for intractable confounding and reverse causation, cross-sectional studies were excluded. We did not consider short-term experimental studies because they are not well-suited to capture long-term patterns, but rather provide important insight into potential underlying biological mechanisms. Our literature search identified 15 studies with metabolic syndrome as an end point and 136 studies with type 2 diabetes as an end point. An additional study of type 2 diabetes by de Koning and colleagues was identified via personal communication.

### Inclusion criteria and data extraction

The criteria for inclusion of studies in our meta-analysis included prospective co-

hort design, end points of metabolic syndrome or type 2 diabetes, presentation of a relative risk (RR) and associated measure of variance (SE or 95% CI), definition, and metric for SSB intake and description of adjustment for potential confounders. After application of these criteria, three studies of metabolic syndrome (11–13) and eight studies of type 2 diabetes (11,14–19) were retained for our meta-analysis. Coefficients and SEs were obtained from Nettleton et al. (11) and Bazzano et al. (18) via correspondence. Data extraction was independently performed by V.S.M. and F.B.H., and there were no differences in extracted information to yield effect estimates comparing extreme quartiles of intake, most often comparing none or  $< 1$  serving/month with  $\geq 1$  or 2 servings/day. Notable exceptions include Odegaard et al. (19) in which the highest category of in-



**Figure 1**—A: Forrest plot of studies evaluating SSB consumption and risk of type 2 diabetes, comparing extreme quantiles of intake. Random-effects estimate (DerSimonian and Laird method). \*Information from personal communication. B: Forrest plot of studies evaluating SSB consumption and risk of metabolic syndrome comparing extreme quantiles of intake. Random-effects estimate (DerSimonian and Laird method).

take was 2–≥3 8-oz servings/week, Montonen et al. (14) in which the comparison between median intakes of the first and fourth quartiles was 0 vs. 143 g/day (note: one 12-oz serving = 336 g), and Paynter et al. (15) in which <1 8-oz serving/day was the reference category. Unless otherwise specified a standard serving size of 12 oz was the metric used.

**Analysis**

A total of eight studies with nine data points were included in our meta-analysis of type 2 diabetes (11,14–19) and three studies were included in our meta-analysis of metabolic syndrome (11–13). STATA (version 9.0; StataCorp, College Station, TX) was used to obtain summary RRs using both random- and fixed-effects models calculated from the logarithm of

the RRs and corresponding 95% CIs of the individual studies. We primarily used a random-effects model because it incorporates both a within-study and an additive between-studies component of variance, is the accepted method to use in the presence of between-study heterogeneity, and is generally considered the more conservative method (20). Significance of heterogeneity of study results was evaluated using the Cochrane Q test, which has somewhat limited sensitivity, and further by the I<sup>2</sup> statistic, which represents the percentage of total variation across studies that is due to between-study heterogeneity (21). Because adjustment for total energy intake and duration of follow-up could be important sources of heterogeneity, we conducted independent meta-regressions using adjustment

for energy and study duration as predictors of effect. Because the association between SSB consumption and these outcomes is likely to be mediated in part by an increase in overall energy intake or adiposity, adjusting for these factors is expected to attenuate the effect. Where possible we used estimates that were not adjusted for energy intake or adiposity and conducted sensitivity analysis by removing studies that only provided energy- or adiposity-adjusted estimates. The potential for publication bias was evaluated using Begg and Egger tests and visual inspection of the Begg funnel plot (22,23).

**RESULTS**

Characteristics of the prospective cohort studies included in our meta-analyses are shown in Table 1. Three studies evaluated risk of metabolic syndrome (11–13) and eight studies (nine data points) evaluated risk of type 2 diabetes (11,14–19). The cohorts included men and women of predominately white or black populations from the U.S., adults from Finland, and Chinese adults from Singapore, with duration of follow-up ranging from 4 to 20 years and number of participants ranging from >3,000 to >91,000. The majority of studies used food frequency questionnaires (FFQs) to evaluate dietary intake and six studies (seven data points) (13, 15–17, 19) provided effect estimates that were not adjusted for total energy or measures of adiposity. Based on data from these studies, including 310,819 participants and 15,043 cases of type 2 diabetes, the pooled RR for type 2 diabetes was 1.26 (95% CI 1.12–1.41) comparing extreme quantiles of SSB intake, illustrating an excess risk of 26% associated with higher consumption of SSB compared with lower consumption (Fig. 1A). Among three studies evaluating metabolic syndrome including 19,431 participants and 5,803 cases, the pooled RR was 1.20 (1.02–1.42) (Fig. 1B). Pooled RR estimates from the fixed-effects model were 1.25 (1.17–1.32) and 1.17 (1.09–1.26) for type 2 diabetes and metabolic syndrome, respectively. Results from a dose-response meta-analysis for type 2 diabetes risk per increase in 1 12-oz serving of SSB/day were RR 1.25 (95% CI 1.10–1.42) from the random-effects model and RR 1.15 (95% CI 1.11–1.20) from the fixed-effects model (not shown).

Although all studies except one (11) showed positive associations, there was significant heterogeneity among studies

in both analyses (for type 2 diabetes:  $I^2$  66% [95% CI 31–83%],  $P$  value, test for homogeneity 0.003; for metabolic syndrome: 76% [22–93%];  $P$  value, test for homogeneity 0.01). In general, larger studies with longer durations of follow-up tended to show stronger associations. Among studies evaluating type 2 diabetes, the one by Nettleton et al. (11) is both the shortest and among the smallest, and the only one to show an inverse although nonsignificant association (11). Removal of this study from our analysis only reduced heterogeneity slightly ( $I^2$  62% [95% CI 17–82%],  $P$  value, test for homogeneity 0.01). In contrast, studies by Schulze et al. (16) and Palmer et al. (17), which are longer and larger, show clearly significant positive associations. Despite this, results from a meta-regression did not find duration of study to be a significant predictor of effect ( $P = 0.84$ ). The study by Montonen et al. (14), which shows a borderline significant positive association, has the fewest number of participants and considerably lower levels of intake relative to those of other studies (median intake of SSB is 143 g/day in highest quartile of intake, where one 12-oz serving is 336 g). Removal of this study from our analysis did not reduce heterogeneity, which is to be expected, given its small percentage weight ( $P$  value, test for homogeneity 0.002). The study by Schulze et al. (16), which is the largest and which used repeated measures of SSB intake, reported the strongest study-specific estimate. Removal of this study from the pooled analysis reduced heterogeneity to borderline significance ( $I^2$  51% [95% CI 0–78%];  $P$  value, test for homogeneity 0.05). Tests for publication bias generally rely on the assumption that small studies (large variance) may be more prone to publication bias, compared with larger studies. Visual inspection of the Begg funnel plot (supplementary Fig. 1A and B, available in an online appendix at <http://care.diabetesjournals.org/cgi/content/full/dc10-1079/DC1>), whereby the SE of log RR (measure of study size) from each study was plotted against the log RR (treatment effect), showed symmetry about the plot, suggesting that publication bias is unlikely, although values for metabolic syndrome may not be particularly informative because of the small number of studies included in the analysis. Studies with a large SE and large effect may suggest the presence of a small-study effect (the tendency for smaller studies in a

meta-analysis to show larger treatment effects). Results from the Begg (type 2 diabetes  $P = 0.75$ ; metabolic syndrome  $P = 1.0$ ) and Egger (type 2 diabetes  $P = 0.75$ ; metabolic syndrome  $P = 0.72$ ) tests also suggest that publication bias is unlikely.

Because the association between SSB consumption and risk of these disease outcomes is mediated in part by energy intake and adiposity, adjustment for these factors will tend to underestimate any effect. Results from our sensitivity analysis in which energy- and adiposity-adjusted coefficients were excluded (11,14,18) showed a slight increase in risk of type 2 diabetes with a pooled RR of 1.28 (95% CI 1.13–1.45) from the random-effects model and RR 1.25 (1.18–1.34) from the fixed-effects model. A greater magnitude of increase was noted in the dose-response meta-analysis when these studies (11,14,18) were excluded: RR 1.35 (1.14–1.59) and RR 1.18 (1.12–1.24) from the random and fixed-effects models, respectively. However, results from a meta-regression did not find adjustment for energy to be a significant predictor of effect ( $P = 0.38$ ). Sensitivity analysis was not possible for studies of metabolic syndrome because they are too few in number; however, both studies that adjusted for these potential mediators of effect had marginal nonsignificant associations (11,12), whereas the study that reported unadjusted estimates showed a strong positive association (13).

**CONCLUSIONS**— Findings from our meta-analyses show a clear link between SSB consumption and risk of metabolic syndrome and type 2 diabetes. Based on coefficients from three prospective cohort studies including 19,431 participants and 5,803 cases of metabolic syndrome, participants in the highest category of intake had a 20% greater risk of developing metabolic syndrome than those in the lowest category of intake. For type 2 diabetes, based on data from eight prospective cohort studies (nine data points), including 310,819 participants and 15,043 cases of type 2 diabetes, participants in the highest category of SSB intake had a 26% greater risk of developing type 2 diabetes than participants in the lowest category of intake.

Because we compared extreme quantiles of SSB intake, most often none or <1 serving/month with  $\geq 1$  or 2 servings/day, categories of intake between studies were not standardized. Therefore, it is possible that random misclassification somewhat

attenuated the pooled estimate; however, results were similar to the dose-response analysis, which used data from all categories. For those studies that did not define serving size, a standard serving of 12 oz was assumed, which may over- or underestimate empirical SSB intake levels but should not materially affect our results. Indeed there is substantial variation in study design and exposure assessment, across studies, which may explain the large degree of between-study heterogeneity we observed. Meta-analyses are inherently less robust than individual prospective cohort studies but are useful in providing an overall effect size, while giving larger studies and studies with less random variation greater weight than smaller studies. Publication bias is always a potential concern in meta-analyses, but standard tests and visual inspection of funnel plots suggested no evidence of publication bias in our analysis. Ascertainment of unpublished results may have reduced the likelihood of publication bias. Because our analysis compared only the top with the bottom categories, we did not use data from the intermediate categories. Thus, the comparison of extreme categories was not statistically significant for the studies of Montonen et al. (14), Paynter et al. (women) (15), and Bazzano et al. (18), even though the overall tests for trend in these studies were significant.

All studies included in our meta-analysis considered adjustment for potential confounding by various diet and lifestyle factors, and for most a positive association persisted, suggesting an independent effect of SSBs. However, residual confounding by unmeasured or imperfectly measured factors cannot be ruled out. Higher levels of SSB intake could be a marker of an overall unhealthy diet as they tend to cluster with factors such as higher intakes of saturated and trans fat and lower intake of fiber (12). Therefore, incomplete adjustment for various diet and lifestyle factors could overestimate the strength of the positive association between SSB intake and risk of metabolic syndrome and type 2 diabetes. However, consistency of results from different cohorts reduces the likelihood that residual confounding is responsible for the findings. Longitudinal studies evaluating diet and chronic disease risk may also be prone to reverse causation, i.e., individuals change their diet because of symptoms of subclinical disease or related weight gain, which could result in spurious associations (24). Although it is not possible

to completely eliminate these factors, studies with longer durations of follow-up and repeated measures of dietary intake tend to be less prone to this process.

In several studies, type 2 diabetes was assessed by self-report; however, it has been shown in validation studies that self-report of type 2 diabetes is highly accurate according to medical record review (25). The majority of studies used validated FFQs to measure SSB intake, which is the most robust method for estimating an individual's average dietary intake compared with other assessment methods such as 24-h diet recalls (26). However, measurement error in dietary assessment is inevitable, but because the studies we considered are prospective in design, misclassification of SSB intake probably does not differ by case status. Such nondifferential misclassification of exposure is likely to underestimate the true association between SSB intake and risk of these outcomes.

SSBs are thought to lead to weight gain by virtue of their high added sugar content, low satiety potential and incomplete compensatory reduction in energy intake at subsequent meals after consumption of liquid calories, leading to positive energy balance (7,8). Although SSBs increase risk of metabolic syndrome and type 2 diabetes, in part because of their contribution to weight gain, an independent effect may also stem from the high levels of rapidly absorbable carbohydrates in the form of added sugars, which are used to flavor these beverages. The findings by Schulze et al. (16) suggested that approximately half of the effects of SSBs on type 2 diabetes were mediated through obesity. In a recent study among >88,000 women followed for 24 years, those who consumed  $\geq 2$  SSBs/day had a 35% greater risk of coronary heart disease compared with infrequent consumers after adjustment for other unhealthy lifestyle factors (RR 1.35 [95% CI 1.1–1.7,  $P_{\text{trend}} < 0.01$ ] (27). Additional adjustment for potential mediating factors including BMI, total energy, and incident type 2 diabetes attenuated the associations, but they remained statistically significant, suggesting that the effect of SSBs is not entirely mediated by these factors.

Because SSBs have been shown to raise blood glucose and insulin concentrations rapidly and dramatically (28) and are often consumed in large amounts, they contribute to a high dietary glycemic load. High glycemic load diets are known

to induce glucose intolerance and insulin resistance particularly among overweight individuals (9) and can increase levels of inflammatory biomarkers such as C-reactive protein, which are linked to type 2 diabetes risk (29). Findings from our cohorts indicate that a high dietary glycemic load also increases risk of developing cholesterol gallstone disease, which is associated with insulin resistance, metabolic syndrome, and type 2 diabetes (30). Endogenous compounds in SSBs, such as advanced glycation end products, produced during the process of caramelization in cola-type beverages may also affect pathophysiological pathways related to type 2 diabetes and metabolic syndrome (31). SSBs may also increase risk indirectly by inducing alterations in taste preferences and diet quality, resulting from habitual consumption of highly sweetened beverages, which has also been noted for artificially sweetened beverages (5).

Short-term experimental studies suggest that fructose, which is a constituent of both sucrose and high-fructose corn syrup in relatively equal parts, may exert particularly adverse metabolic effects compared with glucose. Fructose is preferentially metabolized to lipid in the liver, leading to increased hepatic de novo lipogenesis, the development of high triglycerides, low HDL cholesterol, small, dense LDL, atherogenic dyslipidemia, and insulin resistance (32). Recent evidence has also shown that fructose consumption may promote accumulation of visceral adiposity or ectopic fat deposition (10), two key features of a dysmetabolic state increasing risk of type 2 diabetes and cardiovascular disease (33), despite no difference in weight gain between glucose and fructose conditions (10). In contrast, some studies have shown greater satiety and lower total energy intake after intake of fructose-containing beverages compared with glucose beverages (34). Ghanim et al. (35) found evidence of oxidative and inflammatory stress after intake of glucose but not fructose or orange juice. However, fructose has also been shown to increase blood pressure when administered acutely or when consumed as SSBs, an effect not observed with glucose administration or consumption of aspartame-sweetened beverages (36,37). A number of prospective cohort studies have found positive associations between SSB consumption and incident hypertension (11,13). Fructose is also the only sugar able to increase blood uric acid

concentrations, and SSB consumption has been linked to development of hyperuricemia (serum uric acid level >7 mg/dl for men and >5.7 mg/dl for women) (38) and gout (39). Men who consumed  $\geq 2$  SSBs/day had an 85% greater risk of developing gout compared with infrequent consumers (RR 1.85 [95% CI 1.08–3.16];  $P_{\text{trend}} < 0.001$  for trend). No association was shown with diet soda. A recent randomized controlled trial among men in Spain showed that high doses of fructose increased blood pressure and induced features of metabolic syndrome and that pharmacologically lowering uric acid levels prevented the increase in mean arterial blood pressure (40).

In summary, this meta-analysis has demonstrated that higher consumption of SSBs is significantly associated with development of metabolic syndrome and type 2 diabetes. It provides further support to limit consumption of these beverages in place of healthy alternatives such as water to reduce obesity-related chronic disease risk.

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V.S.M. extracted data, conducted analyses, researched data, and wrote the manuscript. B.M.P. contributed to introduction and reviewed/edited the manuscript. G.A.B. contributed to discussion and reviewed/edited the manuscript. J.-P.D. and W.C.W. reviewed/edited the manuscript. F.B.H. extracted data, researched data, and wrote the manuscript.

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