

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, 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 its role in the development of related chronic metabolic diseases, such as metabolic syndrome (MetSyn) and type 2 diabetes (T2DM), has not been quantitatively reviewed.

Methods: We searched the MEDLINE database up to May 2010 for prospective cohort studies of SSB intake and risk of MetSyn, and T2DM. We identified 11 studies (3 for MetSyn; 8 for T2DM) for inclusion in a random effects meta-analysis comparing SSB intake in the highest to lowest quantiles in relation to risk of MetSyn and T2DM.

Results: Based on data from these studies, including 310,819 participants and 15,043 cases of T2DM, individuals in the highest quantile of SSB intake (most often 1-2 servings/day) had a 26% greater risk of developing T2DM than those in the lowest quantile (none or < 1 serving/month) (RR:1.26 (95% CI: 1.12, 1.41)). Among studies evaluating MetSyn, including 19,431 participants and 5,803 cases, the pooled RR was 1.20 (95% CI: 1.02, 1.42).

Conclusions: In addition to weight gain, higher consumption of SSBs is associated with development of MetSyn, and T2DM. These data provide empirical evidence that intake of SSBs should be limited to reduce obesity-related risk of chronic metabolic diseases.

In recent decades, consumption of sugar sweetened beverages (SSBs), which includes the full spectrum of soft drinks (soda), fruit drinks, and energy and vitamin water drinks has been steadily increasing to varying degrees across the globe. For example, in the US between the late 1970's and 2006 the per capita consumption of SSBs increased from 64.4 kcal/d to 141.7 kcal.d, representing more than a 2-fold increase(1). Similar temporal patterns have been shown for Mexico where currently over 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 US diet, are comprised 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 a SSB. Increasingly, groups of scholars and organizations such as the American Heart Association are calling for major reductions in consumption of SSB's(5, 6). Findings from well powered prospective epidemiologic 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 MetSyn and T2DM(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 following intake of liquid

calories(7). Due to the high content of rapidly absorbable carbohydrates such as sucrose (50 % glucose and 50% fructose) and high-fructose corn syrup (HFCS) (most often 45% glucose and 55% fructose), in conjunction with the large volumes consumed, SSB's may increase risk of Met Syn and T2DM not only through obesity but also by increasing dietary glycemic load (GL), leading to insulin resistance, β -cell dysfunction, and inflammation(9). Additional metabolic effects of these beverages may also lead to hypertension, promote accumulation of visceral adipose tissue and of ectopic fat due to elevated hepatic *de novo* lipogenesis(10) leading to the development of the high triglycerides, 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 consumption and risk of developing MetSyn and T2DM.

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 sugar- sweetened beverages (SSBs) (soft drinks, carbonated soft drinks, fruitades, fruit drinks, sports drinks, energy and vitamin water drinks, sweetened iced tea, punch, cordial, 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, as well as in a subsequent Medical subheading (MESH) terms search. Due to 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 biologic mechanisms. Our literature search identified 15 studies with MetSyn as an endpoint and 136 studies with T2DM as an endpoint. An additional study of T2DM 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 cohort design, endpoints of MetSyn or T2DM, presentation of an RR and associated measure of variance (SE, or 95% CI), definition and metric for SSB intake and description of adjustment for potential confounders. After applying these criteria, 3 studies of MetSyn (11-13) and 8 studies of T2DM (11, 14-19) were retained for our meta-analysis. Coefficients and SE were obtained from Nettleton et al.(11) and Bazzano et al.(18), via correspondence. Data extraction was independently performed by VSM and FBH, and there were no differences in extracted information, to yield effect estimates comparing extreme quantiles of intake, most often comparing none or < 1 serv/mo to ≥ 1 or 2 serv/d. Notable exceptions include Odegaard et al. where the highest category of intake was 2- ≥ 3 eight-oz servings per week (19), Montonen et al. where the comparison between median intakes of the 1st and 4th quartiles was 0 vs. 143 g/d (note: one 12-oz serv = 336 g)(14) and Paynter et al. where <one, 8-oz serv/d was the reference category(15). Unless otherwise specified a standard serving size of 12-oz was the metric used.

Analysis. A total of 8 studies with 9 data points were included in our meta-analysis of T2DM (11, 14-19) and 3 studies were included in our meta-analysis of MetSyn(11-13). STATA version 9.0 (StataCorp, College Station, TX) was used to obtain summary

RR's using both random and fixed effects models calculated from the logarithm of the RR's and corresponding 95% CI's of the individual studies. We primarily used random-effects models since they incorporate both a within-study and an additive between-studies component of variance and 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^2 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. Since 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, which only provided energy or adiposity-adjusted estimates. 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 MetSyn (11-13) and 8 studies (9 data points) evaluated risk of T2DM (11, 14-19). The cohorts included men and women, of predominately white or black populations from the USA, adults from Finland and Chinese adults from Singapore, with duration

of follow-up ranging from 4 to 20 y and number of participants ranging from over 3000 to over 91,000. The majority of studies used FFQ's to evaluate dietary intake and 6 studies (7 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 T2DM, the pooled RR for T2DM was RR: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 to lower consumption (figure 1a). Among 3 studies evaluating MetSyn including 19,431 participants and 5,803 cases, the pooled RR was 1.20 (1.02, 1.42) (figure 1b). Pooled estimates from the fixed effects model were RR: 1.25 (95% CI 1.17, 1.32) and RR: 1.17 (95% CI 1.09, 1.26) for T2DM and MetSyn respectively.

Although all studies except one(11) showed positive associations, there was significant heterogeneity between studies in both analyses (For T2DM: I^2 66 % 95% CI: 31%, 83%; p-value, test for homogeneity 0.003 and for MetSyn: I^2 76 % 95% CI: 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 T2DM, the one by Nettleton(11) is both the shortest and among the smallest and the only one to show an inverse though non-significant 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 and Palmer, which are longer and larger, show clearly significant positive associations(16, 17). 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, which shows a borderline significant

positive association, has the fewest number of participants and considerably lower levels of intake relative to other studies (median intake of SSB is 143 g/d in highest quartile of intake, where one 12 oz serv 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)(14). The study by Schulze which is the largest, and used repeated measures of SSB intake, reported the strongest study specific estimate (16). 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 to larger studies. Visual inspection of Begg's funnel plot (Supplemental Figure 1a, b in the online appendix at <http://care.diabetesjournals.org>), whereby the S.E. 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 MetSyn may not be particularly informative due to the small number of studies included in the analysis. Studies with a large SE and large effect may suggest presence of a small-study effect (the tendency for smaller studies in a meta-analysis to show larger treatment effects). Results from the Begg (T2DM p-value 0.75; MetSyn p-value 1.0) and Egger (T2DM p-value 0.75; MetSyn p-value 0.72) tests also suggest that publication bias is unlikely.

Since the association between SSB consumption and risk of these disease outcomes is mediated in part by energy intake and adiposity, adjusting for these factors will tend to underestimate any effect. Results from our sensitivity analysis where energy and adiposity adjusted coefficients were excluded (11, 14, 18) showed a slight increase in risk of

T2DM with a pooled RR of 1.28 (95% CI: 1.13, 1.45). 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 MetSyn because they are too few in number, however both studies that adjusted for these potential mediators of effect had marginal non-significant associations(11, 12) while the study that reported unadjusted estimates has showed a strong positive association(13).

DISCUSSION

Findings from our meta-analyses show a clear link between SSB consumption and risk of MetSyn and T2DM. Based on coefficients from 3 prospective cohort studies including 19,431 participants and 5,803 cases of MetSyn, participants in the highest category of intake had a 20% greater risk of developing MetSyn than those in the lowest category of intake. For T2DM, based in data from 8 prospective cohort studies (9 data points), including 310,819 participants and 15,043 cases of T2DM, participants in the highest category of SSB intake had a 26% greater risk of developing T2DM compared to participants in the lowest category of intake.

Since we compared extreme quantiles of SSB intake, most often none or < 1 serv/mo with ≥ 1 or 2 serv/d, categories of intake between studies were not standardized. Therefore, it is possible that random misclassification somewhat attenuated the pooled estimate. 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 due to difficulties in creating standard units across studies, we did not use data from the intermediate categories. Thus, the comparison of extreme categories was not statistically significant for the Montonen(14), Paynter (women)(15) and Bazzano(18) studies, even though the overall tests for trend in these studies were significant. Although our summary result was robustly positive, the overall results would likely be even more significant if we had been able to use all the data.

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 it tends 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 MetSyn and T2DM. 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. persons change their diet because of symptoms of subclinical disease or related weight-gain, which could

result in spurious associations(24). While not possible to completely eliminate, studies with longer durations of follow-up and repeated measures of dietary intake, tend to be less prone to this process.

In several studies, T2DM was assessed by self-report, however, it has been shown in validation studies that self report of T2DM 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 to other assessment methods such as 24-hour diet recalls(26). However, measurement error in dietary assessment is inevitable, but since the studies we considered are prospective in design, misclassification of SSB intake does not likely differ by case status. Such nondifferential misclassification of exposure is likely to underestimate the true association between SSB intake and risk of these outcomes.

SSB's 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 following consumption of liquid calories leading to positive energy balance(7, 8). While SSB's increase risk of MetSyn and T2DM in part due to 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 SSB's effects on T2DM was mediated through obesity. In a recent study among over 88,000 women followed for 24 years, those who consumed ≥ 2 SSBs per day had a 35% greater risk of coronary heart disease compared to infrequent consumers, after adjusting for other unhealthy lifestyle factors (RR= 1.35, 95% CI: 1.1, 1.7, p-trend <0.01)(27). Additional adjustment for

potential mediating factors including BMI, total energy and incident T2DM 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 (GL). High GL 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, linked to T2DM risk(29). Findings from our cohorts indicate that a high dietary GL also increases risk of developing cholesterol gallstone disease, which is associated with insulin resistance, Met Syn and T2DM(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 T2DM and MetSyn (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 HFCS in relatively equal parts, may exert particularly adverse metabolic effects compared to glucose. Fructose is preferentially metabolized to lipid in the liver, leading to increased hepatic *de novo* lipogenesis, the development of the high triglyceride – 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

T2DM and CVD(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 following intake of fructose containing beverages compared to glucose beverages(34). Ghanim and colleagues found evidence of oxidative and inflammatory stress following intake of glucose but not fructose or orange juice(35). 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 ≥ 2 SSBs per day had an 85% greater risk of developing gout compared to infrequent consumers (RR=1.85, 95% CI: 1.08, 3.16; $p < 0.001$ 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 MetSyn, and that pharmacologically lowering uric acid levels prevented the increase in mean arterial blood pressure (40).

In conclusion, this meta-analysis has demonstrated that higher consumption of SSBs is significantly associated with development of MetSyn, and T2DM. 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.

Author Contributions. VSM extracted data, conducted analyses, researched data, wrote manuscript. BMP contributed to introduction,

reviewed/edited manuscript. GAB contributed to discussion reviewed/edited manuscript. JPD reviewed/edited manuscript. WCW reviewed/edited manuscript. FBH extracted data, researched data, wrote manuscript.

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Table 1: SSB intake and Risk of Type 2 Diabetes and Metabolic Syndrome

Ref	Population (cases)	Mean baseline age (SD) or age range Y	Duration Y	Dietary assessment method	Outcome	Results	Adjustment for potential confounders
Montonen, 2007 ¹⁴	2,360 adults, Finnish Mobile Clinic Health Examination, Finland (177)	40-69	12	Diet History	T2DM ^a	RR (95% CI) between extreme quartiles of median SSB intake (0 vs. 143 g/d): 1.67 (0.98, 2.87); p-for- 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, 2006 ¹⁵	12,204 adults ARIC study, USA (718 Men, 719 Women)	45-64	9	FFQ	T2DM ^b	Men: RR (95% CI) between extreme quartiles of SSB intake (<1 8-oz serv/d vs. ≥ 2 8-oz serv/d): 1.09 (0.89, 1.33); p- for -trend, 0.68. Women: RR (95% CI) between extreme quintiles of SSB intake: 1.17 (0.94, 1.46); p- for- trend, 0.05	Race, age
Schulze, 2004 ¹⁶	91,249 women NHS II, USA (741)	24-44	8	133 -item FFQ	T2DM ^c	RR (95% CI) between extreme quartiles of SSB intake (<1 serv/mo vs. ≥1 serv/d: 1.83 (1.42, 2.36); p- for- trend, <0.001	Age, alcohol intake, physical activity, family history of diabetes, smoking, post- menopausal hormone use, oral contraceptive use, cereal fiber, magnesium, trans-fat, ratio of polyunsaturated to saturated fat, diet soft drinks, fruit juice, fruit punch
Palmer, 2008 ¹⁷	43,960 women BWHS, USA (2713)	21-69	10	68 -item FFQ	T2DM ^d	RR (95% CI) between extreme quintiles of SSB intake (<1 12-oz serv/mo vs. ≥ 2 12-oz serv/d: 1.24 (1.06, 1.45); p- for -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, 2009 ¹⁸ author correspondence	71,346 women NHS, USA (4529)	38-63	18	FFQ	T2DM ^c	RR (95% CI) between extreme quintiles of SSB intake: (<1 12-oz serv/mo vs. 2-3 12-oz serv/d): 1.31 (0.99, 1.74); p-for-trend, <0.001	BMI, physical activity, family history of diabetes, post-menopausal hormone use, alcohol use, smoking, and total energy intake

Odegaard, 2010 ¹⁹	43,580 adults, Singapore Chinese Health study (2273)	45-74	5.7	FFQ	T2DM ^c	RR (95% CI) between extreme quintiles of SSB intake: (none vs. ≥ 2 8-oz serv/wk): 1.42 (1.25, 1.62); p-for-trend, <0.0001	Age, sex, dialect, year of interview, educational level, smoking, alcohol, physical activity, saturated fat, dietary fiber, dairy, juice, coffee
De Konig, 2010 personal communication	41,109 male health professionals, USA (2760)	40-75	20	FFQ	T2DM ^c	RR (95% CI) between extreme quartiles of median SSB intake (0 vs. 0.79 serv/d): 1.14 (1.03, 1.28); p-for-trend, 0.0024	Age, smoking, physical activity, alcohol, coffee, family history of T2DM
Nettleton, 2009 ¹¹ author correspondence	5,011 adults, MESA, USA (413)	45-84	5	FFQ	T2DM ^e	RR (95% CI) between extreme quartiles of SSB intake (0 vs. ≥ 1 serv/d): 0.86 (0.62, 1.17); p-for trend, 0.09	Study site, age, sex, race, energy intake, education, physical activity, smoking, at least weekly supplement use, whole grains, refined grains, nuts/seeds, vegetables, white potatoes, coffee, diet soda, red meat, processed meat, high-fat dairy, low-fat dairy, waist circumference
Nettleton, 2009 ¹¹ author correspondence	3,878 adults, MESA, USA (871)	45-84	5	FFQ	MetSyn ^f	RR (95% CI) between extreme quartiles of SSB intake (0 vs. ≥ 1 serv/d): 1.15 (0.92, 1.42); p- for -trend, 0.65	Study site, age, sex, race, energy intake, education, physical activity, smoking, at least weekly supplement use, whole grains, refined grains, nuts/seeds, vegetables, white potatoes, coffee, diet soda, red meat, processed meat, high-fat dairy, low-fat dairy, waist circumference
Dhingra, 2007 ¹³	6,039 adults, Framingham Offspring study, USA (1150)	52.9	4	FFQ	MetSyn ^g	RR (95% CI) between extreme quartiles of soft drink intake (0 vs. ≥ 1 12-oz serv/d): 1.39 (1.21, 1.59)*	Age and sex

Lutsey, 2008 ¹²	9514 adults ARIC, US (3782)	45-64	9	66-item FFQ	MetSyn [†]	RR (95% CI) between extreme tertiles of SSB intake (0 vs. 1 median serv/d): 1.09 (0.99, 1.19); p -for- 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
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SSB, sugar sweetened beverages; serv, serving; RR, relative risk, FFQ, food frequency questionnaire; T2DM, type 2 diabetes; MetSyn, metabolic syndrome; CHD, coronary heart disease; NHS, Nurses Health Study; MESA, Multi-ethnic study of atherosclerosis; BWHS, Black women’s health study; ARIC, Atherosclerosis risk in communities study

a National register confirmed by medical record

b Presence of one of the following: 1) fasting glucose \geq 126 mg/dl, 2) non-fasting glucose \geq 200 mg/dl, 3) current use of hypoglycemic meds 4) self-report physician diagnosis

c self report of physician diagnosis and supplemental questionnaire

d Confirmed self report of physician diagnosis

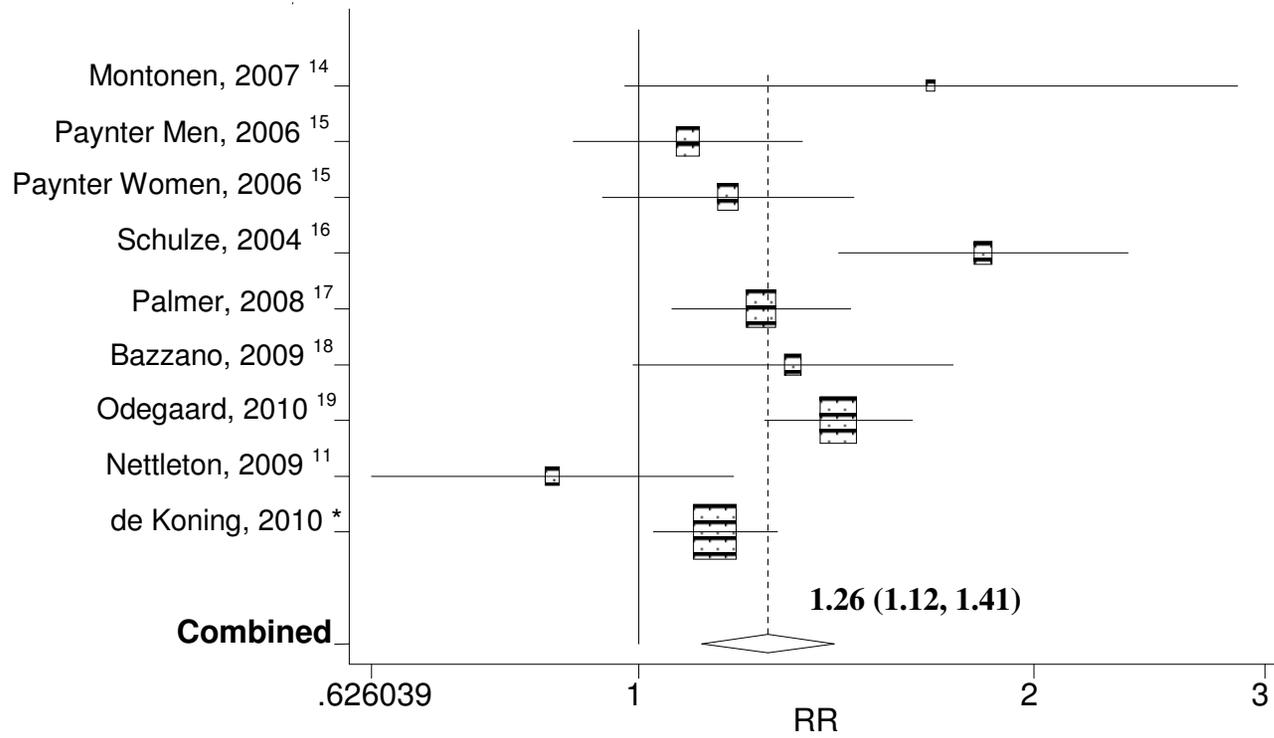
e Presence of one of the following: 1) fasting glucose \geq 126 mg/dl, 2) current use of hypoglycemic meds 3) self-report physician diagnosis

f 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 \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

g 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 \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 non-diet soft drinks

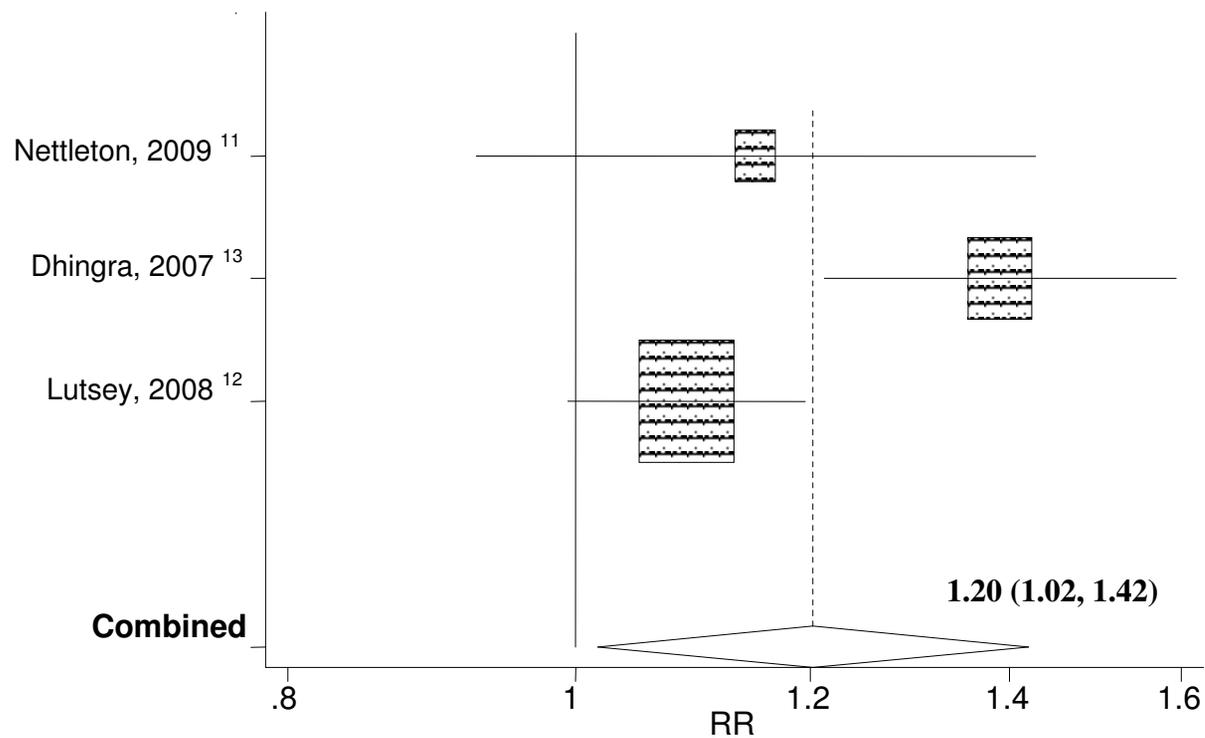
Figure 1a



Forrest plot of studies of evaluating SSB consumption and risk of T2DM, comparing extreme quantiles of intake. Random-effects estimate (DerSimonian and Laird method)

* from personal communication

Figure 1b



Forrest plot of studies evaluating SSB consumption and risk of MetSyn comparing extreme quantiles of intake. Random-effects estimate (DerSimonian and Laird method)