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Fructose and Risk of Cardiometabolic Disease

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Abstract

Fructose and glucose in soft drinks and fruit drinks account for just under 50 % of added sugars. Their intake has risen five-fold between 1950 and 2000, and this increase in intake of simple sugars has raised health concerns. The risks of cardiovascular disease, obesity and the metabolic syndrome have all been related to consumption of sugar-sweetened beverages in several, but not all meta-analyses. Fructose and sugar-sweetened beverages have also been related to the risk of gout in men, and to non-alcoholic fatty liver disease. Studies show that the calories in sugar-sweetened beverages do not produce an adequate reduction in the intake of other foods, leading to increased caloric intake. Plasma triglycerides are increased by sugar-sweetened beverages, and this increase appears to be due to fructose, rather than to glucose in sugar. Several 10-week to 26-week randomized trials of sugar-containing soft drinks (50 % fructose) show increases in triglycerides, body weight, and visceral adipose tissue; there were also increases in muscle fat and liver fat, which might lead to non-alcoholic-fatty liver disease.

Keywords

Metabolic syndrome; diabetes; obesity; food intake; soft drinks; hypertension; dyslipidemia; triglycerides; visceral fat; sucrose; HFCS

Introduction:

The prevalence of obesity began to increase in the 1980's and now more than 30 % of Americans are classified as obese and over 60 % are classified as overweight [1, 2]. In contrast, the prevalence was only 14 % in 1972. The increase in obesity reflects a chronic, small excess of energy intake over energy expenditure [3, 4•]. The USDA has estimated that total calories consumed have increased by about 425 per day over the last 50 years [5]. Most food items are now consumed in greater quantities, but some have increased more than others, including soft drinks and other sources of added sugars [6, 7].

In this review on the consumption of sugar-containing beverages, I will summarize data on the relation of sugar-sweetened beverages to the risks of developing cardiometabolic disease, becoming obese, and developing the metabolic syndrome. Then I will also explore

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the mechanisms that may account for the relation of high consumption of sugar-sweetened beverages to cardiometabolic diseases and obesity.

Added sugars are caloric sweeteners added to processed and prepared foods, in most added sugars, fructose represents about 50 % of the calories, when sugar and high fructose corn syrup (HFCS) are included [8].

Change in Beverage Intake

Soft drink consumption has been an important component in the increase in calorie intake in the last 40 years [6]. Carbonated soft drinks were developed more than a century ago, and now provide more than 20 % of calorie intake for some people [6]. Sugar intake has shown a remarkable increase since the time of the American Revolution. In 1750, the average American consumed four pounds of sugar per year. This rose to 20 pounds per person by 1850 and showed a further rise to 120 pounds per year per person by 1994. By the early 21st century, it exceeded 160 pounds per capita. Data from the National Health and Nutrition Survey show that soft drinks and fruit drinks provided over 40 % of the “added-sugars” that are in the diet. Between 1950 and 2000, the consumption of soft drinks had risen from 10 gallons per person per year to just over 50 gallons per person per year [7]. This is equivalent to about one 16-ounce soft drink per person per day. Thus, the sugar in soft drinks has been an important outlet for use of the growing production of sugar.

Soft Drinks and Their Relation to Increases in Health Risks

Sugar Sweetened Beverages and Cardiometabolic Disease

Consumption of soft drinks predicts the risk of developing cardiometabolic disease, as seen in the increased relative risk in a meta-analysis. Malik et al. [9, 10] identified ten prospective cohort studies evaluating sweetened soft drink consumption and weight gain (Table 1). Six of the studies related soft drink consumption to risk for diabetes mellitus [10–16], three to the risk of the metabolic syndrome [16–18], and one to the risk of coronary heart disease [12]. This meta-analysis included 294,617 participants with 10,010 cases of type 2 diabetes, 6,236 cases of the metabolic syndrome and 3,105 cases of coronary heart disease. There was a clear and consistent positive association between consumption of sweetened soft drinks and weight-gain, particularly in larger studies with longer durations of follow-up. Individuals in the highest quantile of soft drink intake had a 24 % greater risk of cardiometabolic disease than those in the lowest quantile [RR:1.24 (95 % CI: 1.12, 1.34)]. This increased to 30 % in studies that adjusted for mediating effects of energy intake and excluded body mass index (BMI) from analysis [RR: 1.31 (95 % CI: 1.16, 1.48)]. The authors concluded that higher consumption of calorie-sweetened soft drinks is associated with weight gain and increased risk of cardiometabolic diseases [9]. Fructose intake has also been related to the level of small dense LDL-cholesterol in children [20], and Dhingra et al. reported a relationship of the metabolic syndrome to consumption of both calorie-sweetened beverages and beverages sweetened with artificial sweeteners [16].

Sugar Sweetened Beverages and Obesity

A study by Ludwig et al. [21] focused attention on the relationship between soft-drink consumption and obesity. They noted that in children the baseline intake of soft drinks predicted future weight gain. He and his colleagues also showed that changes in the intake of soft drinks predicted future weight gain. This early study has been buttressed by many other studies and meta-analyses that have been done subsequently. Consuming two or more servings per day of calorie-sweetened beverages at 5 years of age, but not the consumption of either milk or fruit juice, was positively associated with adiposity from ages 5–15 years in 170 non-Hispanic white girls. [22], A meta-analysis by Malik et al. [23] that re-analyzed data initially published by Forchet et al. found a significant positive relationship between in the intake of soft drinks and obesity in children.

Most cross-sectional and longitudinal epidemiological studies in adults have also shown either a positive relationship or no relationship between soft drink consumption and the risk of obesity; essentially none have found that increased intake of soft drinks is protective against obesity, as might have been expected if there was a random distribution of body weight in response to drinking sugar-containing beverages. In the meta-analysis of Vartanian et al., [24] the five longitudinal studies all reported a positive relationship of beverage intake and obesity, with moderate effect size of 0.24 or r values from the regression analysis. In four long-term experimental studies ,the effect size was even larger (0.30) and even in ten of 12 cross-sectional studies, there was a positive relationship, with an average modest effect size of 0.13 [24]

In another meta-analysis, Olsen and Heitman [25] found that the majority of 14 prospective studies and five experimental studies found a positive association between the intake of calorically sweetened beverages and obesity. Three experimental studies also found positive effects of calorically sweetened beverages and changes in body fat, but two did not find these effects; none showed beneficial effects on weight. In their meta-analysis, eight prospective studies were adjusted for energy intake and seven of these resulted in essentially the same associations. On the basis of their meta-analysis, Olsen and Heitman concluded that a high intake of calorically sweetened beverages can be regarded as a determinant for obesity [25].

Two recent meta-analyses [26•, 27] using different inclusion criteria or analytical methods have reached different conclusions. One meta-analysis examined the effect replacing carbohydrate in the diet with either isocaloric (n = 13 studies) or hypercaloric (n = 2 studies) amounts of fructose. Sievenpiper et al. [26•] found that isocaloric substitution of fructose for carbohydrate had no effect on body weight, as one would expect. They also showed that hypercaloric diets, whether with added fructose or carbohydrate, increased body weight, again confirming other studies [28•]. Fructose added alone to the food supply represents only a few percent of total dietary fructose. The overwhelming amount comes from the fructose in sucrose or from HFCS, both of which were excluded from this meta-analysis.

Another meta-analysis by Sun and Empie [27] did not find any relationship between BMI and consumption of sugar-containing soft drinks. It is not immediately clear why this meta-analysis is discordant from the others. However, there was no evidence that consumption

of sugar-containing soft drinks reduced BMI. If there was a normally distributed statistical relationship between consumption of sugar-containing beverages and BMI, one might have expected consumption of sugar-containing soft drinks to reduce BMI, but this was not observed.

Clinical Studies Evaluating Effects of Sucrose, Glucose or Fructose on Metabolic Responses in Human Beings

Several human studies have examined the effect of sugar, glucose or fructose on metabolic responses. In one study using a Latin Square design, 20 healthy men and women ate a standard meal at 7:30 AM, and triglycerides were measured over the next 7 hours [29]. Each test meal was separated from the next by at least 72 hours. The effect of sucrose, glucose or fructose on the 7-hour increase in triglycerides was measured along with the effects of water and other appropriate controls. A 100 g load of sucrose was compared to 50 g of fructose or 50 g of glucose that provided the same amount of glucose or fructose that would be provided by the 100 g of sucrose. The rise in triglycerides was not significantly different between sucrose and fructose, but both were significantly higher than glucose, leading the authors to conclude that it was the fructose in sucrose that was responsible for the rise in triglycerides produced by sucrose [29].

Three randomized clinical trials lasting 10–26 weeks have examined the longer-term effect of controlling beverage intake on selected metabolic outcomes. The first 10 week trial compared two groups of young individuals drinking a fixed amount of sugar-sweetened cola versus aspartame-sweetened cola [30]. A total of 41 overweight men and women were entered into this 10 week parallel arm study. One group of 21 participants received 3.4 MJ (813 kcal) of sugar-containing beverages, and the other 20 participants received about 1 MJ (240 kcal) of artificially sweetened beverages containing no sugar. Body weight and fat mass increased by 1.6kg and 1.3kg, respectively, in the group drinking sugar-sweetened beverages and decreased by 1.0kg and 0.3kg, respectively, in the group drinking artificially sweetened beverages containing no sugar. Blood pressure increased by 3.8/4.1 mmHg in the sugar consuming group [30]. In addition, concentrations of several inflammatory markers were increased in the group consuming sucrose-containing beverages (haptoglobin by 13 %, transferring by 5 % and C-reactive protein by 6 %), compared to a decrease for these same indices in the group consuming aspartame-flavored (artificially sweetened) beverages (16 % decrease for haptoglobin, 2 % decrease for transferring, and 26 % for c-reactive protein) [31].

The second study lasted 12 weeks, with a 2-week baseline period followed by a 10 week intervention, during which subjects received an energy balanced diet with 55 % carbohydrate [32]. A total of 32 overweight men and women (BMI 29) were randomly assigned to drink 25 % of their energy as fructose ($N = 15$) or glucose ($N = 17$) for 12 weeks. The first 2 weeks and last 2 weeks were spent in the metabolic ward. The basal diet was 55 % carbohydrate, 30 % fat and 15 % protein. At 2 weeks, 10 weeks and 12 weeks, 24-hour triglycerides rose much more during the nighttime in the individuals drinking the fructose-sweetened beverages than in those given glucose-containing beverages. Body weight and total body fat increased significantly in both groups, but the increase did

not differ between groups. De-novo lipogenesis, measured with stable isotopes, increased significantly during the study in the fructose-beverage group, but not in the glucose-beverage group. More ominously, visceral fat increased significantly as measured by computed tomography (14.2 % in the fructose group and 3.2 % in the glucose group). In contrast, the smaller increase in subcutaneous fat did not differ significantly between groups [32].

The third randomized controlled trial lasted 6 months [33††]. Participants received one of four treatments: 1 L/day of sugar-sweetened cola (« two 16 oz beverages); 1 L/day of milk; 1 L/day of aspartame-sweetened cola; or 1 L/day of water. The carbohydrate was 100 g/day from cola (50 % fructose) and 47 g/day from milk (no fructose). The subject's activity and dietary intake were collected at the beginning and end of the study. The results are summarized in Table 2. Body weight and total body fat did not change significantly, although there was a tendency ($P = 0.07$) for an increase in subcutaneous adipose tissue in the cola-drinking group. Visceral fat, liver fat, muscle fat, triglycerides, total cholesterol and systolic blood pressured all showed significant differences in the group drinking the cola beverage, usually being higher than the others. Thus, the consumption of about two 16-ounce cola beverages per day (one liter) was sufficient to produce detrimental changes similar to those seen in the metabolic syndrome [33••].

Potential Mechanisms for the Relation of Sugar-Sweetened Beverage Intake and Cardiovascular Disease

Several potential mechanisms can be suggested for a relationship of sugar-containing soft drinks and cardiometabolic diseases. These would include the reduced response to the calories in beverages, with increased caloric intake as a consequence; dyslipidemia reflected in increased triglyceride production; an increase in blood pressure; and an increase in uric acid in relation to the intake of calorically sweetened soft drinks (a reflection of fructose intake) [34, 35].

Beverages and Off-setting Intake of Other Foods

Energy obtained from beverages appears to be sensed differently from similar quantities of energy ingested as solid food; that is, the energy in beverages does not produce an offsetting decrease in calories as solid food, whereas solid food produces an offsetting reduction in the intake of other foods. Using a pre-meal load followed by measurement of food intake at lunch, Rolls and her colleagues reported that the intake of solid food at lunch did not change significantly when there was no preload, or when the preload was water or a cola beverage [36]. Hence, the calories in the cola beverage were "add-on" calories, without any offsetting reduction in other foods [26•].

To expand on the relationship of beverage intake and compensatory or offsetting reduction in the intake of solid food, Mattes and his associates have compared liquid versus solid forms of three foods that are predominantly rich in fat, protein, or carbohydrate [37, 38]. In each case, the intake of a beverage did not suppress the intake of the other components of a lunch meal or the 24-hour food intake by the amount of calories ingested in the beverage. In contrast, the intake of a solid preload of comparable calorie value was associated with an appropriate offsetting reduction in the caloric intake of other foods. Thus, the process

by which calorie ingestion is registered at the pyloric value or in the intestine to provide information about energy content appears to be sub-optimal for suppressing food intake if the calories are in liquid form, but not when they are in solid form [38].

Dyslipidemia

Both fructose and glucose enter the portal circulation of blood from the intestine to the liver [39, 40]. Since the transport molecule (glut5) for fructose is absent into most cells, the liver and kidney are the main sites for fructose metabolism. Upon entering the liver, glucose is phosphorylated at the 6-position to form glucose-6-phosphate, whereas fructose is phosphorylated at the 1-position by ketohexokinase to form fructose-1-phosphate. The fructose-1-phosphate is readily converted to triose phosphates, which provide the backbone for triglycerides. In contrast, glucose-6-phosphate is not so readily converted to triglyceride, because its metabolism is regulated by phosphofructokinase. This probably explains why fructose, but not glucose, stimulates the formation of lipids in the liver and increases circulating levels of triglycerides, particularly at night [31, 40, 41].

Blood Pressure

Fructose increases blood pressure and thermogenesis more than glucose in some studies [42, 43]. When a 75 g oral load of glucose or fructose was given to 17 volunteers, fructose stimulated oxygen consumption more than glucose but produced a much smaller stimulation of insulin [43]. Fructose increased the respiratory quotient more than glucose, which is consistent with the de novo lipogenesis measured in studies by Stanhope et al. [32]. Both obese and diabetic patients had a similar stimulation of oxygen uptake after infusion of glucose that was smaller than the response to fructose [43]. When fructose, glucose or water were given to healthy male volunteers, blood pressure was stimulated by fructose, but not by water or glucose [42]. To further explore the relation of fructose to blood pressure, Ha et al. [44] did a meta-analysis on studies where fructose was substituted for other carbohydrates either isocalorically (13 studies) or with added calories (two studies). Overall, they found that fructose intake in the 13 isocaloric exchange studies significantly decreased diastolic (mean difference: −1.54 [95 % CI: −2.77 to −0.32]) and mean arterial pressure (mean difference: −1.16 [95 % CI: −2.15 to −0.18]). There was no significant effect of fructose on systolic blood pressure (mean difference: −1.10 [95 % CI: −2.46 to 0.44]). The two hypercaloric studies where fructose was substituted for other carbohydrates found no significant effect on mean arterial blood pressure. Most studies were small and the methods variable, and the authors concluded that more high quality studies were needed. Moreover, this meta-analysis did not include fructose from either sucrose or HFCS. Fructose added to the diet separately from its role as half of the sucrose molecule, or in HFCS, accounts for less than 5 % of the added sugars. Since added fructose is a relatively small component of the diet, the meta-analysis of Ha et al. [44] does not address the impact of the intake of fructose from sucrose and HFCS, the question which is addressed by Maersk et al. [33••] and Raben et al. [30], where beverages containing sucrose (50 % fructose) increased blood pressure.

Metabolic Syndrome

Ingesting two16-ounce sugar containing cola beverages for 6 months produced a variety of features of the metabolic syndrome including an increase in visceral fat, an increase in blood pressure, and an increase in triglycerides [33††]. Those with the metabolic syndrome have an increased risk of developing type 2 diabetes and cardiovascular disease [45].

Uric Acid

Using data from 14,761 participants ≥ 20 years of age from the Third National Health and Nutrition Examination Survey (1988-1994), Choi et al. found that serum uric acid levels increased with increasing sugar-sweetened soft drink intake. Both fructose and a related D-tagatose can increase blood uric acid concentrations [40, 46]. The metabolism of fructose in the liver generates adenosine 5'phosphate that is a substrate for conversion to uric acid, which has been shown to reduce endothelial nitric oxide production. Moreover, elevated blood uric acid has been shown to reduce endothelial nitric oxide production. Thus, SSBs may contribute to increased risk of developing CHD by means of the uric acid/nitric oxide pathway [39, 40]. In a meta-analysis of fructose replacing carbohydrate in the diet, Wang et al. [47] identified 21 trials with a total of 425 individuals, but excluded fructose from sugar or HFCS. Isocaloric substitution of fructose did not affect uric acid; howver, with hypercaloric diets, overfeeding by 35 %, fructose substitution increased uric acid in nondiabetic individuals, indicating that fructose can indeed increase uric acid ,even with relatively small substitution [47, 48]

Discussion

This review has examined some of the relationships between the intake of beverages sweetened with fructose from either sucrose or HFCS and the risk for disease, and some of the potential mechanisms for these effects. Many of the epidemiological studies show a positive relationship between the intake of sugar-sweetened beverages and cardiometabolic diseases and obesity, and interestingly none of them show a protective or beneficial effect, which is what one might expect if there were no relation between intake of sugar-sweetened soft drinks and obesity [10••, 23, 24]. Thus, risk of diabetes the risk of cardiovascular disease, the risk of the metabolic syndrome and the risk of gout all appear to be increased with the consumption of sugar-sweetened soft drinks [10••, 18].

Soft drinks have also been implicated in the risk for developing non-alcoholic fatty liver disease and the often-associated metabolic syndrome [50], Alcohol and a number of toxins are well known risk factors for fatty liver and subsequent fibrosis and cirrhosis. Over the past 40 years a new entity, non-alcoholic fatty liver disease, has come to the fore as a precursor of diabetes and CVD and as a major cause of liver failure and liver transplant. The rise in intake of sugar-sweetened soft drinks has paralleled this rising incidence of non-alcoholic fatty liver disease. Although association does not prove causation, it can serve as the basis for generating hypotheses and for additional studies.

Several mechanisms may account for the relationship between the intake of sugar-sweetened soft drinks and the diseases discussed above. First, the sugar in sugar-sweetened beverages

provides energy (calories) to the body. It is an excess of energy intake over expenditure that is continued over months to years that produces obesity [3,4]. Certainly, the calorie content of soft drinks can contribute to this cumulative calorie load.

A second component of the response to beverages is that they do not elicit an offsetting degree of calorie compensation as solid foods do [37, 38]. Many kinds of beverages have this effect, and in some studies beverages may actually stimulate additional intake of calories from solid foods rather than decrease their intake to account for the calories in the beverage [38]. In addition, when a single food is prepared in solid, semi-solid and liquid forms, the reduction in intake of solid food is appropriate for the amount of energy ingested with the solid and semi-solid forms, but not when the same number of calories from the same fruit are provide as a liquid [37].

Fructose is predominantly metabolized in the liver, which contains abundant glut-5, the transporter protein that facilitates the entry of fructose into cells. The first step in the metabolism of fructose is phosphorylation by the transfer of one phosphate from adenosine 5-triphosphate to fructose and producing, as a by-product adenosine 5-diphosphate, which can be further metabolized to uric acid [38, 39]. The phosphorylated fructose is a ready substrate for aldolase, which produces trioses that serve as the backbone for triglycerides. This probably accounts for the increase in de novo lipogenesis seen when fructose-containing beverages are fed acutely [38] or chronically [32].

In the 6-month study with two 16-ounce cans of cola beverage each day, there was an increase in visceral fat, muscle fat, systolic blood pressure without a significant change in body weight. This indicates that a dose of 1 liter per day of cola beverage for 6 months, equivalent to two 16-ounce cola beverages per day, is sufficient to produce the features of the metabolic syndrome in some people [29, 32, 40].

Conclusion

In conclusion, sugar consumption in America has increased over 40 fold since 1750. Over 40 % of the added sugars are found in soft drinks and fruit drinks. Beverage consumption continues to rise and is now, on average, 500 mL/day, or about one 16-ounce beverage per day; many people consume more than two 500 mL beverages per day. Sugar-containing soft drinks increase the risk of cardiometabolic disease, the risk of diabetes and the risk of obesity. Soft drinks and fructose intake are also related to gout, the metabolic syndrome and the risk of non-alcoholic fatty liver disease. Sugar-sweetened beverages provide “add-on” calories, since calories in beverages produce incomplete caloric compensation. Three randomized studies reached similar conclusions about the metabolic effects of sugar and fructose. Study 1 showed weight gain, increased blood pressure and inflammatory markers with sugar-sweetened beverages. Study 2 showed increased triglycerides, de novo lipogenesis and visceral fat with fructose, but not glucose beverages. Study 3 showed increased triglycerides, total cholesterol, blood pressure, visceral fat, liver fat and muscle fat with cola beverage compared to milk, diet cola or water. The possibility that current consumption levels of calorically sweetened beverages may produce components of the

metabolic syndrome in some people should increase efforts to reduce the intake of these products.

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milk have “sugar” but only the sucrose in the cold has fructose – the milk sugar is composed of glucose and galactose. During the 6 months when the equivalent of two 16 oz beverages were ingested each day, the cola group showed increased visceral fat, liver fat, muscle fat, cholesterol and systolic blood pressure, in comparison with milk or all other groups combined. This suggests that within 6 months, two 16 oz sugar-containing beverages can mimic the metabolic syndrome.

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Table 1:

SSB Intake and Risk of Cardiometabolic Disease

Ref	Population	Mean baseline age (SD) or age range Y	Duration Y	Dietary assessment method	Outcome	Results	Adjustment for potential confounders
Montonen, 2007 [33]	4304 adults, Finnish Mobile Clinic Health Examination, Finland	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 [34]	12 204 adults ARIC study, USA	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 [23]	51603 women NHS II, USA	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 [28]	43 960 women BWHS, USA	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 [36]	71 346 women NHS, USA	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
Nettleton, 2009 [35]	5011 adults, MESA, USA	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 [35]	3878 adults, MESA, USA	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

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[a] National register confirmed by medical record

[b] Presence of one of the following: 1) fasting glucose 3 126 mg/dl, 2) non-fasting glucose 3 200 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 3 126 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 _102 (men) or _88 cm (women), 2) triglycerides _150 mg/dl, 3) HDL cholesterol _40 (men) or _50 mg/dl (women), 4) blood pressure _130/85 mmHg or antihypertensive treatment and 5) fasting glucose _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 ≥102 (men) or ≥88 cm (women), 2) triglycerides >150 mg/dl, 3) HDL cholesterol ≤40 (men) or ≤50 mg/dl (women), 4) blood pressure ≥135/85 mmHg or antihypertensive treatment and 5) fasting glucose ≥100 mg/dl or antihyperglycemic treatment/ insulin

Table 2 .

Some metabolic responses after 6 months of drinking 1 liter per day of one of four beverages each day.

Variable	Cola	Milk	Diet Cola	Water	*P* (overall)
Body weight	3±	1±	−0.5±	0.5±	=0.8
Body fat	3.14±3.7	1.42±2.5	−0.52±2.5	0.49±2.6	
Subcutaneous fat	4.98±2.8	3.10±2.9	−2.79±2.7	−4.3±2.7	=0.07
Visceral fat	23±9	−8±8*	1±8	−0.5±8	=0.03
Liver fat	130±40	−10±4*	−5±35*	2±40*	=0.01
Muscle fat	200±70	−20±60	−30±60	80±60	<0.05
Triglycerides	32.7±8.6	−0.30±8.1*	−14.1±8.1*	−14.2±7.7*	=0.001
Cholesterol	11.4±3.2	0.63±3.0	−5.9±3.0*	−0.16±2.8*	=0.004
Systolic blood pressure	3±3	−7±3*	−7±3*	0±3	=0.01

Data Adapted from Maersk et al. Am J Clin Nutr [31]

*P<0.05 compared to cola