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Adverse metabolic effects of dietary fructose: Results from recent epidemiological, clinical, and mechanistic studies

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Abstract

Purpose of review—The effects of dietary sugar on risk factors and processes associated with metabolic disease remains a controversial topic, with recent reviews of the available evidence arriving at widely discrepant conclusions.

Recent findings—There are many recently published epidemiological studies that provide evidence that sugar consumption is associated with metabolic disease. Three recent clinical studies, which investigated the effects of consuming relevant doses of sucrose or high fructose corn syrup along with *ad libitum* diets, provide evidence that consumption of these sugars increase risk factors for cardiovascular disease (CVD) and metabolic syndrome. Mechanistic studies suggest that these effects result from the rapid hepatic metabolism of fructose catalyzed by fructokinase C, which generates substrate for *de novo* lipogenesis and leads to increased uric acid levels. Recent clinical studies investigating the effects of consuming less sugar, via educational interventions or by substitution of sugar-sweetened beverages for non-calorically sweetened beverages, provide evidence that such strategies have beneficial effects on risk factors for metabolic disease or on BMI in children.

Summary—The accumulating epidemiological evidence, direct clinical evidence, and the evidence suggesting plausible mechanisms support a role for sugar in the epidemics of metabolic syndrome, CVD and type 2 diabetes.

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Keywords

Fructose; sucrose; high fructose corn syrup; sugar; metabolic disease

Introduction

In August 2009, the American Heart Association Nutrition Committee recommended that women consume no more than 100 kcal/day and men consume no more than 150 kcal/day of added sugar (1). In June 2010, the Report of the Dietary Guidelines Advisory Committee (DGAC) on the Dietary Guidelines for Americans 2010, suggested a maximal intake level of 25% or less of total energy from added sugars (2). While this latter guideline is not recommending people consume 25% of their energy as added sugar, it does imply that after due consideration of the evidence DGAC concluded that consumption of added sugar at this level is not associated with any adverse metabolic effects. The difference in these 2 guidelines, equivalent to almost three 12-ounce servings of soda for the average woman and more than 3.5 for the average man, illustrates the state of controversy that existed concerning the effects of sugar consumption on the development of metabolic disease in 2010.

Are we any nearer a consensus now, 3 years later? The discrepant conclusions summarized below from review articles evaluating the available data to 2012 suggest we are not.

- Data from prospective and intervention studies clearly point to high fructose consumption, mainly in the form of sugar-sweetened beverages (SSB) as risk factor for metabolic diseases in humans (3).
- Although some studies hint towards some potential adverse effects of excessive fructose consumption especially when combined with excess energy intake, the results from clinical trials do not support a significant detrimental effect of fructose on metabolic health when consumed as part of a weight-maintaining diet in amounts consistent with the average-estimated fructose consumption in Western countries (4).
- Intake of free sugar or SSB is a determinant of body weight (5).
- Randomized controlled trials at levels even exceeding normal human consumption have been inconclusive related to SSB and obesity (6).

This review will present the recent epidemiological, clinical, and mechanistic studies pertaining to the effects of dietary sugar on risk factors and processes associated with metabolic disease, and provide the perspective of researchers directly involved in clinical investigations of this topic.

Epidemiological studies

Recent studies add to the already considerable epdemiological evidence that sugar consumption is associated with metabolic disease.

- Men from the Health Professionals Follow-Up Study in the top quartile of SSB intake had a 20% higher relative risk of coronary heart disease than those in the bottom quartile (7).
- In Hispanic adults, plasma TG, metabolic syndrome and waist circumference were associated with consumption of instant SSB and/or regular soda (8).
- In the Nurses' Health Study II, one serving/d of SSB was associated with increased risk for type 2 diabetes (T2DM) (9).
- In participants from the Nurses' Health Study, Nurses' Health Study II and the Health Professionals Follow-Up Study, SSB consumption was associated with a higher risk of T2DM; coffee intake was associated with a lower risk, irrespective of the caffeine content. (10)
- In an analysis across 94 countries, every additional percentage point of calories from sugar/sweeteners were associated with 5% higher prevalence of diabetes (11).
- An increased consumption of 100-mL/day of SSB was associated with increased HOMA IR and systolic blood pressure among children ≥85 percentile for BMI in the Quebec Adiposity and Lifestyle Investigation in Youth Study, and with increased systolic blood pressure and waist circumference in children with impaired glucose tolerance (12).
- In healthy adults in Scotland, uric acid levels were positively associated with SSB consumption (13).
- SSB consumption was positively associated with serum uric acid concentrations in adolescents in Taiwan, as was BMI, body fat, and systolic blood pressure. 25% of the 2727 subjects consumed more than 500 ml of SSB/day (14).
- Among participants of the Nurses' Health Study, Nurses' Health Study II and Health Professionals Follow-Up Study substitution of water, coffee, tea, diet beverages, or low-fat milk for one serving of SSB was associated with weight loss, with the greatest effect occurring with water (15). The genetic association with BMI was stronger among participants with higher intake of SSB than those with lower intake (16).
- In adults, frequency of SSB, but not diet beverage, intake was positively associated with proportion of visceral (VAT) to subcutaneous abdominal adipose tissue (SAT) (17).
- In teenagers, fructose intake was associated with VAT, but not SAT (18).

In contrast to the above reports, an analysis of the NHANES 1999-2006 indicated that fructose and non-fructose sugar consumptions at levels representative of the American diet were not associated with indicators of the metabolic syndrome (19).

Clinical studies – Interventions with increased sugar intake

Recent clinical studies have investigated the effects of fructose or sugar consumption by providing subjects with SSB or control beverages that were consumed along with *ad libutum*

quantities of the subjects' usual diets. The longest of these studies was conducted in Denmark where subjects consumed 1 liter/d of sucrose-sweetened cola (~20% energy requirements (ER)), isocaloric amounts of low-fat milk, 1 liter/d aspartame-sweetened beverages, or 1 liter/d water for 6 months. Body weight at the end of the intervention period was not significantly different from baseline in any group. Subjects consuming sucrose exhibited increased VAT, liver and muscle TG, and fasting TG and cholesterol levels, while the other 3 groups did not. The sucrose-induced increase of liver TG was significantly larger compared with all 3 of the other groups, and the increase in visceral fat was significantly greater compared with the subjects who consumed low-fat milk and who exhibited a comparable change in body weight (Sucrose: +1.3%; Milk: +1.4%) (20).

Aeberli and colleagues have published two recent reports in which young men participating in 6-arm (21) or 4-arm crossover trials (22) consumed low (40 g/d, ~6.5% ER) or moderate (80 g/d, ~13% ER) amounts of fructose, glucose, or sucrose as beverages along with *ad libitum* diets for 3 weeks. In the 6-arm crossover, LDL particle size was reduced compared with baseline during consumption of moderate fructose or sucrose, and redistribution to a more atherogenic LDL subclass distribution was observed after these interventions plus the low fructose intervention. These 3 interventions also increased waist:hip ratio, even though low glucose was the only intervention that resulted in significant weight gain compared with baseline (21). In the 4-arm crossover, total and LDL cholesterol were increased after moderate fructose or sucrose compared with moderate glucose consumption. Hepatic insulin sensitivity, indexed by endogenous glucose production during euglycemic-hyperinsulinemic clamps, was decreased during moderate fructose compared with moderate glucose consumption, while whole body insulin sensitivity was not different (22).

Our group demonstrated that young, healthy subjects consuming 25% ER as HFCS-sweetened beverages for 2 weeks exhibited significant increases of fasting LDL, non-HDL-cholesterol and apolipoprotein B (apoB), and postprandial TG, remnant-cholesterol and -TG, and small dense LDL (sdLDL), which were comparable to those observed in subjects consuming fructose, and greater than those in subjects consuming glucose (23). In contrast, Silbernagel et al. reported that when subjects consumed 150 g/d of fructose or glucose, the only significant difference between groups was an increase of fasting TG concentrations in the fructose group (24). They did not measure postprandial TG, fasting apoB or sdLDL. Given the similarities between this study (24) and our group's study (23) (both parallel arm, subjects of comparable age and BMI, similar amounts of sugar consumed), it is interesting to consider why there were numerous differential effects between glucose and fructose on lipids in our study, and only one in this study. A potential reason for the lack of group differences in the study by Silbernagel et al. was the highly significant weight gain that occurred in subjects consuming glucose (+1.7 ± 0.4 kg, $P = 0.001$ vs baseline, $P = 0.056$ vs fructose), but not in subjects consuming fructose (+0.2 ± 0.6 kg) (24). This difference may possibly be due to fructose malabsorption (25), which they did not assess. As shown in Figure 1, sub-division of the 48 subjects who participated in our study (23) into groups that gained or did not gain body weight, illustrates that weight gain has a marked effect on the sugar-induced increases of fasting cholesterol, LDL and apoB concentrations.

The studies by Maersk et al. (20), Aeberli et al. (21, 22) and Stanhope et al. (23) provide direct evidence that consumption of sugar can increase risk factors for metabolic disease. These results are relevant to public health in that the sugars investigated included the commonly-consumed sugars (sucrose and HFCS as opposed to pure fructose) and in quantities comparable to that consumed by a significant number of people (21, 22), and within the maximal intake level of 25% suggested by DGAC (2). Obtaining stronger evidence will require clinical trials in which all study food is formulated and provided throughout the investigation to ensure that there are no diet variations between the experimental groups or interventions that may confound results.

Clinical studies providing mechanistic insights

Other recent clinical studies investigating the effects of hyper-energetic feeding protocols and/or pure fructose have provided mechanistic insights. In an overfeeding study in which diets were supplemented with 1000 kcal/d as candy/SSB, within 3 weeks subjects exhibited increased body weight (+2%), liver fat (+27%) and increased DNL. The increase of DNL was proportional to the increase in liver fat (26). While the lack of a control group prevents differentiating the effects of sugar from those of overfeeding, these results suggest that DNL is involved in the process by which surplus sugar in the context of positive energy balance increases liver fat. Importantly, our group has previously reported that DNL was increased in subjects consuming fructose with energy-balanced, steady state meals, but not in subjects consuming glucose (27).

However, a recent review of fructose metabolism and isotopic tracer studies concluded that a small percentage of ingested fructose (<1%) appears to be directly converted to plasma TG (28). This figure is clearly an underestimation, based on acute feeding studies that do not take into account that DNL-derived lipid can spend from 24 to over 72 hours in the liver prior to being packaged into very low density lipoprotein (VLDL) and secreted into the circulation (29, 30). The actual percentage of fructose converted to fat is difficult to quantify, especially under physiologically relevant meal-fed conditions, and has yet to be determined. Accurate estimations will require assessments of DNL and VLDL production, secretion and clearance using non-steady state tracer kinetic models. However, the above studies and others demonstrate that DNL is upregulated concurrently with fructose-induced postprandial hypertriglyceridemia (27, 31, 32) and liver fat accumulation (26). The seminal study from Donnelly et al. (29) shows that in patients with NAFLD, 26% of both intra-hepatic fat and VLDLTG are made *de novo* (29). Furthermore, when hepatic DNL is induced, not only are new lipids synthesized and non-esterified fatty acids re-esterified, but hepatic lipid oxidation is down-regulated. Our group has recently reported that the subjects who exhibited increased DNL during fructose consumption, also exhibited inhibition of post-meal lipid oxidation (33). These combined events create an imbalance between hepatic lipid “input” and “export”, leading to net intrahepatic fat accumulation. While we did not measure hepatic lipid in these subjects, the 17% decrease in insulin sensitivity (27) supports the concept that hepatic DNL is a mechanism leading to increased hepatic lipid production, hepatic lipid accumulation, and thereby to hepatic insulin resistance (34).

Bortolotti et al. invetigated the hypothesis that high dietary protein content would reverse the inhibition of lipid oxidation and the increase in postprandial TG levels caused by fructose consumption. The concurrent feeding of fructose and protein did not increase lipid oxidation, and in opposition to the hypothesis, it increased postprandial TG levels. The authors suggest that the supplemental protein may have enhanced hepatic VLDL synthesis, assembly and secretion (35).

Our group has also recently reported that 10-weeks consumption of fructose, but not glucose, led to significantly increased 24-h uric acid profiles (36), which suggests that the epidemiological associations (13, 14, 37-39) between sugar consumption and uric acid levels are causal. Fasting concentrations of markers of inflammation; monocyte chemoattractant protein-1, plasminogen activator inhibitor-1, and E-selectin; as well as retinol binding protein-4 and the liver enzyme, gamma glutamyl transferase, were also increased in these same subjects consuming fructose (36, 40).

Our recent report of the postprandial glucose and insulin responses in the subjects consuming glucose or fructose for 10 weeks (41) has clinically relevant implications to the potential role of the glycemic index (GI) in metabolic disease risk. The adverse metabolic effects of dietary sugars have been attributed by some to GI (42, 43). The GI of fructose is 23 compared with 100 for glucose. The calculated relative GI of the baseline high complex carbohydrate diet, the high glucose and the high fructose intervention diets, consumed during the 24-h blood collections in our studies, were 64, 83 and 38, respectively. As expected, for this study (27), and our more recent 2-week study (23), the glucose and insulin excursions of the diets paralleled the GI, with exposure being highest on the glucose diet, intermediate on the complex carbohydrate baseline diet, and lowest on the fructose diet. However, it was subjects consuming the high fructose diets with the lowest GI and glycemic exposure, who exhibited increased VAT and decreased insulin sensitivity (27) and increases of LDL, apoB, and postprandial TG (23, 27). In contrast, when subjects consumed high glucose diets, postprandial plasma glucose and insulin excursions increased substantially (23, 27), however insulin sensitivity (27) and postprandial TG exposure, LDL, and apoB remained unchanged (23, 27). Thus, these results do not support the hypothesis that elevated postprandial glucose and/or insulin excursions contribute to dyslipidemia and insulin resistance. They also demonstrate that studies investigating the relationship of dietary carbohydrates to risk factors for metabolic diseases should accurately determine the glucose and fructose contents of the diets. Dietary fructose may be an important contributor to the inconsistent reported effects of dietary GI on metabolic disease risk. It is likely that other differences between high and low GI diets, with alterations in dietary fiber content being the most likely confounder, underlie these inconsistencies. Nonetheless, the available evidence indicates that it is the fructose and not the glucose component of sucrose and HFCS that is primarily responsible for their adverse metabolic effects.

As the prevalence of pediatric obesity and metabolic syndrome increase, investigations of the effects of sugar consumption in children are needed. The 24-h TG profile was measured in children, with or without nonalcoholic fatty liver disease (NAFLD), during consumption of fructose and glucose in crossover feeding trials (44). As previously shown in adults (45, 46), postprandial TG levels were higher during fructose compared with glucose

consumption in all children. Importantly, the fructose-induced increases in TG were higher in children with NAFLD than those without NAFLD (44).

Clinical studies – interventions to reduce sugar intake

Several recent clinical studies have demonstrated beneficial effects on metabolic parameters by providing subjects with educational programs aimed at reducing sugar/fructose consumption. Obese African-American and Latino adolescents participated in a 16-week nutrition education intervention focused on decreasing added sugar intake to ≤10% of daily calories and increasing fiber intake. Despite unchanged BMI, subjects exhibited improved insulin sensitivity compared with the control group (47). Goran et al. have recently reviewed the inter-relationship between genetic factors, liver fat, and sugar consumption, (48) which appear to make Latino children (49) and adults (50) particularly vulnerable to the adverse effects of sugar.

In another study, patients with chronic kidney disease followed dietary instructions and lowered fructose consumption to 12 g/d. After 6 weeks, they exhibited significant decreases in fasting insulin, high sensitivity C-reactive protein and soluble intercellular adhesion molecule, and nonsignificant ($P<0.1$) decreases in blood pressure and uric acid levels (51).

Three recent studies provide evidence that dietary education programs designed to reduce sugar and fructose consumption (52), or blinded (53) or unblinded (54) replacement of SSB with noncaloric-sweetened beverages have beneficial effects on BMI in children. Previous studies suggest that consumption of non-caloric sweeteners compared with sucrose or HFCS also has beneficial effects on BMI in adults (55-57). The explanation for these results could be as simple as people tend to over-eat sugar because they like the sweet taste. However, recent studies on the central effects of sugars in the brain (58-60), made possible by functional magnetic resonance imaging technology, suggest the answer could be more complicated. The most recent of these studies reports that consumption of a fructose-sweetened beverage resulted in greater hypothalamic activation, which would be associated with less appetite suppression, than consumption of a glucose-sweetened beverage in young healthy adults (59). Corroborating these results, the subjects recorded significantly higher ratings of fullness and satiety after the glucose, but not fructose, drink (59).

These data provide a plausible link for the associations between the consumption of sugar-sweetened beverages and body weight gain (16, 61-63). Confirming this link will be important not only for combating the obesity epidemic, but also the obesity-related increases of metabolic syndrome, CVD and T2DM. Recent research (20-23, 27) and older research (64-69) demonstrate that consumption of fructose and fructose-containing sugars has adverse effects on risk factors for metabolic disease that are independent of body weight gain. These results, the results in Figure 1, and the potential link between sugar consumption and body weight gain suggest that sugar promotes the development of metabolic disease through two mechanisms; directly via the adverse effects of fructose on lipid and carbohydrate metabolism, and indirectly by promoting body weight gain (See Figure 2).

Animal and *in vitro* studies investigating mechanisms of the metabolic effects of fructose

Numerous recent studies, more than can be discussed in this review, have investigated the links between dietary fructose and adverse metabolic effects in animal models or *in vitro* systems. We have included a few studies that provide insight into the underlying mechanisms by which fructose induces lipid dysregulation.

The initial phosphorylation of dietary fructose is largely catalyzed by fructokinase, which is not regulated by hepatic energy status. This results in high levels of fructose uptake by the liver with little of the ingested fructose reaching the systemic circulation. Ishimoto et al. have provided compelling evidence concerning the importance of fructokinase in mediating the adverse effects of fructose (70). They report that fructokinase exists as two isoforms: fructokinase A which is widely distributed and has low affinity for fructose; and fructokinase C, which is expressed primarily in liver, intestine, and kidney and has high affinity for fructose. They demonstrated that fructose-induced metabolic syndrome is prevented in knockout mice lacking both isoforms, but is exacerbated in fructokinase A knockout mice compared with wild-type mice (70). These results demonstrate that fructokinase C is the key driver of the adverse effects induced by fructose. It also suggests that fructokinase A offers some protection against the adverse effects of fructose by allowing for some fructose metabolism in peripheral tissues.

Recent studies have investigated the regulation and effects of fructose-induced DNL. Erion et al. compared the effect of treatment with carbohydrate response element-binding protein (ChREBP) and control antisense oligonucleotides (ASO) in rats fed high fructose or high fat diets (71). Treatment with ChREBP ASO decreased plasma TG concentrations compared with control ASO in both diet groups, but hepatic lipid content and insulin sensitivity were unaffected. The reduction in plasma TG was more pronounced in the fructose-fed group and attributed to measured decreases of hepatic expression of fructokinase, lipogenic genes, and microsomal TG transfer protein, and decreased hepatic TG secretion (71).

Ren et al. compared mice fed high fat diet or high fructose diets. Liver lipid levels increased within 3 days and indicators of impaired glucose tolerance and insulin signaling were exhibited within one week in both groups. As expected, DNL and lipogenic gene expression were increased in fructose-fed mice and decreased in fat-fed mice. Interestingly, fructose feeding activated two endoplasmic reticulum stress pathways, but high fat feeding did not. The authors suggest that endoplasmic reticulum stress is involved in DNL *per se* rather than resulting from hepatic steatosis or insulin resistance (72).

Extensive recent work by Richard Johnson and co-workers suggests that fructose-induced increases of uric acid may contribute to the adverse effects of fructose. They report that in fructose-exposed human hepatocytes, uric acid upregulates fructokinase expression (73) and inhibits AMP-activated kinase activity (74), thus amplifying the lipogenics effects of fructose. A series of experiments involving hepatocytes, allopurinol-treated mice, and hyperuricemic patients with low BMI provides evidence that the lipogenic effects of fructose may be partially mediated through direct effects of uric acid to stimulate hepatic fat

accumulation (75). Most recently Tapia et al. studied 3 groups of rats receiving: 1. Uricase inhibitor treatment, 2. SSB, 3. Uricase inhibitor + SSB. Uricase inhibitor induced glomerular hypertension and SSB induced insulin resistance. In combination, they produced both effects, plus synergistic effects on systemic and glomerular pressure, plasma glucose, hepatic TG, and oxidative stress (76).

Conclusion

The extent to which the adverse metabolic effects of dietary sugar consumption result from direct effects of fructose on lipid and carbohydrate metabolism, to indirect effects resulting from increased body weight and adiposity, or to direct metabolic actions that are exacerbated by weight gain, has not been determined.

However, the accumulating epidemiological evidence, direct clinical evidence, and the evidence suggesting plausible mechanisms support a role for sugar in the epidemics of metabolic syndrome, CVD and T2DM.

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Key points

- Recently published epidemiological studies that provide evidence that sugar consumption is associated with metabolic disease.
- Three recent clinical studies, which investigated the effects of consuming relevant doses of sucrose or high fructose corn syrup along with *ad libitum* diets, provide evidence that consumption of these sugars increase risk factors for cardiovascular disease and metabolic syndrome.
- Mechanistic studies suggest that the adverse effects of sugar consumption result from the rapid hepatic metabolism of fructose catalyzed by fructokinase C, which generates substrate for *de novo* lipogenesis and leads to increased uric acid levels.
- Recent clinical studies investigating the effects of consuming less sugar, via educational interventions or by substitution of sugar-sweetened beverages for non-calorically sweetened beverages, provide evidence that such strategies have beneficial effects on risk factors for metabolic disease or on BMI in children.

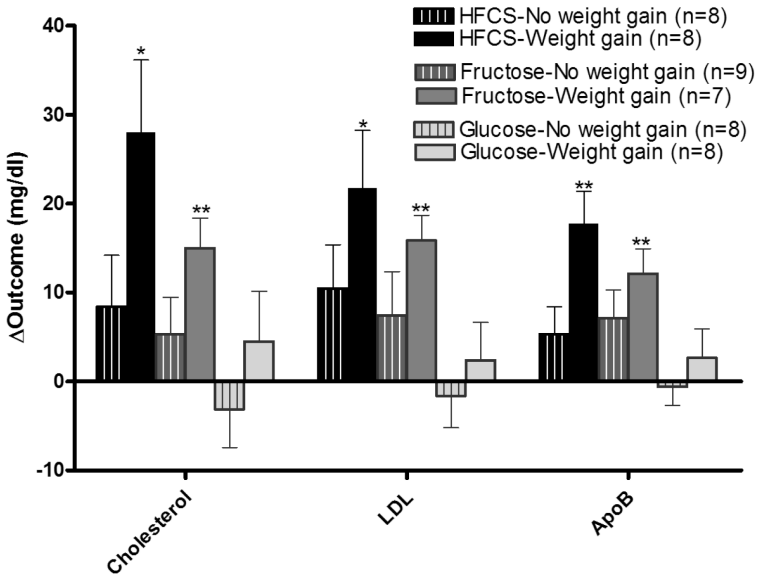

Figure 1. Effect of body weight gain on the changes of fasting cholesterol, LDL and apoB in subjects consuming sugar

Changes in fasting lipid outcomes in subjects who gained and did not gain body weight while consuming 25%E HFCS-, fructose-, or glucose-sweetened beverages for 2 weeks with ad libitum diets (*P < 0.05, **P < 0.01; 2 week vs baseline).

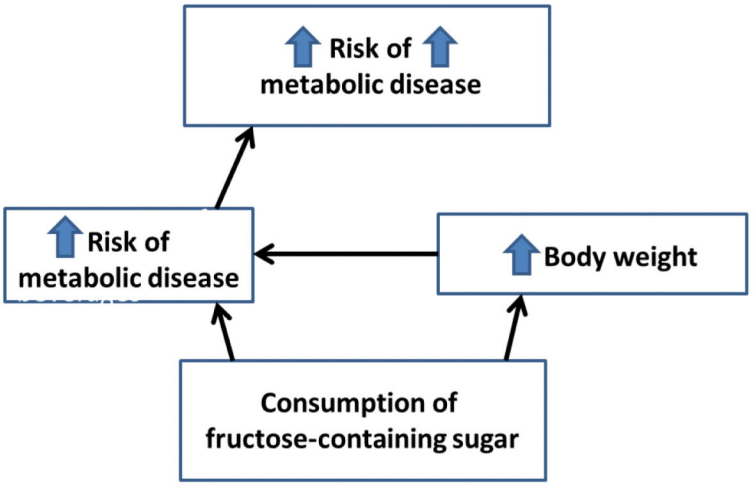

Figure 2. Two mechanisms by which sugar increases metabolic risk

Consumption of sugar increases risk for metabolic disease via the direct effects of fructose on lipid and carbohydrate metabolism. Consumption of sugar may also promote body weight gain. The increased body weight/adiposity further increases risk for metabolic disease. Thus consumption of sugar increases risk for metabolic disease both directly and via effects to promote weight gain.