HHS Public Access

Author manuscript

Crit Rev Clin Lab Sci. Author manuscript; available in PMC 2017 February 01.

Published in final edited form as:

Crit Rev Clin Lab Sci. 2016 February ; 53(1): 52–67. doi:10.3109/10408363.2015.1084990.

Sugar consumption, metabolic disease and obesity: The state of the controversy

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Abstract

The impact of sugar consumption on health continues to be a controversial topic. The objective of this review is to discuss the evidence and lack of evidence that allows the controversy to continue, and why resolution of the controversy is important.

There are plausible mechanisms and research evidence that support the suggestion that consumption of excess sugar promotes the development of cardiovascular disease (CVD) and type 2 diabetes (T2DM) both directly and indirectly. The direct pathway involves the unregulated hepatic uptake and metabolism of fructose, which leads to liver lipid accumulation, dyslipidemia, decreased insulin sensitivity and increased uric acid levels. The epidemiological data suggest that these direct effects of fructose are pertinent to the consumption of the fructose-containing sugars, sucrose and HFCS, which are the predominant added sugars. Consumption of added sugar is associated with development and/or prevalence of fatty liver, dyslipidemia, insulin resistance, hyperuricemia, cardiovascular disease and type 2 diabetes, and many of these associations are independent of body weight gain or total energy intake. There are diet intervention studies in which human subjects exhibited increased circulating lipids and decreased insulin sensitivity when consuming high sugar compared with control diets. Most recently, our group has reported that supplementing the *ad libitum* diets of young adults with beverages containing 0, 10, 17.5 or 25% of daily energy requirement (Ereq) as high fructose corn syrup (HFCS) increased lipid/lipoprotein risk factors for cardiovascular disease (CVD) and uric acid in a dose response manner. However, un-confounded studies conducted in healthy humans under a controlled, energy-balanced diet protocol that allow determination of the effects of sugar with diets that do not allow for body weight gain are lacking. Furthermore, there are recent reports that conclude that there are no adverse effects of consuming beverages containing up to 30% Ereq sucrose or HFCS, and the conclusions from several meta-analyses suggest that fructose has no specific adverse effects relative to any other carbohydrate.

Dr. Stanhope has no conflicts of interest to report.

Declarations of interest:

The studies conducted by Drs. Havel and Stanhope's research group were supported with funding from NIH grants R01 HL-075675, 1R01 HL-091333, 1R01 HL-107256 and a Multi-campus Award from the University of California, Office of the President (UCOP #142691). These projects also received support from Grant Number UL1 RR024146 from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH), and NIH Roadmap for Medical Research. Dr. Stanhope is supported by a Building Interdisciplinary Research Careers in Women's Health award (K12 HD051958) funded by the National Institute of Child Health and Human Development (NICHD), Office of Research on Women's Health (ORWH), Office of Dietary Supplements (ODS), and the National Institute of Aging (NIA).

Consumption of excess sugar may also promote the development the development of CVD and T2DM indirectly by causing increased body weight and fat gain, but this is also a topic of controversy. Mechanistically, it is plausible that fructose consumption causes increased energy intake and reduced energy expenditure due to its failure to stimulate leptin production. Functional magnetic resonance imaging of the brain demonstrates that the brain responds differently to fructose or fructose-containing sugars compared with glucose or aspartame. There are epidemiological studies which show sugar consumption is associated with body weight gain, and there are intervention studies in which consumption of *ad libitum* high sugar diets promoted increased body weight gain compared with consumption of *ad libitum* low sugar diets. However, there are no studies in which energy intake and weight gain were compared in subjects consuming high or low sugar, blinded, *ad libitum* diets formulated to ensure both groups consumed a comparable macronutrient distribution and the same amounts of fiber. There is also little data to determine whether the form in which added sugar is consumed, as beverage or as solid food, affects its potential to promote weight gain.

It will be very challenging to obtain the funding to conduct the clinical diet studies needed to address these evidence gaps, especially at the levels of added sugar that are commonly consumed. Yet, filling these evidence gaps may be necessary for supporting the policy changes that will help to turn the food environment into one that does not promote the development of obesity and metabolic disease.

Keywords

Fructose; sucrose; high fructose corn syrup; diet; food environment; triglyceride; uric acid; metabolic syndrome; cardiovascular disease; type 2 diabetes

Introduction

The impact of added sugar consumption on heath continues to be a controversial topic. In recent counterpoint reviews Bray and Popkin concluded that sugar-sweetened beverages play a role in the epidemics of obesity, metabolic syndrome, and fatty liver disease (1), while Kahn and Sievenpiper concluded that there is no clear or convincing evidence that any dietary or added sugar has a unique or detrimental impact relative to any other source of calories on the development of obesity or diabetes (2). Therefore the objective of this review is to discuss the evidence and lack of evidence that allows the controversy to continue. The evidence is divided into two topics: the direct and the indirect effects of added sugar consumption on the development of metabolic disease. Studies needed to help resolve the controversy will be described, as well as the challenges involved in conducting these studies and reasons they are needed.

The term added sugar consumption in this review refers to sugars not naturally-occurring in foods and these consist mainly of sucrose and high fructose corn syrup (HFCS). It also refers to the sugars added to both beverage and solid foods, even though it cannot be assumed that sugar in solid food and sugar in beverage have equivalent effects. This is discussed later in the review. The term metabolic disease is used to specifically refer to cardiovascular disease (CVD), type 2 diabetes (T2DM), and non-alcoholic fatty liver disease

(NAFLD). Metabolic disease was chosen over metabolic syndrome because it is beyond the scope of this review to discuss in detail the evidence and mechanisms related to sugar and its associations with hypertension and central obesity.

The potential for both direct and indirect effects of added sugar consumption on metabolic disease

There is evidence to suggest that diets high in added sugar promote the development of metabolic disease both directly and indirectly (Figure 1). Directly, the fructose component in sugar causes dysregulation of lipid and carbohydrate metabolism. Indirectly, sugar promotes positive energy balance, thus body weight and fat gain, which also cause dysregulation of lipid and carbohydrate metabolism. Due to the direct and indirect pathway, we have suggested that risk for metabolic disease is exacerbated when added sugar is consumed with diets that allow for body weight and fat gain (3).

The direct effects of added sugar consumption on the development of metabolic disease

The prevalence of metabolic syndrome, cardiovascular disease and type 2 diabetes are strongly associated with the presence of overweight and obesity. This has led to the widespread belief that diet impacts metabolic disease solely through the effects of excess body weight and fat. The sugar-related industries are campaigning vigorously to reinforce this belief and “educate” the public that the only dietary culprit is excess calories (4, 5). However, if sugar consumption has direct effects that increase risk factors for metabolic disease in the absence of positive energy balance, this assertion is not true, and the public and health care providers need to be informed accordingly.

There is considerable epidemiological evidence suggesting intake of added sugars and/or sugar-sweetened beverages are associated with the presence of unfavorable lipid levels (6–8), insulin resistance (9, 10), fatty liver (11, 12), T2DM (13–17), cardiovascular disease (CVD) (18, 19), metabolic syndrome (20–24), visceral adiposity (25, 26), and hyperuricemia (27–29). For the majority of these studies, the reported associations were not attenuated by adjustment for body mass index (BMI) or total energy intake (6–8, 10, 13–23, 27, 28). Recent evidence from National Health and Nutrition Examination Survey III is especially alarming (30). The adjusted (included adjustment for total energy intake) hazard ratios of CVD mortality across quintiles (Q) of percentage of daily calories consumed from added sugar (**Q1**: 0–9.59; **Q2**: 9.6–13.09; **Q3**: 13.1–16.69; **Q4**: 16.7–21.29; **Q5**: ≥21.3% of daily calories) were **Q1**: 1.00 (reference), **Q2**: 1.07, **Q3**: 1.18, **Q4**: 1.38, and **Q5**: 2.03 (n=11,733) (30). These data not only suggest that the higher the intake of added sugar, the greater the risk (30); they also show that the average level of added sugar consumption in the US, 15% of daily calories (30), is associated with an 18% increase in risk for CVD mortality.

Is it really possible that, independently of total energy intake, the average level of sugar consumption in this country is increasing risk for CVD death by 18%? This question cannot be answered based on these data alone, since epidemiological data can only demonstrate associations, not cause and effect. To prove added sugar consumption at the US average intake level, or even at levels exceeding the average intake, is independently promoting or contributing to development of CVD or T2DM, we need plausible mechanisms by which

added sugar is specifically able to do so and direct experimental evidence from clinical diet intervention studies demonstrating that high sugar diets increase risk factors for CVD or T2DM compared with control diets.

Plausible mechanisms by which consumption of sugar may independently contribute to the development of CVD and T2DM

Our group has reported that subjects consuming fructose-sweetened beverages for ten weeks exhibited increased de novo lipogenesis (DNL), dyslipidemia, and circulating uric acid levels and reduced fatty acid oxidation and insulin sensitivity, while subjects consuming glucose-sweetened beverages did not, despite comparable body weight gain (31–33). These results, our more recent results and the results of many colleagues support the plausibility of the mechanisms, described below and illustrated in Figure 2, by which consumption of added, fructose-containing sugars may mediate or contribute to metabolic disease.

Hepatic glucose metabolism is regulated by insulin and hepatic energy needs, and this allows much of ingested glucose, from starch or a glucose-sweetened beverage, arriving via the portal vein to bypass the liver and reach the systemic circulation. In contrast, the initial phosphorylation of dietary fructose is largely catalyzed by fructokinase, which is not regulated by hepatic energy status. This results in unregulated fructose uptake by the liver, with most of the ingested fructose being metabolized in the liver and very little reaching the systemic circulation (34). The fructose overload in the liver results in excess substrate that leads to increased *de novo* lipogenesis (DNL) (33). DNL increases the intra-hepatic lipid supply directly (35, 36), via synthesis of fatty acids, and indirectly, by inhibiting fatty acid oxidation (31). Increased levels of intra-hepatic lipid content promote very low density lipoprotein 1 (VLDL1) production and secretion (37), which leads to increased levels of postprandial TG and dyslipidemia (38).

Increased levels of hepatic lipids may also promote hepatic insulin resistance (39), possibly by increasing levels of diacylglycerol (DAG), which activates novel protein kinase C (nPKC) and leads to serine phosphorylation of the insulin receptor and insulin receptor substrate 1 (IRS-1) and impaired insulin action (40). Due to selective insulin resistance, DNL is even more strongly activated in the insulin resistant liver (41). This has the potential to generate a vicious cycle: i.e. DNL increases liver lipid, which increases hepatic insulin resistance, which further increases DNL (Figure 2--circular arrows). This cycle would be expected to further exacerbate VLDL production and secretion by increasing the intra-hepatic lipid supply (37). Hepatic insulin resistance may also indirectly increase VLDL production and secretion by 1) increasing apolipoprotein B (apoB) availability (42, 43), the protein backbone of VLDL; 2) up-regulating microsomal triglyceride-transfer protein expression (41), which catalyzes the assembly of TG and apoB into VLDL; and 3) increasing the production of apolipoprotein CIII (apoCIII) (44). There is evidence to suggest that apoCIII plays a critical role in promoting the second-step incorporation of lipid into VLDL, which converts VLDL2 (smaller, TG-poor particles) into larger, TG-rich VLDL1 particles (45, 46). The overproduction of VLDL1 has been described as the underlying defect that leads to the dyslipidemia that is characteristic of patients with type 2 diabetes and metabolic syndrome

(38). Furthermore, apoCIII promotes hypertriglyceridemia by inhibiting both lipoprotein lipase activity and the clearance of TG-rich lipoproteins by hepatic receptors (47).

Thus, there is increased exposure of the vasculature to TG, which can lead to intramyocellular lipid accumulation. Intramyocellular lipid concentrations are correlated with reduced whole body insulin sensitivity in humans (48). It is possible, but not definite (49), that this relationship is mediated by the same mechanism described for the development of hepatic insulin resistance; DAG-mediated activation of nPKC resulting in serine phosphorylation of the insulin receptor or IRS-1 (50). It is also possible that other factors such as inflammation and oxidative stress (51), are contributors to, or possibly mediators of, muscle insulin resistance (52).

The fructokinase-catalyzed phosphorylation of fructose to fructose-1-phosphate, which results in conversion of adenosine triphosphate (ATP) to adenosine monophosphate (AMP) and a depletion of inorganic phosphate, leads to uric acid production via the purine degradation pathway (53). Uric acid is a potential mediator of metabolic disease with most recent studies, but not all (54), showing that it is strongly associated and predictive of metabolic syndrome, fatty liver and CVD (55–57). Our recent data (58) demonstrate that uric acid and apoCIII are, at the very least, strong biomarkers, and possibly mediators, of independent pathways by which consumption of HFCS increases risk factors for CVD.

There is also evidence to suggest that fructose may promote inflammatory responses (59) that can further impair hepatic insulin signaling. Studies in mice and non-human primates show that direct exposure of fructose to the intestine increases intestinal translocation of endotoxin (60, 61). Fructose exposure, compared with glucose exposure, has also been shown to cause activation of c-jun NH_2-terminal kinase, increased serine phosphorylation of IRS-1 and reduced insulin-stimulated tyrosine phosphorylation of IRS-1 and IRS-2 in isolated hepatocytes (62).

Thus fructose overload in the liver may mediate a cascade of events by which risk for metabolic disease is increased.

Direct experimental data from diet intervention studies

In addition to plausible mechanisms, we also need direct experimental data from clinical diet intervention studies that show that consumption of added sugar at commonly-consumed levels increases risk factors for metabolic disease compared with a diet containing low amounts of added sugar. There are at least twelve diet intervention studies in humans that document increased risk factors for metabolic disease in human subjects consuming added sugar (specifically sucrose or high fructose corn syrup (HFCS)) (34, 35, 58, 63–73). Yet, despite these studies and the plausible mechanisms to support the epidemiological data, the weight-independent role of sugar consumption at commonly-consumed levels in the epidemics of metabolic disease remains highly controversial. There are 3 major reasons for this:

1. The diet intervention studies that have investigated the effect of added sugar consumption at the levels that are consumed by most Americans have limitations that preclude their being definitive.

2. The diet intervention studies that have investigated the effect of added sugar consumption under energy-balanced conditions to allow determination of the weight-independent effects of sugar consumption have limitations that preclude their being definitive.
3. There is evidence from diet intervention studies that suggests that there are no adverse health effects associated with consumption of added sugar.

1) The diet intervention studies that have investigated the effect of added sugar consumption at the levels that are consumed by most Americans—58% of men and women aged 19–30 years, and 63% of men and women aged 31–50 years consume between 5 and 20% of their daily energy as added sugar (74), and as stated previously, the average intake in US is 15% of energy (30). There are 3 published studies which suggest that consumption of added sugar at 20% Ereq or less can increase risk factors for metabolic disease. In all three of these studies, there were no differences between experimental groups or interventions in body weight gain.

- Men and women consuming 1 liter/d of sucrose-sweetened cola (~20%Ereq) for 6 months along with their usual *ad libitum* diets had increases in liver TG and fasting plasma TG concentrations compared with those who consumed isocaloric amounts of low-fat milk, or iso-volumetric amounts of aspartame-sweetened beverage or water (35). Sucrose consumption also increased visceral fat volume compared with milk consumption, despite comparable body weight gain; and it increased plasma cholesterol concentrations compared with aspartame and water consumption (35).
- A group in Switzerland reported that young, healthy men exhibited increased low-density lipoprotein-cholesterol (LDL-C) and small dense LDL-C levels when they consumed 80 g/d sucrose (~13%Ereq) in beverage along with their usual *ad libitum* diets for 3 weeks compared with when they consumed 80 g/d glucose in beverage (63, 64).
- Young men and women consuming the 10% Ereq as HFCS-sweetened beverages along with *ad libitum* diets had increased levels of nonHDL-C, LDL-C, apoB and postprandial TG compared with their baseline levels (and also compared with the 0% dose group for postprandial TG). The participants consuming 17.5% (and 25%) Ereq as HFCS-sweetened beverages had significant increases in all of these outcomes, plus increased uric acid and postprandial apoCIII, compared with both their baseline levels and the 0% dose group (58).

The obvious limitation of these studies is that the sugar-sweetened beverages were consumed with the subjects' own usual *ad libitum* diets for all or part of the study, thus the total amount of added sugar that the participants consumed is unknown. Furthermore, it cannot be stated with certainty that there were no diet variations between the experimental groups or interventions that may have confounded the study results.

2) Diet intervention studies that investigated the weight-independent effect of sugar consumption—There are very few studies conducted under standardized, energy-balanced conditions upon which to base definitive conclusions regarding the effects of sugar

consumption when results are not confounded by potential positive energy balance and diet variations between the experimental groups or interventions. In the studies described below, subjects did not exhibit weight gain because they consumed sugar (at ≤30% Ereq) as part of an energy-balanced diet that was prepared/provided as per experimental protocol throughout the entire study.

- In a 6-week cross-over study, healthy men who consumed energy-balanced diets containing high (25%Ereq) or low (10% Ereq) amounts of sucrose, exhibited increased levels of total cholesterol and LDL-C during the high sucrose diet (65). However, the authors (study funded by the Dutch Sugar Bureau) attributed the increases of cholesterol and LDL-C to a difference in the saturated fat content of the 2 diets.
- Reiser et al. conducted an energy-balanced 6-week crossover study comparing a 30% Ereq sucrose diet with a iso-caloric starch diet in men and women. Fasting TG, cholesterol, (71) glucose and insulin levels, and insulin responses to an oral sucrose load were increased during the sucrose intervention (72). However, 30% Ereq is above the suggested maximal intake level for consumption of added sugars in the Report of the Dietary Guidelines Advisory Committee on the Dietary Guidelines for Americans 2010 (75). Also the distribution of energy in the provided diet; 10% Ereq at breakfast, 90% Ereq at dinner; was an atypical meal pattern that could have affected metabolic responses.
- Reiser et al. measured the same parameters in participants of a crossover study in which energy-balanced diets containing 5, 18, or 33% Ereq as sucrose were consumed (70). Fasting lipids (69), glucose and insulin, and the glucose and insulin responses to the oral sucrose test (70) were all increased during the 18% and 33% Ereq sucrose diets compared with the 5% Ereq sucrose diet. However, the 24 subjects (36 years, 25 kg/m^2) enrolled in this study, were chosen out of 150 potential participants for their exaggerated responses to an oral sucrose test. Also the distribution of energy in the provided diet; 25% at breakfast, 75% at dinner; was not typical of the usual 3 meal/day pattern. And finally, the fat content of the diets in both of the studies conducted by Reiser et al. (69–72) was 41.5–43% Ereq. There are plausible mechanisms by which diets that are high in both sugar and fat may lead to more adverse outcomes than high sugar/low fat diets or high fat/low sugar diets (76).
- Most recently, Lewis et al. conducted a randomized crossover study in which older (mean = 46 years), obese (31.7 kg/m^2) participants consumed low sucrose (sucrose 5.2%, total sugar 17.1% of daily calories) or high sucrose (sucrose 14.9%, total sugar 30.2% of daily calories—details about non-sucrose sugar are not provided) diets for 6 weeks (66). While there were no differences in peripheral glucose utilization and suppression of endogenous glucose production during a two-step hyperinsulinaemic euglycaemic clamp, fasting and oral glucose tolerance area under the curve (AUC) were higher for both glucose and insulin after the high sucrose diet than after the low.

The results from these 4 studies suggest that added sugar consumption, even at 18% Ereq, increases risk factors for metabolic disease when consumed with a diet that does not allow for weight gain; however these studies have limitations that narrow their generalizability to the typical western diet and/or to healthy adults. These limitations are why Dr. Luc Tappy in his 2012 review stated: "… 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. However, definitive studies are missing" (77). Three years later, these studies are still missing. This is why Kahn and Sievenpiper are still concluding that "there is no clear or convincing evidence that any dietary or added sugar has a unique or detrimental impact relative to any other source of calories on the development of obesity or diabetes. Sugar is purely a highly palatable source of energy; …" (2).

3. Direct experimental evidence that suggests that there are no adverse health effects associated with consumption of added sugar—The missing studies (77) allow the controversy concerning the independent role of added sugar in the epidemics of metabolic disease to continue. However, the controversy is further fueled by direct experimental evidence, such as described below, that suggests that there is no adverse health effects associated with consumption of added sugar.

- Investigators of a recent dose-response study, in which *ad libitum* diets of men and women were supplemented with beverages containing 8, 18 or 30% Ereq from sucrose or HFCS for 10 weeks (78, 79), have reported that consumption of added sugar does not increase fasting cholesterol and LDL-C (78), and that there were no differences between the three levels of sugar in 24-hour circulating TG and uric acid concentrations (79).
- Wang et al. reported that their meta-analysis does not support a uric acid-increasing effect of isocaloric fructose intake in nondiabetic participants (80).
- In a more recent meta-analysis, Wang et al. concluded that fructose in isocaloric exchange for other carbohydrate does not increase postprandial TG (81).

These reports share a commonality in that they were industry-funded or were conducted by investigators who have received consulting fees from industries with a strong financial interest in maintaining high levels of sugar consumption. Does this conflict of interest influence the conclusions? Two recent studies that examined whether industry funding or the disclosure of potential conflicts of interest influenced the results of published systematic reviews conducted in the field of sugar-sweetened beverages and weight gain or obesity suggest it may (82, 83). Both studies concluded that reviews with conflicts of interest were more likely to present a conclusion of no or lesser association between sugar-sweetened beverages and weight gain or obesity than those without them (82, 83).

Even so, the discrepancies between the results from the study in which the *ad libitum* diets of healthy adults were supplemented with beverages containing 8, 18, or 30% Ereq as sucrose or HFCS (78, 79), and the results from our recent study, in which we supplemented the *ad libitum* diets of healthy adults with beverages containing 0, 10, 17.5 or 25% Ereq as HFCS (58), are startling. As a striking example, Yu et al. reports no differences in the 24-h

uric acid AUC “response to the 6 different interventions at baseline or posttesting” (79). In our recent study (58), the participants consuming 25%Ereq HFCS exhibited an increase in the 24-h uric acid AUC that was significant at $P = 0.0000006$ (paired t test) compared to their baseline levels and at $P = 0.00008$ (unpaired t test) compared to the increase of uric acid in participants consuming 10% Ereq HFCS. In the 4-group analysis of covariance the significance of both of these comparisons was $P < 0.0001$.

How is it possible for two similarly-designed studies to yield such discrepant results? Possible reasons that Yu et al. (79) were able to report a null finding include: 1. The vehicle by which the sugar was provided to the participants; 2. The statistical analyses; 3. The monitoring of compliance.

1. **Vehicle:** Yu et al. provided the sugar in low fat milk and each subject was required to consume three 8-oz servings of milk/day (79) (presumably the servings consumed by the 30% group contained ~50 grams of sugar/8 oz). This is more than 3 times the amount of milk consumed by the average American (84), thus this vehicle very likely resulted in a substantial increase of milk consumption in the majority of the participants. There is no report of a control group who consumed milk without the added sugar, therefore this study is unable to differentiate the effects of increased milk consumption from the effects of increased sugar consumption. This is a very important limitation given that milk consumption is associated with decreased risk of metabolic syndrome (85), CVD and diabetes (86, 87).

   The use of milk as a vehicle introduced other limitations including the strong possibility that some of the subjects found the sweetened milk beverages difficult to consume over time due to lactose intolerance. Lactose intolerance may have caused the high dropout rate acknowledged in the paper and may have affected the compliance of those participants who did complete the study.

   Two reasons are provided in the paper as to why low-fat milk was used as a vehicle for this study. The first reason provided is, “To enhance participant compliance over the 10-week study” (79). As stated above it would seem more likely that the milk vehicle would undermine compliance in participants with lactose intolerance. It also seems likely that some or most of the participants would find the sweetened milk unpalatable compared to the usual sugar-sweetened sodas and fruit-flavored drinks; especially the high dose beverages that contained 50 grams of sugar/8 oz milk (most sodas contain 35–40 grams sugar/12 oz). Since sweetened milk is normally consumed with a chocolate flavoring, there is the possibility that some participants of this study may have improved the palatability of the sweetened milk by adding cocoa. This would introduce an additional confounder, as approximately 70 human intervention studies indicate that cocoa and cocoa-containing products beneficially affect endothelial function, blood pressure, and cholesterol levels (88).

   The second reason provided for the use of the low fat milk vehicle is, “Furthermore, previous investigations that used carbonated soft drinks suffered from the confounding problem of significant inversion of sucrose into its components of

fructose and glucose because of the mildly acidic environment of these beverages." (79) This explanation is inadequate simply because water would have served the same purpose. Sucrose does not hydrolyze in water. Therefore, given its advantages over milk with regard to its being non-caloric and not able to confound metabolic outcomes, it is scientifically inexplicable why water was not used as a vehicle for this study.

2. **Statistical analyses:** The statistical model utilized by Yu et al. (79) was a 6 group one-factor (time) ANOVA. With this analysis and 23 subjects per group, the study was powered to detect differences of 1.08 standard deviation or greater with 80% power. This means that only very dramatic differences could be detected between groups. A more suitable analysis could have been utilized; a two-factor ANOVA (type of sugar and dose of sugar), which would take advantage of the 2 by 3 factorial design. With 46 subjects per group (pooled by dose), the investigators could have detected differences of 0.66 standard deviation among the three dosage groups with 80% power. With 69 per group (pooled by sugar), they could detect differences of 0.48 standard deviation between the two sugar types with 80% power. It is not possible to evaluate whether this analysis could have affected the conclusion regarding uric acid because the group data are not reported in the paper (79). The sensitivity of the statistical model would have also been improved by including adjustment for sex. In our study (58), the HFCS-induced increases in 24-h uric acid AUC were higher in men than women ($P = 0.008$, effect of sex).

3. **Monitoring of compliance:** Yu et al. (79) report that compliance to milk consumption was measured with daily dietary logs and state that "tight control" over free living diet consumption was a strength of the study. This is unlikely to be true as inaccurate reporting of food consumption is a well-documented occurrence in dietary research studies (89, 90). Using a biomarker (e.g. riboflavin (58)) in the experimental beverages that can be recovered and measured in urine, and informing the participants of this, provides a more objective index of compliance and also provides motivation for subject compliance.

The reports by Yu et al. (79) and Bravo et al. (78) are on subsets of subjects studied as part of a large randomized control trial (RCT) funded by the Corn Refiners Association for ten million dollars (91). It is the largest RCT (n=352 (92)) yet conducted on the effects of sugar consumption. It has generated several more publications with null findings (93, 94), and will have a marked influence on the conclusions of future meta-analyses. The Principal Investigator of the study, Dr. James Rippe, receives a $41,000/month retainer from the Corn Refiners Association (91). In an interview Dr. Rippe said the corn industry's payments did not influence the conclusions of his research, "We presented academic research based on the highest gold standard" (91). Yet, the inexplicable use of milk as a vehicle for the study, the lack of a control group, the use of a suboptimal statistical model, and the lack of objective compliance monitoring do not represent gold standard research. Instead they give the appearance that the objective of this industry-sponsored study was not to answer an important public health question, but to generate results that will assure the public that the current level of sugar consumption is safe and maintain the state of controversy.

Meta-analyses

Conclusions from meta-analyses, in which results from all qualifying studies are combined, may have more potential to clarify the role of sugar consumption in the development of metabolic disease than any single study. However the conclusions from recent meta-analyses of intervention studies cover the range from yes to equivocal to no regarding the effects of fructose or sugar consumption on risk factors for metabolic disease. Recent meta-analyses conclude that fructose and/or sugar consumption increase total and LDL-C (95); TG, total and LDL-C, and blood pressure (96), and have significant effects on most components of metabolic syndrome (increased systolic blood pressure, fasting glucose and TG, decreased HDL) (97). Another recent meta-analyses concludes that the available evidence is not sufficiently robust to draw conclusions regarding effects of fructose, HFCS, or sucrose consumption on NAFLD (98). And, as stated earlier recent, Wang et al. concluded that there were no relationships between fructose consumption and levels of uric acid (80) or postprandial TG (81).

Since the diet intervention studies conducted by our group have demonstrated a very marked and consistent effect of fructose or sugar consumption to increase uric acid (32, 58) and postprandial TG (33, 58, 73, 99), it is worth examining the meta-analyses that focused on these two outcomes. Specifically, Wang et al. reported that their meta-analysis does not support a uric acid-increasing effect of isocaloric fructose intake in nondiabetic participants (80). In contrast, the 24-h AUC for uric acid increased in participants in our recently-completed study who consumed either 17.5% (+14%; $P = 0.0000002$, paired t test, n=22) or 25% Ereq (+19%; $P = 0.000000007$, paired t test, n=28) of Ereq as fructose-sweetened beverages for 2 weeks (unpublished data). Both groups gained less than 0.1 kg, thus these results are not confounded by weight gain or a hyper-energetic diet. A close examination of some of the studies that met the inclusion criteria for the meta-analyses conducted by Wang et al. (80) may help explain discordance between their conclusion and our results. Of the nine studies that were grouped as ‘isocaloric, no diabetes’, there were four studies in which the effect of fructose consumption to increase circulating uric acid in comparison to the control carbohydrate was zero or less. For two of these studies (100, 101), the comparison or control carbohydrate was sucrose, a fructose-containing sugar that is also likely to increase uric acids levels. Indeed, as already noted, we have recently reported that consumption of beverages containing 17.5 or 25% Ereq as HFCS, the other commonly-consumed fructose-containing added sugar, increased both fasting and 24-h uric acids levels (58). In the other two studies it appears that both the fructose and control diets were energy-restricted (102, 103). Since uric acid production via the purine degradation pathway is increased by hepatic substrate overload leading to generation of excess AMP and a depletion of inorganic phosphate, energy-restricted diets are not likely to lead to increased uric acid levels. Also in the study conducted by Madero et al. the “high” fructose diet consisted of 60 grams “natural” fructose/day from fruit (103). The inclusion of these four studies in a meta-analysis (80) consisting of only 9 total studies grouped as ‘isocaloric, no diabetes’ makes a null conclusion unsurprising.

In a more recent meta-analysis, Wang et al. concluded that fructose in isocaloric exchange for other carbohydrate does not increase postprandial TG (81). Again our recent results

suggest otherwise. The 24-h AUC for TG increased in participants who consumed either 17.5% (+16%; $P = 0.003$, paired t test, n=22) or 25% Ereq (+20%; $P = 0.00003$, paired t test, n=28) as fructose-sweetened beverages for 2 weeks and gained less than 0.1 kg body weight (unpublished data). Figure 2 of the meta-analysis (81) shows of the five studies of "otherwise healthy" subjects, there were two in which the effect of fructose consumption to increase circulating postprandial TG in comparison to the control carbohydrate was only slightly above zero. Again, for one of these studies (101) the control carbohydrate was sucrose, which would be expected to increase postprandial TG and obscure the effect of fructose. In the other study (104), the postprandial testing period occurred from pre-breakfast to 4-h post-breakfast, which is of insufficient duration to detect an increase in postprandial TG. In our sustained consumption studies with 24-h blood collection protocols (33, 58, 73, 99), we did not observe the effects of fructose/fructose-containing sugars compared with glucose or starch to increase postprandial TG until after lunch, with the most marked differences between the carbohydrates occurring 4–5 hours after dinner. Given the limited number of fructose intervention studies that have reported measures of postprandial TG in healthy humans, the inclusion of these two studies had a marked effect on the null conclusion reported by Wang et al. (81).

Summary - The direct effects of added sugar consumption on the development of metabolic disease

While the epidemiological evidence, the plausibility of the mechanisms, and the results from diet intervention studies provide strong support for a direct causal/contributory role of sugar consumption in the epidemics of metabolic disease, as stated in 2012 by Dr. Tappy (77), definitive studies are missing. These missing studies preclude a resolution to the controversy, while the null findings from industry-funded studies and industry-supported investigators escalate it.

Needed studies

What studies would help resolve the controversy? We need clinical trials, lasting at least 4 weeks (longer would be better) in which healthy subjects consume added sugar as part of energy-balanced diets that are prepared/provided as per experimental protocol throughout the entire study. The optimal study would include a range of added sugar consumption levels including 5% (approximately the daily calorie level recommended by the American Heart Association (105)), 10% (the new daily calorie limit proposed in the Scientific Report of the 2015 Dietary Guideline Advisory Committee (106)), 15% (the average daily calorie level consumed in US (30)), and 25% Ereq (the current upper level recommendation in the 2010 report of the Dietary Guideline Advisory Committee (75)). The diets need to be formulated such that the level of fat is consistent with dietary recommendations and there are no macronutrient, fiber, saturated fat, trans fat differences between groups that can confound results. Compliance needs to be monitored objectively (biomarkers), and also perhaps by utilizing mobile phone technology (107–109).

When will such studies be conducted? This author can only offer the perspective of a US researcher who has pursued funding from NIH to answer questions related to the role of added sugar/diet in the development of metabolic disease utilizing standardized dietary

protocols. The hurdles that make obtaining funding for such studies extremely challenging include the expense of these studies, plus the fact that clinical diet intervention studies are often perceived by the NIH reviewers as descriptive, lacking innovation, and even lacking significance.

Expense: It is difficult to design a clinical diet intervention study that is adequately powered and of sufficient duration, and includes a standardized dietary protocol (meaning providing standardized meals, not standardized diet prescriptions), with costs within the usual NIH budget limit ($500,000/year for five years). It has become even more difficult in recent years because NIH is no longer subsidizing essential research expenses, such as facility and nursing costs, through its Clinical and Translational Science Center awards.

Descriptive: Yet, even when a researcher finds a way to budget a diet intervention study within the NIH funding limits, reviewers often reject the proposal because it is descriptive. This means the proposal only seeks to answer a public health question concerning the effect of diet, but does not include the mechanistic studies needed to illuminate the metabolic pathways affected by the diet. In human subjects, these mechanistic studies usually require the use of stable isotopes and mass spectrophotometer analyses. These procedures can easily double or triple the cost of the proposed trial to well beyond the NIH budget limits.

Lack of innovation: An important component by which NIH applications are judged and scored is innovation, eg. does the proposal seek to investigate a new therapeutic target; will it utilize a novel procedure? Due to the ethical constraints regarding what procedure can be performed, studies involving human subject are far less likely to contain innovative aspects than those utilizing animal models. Innovation is likely to be even more limited when the investigator is simply proposing to answer the question: Will Diet A increase risk factors for metabolic disease in human subjects more than Diet B? With only 10–18% of the submitted NIH proposals receiving fundable scores, a proposal that receives a poor innovation score has little or no chance for funding, even if it receives very high scores on all other components.

Lack of significance: An equally important scoring component of NIH proposals is the reviewers' assessment of the significance of the research with regard to human health. With the prevalence of CVD, T2DM, obesity, and metabolic syndrome causing such public health burdens, one would think that a proposal seeking to answer a public health question that could attenuate these epidemics would score well on the assessment of significance. Our group has had many opportunities to find this is often not true with regard to our proposed investigations of sugar consumption. Ten to fifteen years ago it was often not true because some reviewers were highly skeptical of the hypothesis that dietary sugar could really be a mediator or contributor to our serious public health issues. At that time it could be suggested that this hypothesis had already been disproven, given that John Yudkin had proposed/investigated the same hypothesis in the 1960s through 1980s (110–112). More recently, though, many reviewers have assessed the significance of our proposals as low for the opposite reason. They have stated that everyone, except those associated with the sugar industries, knows that consumption of

sugar is bad for health. This change in attitude is validation of the research of John Yudkin (too late to affect him personally) and a testament to the recent investigators conducting research on the adverse metabolic effects of sugar consumption. However, it undermines our ability to demonstrate that added sugar at commonly-consumed levels has a direct, weight independent effect on the development of metabolic disease; and to determine at what levels of consumption this effect occurs.

This is unfortunate because it leaves a void in our scientific knowledge, but it is even more unfortunate from a public health perspective. All of us, whether normal weight or overweight, need to be armed with the knowledge that added sugar at commonly-consumed levels has direct, weight-independent effects on the development of metabolic disease as we continue to face numerous opportunities every day to indulge in palatable, high sugar treats. Parents need this information as they supervise the diets of their children (including normal weight children) and try to instill healthy life-long habits. The belief that our public health crisis is mediated solely through the prevalence of overweight and obesity has clearly not attenuated the crisis. Perhaps the knowledge and understanding that sugar is not simply a source of extra calories (that can be balanced with a little extra exercise later—even though later often never happens), rather it is also a direct contributor to the development of metabolic disease, will be more effective at slowing our epidemics of metabolic disease.

The indirect effects of added sugar consumption on the development of metabolic disease

The prevalence of metabolic syndrome, cardiovascular disease and type 2 diabetes are strongly associated with the presence of overweight and obesity, and there is little argument that this relationship is one of cause (overweight/obesity) and effect (metabolic disease). Therefore, if added sugar consumption promotes body fat gain relative to other macronutrients, this is a second and indirect pathway by which high sugar diets may contribute to the development of metabolic disease. However, the question of whether consumption of added sugar promotes body weight and fat gain is also controversial as indicated by the titles of recent reviews: “Resolved: there is sufficient scientific evidence that decreasing sugar-sweetened beverage consumption will reduce the prevalence of obesity and obesity-related diseases” (113), and “Will reducing sugar-sweetened beverage consumption reduce obesity? Evidence supporting conjecture is strong, but evidence when testing effect is weak” (114).

Again, conflict of interest fuels the controversy (82, 83). However, some of the conflicting conclusion can also be explained by dividing the question; does consumption of added sugar promotes body weight and fat gain; into two separate questions, and realizing that investigators are sometimes not addressing the same question (115–119). The two questions are:

1. Does consumption of a high sugar diet promote more weight gain than consumption of a low sugar diet that is consumed in iso-caloric quantities?
2. Does consumption of an *ad libitum* diet that is high in added sugar promote increased energy intake, and thus increased body weight gain, compared with consumption of an *ad libitum* diet that is low in sugar?

Question 1 is specifically asking whether sugar (or fructose) has inherent properties that make it more able to promote weight gain than an isocaloric amount of any other food. Investigators who conclude that sugars have no special role in body weight control other than as one of many sources of energy (118) are focusing on Question 1. When these investigators examine a free-living population for evidence of a relationship between sugar consumption and weight gain, total energy intake is a confounder for which they adjust in their statistical model (115).

There is a mechanism by which a high sugar diet could promote more weight gain than consumption of a low sugar diet that is consumed in iso-caloric quantities. Our group has hypothesized that fructose consumption could promote weight gain because it does not stimulate insulin secretion or leptin production (120). Leptin production by adipocytes is regulated by insulin-mediated glucose metabolism (121). Ingestion of fructose does not result in meal-related increases of plasma glucose or insulin concentrations, therefore both short (34, 122) and long-term (123) studies demonstrate that meals accompanied with fructose-sweetened beverages result in reduced circulating leptin concentrations compared with glucose-sweetened beverages. Leptin acts, along with insulin, in the hypothalamus to regulate food intake and energy metabolism via neuropeptide systems including neuropeptide-Y and melanocortins. Accordingly, leptin-deficient patients exhibit increased hunger and impaired satiety (124). Additionally, functional magnetic resonance imaging (MRI) studies have shown that the areas of the brain associated with pleasure and reward are markedly activated when leptin-deficient patients are shown pictures of food, but this activation decreases to the level of normal subjects following 7 days of leptin administration (125). Leptin-responsive neurons also project to pathways which that activates signals to the periphery involved in promoting energy expenditure and fat oxidation. Thus, leptin is a key regulator of energy homeostasis (125). Therefore, it is plausible that, compared to an isocaloric high starch or glucose diet, a high fructose diet could reduce leptin production and circulating leptin concentrations, leading to decreased energy expenditure and increased body weight gain.

There are a several epidemiological studies that report a significant positive relationship between sugar-sweetened beverage consumption and BMI, even with adjustment for total energy intake (126–130). This does suggest that it is possible that consumption of fructose could have effects on body weight that are independent of total energy intake. However, there are no data from diet intervention studies to support this, including the data our own study. Food intake appeared to be similar and weight gain was comparable between the subjects consuming 25% Ereq as fructose- or glucose-sweetened beverages with *ad libitum* diets for 8 weeks (33). However, in these same subjects, we also observed a fructose-induced decrease in 24-h leptin levels (123), and a decrease in fasting energy expenditure that was not observed with glucose consumption (31). Why then did the subjects consuming fructose fail to show increased body weight gain compared with the subjects consuming glucose? The first and most obvious answer is duration of intervention. The reduction of energy expenditure exhibited by the subjects consuming fructose equated to a gain of 1.6 kg if maintained for one year (31). While this is a clinically significant outcome that could contribute to obesity over time, it would likely not be detectable in an intervention lasting less than one year. Furthermore, the body weight results from our study, and the other

studies investigating the effects of fructose on energy intake and weight gain, could be confounded by fructose malabsorption. Consumption of fructose as a monosaccharide can overwhelm the absorptive capacity of the small intestine leading to fructose malabsorption and gastrointestinal distress (131), which can affect energy availability and intake. However, fructose malabsorption is low in normal subjects consuming sucrose or HFCS, because fructose when ingested along with glucose is much more completely absorbed than when ingested as pure fructose (132). Therefore studies comparing the isocaloric consumption of high and low sucrose or HFCS diets on body weight gain are not likely to be confounded by fructose malabsorption. Yet, even so, the costs of such studies, with the duration and power to ensure a clinically relevant answer, is likely to prevent its ever being conducted. Thus it is probable that we will never obtain a definitive answer to the question as to whether a high sugar diet promotes more weight gain than consumption of a low sugar diet that is consumed in iso-caloric quantities.

However, the typical western diet is consumed *ad libitum*, and the fact that the majority of adults are overweight (in the US, 56% of the women and 67% of men aged 20–39 have BMI ≥25 kg/m^2 (133)) provides evidence that this *ad libitum* diet is being consumed in amounts beyond energy requirement. Therefore Question 2 concerning whether sugar (or fructose) has inherent properties that make it more likely to promote overeating than other macronutrients is far more relevant to the obesity epidemic. For researchers investigating this possibility, total energy intake is not a confounder, but instead an intermediary variable in the relationship between sugar consumption and body weight gain (83).

The answer to this question, whether sugar (or fructose) has inherent properties that make it more likely to promote overeating than other macronutrients, could be as simple as people tend to over-eat sugar because they like the sweet taste. Yet, recent studies on the central effects of sugars in the brain (134–142), made possible by functional magnetic resonance imaging (fMRI) technology, suggest the answer could be more complicated. Luo et al. reported that consumption of a fructose-sweetened beverage resulted in greater brain reactivity to food cues than consumption of a glucose-sweetened beverage in young healthy adults (143). Corroborating these results, fructose versus glucose led to greater hunger and desire for food and a greater willingness to give up long-term monetary rewards to obtain immediate high-calorie foods (143). Stice et al. reported that a high sugar milk shake was more effective at recruiting reward regions of the brain than an equi-caloric high-fat milkshake (142). A high sucrose beverage induced greater activation in the nucleus tractus solitarius than a non-nutritive beverage matched for sweetness in lean and obese women (138). The authors of this study also noted pattern differences between the lean and obese women that may suggest altered interaction between homeostatic and reward networks in obese individuals (138). Gearhardt et al. reported that the neural activation patterns associated with addictive-like eating behavior are similar to those associated with substance dependence (136). In line with this, reward activation to consumption of an ice cream-based chocolate milkshake was reduced in frequent compared with non-frequent consumers of ice cream, which the authors suggest may parallel the tolerance observed in drug addiction (134). Our group reported that women consuming sucrose-sweetened beverage had inhibited responses to stress, which included greater activation in the hippocampus and lowered cortisol levels, compared with women consuming aspartame-sweetened beverages (144).

These results offer a potential mechanistic explanation for sugar often being perceived as a stress-relieving or comfort food.

While these fMRI studies hold great promise for illuminating the brain responses to the various macronutrients and eating patterns, sustained diet intervention studies will still be necessary to correlate patterns of activation in the various regions of the brain to long term eating behavior. They are also necessary to simply answer the question whether people tend to consume more energy when consuming sugar. The following studies suggest that they do:

- Tordoff et al (145) reported that men and women (BMI just over 25) consuming HFCS-sweetened beverages (~20%E) consumed more energy and gained weight compared with baseline consumption. When the same subjects consumed aspartame-sweetened drinks they consumed less energy and did not gain weight.
- Raben et al (146) reported that body weight (+1.6 kg) and fat mass (+1.3 kg) increased in overweight men and women consuming sucrose-sweetened beverages/snacks (~28%E) for 10 weeks and decreased (−1.0 and −0.3 kg, respectively) in men and women consuming comparable beverages/snacks containing non-caloric sweeteners; the between-group differences were highly significant.
- Reid et al (147) reported that, compared with baseline, normal-weight women consuming sucrose-sweetened beverages (~21%Ereq) for 4 weeks increased energy intake and women consuming aspartame-sweetened beverages decreased energy intake. The body weight gain was significantly greater in the sucrose group.
- Our groups has reported that young men and women consuming the 0 (aspartame), 10,17.5 or 25% Ereq as HFCS-sweetened beverages along with ad libitum diets for 2 weeks exhibited a dose response increase in body weight, with the high dose group gaining the most weight (+0.8 kg, $P < 0.01$ compared with baseline body weight) (58).

These studies however fail to provide definitive evidence to answer the question due to the limitation that the experimental sweetened beverages and snacks were consumed with the subjects' usual *ad libitum* diets. Therefore it cannot be known with any degree of certainty that there were not dietary variations between the experimental groups or interventions that could have confounded the results.

There appears to be only one investigation in which *ad libitum* consumption of a high sugar diet was investigated under controlled dietary conditions. Raben et al. have compared the *ad libitum* consumption of a high sugar diet (23%Ereq sucrose from both solid food and beverage) with a high complex carbohydrate diet (2%Ereq sucrose), while providing all of the food consumed during the study and maintaining similar proportions of protein and fat during both interventions (148). In this 14-day crossover study, subjects consumed more energy and gained more weight during consumption of the sucrose diet (+0.2 kg) than the complex carbohydrate diet (−0.7 kg) (148). However, as the Principal Investigator of this study points out (149), these results could possibly be explained by the complex carbohydrate diet containing more fiber than the sucrose diet. Another possible confounder was the lack of blinding. While the investigators attempted to match the palatability of the

diets as closely as possible, they did not supplement the high complex carbohydrate diet with non-caloric sweeteners. Post-intervention questionnaires indicated that subjects were aware that they were consuming a high sugar or low sugar diet (148). A study by Ng et al. suggests that this is an important issue (139). Using fMRI, they demonstrated that areas of the brain associated with reward valuation were more activated when subjects consumed a milk shake labeled “regular” compared with an identical milk shake labeled “low-fat” (139). Similarly, Crum et al. reported that ghrelin levels of participants decreased following consumption of a 380 calorie milkshake that was labelled “indulgent, 620 calories”, but ghrelin did not decrease following consumption of the identical milkshake when it was labelled “sensible, 140-calories” (150). These findings suggest that preconceptions regarding diet composition, even when they are inaccurate, can affect the brain and ghrelin responses to the diet, and therefore, possibly energy intake as well.

Thus we lack the direct experimental data to definitively answer Question 2: Does consumption of an *ad libitum* high sugar diet promote increased energy intake, and thus increased body weight gain, compared with consumption of an *ad libitum* low sugar diet? Clinical trials in which blinded, *ad libitum* diets, containing high and low amounts of sugar, that have been carefully formulated to ensure that there will be no confounding dietary differences (e.g. dietary fiber, saturated fat) between the study groups are needed. Studies are also needed to compare the effects of sugar consumed in beverages versus solid food. While beverage is the leading single food contributor to sugar consumption, over 60% (151) of added sugar is consumed from solid food sources. This proportion may increase (152) with recent public health initiatives (tax, size limits and warning labels) focusing specifically on decreasing consumption of sugar-sweetened beverage. Yet, nearly all the sustained-consumption sugar intervention studies, with the notable exception being the aforementioned studies by Reiser et al, (69–72) have provided the experimental sugar as either solely or mainly as sugar-sweetened beverage. Sugar-sweetened beverage have been the main public health focus because many acute studies, consisting of liquid or solid food preloads followed by *ad libitum* consumption of one or two meals, suggest that in comparison to solid food forms, beverages hold weak satiety properties that lead to failure to adjust intake at subsequent eating occasions for energy supplied by the beverages.(153–155) Thus, liquid sugar may promote greater energy intake and weight gain than consuming sugar in solid food. Currently, though, there is only one published, sustained consumption diet intervention study that has compared the effects of consuming the 2 forms of added sugar (sugar-sweetened beverage or in solid food) with usual *ad libitum* diets on body weight and food intake. In this 4-week crossover study, participants reported greater energy intake while consuming 25% Ereq as sugar-sweetened beverage than as jelly beans (156). Body weight gain, however, was not significantly different between the sugar-sweetened beverage (+0.5 kg) and jelly bean (+0.2 kg) diets. Longer studies with standardized diets, and which provide the added sugar in solid food in a greater variety of more palatable and typically-consumed foods (e.g. sugar-coated cereal, cookies, cake, candy), will provide much-needed data to help address this important question.

It is also possible that sugar in liquid and sugar in solid food may have differential effects that are independent of energy intake and weight gain. Because sugar in liquid is digested and delivered to the liver more quickly than sugar in solid food, it may promote a greater

substrate overload (more substrate in a shorter time frame) in the liver. This could lead to greater increases in DNL, hepatic lipid accumulation and postprandial TG in participant consuming sugar-sweetened beverage compared to those consuming sugar in solid food. Evidence from sustained consumption studies to support this is lacking. Metabolic results (i.e. DNL, liver lipid accumulation, postprandial TG levels), which could serve as indicators of increased hepatic overload, have not been reported from the sugar-sweetened beverage versus jelly bean study (156), and there appears to be no other long-term diet intervention studies that have concurrently investigated the effects of consuming added sugar as sugar-sweetened beverage and from solid food.

Obtaining the NIH funding to answer Question 2 or questions about the differences between liquid and solid sugar faces all the same hurdles already outlined; reviewers are likely to consider them expensive, descriptive, lacking innovation, and lacking significance. However, our laboratory has received NIH funding to conduct an 8-week RCT to test the hypothesis that consumption of an *ad libitum* diet along with 25% Ereq as HFCS-sweetened beverage will increase energy intake and body weight gain compared with consumption of the same *ad libitum* diet along with aspartame-sweetened beverages. The ad libitum diet will be provided throughout the intervention at 125% Ereq and will be carefully formulated to ensure that all participants will consume a comparable macronutrient distribution. Stable isotopes will be used to assess DNL and VLDL kinetics under meal-fed conditions.

Within this study, we will also test the hypothesis that sugar consumption in the absence of positive energy balance and weight gain has adverse effects on risk factors for metabolic disease by also studying participants who will consume the aspartame-sweetened beverages or the 25% Ereq HFCS-sweetened beverages with energy-balanced meals. This study design will allow us to compare the contribution of sugar with the contribution of energy level and body weight gain to the changes in risk factors, and to compare the effects of sugar versus sugar + weight gain on DNL and VLDL kinetic in non-steady state conditions. However, the answers generated by this study will not be applicable to the commonly-consumed levels of sugar (74) or to sugar consumed in solid food. Our efforts to obtain the funding to study groups consuming sugar in beverage or sugar in solid food at levels ranging from 5 to 20% Ereq under a standardized dietary protocol have, so far, been unsuccessful.

Thus the controversies regarding the role of sugar consumption at commonly-consumed levels in the obesity epidemic and in the epidemics of metabolic disease are likely to continue. Is this so important? The primary objectives of conducting this research are to improve the diet of the general population and attenuate the epidemics of metabolic disease. Maybe this can and will be achieved despite the controversy. However, Petrunoff et al. conducted focus groups to investigate parents' beliefs regarding providing their pre-school children with high sugar and/or fat snacks that are low in nutrients. They reported that parents mainly believed that these foods can be provided frequently as long as their children are eating a healthy balance of foods (157). On an online survey completed by 3361 US adults 18 years and older, less than 40% of participants identified added sugars as a primary concern when choosing beverages (158). A Gallup poll conducted in July 2014 reported that the number of American who avoid consuming soda has increased by 12% since 2004, however, the number that avoid consuming sugar has only increased from 51 to 52% in the

same time period (152). Interestingly, the number that reported consuming sugar has increased from 21 to 27% (152), suggesting that some of the people who now actively avoid soda have decided that sugar in solid food is acceptable. Caregivers of African-American children demonstrated a good understanding of the relationship between an unhealthy diet and obesity and metabolic disease. Yet they also expressed concern that their ability to provide a healthy diet was undermined by child preference for foods higher in fat and sugar, lower pricing of less healthy foods, limited access to healthier food retailers and targeted advertisements (159).

The concerns of these caregivers (159) are validated in an interesting perspective offered by Chandon et al., who described in detail how food marketing has made us fat by providing increased access to ‘continuously cheaper, bigger, and tastier calorie-dense food’ (160). They then contend that researchers have over-estimated the impact that deliberate decision-making has on food intake and have underestimated the impact that peripheral factors and mindless habitual behavior have on food intake (160). In other words they suggest that nutrition and health education has little chance against our palatable and inescapable food environment.

This suggests then that slowing the epidemics of obesity and metabolic disease can only occur through changes in the food environment. One such change is to make ‘cheaper, bigger, and tastier calorie-dense food’ less cheap through soda and junk food taxes. This tactic may prove effective. Mexico implemented a tax on sugar-sweetened beverages (seven cents/liter) and junk food in January 2014. The purpose is to target the epidemics of obesity and T2DM in Mexico, which are among the highest on the planet, by reducing sugar consumption and generating revenue that will be targeted for health programs and providing drinking water in schools. While the early data from Mexico’s National Institute of Public Health suggest in the first three months of 2014, purchases of sugary drinks dropped by 10% compared with the same period in 2013 (161), it will take longer to determine whether the decrease will continue and whether it and the programs funded by the tax will translate into positive health outcomes. In November 2014, a bill to tax sugar-sweetened beverages at one cent/oz was approved by voters by a 3 to 1 margin in Berkeley California, despite an opposition campaign funded by industry for $2.1 million (162).

This represents the highest soda tax to be approved by US voters. Whether voters in other states and cities will follow the lead of the progressive Berkeley voters remains to be seen. A two cents/oz tax did not receive the requisite 2/3 majority from San Francisco voters in the same election; however it did receive 55% of the vote. The American Beverage Association spent over $9 million campaigning against this measure, outspending the pro-tax campaign by 30 to 1 (162).

This is not the first time that efforts to change the food environment were defeated by the deep pockets of the industry. In 2012, the American Beverage Association spent $2.5 million to defeat a soda tax in Richmond California, outspending the pro-tax campaign by 50 to 1 (163). In 2010, the American Beverage Association’s lobby efforts toward getting the Philadelphia City Council to reject the mayor’s proposal to tax sugary drinks at two cents/oz included a donation of $10 million to the Children’s Hospital of Philadelphia to fund

research into and prevention of childhood obesity (164). Maryland repealed its snack tax in 1997 when Frito-Lay threatened not to build a planned local plant (165). Louisiana halved and then repealed their soft drink tax in 1997 in response to Coca-Cola's contracting to build a bottling facility in the state (165).

And this is why we do need to conduct the well-controlled clinical trials to generate the direct experimental data to resolve the controversies regarding the role of sugar consumption in the epidemics of metabolic disease and obesity. Health advocates proposing to improve the food environment will never have money to compete with the deep pockets of industry. They need to be armed with the direct experimental data that definitely demonstrates a causal role of added sugar consumption in the health epidemics.

The current gaps in knowledge allow the industry to arm their lobbyist with statements like:

- When the full body of science is evaluated during a major review of scientific literature, experts continue to conclude that sugars intake is not a causative factor in any disease, including obesity (166).
- The majority of nutrition experts agree that high fructose corn syrup is safe (167).
- When it comes to risk for heart disease, there is nothing unique about the calories from added sugars, or sugar-sweetened beverages for that matter (168).

This allows lawmakers and voters to make immediate financial concerns a priority over long-term health concerns. When we have obtained the definitive evidence that shows that sugar at commonly-consumed levels is an independent and modifiable risk factors for metabolic disease; when we have the definitive evidence that shows that consumption of sugar promotes weight and body fat gain; possibly concerns about the health of our children and the health care costs burden on society will take precedence.

Conclusion

There are epidemiological data, plausible mechanisms and clinical data from diet intervention studies that provide strong support for a direct causal/contributory role of sugar in the epidemics of metabolic disease, and for an indirect causal/contributory role mediated by sugar consumption promoting body weight and fat gain. Yet these are still controversial topics. Clinical diet intervention studies in healthy men and women that definitively demonstrate that sugar consumption at commonly-consumed levels can increase risk factors for metabolic disease in the absence of body weight and fat gain are missing. Also missing are clinical trials in which the effects of an *ad libitum* high versus low sugar diet on energy intake and body weight gain are compared using a blinded and carefully-formulated dietary protocol that ensures all other dietary variables are comparable between the study groups. The controversy is further fueled by industry-funded studies that report that there are no adverse effects of consuming beverages containing up to 30% Ereq sucrose or HFCS and by the null conclusions of recent meta-analyses. Obtaining the funding to conduct the expensive clinical studies needed to fill the evidence gaps and resolve the controversy will be very challenging. However, obtaining this definitive evidence may be necessary in order to make progress in implementing the policies that will change the food environment into one that

does not promote the development of obesity and metabolic disease; especially for implementing policies that may threaten the profits of the sugar and beverage industries.

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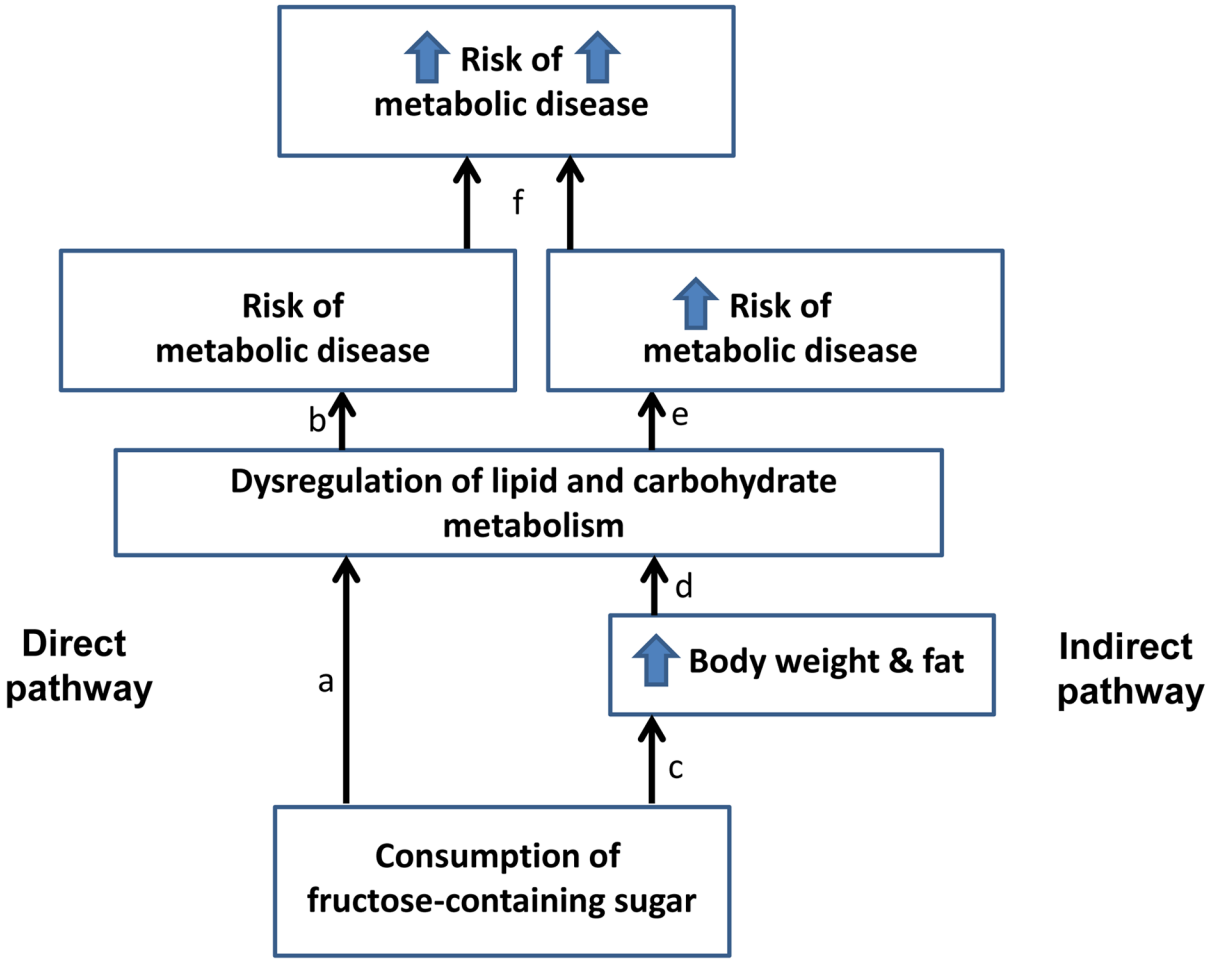

Figure 1. Two pathways by which sugar increases metabolic risk

Direct pathway: Consumption of sugar leads to dysregulation of lipid and carbohydrate metabolism (**a**) which increases risk for metabolic disease (**b**). Indirect pathway: Consumption of sugar promotes body weight and fat gain (**c**) which leads to dysregulation of lipid and carbohydrate metabolism (**d**) which increases in risk for metabolic disease (**e**). Thus, it is possible that risk for metabolic disease is exacerbated when added sugar is consumed with diets that allow for body weight and fat gain (**f**).

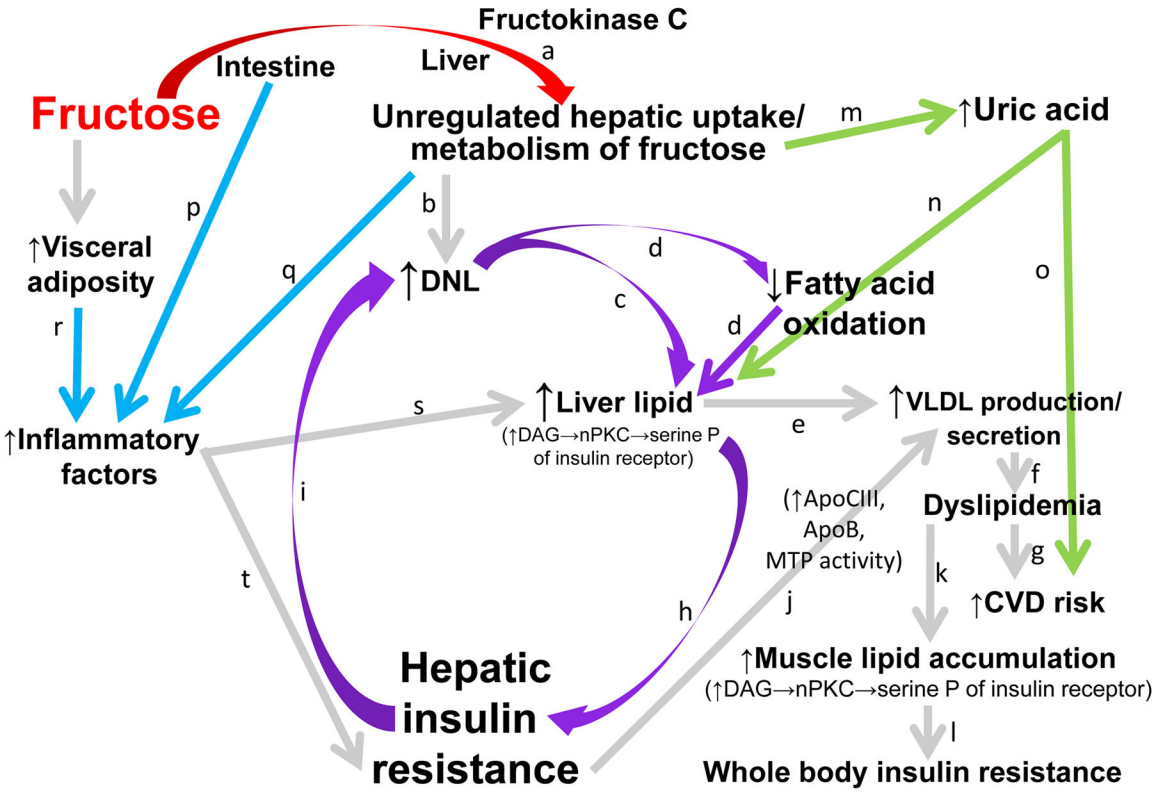

Figure 2. Potential mechanisms by which consumption of fructose affects lipid metabolism and hepatic insulin sensitivity

The initial phosphorylation of dietary fructose in the liver is largely catalyzed by fructokinase C (**a**), which is not regulated by hepatic energy status. This results in unregulated fructose uptake and metabolism by the liver. The excess substrate leads to increased de novo lipogenesis (DNL)(**b**). DNL increases the intra-hepatic lipid supply directly, via synthesis of fatty acids (**c**), and indirectly, by inhibiting fatty acid oxidation (**d**). Increased levels of intra-hepatic lipid content promote very low density lipoprotein (VLDL) production and secretion (**e**). This leads to increased levels of circulating TG and low density lipoprotein cholesterol (dyslipidemia (**f**)), risk factors for cardiovascular disease (CVD) (**g**). Increased levels of hepatic lipids may also promote hepatic insulin resistance by increasing levels of diacylglycerol, which may activate novel protein kinase C (nPKC) and lead to serine phosphorylation (serine P) of the insulin receptor and insulin receptor substrate 1 (IRS-1) and impaired insulin action (**h**). Due to selective insulin resistance, DNL is even more strongly activated in the insulin resistant liver DNL (**i**), which has the potential to generate a vicious cycle (**circular arrows**). This cycle would be expected to further exacerbate VLDL production and secretion via increased intra-hepatic lipid supply. Hepatic insulin resistance also exacerbates VLDL production/secretion (**j**) by increasing apolipoprotein (apo)B availability and apoCIII synthesis, and by up-regulating microsomal triglyceride-transfer protein expression (MTP). This exacerbates and sustains exposure to circulating TG, leading to muscle lipid accumulation (**k**), impaired insulin signaling, and whole body insulin resistance (**l**). The fructokinase-catalyzed phosphorylation of fructose to fructose-1-phosphate, which results in conversion of adenosine triphosphate (ATP) to

adenosine monophosphate (AMP) and a depletion of inorganic phosphate, leads to uric acid production via the purine degradation pathway (**m**). High levels of uric acid are associated and may contribute to increased risk for development of fatty liver (**n**), CVD (**o**), and metabolic syndrome. Fructose exposure in the intestine (**p**) and liver (**q**), and fructose-induced increases of visceral adipose (**r**) may promote inflammatory responses that further promote liver lipid accumulation (**s**) and/or impair hepatic insulin signaling (**t**).