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Research Update

Sickeningly Sweet: Does Sugar Cause Type 2 Diabetes? Yes

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The metabolic syndrome, of which type 2 diabetes mellitus is a hallmark disease, affects more than 25% of the adult population in the United States (U.S.) (1). Specifically, type 2 diabetes currently exhibits a U.S. prevalence of 9.3%, while prediabetes is currently estimated to be present in up to 40% of adults. It is assumed that the epidemic rise in obesity is the cause of this upswing in the rate of type 2 diabetes. However, there are 4 separate reasons to doubt this thesis.

1) Although obesity prevalence and diabetes prevalence correlate, they are not concordant; there are countries in which populations are obese without having diabetes (such as Iceland, Mongolia and Micronesia), and there are countries in which populations have diabetes without being obese (such as India, Pakistan and China, which manifest a 12% diabetes rate). This lack of concordance is further reinforced by looking at years of life lost because of diabetes as opposed to obesity (3).
2) People forget that 20% of morbidly obese individuals are metabolically healthy and have normal life spans (4–6), while up to 40% of normal-weight adults harbour metabolic perturbations similar to those that occur with obesity, including hypertension, dyslipidemia, nonalcoholic fatty liver disease and cardiovascular disease (7,8).
3) The trend of diabetes in the U.S. between 1988 and 2012 has demonstrated a 25% increase in prevalence in both the obese and the normal-weight populations (9)
4) The aging process does not explain the prevalence of type 2 diabetes; children as young as 1 through 10 years of age now manifest these same biochemical processes (10,11). Thus, although obesity may be a marker for the pathology, it is clearly not the cause because normal-weight people have type 2 diabetes too. So what is the cause, a cause that everyone is exposed to? And how is it that children experience this degree of metabolic dysfunction?

The Concept of Toxicity

The food industry argues that obesity obeys the first law of thermodynamics, that obesity is about energy balance—that obesity is a manifestation of 2 behaviours: increased intake (gluttony) and decreased expenditure (sloth)—and that blame is to be ascribed to the individual, because "a calorie is a calorie." But obesity is not the issue. Type 2 diabetes is the issue, and a protein calorie is different from a fat calorie, which is different from a carbohydrate calorie; a calorie is *not* a calorie (12). Where those calories come from determine where in the body they go.

The concept that sugar might be the inciting factor in type 2 diabetes is not new; in fact, John Yudkin of the United Kingdom posited this idea more than 40 years ago (13). However, many people, including scientists, have negative visceral reactions to the concept that a food can be toxic. The *Merriam-Webster Dictionary* defines *toxic* as "the degree to which a substance can damage an organism." Note that there is no distinction between acute and chronic toxicity. Sugar is made of 2 molecules, glucose and fructose. Glucose is the energy of life. Every cell on the planet can burn glucose for energy. Glucose is so important that if one does not consume it, the liver makes it (gluconeogenesis). Conversely, dietary fructose, while an energy source, is otherwise completely vestigial; there is no biochemical reaction in any vertebrate that requires it.

Just because something is an energy source does not make it a food. Can you name an energy source that is not nutrition, in which there is no biochemical reaction in the human body (or in any organism) that requires it, that causes disease when consumed at high dosages, yet we love it anyway, and it's addictive? Answer: alcohol. It's loaded with calories, but it's not nutrition. There's no biochemical reaction that requires it (40% of Americans don't consume alcohol, and they're not sick). At high dosages, alcohol causes fatty liver disease. Clearly, alcohol is *not* a food; it's a toxin in high dosages. Alcohol is not dangerous because of its calories or its effects on weight. Alcohol is dangerous because it's alcohol (14); the biochemistry of the molecule makes it toxic.

There are 2 molecular mechanisms that delineate the toxicity of fructose (Figure 1) (15).

1) Only the liver has the fructose-specific Glut5 transporter; thus, in the fed state, the overwhelming majority of fructose metabolism occurs in the liver. Fructose is rapidly metabolized to fructose-1-phosphate (F1P) via fructokinase, an

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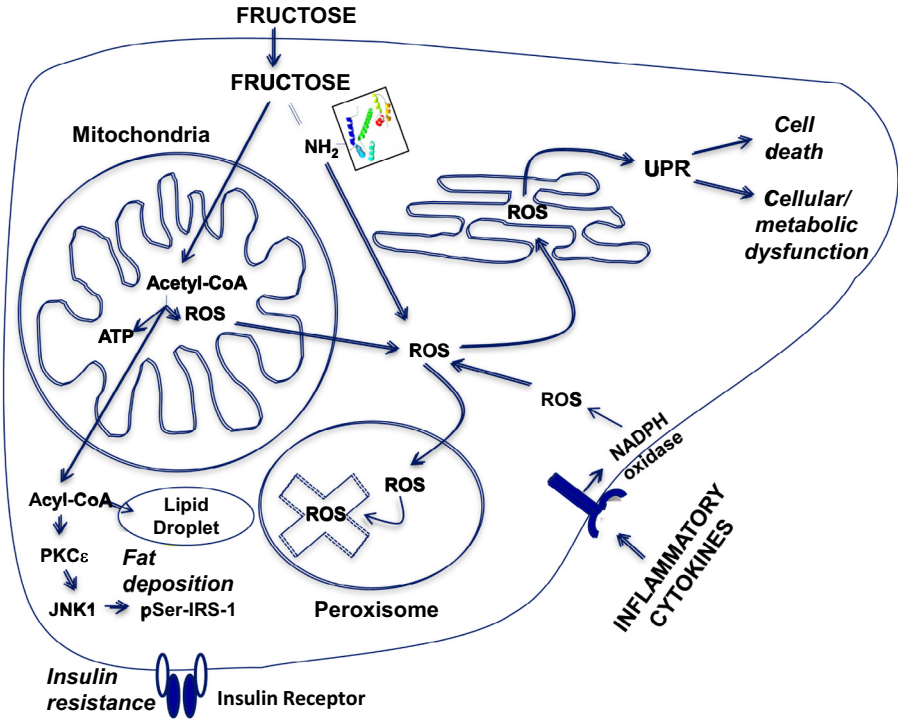

Figure 1. The consequences of hepatic fructose metabolism. Dietary fructose, due to its metabolic processing in the mitochondria and the fructosylation of protein ε-amino groups via the Maillard reaction, and circulating inflammatory cytokines, due to their receptor-mediated activation of NADPH oxidase, increase intracellular levels of ROS. In the absence of sufficient peroxisomal quenching and degradation, the ROS moieties lead to the UPR response, causing either cell death (apoptosis) or cellular/metabolic dysfunction. The formation of acetyl-CoA also leads to lipid deposition and insulin resistance through the activation of inflammatory pathways (from (17)). *ATP,* adenosine triphosphate; *CoA,* coenzyme A; *NADPH,* nicotinamide adenine dinucleotide phosphate; *ROS,* reactive oxygen species; *UPR,* unfolded protein response.

insulin-independent process which also bypasses the negative feedback regulation of phosphofructokinase in the glycolytic pathway. Thus, fructose metabolism generates lipogenic substrates (e.g. glyceraldehyde-3-phosphate and acetyl-CoA) in an unregulated fashion, and they are are delivered straight to the mitochondria but also simultaneously drive hepatic "de novo" lipogenesis (DNL), which will either be exported as triglyceride or possibly overwhelm the liver's lipid export capacity, leading to intrahepatic lipid deposition and hepatic steatosis. F1P also stimulates the sterol regulatory element binding transcription factor 1c (SREBP-1c) gene via peroxisome proliferator-activated receptor-gamma coactivator (PGC)-1 beta (16), independent of insulin, which activates the genes involved in DNL. Also, F1P activates dual-specificity mitogen-activated protein kinase 7 (MKK7), which subsequently stimulates c-jun N-terminal kinase-1 (JNK-1), serine phosphorylates IRS-1, inactivating it and leading to hepatic insulin resistance.

2) Because of its unique stereochemistry, the ring form of fructose (a 5-membered furan with axial hydroxymethyl groups) is under a great deal of ionic strain, which favours the linear form of the molecule, exposing the reactive 2-keto group, which can readily engage in the nonenzymatic fructosylation of exposed amino moieties of proteins via the Maillard reaction in the same way that the 1-aldehyde position of glucose is reactive with proteins. The Maillard reaction generates reactive oxygen species (ROS), which must be quenched by an antioxidant at the risk of cellular damage. Thus, fructose generates excessive ROS, which can lead to cellular damage and promotes the unfolded protein response (UPR), leading to metabolic syndrome (17).

Dissociating Sugar from Its Calories and Its Effects on Weight

Many case-control studies (18,19) point to fructose as a primary cause of type 2 diabetes, but these studies are not controlled for calories. In order to prove that fructose (and, therefore, sugar) is specifically toxic, the molecule must be dissociated from its inherent calories and its effects on weight. Furthermore, standard cross-sectional or correlational studies without time-factor analysis components are not acceptable because they cannot distinguish reverse or intermediate causality; they are like the snapshot rather than the movie. Last, the food industry is quick to point out that most fructose studies are performed in rodents that are given large doses over short periods of time. In defense, a recent study in rats shows that sugar at normal levels of consumption can cause morbidity and mortality (20), and a primate study demonstrates similar detrimental effects (21). Nonetheless, in order to prove toxicity, I must limit my argument to human studies using doses routinely consumed.

Prospective Cohort Studies

Two recent studies, both controlled for calories and adiposity and with time analyses, support sugar as a specific and direct causative agent of type 2 diabetes. First, a prospective cohort analysis of the European Prospective Investigation into Cancer and Nutrition (EPIC-Interact) study found that sugar-sweetened beverage (SSB) consumption increased the risks for developing diabetes over a 10-year period. The multivariate modelling, which adjusted for both energy intake and adiposity (body mass index), demonstrated that each SSB consumed increased the hazard risk ratio by 1.29 (95% CI 1.02, 1.63) exclusive of energy intake or body mass index (22). In

the U.S., people are currently consuming the equivalent of 2.5 servings of SSBs per day, so people's hazard ratios may well approach 1.68.

A second group performed a meta-analysis of studies that isolated consumption of soda (n=17) and fruit juice (n=13), controlled for calories and adjusted for adiposity (23). This meta-analysis showed that both soda and fruit juice specifically increase the relative risk ratio for diabetes (1.27, 1.10, respectively) over time. Furthermore, this study specifically took into account the fact that food industry-sponsored studies commonly demonstrate publication and information bias and calibrated for these biases.

Econometric Analysis

Our group performed an econometric analysis to assess which foods were specifically implicated in causing diabetes (2). We melded 3 freely available databases: 1) the Food and Agriculture Organization statistics database (FAOSTAT, a branch of the World Health Organization), which lists food availability per person by country, for the years 2000 to 2010, and by line item (total calories, fruits [excluding wine], meats, oils, cereals, fibre-containing foods, and sugar/sweeteners); 2) The International Diabetes Federation (IDF) database, which lists diabetes prevalence per country for the years 2000 to 2010; and 3) the World Bank World Development Indicators Database for the years 2000 to 2010, in which gross domestic product is expressed in purchasing power parity in 2005 U.S. dollars for comparability among countries to control for poverty. It also controls for urbanization, aging, physical activity and obesity. We asked which foods' availabilities predict change in diabetes prevalence, country by country, over the decade.

We performed this analysis using generalized estimating equations with a conservative fixed-effects approach (the Hausman test) and a hazard model to control for selection bias (the Heckman selection test); period effects controlled for secular trends that may have occurred as a result of changes in diabetes detection capacity or importation policies. Most important, we had longitudinal data between 2000 and 2010, which allowed us to determine which dietary changes preceded the changes in diabetes prevalence (the Granger causality test).

Food industry-backed scientists have attacked this study as being an example of an "ecological study," which, by convention, is hierarchically considered to be of low quality. Rather, this is an "econometric analysis," which is much more rigorous because it assesses multiple points in time, discerns complex relationships between internal and external motivating factors (adjusted over time), and allows for determination of causation (the Granger causality test). In fact, econometric analyses are hierarchically of higher quality than all studies except randomized controlled trials (24). Other investigators have derided this analysis because the FAOSTAT database assesses food availability rather than consumption. Rather, we view this as a positive rather than a negative factor because availability is easily quantifiable and not subject to the vicissitudes of individual recall and food wastage.

We showed that changes in sugar availability predicted the prevalence of diabetes between 2000 and 2010, exclusive of total calories, other foodstuffs, aging, obesity, physical activity or income. For every 150 calories per day in excess, diabetes prevalence increased 0.1%, but if those 150 calories happened to be a can of soda, diabetes prevalence increased 11-fold, by 1.1% (2). These data meet the Bradford Hill criteria for "causal medical inference" because we demonstrated that dose (more sugar, more diabetes); duration (longer sugar exposure, more diabetes); directionality (the few countries where sugar availability went down experienced a reduction in diabetes); and, most important, for causation precedence (3 years between change in sugar availability and change in diabetes prevalence).

Interventional Starch-for-Sugar Exchange

Our recent article in the journal *Obesity* (25) documents the effects of isocaloric substitution of sugar with starch in 43 Latino and African American children with metabolic syndrome over a 10-day period. After recruitment, we performed food questionnaires and interviews using sophisticated software to assess their total caloric consumption, as well as specific macronutrient and fibre intake. On day 0, we assessed their metabolic health on the basis of their home diets by using baseline analyte levels, oral glucose tolerance testing and dual-energy x-ray absorptiometry (DEXA) scanning. And then, for the next 9 days, we catered their meals so as to provide the same caloric content, the same fat, protein and fibre content and the same amount of total carbohydrate, but we reduced the percentage of calories from dietary sugar from a mean of 28% to 10%. We took the chicken teriyaki out; we put the turkey hotdogs in. We took the sweetened yogurt out; we put the baked potato chips in. We took the donuts out; we put the bagels in. We gave them unhealthy processed food, but it was food that had no added sugar. They were allowed fruit but not fruit juice. We gave them a scale to take home and called them every day. If their weights were declining, we made them eat more. They were given extra snacks to prevent weight loss. Then we studied them again 10 days later.

In short, every aspect of their metabolic health improved, with essentially no changes in weight. Blood pressure reduced by 5 mm Hg, triglycerides by 33 mg/dL, low-density lipoprotein by 10 mg/dL, and lactate by 0.3 mg/dL. Baseline glucose levels reduced by 5 mg/dL, glucose area under the curve dropped by 8%, fasting insulin dropped by 10 mU/L, insulin area under the curve dropped 25%—all improved—on the same number of calories and without weight loss, just by removing the added sugar—and in just 10 days! This study alone does not prove that sugar causes metabolic syndrome, but when taken with other studies (2,26,27), Koch postulates for causation were fulfilled.

Other Foodstuffs Specifically Linked to Metabolic Syndrome

To be clear, there are at least 3 other consumable substances that promote metabolic syndrome unrelated to their calories.

1) Transfats cannot be completely metabolized by mitochondria due to the trans-double bond, and they generate increased ROS. Transfats have long been assumed to contribute to chronic metabolic disease, especially atherosclerosis.
2) The branched-chain amino acids (BCAAs) valine, leucine and isoleucine are essential amino acids that account for more than 20% of the amino acids in the typical Western diet. In the anabolic state, they build muscle. However, when provided in excess beyond anabolic requirements, these classic ketogenic amino acids must be deaminated in the liver to be diverted toward energy utilization. This supplies too much acetyl-CoA to liver mitochondria, leading to liver-fat formation, and BCAA serum concentrations correlate with metabolic syndrome (28).
3) Cross-sectional and prospective studies implicate a dose-dependent effect of alcohol in metabolic syndrome and suggest that chronic consumption of large amounts of ethanol worsen insulin sensitivity. Ethanol is converted by alcohol dehydrogenase-1B to form acetaldehyde, generating nicotinamide adenine dinucleotide hydrogen (NADH), which promotes ROS formation and must be quenched by hepatic antioxidants to prevent liver damage. Furthermore, alcohol is metabolized to acetyl-CoA, which preferentially undergoes DNL under the excess of the reducing power of alcohol, driving fatty liver disease. While clearly a concern in adults,

it is unlikely that alcohol contributes significantly to metabolic syndrome in children.

Transfats, BCAAs, alcohol and fructose share 4 biochemical properties: 1) they are metabolized for energy primarily within the liver; 2) they are not insulin regulated; 3) they do not have a "pop-off" mechanism to form glycogen for storage and 4) they overwhelm mitochondrial β-oxidative capacity, leading to ROS generation and excessive DNL, which drives hepatic insulin resistance, hepatic steatosis and the UPR, which results in metabolic syndrome (17).

The Fallacies of Systematic Reviews and Meta-Analyses

Dr. J.L. Sievenpiper, my opponent in this debate, proffers numerous systematic reviews and meta-analyses, hierarchically considered to be the highest quality evidence. They state that fructose does not contribute to obesity (29,30). But this debate is not about obesity; it is about chronic metabolic disease. He provides other meta-analyses stating that fructose contributes to metabolic comorbidities only when provided in excess (31–33). However, systematic reviews and meta-analyses in general have recently come under fire for several reasons (34):

1) Publication bias. The food industry publishes numerous negative studies to help their causes, while independent investigators are loathe to publish negative studies. Thus, the truth is diluted.
2) Between-study heterogeneity. Alterations in dosage, utilizing lean vs. obese and insulin-sensitive vs. insulin-resistant subjects make comparisons difficult.
3) Random-effects modelling giving greater weight to smaller studies. Dr. Sievenpiper frequently acknowledges that the data in his analyses are of poor quality (35).

Furthermore, Dr. Sievenpiper's meta-analyses suffer specifically from the following 3 inadequacies.

a) Controlled-feeding studies are not physiologic. They neglect the neuroendocrine control of feeding. Fructose does not suppress ghrelin, so people may eat more. Because fructose does not acutely raise leptin, the hypothalamus may not sense that the person has eaten. Because fructose decreases dopamine-receptor density in the brain centre driving reward, *ad lib* studies may be more appropriate.
b) The paradigm of isocaloric fructose-for-glucose exchange. Fructose administered alone is incompletely absorbed, generating pain, bloating and diarrhea (36), similar to the feeling children experience on Halloween; this is why crystalline fructose is rarely used as a sweetener. Thus, the apparent dose and the received dose may be dichotomous. Furthermore, DNL is low when either glucose or fructose is administered alone, but they are synergistic when administered together (37). There is no fructose alone in nature; there is just sucrose (and now high-fructose corn syrup). Therefore, fructose-for-glucose exchange studies are completely artifactual.
c) Lack of subclassification of industry-sponsored vs. independent studies. Analysis of food industry-sponsored studies demonstrates an odds ratio of a conclusion favourable to the industry of 7.61 (38). Furthermore, a meta-analysis of meta-analyses showed that 5 of 6 food industry-sponsored studies showed that sugared beverages do not cause weight gain, whereas 10 of 12 independent studies showed that they did (39). In fact, the 1 meta-analysis that takes funding source into account finds that sugar consumption does predict diabetes (23), yet none of Dr. Sievenpiper's analyses are stratified by funding source.

These 6 points, taken together, deflate the opposition's argument.

Conclusions

Most people consider sugar (i.e. fructose-containing compounds) to be just "empty" calories. Rather, the studies mentioned herein demonstrate that the fructose moiety of sugar is toxic in chronically high dosage unrelated to its calories and is a significant contributor to metabolic syndrome. Sugar recapitulates all the chronic detrimental effects on long-term health, as does alcohol (15). This is why our children now get the diseases related to alcohol (type 2 diabetes, nonalcoholic fatty liver disease) without consuming alcohol. Sugar meets all the public health criteria for regulation (40). The Canadian documentary *Sugar Coated* (2015) (41) exposes the corporate fraud and tactics of the sugar industry in the 1970s to dismiss the science in order to obtain Generally Recognized as Safe (GRAS) status by the U.S. Food and Drug Administration. It is time to revisit this issue, to reclassify sugar from *food* to *food additive* and, just as we did with transfats, remove it from the GRAS list for the good of public health.

Disclosures

Dr. Lustig has never accepted money from the food industry and has no disclosures with respect to this article. However, Dr. Lustig has authored 3 popular books as a public health service: *Fat Chance: Beating the odds against sugar, processed food, obesity, and disease*; *Sugar Has 56 Names: A shopper's guide*; and *The Fat Chance Cookbook*. He is also the unpaid president of the nonprofit Institute for Responsible Nutrition.

References

1. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: Findings from the third National Health and Nutrition Examination Survey. JAMA 2002;287:356–9.
2. Basu S, Yoffe P, Hills N, Lustig RH. The relationship of sugar to population-level diabetes prevalence: An econometric analysis of repeated cross-sectional data. PLoS ONE 2013;8:e57873.
3. Sepúlveda J, Murray C. The state of global health in 2014. Science 2014;345:1275–8.
4. Chan JM, Rimm EB, Colditz GA, et al. Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men. Diabetes Care 1994;17:961–9.
5. McLaughlin T, Abbasi F, Cheal K, et al. Use of metabolic markers to identify overweight individuals who are insulin resistant. Ann Intern Med 2003;139:802–9.
6. Chen DL, Liess C, Poljak A, et al. Phenotypic characterization of insulin-resistant and insulin-sensitive obesity. J Clin Endocrinol Metab 2015;100:4082–91.
7. Abbasi F, Chu JW, Lamendola C, et al. Discrimination between obesity and insulin resistance in the relationship with adiponectin. Diabetes 2004;53:585–90.
8. Voulgari C, Tentolouris N, Dilaveris P, et al. Increased heart failure risk in normal-weight people with metabolic syndrome compared with metabolically healthy obese individuals. J Am Coll Cardiol 2011;58:1343–50.
9. Menke A, Casagrande S, Geiss L, Cowie CC. Prevalence of and trends in diabetes among adults in the United States, 1988–2012. JAMA 2015;314:1052–62.
10. Wiegand S, Maikowski U, Blankenstein O, et al. Type 2 diabetes and impaired glucose tolerance in European children and adolescents with obesity: A problem that is no longer restricted to minority groups. Eur J Endocrinol 2004;151:199–206.
11. Biltoft CA, Muir A. The metabolic syndrome in children and adolescents: A clinician's guide. Adolesc Med State Art Rev 2009;20:109–20.
12. Lustig RH. Fat chance: Beating the odds against sugar, processed food, obesity, and disease. New York, NY: Hudson Street Press; 2012.
13. Yudkin J. Pure, white, and deadly. New York: Viking, 1972.
14. Lustig RH. Fructose: Metabolic, hedonic, and societal parallels with ethanol. J Am Diet Assoc 2010;110:1307–21.
15. Lustig RH. Fructose: It's "alcohol without the buzz". Adv Nutr 2013;4:226–35.

16. Nagai Y, Yonemitsu S, Erion DM, et al. The role of peroxisome proliferator-activated receptor gamma coactivator-1 beta in the pathogenesis of fructose-induced insulin resistance. Cell Metab 2009;9:252–64.
17. Bremer AA, Mietus-Snyder ML, Lustig RH. Toward a unifying hypothesis of metabolic syndrome. Pediatrics 2012;129:557–70.
18. Malik VS, Popkin BM, Bray GA, et al. Sugar-sweetened beverages, obesity, type 2 diabetes mellitus, and cardiovascular disease risk. Circulation 2010;121:1356–64.
19. Bray GA. Energy and fructose from beverages sweetened with sugar or high-fructose corn syrup pose a health risk for some people. Adv Nutr 2013;4:220–5.
20. Ruff JS, Suchy AK, Hugentobler SA, et al. Human-relevant levels of added sugar consumption increase female mortality and lower male fitness in mice. Nat Commun 2013;4:2245.
21. Bremer AA, Stanhope KL, Graham JL, et al. Fructose-fed rhesus monkeys: A non-human primate model of insulin resistance, metabolic syndrome, and type 2 diabetes. Clin Transl Sci 2011;4:243–52.
22. EPIC-Interact Consortium. Consumption of sweet beverages and type 2 diabetes incidence in European adults: Results from EPIC-InterAct. Diabetologia 2013;56:1520–30.
23. Imamura F, O'Connor LYZ, Mursu J, et al. Consumption of sugar-sweetened beverages, artificially sweetened beverages, and fruit juice and incidence of type 2 diabetes: Systematic review, meta-analysis, and estimation of population attributable fraction. BMJ 2015;351:h3576.
24. Barker FG. What is medical evidence? Clin Neurosurg 2009;56:24–33.
25. Lustig RH, Mulligan K, Noworolski S, et al. Isocaloric fructose restriction and metabolic improvement in children with obesity and metabolic syndrome. Obesity (Silver Spring) 2016;24(2):453–60. Epub Oct 27.
26. Stanhope KL, Schwarz JM, Keim NL, et al. Consuming fructose-, not glucose-sweetened beverages increases visceral adiposity and lipids and decreases insulin sensitivity in overweight/obese humans. J Clin Invest 2009;119:1322–34.
27. Maersk M, Belza A, Stødkilde-Jørgensen H, et al. Sucrose-sweetened beverages increase fat storage in the liver, muscle, and visceral fat depot: A 6-month randomized intervention study. Am J Clin Nutr 2012;95:283–9.
28. Newgard CB, An J, Bain JR, et al. A branched-chain amino acid-related metabolic signature that differentiates obese and lean humans and contributes to insulin resistance. Cell Metab 2009;9:311–26.
29. Te Morenga L, Mallard S, Mann J. Dietary sugars and body weight: Systematic review and meta-analyses of randomised controlled trials and cohort studies. BMJ 2013;346:e7492.
30. Sievenpiper JL, de Souza RJ, Mirrahimi A, et al. Effect of fructose on body weight in controlled feeding trials: Asystematic review and meta-analysis. Ann Intern Med 2012;156:291–304.
31. Cozma AI, Sievenpiper JL, de Souza RJ, et al. Effect of fructose on glycemic control in diabetes: A systematic review and meta-analysis of controlled feeding trials. Diabetes Care 2012;35:1611–20.
32. Wang D, Sievenpiper JL, de Souza RJ, et al. Effect of fructose on postprandial triglycerides: A systematic review and meta-analysis of controlled feeding trials. Atherosclerosis 2014;232:125–33.
33. Sievenpiper JL, Carleton AJ, Chatha SJ, et al. Heterogeneous effects of fructose on blood lipids in individuals with type 2 diabetes: Systematic review and meta-analysis of experimental trials in humans. Diabetes Care 2009;32:1930–7.
34. Satija A, Yu E, Willett WC, Hu FB. Understanding nutritional epidemiology and its role in policy. Adv Nutr 2015;6:5–18.
35. Chiu S, Sievenpiper JL, de Souza RJ, et al. Effect of fructose on markers of non-alcoholic fatty liver disease (NAFLD): A systematic review and meta-analysis of controlled studies. Eur J Clin Nutr 2014;68:416–23.
36. Rumessen JJ, Gudmand-Hoyer E. Absorption capacity of fructose in healthy adults: Comparison with sucrose and its constituent monosaccharides. Gut 1986;27:1161–8.
37. Hudgins LC, Parker TS, Levine DM, Hellerstein MK. A dual sugar challenge test for lipogenic sensitivity to dietary fructose. J Clin Endocrinol Metab 2011;96:861–8.
38. Lesser LI, Ebbeling CB, Goozner M, et al. Relationship between funding source and conclusion among nutrition-related scientific articles. PLoS Med 2007;4:e5.
39. Bes-Rastrollo M, Schulze MB, Ruiz-Canela M, Martinez-Gonzalez MA. Financial conflicts of interest and reporting bias regarding the association between sugar-sweetened beverages and weight gain: A systematic review of systematic reviews. PLoS Med 2013;10:e1001578.
40. Lustig RH, Schmidt LA, Brindis CD. The toxic truth about sugar. Nature 2012;487:27–9.
41. Sugar Coated. Movie Documentary, Michele Hozer, director, Janice Dawe, producer. Cutting Factory 2015;http://sugarcoateddoc.com/.