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Commentary

Sickeningly Sweet: Does Sugar Cause Chronic Disease? No

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Introduction

Sugars have emerged as 1 of the most important public health concerns. Special attention has focused on the fructose moiety of sugars owing to its unique metabolic and endocrinologic responses. Low-quality ecologic studies (1–3), animal models of overfeeding at levels of exposure far beyond mean population levels of intake (4) and select human interventions lacking control for energy (5) have been used to implicate fructose-containing sugars in the epidemics of obesity and diabetes. Although experimental models have been invoked to offer plausible biochemical mechanisms to support these positions, whereby fructose acts as an unregulated substrate for de novo lipogenesis, depletes intracellular adenosine triphosphate and impairs satiety signalling through insulin, leptin and ghrelin (6–9), the clinical translation of these mechanisms remains in question.

Whether sugars at real-world levels of exposure in free-living people cause diabetes and other cardiometabolic diseases requires careful deliberation. Systematic reviews and meta-analyses of controlled trials and prospective cohort studies are universally considered the highest level of evidence to inform public health policy and clinical practice guidelines. Prospective cohort studies provide the best protection against bias in observational studies owing to their long longitudinal follow up, ability to adjust for multiple confounding factors and assessment of clinical outcomes rather than surrogate biomarkers. Randomized and nonrandomized controlled trials provide the best protection against bias because they control for confounding factors, allowing for isolation of the effect of interest. This counterpoint to the article by Dr. Robert Lustig (10) in the current issue of *Canadian Journal of Diabetes* argues that if one applies an evidence-based framework assessing the totality of the highest level of evidence from prospective cohort studies and controlled trials, then a causal relationship between sugars and chronic disease is far from proven.

Evidence from prospective cohort studies

Prospective cohort studies assessing the relationships between sugars and chronic diseases have been complicated by the formats in which the sugars are consumed. Individual large cohort studies and systematic reviews and meta-analyses of available cohort studies do show that sugar-sweetened beverages (SSBs) as sources of free sugars are associated with increased risks for weight gain (11,12), metabolic syndrome (13), diabetes (13,14), hypertension (15), coronary heart disease (16,17), stroke (18) and gout (19,20). Pooled analyses involving the same cohorts, however, have failed to show the same adverse association for total sugars, sucrose or fructose, which necessarily include SSBs, and a protective association is even seen between sucrose and diabetes (11,21–37). The only exception is an adverse association between fructose and gout (38). Important food sources of free sugars other than SSBs have also failed to show adverse associations with cardiometabolic diseases. For example, cakes and cookies (39) and sherbet (40) have shown no association with diabetes, while whole fruit (41), yogourt (40), whole-grain cereals (42) and ice cream (40) have even shown protective associations with diabetes (Figure 1).

In the absence of an adverse association with sugars per se, why do SSBs alone appear to be the special case? One reason may relate to energy. The observed associations do not remain significant at intermediate levels of exposure near the 50th percentile for intake in the United States; that is, they are restricted to the highest quantiles of exposure, with the single exception of gout (38). Any positive associations also become nonsignificant or are markedly attenuated after adjustment for total energy intake (12), suggesting that any effects of SSBs on cardiomebatolic diseases appear to be highly mediated by energy. In this regard, many prospective cohort studies report energy unadjusted models as energy is considered to be on the causal pathway between the exposure (sugars) and weight-related outcomes (obesity, metabolic

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Food source of sugars	Cohort comparisons	Participants	Cases	Median Follow up	Risk ratios with 95% CIs	I^2
SSBs (14)	17	464,937	38,253	12y	1.27 (1.10 to 1.46)	73%*
Fruit drinks (44)	4	191,686	12,375	19y	1.28 (1.04 to 1.59)	43%
100% fruit juice (14)	13	440,937	35,722	12y	1.10 (1.01 to 1.20)	30%
Yogourt (40)	8	187,170	15,893	10y	0.86 (0.75 to 0.98)	59%*
Sherbet (40)	2	78,437	2,846	11y	0.90 (0.79 to 1.03)	0%
Ice cream (40)	2	78,437	2,846	11y	0.83 (0.73 to 0.95)	0%
Cakes, cookies (39)	8	16,154	778	16y	0.96 (0.86 to 1.07)	35%
Cereal (whole grain) (42)	3	128,314	4,202	10y	0.72 (0.55 to 0.93)	78%
Fruits (41)	11	424,677	22,995	11y	0.93 (0.88 to 0.99)	0%

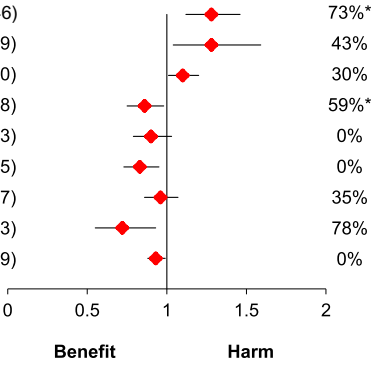

Figure 1. Summary estimates from pooled prospective cohort studies and systematic reviews and meta-analyses of prospective cohort studies of the relationships of various sources of sugar to incident type 2 diabetes in adults. Summary estimates *(diamonds)* were derived from pooled risk ratios for comparison of extreme quantiles, the highest level of exposure compared to the lowest level of exposure. The 1 exception was for cakes and cookies, which compared the highest level of exposure to the middle level of exposure, the reference exposure that was associated with the lowest risk. Data are expressed as risk ratios with 95% confidence intervals (CI). *Asterisks* indicate significant interstudy heterogeneity as assessed by the Cochran Q statistic and quantified by the I^2 statistic at a significance level of $p<0.10$. *SSBs,* sugar-sweetened beverages.

syndrome, diabetes, etc.). Intake of sugars in the liquid form provided by SSBs may not be compensated for by a decrease in total energy intake, promoting weight gain, a main risk factor for cardiometabolic diseases. A pooled analysis of acute preload trials has shown that liquid calories were less compensated for than solid calories (43). Longer term trials designed to assess whether this lack of compensation results in weight gain, however, have been inconclusive (43). Liquid calories from 100% pure fruit juice have also not shown reliable associations with diabetes or cardiometabolic diseases (14,44).

Another possibility is that SSBs are markers of unhealthy lifestyles (45–48). Food and lifestyle choices do not exist in isolation. An approach that only looks at a single food or lifestyle behaviour may be inadequate for disentangling complicated interactions among different foods and the dietary and lifestyle patterns they comprise under free-living conditions. In this regard, the associations seen for SSBs are at risk for residual confounding from important collinearity effects. Higher SSB intake is associated with higher caloric intake, less physical activity, smoking and poorer dietary patterns (16,45,46), which may be difficult to measure and adjust for in observational studies (47). Dietary pattern analyses, which take advantage of this collinearity, have identified 2 distinct dietary patterns in the Harvard cohorts: a Western dietary pattern characterized typically by high intakes of processed meats, red meats, refined grains, French fries, sweets and desserts and sugary beverages and a Prudent dietary pattern characterized typically by high intakes of vegetables, fruit, legumes, fish, poultry and whole grains. The Western dietary pattern has been associated with cardiometabolic disease outcomes that include weight gain and increased risk for diabetes, coronary heart disease (CHD) and mortality resulting from CHD in energy-adjusted models (48–52). Each individual component of a Western dietary pattern is associated with equal or greater risk for diabetes than SSBs alone. The effect sizes for weight gain of more than 7.03 kg over 8 years (48), diabetes relative risks (RRs), 2.56 to 2.93 (49–52), and CHD RR, 1.46) (53) are larger than those reported for SSBs alone (11–17), and these associations remain unchanged even after adjustment for SSBs, as seen in the 2 analyses in which this adjustment was made (48,49). In contrast, total sugars and total fructose-containing sugars tend not to be associated with these dietary factors in the available cohorts (21–37).

Evidence from controlled trials of fructose

Controlled trials have been similarly equivocal for the independent effects of fructose, the presumed culprit, on cardiometabolic risk. A carefully conducted series of systematic reviews and meta-analyses (54–64) of more than 50 controlled trials in more than 1000 participants of the effects of fructose across a wide dose range have failed to show signals of harm of fructose in “substitution” trials, in which fructose was provided in isocaloric substitutions for other carbohydrates likely to replace it (Figure 2). Contrary to the prevailing concerns, pooled analyses of the totality of the evidence from the substitution trials show that fructose leads to clinically meaningful improvements in glycemic control as assessed by glycated blood proteins in people with and without diabetes (60,64). The reduction is equivalent to a 0.57% reduction in glycated hemoglobin (A1C) levels, which is at the lower limit of efficacy of oral antihyperglycemic agents of 0.5% (65) and exceeds the Federal Drug Administration threshold of 0.3% for the development of new oral antihyperglycemic agents (66). Favourable results are also seen for blood pressure, without any adverse effects on other cardiometabolic risk factors, including body weight, fasting lipids, postprandial lipids, whole-body and hepatic insulin resistance, uric acid, and markers of nonalcoholic fatty liver disease (NAFLD) in people with varying metabolic phenotypes (54–64).

An adverse effect of fructose is seen reliably under certain conditions. Dose thresholds for harm have been reported previously for the effects of fructose on fasting triglycerides >60 grams per day in people with type 2 diabetes and >100 grams per day in participants with mixed phenotypes and postprandial triglycerides >50 grams per day in participants with mixed phenotypes (55,56). Increases in both fasting and postprandial triglycerides have also been shown when pooled analyses of controlled and individual controlled trials are restricted to fructose in isocaloric comparisons with glucose at very high doses (>100 grams per day) (67,68). These findings, however, have not been reproduced in dose-response and subgroup analyses in updated systematic reviews and meta-analyses (58,59). The most consistent signal for harm remains restricted to “addition” trials, in which excess calories from fructose are added to diets and compared to the same diet alone without the excess calories. Systematic reviews