Fructose as a Driver of Diabetes: An Incomplete View of the Evidence

To the Editor: We are concerned that the article by DiNicolantonio et al[1] published in the March 2015 issue of *Mayo Clinic Proceedings* that implicated added fructose as a driver of type 2 diabetes misrepresented the data by placing undue emphasis on low-quality evidence from ecological observations, animal models of fructose overfeeding, and selected human studies assessed in isolation. It also ignored important biological mechanisms by which fructose may assist in the metabolic handling of glucose. If one considers the totality of the highest-quality evidence from controlled feeding trials and prospective cohorts, then different conclusions are reached.

A series of carefully conducted systematic reviews and meta-analyses[2-9] of more than 50 controlled trials that included over 1000 participants of the effect of fructose across a wide dose range have failed to document a signal for harm of fructose in isocaloric substitution for other carbohydrates likely to replace it (Figure 1). Contrary to the hypothesis put forward by DiNicolantonio et al,[1] pooled analyses of the totality of the evidence from these trials show that fructose in isocaloric exchange for other sources of carbohydrate leads to clinically meaningful improvements in glycemic control as assessed by glycated blood proteins (equivalent to a 0.57% reduction in hemoglobin A_{1c}, which exceeds the US Food and Drug Administration threshold of 0.3% for the development of new oral antihyperglycemic agents) in individuals with and without diabetes.[2,3] Favorable results are also seen in blood pressure, without any adverse effects on other cardiometabolic risk factors including insulin sensitivity, body weight, fasting lipid levels, postprandial lipid levels, uric acid concentration, and markers of nonalcoholic fatty liver disease in individuals with varying metabolic phenotypes.[2-9] DiNicolantonio et al implied that bias from industry funding might explain these favorable results among the available controlled trials, but very few of these trials were funded exclusively by industry. The majority were funded by a combination of agency and industry or agency alone, and there was no evidence of publication bias across the end points.[2-9]

Prospective cohort studies, which provide the greatest protection against bias among observational studies because of their long longitudinal follow-up and the ability to adjust for multiple confounding factors, have also failed to document a direct relationship between fructose and diabetes. Although pooled analyses of the available cohorts have revealed that sugar-sweetened beverages (SSBs) as a source of free fructose are associated with an increased risk of diabetes when the highest and lowest levels of exposure are compared,[10,11] pooled analyses involving many of the same cohorts have not found the same relationship for total sugars, total sucrose, total fructose,[12] or other sources of free fructose such as 100% fruit juice[11] and cakes and cookies[13] (Figure 2). The opposite relationship (benefit) has also been reported for fruit as a source of bound fructose.[14]

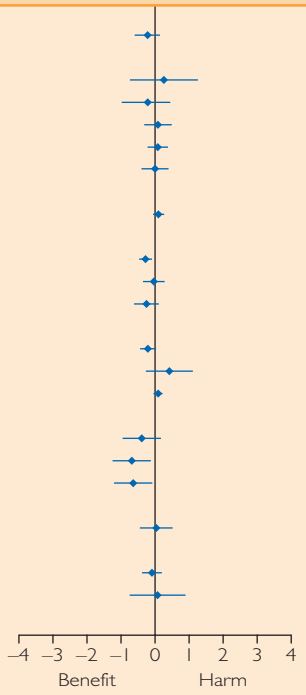
Setting aside these discrepant findings, if one wants to invoke the evidence for SSBs as a proxy for all added fructose-containing sugars, then one has to ask how important a risk factor is the intake of SSBs. A recent comparative risk assessment revealed that the burden of disease and mortality attributable to SSBs (that is, population-attributable fraction) is still much less than that of other established risk factors measured among the cohort studies, ranking 32nd among 57 risk factors globally.[15] Even among the dietary and physical inactivity risk factors, SSBs ranked 12th of 15 for both burden of disease and mortality, and no other sources of added fructose-containing sugars were identified as risk factors.[15]

The question becomes why the higher-level evidence disagrees with the current hypothesis from DiNicolantonio et al.[1] One reason may be that the mechanisms being invoked are not as relevant in humans as in the animal models used to support them. For example, although de novo lipogenesis is extremely high (estimated at $\geq$50%) with excessive fructose feeding (typically 60% of total energy intake) in rodents, a careful review of stable isotope tracer studies reveals that de novo lipogenesis from fructose (as indeed from all carbohydrate) is a minor pathway for fructose disposal in humans (estimated to range from 0%-1% at moderate intake to up to 5% with overfeeding in humans).[16]

Another reason for the differences may lie in biologically plausible pathways that offset any harm and even explain some benefits. Fructose has a very low glycemic index (15), a factor that led to an early interest in fructose in diabetes management. Emerging evidence also shows that low-dose fructose ($\leq$10 g per meal) may benefit glycemic control through its metabolite fructose-1-phosphate by inducing glucokinase activity. This catalytic effect of fructose on hepatic glucose metabolism has been reported to coincide with (1) a decrease in hepatic glucose production under hyperglycemic clamp conditions in patients with type 2 diabetes and (2) an increase in glycogen synthesis by carbon 13 nuclear magnetic resonance spectroscopy under euglycemic clamp conditions in participants without diabetes.[17,18] These mechanisms appear to be sustainable over the long term. A systematic review and meta-analysis of controlled trials of the effect of small "catalytic" fructose doses ($\leq$36 g/d) in exchange for starch reproduced the favorable glycemic effects seen at

Isocaloric substitution trials

Cardiometabolic end point		Comparisons	No.	Standardized mean difference (SMD) with 95% CI	I^2
Body weight[4]		31	637	−0.22 (−0.58, 0.13)	37%*
Fasting lipids[5]	LDL-C	26	327	0.36 (−0.27, 0.50)	11%
	Apo-B	8	176	−0.21 (−0.96, 0.43)	62%*
	Non-HDL-C	26	457	0.09 (−0.30, 0.47)	92%*
	TG	49	815	0.08 (−0.20, 0.36)	62%*
	HDL-C	27	525	0.00 (−0.38, 0.38)	49%*
Postprandial TG[6]		14	290	0.14 (−0.02, 0.30)	54%*
Glycemic control[3]	GBP	19	277	−0.28 (−0.45, −0.11)	56%*
	FBG	47	881	−0.04 (−0.34, 0.26)	78%*
	FBI	34	622	−0.25 (−0.60, 0.09)	70%*
Insulin sensitivity[3]	Whole body	16	265	−0.21 (−0.42, 0.01)	66%*
	Hepatic	3	25	0.42 (−0.25, 1.09)	51%
	HOMA-IR	39	806	0.09 (−0.03, 0.20)	66%*
Blood pressure[7]	SBP	13	352	−0.39 (−0.93, 0.16)	31%
	DBP	13	352	−0.68 (−1.23, −0.14)	47%*
	MAP	13	352	−0.64 (−1.19, −0.10)	97%*
Uric acid[8]		18	390	0.04 (−0.43, 0.50)	0%
NAFLD[9]	IHCL	4	95	−0.09 (−0.36, 0.18)	0%
	ALT	6	164	0.07 (−0.73, 0.87)	0%



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Hypercaloric addition trials

Cardiometabolic end point		Comparisons	No.	Standardized mean difference (SMD) with 95% CI	I^2
Body weight[4]		10	119	1.24 (0.61, 1.85)	30%
Fasting lipids[5]	LDL-C	4	79	0.14 (−0.39, 1.57)	77%*
	Apo-B	2	48	2.00 (0.55, 3.33)	0%
	Non-HDL-C	2	43	0.30 (−1.11, 1.66)	93%*
	TG	8	125	1.20 (0.51, 1.89)	66%*
	HDL-C	4	79	−0.41 (−1.39, 0.57)	0%
Postprandial TG[6]		2	32	0.65 (0.30, 1.01)	22%
Glycemic control[3]	GBP	2	31	−0.33 (−0.62, −0.04)	0%
	FBG	8	98	1.25 (0.59, 1.98)	59%*
	FBI	8	98	0.50 (−0.19, 1.19)	41%
Insulin sensitivity[3]	Whole body	7	74	0.25 (0.12, 0.39)	0%
	Hepatic	3	31	0.38 (0.01, 0.75)	0%
	HOMA-IR	9	113	0.26 (−0.01, 0.52)	77%*
Blood pressure[7]	MAP	2	24	−0.76 (−2.15, 0.62)	24%
Uric acid[8]		3	35	2.26 (1.13, 3.39)	0%
NAFLD[9]	IHCL	5	60	0.45 (0.18, 0.72)	51%*
	ALT	4	59	0.99 (0.01, 1.97)	28%

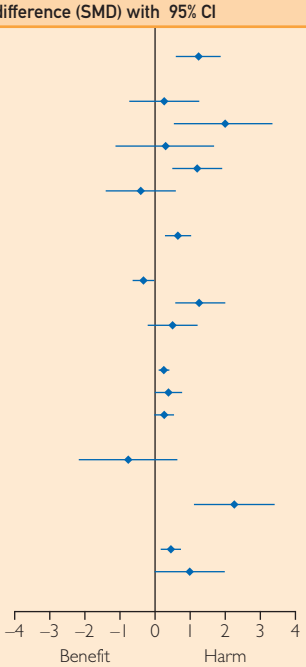

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FIGURE 1. Forest plots of summary estimates from recent meta-analyses of the effect of fructose interventions on cardiometabolic risk factors in controlled dietary trials. The meta-analyses were grouped on the basis of the control of calories in the trial comparisons: A—isocaloric substitution trials, in which fructose was exchanged for other carbohydrate sources under energy-matched conditions; and B—hypercaloric addition trials, in which excess calories from fructose were added to a diet compared with the same diet without the excess calories. Summary estimates (diamonds) were derived from pooled trial-level data. The data for glycemic control and insulin sensitivity in individuals with and without diabetes were derived from an update by Cozma et al.[3] To allow the summary estimates for each end point to be displayed on the same axis, mean differences were transformed to standardized mean differences (SMDs). Pseudo-95% CIs for each transformed SMD were derived directly from the original mean difference and 95% CI. The scales were also flipped for high-density lipoprotein cholesterol (HDL-C), whole-body insulin sensitivity, and hepatic insulin sensitivity so that the direction of the effect for benefit or harm was in the same direction as that for the other end points. Asterisks indicate significant interstudy heterogeneity as assessed by the Cochran *Q* statistic and quantified by the I^2 statistic at a significance level of $P<.10$ (the higher significance level was chosen owing to the poor sensitivity of the test). ALT = alanine aminotransferase; Apo-B = apolipoprotein B; DBP = diastolic blood pressure; FBG = fasting blood glucose; FBI = fasting blood insulin; GBP = glycated blood proteins; HOMA-IR = homeostatic model assessment-insulin resistance; IHCL = intrahepatocellular lipid; LDL-C = low-density lipoprotein cholesterol; MAP = mean arterial pressure; SBP = systolic blood pressure; TG = triglycerides.

higher doses, without any adverse effects on metabolic control over 1 to 52 weeks of follow-up.[19]

Harm from fructose, however, is seen under certain conditions. Dose thresholds for harm have been previously identified for the effect of fructose on fasting and postprandial lipid levels,[2,5] Although these thresholds have not been reproduced in updated meta-analyses,[6] individual trials of fructose feeding at very high doses (>100 g/d) have found increases in fasting and postprandial triglyceride levels in energy-matched comparisons with glucose.[20] The most consistent signal for harm remains restricted to hypercaloric addition trials, in which excess calories from pure fructose are added to a diet, compared with the same diet without these excess calories. Systematic reviews and meta-analyses of the available trials have found that fructose under these conditions leads to weight gain and increases in fasting and postprandial triglyceride levels, fasting glucose levels, whole-body and hepatic insulin resistance, uric acid concentrations, and markers of nonalcoholic fatty liver disease[3-9] (Figure 1). The inability of fructose to induce the same adverse effects in isocaloric substitution for other carbohydrates suggests that the main determinant of this observed harm is excess calories rather than any special

Source	Cohort comparisons	Participants	Cases	Median follow-up	Risk ratio (95% CI)	I^2
Foods						
SSBs[10]	9	310,819	15,043	10 y	1.26 (1.12, 1.41)	66%*
SSBs (fruit drinks)[11]	4	191,686	12,375	19 y	1.28 (1.04, 1.59)	43%
100% Fruit juice[11]	4	137,663	4906	10 y	1.03 (0.91, 1.18)	6%
Cakes, cookies[13]	8	16,154	778	16 y	0.96 (0.86, 1.07)	35%
Fruits[14]	11	424,677	22,995	11 y	0.93 (0.88, 0.99)	0%
Sugars						
Total sugars[12]	13	134,822	13,906	12 y	0.88 (0.74, 1.06)	76%*
Total sucrose[12]	8	213,838	3829	6 y	0.89 (0.80, 0.98)	1%
Total fructose[12]	6	129,478	3613	7 y	1.04 (0.84, 1.29)	71%*

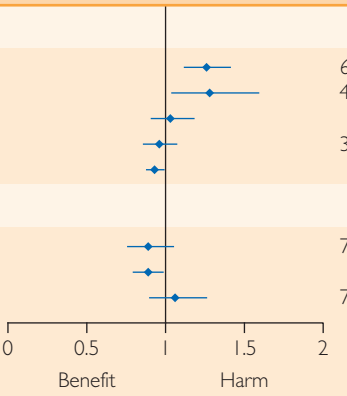

FIGURE 2. Forest plots of summary estimates from recent meta-analyses of the relationship between different sources of sugars and incident type 2 diabetes in adults. Summary estimates (diamonds) were derived from pooled risk ratios for comparison of extreme quantiles (the highest level of exposure compared with the lowest level of exposure). The one exception was for cakes and cookies, which compared the highest level of exposure with the middle level of exposure, the reference exposure that was associated with the lowest risk. Data are expressed as risk ratios with 95% CIs. Asterisks indicate significant interstudy heterogeneity as assessed by the Cochran *Q* statistic and quantified by the I^2 statistic at a significance level of $P<.10$ (the higher significance level was chosen owing to the poor sensitivity of the test). SSBs = sugar-sweetened beverages.

metabolic or endocrine responses to the fructose. Any adverse effects observed under conditions of overfeeding appear to be no more mediated by fructose than by other sources of carbohydrate used to replace it. That these adverse effects appear to be reversible by exercise also suggests that they may not be generalizable to all individuals.[20]

In conclusion, efforts to identify the factors that contribute to the development of type 2 diabetes remain an important goal. These efforts, however, must be conducted using systematic evidence-based approaches that protect against important sources of bias that include confounding from energy. In the case of fructose, the totality of the highest-level evidence from the systematic reviews and meta-analyses of controlled trials and prospective cohort studies fails to implicate fructose as an independent driver of type 2 diabetes.

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In reply—Fructose as a Driver of Diabetes: An Incomplete View of the Evidence

We appreciate the response to our article from Dr Sievenpiper and colleagues, who argue that the highest-level evidence fails to implicate fructose as an independent driver of type 2 diabetes. We respectfully counter that the meta-analyses and systematic reviews the authors present may be misleading and that the totality of data supports our original contention.

As a bottom line, Sievenpiper et al dismiss attributed harms of fructose as the effect of any added calories, noting detriments of fructose consumption in hypercaloric addition trials but not in isocaloric substitution trials. One problem with the logic is that isocaloric substitution is an artificial condition. Free-living individuals do not substitute fructose for other carbohydrates or macronutrients in a calorie-neutral way. When free-living individuals consume more fructose, they tend to consume more calories overall.[1,2] Such overconsumption may result partly from fructose being less satiating (even when compared with glucose).[3] Furthermore, fructose incites insulin resistance[4-6] and leptin resistance,[7,8] which may drive hunger and delay satiety. Thus, hypercaloric addition trials may be more representative of the effects of fructose consumption in the real world. As we stated in our article,[9] and as the forest plot provided by Sievenpiper et al corroborates, there seems to be no question that hypercaloric fructose is associated with a variety of adverse metabolic effects.

Another problem with the cited isocaloric substitution trials may be industry involvement. Sievenpiper et al note favorable effects on hemoglobin A_{1c} and blood pressure in trials substituting fructose for other carbohydrates, explaining that the majority of trials were not funded exclusively by industry but by a combination of industry and agency. This fact should not be at all reassuring because trials that involve industry collaboration in design, analysis, or reporting use less rigorous methods and are more likely to report pro-industry conclusions.[10] A recent meta-analysis found a direct effect of higher sugar intake on systolic blood pressure when industry-funded trials were included but documented an even greater increase in blood pressure when industry-funded trials were excluded[11] (an effect about twice as strong as what might be seen with high-sodium intake[12]). Another systematic review revealed a striking dichotomy: more than 80% of industry-funded studies reported *no* relationship between sugar-sweetened beverage consumption and weight gain, whereas more than 80% of non—industry-funded studies found a positive correlation between intake of sugar-sweetened beverages and weight gain.[13]

There are also measurement issues to consider in the trials cited by Sievenpiper et al. For instance, with regard to blood pressure, the hypertensive effect of sugar might have been missed in trials employing random blood pressure readings because sugar has been found to predominantly elevate blood pressure postprandially.[14-16] Also, 24-hour ambulatory monitoring is more accurate and reliable for measuring blood pressure than single clinic readings.[17] When ambulatory monitoring is used, evidence suggests that blood pressure is significantly increased after just a few weeks of high sugar intake.[18]

Measurement is also an issue for Sievenpiper and colleagues' cited prospective cohort studies. The authors note that such studies have failed to document a direct relationship between fructose and diabetes. Yet, these studies almost inevitably rely on self-reported measures for dietary intake, which are notoriously problematic. In fact, some experts contend that self-reported intake data are wholly inadequate and unacceptable, at least with regard to energy intake.[19] More specifically with regard to sugar, a recent prospective cohort study found that sucrose measured by objective biomarkers was directly associated with body mass index, whereas sucrose measured by self-report was *inversely* associated with body mass index.[20] Thus, the assertion by Sievenpiper et al that studies employing self-reported