Re. “Association of fructose consumption and components of metabolic syndrome in human studies: A systematic review and meta-analysis”

To the Editor:

We read with great interest the article by Kelishadi et al. [1] describing a systematic review and meta-analysis of the adverse effects of fructose on most components of the metabolic syndrome (fasting blood glucose, triglycerides, high-density lipoprotein cholesterol, and blood pressure). We are concerned that the “before–after” comparisons favored by most systems of evidence-based medicine at the design controls for known and unknown confounders allowing for the isolation of the effect of the intervention in question from other prognostic factors. That is, it protects against important confounding from factors that the fructose intervention shares with other dietary interventions under the same conditions. The before–after design used by the authors provides evidence that would be considered by most systems of evidence-based medicine at the level of a case series, rendering it not probative and “very low quality” [3].

If these were the only data available, then we would await higher-quality data on this question. However, the authors themselves have identified higher-quality data from the controlled comparisons within these same feeding trials. If one examines these controlled comparisons carefully, then the inferences drawn are very different. We have published a series of Canadian Institutes of Health Research-funded systematic reviews and meta-analyses of controlled feeding trials of the effect of fructose on cardiometabolic risk factors [clinical trials.gov identifier, NCT01363791]. These syntheses demonstrate that when dietary fructose is consumed in isocaloric substitution for other carbohydrate sources such as starch or glucose (an energy-matched comparison between fructose and a carbohydrate comparator), there are no deleterious effects on body weight, fasting and postprandial lipids, blood pressure, uric acid, glycemic control, insulin, and markers of nonalcoholic fatty liver disease [4–10], although there may be a dose threshold for fasting lipids in some subgroup analyses [10,11]. This lack of effect is true even when fructose provides excess calories (positive energy balance), as long as the carbohydrate comparator is matched for the excess calories. On the contrary, consistent adverse signals are seen when fructose is consumed in imbalanced, hypercaloric comparisons [4–9], in which fructose supplements control diets with excess calories compared with the same control diets alone without the excess calories. In the absence of an effect of fructose in isocaloric comparisons, our syntheses suggest that the effect of fructose seen in hypercaloric comparisons relates more to the excess calories than the fructose. By pooling intervention arms of fructose under isocaloric conditions (meeting energy requirements) together with those under hypercaloric conditions (exceeding energy requirements) without comparison to a control group, the systematic review and meta-analysis in question (in which 50% of the intervention arms were hypercaloric) is unable to separate the effect of fructose from that of excess calories. Taken together, these data make the case for confounding from excess calories that can only be appreciated in controlled comparisons.

Furthermore, the method of aggregating the study results is unclear. In the methods section, the authors claimed to have pooled “mean differences,” yet their forest plots report “standardized mean differences,” with no explanation for the method of standardizing these mean differences. In the absence of a clear congruence between methodology and results reporting, the aggregate analysis is not meaningfully interpretable.

In conclusion, one cannot infer that fructose uniquely affects most components of the metabolic syndrome (fasting blood glucose, triglycerides, high-density lipoprotein cholesterol, and blood pressure) from the present systematic review and meta-analysis of uncontrolled comparisons. The adverse signals disappear in the appropriate controlled comparisons with other carbohydrates under calorie-matched conditions. The implication remains that fructose is no worse than other carbohydrates likely to replace it and that any adverse effects are explained by an imbalance in calories.

References


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