Effect of Important Food Sources of Fructose-Containing Sugars on Non-alcoholic Fatty Liver Disease: A Systematic Review and Meta-Analysis of Controlled Trials

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Objectives: Fructose as a source of excess calories increases non-alcoholic fatty liver disease (NAFLD) markers. Whether this effect is mediated by the food matrix is unknown. We thus conducted a systematic review and meta-analysis of controlled feeding trials assessing the effect of important food sources of fructose-containing sugars at different energy control levels on NAFLD markers.

Methods: MEDLINE, Embase, and Cochrane Library were searched through January 18, 2021 for controlled trials ≥7-days. Four trial designs were prespecified based on energy control: substitution (energy-matched replacement of sugars by other macronutrients); addition (excess energy from sugars added to diets); subtraction (energy from sugars subtracted from diets); and ad libitum (energy from sugars freely replaced by other macronutrients). The primary outcome was intrahepatocellular lipid (IHCL). Secondary outcomes were alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Independent reviewers extracted data and assessed risk of bias. Certainty of evidence was assessed by GRADE.

Results: We included 44 trials (65 trial comparisons, n = 1941) assessing the effect of 8 food sources (sugar-sweetened beverages [SSBs]; sweetened dairy alternative [soy]; fruit juice; fruit; dried fruit; baked goods, desserts and sweets; added nutritive sweetener; and mixed sources) across 4 energy levels. Total fructose-containing sugars increased IHCL in addition trials (standardized mean difference = 1.69 [95% CI, 1.00–2.37], P < 0.001), but no effect in substitution, subtraction and ad libitum trials. There was evidence of interaction by food source in addition trials with SSBs increasing IHCL and ALT, and mixed sources increasing AST. The overall certainty of evidence was high for SSBs on IHCL and ALT in addition trials and high to very low for all other comparisons.

Conclusions: Energy control and food source appear to mediate the effect of fructose-containing sugars on NAFLD markers. High certainty evidence suggests that SSBs providing excess energy increase NAFLD markers, while the evidence is less certain that mixed sources share the same effect and other food sources do not. More high-quality randomized trials of different food sources are needed to improve our estimates (ClinicalTrials.gov identifier, NCT02716870).

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