RESPONSE TO COMMENT ON LEE ET AL.

Relation of Change or Substitution of Low- and No-Calorie Sweetened Beverages With Cardiometabolic Outcomes: A Systematic Review and Meta-analysis of Prospective Cohort Studies. Diabetes Care 2022;45:1917–1930

Jennifer J. Lee,[1] Tauseef Khan,[1,2] and John L. Sievenpiper[1–5]

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We thank Buziau et al. (1) for their letter. Using Mendelian randomization, the authors examined the association between the rs2304681 minor allele in the gene encoding ketohexokinase and cardiometabolic outcomes. rs2304681 is a missense variant that impairs fructose metabolism, thereby acting as a proxy for fructose exposure. This allows for the examination of the association of fructose with cardiometabolic outcomes, a proposed mechanism by which sugar-sweetened beverages (SSBs) contribute to excess cardiometabolic harm.

Several lines of evidence suggest that SSBs contribute to cardiometabolic harm, with guidelines recommending a reduction in consumption. However, the optimal clinical and public health strategies for achieving SSB reduction were hitherto unclear due to limited evidence on the role of replacement beverages (e.g., low- and no-calorie sweetened beverages [LNCSBs]). Our recent findings of a systematic review and meta-analysis of prospective cohort studies (2) and randomized controlled trials (3) demonstrated that LNCSBs can be used as a replacement strategy similar to that for water for reducing cardiometabolic harm from SSBs. These studies also provided evidence that the causal pathway between SSBs and cardiometabolic outcome is via excess energy. New methodologies, including Mendelian randomization, can be a powerful tool to examine diet–disease relationships. However, the causal pathway between the exposure to SSBs and cardiometabolic outcomes, which is driven by excess energy, cannot be reduced to a single nutrient due to the complexity of nutrient interaction, the food matrix in which the nutrients are contained, and other consumption behaviors. Our previous systematic review and meta-analysis of cohort studies showed that fructose intake was not associated with diabetes, hypertension, or cardiovascular disease incidence (4) and had a nonlinear U-shape with cardiovascular disease mortality, indicating that while excess intake can be harmful, moderate intake might be associated with protection. Such a relationship can be understood when looking at the consumption behaviors of fructose (i.e., as part of a food source rather than as a single ingredient). Traditional extreme quantile meta-analyses and dose-response meta-analyses of food sources of fructose showed that SSBs were associated with increased risk of diabetes, metabolic syndrome, and hypertension, while yogurt, fruit, 100% fruit juice, and whole-grain breakfast cereals showed protective associations. Similarly, systematic review and meta-analysis of randomized controlled trials failed to show a harmful effect of fructose in energy-matched substitutions with other carbohydrates on cardiometabolic outcomes, with a signal for harm seen only when fructose provided excess energy (5). When intervention studies were stratified further by food source, cardiometabolic harm was observed only when fructose was consumed as SSBs providing excess energy, while other food sources in energy-matched substitutions failed to show harm. These results align with those of Buziau et al. (1) by demonstrating the signal for cardiometabolic

[1]*Department of Nutritional Sciences, Temerty Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada*
[2]*Toronto 3D Knowledge Synthesis and Clinical Trials Unit, Clinical Nutrition and Risk Factor Modification Centre, St. Michael's Hospital, Toronto, Ontario, Canada*
[3]*Division of Endocrinology and Metabolism, Department of Medicine, St. Michael's Hospital, Toronto, Ontario, Canada*
[4]*Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Ontario, Canada*
[5]*Department of Medicine, Temerty Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada*

Corresponding author: John L. Sievenpiper, john.sievenpiper@utoronto.ca

harm occurs when fructose provides excess energy in the form of SSBs; however, the results do not necessarily extend to fructose from other important food sources. Further investigation of the causal pathway between SSBs and cardiometabolic outcomes and the role of LNCSBs in that pathway are warranted to further understand this relationship.

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