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The Effects of Dietary Sugars on Cardiovascular Disease and Cardiovascular Disease–Related Mortality: Finding the Sweet Spot

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The role of diet for the prevention and treatment of noncommunicable chronic diseases (NCDs) has been object of intense scrutiny in the last several decades. Recent data suggest that dietary factors are responsible for more than 40% of the most common cardiometabolic-related deaths in the United States.[1] Most of the available evidence investigating the relationship between diet and cardiometabolic diseases, however, largely relies on observational studies that investigate the association between macronutrient and micronutrient consumption with the risk of NCDs, such as type 2 diabetes mellitus (T2DM), many forms of cancer, and cardiovascular (CV) diseases (CVDs). Importantly, such studies often investigate the role of diet in healthy individuals or in those with risk factors, providing evidence related to primordial and primary prevention of NCDs, with little evidence related to secondary prevention. Although the relationship between nutrient consumption and cardiometabolic diseases has been investigated for several macronutrients and micronutrients, the role of dietary fats (ie, saturated fats, unsaturated fats, and trans fats) and carbohydrates (ie, complex carbohydrates and simple carbohydrates) have certainly attracted the most attention.

Simple carbohydrates, also known as sugars, include monosaccharides (ie, glucose, fructose, and galactose) and disaccharides (ie, sucrose [glucose plus fructose], lactose [glucose plus galactose], and maltose [glucose plus glucose]). Initial concerns related to sugars' potential detrimental role on CV health were raised in the early 1960s.[2] Around the same time, low-fat diets were widely promoted to prevent coronary heart disease (CHD), although this was found to be ineffective 50 years later.[3,4] In response to these recommendations, consumers increased consumption of dietary carbohydrates, particularly sugars, which were later found to increase serum lipids, a major risk factor for CHD. To further support this preliminary evidence, a large meta-analysis of prospective studies including 173,753 participants found that sugars in the form of sugar-sweetened beverages (SSBs) were associated with greater risk for CHD, with a 16% relative risk (RR) increase of CHD for each additional daily serving.[5] More recently, data involving 127,536 individuals from the Nurses' Health Study and the Health Professional Follow-up Study confirmed a strong positive association between the intake of food rich in refined starches and added sugars with a 10% RR increase of CHD.[6] Conversely, this relationship was not found with food rich in complex carbohydrates (ie, whole grains), which were associated with a 9% RR reduction of CHD,[6] thereby supporting the concept that the quality of carbohydrates perhaps matters more than the total amount of carbohydrates. On the other hand, in a prospective study of the Framingham Heart Study Offspring cohort, intake of SSBs was not associated with increased CVD (ie, stroke).[7] With regards to added sugars, an analysis of the National Health and Nutrition Examination Survey found that added sugars were associated with a greater risk for CVD mortality; however, the greater increase was particularly evident in the very high quintiles of consumption,[8] suggesting that unless they reach a large proportion of daily caloric intake, dietary added sugars could be relatively safe, at least from a CVD mortality standpoint.

The lack of appropriately powered randomized controlled trials investigating the effects of such macronutrients on CHD, CVD in general, and CVD-related mortality remains a major concern. Pharmacologic strategies undergo rigorous CV outcomes trials, an approach that is highly encouraged but seldom used in nutrition research.[9] This methodology would allow the identification of a harm threshold for sugars consumption, if one exists. The American Heart Association[10] as well as the World Health Organization[11] currently recommend that dietary "free sugars," including added sugars and sugars naturally found in foods such as honey, syrups, fruit juices, and fruit juice concentrates,[11] do not exceed 10% of total daily calories, and the 2015−2020 Dietary Guidelines for Americans recommend to not exceed 10% of calories from "added sugars." However, such a threshold requires further validation because it was mostly chosen due to its relationship with the development of dental caries and weight gain, the latter being a major risk factor for T2DM and CVD.

In the current issue of *Mayo Clinic Proceedings*, Khan et al[12] performed a comprehensive systematic review and dose-response meta-analysis of prospective cohort studies including 624,128 individuals in an attempt to provide an answer to this important, yet largely under-investigated area of research. The elegant analysis assessed the role of individual as well as cumulative reported dietary intake (ie, food frequency questionnaires, 24-hour dietary recall, and 7-day food diaries) of simple carbohydrates, which were divided into total sugars (ie, monosaccharides and disaccharides), added sugars (ie, monosaccharides and disaccharides not naturally present in foods like fruits and fruit juices), and the individual sugars.

The results of the analysis are surprising: as opposed to what many would expect, the consumption of total sugars, sucrose, or fructose, was not associated with a linear dose-response association for the incidence of CVD. The consumption of total sugars and fructose alone were, however, associated with a 9% RR increase and an 8% RR increase in CVD mortality, whereas sucrose presented an inverse association with a 6% RR reduction for CVD mortality, with a 7% RR reduction for each 50-g increase of sucrose consumption. Added sugars were not significantly associated with CVD mortality. Importantly, the authors performed an elegant dose-response analysis of sugars consumption with CVD mortality, and they identified thresholds of 26%, 11%, and 13% of calories deriving from total sugars, fructose, and added sugars respectively, using a predefined amount of 2000-kcal diet. For each additional 50 g of total sugars, fructose, and added sugars consumption after the above described thresholds were reached, RR increases of 17%, 39%, and 17% were found, respectively. Importantly, many of the associations found in the overall population were affected by the sensitivity analyses conducted by the authors, suggesting that the effects of sugars consumption may vary significantly based on the population being investigated.

The study by Khan et al[12] provides novel and provocative findings, which suggest that although sugars may not be associated with the incidence of CVD, a very high level of consumption may be associated with greater CVD-related mortality. In addition, the threshold for harm with regards to CVD mortality identified by the authors for total sugars, fructose, and added sugars are clearly greater than what is recommended by major scientific societies (ie, <10%). The study from Khan et al,[12] if confirmed in randomized controlled trials, has the potential to have a great impact on future dietary recommendations to prevent CVD because the estimated added sugars consumption of the United States adult population is already very close to achieving a consumption below the threshold for harm identified in their study.[13-15] In that case, the great effort of reducing dietary sugar to prevent CVD and CVD-related mortality would not be justified by the evidence. The study by Khan et al[12] did not investigate the risk of sugars consumption with cardiometabolic diseases, such as T2DM. In fact, an analysis of the Health Professional Follow-up Study found that the highest quartile of SSB consumption was associated with a 24% RR increase of developing T2DM,[16] an obvious risk factor for the development of CVD and

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CVD-related mortality. Also, sugar intake may be more detrimental to those physically inactive, obese, and with those with components of the metabolic syndrome, whereas this would be less the case in physically active, lean, and/or metabolically healthy individuals.[17,18]

In conclusion, the role of dietary sugars on the risk of CVD and CVD mortality requires further investigation as the current evidence presents conflicting results. As for most clinical nutrition research and related recommendations from major societies, the evidence heavily relies on observational studies. Prospective randomized controlled trials are urgently needed to determine whether sugars, in fact, cause CVD and CVD mortality, and if yes, understanding the underlying mechanisms would also provide important scientific information. In that case, establishing a threshold for harm, as proposed by Khan et al,[12] would further inform scientific societies on the most appropriate dietary daily consumption of sugars. Ultimately, we advocate for the development of operator-independent biomarkers of sugars consumption to allow for a more objective assessment of dietary consumption, which to date, relies on validated, yet memory-based dietary assessments, which some have seriously questioned.[19]

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