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Artificial sweeteners, real risks

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In 2018 the American Heart Association advised that short-term replacement of sugar-sweetened beverages (SSB) with beverages containing low-calorie sweeteners, including artificially-sweetened beverages (ASB), may be an effective and realistic approach to calorie reduction and weight loss in some adults.[1] This advice reflects knowledge about the well-established adverse cardiometabolic effects of SSB and the reality that replacement of SSB with water may not be achievable for many adults habituated to the sweet taste of SSB. In comparison, evidence regarding the negative health effects of low calorie, nonnutritive sweeteners is relatively inconclusive, but growing.

The manuscript by Mossavar-Rahmani and colleagues in this issue of *Stroke*[2] is an important contribution to this epidemiological literature on the relationship between ASB and stroke, coronary heart disease (CHD), and mortality. The investigators used data from the Women's Health Initiative, a large, prospective, observational cohort study. Women who consumed an average of two or more ASB per day (≥24 ounces/day) had an elevated risk of all stroke, ischemic stroke, CHD, and all-cause mortality compared to those who consumed less than one ASB per week, adjusting for demographics, cardiovascular disease history and risk factors, body mass index (BMI), health behaviors, and overall diet quality. These findings are consistent with some, but not all, other prospective cohort studies in diverse US populations that have shown frequent consumption of ASB is associated with an increased risk of vascular outcomes, including stroke, diabetes, and dementia, even after adjusting for vascular disease risk factors[3–4,5,6,7,8,9,10,11]. Mossavar-Rahmani and colleagues have also provided novel findings regarding the association between heavy ASB consumption and specific stroke subtypes, including a strong association with small artery occlusion in

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particular, perhaps implicating hypertension or the metabolic syndrome as a potential mechanism. In addition, the increased risk of stroke, and ischemic stroke specifically, among frequent ASB consumers was observed among black participants, but not whites. These findings deserve further study.

Frequent consumption of ASB during mid- and late-life has now been associated with an increased risk of vascular events in multiple observational studies. But what remains unclear is the causal nature of these associations. Adults who frequently consume ASB may be heterogeneous: some spent their early adult years consuming SSB daily and only switched to ASB in an obese, prediabetic state, while others consumed ASB for decades as part of an overall healthy nutrient-dense diet, and still others rarely consumed SSB and only incorporated ASB into their diet later in life to reduce calorie consumption and lose weight. For some, the incorporation of ASB into the diet may lead to total daily calorie reduction, while for others it may not have this effect. Examining vascular disease risk in these different subsets of ASB consumers may elucidate the potential causal nature of the associations. Thus, in order to better understand the impact of ASB consumption on vascular disease risk, investigators need to better capture the duration, patterns, and reasons for ASB consumption, as well as the role of confounding factors, like obesity and insulin resistance. Weight change and dieting habits prior to enrollment into studies are likely important explanatory factors for the observed associations between ASB consumption and cardiometabolic health.[12] Future studies are also needed to identify the potentially varied impacts of different types of artificial sweeteners. To date, observational epidemiological studies have assessed ASB consumption as a single entity, despite the possibility of heterogeneous effects on cardiometabolic health across an increasing variety of artificial sweeteners.

A notable strength in the study by Mossavar-Rahmani and colleagues was the inclusion of sensitivity analyses excluding participants with a history of diabetes or cardiovascular disease prior to assessment of ASB consumption habits. These analyses are less prone to bias due to reverse causality, whereby some frequent ASB consumers may have started this habit as the result of diabetes or CVD. The associations of frequent ASB consumption with incident stroke, CHD, and all-cause mortality remained relatively unchanged, and were not attenuated, in these analyses, partially allaying concerns about biased associations. These sensitivity analyses cannot entirely exclude the possibility of reverse causality, however, as they did not exclude all participants with prediabetes, overweight and obesity, or the metabolic syndrome.

Perhaps most interesting were the analyses stratified by BMI category. Heavy ASB consumption was associated with an increased incidence of stroke only among the obese, with no association evident among those of normal BMI or overweight. In contrast, all-cause mortality was increased among frequent ASB consumers who were normal weight or overweight, but not definitely among those who were obese. The trends for stroke could be interpreted as supporting the hypothesis that reverse causality explains much of the increased risk for frequent ASB consumers, since it was not observed when the population was limited to those with normal BMI. Alternatively, it can also be interpreted to support the possibility that ASB consumption leads to weight gain as a mediating (causal) pathway. In

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the absence of data on trajectories of SSB and ASB consumption over time and corresponding weight changes, these possible explanations remain hypotheses for further exploration.

The present study, like others on this topic, assessed ASB consumption at a single time point, reflecting consumption habits over a three-month period. The lack of repeated ASB assessments and paucity of data on ASB consumption history and weight fluctuations may be the most important limitations of this and previous cohort studies exploring the health effects of ASB. Although diet quality tends to remain stable in other study populations, particularly among weight-stable adults, a single assessment of ASB consumption may not always reflect long-term exposure.

Experimental evidence provides support for several potential causal mechanisms that could explain an elevated risk of vascular-related diseases among heavy ASB consumers. For example, consumption of artificial sweeteners has been shown to result in sugar cravings and dependence, impaired caloric compensation resulting in appetite stimulation, increased consumption, weight gain, and glucose intolerance.[13–14,15] ASB may even impact glucose tolerance through mechanisms involving altered gut microbiota.[16] Existing data on beverage consumption and obesity is largely cross-sectional, and show that ASB consumption is more frequent among overweight and obese adults.[17] Though short-term clinical trials in humans have provided some encouraging evidence of the potential for ASB to promote weight loss when substituted for SSB, prospective observational studies and those in rodents have yielded highly inconsistent results, with some associating consumption of artificial sweeteners with weight gain.[1,13] However, even with the availability of potential causal mechanisms, the observed associations likely also reflect to some extent residual confounding or reverse causality. It seems likely that at least some of the population switches to heavy consumption of ASB in place of SSB late in life when they are already at a significantly elevated risk for vascular disease, perhaps in part due to decades of frequent SSB consumption. Long-term prospective epidemiological studies with sequential dietary assessments starting in early- or mid-adulthood are necessary to elucidate this bias, characterize individual soda consumption trends in a population, and relate these to trajectories of metabolic risk factors and incident vascular events.

Continued public health campaigns to reduce consumption of SSB are prudent. Replacing SSB with water is challenging for heavy consumers, however. The impact of various replacement choices likely varies over the lifecourse and deserves further investigation. Future studies are necessary to help elucidate the relative vascular risk trajectories of those who habitually consume SSB compared to those who switch to ASB consumption at different stages of adulthood and those who replace SSB with water or other beverages, like coffee or tea. The public health relevance of continued research on vascular health effects of ASB consumption is underscored by its prevalence. Despite the continued decline in recent years, ASB consumption remains high, with 31% of adults reporting low-calorie sweetened beverage consumption in a 2009–2012 survey.[1,18] Until we have more evidence to better understand who, if anyone, benefits from consumption of ASB, we should emphasize water as the healthiest substitute for SSB. If ASB consumption is used to wean off SSB, it should

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be viewed as a time-limited intermediate in the transition to water and other healthier beverages.

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References:

1. Johnson RK, Lichtenstein AH, Anderson CAM, Carson JA, Després JP, Hu FB, et al. Low-Calorie Sweetened Beverages and Cardiometabolic Health: A Science Advisory From the American Heart Association. Circulation. 2018;138:e126–e140. [PubMed: 30354445]
2. Mossavar-Rahmani Y, Kamensky V, Manson J, Silver B, Rapp S, Haring B et al. Artificially Sweetened Beverages & Stroke, Coronary Heart Disease, All-Cause Mortality in the Women's Health Initiative. Stroke. 2019 (In press).
3. Vyas A, Rubenstein L, Robinson J, Seguin RA, Vitolins MZ, Kazlauskaite R, et al. Diet drink consumption and the risk of cardiovascular events: A report from the women's health initiative. J Gen Intern Med. 2015;30:462–468. [PubMed: 25515135]
4. Fung TT, Malik V, Rexrode KM, Manson JE, Willett WC, Hu FB. Sweetened beverage consumption and risk of coronary heart disease in women. Am J Clin Nutr. 2009;89:1037–1042. [PubMed: 19211821]
5. Imamura F, O'Connor L, Ye Z, Mursu J, Hayashino Y, Bhupathiraju SN, Forouhi NG. Consumption of sugar sweetened beverages, artificially sweetened beverages, and fruit juice and incidence of type 2 diabetes: systematic review, meta-analysis, and estimation of population attributable fraction. Br J Sports Med. 2016;50:496–504. [PubMed: 27044603]
6. Bernstein AM, de Koning L, Flint AJ, Rexrode KM, Willett WC. Soda consumption and the risk of stroke in men and women. Am J Clin Nutr. 2012;95:1190–9. [PubMed: 22492378]
7. Gardener H, Moon YP, Rundek T, Elkind MSV, Sacco RL. Diet Soda and Sugar-Sweetened Soda Consumption in Relation to Incident Diabetes in the Northern Manhattan Study. Curr Dev Nutr. 2018;2:nzy008. [PubMed: 29955723]
8. Gardener H, Rundek T, Markert M, Wright CB, Elkind MS, Sacco RL. Diet soft drink consumption is associated with an increased risk of vascular events in the Northern Manhattan Study. J Gen Intern Med. 2012;27:1120–6. [PubMed: 22282311]
9. Pase MP, Himali JJ, Beiser AS, Aparicio HJ, Satizabal CL, Vasan RS, et al. Sugar- and Artificially Sweetened Beverages and the Risks of Incident Stroke and Dementia: A Prospective Cohort Study. Stroke. 2017;48:1139–1146. [PubMed: 28428346]
10. Narain A, Kwok CS, Mamas MA. Soft drinks and sweetened beverages and the risk of cardiovascular disease and mortality: a systematic review and meta-analysis. Int J Clin Pract. 2016;70:791–805. [PubMed: 27456347]
11. de Koning L, Malik VS, Kellogg MD, Rimm EB, Willett WC, Hu FB. Sweetened beverage consumption, incident coronary heart disease, and biomarkers of risk in men. Circulation. 2012;125:1735–41. [PubMed: 22412070]
12. de Koning L, Malik VS, Rimm EB, Willett WC, Hu FB. Sugar-sweetened and artificially sweetened beverage consumption and risk of type 2 diabetes in men. Am J Clin Nutr. 2011;93:1321–7. [PubMed: 21430119]
13. Pereira MA. Sugar-sweetened and artificially-sweetened beverages in relation to obesity risk. Adv Nutr. 2014;5:797–808. [PubMed: 25398745]
14. Swithers SE, Davidson TL. A role for sweet taste: calorie predictive relations in energy regulation by rats. Behav Neurosci. 2008;122:161–173. [PubMed: 18298259]
15. Yang Q Gain weight by "going diet?" Artificial sweeteners and the neurobiology of sugar cravings: Neuroscience 2010. Yale J Biol Med. 2010;83:101–8. [PubMed: 20589192]

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16. Suez J, Korem T, Zeevi D, Zilberman-Schapira G, Thaiss CA, Maza O, et al. Artificial sweeteners induce glucose intolerance by altering the gut microbiota. Nature. 2014;514:181–186. [PubMed: 25231862]
17. Bleich SN, Wolfson JA, Vine S, Wang YC. Diet-beverage consumption and caloric intake among US adults, overall and by body weight. Am J Public Health. 2014;104:e72–8.
18. Sylvetsky AC, Jin Y, Clark EJ, Welsh JA, Rother KI, Talegawkar SA. Consumption of low-calorie sweeteners among children and adults in the United States. J Acad Nutr Diet. 2017;117:441–448. [PubMed: 28087414]