Editorial

Sugar-Sweetened and Artificially Sweetened Beverages in Relation to Stroke and Dementia

Are Soft Drinks Hard on the Brain?

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See related article, p 1139.

Although the consumption of sodas has been decreasing in most Western countries during the past 2 decades, sugar-sweetened beverages (SSBs) are the leading sources of added sugars in the US diet and are increasing on a global level.[1–3] As measured by the recommendation of the 2015 World Health Organization Guideline on the intake of free sugars, a single can of sugar-sweetened soda contains about the upper limit of the recommended 25 to 50 g per day.[4] Moreover, the American Heart Association/American Stroke Association has defined 1 component of an ideal cardiovascular diet as consisting of ≤450 kcal/wk of SSBs. The harmful effects of regular SSB consumption, including weight gain, the metabolic syndrome, and type 2 diabetes mellitus, have been demonstrated in numerous large observational studies.[5–9] Furthermore, a higher intake of SSBs has been repeatedly associated with increased risks of hypertension, coronary heart disease, and stroke, as well as with adverse changes in lipid levels and inflammatory markers.[10,11] A recent estimation based on nationally representative data calculated that >50 000 cardiometabolic deaths in US adults in 2012 can be attributed to high SSB consumption, making SSBs the leading factor associated with cardiometabolic mortality in young and middle-aged adults.[12]

Artificially sweetened beverages (ASBs) are marketed as healthier alternatives to SSBs. Their consumption is rising in the United States, particularly among children.[13] The American Heart Association and American Diabetes Association have given a cautious nod to the use of artificial sweeteners in place of sugar to combat obesity, metabolic syndrome, and diabetes mellitus,[14,15] but there is still uncertainty about the benefits and even healthfulness of ASBs.[16] Several large observational studies, including the Atherosclerosis Risk in Communities Study,[17] the Framingham Heart Study,[18] and the Multi-Ethnic Study of Atherosclerosis,[19] reported a positive association between diet soda consumption and increased risks of the metabolic syndrome and type 2 diabetes mellitus. Results from the Northern Manhattan Study further indicated that diet soda consumption was associated with an increased risk of stroke, myocardial infarction, and vascular death,[20] and a study based on combined data from the Nurses' Health Study the Health Professionals Follow-Up Study reported higher incidence of hemorrhagic strokes in subjects with high regular low-calorie soda intake.[21] Alternatively, other longitudinal studies have not confirmed the association between the intake of ASB and cardiovascular disease risk.[11,22]

In this issue, Pase et al[23] contribute new data to this debate. Using prospective data from the Framingham Offspring Cohort, they analyzed the relationship between recent and long-term consumption of SSBs and ASBs and the risks of incident stroke and dementia. On the basis of participants who completed a validated food frequency questionnaire between 1998 and 2001 and additionally during at least 1 of the 2 previous examination cycles (1991–1995 and 1995–1998), the authors found that during a follow-up of 10 years, higher recent and cumulative intake of artificially sweetened soft drinks was associated with an increased risk of ischemic stroke, all-cause dementia, and Alzheimer's dementia. The effects persisted when analyses were adjusted for total caloric intake, diet quality, physical activity, and smoking status. However, the associations between recent and higher cumulative intake of artificially sweetened soft drinks and dementia were no longer significant after additional adjustment for vascular risk factors and diabetes mellitus.

In the study by Pase et al,[23] the intake of SSBs was not associated with stroke or dementia. This finding could be attributed to selection bias, such that particularly vulnerable participants, that is, long-term SSB consumers with a very high cardiovascular risk died earlier. This could also explain the lower-risk profile of high SSB consumers compared with high ASB consumers the data of which were collected in 1998 to 2001. As already discussed, the results from previous studies of associations between SSB and stroke and the direct causal pathways linking SSB and vascular outcomes provide ample evidence to support World Health Organization and American Heart Association/American Stroke Association initiatives to reduce the consumption of SSBs.

The interpretation of the association between ASB consumption and vascular outcomes is more controversial. Is there a direct or indirect causal pathway or is there an association because of bias from reverse causation? As discussed in the works of Gardener et al[20] and Pase et al,[23] confounding by reverse causation cannot be ruled out in these observational studies. People at increased risk of vascular events because of preexisting vascular risk factors may switch from regular to diet soft drinks in an attempt to control weight and insulin resistance. It is entirely possible that the intake of ASB starts

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after the cardiovascular risk is increased and, therefore, is a marker of a high-risk profile rather than being a causal risk factor for stroke or dementia. The data presented by Pase et al[23] can be interpreted in favor of this hypothesis: compared with people with high intake of SSBs, participants regularly consuming ASB showed a higher prevalence of hypertension, diabetes mellitus, and cardiovascular disease.

Whether the observed associations between ASBs and vascular outcomes reflect reverse causation bias is difficult to elucidate. In the epidemiological literature, adjustment for vascular risk factors has typically attenuated many of the effects of ASBs. This can be interpreted as either a reduction in bias because of confounding or blocking of potential indirect causal pathways through which ASB consumption may impact cerebrovascular health. ASB consumption may occur because of weight gain but could also exacerbate these conditions. Disentangling these effects and their temporality is challenging in epidemiological studies. Sensitivity analyses such as excluding high-risk subjects also attenuated effects in this study, but similar analyses have not resulted in the attenuation of effects in all studies. Sensitivity analyses in which the first several years of follow-up are excluded is also an option to help minimize bias caused by reverse causality, and such analyses have not eliminated the observed relationship between ASB consumption and diabetes mellitus.[24]

From a biological perspective, there are no obvious pathways. Studies on the effects of ASB consumption on weight gain have yielded inconsistent results. There is some experimental work suggesting that artificial sweeteners may increase cravings for high glycemic and high-calorie foods, induce glucose intolerance, or impair caloric compensation, thereby increasing calorie intake and body weight.[25,26] Another proposed mechanism refers to advanced glycation end products, which are produced during the process of caramelization used in some ASBs and SSBs which might be proinflammatory and promote insulin resistance.[18] Other hypothesized mechanisms linking ASB consumption with adverse vascular effects and insulin resistance include hormonal and microbiota effects,[25] and the phosphoric acid in diet soda has also been hypothesized to play a role in vascular outcomes.[8] None of these hypotheses have been adequately proven calling for more experimental studies. In light of inconsistent evidence in the epidemiological literature, coherence with laboratory findings will provide important information to determine causality.

Nevertheless, both, the causal and bias hypotheses, are possible interpretations of these observational data, and further studies are needed. One possibility could be a cohort starting in childhood and following up through adolescence and adulthood thereby closely monitoring changes in nutrition and the development of (subclinical) vascular disease. Long-term prospective studies will help inform the temporality of vascular outcomes in relation to ASB consumption and the sensitive periods during the life course during which ASB consumption may have the greatest impact on brain and heart health. Another, less valid, but faster, option would be a retrospective collection of data on lifetime exposures on nutrition and associated health behaviors to facilitate the characterization and stratification of different exposure groups.[20] In future epidemiological studies, we recommend greater collection of data that may help answer these questions, including previous weight fluctuations, dieting behavior, changes in SSB/ASB consumption over time, and reasons for choosing ASB consumption.

The work by Pase et al[23] highly encourages further discussion and more research into this question, for even small causal effects would have tremendous effects on public health due to the popularity of both ASB and SSB consumption. The current body of literature is inconclusive about the causal nature of the associations between ASB consumption and risk of stroke, dementia, diabetes mellitus, and the metabolic syndrome. The growing number of epidemiological studies showing strong associations between frequent consumption of ASBs and vascular outcomes, however, suggests that it may not be reasonable to substitute or promote ASBs as healthier alternatives to SSBs. Both sugar-sweetened and artificially sweetened soft drinks may be hard on the brain.

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