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Sugar- and artificially-sweetened beverages in relation to stroke and dementia - Are soft drinks hard on the brain?

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Although the consumption of sodas has been decreasing in most Western countries during the last two 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 WHO Guideline on the intake of free sugars, a single can of sugar-sweetened soda contains about the upper limit of the recommended 25–50 grams per day[4]. Moreover, the AHA/ASA has defined one component of an ideal cardiovascular diet as consisting of ≤450 kcal/week of sugar-sweetened beverages. The harmful effects of regular SSB consumption, including weight gain, the metabolic syndrome and type 2 diabetes, 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 more than 50,000 cardio-metabolic deaths in US adults in 2012 can be attributed to high SSB consumption, making SSBs the leading factor associated with cardio-metabolic mortality in young and middle-aged adults[12].

Artificially sweetened beverages (ASBs) are marketed as healthier alternatives to sugar-sweetened beverages. Their consumption is rising in the US, particularly among children[13]. "The American Heart Association (AHA) and American Diabetes Association (ADA) have given a cautious nod to the use of artificial sweeteners in place of sugar to combat obesity, metabolic syndrome, and diabetes"[14,15], but there is still uncertainty about the benefits and even healthfulness of artificially sweetened beverages[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. 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

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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 the current issue, *Pase et al.*[23] contribute new data to this debate. Using prospective data from the Framingham Offspring Cohort, they analysed the relationship between recent and long-term consumption of sugar- and artificially-sweetened beverages and the risks of incident stroke and dementia. Based on participants who completed a validated food frequency questionnaire between 1998 and 2001 and additionally during at least one of the two 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.

In the study by Pase et al. [23], the intake of sugar-sweetened beverages was not associated with stroke or dementia. This finding could be attributed to selection bias, such that particularly vulnerable participants, i.e. 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 to high ASB consumers the data of which were collected in 1998–2001. As already discussed, the results from prior studies of associations between SSB and stroke and the direct causal pathways linking SSB and vascular outcomes provide ample evidence to support WHO and AHA/ASA 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 due to 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 due to pre-existing 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 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. can be interpreted in favor of this hypothesis: Compared to people with high intake of sugar sweetened beverages participants regularly consuming ASB showed a higher prevalence of hypertension, diabetes and cardiovascular disease.

Whether the observed associations between ASBs and vascular outcomes reflect reverse causation bias is difficult to elucidate. In the epidemiologic 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 due to 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 the

current 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 due to reverse causality, and such analyses have not eliminated the observed relationship between ASB consumption and diabetes[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 artificially and sugar-sweetened beverages 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 epidemiologic literature, coherence with laboratory findings will provide important information to determine causality.

Nevertheless, both, the causal and bias hypothesis, 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 as well as 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 life time “exposures” regarding nutrition and associated health behaviours to facilitate the characterization and stratification of different exposure groups[20]. In future epidemiologic studies, we recommend greater collection of data that may help answer these questions including previous weight fluctuations, dieting behaviour, changes in SSB/ASB consumption over time, and reasons for choosing ASB consumption.

The work by Pase et al. 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 regarding the causal nature of the associations between ASB consumption and risk of stroke, dementia, diabetes, and the metabolic syndrome. The growing number of epidemiological studies showing strong associations between frequent consumption of ASBs and vascular outcomes, however, suggest that it may not be reasonable to substitute or promote ASBs as healthier alternatives to SSBs. Both sugar- and artificially- sweetened soft drinks may be hard on the brain.

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