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Perspective

Increased Fructose Intake as a Risk Factor For Dementia

B. C. M. Stephan,[1] J. C. K. Wells,[2] C. Brayne,[1] E. Albanese,[3] and M. Siervo[4]

[1]Institute of Public Health, University of Cambridge, UK.
[2]Childhood Nutrition Research Centre, University College London, Institute of Child Health, UK.
[3]Medical Research Council, Unit for Lifelong Health and Ageing, London, UK.
[4]Human Nutrition and Physiology Unit, University of Naples "Federico II," Italy.

Address correspondence to M. Siervo, MD, MSc, Human Nutrition and Physiology Unit, University of Naples "Federico II," via Pansini 5, 80100, Naples, Italy.

The transition in the world age demographic toward older age is associated with an increased risk of neurodegenerative diseases, such as Alzheimer's disease. Risk profiles for dementia may also be changing. Obesity and type 2 diabetes have increased in prevalence in the last half-century and have been associated with increased dementia risk. Specific changes in nutrition may also represent a direct risk. A diet transition in the United States has occurred in the intake of refined sugar, particularly high-fructose corn syrup (HFCS) from a yearly estimate of 8.1 kg/person at the beginning of the XIX century to a current estimate of 65 kg/person. This article considers the association between refined sugar intake, markers of cardiovascular disease risk, and the possible promotion of the development of dementia.

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The American Heart Association (AHA) has recently released new recommendations to reduce the dietary intake of added sugars. Such changes are advocated due to the established link between high sugar intake and metabolic derangement and adverse health conditions including, for example, obesity and diabetes (1). The statement of the AHA report did not mention the potential effects of added sugars on risk of chronic neurodegenerative diseases, such as dementia, either through a direct influence on pathogenesis or through metabolic diseases, such as diabetes or hypertension. Animal models of dementia suggest that excess consumption of fructose contained in refined sugars like sucrose and high-fructose corn syrup (HFCS) can promote dementia pathogenesis through increased central neuronal insulin resistance and deposition of beta amyloid (associated with Alzheimer's disease, AD) (2,3). Currently, there is a lack of evidence for an effect of fructose on cognitive functions in humans, and a high intake of fructose-based sweeteners might be a significant risk factor for the development of dementia, independent of changes in the world age demographic and mortality rates (4–6). This article will explore the potential link between dietary and health secular trends in the United States, namely the growing consumption of fructose-based sweeteners as a risk factor for dementia in the ageing population.

Secular Trends in Dietary Intake and Risk of Chronic Disease

Data on fructose and refined sugar consumption from European and Asian countries are scarce. In these regions, dietary intake is typically not assessed individually but rather estimated from population food disappearance. As such, the current epidemiological evidence on secular trends and the association between sugar intake and cardiometabolic diseases is derived from data collected in American National Surveys (NHANES) (5) and population-based cohorts including, for example, the Framingham study (7) and the Nurses Health Study (8). We will use available U.S. data to explore the potential association between increased fructose intake and risk of cognitive decline with the assumption that any association can be extrapolated to countries with similar demographic and health/lifestyle behaviors.

Recent diet secular trends include reduced fat intake and increased intake of refined carbohydrate, especially with regard to HFCS (5,9). The powerful sweetening properties of fructose have been exploited by the food industry to increase the palatability and rewarding properties of food products (10). Initially, the food industry used sucrose (formed by one molecule of glucose and one of fructose); however, HFCS (formed by 55% fructose and 41% glucose) is now more commonly used due to ease of production, economic viability, as well as the powerful sweetening effects,

which are likely to induce more addictive consumption behaviors (10,11). Indeed, by the 1980s, HFCS represented about 80% of the refined sugar added to soft drinks, baking products, and ice creams (5,10,12).

Dietary intake of other macronutrients has also changed over the last 50 years. Public health campaigns to reduce saturated fat and cholesterol have been linked to a decline in fat intake. Theoretically, energy intake should have also declined given that fat is more energy dense (9 kcal/g) than either protein (4 kcal/g) or carbohydrate (4 kcal/g). In contrast to prediction, total energy intake has increased over the past 30 years by an average of 150–300 cal/day. This has mostly been accounted for by an increase in sugary drinks (9). In addition, a decline in fiber intake has also been observed (9) as reflected in decreased population consumption of whole grains, mainly fruit and vegetables, and an increase in more refined carbohydrates. Independent to those changes known to affect cognitive and metabolic risk, including, for example, change in the age demographic, increased education, better medical care and nutrition in early life, as well negative changes such as decreased physical activity and increased psychosocial stress, secular trends in dietary intake may adversely affect both metabolic and cognitive health, thereby increasing dementia risk. This may be particularly true in transitional developing countries where population ageing and projected increases in chronic diseases are steepest (6), and early life adverse circumstances, coupled with Westernized dietary and lifestyle habits later in life, constitute an exceptionally detrimental combination of factors (13).

With regard to metabolic disease, the prevalence of overweight and obesity (body mass index $\geq$25 kg/m^2) in the U.S. population was relatively stable till the 1980s, but a major increase in prevalence has been seen, particularly in children and adolescents in the last 30 years (14,15). The prevalence of type 2 diabetes (T2D) has also increased steadily, but caution is needed in interpretation of the cause of change as diagnostic criteria have also been altered in the last 50 years (14). The prevalence of hypertension and hypercholesterolemia show a negative trend (14), but it remains to be elucidated whether this reflects (a) more effective pharmacological treatment, (b) change in dietary intake (decrease in fat and salt intake), or (c) an interaction of the two.

Fructose and Dementia: A Potential Time Bomb

The pathophysiology of dementia is complex and may include genetic, physiological, as well as nutritional elements, some of which may be linked (16) all through the life course (17). With regard to diet, single nutrients as well as specific dietary patterns (eg, Westernized diet compared with a Mediterranean diet) (18–20) have been associated with increased dementia risk (21). Given the multifaceted nature of dementia, the assessment of the proportional contribution of each risk factor to the total risk of dementia is essential to develop more effective and targeted preventative strategies.

In some individuals, the increased prevalence of metabolic diseases and risk of dementia may represent, at least in part, a pathological epiphenomenon of the same dietary secular trend (22). As such, in those countries with intakes similar to the United States, future dementia in some individuals might be associated with the increased intake of added sugars containing fructose. We discuss the possible mechanisms of this association later in the section on the mechanistic connection between fructose and dementia.

Fructose Metabolism

Fructose is an isomer of glucose, which exists in aqueous solutions in two distinct chemical forms in constant equilibrium (a five-ring and a six-ring form) (10). The "open" chemical structure of fructose is more reactive than glucose and interacts rapidly with proteins to form reactive adducts (Maillard reaction) (23). It is this property that has been exploited by the food industry for the preparation of baking products (10). High fructose intake can directly or indirectly induce protein degeneration by increasing the formation of glycated proteins and oxidative stress (23–25).

Fructose is absorbed in the small intestine, which can rapidly adapt to changes in fructose intake. The fructose molecule is uptaken by the enterocyte and transported into the portal vein by an insulin-independent transporter (GLUT-5) (26). Fructose is characterized by a high first-pass hepatic metabolism, and the high hepatic extraction rate is related to the low constant of affinity of the glycolytic enzyme fructokinase, which catalyses the phosphorilation of fructose into fructose-1-phosphate, which accelerates the cellular depletion of ATP (4). Fructose enters the glycolytic pathway bypassing the main energetic gateway of the enzyme phosphofructokinase, and it is converted into glycerol-3-phosphate and pyruvate (27). These molecules will form the structural backbones for the synthesis of triglycerides (de novo lipogenesis, DNL) and glucose (gluconeogenesis, GLN). The newly formed triglycerides will be assembled into very low-density lipoproteins, whereas the new glucose will be released into circulation. These new molecules will increase the glucose plasma pool and will further stimulate the secretion of insulin by the pancreatic beta-cells. Insulin is an anabolic hormone and, in an organism in positive energy balance, determines an increase in the deposition of fat in adipose tissue and other organs (ie, ectopic fat deposition). Fructose also increases the production of uric acid (UA) via an increased production of inosine 5′-phosphate and activation of xanthine oxidase (27). UA is the final byproduct of the metabolism of purines and recent evidence suggests that elevated plasma levels of UA are associated with an increased cardiovascular risk (28).

If these metabolic insults become chronic, they can lead to the development of a state of insulin resistance, which is characterized by an increase in insulin secretion to counteract the decrease in insulin sensitivity in the tissues (29). Excessive fructose intake has also been linked to high blood

pressure and endothelial dysfunction via a reduction in nitric oxide (NO) production (30) and increased energy intake via an increase in orexigenic signaling peptides levels (NPY and AgRP) in the hypothalamus (31).

Fructose does not directly stimulate insulin secretion, and it has a low glycaemic index, which determines smaller increments in plasma glucose levels in healthy participants and T2D (32). This effect was believed to be beneficial, and fructose was recommended as sweetener to participants with diabetes. However, these early studies also demonstrated that fructose was associated with higher levels of postprandial triglycerides and cholesterol in participants with T2D (32). The current guidelines for the nutritional management of diabetes recognize the beneficial effects of low intake of fructose in natural foods like honey and fruit (33). However, the guidelines do not recommend the use of fructose as a sweetening agent due to the effects on plasma lipids (33). Stanhope and colleagues (24) tested in overweight and obese participants the metabolic effects of consumption of fructose- and glucose-sweetened beverages (25% of energy requirements) for 10 weeks. At the end of the trial, the fructose group had more elevated fasting and postprandial insulin and glucose levels compared with the glucose group. A similar study testing the long-term metabolic effects of fructose intake on glucose control in diabetic participants has not been carried out.

Fructose and Dementia: The Mechanistic Connection

To date, no studies exploring the short- or long-term effects of fructose intake on cognition have been undertaken in humans. Results from animal studies show that diets with higher fructose content result in rapid insulin resistance, compensatory hyperinsulinaemia and memory impairment. Rats exposed to a diet with high-fat/refined carbohydrate diets (40% of kilocalories from fat and 40% of kilocalories from sucrose) are found to have poorer memory and impairment in the signaling pathways (p-CREB) involved in neuronal plasticity in the hippocampal areas, when compared with rats on a low-fat/complex carbohydrate diet (34). A high-fat/refined carbohydrate diet even for a short duration (ie, 2 months) was also found to be associated with reduced hippocampal levels of brain-derived neurotrophic factor (BDNF) and impaired spatial learning (35). The simultaneous administration of both high-fat and high-sucrose diets in both studies, however, does not allow determination of the individual effects of each macronutrient (fat vs sucrose) on cognition. In a subsequent study (36) in which rats were fed a diet either supplemented with sucrose or fat, both the sucrose and the fat groups gained more weight and accumulated more visceral fat compared with the control group, but only rats fed with the supplemental sucrose diet displayed deficits in long-term spatial memory (36). The potential link between fructose-induced insulin resistance and cognitive impairment was investigated in two additional studies. The first (37) reported that rats fed diets supplemented with HFCS were more insulin resistant and cognitively impaired on spatial learning and ability tasks than nonsupplemented rats (37). Neuropathologically, they showed reduced dendritic spine density and a reduction in the hippocampal levels of BDNF (37). The second showed that hamsters fed with 60% fructose were characterized by a decrease in neuronal insulin signaling in the cerebral cortex and hippocampus (reduced phosphorylation of the insulin receptor and insulin receptor substrate 1) and an impairment of synaptic function (3).

Overall, the results suggest that insulin resistance status induced by high fructose intake and/or the insulin resistance syndrome (ie, metabolic syndrome) is linked to cognitive decline and neurodegeneration, namely AD type pathology (2, 35–38). This is supported by findings from animal models of AD (2). Insulin resistance (induced by a high-fat diet) has been found to be directly associated with an increase in amyloid deposition linked to an increased intracellular generation of beta amyloid (increase in secretases) and decreased activity of the insulin-degrading enzyme (IDE) (38,39). Furthermore, homozygous deletion of the IDE gene in rats has been linked to a decrease in beta amyloid and insulin degradation and accumulation of beta amyloid and hyperinsulinaemia (40).

The association between high fructose consumption and increased risk of cognitive impairment could also be mediated by the elevation of plasma levels of UA caused by high fructose intake (30). Elevated UA levels represent a biomarker of an increased activity of the xanthine oxidase, which, via an increased generation of reactive oxygen species and reduced levels of NAPDH, could reduce the NO synthesis and consequently increase the risk of atherosclerotic disorders and vascular dementia (VaD) (41). NO is a pleiotropic signaling molecule produced also in the brain by the neuronal form of the NO synthase, and it is directly involved in synaptic neurotransmission and memory formation (42). Two recent epidemiological studies have observed that an elevation of serum UA may be associated with cognitive decline in older participants (43,44), whereas one study found a protective effect (45). In addition, participants with AD have been found to have increased levels of circulating asymmetric dimethylarginine, a endogenous inhibitor of the endothelial and neuronal NO synthases (46).

In humans, no studies have been performed on the short-term and long-term effects of fructose on cognition and dementia risk. A small number of studies have provided preliminary evidence of an association between insulin resistance and brain structural changes whereby participants with T2D show deficits in cognitive performance and alterations of brain structures and volumes in hippocampal and periventricular areas (47-49).

The association between features of the metabolic syndrome (50,51) and of adiposity (52) and cognitive decline and dementia is well established in humans, though mechanisms are not fully understood (53,54). It is reasonable that

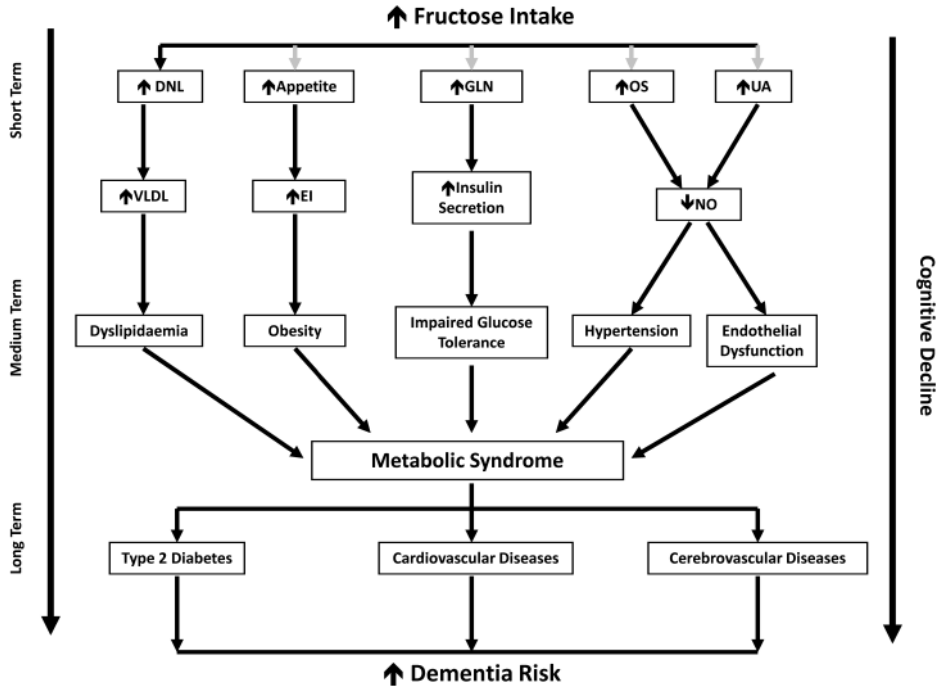

Figure 1. Potential causal mechanisms linking increased fructose intake with an increased risk of dementia. All these effects refer to human and animal studies in which have established a causal link between fructose and metabolic deregulation. The effects are divided according to the time that each effect of fructose would require to take place (short, medium, and long term) and the progression of cognitive decline with the increase severity of the metabolic abnormalities. Acronyms are ↑ = increase, ↓ = decrease, DNL = de novo lipogenesis, NO = nitric oxide production, GLN = gluconeogenesis, VLDL = very low-density lipoproteins, EI = energy intake, OS = oxidative stress, and UA = uric acid. The arrows are color coded to indicate the reliability of the evidence supporting the link between excessive fructose intake and each physiological disruption. Black arrows indicate consistent evidence in humans and animal studies. Gray arrows indicate inconsistent findings collected either in humans or in animal studies.

fructose might on the one hand confound, interact with, or mediate these associations, whereas on the other, its potential importance in neurodegeneration is still relatively unexplained. A recent study has demonstrated in overweight and obese women that high fructose intake is associated with increased DNL, lipid peroxidation, and GLN (24). Animal and human studies strongly suggest that these metabolic factors induce structural changes in key cognitive regions including, for example, the hippocampus (2,37,47). A schematic representation of the putative mechanisms linking high fructose intake to cognitive decline and increased dementia risk is presented in Figure 1.

The question therefore becomes if these findings are strong enough to construct a mechanistic hypothesis to link high fructose intake to increased dementia risk (eg, all cause dementia and its subtypes including AD and VaD) in individuals with a high fructose diet? This article suggests that this is highly plausible, and if true, then the increasing consumption of fructose in the U.S. population could lead to greater dementia risk either directly only or more likely in synergic combination with the concomitant increases in obesity.

Research and Public Health Priorities

Increasing evidence of a detrimental effect of fructose intake on metabolic health supports a possible major public health concern. There is an urgent need to elucidate the mechanisms of this association and determine whether a reduction in fructose intake can reverse any negative effects, particularly over long-term intake. The measures required to test the hypotheses raised in this article are not easily available; therefore, there is a need to (i) identify studies with existing data that can test these hypotheses and (ii) to develop new improved measures and include them in studies with current potential or to set up new studies. The fructose-dementia hypotheses outlined in this article need to be tested outside animal models, and these data are necessary before any public health interventions can be proposed.

Conclusions: Potential Future Risk?

Although the literature from animal studies suggests that increased refined sugar intake is associated with increased risk of neurodegeneration, evidence in humans is lacking. Better insight into the direct (and indirect) link between fructose intake and dementia risk is essential for informing public health policy to possibly ameliorate dementia risk through changing population eating habits and manipulating nutritional factors. Furthermore, worldwide changes in sucrose and HFCS intake also need to be considered to determine whether refined sugar–dementia risk associations are consistent across populations especially with regard to developing countries,

which are moving gradually into the degenerative disease stage while undergoing nutritional transition.

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