

REVIEW

Open Access

# The emerging role of dietary fructose in obesity and cognitive decline

Shaheen E Lakhan<sup>1,2\*</sup> and Annette Kirchgessner<sup>1,3</sup>

## Abstract

The incidence of obesity has increased dramatically over the past several years, and in parallel, so has the prevalence of type 2 diabetes (T2D). Numerous studies have demonstrated that both obesity and T2D are associated with lower cognitive performance, cognitive decline, and dementia. Intake of dietary fructose has also increased. In fact, high-fructose corn syrup (HFCS) accounts for as much as 40% of caloric sweeteners used in the United States. Given the increase in the incidence of Alzheimer's disease (AD), characterized by an age-related decline in memory and cognitive functioning, in this report we review the effects of obesity on cognitive performance and the impact of high fructose intake in promoting cognitive decline. The paper then considers the effects of omega-3 fatty acids (FAs), which have been linked to promising results in cognitive function including ameliorating the impact of a high-fructose diet.

**Keywords:** Obesity, Nutrition, Cognition, Fructose, Diabetes, Dementia, Omega-3 fatty acids

## Background

Obesity is a global health issue that has reached epidemic proportions. Greater than 60% of adults living in the U.S. and Europe are obese (body mass index (BMI)  $\geq 30$  kg/m<sup>2</sup>) [1-4]. Moreover, if obesity continues to increase at the present rate, projections indicate that more than 2.3 million adults will be obese by 2015 [5]. Childhood obesity has also become a global health issue and its incidence is increasing in both developed and developing countries. Available estimates (1980–1990) show that the incidence of childhood obesity increased by two to five times in developed countries, and almost four times in developing countries (e.g., from 4% to 14% in Brazil) [6]. An estimated 18% of U.S. children and adolescents are classified as obese [7]. In a recent study, the prevalence of overweight/obesity among American and Hispanic elementary school students in grade 4 was 44.5% [8].

Over the last three decades, the incidence of global diabetes has more than doubled, with nearly 1 in 10 adults affected worldwide [9]. Among U.S. veterans aged 65–85 years, ~30% had diabetes in 2010 [10], of which the overwhelming majority of the cases were type 2

(T2D). The global prevalence of diabetes for all age groups is projected to rise from 171 million in 2000 to 366 million in 2030 [11]. This is not surprising since obesity is a major risk factor for T2D. In fact, the diabetes epidemic appears to have gone hand-in-hand with the increases in obesity. T2D is linked to metabolic syndrome (MetS), defined by a cluster of symptoms including abdominal obesity, insulin resistance, hyperglycemia, dyslipidemia, and hypertension [12], most commonly associated with cardiovascular disease. The incidence of MetS is also rising. According to the Centers for Disease Control and Prevention, approximately 34% of American adults meet the criteria for MetS [13]. Moreover, nearly one third of overweight/obese adolescents had pediatric MetS [14]. Thus, chronic diseases, such as T2D and MetS, once observed solely in adulthood, are now commonly seen among the obese in childhood and are likely to track into adulthood.

Recent studies indicate that both obesity and T2D are associated with cognitive decline. Not only does midlife obesity increase the risk of developing late-life dementia [15,16], but also lower cognitive performance earlier in life is itself a risk factor for dementia later in life [17]. Interestingly, the fastest decline in cognitive function occurs in those with both obesity and metabolic abnormalities; however, individuals who were obese without

\* Correspondence: slakhan@gnif.org

<sup>1</sup>Global Neuroscience Initiative Foundation, Los Angeles, CA, USA

<sup>2</sup>Neurological Institute, Cleveland Clinic, 9500 Euclid Ave, S100A, 44195, Cleveland, OH, USA

Full list of author information is available at the end of the article

metabolic abnormalities, still developed a significant cognitive decline [18]. T2D is associated with reduced cognitive function [19] and an increased (1.5-2.5-fold) risk of dementia [20]. Impaired cognitive function is frequently exhibited by individuals with poorly controlled diabetes [21]. Cognitive impairment is also linked to MetS [22], and individuals with MetS in midlife are at increased risk of later life cognitive decline and dementia [23]. Similarly, the incidence of Alzheimer's Disease (AD), characterized by a progressive and debilitating decline in memory and cognitive functioning beyond that which is normally experienced with aging is projected to rise, increasing nearly four-fold over the next 40 years [24]. Thus, identifying the risk factors for delaying the onset and preventing the progression of these disorders is of utmost importance.

Although several factors, such as a lack of exercise, are likely contributors to the rising trend in obesity, increases in its prevalence are directly attributable to excessive caloric intake [25]. In addition, there is now strong evidence that excessive consumption of added sugars (sucrose and high-fructose corn syrup (HFCS)), contributes to rising obesity and diabetes rates [9,26]. There has been a substantial increase in the amount of HFCS found in the North American diet, primarily in soft drinks and fruit drinks [27]. Moreover, findings from large cross-sectional and prospective studies show that increased consumption of sugar-sweetened beverages is positively associated with obesity in both children and adults [28]. Thus, consumption of sugar-sweetened beverages appears to be a key contributor to the epidemic of overweight and obesity. In fact, countries with higher availability of HFCS have a higher prevalence of T2D compared to countries with low availability [29,30]. Since this difference was retained or strengthened after adjusting for BMI, the data suggest that countries with higher availability of HFCS have a higher prevalence of T2D independent of obesity [30]. Abundant consumption of fructose is also an important contributor to the MetS [31]. This raises concerns regarding the short and long-term effects of fructose in humans, and the possibility that fructose intake in childhood is associated with poorer academic performance and impaired cognitive function as an adult.

In this paper we review the association of obesity with cognitive performance. Since high fructose intake appears to be related to the current obesity epidemic, we also review the impact of added sugars on cognitive function and the beneficial effects of dietary supplementation of omega-3 fatty acids (FAs) [32-34].

#### **Proper nutrition is essential for cognitive function**

There is no doubt that proper nutrition is essential for cognitive function. Data suggest that the influence of nutrition on cognitive function begins during fetal life

[35,36]. A negative cognitive effect of prenatal caloric restriction has been shown in animals, and studies in humans demonstrate prenatal diet variation in micronutrients negatively affecting childhood cognitive function [37-41]. Prenatal under nutrition also negatively influences cognitive function in later life [36]. de Rooij et al. [36] showed that individuals experiencing famine during the early stage of gestation performed worse on a selective attention task. Since performance on this task usually declines with increasing age, the researchers hypothesized that this decline may be attributed to an increased cognitive aging process [36].

In contrast to the detrimental effects of inadequate nutrition on cognitive function, pre- and postnatal nutritional supplementation enhances cognitive development. In a longitudinal investigation of nutrition and mental development, Freeman et al. [42] found an association between nutritional status and cognitive measures, independent of social factors. Language scores in 3- and 4-year-old children in rural Guatemalan villages were higher in the offspring of mothers who received a high-protein calorie supplement during pregnancy and lactation than in the offspring of mothers who did not. Mothers supplemented with a high calorie diet consumed at least twice as many calories as mothers supplement with a low calorie diet, which may have also contributed to the results.

Even skipping breakfast, which occurs at a rate of 10-30% among children and adolescents in the U.S and Europe [43-45], affects cognitive functioning [46,47]. Skipping breakfast has been shown to negatively affect performance on measures of IQ, the Hagen Central Incidental Test, and the Matching Familiar Figure Test [48]. In contrast, breakfast has beneficial effects on cognitive function. In an internet based study involving children aged 6-16 years, children who ate breakfast performed better on tests of attention and memory than children who skipped breakfast, indicating that breakfast exerts a beneficial effect in maintaining cognitive function during the morning [49]. A very recent cross-sectional study of children aged 6 years showed that children who regularly have breakfast had significantly higher verbal and IQ test scores compared to children who "sometimes" have breakfast [50]. In addition, in a randomized, cross-over trial involving high school students (13-20-years-old), breakfast had positive short-term effects on visual-spatial memory and self-reported alertness; however, breakfast had no effect on sustained attention [51].

#### **Obesity and cognition**

There is no doubt that nutrition is critical for cognition and academic performance; however, food intake in excess of energy needs is linked to the development of obesity

[52] and obesity has been associated with poorer cognitive function [53,54].

In 2005, Jeong et al. [55] examined the association between obesity and cognition using data from a community study of South Korean adults ( $\geq 65$  years). Cognitive function was examined using the Korean Mini-Mental State Examination, and obesity using BMI and waist circumference, as measured at the level midway between the lower rib margin and the iliac crest [56]. Obesity ( $\text{BMI} \geq 25 \text{ kg/m}^2$ ) and poor cognitive performance were associated with above normal waist circumference, and poor cognitive performance was negatively associated with overweight ( $\text{BMI}$ , 23-25  $\text{kg/m}^2$ ) and normal waist circumference. Recently, Benito-Leon et al. [57] assessed cognitive function in a large population-based sample of overweight ( $\text{BMI}$  25-29  $\text{kg/m}^2$ ) and obese ( $\text{BMI} \geq 30 \text{ kg/m}^2$ ) elderly ( $\geq 65$  years) participants compared with normal weight controls living in the same community in central Spain (the Neurological Diseases in Central Spain study (NEDICES)). Subjects underwent assessment of cognitive function, which included the 37-item Mini-Mental State Examination (37-MMSE), a test that measures global cognition, tests of psychomotor speed, verbal fluency, memory and pre-morbid intelligence. The study found that obese/overweight status was associated with the lowest quartiles of the 37-MMSE, the Trail Making Test-A, verbal fluency, delayed free recall, and immediate logical memory and pre-morbid intelligence, indicating that overweight and obese participants performed poorer on cognitive tests than their normal weight counterparts. In other studies different aspects of cognition have been found to be negatively associated with BMI including memory [58,59], vocabulary [60], speed processing and reasoning [60]. These results support the association of obesity and impaired cognition in the elderly.

There is also evidence to support the association of obesity with poorer cognitive performance in midlife. A higher BMI in midlife was found to be associated with lower cognitive scores both in cross-sectional [58] and longitudinal [61] analyses. For example, in a prospective cohort study, Cournot et al. [58] analyzed data from healthy, non-demented, middle-aged men and women at baseline (32 to 62 years) and at follow-up, five years later, to assess the association between BMI and cognitive function. After adjustment for co-variables, including age, sex, educational level, blood pressure, diabetes, and other psychosocial factors, a higher BMI at baseline was associated with lower cognitive scores. Moreover, a higher BMI at baseline was associated with lower cognitive scores at follow-up, 5 years later. The association of BMI with decreased cognitive performance was significant for word-list learning (4 recalls). Several other investigators have reported similar results [54,58,60,62]. A higher BMI was

associated with lower cognitive function scores in healthy, black and non-black adults ( $\geq 65$  years); however, greater BMI was not predictive of cognitive decline as measured by the MMSE at an average follow-up of 6.4 years [62]. Thus, in this study, greater BMI in old age was not predictive of cognitive decline at follow-up.

There is also data to suggest that obesity is associated with impaired cognitive function in children [63]. Obesity has been linked to poorer academic achievement in school age children as well as greater destruction of brain architecture and function during aging [64]. Decreased amplitude and prolonged latency of P300 auditory event-related potentials were observed in children with obesity compared to that of healthy controls [65]. This difference in recordings of P300 auditory event-related potentials in obese children suggests impairment in cognitive functions [66]. Obese children in kindergarten up until the end of third grade, exhibit lower academic test scores [67]. Additionally, severely obese children have been reported to have lower IQs, display poorer school performance, and lower test scores than their overweight classmates [67]. In addition, adolescents with MetS had significantly lower spelling, attention, arithmetic, and overall mental flexibility with a trend for lower overall intelligence [68]. Furthermore, there is an inverse childhood full IQ/obesity association in adults [63]. However, after adjusting for educational attainment, the full IQ/obesity association was not significantly different [63], suggesting that educational level plays a role in the persistence of obesity in later life.

#### **Obesity, dementia and cognitive decline**

Several studies have shown that obesity in midlife is associated with increased risk of dementia in later life [55,69-85]. A 27-year longitudinal, population based study [81] showed that obese people ( $\text{BMI} \geq 30 \text{ kg/m}^2$ ) had a greater risk of dementia (74%) compared with those who were overweight ( $\text{BMI}$  25-29.9  $\text{kg/m}^2$ ) or normal body weight at 40-45-years of age (35%) [81]. Less is known about the association between obesity and cognitive aging. "Cognitive aging" refers to the inevitable cognitive decline that occurs with aging, with no evidence of dementia. The extent to which cognitive decline occurs is highly variable, and strongly affected by various disease processes. In general, cognitive abilities remain stable through adulthood and decline around the age of 65 years [86,87].

In the Swedish Adoption/Twin Study of Aging (SATSA) [88], the association between BMI and cognitive decline was examined among participants with an average age of 42. BMI and global cognitive ability were measured over a 20-year period beginning at age 25. The study showed that higher BMI was inversely related to global cognitive ability with longitudinal decline for both women and men as indicated by latent growth curve analyses. Early midlife

obesity was associated with a steeper decline in general cognitive ability and perceptual speed, with a tendency for a steeper decline in verbal and spatial abilities. Moreover, being stably obese over a longer period of time was associated with lower cognitive function in late life. In contrast, when obesity developed in late life, there was a steeper decline in only verbal ability. Since verbal ability remains stable over the adult life span until very old age [86], this can be seen as evidence that obesity is associated with cognitive decline. However, most studies assessing obesity in late life found no association between late-life obesity and late-life cognitive abilities [62,74]. Dahl and Hassing [74] conducted a systematic review to examine the association between obesity and cognitive aging among individuals without dementia. The reviewed studies showed clear evidence that midlife obesity was associated with cognitive aging, whereas this association was weaker in late life.

Sabia et al. [53] employing the Whitehall II cohort [18], determined whether cognition in late midlife is influenced by lifetime obesity. In this study, BMI at 25 years (early adulthood) was self-reported at baseline and was measured in early midlife (mean age, 44 years) and again in late midlife (mean age, 61 years). Cognition was evaluated in late midlife by using the 30-item MMSE, and tests of memory (verbal memory) and executive function (Alice Heim 4-I, tests of verbal and phonemic fluency). The study found that the proportion of the population that was either overweight or obese increased from 13.6% (age 25) to 63.1% (age 61). Moreover, long-term obesity in adulthood was associated with lower cognitive performance in late midlife. Those who were obese at 2 or 3 occasions had lower mean MMSE scores and scores of memory and executive function, adjusted for age, sex, and education, than did their normal-weight counterparts. Thus, an increase in BMI over the adult life course was associated with lower cognitive performance in late midlife, supporting earlier reports [58]. These data suggest that the association between obesity and cognition starts early in adulthood and continues to develop for many years.

#### **Obesity and cognition: the influence of metabolic factors**

Singh-Manoux et al. [18], employing the Whitehall II cohort, determined the association of BMI and metabolic status with cognition. A cognitive test battery consisting of 4 standard tasks was administered, which consisted of the Alice Heim 4-1, a test of reasoning, in addition to a recall test to test short-term memory, and two measures of verbal fluency. In addition, a global cognitive score was created based on the 3 tests mentioned above. The results indicated that at baseline, obese individuals (BMI  $\geq 30$  kg/m<sup>2</sup>) had lower cognitive scores than normal weight individuals. Moreover, the baseline differences were maintained over the 10-year follow-up. However,

cognitive decline on the global score was only faster among individuals with both obesity and metabolic abnormality. It is important to note, that although this trend was evident for all tests, it was statistically significant only for the global cognitive score.

The influence of metabolic abnormalities on the association between obesity and cognition was also observed in the Italian Longitudinal Study on Aging (ILSA) [89], a prospective study, which investigated the relationship of MetS with the incidence of mild cognitive impairment and its progression to dementia. In this study, the presence of MetS, characterized by abdominal obesity, hypertension, and hypertriglyceridemia, in individuals with mild cognitive impairment (MCI) was associated with a significantly higher incidence rate for progression to dementia over 3.5 years of follow-up. The risk in MCI patients with MetS almost doubled compared with those with MCI without metabolic abnormalities.

Hypertension was found to modulate the association between obesity and cognitive functioning in participants of the Framingham Heart study [90]. In this prospective study, BMI and blood pressure status were related to cognitive performance on tests administered 4-6 years later. The lowest levels of cognitive performance were seen for subjects with both hypertension and obesity as compared to those with either hypertension or obesity or neither of these risk factors. Interestingly, adverse effects of obesity and hypertension on cognitive performance were observed only in aging men. A synergistic influence of concomitant obesity and hypertension on cognition was also observed by Wolf et al. [61]. In this study, which employed the Framingham Offspring Study cohort, midlife measures of obesity and of hypertension were each significantly related to poorer cognitive performance on executive function and visual motor skills. Moreover, the relation of hypertension to cognitive performance was significantly modified by obesity. In addition to MetS and hypertension, diabetes has been linked to poorer cognitive performance; however, in this study, diabetes did not modify the effects of obesity on cognition [54], suggesting that the underlying mechanisms may be different.

#### **Added sugars and cognition**

Obesity is directly attributable to excessive caloric intake [25] and there is now strong evidence that intake of added sugars, mainly fructose and sucrose, contributes to the rising obesity and diabetes rates [9,26]. In particular, high-fructose corn syrup (HFCS)-sweetened beverages play a role in the development of obesity, and increased BMI is associated with their increased consumption. Intake of HFCS-sweetened beverages is also linked to metabolic abnormalities characteristic of the MetS. In addition,

several studies have shown that intake of added sugars is associated with lower cognitive function.

### **Fructose**

Fructose, an isomer of glucose, is a natural sugar found in many fruits. In equal amounts, it is sweeter than sucrose (glucose-fructose) and therefore commonly used as a sweetener. The commercial production of HFCS began in 1967. At that time, the fructose content of the syrup was ~15%. After several modifications, the fructose content was increased to 55% (HFCS-55) and it became the sweetener of choice for the soft drink and ice cream industries. Currently, HFCS accounts for 40% of all added caloric sweeteners [25,91]. Approximately 80% of added sugars in soft drinks, baking products, and ice creams consist of HFCS [25,92,93].

The intake of fructose has significantly increased over the past three decades and is derived largely from sucrose (composed of 50% fructose) and HFCS (42%, 55% or 90% fructose). In the US, yearly per capita caloric sweetener consumption rose around 20% since 1970 [94]. Interestingly, this increase coincides with the obesity epidemic. Data on self-reported food intake from the National Health and Nutrition Examination Survey (NHANES) suggest that ~15% of the US population consumes  $\geq$  25% of energy from added sugars [92]. The largest source of added sugars in the Western diet is sugar-sweetened beverages, which accounts for more than 10% of energy intake [95]. The consumption of sugar-sweetened beverages increased by ~135% between 1977 and 2001 [76] contributing to an increase in the consumption of all caloric sweeteners of ~83 kcal/person/day [77]. It is estimated that nearly 7% of daily caloric consumption in the U.S. is from HFCS [91]. More concerning is the fact that at least 30% of children (1-5 years of age) consumed sugar-sweetened beverages (soft drinks) [96].

The compositional similarity of HFCS to sucrose suggested that it was safe and would be metabolized in a similar manner. Thus, HFCS, like sucrose, was not perceived to pose a significant health risk, with the single exception of promoting dental caries [97,98]. Additionally, fructose does not directly stimulate insulin secretion and has a low glycemic index, which results in smaller increments in plasma glucose levels in healthy individuals and those with T2D [99]. As a result, fructose was accepted as a beneficial dietary component and fructose was recommended as a sweetener to patients with diabetes. However, there are differences in how these sugars are metabolized and utilized in the body. Meals high in fructose have been shown to reduce circulating insulin and leptin levels in women [91]. In contrast, dietary sucrose increases circulating insulin and leptin levels and inhibits eating, which in turn further inhibits food intake [100]. Accordingly, the level of satiety from fructose intake may be less than that of

glucose or sucrose and ultimately add to body weight. In support of this idea, increased fructose intake, particularly in the form of HFCS-sweetened beverages, has been implicated in promoting obesity [101,102]. Results from animal studies showed that rats with access (12 hours) to HFCS gained significantly more body weight than rats given equal access to sucrose (10%), even though they consumed the same number of total calories. Moreover, over the long term, rats with access to HFCS gained significantly more body weight than the sucrose-fed group. The HFCS group exhibited an increase in abdominal fat and elevated circulating triglyceride levels [103]. Studies have also shown that high fructose exacerbated weight-gain in rats that are subsequently maintained on a high-fat diet [104]. Thus, excessive consumption of HFCS may contribute to the rising incidence of obesity.

Intervention studies provide a clear view of the relationship between sugar-containing beverages and body weight in humans. In a well-conducted study by Cox et al. [105] in overweight/obese male and female subjects, consumption of fructose (at 25% of energy requirements for 10 weeks), but not glucose, led to significant decreases in resting energy expenditure, thus contributing to the build-up of excess energy substrates. Furthermore, in one of the population segments at high risk of fructose-related obesity, it was demonstrated that a significant reduction in fructose and/or general sugar intake over a short period of time (3 months) in overweight and obese children might reduce the BMI [106].

Despite these data, we do not have direct evidence that links obesity to the consumption of physiological daily intake of fructose (<100 grams) in humans. In addition, added fructose (< 50 g/day) has no deleterious effect on triglyceride levels, glucose control, or insulin resistance. Nevertheless, consumption of sugar-sweetened beverages is associated with excess calorie intake, and an increased risk of T2D through an increase in body weight [107]. The increasing intake of HFCS paralleled the upward trend in the prevalence of T2D observed in the U.S. during the 20th century [25]. Diets high in added-sugars promote visceral adiposity, dyslipidemia, and insulin resistance/glucose intolerance [28,91,108-111]—all components of the MetS [112]. Moreover, in animal studies, HFCS consumption seems to produce some of these changes associated with the MetS even without increasing the body weight [113]. This has led to the recommendation to limit the daily intake of added-sugars to no more than 10% of total energy [114].

### **Fructose and cognition**

Results from animal studies suggest that fructose intake may be associated with cognitive decline. Stranahan et al. [115] found that rats fed a high-fat, high-glucose diet and given access to HFCS displayed significantly

impaired cognitive function, possibly via the development of insulin resistance. Ross et al. [33] reported that a high fructose diet impairs spatial (hippocampal-dependent) memory in male rats. Their study showed that consuming a high fructose (60%) diet for almost 5 months increased the latency to reach the target and decreased time spent in the target quadrant and the number of target approaches in a spatial water maze probe test. High fructose intake did not influence navigational ability. In addition, the rats were able to learn and retain the location of the platform for short periods of time. Only impairments on the retention tests were recorded associated with high fructose intake (given 48 hours after training), which suggests that consumption of such a diet may impair long-term memory storage or retrieval, or both.

Impaired cognitive function by high fructose was also reported by Agrawal and Gomez-Pinilla [32]. Agrawal and Gomez-Pinilla investigated the impact of a diet deficient in omega-3 FAs (n-3 deficient), to represent the “normal” Western diet, and the MetS on cognition and synaptic plasticity, and concomitant changes in the hippocampus, a region of the brain critical for learning and memory. Rats were randomly assigned to four groups: either with dietary omega-3 FA or a omega-3 FA deficient diet, and each of those were given fructose (15%) or no fructose in their drinking water. Dietary omega-3 FA deficiency impaired spatial learning and memory retention in a Barnes maze, which was further enhanced by the high fructose intake. Changes in cognitive function were accompanied by reduced expression of synaptophysin and synapsin I, synaptic plasticity-associated proteins found in the brain. In addition, high-fructose intake led to insulin resistance and hypertriglyceridemia, suggesting that either factor could impact on cognitive performance (see below). The addition of omega-3 FAs to the diet improved memory and ameliorated the memory impairments induced by fructose intake. All parameters of MetS in the brain related to the fructose treatment were also ameliorated by omega-3 FA intake. Together these results suggest that diets enriched with omega-3 FA can prevent the detrimental effects of fructose on cognition under “normal” conditions, and particularly during metabolic stress [32]. Interestingly, long-term omega-3 FA supplementation has been shown to improve cognitive function in experimental animal models of AD [32].

A recent population-based study investigated the association of fructose intake with cognitive function in humans. Ye et al. [116] examined whether routine intakes of total sugars, added sugars (sucrose and HFCS), sugar-sweetened beverages or sweetened solid foods are associated with declining cognitive function in humans. The study included middle-aged and older Puerto Rican adults ( $n = 737$ ; mean age 56.3), without diabetes. Total sugars were defined as the sum of three free monosaccharides

(glucose, fructose, and galactose) and three free disaccharides (sucrose, lactose, and maltose). Cognitive function was measured with a battery of seven-tests: the MMSE, to assess general cognitive function, a sixteen-word list learning task to assess verbal memory, digit span forward and backward, to assess attention and working memory, clock drawing and figure copying, both to assess visual-spatial organization, verbal fluency, to assess the speed at which one provide exemplars to a category, and the Stroop test, the measure cognitive flexibility, response inhibition and processing speed. Among the participants, ~21% of energy intake was obtained from total sugars, and 12% from added sugars. Fruit drinks, soft drinks, dairy desserts, and sweets provided 22.1%, 12.9%, 11.3% and 10.3% of added sugars, respectively. Total sugars, added sugars, sucrose, glucose and added fructose were each significantly inversely associated with low MMSE scores, in contrast to natural fructose (from fruits and vegetables), which had no effect on cognitive function. Greater consumption of total sugars was also associated with lower word list learning score. These findings suggest that increased consumption of added sugars is associated with lower cognitive function in humans. Interestingly, the association between added sugar intake and MMSE was independent of BMI and age.

#### **Sucrose and cognition**

Several studies have been conducted to explore the association of sucrose intake with cognitive function. Sucrose is composed of 50% fructose. Results from animal studies show that diets with higher sucrose content result in memory impairment. Rats exposed to a sucrose solution (32%) in addition to chow were found to have poorer memory in a novel object recognition task, when compared with rats that only received chow, whereas memory was not affected in rats given a high-fat diet [117]. Interestingly, both the sucrose and high-fat groups became obese when given access to the diets and had increased fasting blood glucose levels; however, only the sucrose fed group showed impairment in object recognition. In addition, the time spent exploring the novel object was negatively correlated with fasting blood glucose levels. Thus, sucrose may be affecting cognitive function independent of its effects on body weight, as the two diets had differential effects on learning performance but not on body weight gain. Several animal studies have shown that Western diet-induced learning and memory impairments can precede the development of diet-induced obesity [24,118]. In addition, the authors hypothesized that the impairment in object recognition in sucrose fed rats, is due, to diet-induced alterations in blood glucose [117]. In another study, young rats fed a supplemental sucrose solution (32%) in addition to chow took significantly more time to find a hidden platform in the Morris Water Maze

(MWM), a widely-used task for assessing spatial memory, that is impaired in rats with damage confined to the hippocampus (see [119] for review). Moreover, when tested 10 days after the initial training trials, sucrose fed rats displayed deficits in long-term spatial memory [79]. As in the previous study, fasting glucose levels were significantly higher in the sucrose-fed rats supporting the idea that these cognitive deficits arise from metabolic insults.

Postprandial memory performance after consuming a meal with high or a low glycemic index was examined in adults with well-controlled T2D [120]. It was shown that the high glycemic meal led to poorer performance in memory tests when administered 1-2 hours after eating. Similarly, a diet with a higher glycemic index led to poorer memory performance in normal weight undergraduate women [121] and in non-diabetic individuals, including children [122]. In summary, simple rather than complex carbohydrates may impair postprandial memory performance.

#### **Underlying mechanisms**

There are several possible mechanisms underlying the association between fructose intake, obesity, MetS and cognitive function. Animal studies have shown that excessive caloric intake impairs hippocampal synaptic plasticity suggesting that the hippocampus may be particularly sensitive to changes in dietary energy intake [123-125]. The hippocampus is a brain region critical for learning and memory. Thus, diet-induced changes in hippocampal neuronal plasticity may affect memory and cognition.

Inflammation is correlated with cognitive decline [126] and dementia [123,127,128], and various inflammatory markers are increased in obese relative to lean individuals [129]. Sugar-sweetened beverages were found in a 10-week intervention study to increase inflammatory activity [130]. IL-1 has been implicated in memory consolidation, whereas IL-6 may mediate hippocampal dysfunction and thus affect memory and cognition [131]. IL-6 and C-reactive protein (CRP) correlated with accelerated functional decline in the elderly, and middle age CRP levels may prognosticate dementia risk [132]. Patients with post-surgical neurocognitive decline, which occurs in 7-26% of patients undergoing surgery [133], were observed to have a significant increase in CRP and IL-1 compared to patients without cognitive decline. Postoperative elevations in IL-6 and CRP were found to correlate with short- and medium-term cognitive dysfunction after coronary artery bypass surgery [134].

Vascular pathologies have been hypothesized to play a role [71]. In fact, there is evidence that the relations between obesity and cognition are modified by the presence of cardiovascular risk factors. In the Framingham Heart Study [90], obesity and hypertension were independently

associated with lower scores on multiple measures of cognitive functioning, and the adverse effects of obesity and hypertension were additive with respect to measures of episodic memory and visual-spatial constructive abilities. The highest level of performance was observed in the absence of obesity and hypertension, the second highest for those with either hypertension or obesity, and the lowest for those with both obesity and hypertension [90].

It is now known that many of the diagnostic characteristics that define the MetS are individually related to cognitive impairment. Recently, Yau et al. [68] documented lower cognitive performance and alterations in brain structure among adolescents with MetS. Adolescents with MetS scored significantly lower on tests of arithmetic, spelling, attention, and mental flexibility and displayed a trend for lower overall intelligence. They also had, in a metabolic syndrome-dose-related fashion, smaller hippocampal volumes. Excessive fructose intake has been linked to increased lipogenesis, glycogenesis, oxidative stress and uric acid production [135], and these metabolic changes are also associated with the MetS, which in turn, may lead to cognitive dysfunction [136]. Two epidemiological studies have reported an association between elevated uric acid and cognitive decline in older individuals [137,138], whereas one study found a protective effect [139].

Results suggest that insulin resistance induced by high fructose is linked to cognitive decline [140]. Rats fed diets supplemented with HFCS were more insulin resistant and cognitively impaired on spatial learning and ability tasks than non-supplemented rats [115]. Agrawal and Gomez-Pinilla [32] found that fructose intake and DHA deficiency increased hippocampal insulin resistance, as shown by a decrease in insulin receptor signaling. Insulin resistance results from impaired signaling at the level of the insulin receptor primarily as a result of altered phosphorylation. Phosphorylation of the insulin receptor and its distal signaling molecule Akt were reduced in rats fed the omega-3 FA-deficient diet, and that these effects were aggravated by high fructose intake. Inclusion of omega-3 FAs in the diet restored insulin signaling. A role of insulin resistance in memory impairment is supported by the observation that exogenous insulin enhances memory even in individuals with AD [141]. Since memory deficits are positively correlated with increases in insulin resistance, this suggests that insulin signals neurons directly in the brain. Insulin can cross the blood-brain barrier (BBB) [142]. However, insulin receptor knockout mice perform normally in spatial learning and memory tests [143], which suggests that other mechanisms are involved.

In rats, high fructose intake resulted in hyperinsulinemia, hyperglycemia, and an increase in triglyceride (TG) levels [32]. In the study by Agrawal and Gomez-Pinilla [32], insulin resistance index increased in proportion to TG levels, and given the association of cognitive impairment

with elevated TG levels, high fructose intake may prime the brain to insulin resistance by its effects on TGs. In fact, the application of TGs to hepatic cells decreases insulin's ability to trigger its signaling cascade [144]. In addition, TGs can penetrate the BBB [145] and an injection of TGs directly into the brain impairs memory [124]. Data also suggest that neuronal cells can metabolize fructose [146]; however, it is not known whether fructose can penetrate the BBB.

#### **The beneficial effects of omega-3 FAs**

Omega-3 FAs (eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)) are diet-dependent factors critical to normal brain development and function [147], that have been shown to exert beneficial effects on cognition. DHA, the principle omega-3 (PUFA) in brain, has effects on neuronal membrane activity, which modulates cell signaling [148]. DHA status is dependent on dietary supplementation because mammals are inefficient at producing DHA from precursors. In humans [149] and rats [150], DHA concentration in the brain decreases with age. This appears to be related to the age-related deterioration in CNS functions [149]. Data from animal studies support this idea. Rodents fed a low omega-3 FA diet showed significant cognitive deficits [150] that were reduced by DHA supplementation [151]. In addition, DHA supplementation improved memory performance in aged mice [152]. DHA levels in the hippocampus decrease with age and AD and impairs hippocampal-dependent spatial learning memory ability. This implies that adequate levels of DHA are required for optimal cognitive performance.

Supplementation with omega-3 FAs can counteract the effects of a high fructose diet on memory [32]. In rodents, dietary omega-3 FA deficiency was associated with a decline in spatial memory in proportion to the intensity of insulin resistance, which was further aggravated by high fructose intake. There was no difference in body weight or total caloric intake; therefore, obesity did not appear to be a major contributor to altered memory functions in this model. Based on these data, it appears that omega-3 FA deficiency increases the vulnerability to the effects of high fructose, as evidenced by disruptions of insulin signaling and impaired cognitive functions.

A potential mechanism has been proposed [153] by which DHA supports the development and maintenance of spatial learning memory. DHA is synthesized and taken up by neurons of the developing brain and hippocampus, which incorporate it into membrane phospholipids, especially phosphatidylethanolamine. This results in enhanced neurite outgrowth, synaptogenesis and neurogenesis. In support of this idea, exposure to omega-3 FAs increased synaptic protein expression to increase the dendritic spine density, and enhanced synaptic plasticity by increasing neurogenesis in the hippocampus. Retinoid signaling may

be involved in the effects of DHA on learning memory performance as DHA supplementation appeared to increase retinoid X receptor expression compared with the untreated old group [154].

Dietary DHA appears to be a promising target to protect against the detrimental effects of high fructose intake on cognitive performance. Animal studies have shown that consumption of a DHA enriched diet restores brain DHA levels [155], enhances learning and memory tasks in aged animals [155,156], and significantly reduces beta amyloid, plaques, and tau in transgenic AD models [157,158]. Evidence from clinical studies indicates that dietary supplementation with omega-3 FAs improves cognitive performance in healthy children and adults [159] and is somewhat effective in preventing or ameliorating cognitive decline in the aged [160]; however, these findings are not consistent across studies [161,162]. Dietary supplementation with omega-3 FAs has little or no effects in underperforming individuals, and patients with mild to moderate AD [163]. Nevertheless, individuals (aged 65–94 years) who consumed fish at least once per week were found to have a reduced risk of AD at ~ 4 years follow-up compared to those who rarely or never ate fish [164]. Clearly, additional studies examining the effects of longer duration dietary supplementation with omega-3 FAs may identify greater change in cognitive function in study subjects.

#### **Conclusion**

The association of obesity with chronic diseases, such as T2D and MetS is well known. What has recently emerged is the association of obesity with cognitive decline and that intake of added sugars may mediate the influence of obesity on cognitive function. The intake of fructose, along with HFCS has increased over the past three decades. With the rising trend in childhood obesity, causing children to be at risk of diabetes and MetS, the potential contribution of fructose to lower academic performance in adolescents is becoming increasingly realized. Although obesity may not be enough to warrant concern among parents, the lower academic potential of obese adolescents strongly argues for early treatment of childhood obesity and comprehensive intervention, including a limitation of sweetened soft drinks, especially those containing HFCS. Equally important is exploring the role of dietary omega-3 FAs, which appear to have beneficial effects on cognitive function and attenuate high-fructose associated cognitive decline.

#### **Abbreviations**

AD: Alzheimer's disease; BMI: Body mass index; CRP: C-reactive protein; DHA: Docosahexaenoic acid; EPA: Eicosapentaenoic acid; HFCS: High-fructose corn syrup; IL-1: Interleukin-1; IL-6: Interleukin-6; ILSA: Italian Longitudinal Study on Aging; Omega-3 FA: Omega-3 fatty acids; SATSA: Swedish Adoption/Twin Study of Aging; T2D: Type 2 diabetes; TG: Triglycerides; MetS: Metabolic syndrome; MMSE: Mini-Mental State Examination.



### Competing interests

The authors declare that they have no competing interests.

### Authors' contributions

Both authors participated in the preparation of the manuscript, and read and approved the final manuscript.

### Author details

<sup>1</sup>Global Neuroscience Initiative Foundation, Los Angeles, CA, USA.  
<sup>2</sup>Neurological Institute, Cleveland Clinic, 9500 Euclid Ave, S100A, 44195, Cleveland, OH, USA. <sup>3</sup>School of Health and Medical Sciences, Seton Hall University, South Orange, NJ, USA.

Received: 4 April 2013 Accepted: 7 August 2013

Published: 8 August 2013

### References

1. WHO: Obesity: preventing and managing the global epidemic: report of a WHO consultation. *World Health Organ Tech Rep Ser* 2000, **894**:1–253.
2. WHO: WHO technical report. In *Obesity-preventing and managing the global epidemic*. Geneva: World Health Organization; 2000.
3. Hedley AA, Ogden CL, Johnson CL, et al: Prevalence of overweight and obesity among US children, adolescents, and adults, 1999–2002. *JAMA* 2004, **291**:2847–2850.
4. Visscher TL, Seidell JC, Menotti A, et al: Underweight and overweight in relation to mortality among men aged 40–59 and 50–69 years: the Seven Countries Study. *Am J Epidemiol* 2000, **15**:660–666.
5. *Controlling the global obesity epidemic*. 2011.
6. Flynn MA, McNeill DA, Maloff B, Mutasingwa D, Wu M, Ford C, Tough SC: Reducing obesity and related chronic disease risk in children and youth: a synthesis of evidence with “best practice” recommendations. *Obes Rev* 2006, **Suppl 1**:7–66.
7. Halbach SM, Flynn J: Treatment of obesity-related hypertension in children and adolescents. *Curr Hypertens Rep* 2013, **15**(3):224–231.
8. Moreno G, Johnson-Shelton D, Boles S: Prevalence and prediction of overweight and obesity among elementary school students. *J Sch Health* 2013, **83**:157–163.
9. Danaei G, Finucane MM, Lu Y, Singh GM, Cowan MJ, et al: National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants. *Lancet* 2011, **378**:31–40.
10. Steinman M, Lee S, John Boscardin W, Miao Y, Fung K, Moore K, et al: Patterns of multimorbidity in elderly veterans. *J Am Geriatr Soc* 2012, **60**:1872–1880.
11. Wild S, Roglic G, Green A, Sicree R, King H: Global prevalence of diabetes. *Diabetes Care* 2004, **27**:1047–1053.
12. Katsumata Y, Todoriki H, Higashiusato Y, Yasura S, Willcox DC, et al: Metabolic syndrome and cognitive decline among the oldest old in Okinawa: in search of a mechanism: the KOCO project. *J Gerontol A Biol Sci Med Sci* 2012, **67A**:126–134.
13. Ervin RB: Prevalence of metabolic syndrome among adults 20 years of age and over, by sex, age, race and ethnicity, and body mass index: United States. *Nat Statistics Rep* 2009, **13**:1–8.
14. De Rerranti SD, Gauvreau K, Ludwig DS, Neufeld EJ, Newburger JW, Rifal N: Prevalence of the metabolic syndrome in American adolescents: findings from the third national health and nutrition examination survey. *Circulation* 2004, **110**:2494–2499.
15. Xu WL, Atti AR, Gatz M, Pedersen NL, Johansson B, Fratiglioni L: Midlife overweight and obesity increase late-life dementia risk. *Neurology* 2011, **76**:1568–1574.
16. Stewart R, Masaki K, Xue QL, Peila R, Petrovitch H, White LR, Launer LJ: A 32-year prospective study of change in body weight and incident dementia: the Honolulu-Asia aging study. *Arch Neurol* 2005, **62**:55–60.
17. Elias MF, Beiser A, Wolf PA, Au R, White R, D'Agostino RB: The preclinical phase of Alzheimer disease: a 22-year prospective study of the Framingham cohort. *Arch Neurol* 2000, **57**:808–813.
18. Singh-Manoux A, Czernichow S, Elbaz A, Dugravot A, Sabia S, Hagger-Johnson EJ, et al: Obesity phenotypes in midlife and cognition in early old age: the Whitehall II cohort study. *Neurology* 2012, **79**:755–762.
19. Strachan MW: R D Lawrence Lecture 2010: the brain as a target organ in Type 2 diabetes: exploring the links with cognitive impairment and dementia. *Diabet Med* 2011, **28**:141–147.
20. Strachan MW, Reynolds RM, Marioni RE, Price JF: Cognitive function, dementia and type 2 diabetes mellitus in the elderly. *Nat Rev Endocrinol* 2011, **7**:108–114.
21. Gold SM, Dziobek I, Sweat V, Tirsi A, Rogers K, et al: Hippocampal damage and memory impairments as possible early brain complications of type 2 diabetes. *Diabetologia* 2007, **50**:711–719.
22. Panza F, Firsardi V, Capurso C, Imbimbo BP, Vendemiale G, et al: Metabolic syndrome and cognitive impairment: current epidemiology and possible underlying mechanisms. *J Alzheimers Dis* 2010, **21**:691–724.
23. Yaffe K, Weston AL, Blackwell T, Krueger KA: The metabolic syndrome and development of cognitive impairment among older women. *Arch Neurol* 2009, **66**:324–328.
24. Kanoski SE, Davidson TL: Different patterns of memory impairments accompany short- and longer-term maintenance on a high-energy diet. *J Exp Psychol Anim Behav Process* 2010, **36**:313–319.
25. Gross LS, Li L, Ford ES, Liu S: Increased consumption of refined carbohydrates and the epidemic of type 2 diabetes in the United States: an ecologic assessment. *Am J Clin Nutr* 2004, **79**:774–779.
26. Tappy L, Le KA, Tran C, Paquot N: Fructose and metabolic diseases: new findings, new questions. *Nutrition* 2010, **26**:1044–1049.
27. Bray GA, Popkin BM: Calorie-sweetened beverages and fructose: what have we learned 10 years later. *Pediatr Obes* 2013, **8**(4):242–248.
28. Malik VS, Schulze MB, Hu FB: Intake of sugar-sweetened beverages for its effects to increase visceral adiposity and induce dyslipidemia and insulin resistance. *Curr Opin Lipidol* 2006, **19**:16–24.
29. Goran MI, Ulijaszek SJ, Ventura EE: High fructose corn syrup and diabetes prevalence: a global perspective. *Glob Public Health* 2013, **8**:55–64.
30. Goran MI, Ulijaszek SJ, Ventura EE: High fructose corn syrup and diabetes prevalence: a global perspective. *Glob: Public Health*; 2012.
31. Sun SZ, Anderson GH, Flickinger BD, Williamson-Hughes PS, Empie MW: Fructose and non-fructose sugar intakes in the US population and their associations with indicators of metabolic syndrome. *Food Chem Toxicol* 2011, **49**:2875–2882.
32. Agrawal R, Gomez-Pinilla F: Metabolic syndrome in the brain: deficiency in omega-3 fatty acid exacerbates dysfunctions in insulin receptor signalling and cognition. *J Physiol* 2012, **590**:2485–2499.
33. Ross AP, Bartness TJ, Mielke JG, Parent MB: A high fructose diet impairs spatial memory in male rats. *Neurobiol Learn Mem* 2009, **92**:410–416.
34. Costello DA, Claret M, Al-Qassab H, Plattner F, Irvine EE, et al: Brain deletion of insulin receptor substrate 2 disrupts hippocampal synaptic plasticity and metaplasticity. *PLoS One* 2012, **7**:e31124.
35. Burkhalter TM, Hillman CH: A narrative review of physical activity, nutrition, and obesity to cognition and scholastic performance across the human lifespan. *Adv Nutr* 2011, **2**:2015–2065.
36. De Rooij SR, Wouters H, Yonker JE, Painter RC, Roseboom TJ: Prenatal undernutrition and cognitive function in late adulthood. *Proc Natl Acad Sci* 2010, **107**:16881–16888.
37. Simonson M, Chow BF: Maxe studies on progeny of underfed mother rats. *J Nutr* 1970, **33**:373–385.
38. Bush M, Leathwood PD: Effect of different regimens of early malnutrition on behavioral development and adult avoidance learning in Swiss white mice. *Br J Nutr* 1975, **33**:373–385.
39. Rogers PJ, Tonkiss J, Smart JL: Incidental learning is impaired during early-life undernutrition. *Dev Psychobiol* 1986, **19**:113–124.
40. Ranade SC, et al: Different types of nutritional deficiencies affect different domains of spatial memory function checked in a radial arm maze. *Neuroscience* 2008, **152**:859–866.
41. Bhat V, et al: Vitamin B12 status of pregnant Indian women and cognitive function in their 9-year-old children. *Food Nutr Bull* 2008, **29**:249–254.
42. Freeman HE, Klein RE, Kagan J, Yarbrough C: Relations between nutrition and cognition in rural Guatemala. *Am J Public Health* 1977, **67**:233–239.
43. Rampersaud GC, Pereira MA, Girard BL, Adams J, Metz J: Breakfast habits, nutritional status, body weight, and academic performance in children and adolescents. *J Am Diet Assoc* 2005, **105**(5):743–760.
44. Siega-Riz A, Popkin B, Carson T: Trends in breakfast consumption for children in the United States from 1965–1991. *Am J Clin Nutr* 1998, **67**:7485–7565.

45. Pollitt E, Lewis NL, Garza C, Shulman RJ: **Fasting and cognitive function.** *J Psychiat Res* 1982–1983, **17**:169–174.
46. Wesnes KA, Pincock C, Richardson D, Helm G, Hails S: **Breakfast reduces decline in attention and memory over the morning in schoolchildren.** *Appetite* 2003, **41**:329–331.
47. Mahoney CR, Taylor HA, Kanarek RB, Samuel P: **Effect of breakfast composition on cognitive processes in elementary school children.** *Physiol Behav* 2005, **85**:635–645.
48. Craig A, Richardson E: **Effects of experimental and habitual lunch-size on performance, arousal, hunger and mood.** *Int Arch Occup Environ Health* 1989, **61**:313–319.
49. Wesnes KA, Pincock C, Scholey A: **Breakfast is associated with enhanced cognitive function in schoolchildren: an internet based study.** *Appetite* 2012, **59**:646–649.
50. Liu J, Hwang WT, Dickerman B, Compher C: **Regular breakfast consumption is associated with increased IQ in kindergarten children.** *Earlyl Hum Dev* 2013, **89**(4):257–262.
51. Widenhorn-Muller K, Hille K, Klenk J, Weiland U: **Influence of having breakfast on cognitive performance and mood in 13-to-20-year-old high school students: results of a crossover trial.** *Pediatrics* 2008, **122**:279–284.
52. Hu F, Van Dam R, Liu S: **Diet and risk of Type II diabetes: the role of types of fat and carbohydrate.** *Diabetologia* 2001, **44**:805–817.
53. Sabia S, Kivimaki M, Shipley MJ, Marmot MG, Singh-Manoux A: **Body mass index over the adult life course and cognition in late midlife: the Whitehall II Cohort study.** *Am J Clin Nutr* 2009, **89**:601–607.
54. Elias MF, Elias PK, Sullivan LM, Wolf PA, D'Agostino RB: **Obesity, diabetes and cognitive deficit: the Framingham heart study.** *Neurobiol Aging* 2005, **26**:11–16.
55. Jeong SK, Nam HS, Son MH, Son EJ, Cho KH: **Interactive effect of obesity indexes on cognition.** *Dement Geriatr Cogn Disord* 2005, **19**:91–96.
56. Okosun IS, Liao Y, Rotimi CN, Choi S, Cooper RS: **Predictive values of waist circumference for dyslipidemia, type 2 diabetes and hypertension in overweight White, Black, and Hispanic American adults.** *J Clin Epidemiol* 2000, **53**:401–408.
57. Benito-Leon J, Mitchell AJ, Hernandez-Gallego J, Bermejo-Pareja F: **Obesity and impaired cognitive functioning in the elderly: a population-based cross-sectional study (NEDICES).** *Eur J Neurol* 2013.
58. Cournot M, Marquie JC, Ansiau D, Martinaud C, Fonds H, Ferrieres J, Ruidavets JB: **Relation between body mass index and cognitive function in healthy middle-aged men and women.** *Neurology* 2006, **67**:1208–1214.
59. Gunstad J, Paul RH, Cohen RA, Tate DF, Gordon E: **Obesity is associated with memory deficits in young and middle-aged adults.** *Eat Weight Disord* 2006, **11**:e15–19.
60. Kilander L, Nyman H, Boberg M, Lithell H: **Cognitive function, vascular risk factors and education: a cross-sectional study based on a cohort of 70-year-old men.** *J Intern Med* 1997, **242**:313–321.
61. Wolf PA, Beiser A, Elias MF, Au R, Vasan RS, Seshadri S: **Relation of obesity to cognitive function: importance of central obesity and synergistic influence of concomitant hypertension: the Framingham heart study.** *Curr Alzheimer Res* 2007, **4**:111–116.
62. Sturman MT, De Leon CF, Bienias JL, Morris MC, Wilson RS, Evans DA: **Body mass index and cognitive decline in a biracial community population.** *Neurology* 2008, **70**:360–367.
63. Yu ZB, Han SP, Cao XG, Guo XR: **Intelligence in relation to obesity: a systematic review and meta-analysis.** *Obes Rev* 2010, **11**:656–670.
64. Li X: **A study of intelligence and personality in children with simple obesity.** *Int J Obes Relat Metab Disord* 1995, **19**:355–357.
65. Tascilar ME, Turkkahraman D, Oz O, Yucl M, Taskesen M, Eker I, et al: **P300 auditory event-related potentials in children with obesity: is childhood obesity related to impairment in cognitive functions.** *Pediatr Diabetes* 2011, **12**:589–595.
66. Khaliq F, Alam KK, Vaney N, Singh TB: **Sensory, cognitive and motor assessment of children with poor academic performance: an auditory evoked potential study.** *Indian J Physiol Pharmacol* 2010, **54**:255–264.
67. Datar A, Sturm R: **Childhood overweight and elementary school outcomes.** *Int J Obes* 2006, **30**:1449–1460.
68. Yau PL, Castro MG, Tagani A, Tsui WH, Convit A: **Obesity and metabolic syndrome and functional and structural brain impairments in adolescence.** *Pediatrics* 2012, **130**:e856–864.
69. Anstey KJ, Cherbuin N, Budge M, Young J: **Body mass index in midlife and late-life as a risk factor for dementia: a meta-analysis of prospective studies.** *Obes Rev* 2011, **12**:e426–e437.
70. Gorospe EC, Dave JK: **The risk of dementia with increased body mass index.** *Ageing* 2007, **36**:23–29.
71. Gustafson D: **Adiposity indices and dementia.** *Lancet Neurol* 2006, **5**:713–720.
72. Gustafson D, Rothenberg E, Blennow K, Steen B, Skoog I: **An 18-year follow-up of overweight and risk of Alzheimer disease.** *Arch Intern Med* 2003, **163**:1524–1528.
73. Beydoun MA, Beydoun HA, Wang Y: **Obesity and central obesity as risk factors for incident dementia and its subtypes: a systematic review and meta-analysis.** *Obes Rev* 2008, **9**:204–218.
74. Dahl AK, Hassing LB: **Obesity and cognitive aging.** *Epidemiol Rev* 2012, **35**(10):22–32.
75. Berrino F: **Western diet and Alzheimer's disease.** *Epidemiol Prev* 2002, **26**(3):107–115.
76. Pasinetti G, Eberstein J: **Metabolic syndrome and the role of dietary lifestyles in Alzheimer's disease.** *J Neurochem* 2008, **106**:1503–1514.
77. Benton D, Maconie A, Williams C: **The influence of the glycemic load of breakfast on the behaviour of children in school.** *Physiol Behav* 2007, **92**:717–724.
78. Eskelinen M, Ngandu T, Helkala E, Tuomilehto J, Nissinen A, Soininen H, et al: **Fat intake at midlife and cognitive impairment later in life: a population-based CAIDE study.** *Int J Geriatr Psychiatry* 2008, **23**:741–747.
79. Jurdak N, Lichtenstein AH, Kanarek RB: **Diet-induced obesity and spatial cognition in young male rats.** *Nutr Neurosci* 2008, **11**:48–54.
80. Morris MC, Evans DA, Bienias JL, Tangney CC, Wilson RS: **Dietary fat intake and 6-year cognitive change in an older biracial community population.** *Neurology* 2004, **62**:1573–1579.
81. Whitmer RA, Gunderson EP, Barrett-Connor E, Quesenberry CP Jr, Yaffe K: **Obesity in middle age and future risk of dementia: a 27 year longitudinal population based study.** *BMJ* 2005, **330**:1360.
82. Luchsinger JA, Tang MX, Shea S, Mayeux R: **Caloric intake and the risk of Alzheimer's disease.** *Arch Neurol* 2002, **59**:1258–1263.
83. Kivipelto M, Ngandu T, Fratiglioni L, et al: **Obesity and vascular risk factors at midlife and the risk of dementia and Alzheimer disease.** *Arch Neurol* 2005, **62**:1556–1560.
84. Rosengren A, Skoog I, Gustafson D, Wilhelmsen L: **Body mass index, other cardiovascular risk factors, and hospitalization for dementia.** *Arch Intern Med* 2005, **165**:321–326.
85. Kivipelto M, Helkala EL, Hanninen T, et al: **Midlife vascular risk factors and late-life mild cognitive impairment: a population-based study.** *Neurology* 2001, **56**:1683–1689.
86. Finkel D, Reynolds C, McArdle JJ, et al: **Latent growth curve analyses of accelerating decline in cognitive abilities in late adulthood.** *Dev Psychol* 2003, **39**:535–550.
87. Schaie KW: *Developmental influences on adult intelligence- the Seattle longitudinal study.* New York: Oxford University Press; 2005.
88. Dahl A, Hassing LB, Fransson E, et al: **Being overweight in midlife is associated with lower cognitive ability and steeper cognitive decline in late life.** *J Gerontol A Biol Sci Med Sci* 2010, **65**:57–62.
89. Solfrizzi V, Scafato E, Capurso C, D'Introno A, Colacicco AM, Frisardi V, et al: **For the Italian longitudinal study on aging working group, metabolic syndrome, mild cognitive impairment, and progression to dementia: the Italian longitudinal study on aging.** *Neurobiol Aging* 2009, **32**:1932–1941.
90. Elias MF, Elias PK, Sullivan LM, Wolf PA, D'Agostino RB: **Lower cognitive function in the presence of obesity and hypertension: the Framingham heart study.** *Int J Obes* 2003, **27**:260–268.
91. Bray GA, Nielsen SJ, Popkin BM: **Consumption of high-fructose corn syrup in beverages may play a role in the epidemic of obesity.** *Am J Clin Nutr* 2004, **79**:537–543.
92. Marriott BP, Olsho L, Hadden L, Connor P: **Intake of added sugars and selected nutrients in the United States, National Health and Nutrition Examination Survey (NHANES) 2003–2006.** *Crit Rev Food Sci Nutr* 2010, **50**:228–258.
93. Hanover L, White J: **Manufacturing, composition, and applications of fructose.** *Am J Clin Nutr* 1993, **58**:724S–732S.
94. Wells HF, Buzby JC: **A report from the economic research service: dietary assessment of major trends in U.S. food consumption, 1970–2005.** United States Department of Agriculture; Washington, DC. *Economic Information Bulletin* 2008, **33**:1–20.
95. Popkin BM, Armstrong LE, Bray GM, Caballero B, Frei B, Willett WC: **A new proposed guidance system for beverage consumption in the United States.** *Am J Clin Nutr* 2006, **83**:529–542.

96. Fulgoni VL, Quann EE: National trends in beverage consumption in children from birth to 5 years: analysis of NHANES across three decades. *Nutr J* 2012, **11**:92.
97. Glinsmann WH, Irausquin H, Park YK: Evaluation of health aspects of sugars contained in carbohydrate sweeteners: reports of sugars task force. *J Nutr* 1986, **116**:S1–216.
98. Glinsmann WH, Bowman BA: The public health significance of dietary fructose. *Am J Clin Nutr* 1993, **58**:820S–823S.
99. Bantle J: Dietary fructose and metabolic syndrome and diabetes. *J Nutr* 2009, **139**:1263S–1268S.
100. Saad MF, Khan A, Sharma A, Michael R, Riad-Gabriel MG, Boyadjian R, et al: Physiological insulinemia actually modulates plasma leptin. *Diabetes* 1998, **47**:544–549.
101. Ritzkalla SW: Health implications of fructose consumption: a review of recent data. *Nutr Metab* 2010, **7**:82.
102. Bray G: How bad is fructose? *Am J Clin Nutr* 2007, **86**:895–896.
103. Bocarsly ME, Powell ES, Avena NM, Hoebel BG: High-fructose corn syrup causes characteristics of obesity in rats: increased body weight, body fat and triglyceride levels. *Pharmacol Biochem Behav* 2010, **97**:101–106.
104. Shapiro A, Mu W, Roncal C, Duerenberg P: Fructose-induced leptin resistance exacerbates weight gain in response to high-fat feeding. *Am J Physiol Regul Integr Comp Physiol* 2008, **295**:R1370–1375.
105. Cox CL, Stanhope KL, Schwarz JM, Graham JL, Hatcher B, Griffen SC, et al: Consumption of fructose-sweetened beverages for 10 weeks reduces net fat oxidation and energy expenditure in overweight/obese men and women. *Eur J Clin Nutr* 2012, **66**:201–208.
106. Maier IB, Stricker L, Ozel Y, Wagnerberger S, Bischoff SC, Bergheim I: A low fructose diet in the treatment of pediatric obesity: a pilot study. *J Nutr* 2011, **142**:251–257.
107. Everitt AV, Hilmer SN, Brand-Miller JC, Jamieson HA, Truswell AS, et al: Dietary approaches that delay age-related diseases. *Clin Interv Aging* 2006, **1**:11–31.
108. Havel P: Dietary fructose: implications for dysregulation of energy homeostasis and lipid/carbohydrate metabolism. *Nutr Rev* 2005, **63**:133–157.
109. Malik VS, Popkin BM, Bray GA, Despres JP, Hu FB: Sugar-sweetened beverages, obesity, type 2 diabetes mellitus, and cardiovascular disease risk. *Circulation* 2010, **121**:1356–1364.
110. Elliott SS, Keim NL, Stern JS, Teff K, Havel PJ: Fructose, weight gain, and the insulin resistance syndrome. *Am J Clin Nutr* 2002, **76**:911–922.
111. Stanhope K: Role of fructose-containing sugars in the epidemics of obesity and metabolic syndrome. *Annu Rev Med* 2012, **63**:329–343.
112. Bremer AA, Stanhope KL, Graham JL, Cummings BP, Wang W, Saville BR, Harvel PJ: Fructose-fed rhesus monkeys: a nonhuman primate model of insulin resistance, metabolic syndrome, and type 2 diabetes. *Clin Transl Sci* 2011, **4**:243–252.
113. Ferder L, Ferder MD, Inserra F: The role of high-fructose corn syrup in metabolic syndrome and hypertension. *Curr Hypertens Res* 2010, **12**:105–112.
114. Aller EE, Abete I, Astrup A, Martinez JA, Van Baak MA: Starches, sugars and obesity. *Nutrients* 2011, **3**:341–369.
115. Stranahan AM, Norman ED, Lee K, et al: Diet-induced insulin resistance impairs hippocampal synaptic plasticity and cognition in middle-aged rats. *Hippocampus* 2008, **18**:1085–1088.
116. Ye X, Gao X, Scott T, Tucker KL: Habitual sugar intake and cognitive function among middle-aged and older Puerto Ricans without diabetes. *Br J Nutr* 2011, **106**:1423–1432.
117. Jurdak N, Kanarek RB: Sucrose-induced obesity impairs novel object recognition learning in young rats. *Physiol Behav* 2009, **96**:1–5.
118. Murray AJ, Knight NS, Cochlin LE, McAleese S, Deacon RM, Rawlins JN, et al: Deterioration of physical performance and cognitive function in rats with short-term high-fat feeding. *FASEB J* 2009, **23**(12):4353–4360.
119. D'Hooge R, De Deyn PP: Applications of the Morris water maze in the study of learning and memory. *Brain Res Brain Res Rev* 2001, **36**:60–90.
120. Papanikolaou Y, Palmer H, Binns MA, Jenkins DJ: Better cognitive performance following a low-glycemic-index compared with a high-glycemic-index carbohydrate meal in adults with type 2 diabetes. *Diabetologia* 2006, **49**:855–862.
121. Nabb S, Benton D: The influence on cognition of the interaction between the macro-nutrient content of breakfast and glucose tolerance. *Physiol Behav* 2006, **87**:16–23.
122. Kanoski SE, Davidson TL: Western diet consumption and cognitive impairment: links to hippocampal dysfunction and obesity. *Physiol Behav* 2011, **103**:59–68.
123. Molteni R, Barnard RJ, Ying Z, Roberts CK, Gomez-Pinilla F: A high-fat, refined sugar diet reduces hippocampal brain-derived neurotrophic factor, neuronal plasticity, and learning. *Neuroscience* 2002, **112**:803–814.
124. Farr SA, Yamada KA, Butterfield DA, Abdul HM, Xu L, Miller NE, et al: Obesity and hypertriglyceridemia produce cognitive impairment. *Endocrinology* 2008, **149**:2628–2636.
125. Stranahan AM, Norman ED, Lee K, Cutler RG, Telljohann R, Egan JM, Mattson MP: Diet-induced insulin resistance impairs hippocampal synaptic plasticity and cognition in middle-aged rats. *Hippocampus* 2008, **18**:1085–1088.
126. Weaver JD, Huang MH, Albert M, et al: Interleukin-6 and risk of cognitive decline: MacArthur studies of successful aging. *Neurology* 2002, **59**:371–378.
127. Yaffe K, Lindquist K, Penninx BW, et al: Inflammatory markers and cognition in well-functioning African-American and white elders. *Neurology* 2003, **61**:76–80.
128. Engelhart MJ, Geerlings MI, Meijer J, et al: Inflammatory proteins in plasma and the risk of dementia: the Rotterdam study. *Arch Neurol* 2006, **61**:668–672.
129. Vachharajani V, Granger DN: Adipose tissue: a motor for the inflammation associated with obesity. *IUBMB* 2009, **6**:424–430.
130. Sorensen LB, Raben A, Stender S, et al: Effect of sucrose on inflammatory markers in overweight humans. *Am J Clin Nutr* 2005, **82**:421–427.
131. Cerejeira J, Firmino H, Vaz-Serra A, et al: The neuroinflammatory hypothesis of delirium. *Acta Neuropathol* 2010, **119**:737–754.
132. Hudetz JA, Gandhi SD, Iqbal Z, et al: Elevated postoperative inflammatory biomarkers are associated with short- and medium-term cognitive dysfunction after coronary artery surgery. *J Anesth* 2011, **25**:1–9.
133. Steinmetz J, Christensen KB, Lund T, Lohse N, Rasmussen LS: Long-term consequences of postoperative cognitive dysfunction. *Anesthesiology* 2009, **110**(3):548–555.
134. Kalman J, Juhasz A, Bogats G, Babik B, Rimanczy A, et al: Elevated levels of inflammatory biomarkers in the cerebrospinal fluid after coronary artery bypass surgery are predictors of cognitive decline. *Neurochem Int* 2006, **48**:177–180.
135. Stephan BC, Wells JC, Brayne C, Albanese E, Siervo M: Increased fructose intake as a risk factor for dementia. *J Gerontol A Biol Sci Med Sci* 2010, **65**:809–814.
136. Yaffe K, Kanaya A, Lindquist K, et al: The metabolic syndrome, inflammation, and risk of cognitive decline. *JAMA* 2004, **292**:2237–2242.
137. Schretlen DJ, Inscore AB, Jinnah HA, et al: Serum uric acid and cognitive function in community-dwelling older adults. *Neuropsychology* 2007, **21**:136–140.
138. Ruggiero C, Cherubini A, Lauretani F, et al: Uric acid and dementia in community-dwelling older persons. *Dement Geriatr Cogn Disord* 2009, **27**:382–389.
139. Euser SM, Hofman A, Westendorp RG, Breteler MM: Serum uric acid and cognitive function and dementia. *Brain* 2009, **132**:377–382.
140. Cao D, Lu H, Lewis TL, Li L: Intake of sucrose-sweetened water induces insulin resistance and exacerbates memory deficits and amyloidosis in a transgenic mouse model of Alzheimer disease. *J Biol Chem* 2007, **282**:36275–36282.
141. Craft S, Asthana S, Newcomer JW, Wilkenson CW, Matos IT, et al: Enhancement of memory in Alzheimer disease with insulin and somatostatin, but not glucose. *Arch Gen Psychiatry* 1999, **56**(12):1135–1140.
142. Banks WA, Jspan JB, Huang W, Kastin AJ: Transport of insulin across the blood-brain barrier: saturability at euglycemic doses of insulin. *Peptides* 1997, **18**:1423–1429.
143. Reagan L: Insulin signaling effects on mood and memory. *Curr Opin Pharmacol* 2007, **7**(1):633–637.
144. Kim DS, Jeong SK, Kim HR, Kim DS, Chae SW, Chae JH: Effects of triglyceride on ER stress and insulin resistance. *Biochem Biophys Res Commun* 2007, **363**:140–145.
145. Drew PA, Smith E, Thomas PD: Fat distribution and changes in the blood brain barrier in a rat model of cerebral arterial fat embolism. *J Neurosci Sci* 1998, **156**:138–143.
146. Funari VA, Crandall JE, Tolan DR: Fructose metabolism in the cerebellum. *Cerebellum* 2007, **6**:130–140.

147. Neuringer M, Anderson GJ, Connor WE: **The essentiality of n-3 fatty acids for the development and function of the retina and brain.** *Annu Rev Nutr* 1988, **8**:517–541.
148. Uauy R, Dangour AD: **Nutrition in brain development and aging: role of essential fatty acids.** *Nutr Rev* 2006, **64**:S24–S33.
149. Soderberg M, Edlund C, Kristensson K, Daliner G: **Fatty acid composition of brain phospholipids in aging and in Alzheimer's disease.** *Lipids* 1991, **26**:421–425.
150. Suzuki H, Park SJ, Tamura M, Ando S: **Effect of the long-term feeding of dietary lipids on the learning ability, fatty acid composition of brain stem phospholipids and synaptic membrane fluidity in adult mice: a comparison of sardine oil diet with palm oil diet.** *Mech Ageing Dev* 1998, **101**:119–128.
151. Moriguchi T, Salem N Jr: **Recovery of brain docosahexaenoate leads to recovery of spatial task performance.** *J Neurochem* 2003, **87**:297–309.
152. Sugimoto Y, Taga C, Nishiga M, Fujiwara M, Konishi F, Tanaka K, Kamel C: **Effect of docosahexaenoic acid-fortified *Chlorella vulgaris* strain CK22 on the radial maze performance in aged mice.** *Biol Pharm Bull* 2002, **25**:1090–1092.
153. Su H: **Mechanisms of n-3 fatty acid-mediated development and maintenance of learning memory performance.** *J Nutr Biochem* 2010, **21**:364–373.
154. Dyall SC, Michael GJ, Michael-Titus AT: **Omega-3 fatty acids reverse age-related decreases in nuclear receptors and increase neurogenesis in old rats.** *J Neurosci Res* 2010, **88**:2091–2102.
155. Moranis A, Delpech JC, De Smedt-Peyrusse V, Aubert A, Guesnet P, et al: **Long term adequate n-3 polyunsaturated fatty acid diet protects from depressive-like behavior but not from working memory disruption and brain cytokine expression in aged mice.** *Brain Behav Immun* 2011, **26**:721–731.
156. Labrousse VF, Nadjar A, Joffre C, Costes L, Aubert A, Gregoire S, et al: **Short-term long chain omega3 diet protects from neuroinflammatory processes and memory impairment in aged mice.** *PLoS One* 2012, **7**:e36861.
157. Green KN, Martinez-Coria H, Khashwji H, et al: **Dietary docosahexaenoic acid and docosapentaenoic acid ameliorate amyloid-beta and tau pathology via a mechanism involving presenilin 1 levels.** *J Neurosci* 2007, **27**:4385–4395.
158. Lebbadi M, Julien C, Phivllay A, Tremblay C, Emond V, Kang JX, Calon F: **Endogenous conversion of omega-6 into omega-3 fatty acids improves neuropathology in an animal model of Alzheimer's disease.** *J Alzheimers Dis* 2011, **27**:853–869.
159. Richardson AJ, Burton JR, Sewell RP, Sprechkelsen TF, Montgomery P: **Docosahexaenoic acid for reading, cognition and behavior in children aged 7–9 years: a randomized, controlled trial (the DOLAB Study).** *PLoS One* 2012, **7**:e43909.
160. Yurko-Mauro K: **Cognitive and cardiovascular benefits of docosahexaenoic acid in aging and cognitive decline.** *Curr Alzheimer Res* 2010, **7**:190–196.
161. Dangour AD, Allen E, Elbourne D, Fasey N, Fletcher AE, Hardy P, et al: **Effect of 2-y n-3 long-chain polyunsaturated fatty acid supplementation on cognitive function in older people: a randomized, double-blind, controlled trial.** *Am J Clin Nutr* 2010, **91**:1725–1732.
162. Sydenham E, Dangour AD, Lim WS: **Omega 3 fatty acid for the prevention of cognitive decline and dementia.** *Cochrane Database Syst Rev* 2012, **13**, CD005379.
163. Quinn JF, Raman R, Thomas RG, Yurko-Mauro K, Nelson EB, Van Dyck C, et al: **Docosahexaenoic acid supplementation and cognitive decline in Alzheimer disease: a randomized trial.** *JAMA* 2010, **304**:1903–1911.
164. Morris MC, Evans DA, Bienias JL, Tangney CC, Bennett DA, Wilson RS, et al: **Consumption of fish and n-3 fatty acids and risk of incident Alzheimer's disease.** *Arch Neurol* 2003, **60**:940–946.

doi:10.1186/1475-2891-12-114

Cite this article as: Lakhan and Kirchgessner: **The emerging role of dietary fructose in obesity and cognitive decline.** *Nutrition Journal* 2013 **12**:114.

**Submit your next manuscript to BioMed Central and take full advantage of:**

- Convenient online submission
- Thorough peer review
- No space constraints or color figure charges
- Immediate publication on acceptance
- Inclusion in PubMed, CAS, Scopus and Google Scholar
- Research which is freely available for redistribution

Submit your manuscript at  
www.biomedcentral.com/submit

