The effect of increased sugar intake and type-2 diabetes mellitus on the incidence of Alzheimer's disease

Olivia Zhang

Introduction

Alzheimer's disease is a neurodegenerative disease that can lead to dementia, the general term for cognitive ability loss, such as memory and thinking. Currently, at least 55 million people worldwide are living with Alzheimer's disease or similar neurodegenerative diseases (*Dementia*, 2023). It is most common among elderly people, as the risk of developing Alzheimer's disease increases significantly after the age of 65 (Liu et al., 2022). While about 10% of Alzheimer's cases are people aged 65 or younger, about one in 13 people aged 65 to 84 and one in three people aged 85 and older have Alzheimer's disease (Fox, 2019). According to the Alzheimer's Association, 1 in 3 older Americans die due to Alzheimer's, which is more than those who die from breast cancer and prostate cancer combined (*Home | Alzheimer's Association*, 2024).

Alzheimer's disease progresses gradually, from mild memory loss in the early stage to cognitive decline, difficulty in making decisions, and a lack of communication skills. Eventually, a patient may be bedridden and suffer from seizures (Fox, 2019). Personality changes – most commonly agitation, aggression, as well as depression – can develop (*Alzheimer's Caregiving*, 2024). These personality changes are due to the damage to the frontal lobes and cerebral cortex, areas of the brain which manage communication, behavior, and logical thinking (*Behavior & Personality Changes*, 2024). Other factors may also contribute to these personality changes, such as noisy environments and the presence of sight or hearing health issues (*Alzheimer's Caregiving*, 2024). Hallucinations and insomnia may also develop.

Alzheimer's disease may be caused by a combination of Beta-amyloid plaques, particular genetic mutations, and harmful health behaviors. The pathogenesis of Alzheimer's disease is the accumulation of B-amyloid (AB) peptides, which are essentially peptides that clot blood flow in the brain by forming amyloid senile plaques (Weller & Budson, 2018). The amyloid precursor protein, PSEN I or PSEN 2, may have a mutation which makes the B-amyloid peptides accumulate at higher rates, increasing the plaques (Khan et al., 2020) or, the AB peptides may form dimers, which are compounds formed from two AB monomers. These dimers can form higher order oligomers, which promote the formation of plaques (Fox, 2019; Khan et al., 2020). Additionally, the disease is marked by neuronal death, caused by the tangling of neurons due to complex processes like over-phosphorylation and the redistribution of the tau proteins, a groups of proteins which help maintain the shape of the axons of neurons, so that messages can be passed (Calsolaro & Edison, 2016; Khan et al., 2020; Pîr et al., n.d.). Many patients also experience neuroinflammation (Fox, 2019).

Genetic and environmental factors also play a role in the incidence of Alzheimer's (Figure 1). The APOE4 allele is a major cause of late-onset Alzheimer's, as it increases the likelihood of beta-amyloid plaque formation (Scheltens et al., 2021). There are also other genetic risk factors, such as certain variations in the *C9ORF72* gene and the *TOMM40* gene, that also increase risk of plaque formation (Fox, 2019). Environmental factors, like insufficient exercise, diet, and sleep also can contribute to increased risk of developing Alzheimer's disease (*Dementia*, 2023).

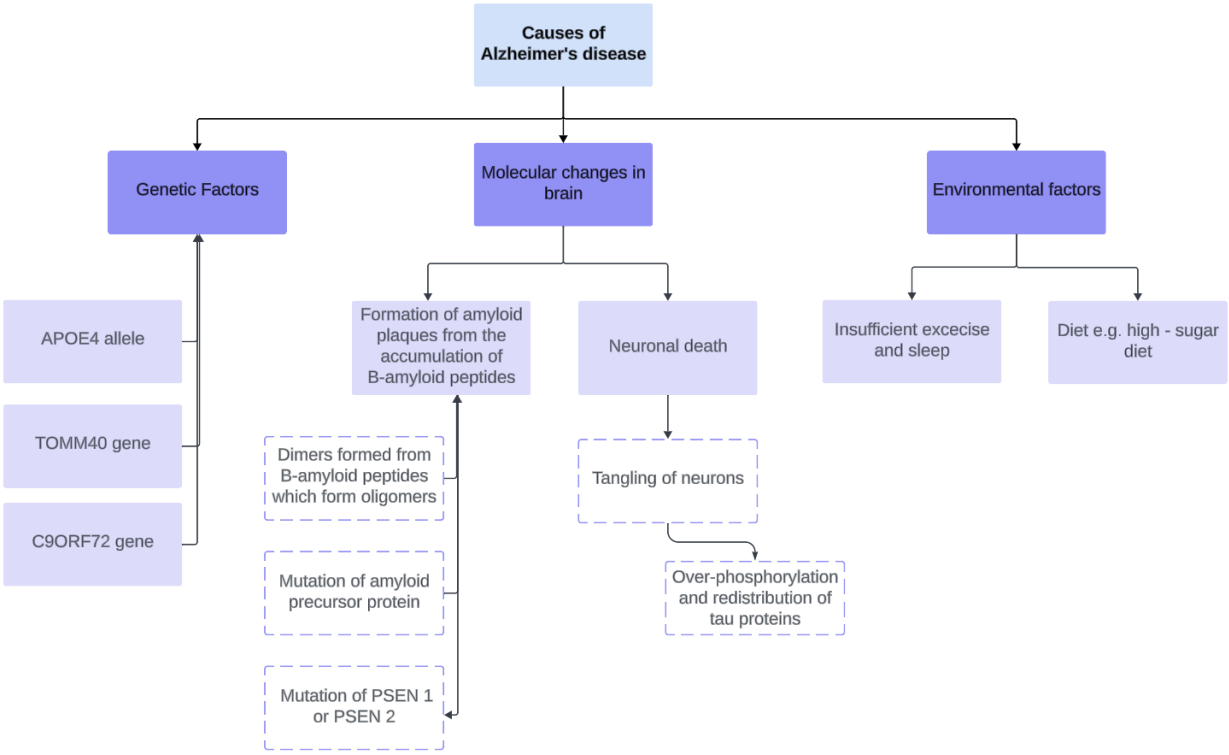

Figure 1: Examples of molecular, genetic and environmental factors that can increase risk of Alzheimer's disease.

Although there is currently no treatment available that reverses disease damage, drugs that help with symptom management are available and focus mainly on preventing further neurodegeneration and disease progression (Fox, 2019). Examples of these drugs include cholinesterase inhibitors like Donepezil, galantamine, and rivastigmine, that enhance the effect of acetylcholine (a chemical that enhances muscle movement) in a synapse. This allows for better communication between nerve cells, hence improving memory, communication skills, and the ability to think more clearly (Khan et al., 2020). In addition, a drug called memantine may be used, which improves cognitive function by helping to protect nerve cells from damage (Kuns et al., 2024). Antidepressant drugs that relieve mood changes and agitation are also used in moderate to severe cases (Arvanitakis et al., 2019).

Lifestyle changes are also available and together with medications offer a more holistic approach. A healthy diet low in fat, sugars, and red meat may be adopted by a patient, as well as more frequent exercise and refraining from excessive smoking and drinking (Serrano-Pozo & Growdon, 2019). Together these lifestyle changes may decrease obesity, a risk factor for AD. Music therapy, communication skills

training, and art therapy are also used to alleviate the agitation felt in patients and to improve their communication skills (Arvanitakis et al., 2019).

In this review paper, I will explore the effect of a particular environmental factor - high sugar dietary intake- on the incidence of Alzheimer's disease. I aim to give insight into the impact of high fructose corn syrup, lactose, alcohol, and other carbohydrate sugars (glucose, fructose) causing type 2 diabetes mellitus and its link to Alzheimer's disease.

Type 2 Diabetes Mellitus

When carbohydrates are digested, they are broken down into glucose by amylase, which is an essential digestive enzyme. This breakdown of glucose increases our blood glucose levels, which will then be lowered by the hormone insulin, which is released from our pancreas, to maintain homeostasis. Insulin enables the transport of glucose to muscle cells for energy and enables the storage of extra glucose in the form of glycogen, particularly in liver cells.

Type 2 diabetes mellitus (T2DM) develops because of insulin resistance. Insulin resistance is where the body is less sensitive to insulin and thus does not perform the downstream effects of insulin as well (Burillo et al., 2021). A patient may also possess decreased sensitivity of beta cells (which produce insulin) in pancreatic islets, hence less insulin secretion, which can lead to uncompensated insulin resistance (Fox, 2019). Therefore, hyperglycemia occurs, where there is too much glucose in our blood, also referred to as high blood sugar (Macauley et al., 2015). T2DM is caused by various factors, such as hypertension, high sugar diet, and obesity (Macauley et al., 2015). T2DM is diagnosed by an impaired glucose tolerance test, or the detection of a fasting glucose level of greater than 126 mg/dL ('Professional Practice Committee', 2020). This is significantly higher than a healthy individual's glucose level, normally 70 to 99 mg/dL ('Professional Practice Committee', 2020). In addition, a blood test to evaluate the patient's HbA1c level can be done, which reflects the patient's average blood sugar level for the past few months is detected (Little, 2022). If the patient's HbA1C is 6.5% or higher, then the patient will likely be diagnosed with diabetes (Little, 2022).

According to the International Diabetes Federation (IDF), there are currently more than 537 million people worldwide living with diabetes, and 90% of these patients diagnosed have type 2 diabetes mellitus (*Facts & Figures*, 2024). The true amount of cases may be even higher because there may be many undiagnosed patients. By 2045, the IDF predicts that 1 in 8 adults will have diabetes, which is around 783 million people (*Facts & Figures*, 2024), posing a threat to human health.

In the long term, type 2 diabetes mellitus may cause kidney failure, limb amputations, or blindness (Fox, 2019). Diabetes is also a major cause of circulatory illnesses, like atherosclerosis, or the buildup of cholesterol causing the narrowing of arteries, blocking blood flow (Fox, 2019). The most common medication to treat T2DM is metformin, which can help lower the blood sugar level (Majety et al., 2023). For more severe patients, insulin may be injected to lower blood sugar levels (Fox, 2019). In addition to the pharmaceutical treatments for type 2 diabetes mellitus, lifestyle changes, such as controlling carbohydrate intake, exercising regularly, and reducing sedentary time can , lower the chance of becoming obese and, therefore may decrease risk of less likely to develop T2DM (Zheng et al., 2018).

Link between type 2 diabetes mellitus and Alzheimer's disease

The risk of having Alzheimer's disease is 65% higher in people living with type 2 diabetes mellitus than people without T2DM (Barbagallo & Dominguez, 2014). A study shows that glucose intolerance, a symptom of T2DM, may occur in 80% of Alzheimer's disease patients (Barbagallo & Dominguez, 2014). Type 2 diabetes increases the likelihood that the brain's neurovascular unit, which includes components of the brain which regulate blood flow, neuroglia, and neurons, will develop Alzheimer's disease because they are more vulnerable (Janoutová et al., 2022). This is mainly due to the insulin resistance and hyperglycemia experienced in T2DM (Janoutová et al., 2022).

The brain is very dependent on glucose for energy. Therefore, brain glucose metabolism, a mechanism where glucose diffused into brain cells produces ATP for energy, is important in the brain (Ritter, 2017). Insulin arbitrates neuron and glial growth- the process for developing new neurons (Macauley et al., 2015). Insulin resistance, a pathology of T2DM, results in a high concentration of insulin in the blood, which damages the neurons, leading to amyloid plaque formation, tau phosphorylation and consequent neurofibrillary tangles, and memory loss, all causes of Alzheimer's disease (Wei et al., 2021; Zhao & Townsend, 2009). One study shows that amyloid plaques are usually present in areas where many insulin receptors are present, as there is an increased insulin production due to insulin resistance (Rebelos et al., 2021).

Insulin resistance also results in neuroinflammation, a hallmark of Alzheimer's disease (Wei et al., 2021). Also, reduced cerebral blood flow caused by glucotoxicity, or high glucose levels because of insulin resistance, can result in neuronal death, a molecular change demonstrated in Alzheimer's patients (Janoutová et al., 2022). Hyperglycemia, or high blood glucose levels, can increase B-amyloid peptide levels and cause neuroinflammation (Burillo et al., 2021; Macauley et al., 2015). Glucose can also cause the adipose tissue cells to secrete more AB peptides, hence forming amyloid plaques (Cross, 2023). Therefore, controlling or preventing T2DM lowers or delays the chance of developing Alzheimer's disease (Wee et al., 2023).

Diabetes and carbohydrate sugar intake

The World Health Organization recommends that sugar consumption should be less than 10% of the total energy intake per day, roughly 12.5 teaspoons (*Guideline*, 2024). However, in 2023 and 2024, around 177.33 million tons of sugar were consumed worldwide. This means people averaged around 34.5 teaspoons per day, 22 more teaspoons than the recommended amount. Predictions state this will increase to 178.79 million tons by 2025 (Shahbandeh, 2024).

A diet high in carbohydrate sugars - mainly glucose and fructose - can lead to type 2 diabetes mellitus (Liyanage et al., 2019). Excessive glucose intake results in high glycemic index, as carbohydrates are digested too fast, causing hyperglycemia (Ma et al., 2022). High amounts of fructose consumption is more likely to lead to obesity (Ma et al., 2022). Hyperglycemia and obesity are conditions present in T2DM patients. Both glucose and fructose result in impaired insulin sensitivity, causing insulin resistance (Ma et al., 2022).

Insulin resistance can affect brain glucose metabolism by causing the brain to not have enough glucose for energy. This can impact and cause a decline in cognitive abilities like thinking. Additionally, a diet high in sugar leads to neuroinflammation, which is also present in AD patients (Liyanage et al., 2019). Therefore, a diet high in sugars may lead to increased risk of developing Alzheimer's disease (Ma et al., 2022).

High fructose corn syrup (HFCS) is a sweetener made from carbohydrate sugars glucose and fructose present in sugary beverages and junk food. The amount of HFCS consumed has increased rapidly globally (Ma et al., 2022). According to the US Department of Agriculture, the intake of sugary beverages has increased by 500% in the past 50 years per capita in the US (Kokubo et al., 2019). Recently, it was found that around 12% of the infants drank sugar-sweetened beverages, and later in life, this then led to a higher consumption of processed sugars rather than fresh vegetables and fruits (Kokubo et al., 2019). Similar trends have also been reported outside the United States. For example, in Brazil the intake of sugary drinks quadrupled from 1974 to 2003. In 2009, Brazilian adults drank about 100 ml of sugar-sweetened beverages per day, more than the recommended amount, of 29 ml per day (Kokubo et al., 2019).

The number of cases of T2DM and obesity, both risk factors for AD, has grown. More people are at risk for AD due to the high consumption of sugary beverages, as well as added sugar in many processed foods, which results in obesity (Liyanage et al., 2019). Hence, HFCS present in these beverages also increases the incidence of AD. An experimental paper concluded that high glucose and fructose consumption over 12 years increased the risk of developing T2DM in men and women (Montonen et al., 2007). Out of the types of food they had, sugary beverages, like sweetened berry juice, were thought to be the most associated with increased risk of T2DM (Montonen et al., 2007). One study suggested that switching to ketone metabolism with a ketogenic diet - a diet that involves low carbohydrate and high-fat intake, instead of glucose metabolism, may lower the incidence of Alzheimer's disease as it decreases the chance of obesity (Takeishi et al., 2021). Improvements to diet may protect neurons from neurodegeneration and ultimately neuronal death (Takeishi et al., 2021).

However, other types of sugar like lactose, a type of sugar most commonly found in milk, lead to a decreased incidence of Alzheimer's disease, unlike carbohydrate sugars. Another source of sugar is found in alcohol. Drinking a light to regular amount of alcohol, could also reduce the risk of developing Alzheimer's disease, especially wine (Xie & Feng, 2022).This is because it has a neuroprotective effect, increases insulin sensitivity, and improves blood flow, hence preventing neuronal death (Peng et al., 2020). In addition, wine contains phenolic compounds naturally found in the grapes, which have anti-inflammatory effects against the neuroinflammation present in AD (Reale et al., 2020). However, excessive drinking in midlife, or consuming more than 14 units of alcohol per week, increases the incidence of Alzheimer's disease (Peng et al., 2020). Ethanol, produced by fermented glucose found in alcohol, has a negative impact on the neurotransmitter systems, leading to neurodegeneration (Peng et al., 2020). Ethanol also links to the impairment of the brain glucose metabolism, leading to dementia (Peng et al., 2020).

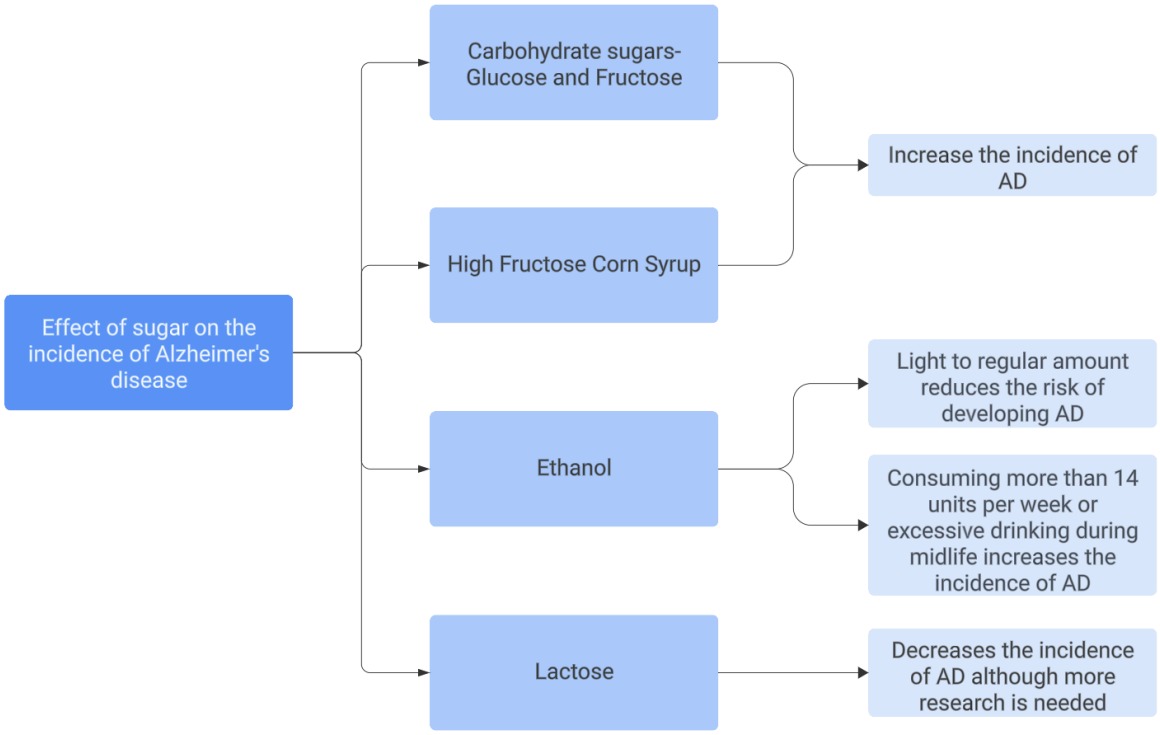

Figure 2: Effect of different types of sugars on the incidence of Alzheimer's disease.

Conclusion

Alzheimer's disease is a neurodegenerative disease caused by multiple factors - inherited genes, harmful health behaviors, and the formation of Beta-amyloid plaques, tau tangles and neuroinflammation. However, treatments, such as lifestyle are still limited to managing the disease, not reversing it. In this review, the effect of increased sugar intake from different sources is explored.

While the incidence of Alzheimer's is significantly higher with increased sugar intake and the presence of T2DM, increased carbohydrate sugar intake can also cause T2DM to develop (Figure 2). Insulin resistance, a pathology of T2DM, may lead to the development of Alzheimer's disease. However, unlike carbohydrate sugars like glucose and the sweetener HFCS, lactose, and ethanol may reduce the incidence of AD. But if a limit is exceeded, excessive ethanol intake can also increase the likelihood of AD developing.

A way to prevent Alzheimer's disease is to lower one's dietary sugar intake, especially if they are diabetic or carry inherited genes associated with AD. A low-sugar diet could also be implemented in AD patients to manage the disease and prevent further neurodegeneration.

More awareness should be raised to the public on the prominent link between T2DM and Alzheimer's disease, explaining the harmful effects of sugar on individuals. This information should not be exclusive to elderly people, but also available to adolescent children as well as people in their early adulthood. This is due to the increasing number of young people under the age of 40 living with T2DM. A recent report published by Diabetes UK in 2024 indicates that the number of T2DM patients under 40 has increased by 40% in 5 years (Endocrinology, 2024).

The existing literature was limited in study populations, and more focus should be directed towards young people under the age of 40. More work should be conducted on a larger, more diverse population. Further research on the effect of lactose on lowering the risk of developing AD and whether exceeding a limit will lead to increased risk is needed. If this relationship is positive, new medication containing lactose can be developed to treat AD. The shared molecular mechanisms between AD and T2DM should be studied more closely so that antidiabetic medicine can treat AD. A low-sugar diet should also be tested for its possibility of reversing disease damage and decreasing neuroinflammation. Overall, high sugar diets leading to T2DM do increase the incidence of Alzheimer's disease as they cause neuroinflammation and the formation of amyloid plaques.

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