



Different Dietary Patterns and their Effects on Alzheimer's

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Abstract

Alzheimer's disease (AD) is among the most common neurodegenerative diseases worldwide, yet the factors that drive it remain misunderstood. Growing evidence links diet, obesity, and the gut-brain axis to neurodegeneration, and three genes involved in metabolism and amyloid biology (SIRT1, APP, and LEP) correlated with diet. This review examines what is known about how four dietary patterns affect brain health: the US Western diet, the Japanese diet, the Mediterranean (including MIND) diet, and intermittent fasting. The United States and Japan, two high-income countries with very different diets, are compared directly using food-group intake, ultra-processed food intake (USA 55.0%, Japan 38.2% of calories), obesity rate, life expectancy, and early-onset dementia prevalence. Japan has a comparatively older population and therefore a higher all-age dementia prevalence than the United States, despite having a lower early-onset dementia prevalence. The Mediterranean diet and intermittent fasting are discussed through clinical, observational, and laboratory research rather than population data. These findings are hypothesis-generating and motivate gene-expression and longitudinal studies of diet, obesity, and brain health.

Introduction

Over 7 million Americans are living with Alzheimer's Disease (AD), making it one of the most prominent diseases affecting the United States ("2026 Alzheimer's Disease Facts and Figures"). Outside of the US, approximately 55 to 57 million people internationally are diagnosed with AD, making it an international crisis as well (World Health Organization). AD is a neurodegenerative disease that more commonly affects the ageing population (>65 years of age), but less commonly, can be early onset (diagnosis at 45-65 years of age). AD is a type of dementia that causes a gradual loss in memory, the ability to perform tasks, mood changes, and gradual progression into a loss of autonomy. Often AD begins in the hippocampus before spreading to the entorhinal cortex and eventually spreading to the frontal, temporal, and parietal lobes. Data shows that this neurological decline is from the accumulation of amyloid plaques between neurons, which prevents sufficient neuronal communication (National Institute on Aging, "What Happens to the Brain in Alzheimer's Disease?"), and tau tangles, which are intracellular aggregates of hyperphosphorylated tau protein. Normally, tau stabilizes the microtubules that carry nutrients and signaling molecules along axons; when tau detaches, this transport fails and neurons eventually die (Biochemical Pharmacology). There are known genetic variations in the apolipoprotein E (APOE) gene, a gene carrying instructions for transporting lipids and cholesterol throughout the bloodstream, that greatly increase the chances of developing AD. In particular, individuals with specific point mutations in the APOE gene, commonly referred to as APOE3 and APOE4, show an increasing susceptibility to developing AD (Husain et al.).

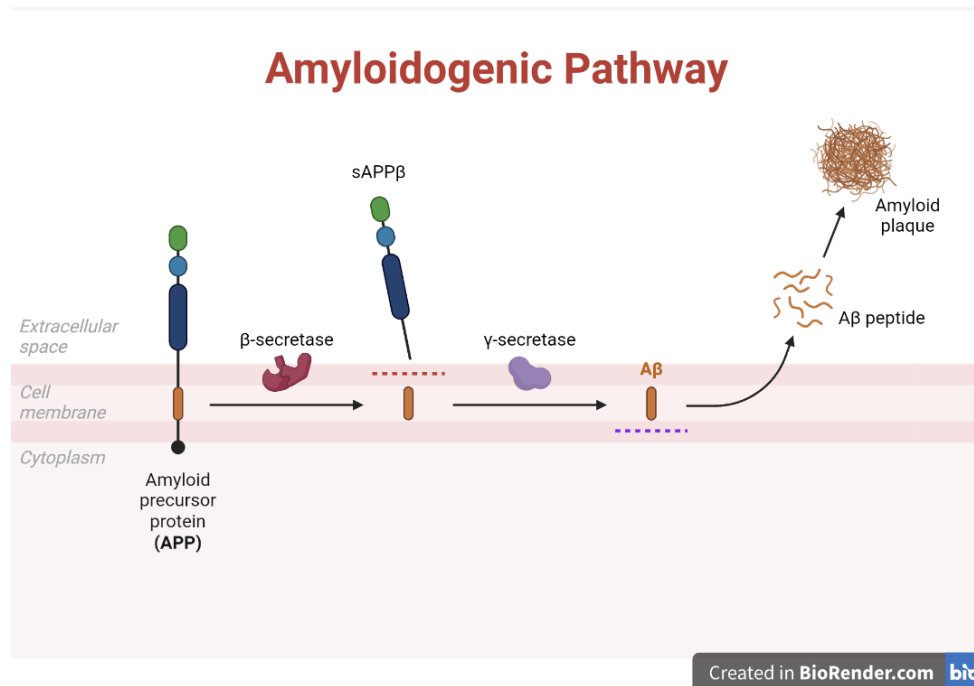


Fig 1: Amyloid Plaque Formation

This figure displays the process of how the Amyloid Precursor Protein pathway that is meant to form Amyloid Beta peptides can lead to amyloid plaque formation in the brain.

Despite an increasing amount of research in AD, it still remains unknown what specific factors are contributing to the accumulation of amyloid plaques and formation of tau tangles that are associated with AD. Interestingly, recent data supports a connection between the gut brain axis and neurodegenerative diseases. AD, a well-known neurodegenerative disease, is lacking data in this field. Obesity, which is closely tied to the Western diet, has also been associated with a higher risk of developing dementia later in life when it is present in middle age. Furthermore, Sirtuin 1 (*SIRT1*), Amyloid precursor protein (*APP*), and Leptin (*LEP*) are sensitive to diet and body weight and have been connected to amyloid production, so they could potentially play a role in the development of AD. However, whether these genes mechanistically contribute to AD pathology in humans remains unclear. It is important to note that these three genes are only a small part of a much larger picture. Brain health and AD risk are likely governed by many factors that we do not yet understand, including other genes, the gut microbiome, inflammation, and other socioeconomic factors that can affect the onset of AD/AD in a population. For this reason, this review focuses on the known effects of each diet on brain health, and uses *SIRT1*, *APP*, and *LEP* as examples of how diet may affect molecular pathways involved in AD rather than the only possible mechanisms.

APP encodes for amyloid precursor protein, which is found throughout the body's tissues and organs, including the brain and spinal cord. It is hypothesized that *APP* aids in protein binding to cells, ultimately influencing neuronal connections. *APP* is cut by enzymes into smaller fragments, two of which are the soluble amyloid precursor protein (sAPP) and the amyloid beta peptide. These fragments, though they are still being studied, are believed to assist in the formation of neurons and the ability of the brain to adapt and change over time. The

overproduction and accumulation of amyloid beta peptides in the brain cause amyloid plaques to form, which is directly linked to the onset of Alzheimer's ("APP Gene: MedlinePlus Genetics").

LEP provides instructions for producing leptin, which is a hormone regulating hunger relative to body weight. Fat cells release leptin in proportion to their concentration, so as the amount of fat cells increase, leptin levels rise accordingly. Leptin crosses the blood brain barrier to bind to receptors in the hypothalamus region in the brain. This stimulates a signaling pathway that produces a feeling of satiety in the body. Obesity can increase the production and decrease the body's response to leptin, as the amount of leptin produced is proportional to the amount of fat cells in the body. Obesity can lead to hyperleptinemia or leptin resistance. Because leptin crosses the blood brain barrier as a regulator of amyloid plaques, leptin resistance can cause excess buildup of amyloid plaques in the brain ("LEP Gene: MedlinePlus Genetics").

Like the LEP gene, the SIRT1 gene codes for a protein that acts as a metabolic regulator. SIRT1 links the metabolic status of cells to the structure of chromatin formed by DNA and gene expression, allowing it to influence a wide range of genetic processes including energy metabolism and stress management. Expression of SIRT1 is controlled by layers of signaling pathways that lead to different metabolic regulations. Specifically, SIRT1 controls glucose and lipid metabolism in the liver, promoting the mobilization of fat in white adipose tissue, regulation of insulin secretion in the pancreas, and modulation of nutrient availability in the hypothalamus (Li). SIRT1 may contribute to Alzheimer's disease pathology by regulating ADAM10, an α -secretase involved in the non-amyloidogenic processing of amyloid precursor protein. Experimental studies have investigated the SIRT1–RAR β –ADAM10 pathway and its relationship with amyloid- β production, although the strength and reproducibility of the evidence should be evaluated across independent studies (Lee et al.; Sun et al.)

Taken together, these three genes connect nutrition to the core biology of AD. APP is the source of the amyloid beta peptide itself. LEP reports the body's fat stores to the brain and, when dysregulated by obesity, may impair the brain's control over amyloid production. SIRT1 senses energy status and, when active, promotes neuronal health and reduces the production of amyloid plaques. These genes are especially relevant to AD because all three are linked to diet, and because dietary patterns that raise adipose fat levels, insulin resistance, and inflammation would be expected to push all three in a harmful direction at once, while dietary patterns rich in omega-3 fatty acids, polyphenols, and periods of caloric restriction would push them in a protective direction.

In this review paper, four dietary patterns will be examined for their known effects on brain health: the US Western diet, the Japanese diet, the Mediterranean (including MIND) diet, and intermittent fasting. The United States and Japan were used as representative populations for the Western and Japanese diets because they have the most data aligning with Alzheimer's prevalence and obesity, and their dietary patterns are distinct and widely followed across the population. To perform these comparisons, an analysis of data from multiple datasets regarding the dementia prevalence, age, obesity rate, and dietary factors such as the amount of meat, fish, sugar, saturated fat, ultra-processed foods, fruit, and vegetable consumption was completed. Two measures were added to reduce confounding variables. First, early-onset dementia (dementia prevalence for ages from 65 and below) was used in addition to overall dementia prevalence because overall dementia prevalence is dominated by the age of a population. For example, a country like Japan with a comparatively older population will have more dementia regardless of diet. Second, the share of total calories that comes from ultra-processed foods was included, as it is a more direct measure of the "Western" dietary

pattern than individual nutrients. The Mediterranean diet and intermittent fasting are discussed mechanistically, using clinical trials, cohort studies, and laboratory research, rather than by comparing populations. This paper aims to summarize what is known about how diet affects the brain, and to possibly promote lifestyles and diets that delay or prevent AD in the global population.

Western Diet

AD represents a major and growing public health crisis in the United States, where 7 million Americans are reported to struggle with AD. The Western Diet is characterized by a high intake of sugars, saturated fats, and ultra-processed foods (Centers for Disease Control and Prevention). Furthermore, compared to the Japanese diet, the Western diet is categorized to consume relatively lower amounts of fruits and vegetables. Ultra-processed foods account for 55.0 percent of total calories consumed in the United States (Williams et al.), which is higher than the Japanese population's consumption of ultra-processed foods (38.2%) (Koiwai et al.). This is consistent with national survey data showing that ultra-processed foods make up more than half of calories consumed by Americans and supply nearly 90 percent of the energy that comes from added sugars (Steele et al.). (Figure 1).

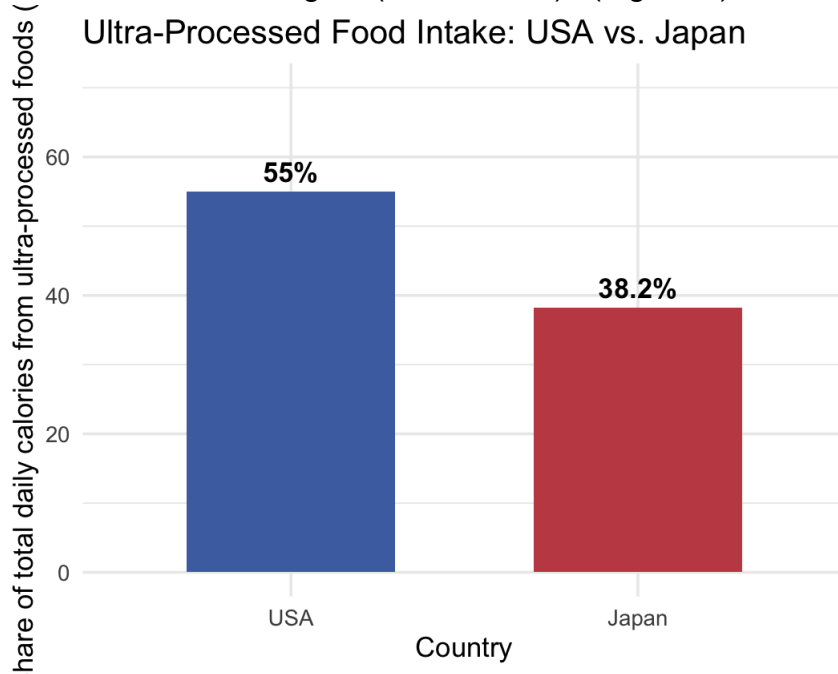


Fig 2 Ultra Processed Food Intake

This figure compares the Ultra-Processed Food intake in percent of total calories consumed in The United States and Japan.

These dietary patterns can be linked to obesity and insulin resistance, which are risk factors for dementia (Wong et al.). The relatively high amounts of saturated fats, ultra-processed foods, and sugars in the western diets promote the storage of adipose tissue in the body. The storage of adipose tissue leads to obesity and inflammation, which are linked to AD (Obradovic et al.). Additionally, the intake of ultra-processed foods, which are often high in sugar and fats, are proven to cause overeating (National Institutes of Health). Sugars and fats impair the

transport of leptin across the blood-brain barrier by inhibiting leptin from binding to transporters in vascular endothelial cells. Leptin is a hormone that is typically transported to the brain to induce satiation signaling and inhibit hunger pathways, and therefore, when prevented from entering into the brain, causes erroneous hunger signaling. The resulting increase in caloric consumption without caloric expenditure leads to the build up of fat tissue in the body and even obesity.

Obesity promotes the build up in short chain fatty acids, which causes pro-inflammatory mediators to release, resulting in organ damage. This can lead to the delivery of oxygen to the brain to be compromised, leading to the inflammation of neurons in the brain. In particular, as body fat increases, so does the expression of the LEP gene, which leads to chronic hyperleptinemia. Leptin crosses the blood-brain barrier and binds to the LEPR receptor in the hippocampus and cerebral cortex, and communicates when the body is satiated, suppresses appetite, and helps regulate metabolism. Hyperleptinemia caused by obesity promotes leptin resistance, causing neurons to be unable to effectively respond to leptin signals (Flores-Cordero et al.). This is concerning as leptin is an important regulator of the formation of β -amyloid plaques. In particular, leptin decreases the activity of β -secretase (BACE1) and components γ -secretase, which are enzymes that help form these toxic plaques that are known to be key contributing factors to the onset of AD. Leptin resistance causes leptin to no longer suppress BACE1 activity, which leads to an increase in the production and activity of β and γ secretase. Thus linking hyperleptinemia from obesity to increasing the production of amyloid plaques and the likelihood of developing AD (Niedowicz et al.; Marwarha et al.; Hamilton and Harvey; Niedowicz et al.).

The Western diet is linked to APP as high-fat diets increase amyloidogenic processing of APP and amyloid beta accumulation, as studied in an experiment involving rodents (Bao et al.). Insulin resistance, common in Western-diet obesity, adds a second pathway. Obesity is associated with insulin resistance and high insulin levels (hyperinsulinaemia), which may cause the insulin-degrading enzyme (IDE) to focus on breaking down insulin instead of amyloid- γ , allowing amyloid- γ to accumulate in the brain and contribute to Alzheimer's disease. This pathway to amyloid plaques links obesity and western diets to APP expression. APP itself is not known to change greatly with diet; what appears to change is how APP is cut and how its fragments are cleared (Qiu and Folstein).

Obesity causes SIRT1 expression to reduce. SIRT1 is a metabolic regulator, and its expression increases during caloric restriction and decreases during high caloric intake. Because of the Western Diet's plethora of processed and high calorie foods, SIRT1 expression is reduced. Because SIRT1 promotes ADAM10 and deacetylates tau, reduced SIRT1 would be expected to mechanistically link decreased SIRT1 expression and increased AD prevalence (Pardo and Boriek).

Japanese Diet

Japan has one of the highest number of individuals living with dementia due to its ageing population. Approximately 4.4 to 4.6 million Japanese adults live with dementia, with Alzheimer's disease affecting approximately 4 to 5 percent of the Japanese population (Behera et al.). This has been found to be correlated to Japan's life expectancy being one of the highest in the world at approximately 80 to 90 years old, and Japan's large ageing population (its median age being approximately 50 years old). Because age is the strongest risk factor for dementia, Japan's large dementia burden in all-age data is expected even if diet is protective at

a given age. This is why the early-onset estimate is a fairer comparison: Japan's rate (50.9 per 100,000) is reported to be the lowest of the three industrialized countries (Awata et al.). The Japanese diet is characterized by a high consumption of seafood, soy products, seaweed, herbs, vegetables, mushrooms, fermented foods, and rice while containing relatively low amounts of saturated fats, red meats, sugar, and ultra-processed foods (Fig 3).

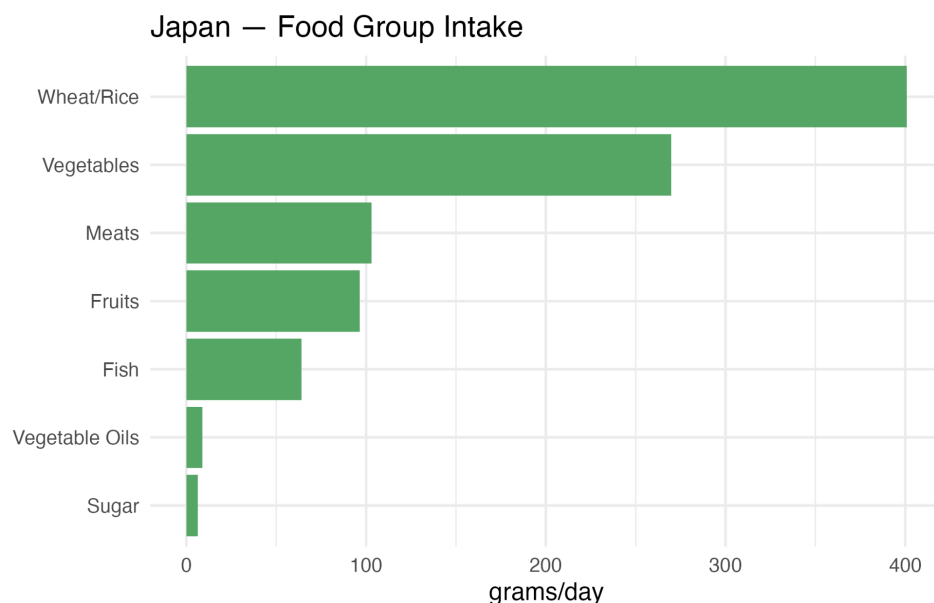


Fig 3. Japan Food Group Intake

This graph displays the average Japanese intake of different foods in grams per day.

Research within Japan suggests that dietary choices matter for the brain. In the Hisayama study, a long-running cohort in Fukuoka, adults in the highest quartile of vegetable intake had a 27 percent lower risk of dementia and a 31 percent lower risk of AD than those in the lowest quartile (Kimura et al.). In the Yabu cohort study, older adults who ate the most varied diets had an 18 percent lower risk of disabling dementia over a median follow-up of 6.8 years than those who ate the least varied diets (Murayama et al.).

A staple of the Japanese diet, fish, is high in Omega-3 fatty acid DHA. DHA Omega 3 strengthens brain cells and promotes healthier neuron memory, which leads to a reduction of the APP processing pathway that produces the amyloid plaques that are known to be a direct link to the onset of AD (Chávez-Castillo et al.). In addition to suppressing the APP processing pathway, DHA reduces the expression of a pathway that produces tau tangles, another known driver of AD. When synthesized, DHA is converted to neuroprotectins and resolvins that reduce long term inflammation (Galizzi; Chavez-Castillo et al.; Cole and Frautschy).

There is no publicly available data linking components of the Japanese diet to SIRT1 expression. However, the Japanese lack of consumption of sugar and vegetable oils combined with their diverse diet of whole foods is correlated with their relatively low obesity rate (Figure 3, 7), and causes it to have less leptin resistance, therefore allowing leptin to regulate amyloid plaques and suppress their accumulation.

U.S Japan Comparison

The United States and Japan are an informative comparison because both are high-income countries with long life expectancies (Figure 7), yet they differ greatly in diet, obesity, and early-onset dementia. About 40.3 percent of US adults have obesity while Japan has one of the lowest adult obesity rates in the world at --%. Ultra-processed foods make up 55.0 percent of calories in the United States and 38.2 percent in Japan (Figure 1). Japan's all-age dementia prevalence is higher than that of the United States, while its early-onset dementia prevalence is lower (Figure 4).

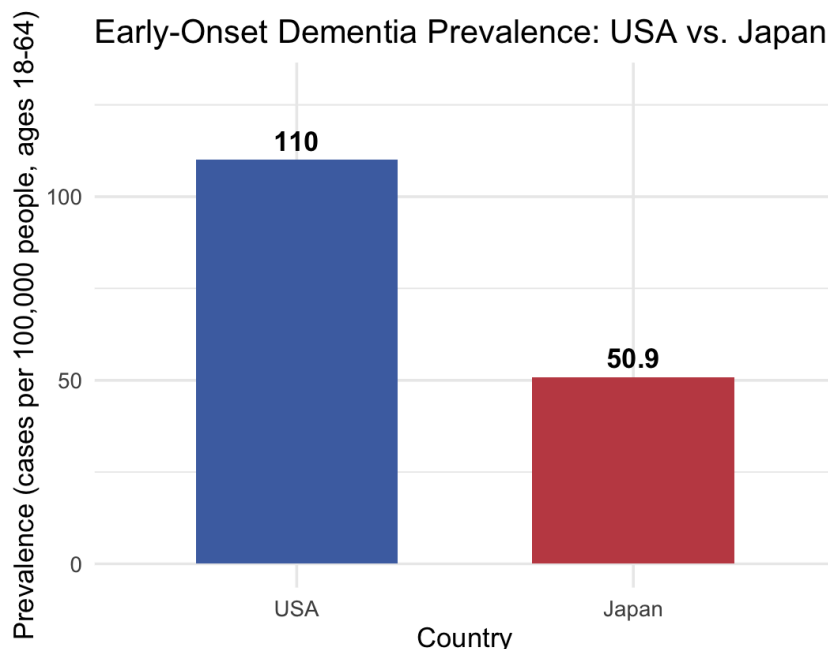


Fig 4. Early Onset Dementia Prevalence

This figure displays the early onset dementia prevalence in the USA and Japan per 100,000 people.

Mediterranean Diet

The traditional Mediterranean diet is characterized by a high intake of olive oil, vegetables, fruits, legumes, whole grains, nuts, and herbs. It also includes moderate amounts of fish and seafood, which are rich in omega-3 fatty acids, as well as yogurt and cheese ("Faostat"). The Mediterranean diet emphasizes whole foods that are naturally rich in monounsaturated fats, omega-2 fatty acids, and dietary fiber, which are proven to benefit cardiovascular health and suppress inflammation in the body (American Society for Nutrition). Observational studies have consistently linked the Mediterranean diet to better brain outcomes. A meta-analysis of prospective cohort studies found that people with the highest adherence to the Mediterranean diet had 33 percent less risk of developing mild cognitive impairment (MCI) or AD than those with the lowest adherence, and among cognitively normal people, higher adherence was associated with a 36 percent lower risk of AD (Bao et al.).

Similar to the Mediterranean diet, researchers have highlighted the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND Diet) whose main focus is to promote brain health and reduce cognitive decline. This diet features leafy greens, vegetables, fruits (specifically berries), whole grains, beans, nuts, moderate intakes of fish, and olive oil while

limiting red meat, sweets, and saturated fats (butter, margarine, fried food) (National Institute on Aging, “What Do We Know About Diet and Prevention of Alzheimer’s Disease?”). A study investigating the relations between the MIND Diet and Alzheimer’s risk identified that consistently following the MIND Diet over the span of approximately 4.5 years is associated with up to a 53 percent lower risk of developing Alzheimer’s disease (Morris et al.). However, these were observational findings. In a randomized trial of 604 older adults who were overweight, had a suboptimal diet, and had a family history of dementia, the MIND diet did not improve cognition more than a control diet with mild caloric restriction over three years, as both groups improved slightly (Barnes et al.). This does not rule out a benefit, as the control group already ate a relatively healthy diet and three years may be too short to affect a disease that develops over decades, but it shows that the benefits of these diets are still being tested.

A staple of both the Mediterranean and MIND diets is olive oil, which is rich in phenolic compounds such as hydroxytyrosol, tyrosol, and oleuropein that lower the levels of pro-inflammatory mediators, contributing to the anti-inflammatory properties of these diets. Furthermore, the Mediterranean and MIND diets also contain a surplus of fish, which consist of DHA Omega 3 (Cicerale et al.). As mentioned in the Japanese Diet section, DHA processing pathway shifts the expression of the APP processing pathway from producing excess amyloid plaques, which lowers amyloid plaque accumulation and tau tangle accumulation.

The Mediterranean diet is also proven to upregulate SIRT1 expression according to a study that randomly assigned participants to follow a mediterranean diet and tested the levels of sirtuin (the protein that SIRT1 gene encodes for) in participants’ blood and plasma (Hidalgo-Moyano et al.). As discussed in the introduction, SIRT1 promotes the ADAM10 pathway, which cuts APP in a non amyloidogenic way and therefore can be associated with the reduction of AD.

The Mediterranean diet is also proven to lower obesity due to its emphasis on whole foods and generally low calorie meals (Muscogiuri et al.). As mentioned in the Western and Japanese diet sections, lower obesity is correlated with lower AD due to lower leptin resistance and more amyloid regulation.

Intermittent Fasting

Intermittent fasting (IF) is an eating pattern, rather than a particular type of diet, in which periods of abstaining from or strongly limiting calories for 12 to 48 hours alternate with periods of regular food intake. Common forms include time-restricted eating, alternate-day fasting, and the 5:2 diet, in which calories are greatly reduced on two days of the week (Gudden et al.). IF is of interest to brain health because a fast of roughly 12 to 36 hours causes a metabolic switch from the use of glucose to the use of fatty acids and ketones (Anton et al.), and ketones become the preferred fuel for the brain during fasting (Gudden et al.). This switch is thought to trigger an adaptive stress response that promotes healthspan (Seidler and Barrow). In animal models, IF has been consistently reported to raise brain-derived neurotrophic factor (BDNF), a protein linked to synaptic plasticity, learning, and memory (Seidler and Barrow). Reviews of preclinical work also report that IF supports neurogenesis in the hippocampus and lowers neuroinflammation in several mouse models, including models of AD (Beveridge et al.). In one study of mice that model AD, IF improved cognition and prevented amyloid β deposition, and the ketone β -hydroxybutyrate may partly explain this by restoring the polarity of aquaporin-4, a protein that helps clear amyloid β from the brain (Zhang et al.). These findings come from animals, and human evidence remains limited (Gudden et al.; Beveridge et al.)

Fasting has been linked to higher SIRT1 expression in humans. In a study of nine volunteers, six days of total fasting more than doubled SIRT1 mRNA in subcutaneous fat tissue, and lean women had more than twice the SIRT1 expression of women with obesity (Pedersen et al.). Because this study used total fasting rather than intermittent fasting, it shows that fasting can raise SIRT1, but it does not show the effect of intermittent fasting patterns specifically. In separate work in cultured cells, SIRT1 reduced NF- κ B signaling in microglia that had been stimulated by amyloid beta, and this protected neurons from amyloid beta toxicity (Chen et al.). Amyloid beta peptides are widely presumed to contribute to AD, so this suggests one way fasting could influence amyloid-related damage: by raising SIRT1, which in turn limits inflammatory signaling. However, the two studies used different tissues (human fat tissue and cultured microglia), and neither tested whether fasting changes SIRT1 in the brain or whether this lowers AD risk. This connection is therefore a hypothesis that needs direct testing.

Intermittent fasting also causes lower obesity, as it utilizes caloric restriction and shifts the body from burning glucose to burning stored fat (Garegnani et al.). Therefore, during intermittent fasting, leptin production is expected to be low, and leptin falls rapidly with fasting and negative energy balance, which keeps the brain leptin-sensitive and avoids the hyperleptinemia and leptin resistance described in the Western diet. This can potentially lead to lower AD risk.

Data Collection Methods

Data for this project was drawn from publicly available sources and research papers (cited below) and specific food group/macronutrient information from various national surveys such as NHANES and FAOSAT. All data were cleaned, merged, and visualized in R using the tidyverse package family. Because each source reported data in a different raw format, each dataset required a distinct cleaning step before analysis. Some comparative data were compiled from different databases and turned into visualized format in R Studio. Images were formed using the digital editing tool: BioRender.

Discussion

In this paper, I chose to elucidate whether diet plays a role in AD prevalence. The five populations discussed in this paper include a wide range of dietary patterns and either a high or low AD prevalence. While there are some limited correlations between diet and AD prevalence, the strength of that correlation depends on the specific diet.

Across the four diets, the three genes point in a consistent direction. The Western diet is expected to raise LEP signaling that the brain resists, lower SIRT1, and favor amyloidogenic APP processing. The Mediterranean and Japanese diets, rich in fish-derived DHA and polyphenols, are expected to support SIRT1 and non-amyloidogenic APP processing, and to keep leptin signaling intact through lower adiposity. Intermittent fasting is expected to raise SIRT1 and preserve leptin sensitivity. These are interpretations of published experimental and observational work. No gene expression was measured in any of these populations in this paper.

Several limitations restrict how strongly these findings can be interpreted. The study establishes correlation, but without experimental trial, causation cannot be established. There are many other variables not accounted for in this study, including education, healthcare access, physical activity, smoking, cardiovascular health, and genetic background.

Conclusion



This paper compares dietary patterns, obesity, and dementia prevalence across five populations and examined three diet-responsive genes, *SIRT1*, *APP*, and *LEP*, that may correlate diet to the prevalence of Alzheimer's disease. Obesity was a common thread in this comparison: Japan, with far lower obesity and lower ultra-processed food intake, had a lower early-onset dementia prevalence than the United States, which had the highest obesity and the highest ultra-processed food intake. Japan's higher all-age dementia prevalence reflects its older population rather than its diet. The Mediterranean diet and intermittent fasting, which were examined through clinical trials, cohort studies, and laboratory research, have also been linked to better brain outcomes, although the evidence is stronger for the Mediterranean diet than for intermittent fasting in humans. We therefore conclude that the data are consistent with, but do not prove, the hypothesis that Western-diet obesity raises AD risk, and that Mediterranean, Japanese, and fasting-based dietary patterns may protect the brain. Pathways involving leptin, *SIRT1*, and amyloidogenic *APP* processing offer plausible mechanisms, but many other factors that are not yet understood are likely involved. These findings will hopefully promote targeted gene-expression and longitudinal studies of diet, obesity, and dementia.

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