Understanding Cardiovascular, Metabolic, and Lifestyle Risk Factors in Alzheimer's Disease Prevention

Sia Gullapalli

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Alzheimer's disease has been identified and named in the scientific community for over one-hundred years; however, it still takes an average of 122,000 lives each year, specifically in individuals sixty-five and older. This literature review of Alzheimer's disease (AD) risk factors and prevention methods identified and summarized four potential AD risk factors which include cardiovascular issues, diabetes, diet, and stress. Based on the peer-reviewed research articles referenced, all four potential factors were found to be associated with increased probability of being diagnosed with AD; however, some were found to be more connected to AD diagnosis compared to others. Accordingly, the every-day prevention approaches identified included, an increased focus on an individual's heart, anti-diabetic medication, a mediterranean-like diet, and the practice of doing meditation regularly. Specific methods of going about these preventive modalities were also highlighted, such as focusing on meditating with a certain technique and consuming a diet with many antioxidant vitamins and oils. Fully characterizing the risk factors for AD has the potential to help reduce the number of AD diagnoses per year as well as giving its victims a fighting chance for survival.

Keywords: AD, prevention, risk factors

Introduction

This paper explores several risk factors and prevention methods for AD. AD is a neurodegenerative disease where brain cells shrink and eventually die, which causes a gradual decline in memory and cognition in the patient with the diagnosis. Though the exact cause of AD has not been verified, more often than not the causes vary from genetic mutations in the amyloid precursor protein (APP), environmental factors such as exposure to aluminum, and degeneration of anatomical pathways, specifically cortical-cortical pathways. Specifically, the hippocampus and its connected structures are found to be affected first when individuals first get diagnosed with AD. The hippocampus is a necessary part of the brain for retrieving memories which is why AD patients have a difficult time remembering. AD is a major problem in society as data reflects that 2.32 million people in 1997 in the United States had been diagnosed with AD[1]. According to a recent study, "it is projected that the prevalence will nearly quadruple in the next 50 years, by which time approximately 1 in 45 Americans will be afflicted with the disease[1]. With this high diagnosis rate, adults, aged sixty-five and older, have a predicted average survival time of four to eight years right after being diagnosed with AD (Alzheimer's Association, 2022). This problem is essential to address as currently, among Americans ages 65 and older, AD is the fifth-leading cause of death, and it takes a significant mental and physical toll on the patients and their families[1]. Even though early research on AD risk factors and prevention stated that the diagnosis of AD was solely based on aging, it has been found in numerous current studies that certain risk factors can be prevented in the mid-life stage which has the potential to reduce individuals' risk for developing AD.

Methods

A systematic literature search was carried out concerning the risk factors of AD and its methods of prevention. Extensive searches were conducted in several electronic databases, including PubMed, Scopus, and Google Scholar. Some of the keywords used while searching the literature include "Alzheimer's disease," "risk factors," "prevention," "cardiovascular health," "diabetes," "Mediterranean diet," and "stress management," among others. The inclusion filters were placed in order to narrow the search in terms of English language peer reviewed articles, published between 2010 and 2024. The actual search was conducted in January-March 2024.

The inclusion will also be very specific: the date of publication should fall in the year 2010 up to 2024; the articles to be included will include original research, systematic reviews, or meta-analysis. Articles targeted established risk factors that increase the incidence of AD and propose ways of preventing the disease. Studies that do not specifically address AD, opinion pieces, editorials, or case reports were excluded. The methods for choosing relevant papers included searching keywords such as "AD, prevention methods, meta-analysis, and prevention."

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Adding on, the process for resolving discrepancies in certain studies included looking at their methods of collecting information and looking at more primary-based studied for a second opinion.

In addition, an standardized data extraction form was utilized to extract data from eligible studies. Information sought included authors and the year of publication, study design (cohort study, case-control study, randomized controlled trial), characteristics of the population under study, identified risk factors and their association with AD, suggested methods of prevention, and key findings and conclusions. This ensured that relevant data collection was comprehensive and uniform. Heterogeneity was avoided by utilizing three main study types: systematic literature reviews, population-based studies, and meta-analyses.

Data synthesis was done using the thematic analysis approach. The identified studies were classified into the pinpointed risk factors such as cardiovascular health, diabetes, dietary choices, and management of stress. Findings in each of the identified themes were summarized through a narrative synthesis, which highlighted the established associations of various risk factors and their prevention strategies with AD. It provided a systematic method to outline insights that could allow the identification of shared themes across studies.

The appropriateness regarding design, sample size, methods of data collection, and clarity of the conclusion were considered in rating each study with the application of the JBI-critical appraisal tools for quality assessment to approach the validity and, if appropriate, reliability of the research systematically. Therefore, such quality assessment helps to ensure that only high-quality research contributes to the findings in this literature review.

Literature Review

Numerous types of cardiovascular issues are linked with the diagnosis of AD in individuals. For instance, in a population-based study conducted by Kivipelto et al. (2001)[2], high systolic blood pressure (>/=160 mm Hg) and elevated levels of serum cholesterol concentration (>/=6.5 mmol/l) in individuals at their midlife displayed significantly higher chance of being diagnosed in their later life with AD. Even after adjusting for "age, body mass index, education, vascular events, smoking status, and alcohol consumption," it was still found, through the participants' history, that arterial blockage as a result of high systolic blood pressure combined with elevated levels of cholesterol are linked with AD risk[2]. Raised systolic blood pressure occurs due to artery stiffness or an overactive thyroid (hyperthyroidism). It can cause a lack of blood flow to the brain and other body parts[3]. As for high serum cholesterol concentration, many factors," such as hyperthyroidism, consumption of fatty foods, and stress, contribute to this issue, which results in decreased arterial compliance within the brain[3]. Re-examination of patients' medical history within the same study demonstrated that individuals diagnosed with AD were significantly more likely to have a family history of cerebrovascular disease and myocardial infarction. These issues are both "almost invariably expressed as a transient ischaemic attack". Additionally, in a systematic literature review conducted by Barnes & Yaffe (2014)[4], which aimed to summarize potentially modifiable risk factors for AD, it was found that within individuals at the midlife stage, hypertension was consistently associated with increased risk of AD during their late life as four out of five studies reviewed, reported a significant association in fully adjusted models.

Hypertension has a strong connection with high systolic blood pressure as both occur when the pressure in the blood vessels is too high, making this finding similar to the population-based study by Kivipelto et al. (2001)[2]. Because hypertension, high cholesterol, high systolic blood pressure, and heart disease are found to be linked with the diagnosis of AD, focusing resources on these cardiovascular elements could assist in reducing the number of people who have the potential to be diagnosed with AD in the future. Along with cardiovascular issues, specifically the ones mentioned above, diabetes has also been found to be linked with the diagnosis of AD within individuals.

Historically, type one diabetes has been explored as another potentially preventable risk factor for the diagnosis of AD in individuals at the late-life stage. According to the World Health Organization, type one diabetes is a chronic disease in which the pancreas or the body does not produce the required amount of insulin or is ineffective in using the insulin it produces[5]. In the systematic review written by Barnes & Yaffe (2014)[4], type one diabetes was investigated as a potential modifiable risk factor in addition to cardiovascular symptoms. The review ultimately found that the diagnosis of AD was associated with an individual's diabetic history and treatments. It identified a meta-analysis by Lu and colleagues, which consisted of eight prospective population-based studies that examined the association between diabetes mellitus and the risk of AD. Two of the studies reported a statistically significant increase in AD risk, while five found a non-significant increase resulting in a combined relative risk (RR) estimate of 1·39 (95% CI 1·17–1·66). However, the latter noted that AD risk was extremely close to the point of significant increase. In another study by Goodarzi et al. (2023)[6], in which an anti-diabetic drug was used to treat AD, it noted that there is an insulin pathway alteration that may be connected with tau protein phosphorylation and amyloid-β protein deposition, which are both essential factors in AD. They highlighted that because of this connection, there is a possibility of utilizing anti-diabetic medication, such as insulin, metformin, Glucagon-like peptide-1 receptor agonist (GLP1R), and thiazolidinediones (TZDs), to prevent AD in individuals due to the medications' possible neuroprotective effects[6]. As Intranasal insulin delivery targets the insulin pathway mutations that cause tau protein phosphorylation and amyloid-β protein

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deposition, it directly suppresses factors which ultimately have been found to cause AD. Metformin's neuroprotective effects are thought to stem from its ability to activate AMP-activated protein kinase (AMPK), reduce oxidative stress, and inhibit tau protein hyperphosphorylation. It may also improve mitochondrial function, which is critical in neurodegenerative processes. TZDs target peroxisome proliferator-activated receptor-gamma (PPAR-γ) pathways, which improve insulin sensitivity, reduce inflammation, and decrease amyloid-β production. However, concerns about side effects like weight gain and cardiovascular risks may limit their use. These therapeutic approaches underscore the potential for repurposing anti-diabetic medications to target specific pathophysiological mechanisms of AD such as inhibiting insulin resistance, reducing tau protein hyperphosphorylation, and mitigating amyloid-β aggregation, thereby addressing critical factors contributing to disease onset and progression. Specifically, out of anti-diabetic medications of Insulin, metformin, Glucagon-like peptide-1 receptor agonist GLP1R, and TZDs, GLP1R is found to work the best as prevention for AD as they have dual action. GLP1R both enhance insulin sensitivity and anti-inflammatory and neuroprotective effects, reducing amyloid-β accumulation and tau pathology while promoting neurogenesis. However, the other anti-diabetic medications mentioned also could potentially be beneficial for AD prevention. If further explored, preventing AD through the focus on type one diabetes and the usage of anti-diabetic medication could potentially reduce AD in the human population. In addition, an individual's diet and lifestyle choices have the possibility of being linked to cerebral perfusion, an essential factor in developing AD.

An individual's dietary choices are another contributing risk factor to neurodegenerative diseases, specifically AD. In a study by Hoscheidt et al. (2022), eighty-seven participants in Seattle and North Carolina with normal cognitive functioning and no history of hypertension (blood pressure $>$ 140/90) or usage of diabetes medications received either a Western or a Mediterranean-like diet (Med-diet). The Western-like diet (West-diet) is high in saturated fat, glycemic index, and sodium, while the Med-diet is low in saturated fat, has a lower glycemic index, and contains less sodium[7]. For context, The glycemic index (GI) is a numerical system that ranks carbohydrates in foods based on how quickly and how much they raise blood sugar (glucose) levels after being consumed. It measures the rate at which carbohydrate-containing food is digested and absorbed, causing a rise in blood sugar. A higher-GI diet causes frequent spikes in blood sugar levels which can cause oxidative stress and chronic inflammation and therefore injuring the brain. The participants were then assessed based on cerebrospinal fluid (CSF) biomarkers, cognition, and cerebral perfusion to determine whether the responses between the two groups were significantly different. It was found that the Med-diet lowered Aβ40 levels and moved the Aβ42/40 ratio, which is interconnected with reduced AD risk and a trend for enhancing cognition and cerebral perfusion (REF). According to the study, " The West-diet increased and the Med-diet reduced total cholesterol levels for both NC and MCI groups similarly (diet x time F= 21.89, P = .0001;)"[7]. (The Aβ42/40 ratio is a key biomarker used in the study and diagnosis of AD and other neurodegenerative conditions. It refers to the ratio of two isoforms of amyloid-beta (Aβ) peptides: Aβ42 and Aβ40, which are derived from the cleavage of the APP. The Aβ42/40 ratio links type 1 diabetes to AD by reflecting the imbalance of amyloid-beta peptides in the brain, with a lower ratio indicating increased amyloid plaque formation, which is exacerbated by insulin resistance and hyperglycemia. This ratio serves as a biomarker for AD risk, showing how diabetes-related metabolic dysfunctions promote amyloid accumulation and contribute to AD pathology.

On the contrary, the same study noted that the West diet increased Aβ40, lowered the Aβ42/40 ratio, and reduced cerebral perfusion, which are patterns associated with an increase in AD risk. Therefore, it was noted that "diet can be a powerful tool for prevention or modulation of disease progression in AD"[7]. Adding on, in another systematic review conducted by Stefaniak et al. (2022), that aimed to explore the principles of rational nutrition for older adults with AD, they highlighted that a diet that is rich in neuroprotective substances such as antioxidants, B vitamins, and polyunsaturated fatty acids contributes to the reduced risk of developing AD in the future. This is because antioxidant vitamins reduce oxidative stress, suppress inflammation signaling cascades, and suppress β-amyloid-induced lipid peroxidation, which are all factors that potentially could contribute to the damage of certain parts of the brain[8]. Through their sources, the study also concluded that the deficiency of vitamins E and C, as well as folates of vitamins B6 and B12, could be a contributing factor in the progression of AD (Cremonini et al., 2019). DNA methylation and homocysteine metabolism require folic acid, vitamin B6, and vitamin B12 as essential cofactors[8]. This makes their deficiency able to contribute to AD through an increase in oxidative damage to the brain and heart as well as an increase in homocysteine levels, which impairs reference memory and cortical levels of acetylcholine[9]. Therefore, individuals who consume a diet rich in vitamins, antioxidants, and folic acids may have a lower risk of developing AD potentially lowering AD from being the fifth-leading cause of death among adults sixty-five and older. Along with poor diet choices, such as ones with large amounts of saturated fats and oil, excessive amounts of stress in individuals' everyday lives are linked with developing AD.

Another potential risk factor for developing AD is an individual's stress levels in their everyday life. In a systematic review conducted by Khalsa (2015), different lifestyle choices regarding stress and the act of meditation were explored as potential risk factors and treatments for AD. Through three combined studies, they concluded that excessive amounts of stress have

a possibility of injuring the brain's hippocampal cells by the release of the hormone known as cortisol in response to pituitary and hypothalamic stimulatory signals [10]. The same study concluded that such injury could lead to damage to critically important emotion regulating brain structures and memory, which are key components in the diagnosis of AD. In the same review, it was also reported that people with stress-prone personalities, noting higher levels of work-related stress, "enduring early childhood stress such as abuse, trauma, and neglect and suffering from midlife stress" were more prone to decreased memory performance and a greater risk of AD in their later life" [10].

Meditation was found to be of help towards this issue as it mitigates the extensive adverse biochemical effects that come into the body due to excessive amounts of stress. Another study conducted by Innes et al. (2014) also recognized stress as an underlying risk for AD. They noted that chronic stress has the potential to lead to inflammatory changes in the brain as well as deleterious neuroendocrine function, reduced neuronal survival, impaired synaptic plasticity, and other adverse functional/morphological changes to the prefrontal cortex, hippocampus, and other essential parts of the brain [11]. These neurological changes can exceedingly affect an individual's learning process, memory, mood, and sleep, leading to ongoing brain damage [11]. As diabetes, stress, diet, and cardiovascular diseases often co-occur, the possibility of mixing prevention options remains open for patients diagnosed with AD. For example, for diabetes and cardiovascular symptoms, insulin as well as heart medication can be taken at the same time to further prevent AD; however, it could also put patients at risk for liver failure and other diseases [12]. For those reasons, individuals who are constantly being stressed have the possibility of being at a potential risk for developing AD in the late stages of their lives. Adding on, stress, along with cardiovascular problems, diabetes, and dietary issues, can become key risk factors and focus for the prevention of AD.

Conclusion

If mitigating potential risk factors for AD, including cardiovascular issues, diabetes type 1 and type 2, dietary choices, and excessive amounts of stress is further explored, there is potential that it can reduce the number of upcoming AD diagnoses in the coming years. Cardiovascular problems such as hypertension, high cholesterol, high systolic blood pressure, and heart disease, were found in multiple clinical studies and systematic reviews to be associated with decreased arterial compliance, therefore damaging the brain in the process. Diabetes I and II were found to be linked with increased AD risk through the insulin pathway alteration with the amyloid-β protein deposition and tau protein phosphorylation. Because of this connection, it is possible to conclude that anti-diabetic medications have the potential to reduce an individual's risk of developing AD due to their neuroprotective properties regarding the insulin pathway alteration. As for diet, multiple studies overlapped with the concept that a diet rich in vitamins, antioxidants, and folic acids gives individuals a lower risk of being diagnosed with AD. The main reason behind this is that antioxidant vitamins suppress inflammation signaling cascades, reduce oxidative stress, suppress inflammation signaling cascades, and suppress β-amyloid-induced lipid peroxidation, which are all factors that potentially could contribute to the damage of certain parts of the brain. For the last reviewed potential risk factor, stress also was found to be connected with increased AD risk. In the study conducted by Innes et al. (2014), chronic stress could potentially lead to inflammatory changes in the brain, specifically regarding the prefrontal cortex and hippocampus parts.

Potential future studies for this issue could focus on more everyday activities that individuals in their early to mid-life could do to reduce their risk for AD disease, specifically regarding the risk factors explored in this review. Some examples of everyday activities could be specific exercises, meditation techniques, or dietary actions that people could do or change about their lifestyle. While most AD disease research funds go towards treating the disease, focusing on the prevention and risk factors of AD could be an extremely effective technique in reducing the number of cases overall in the world. By zeroing in on the root cause of AD disease, many people who are prone to being diagnosed with it could have a fighting chance in the future.

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