



The influence of diet patterns on Alzheimer's risk: a concise systematic review

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Highlights

- ✓ Oxidative stress may induce overproduction of altered proteins, aggregation, oxidation, and membrane changes found in widespread degenerative diseases and suggests a central role for oxidation in the pathogenesis of degenerative diseases, including AD. Therefore, antioxidants that neutralize the effects of oxidative stress are promising therapeutics for preventing AD and several degenerative diseases. Vitamins, minerals, flavonoids, and polyphenols are known to be beneficial agents against age-related illnesses and have been shown to improve cognitive functions. Thus, dietary compounds are promising therapeutics for AD and other age-related degenerative diseases.
- ✓ The benefits of many different types of natural compounds present in a balanced diet can outweigh the risks of supplementing. Fruits and vegetables are fortified with moderate amounts of various antioxidants and other essential elements. Individual or synergistic effects of varieties of compounds found in fruits and vegetables can play a transformative role in mitigating oxidative stress. Eating habits can also influence the composition of the gut microbiota, which in turn can positively or negatively affect cognitive behavior, depending on its composition.

Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder responsible for the main

cause of dementia, and the increasing worldwide prevalence of AD is a major public health concern. Studies suggest that diet and nutrition may be important modifiable risk factors for AD. In addition, intestinal microbial metabolites and their effects on host neurochemical changes can increase or decrease the risk of AD. The aim of this literature review article is to discuss the relationship between dietary patterns, foods, gut microbiota, micro and macronutrients, and cognitive disorders, especially Alzheimer's. The results show that the excessive generation and accumulation of reactive pro-oxidant species over time can damage proteins, lipids, carbohydrates, and nucleic acids. Over time, this oxidative stress can contribute to a variety of age-related degenerative diseases. Therefore, antioxidant foods and healthy eating patterns, such as the Mediterranean diet, can contribute to reducing oxidative stress and consequently reducing the risk of Alzheimer's.

Keywords: Alzheimer's disease. Diet. Gut microbiota. Prevention. Treatment.

Introduction

Alzheimer's disease (AD) is the most common form of dementia. It is estimated that more than 46 million people are affected worldwide. Several factors contribute to the risk of developing late-onset Alzheimer's disease, including older age, genetic factors, family history, history of head injury, hypertension in middle age, obesity, diabetes, and hypercholesterolemia [1].

Medications available for the treatment of AD have only symptomatic effects, and there is an unmet need

to prevent the onset of AD, as well as to delay disease progression due to mild cognitive impairment (MCI) in the absence of disease-modifying therapies. In the last decade, one of the hypotheses raised was the association between lifestyle factors, such as diet and eating habits, and the occurrence of AD and dementia. Dietary factors can affect the risk of cardiovascular disease (CVD), also influencing the risk of AD and dementia [2].

A growing body of evidence suggests that certain diets are associated with a lower incidence of AD, so maintaining a healthy diet can have an impact on many of these possible risk factors for cognitive decline [2]. Therefore, high monounsaturated fatty acids (MUFA) in the diet and polyunsaturated n-3 fatty acids (n-3 PUFA), high fish consumption, together with high levels of antioxidants from fruits and vegetables and regulated gut microbiota, may have a beneficial effect on the risk of dementia [3,4]. However, the diet must be considered as a "whole", consisting of a complex of nutritional principles, foods, micronutrients and macronutrients that interact with each other. Combinations of foods and nutrients in certain patterns can act synergistically to provide stronger health effects than those conferred by their food components.

The National Association on the Aging and Alzheimer's (NIA-AA) guidelines for AD and cognitive decline due to AD pathology [5] have introduced some evidence suggesting a direct relationship between diet and dietary changes in brain structure and activity, thus opening the era of Brain imaging biomarkers in nutritional epidemiology.

Thus, this brief systematic review article aimed to discuss the relationship between dietary patterns, foods, gut microbiota, micro and macronutrients and cognitive disorders, especially Alzheimer's.

Methods

Study Design

The present study followed a concise systematic review model, following the rules of systematic review - PRISMA (Transparent reporting of systematic reviews and meta-analysis-HTTP: [//www.prisma-statement.org/](http://www.prisma-statement.org/)) [6].

Search Strategy and Information Sources

The search strategies for this review were based on the descriptors: "*Alzheimer's disease. Diet. Gut microbiota. Prevention. Treatment*". The research was carried out from April 2021 to July 2021 and developed based on Google Scholar, Scopus, PubMed, Scielo, and

Cochrane Library. Also, a combination of the keywords with the Booleans "OR", "AND", and The operator "NOT" were used to target the scientific articles of interest. The selected articles used as inclusion criteria the period from 2009 to 2021, were considered the researches of the last 12 years. All types of studies were selected. available, prospective, retrospective, case-control, cross-sectional, case reports, in vitro and in vivo studies, as well as systematic and literature reviews were excluded. Alzheimer's or other cognitive disorders.

Study Quality and Bias Risk

Quality was classified as high, moderate, low, or very low to the risk of bias, clarity of comparisons, precision, and consistency of the analyzes. The most evident highlight was for systematic review articles or meta-analysis of randomized clinical trials, followed by randomized controlled trials. The low quality of evidence was attributed to case reports, editorials, and brief communications, according to the GRADE instrument [7]. The risk of bias was analyzed according to the Cochrane instrument [8].

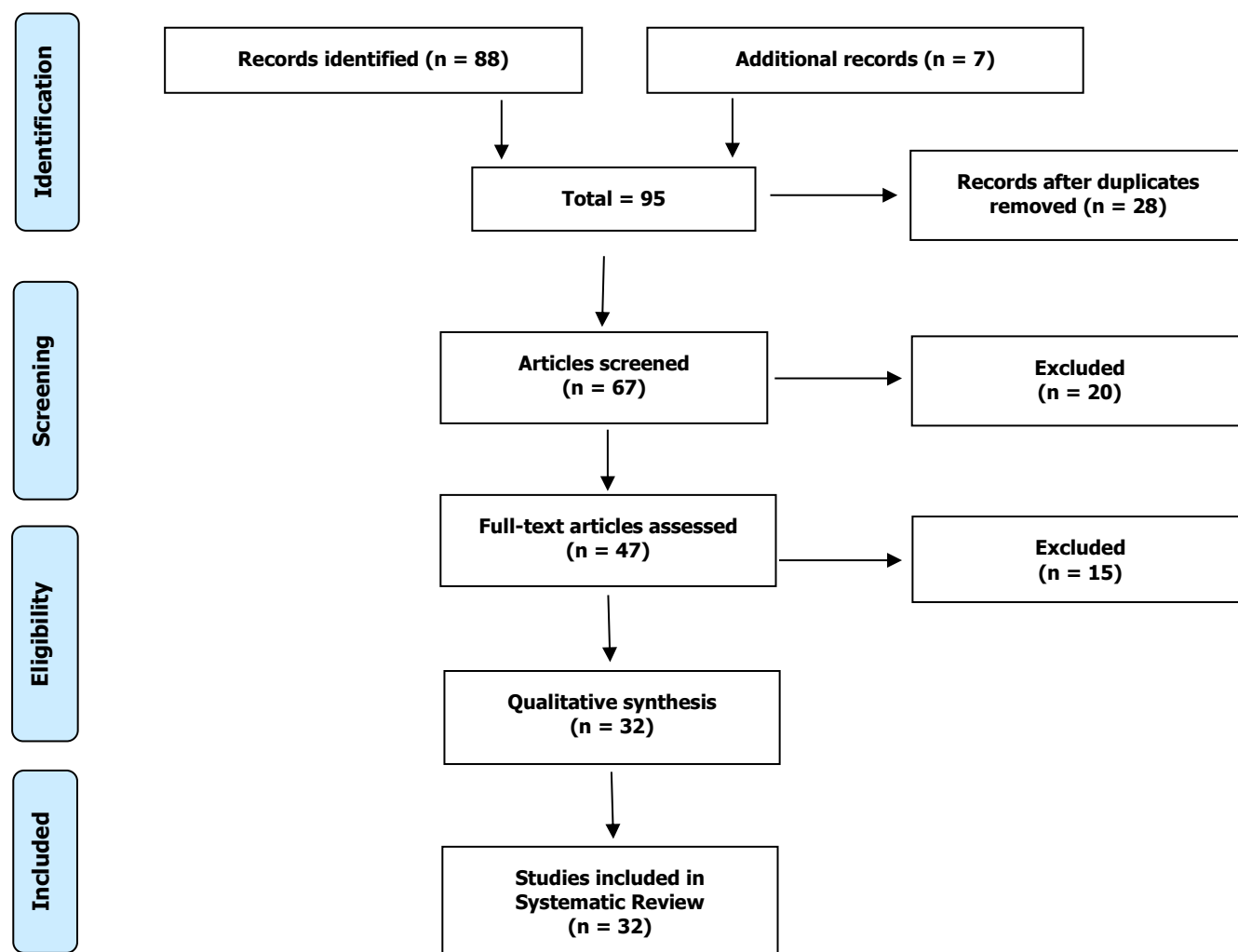
Results

As a corollary to the literary search system, a total of 95 studies were compared that were submitted to the eligibility analysis and, after that, 32 studies of high to medium quality were selected, considering in the first instance the level of scientific evidence of studies in type of study as meta-analysis, randomized, prospective and observational. The biases risk not compromising the scientific basis of the studies (Figure 1).

Oxidative stress and Alzheimer's disease

As aging takes place, cells gradually degenerate. Aging cell degeneration is a highly complex process with several mechanisms and processes involved. Redox cellular metabolic reactions occur during aging that induces harmful genetic and biochemical alterations [9]. An increased production of reactive oxygen species (ROS) and nitrogen damage cellular proteins, lipids, carbohydrates, and nucleic acids through oxidative stress, contributing to cell degeneration during aging [10]. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are short-lived, but increased redox reactions continually generate new ROS and RNS, and are believed to contribute to the onset of several degenerative diseases, including cancer, diabetes, Alzheimer, and Parkinson [9].

Metabolic and physiological behavior changes rapidly with aging. Thus, high-performing cells and

Figure 1. Study eligibility.

tissues, including postmitotic cells (brain and cardiac), are likely to be severely affected by ROS overload. This is one of the fundamental bases for the hypothesis of degenerative diseases induced by oxidative stress in the elderly [10]. Normal metabolic processes or cellular tensions continually generate ROS and RNS and build up over time. High levels of pro-oxidant impairment and weakened anti-oxidative defense mechanisms are more common in the elderly, suggesting that the elderly population is more affected by associated degenerative diseases.

AD is a complex and chronic neurodegenerative disorder related to aging. The mechanisms of AD are largely unknown. It is believed that inflammation, the intracellular release of calcium ions, autophagy, apoptosis, and, mainly, overproduction and aggregation (crosslinking) of A β peptides are involved in the neurodegeneration of AD [11]. Neuronal cells, among others, are particularly susceptible to degeneration induced by oxidative stress [12]. Neurons are metabolically active cells and use large amounts of oxygen, approximately a quarter of the total oxygen

consumed in the body, during metabolism. As a result, neuronal cells generate enormous amounts of ROS and RNS and are subject to free radical attacks. Compared to other cells, neurons comprise a low level of antioxidant defense molecules and contain a greater amount of polyunsaturated fatty acids prone to oxidation [12].

Lipid oxidation is one of the pathological markers found in AD brain tissue [10]. Highly oxidizable polyunsaturated fatty acids, such as arachidonic and docosahexaenoic acids, are present in the brain, and lipid peroxidation damages neuronal membranes, thus favoring damage to brain structures. Pro-oxidant overload is associated with age-related degenerative diseases and antioxidant defense mechanisms may play vital roles in dampening pro-oxidant activity and helping to prevent disease progression. Thus, increasing antioxidant pathways and/or neutralizing pro-oxidants by exogenous antioxidants may provide viable preventive options for degenerative diseases [12].

Gut microbiota, Diet, and Alzheimer's Disease

The health and diversity of the gut microbiota are directly dependent on the foods we consume. The gut microbiota appears to play an important role in increasing or decreasing the risk of AD. The gastrointestinal tract, from the esophagus to the anus, is lined with a layer of epithelial cells, which form the barrier of the intestinal mucosa to protect the body from infection by pathogenic microorganisms and prevent particles, chemicals, bacteria, and other health damage. They play important roles in protecting the host's health [13]. When intestinal permeability problems occur, which is called a leaky gut, disruption of intestinal barrier functions causes bowel leakage accompanied by increased inflammatory levels and resulting in the occurrence of disease [14].

The integrity of the blood-brain barrier (BBB) is vital for brain development and function. In the past, it was believed that the BBB was impermeable and could prevent possible harmful substances from entering the brain. It has recently been discovered that many substances can threaten the integrity of the BBB, causing all types of molecules, including proteins, viruses, and even bacteria, to enter the brain and threaten brain health [15].

Changes in the intestinal environment can gradually destroy the brain's ability to protect it from toxic substances. Inflammation induced by leaky bowel will result in a leaky brain, which is the increased permeability of the BBB. The destruction of the balance of the gut microbiota is directly related to the leaky intestine [16]. Stress, infection by pathogens, and antibiotics can destroy the gut microbiota and lead to increased intestinal permeability.

Lipopolysaccharide (LPS) is a combination of lipids and sugar and an important component of the cell wall of gram-negative bacteria. There are about 50% to 70% of gram-negative bacteria in the normal gut microbiota. LPS which is an endotoxin induces severe inflammation in the body if it enters the bloodstream. Under healthy conditions, LPS is blocked from the bloodstream by the tight junctions that exist between intestinal epithelial cells [16].

When bowel permeability is increased, LPS finds its way into the bloodstream and results in inflammation. Therefore, LPS levels in the blood represent not only inflammation but also a leaky gut. Studies found that plasma LPS levels in AD patients were three times higher than in healthy controls [17]. Increased concentrations of plasma LPS and fecal calprotectin indicate an altered intestinal barrier function and increased intestinal inflammation and permeability in AD

patients. These results also confirm that the gut microbiota can participate in the pathogenesis of AD [18].

Several experimental and clinical studies have revealed the role of the gut microbiota in host cognition, and its aging-associated dysbiosis leads to neurodegeneration. Intestinal microbial dysbiosis leads to the secretion of amyloid and lipopolysaccharides (LPS), which disrupts gastrointestinal permeability and the blood-brain barrier. Thus, it modulates the inflammatory signaling pathway, promoting neuroinflammation, neuronal damage, and, ultimately, leading to neuronal death in AD. A recent study revealed the antimicrobial property of the A β peptide as an innate immune response against pathogenic microbes [19-22].

Effects of Nutrients on Alzheimer's Prevention

As already shown, oxidative stress results in cell damage. Thus, looking for ways to promote antioxidant effects can prevent the occurrence of AD [23].

Vitamins and Minerals

Vitamin A and β -carotene may be key molecules for the prevention and therapy of AD, due to their ability to inhibit the formation of A β oligomers and fibrils. Low serum and plasma concentrations of vitamin A and β -carotene were observed in AD patients, and a higher plasma level of β -carotene was associated with better memory performance [23].

Another vitamin important in reducing A β oligomer formation and oxidative stress is vitamin C. Overall, there is a large body of evidence that maintaining healthy levels of vitamin C may play a protective role against AD [24]. B-complex vitamins can contribute to AD by inhibiting oxidative stress and lowering homocysteine concentrations. High homocysteine concentrations have been associated with an increased risk of AD, and homocysteine was significantly elevated in AD patients; supplementation in high doses of vitamin B6, B12, and folate reduces plasma homocysteine concentrations in AD patients; treatment to lower homocysteine may be a therapeutic target for AD [25].

Vitamin D may have little association with A β mechanisms and its potential association with AD may involve other pathways, such as antioxidant, vascular, anti-inflammatory, or metabolic pathways. A meta-analysis of 10 studies showed that AD cases had lower serum vitamin D concentrations than the corresponding controls [26].

Current knowledge does not provide evidence of a role for selenium (Se) in the treatment of AD, but it is

believed that there is a possible preventive relevance, and it has been reported that selenium plays an important role in antioxidant defense. AD patients had a significantly lower plasma selenium level compared to controls [25].

Polyphenols

Polyphenols are natural antioxidants that provide protective effects for AD through a variety of biological actions, such as interaction with transition metals, inactivation of free radicals, inhibition of the inflammatory response, modulation of the activity of different enzymes, and effects on intracellular signaling pathways and in gene expression. A randomized, double-blind, controlled clinical trial of polyphenol supplementation in 100 subjects showed that polyphenols contained in antioxidant beverages can benefit AD patients by decreasing homocysteine concentrations in AD patients [27,28]. The study by Eskelinen et al., (2009) [29] followed 1,409 individuals in Finland aged 65 to 79 years for 21 years and found that people who drank three to five cups of coffee daily in middle-age showed a 65% lower risk of AD compared to people who did not drink or drank less than two cups a day.

The effect of coffee can be explained in two ways. First, the gut microbiota can easily digest the fiber in coffee beans and collect its energy to support their growth. Simultaneously, they can reduce the ratio of Firmicutes to Bacteroidetes bacteria, and this change in the ratio of Firmicutes to Bacteroidetes is associated with reduced inflammation. Second, the body's ability to utilize coffee polyphenols is also largely influenced by the gut microbiota. After consumption, polyphenols need to be broken down by the gut microbiota into small molecules that are easily absorbed by the human body. Therefore, to obtain sufficient health benefits and increase the bioavailability and activity of polyphenols it is necessary to have a healthy gut microbiota [16]. The protective role of other antioxidants and nutrients may also depend on the balance of the gut microbiota to some extent. The healthy gut microbiota can increase its biological activity and utilization and thus exert its protective role in the brain to the fullest and reduce the risk of AD.

Diets and Alzheimer

Western Diet

The Western diet is characterized by an increased intake of red meat and processed products, refined grains, sweets, and desserts. The high-fat Western diet

may contribute to the development of AD, affecting A β deposition and oxidative stress [32]. In contrast, a study with 3054 participants evaluated participants who consumed a healthy diet, defined as positively correlated with the consumption of fruits, whole grains, fresh dairy products, vegetables, breakfast cereals, tea, good fats, nuts, and fish and negatively correlated with meat, poultry, refined grains, animal fat, and processed meat. Participants with the highest compared with the lowest adherence to a healthy diet had better cognitive function [33].

Mediterranean Diets

The Mediterranean diet, a typical diet of the Mediterranean region, is characterized by high consumption of fruits, vegetables, cereals, bread, potatoes, poultry, beans, nuts, oil, and fish; moderate consumption of alcohol (wine); lower consumption of red meat and dairy products. Adherence to the Mediterranean diet may not only affect AD risk, but also AD mortality. A meta-analysis of eighteen cohort studies with 2,190,627 individuals showed that adherence to the Mediterranean diet was associated with a significant reduction in overall mortality and neurodegenerative diseases [34]. The Mediterranean diet appeared to benefit the health of Crohn's disease patients, reflected by a tendency to reduce biomarkers of inflammation, in addition to normalization of the gut microbiota with an increase in Bacteroidetes and Clostridium and a decrease in Proteobacteria and Bacillaceae [35]. The Mediterranean diet can play important roles in disease control, including AD by balancing the gut microbiota [13].

Conclusion

Moderate amounts of various antioxidants found in a healthy natural diet can effectively mitigate free radical attacks and neutralize unregulated pro-oxidants, maintaining required levels of essential pro-oxidants in the cellular system, with the potential to mitigate disease-induced oxidative stress degenerative diseases, including AD. As oxidative stress can start early in life, preventive dietary intervention can be highly beneficial in preventing the progression of degenerative diseases.

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Data sharing statement

No additional data are available.

Conflict of interest

The authors declare no conflict of interest.

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