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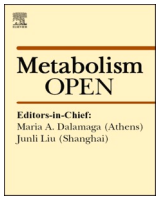

Prevention of Alzheimer's disease through diet: An exploratory review

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ABSTRACT

Introduction: This exploratory review article describes about the genetic factors behind Alzheimer's disease (AD), their association with foods, and their relationships with cognitive impairment. It explores the dietary patterns and economic challenges in AD prevention.

Methods: Scopus, PubMed and Google Scholar were searched for articles that examined the relationships between Diets, Alzheimer's Disease (AD), and Socioeconomic conditions in preventative Alzheimer's disease studies. Graphs and Network analysis data were taken from Scopus under the MeSH search method, including words, Alzheimer's, APoE4, Tau protein, APP, Amyloid precursor protein, Beta-Amyloid, Aβ, Mediterranean Diet, MD, DASH diet, MIND diet, SES, Socioeconomic, Developed country, Underdeveloped country, Preventions. The network analysis was done through VOS viewer.

Results: Mediterranean diet (MD) accurately lowers AD (Alzheimer's Disease) risk to 53% and 35% for people who follow it moderately. MIND scores had a statistically significant reduction in AD rate compared to those in the lowest tertial (53% and 35% reduction, respectively). Subjects with the highest adherence to the MD and DASH had a 54% and 39% lower risk of developing AD, respectively, compared to those in the lowest tertial. Omega-6, PUFA, found in nuts and fish, can play most roles in the clearance of Aβ. Vitamin D inhibits induced fibrillar Aβ apoptosis. However, the high cost of these diet components rise doubt about the effectiveness of AD prevention through healthy diets.

Conclusion: The finding of this study revealed an association between diet and the effects of the chemical components of foods on AD biomarkers. More research is required to see if nutrition is a risk or a protective factor for Alzheimer's disease to encourage research to be translated into therapeutic practice and to clarify nutritional advice.

1. Introduction

In three years of the Covid-19 pandemic, the death toll in 2019 was 5.44 M and the number of affected people was 290 M. On the other hand, the official death toll for Alzheimer's disease (AD) in 2019 was 121,499 and the number of affected people was 13.6 M [1]. With the rate of 1 person getting affected every 3 s, by 2050, the number of affected people in a year will be 13.8 M, where 7.0 M will be 87 years old [2]. Thus, with these mortality rates, scientists are considering Alzheimer's Disease as a silent future pandemic with worse consequences than Covid-19. Hence, it will be a major health concern and a substantial economic burden for families and nations (see Fig. 3 and 4).

In 2020 US spent $256.7 billion, assuming that the death number will rise to $600 billion only in the US by 2050 to bear the burden of AD and, more importantly, to give proper care to AD-diagnosed people, highlighting the threats of AD as a silent epidemic of the future world [3–6]. Besides, it has been over a century since people started searching for a cure for AD. According to the Scopus database, until 2009, the literature search was all about mutations, genes, inflammations, neurotoxicchemicals, and many other factors related to AD cure. In 2009,

Abbreviations: AD, Alzheimer's Disease; MD, Mediterranean Diet; DASH, Dietary Approaches to Stop Hypertension; MIND, Mediterranean-DASH Intervention for Neurodegenerative Delay; APP, Amyloid precursor protein; Aβ, Amyloid beta; MCI, Mild cognitive impairment; DHA, Decosahexaenoincacid; n-3, Omega-3; n-6, Omega-6; PUFA, Poly unsaturated fatty acid; MUFA, Monounsaturated fatty acids; SES, Socioeconomic status; EPA, Eicosapentaenoic acid; FA, Fatty acid.

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the concept of preventing AD by primary preventive measures came for the first time. In 2013, the word prevention with diets started more significantly and firmly in AD. The primary focus for AD has shifted towards the prevention rather than seeking a cure.

There are two big reasons for this change. Firstly, many recent studies have shown that targeting drug treatment to some biomarkers (which are also called secondary prevention), such as tau protein and Beta-Amyloid, which are also believed to have a critical role in Alzheimer's pathogenesis, did not show any positive feedback so far [7–10]. In contrast, the positive signs are blooming yearly regarding the primary prevention factors mainly focused on healthy diets [11,12]. Secondly, the success of prevention factors is increasing in AD-diagnosed patients, thus recovering the economic challenges. For example, dementia is one of the multiple branches of Alzheimer's disease. Currently, 70% of older age dementia are developing AD [13], and 10% of mild cognitive impairment (MCI) are developing AD, which will be expected to rise to 100% by 2050 [14]. Taking these statistics as an alarming point for health and economic research, scientists and health professionals are focusing on the cure to prevention, especially from secondary to primary prevention. Therefore, this exploratory review aims to investigate the link between diet and Alzheimer's disease (AD), examine preventive strategies against AD development, and emphasize the importance of selecting dietary components based on geographical and economic factors to successfully prevent AD.

2. Methods

2.1. Search strategy

This study was designed based on the Preferred Reporting Items for Exploratory Reviews and Meta-Analyses (PRISMA) protocol. In this review study, we performed a literature search on electronic databases, including PubMed, Scopus, and Google Scholar for related publications till January 2022.

An exploratory search was performed by two researchers independently using MeSH and non-MeSH keywords as follows: "Alzheimer's", "APoE4" "Tau protein", "APP", "Amyloid precursor protein", " Beta-Amyloid", "Aβ", "Mediterranean Diet", "MD", "DASH diet", "MIND diet", "SES"," Socioeconomic", "Developed country", "Developing country", "Underdeveloped country", "Preventions", "Mediterranean-DASH Intervention for Neurodegenerative Delay", "APP", "Amyloid precursor protein", "Aβ-Amyloid beta", "MCI", "Mild cognitive impairment", "DHA", "Decosahexaenoinc acid", "n-3 – Omega-3", "n-6 – Omega-6", "Poly unsaturated fatty acid", "Monounsaturated fatty acids", "Socioeconomic status", "Eicosapentaenoic acid", "Fatty acid".

Furthermore, references to these articles were examined to identify other relevant articles that we had not found in our initial search. In addition, we did not consider any language, location, and time restrictions in the search strategy.

2.2. Inclusion and exclusion criteria

In this review, inclusion criteria were (1) studies examining all dietary patterns using dietary assessment tools, includingfood consumption record, dietary record, dietary history, food frequency questionnaire, 24-hour dietary recall; (2) studies examining all possible biological markers of Alzheimer's disease; (3) studies conducting all possible physical and habitual cause of AD; (4) studies examining on socioeconomic status and it's effect on health care (5) studies conducted on adults (not including the studies conducted with using animal model); (6) studies designing observation (prospective or retrospective or cross-sectional or case-control studies) (7) studies were examined from the beginning of AD disease researches till current time.

Following the purpose of the study, we considered studies with long-time exposure (dietary pattern). Therefore, we included a short trial evaluating the effect of the economy on maintaining an effective diet. Short communications, comments, or letters were excluded for this study.

Furthermore, we considered mainly original studies with meta-analysis. Overall, in the initial search, we found 1602 relevant articles; after removing the duplicated studies and screening for topic of interest, we selected 157 articles for review with more details. Among these articles, we excluded 30 studies that were not AD-related but some other cognitive diseases. A total of 57 articles were excluded since they did not relate AD directly to diets. 32 articles were excluded due to no physical and habitual relationship with AD. Furthermore, 20 articles were excluded for socioeconomic irrelevancy. Finally, 18 studies were included in the current review study where the majority (N = 16) were from the USA.

2.3. Data extraction and dietary pattern evaluation

The study's information was extracted from a checklist designed for this study. This checklist included the first author, year of publication, study design, country of origin, sample size, gender, studied age range, dietary pattern assessment tools, kind of diet, and the most important outcome. The introduced dietary patterns of these studies were categorized by researchers into 2 or more groups: healthy and unhealthy diets. A healthy diet tended to contain a high intake of fruits, vegetables, fish, poultry, whole grain, olive oil, red wine, and people associated with physical exercise. An unhealthy diet was characterized by a high intake of red and processed meat, Sugar-sweetened beverages (SSB), refined grain, high-fat foods such as high-fat dairy, a high intake of eggs, and less or no connection with physical and cognitive exercise.

3. Alzheimer's disease and other associated factors

3.1. Dementia, MCI (Mild Cognitive Impairment), and Alzheimer's disease

There are slight differences between Dementia, MCI, and AD, although all of these result from inflammation and toxicity in the brain tissue. The similarities and dissimilarities between these three terms are summarized in Table 1.

Pathological connection among these three terms (Dementia, MCI, and Alzheimer's) also has a significant relationship with preventing AD. These include different types of diets, physical activities, education, SES, health conditions such as cardiovascular diseases, hypertension, depression, obesity etc., [23,24]. Furthermore, primary prevention factors are all the same for neuro-inflammatory diseases, while secondary prevention factors are slightly different from each other. From this point of view, focusing more on these secondary prevention factors

Table 1
Description of the similarities and dissimilarities among Dementia, MCI, and Alzheimer's disease.

Dementia	MCI	Alzheimer's
A cluster of many neuropathogenesis presents some common syndromes [15].	It is a transitional state between developing dementia and normal brain [16]	A branch of dementia [17].
Types of dementia depends on which part it will be developed. For example, Dementia in the hippocampus AD, Vascular Dementia, Dementia with Lewy bodies, Frontotemporal dementia, and Mixed dementia [18].	It has three branches e.g., amnestic MCI (aMCI), single-domain non-amnestic MCI, and multiple-domain MCI [19].	There are two types of AD, Early onset and Late-Onset type, depending on which time of life it develops [20].
It is developed from amnestic MCI [21].	Later, it can be developed into dementia or a normal state [14].	Dementia developed in AD [22].

will be more beneficial in person and for countries' economies and cost-effective than AD biomarkers. Because after suffering from any of these three diseases, a person becomes a burden to their loved ones. Moreover, both health care and caregivers often fall into depression and more importantly, the economic status falls as well because it stays lifelong once it is getting developed in the human body [25–28].

3.2. Secondary preventions of Alzheimer's disease

Mutation in genes and oxidative stress-induced inflammation in the brain are the two major pathological factors in AD. This initiates many other components to make inflammations and further induces the breakdown of neural connections in the brain [29,30]. In AD, one of the secondary preventions refers to the identification of the presence of the mutated genes such as APP, PSEN1, PSEN2, APOE4, TERM2, ABSA7, CR1, CD33, PICALM, NME6, CLU, BIN1, INPP3D, EPHA1, ZCWPW1, SORL1 [31,32].

Depending on their roles, these genes have higher, medium, and lower risk criteria. For example, APP, PSEN1, and PSEN2 are early-onset AD genes and directly affect Amyloid production [32–34]. They do not have much influence in AD. However, early diagnosis and primary prevention steps can reduce the risk of AD development in the elderly age. Among all these genes, two genes, including APOE4 and BIN1, are involved in cholesterol metabolism and trafficking [35,36] and thus play a massive role in AD. They increase the severity of the disease and early age onset more than any other genes. From a pathological perspective, Amyloid and Tau play the most significant role in the development of AD [37].

3.3. Lipid metabolism and genes in AD

Lipid metabolism is essential for the brain to function correctly [38]. Aβ deposition is one of the main pathological hallmarks of AD derived from Amyloid precursor protein (APP). In the brain, APP secretes and works as a transmembrane protein that cleaves lipid bilayer. β-secretase can cleave APP to form APP C99, which is then subjected to further, sequential cleavages by γ-secretase to yield amyloid peptides such as Aβ40 and Aβ42, for the relation of genetic factors with lipid and lipid metabolism researchers had a great interest in linking lipid metabolism and AD.

3.4. Biomarkers of Alzheimer's disease

3.4.1. APOE4

APOE or apolipoprotein E has three isomeric forms apoE2, apoE3, and apoE4 [39]. Among these three, apoE4 is the most frequent factor in AD [40]. Lipid effects on apoE4 are more due to its size and other unknown reasons. Because the apoE4 carrier carries the highest lipid level consumed apoE particles compared with the apoE2 and apoE3 groups [41]. Notably, Docosahexaenoic acid (DHA) plays a significant role in preventing AD development [41].

3.4.2. Tau protein

Tau protein maintains microtubule structures in neurons by keeping the flow of nutrients and neurotransmitters through a tiny microtubule pathway [42] unless Tau protein gets hyperpolarized by beta-Amyloid protein resulting in neurofibrillary tangles by the breakdown and death of neural cells [43].

3.4.3. APP and beta-amyloid

The formation of AD in the hippocampus makes remembering memories difficult [44], making it troublesome to remember incidents in the early stage of AD and dementia [45]. Every neuron cells contain APP. When beta-Amyloid gets produced from APP in the brain, three enzymes, alpha, beta, and gamma-secretases, cause cleavage in different parts of the protein, resulting in soluble fragments that are digested in the proteasome [44]. This helps to initiate the formation of senile plaques around neuron cells, which interrupt signal transmission among neuron cells [46].

3.4.4. Microglia

By measuring the amount and seeing the activities of microglia in the brain, an assumption about AD can be made because of its phagocytosis nature [47]. It gets expressed in every possible AD factor, but Aβ is the most concerning factor in AD pathology. In the brain, microglia usually work as a delete button, which works when syntactical connections stop working for a while. Then it detects neural connection as an unnecessary connection and during sleep, they go there, do phagocytosis, and erase the specific connection. In the case of AD [48], things also happen like this: when Aβ of senile plaques formed around neural connection, the transaction of signals between two neurons gets interrupted [49]. Microglia predicts this thing as an unnecessary connection and they erase these connections as well [50]. This can also cause neural damage in AD because, in Alzheimer's, the numbers of Aβ plaques are so high [51]. It is also one of the reasons why people cannot remember long-term memories in AD.

3.4.5. PSEN1 and PSEN2

PSEN1 and PSEN2 are considered the early-onset genetic factors. This does not play a significant role in AD or play any high risk except in some very specific regions of Latin America. It is really hard to find anywhere around the world, where it puts much risk of Alzheimer's disease [49,52].

3.4.6. CR1 and BIN1

Variant mutation in CR1 (located on chromosome 1) prevent the complement receptor type 1 (CR1) protein [53] and is associated with the development of AD [54]. Amphiphysin2, also known as Bridging Integrator 1 (BIN1), is located in chromosome 2 [55]. Various BIN1 is involved in synaptic vesicle endocytosis in the central nervous system [56]. Many studies presume that there is some direct link between AD and BIN1 but the between mechanisms of BIN1-mediated AD is still unknown [57]. Several studies found that genetic variation in BIN1 augments AD risk by changing tau pathology [58].

3.4.7. CA2AP and CD33

Being on chromosome 6, CA2AP regulates the actin protein's cytoskeleton by involving in the molecular scaffolding of actin [59,60]. A recent meta-analysis study has shown that the rs10948363 SNP of CA2AP is a risk factor for AD [61]. However, the gene expression of CA2AP does not change in AD-developed brains [62]; rather, it helps the formation of neuritic plaque [63]. On the other hand, CD33 has an exceptionally intimate association with microglial and myeloid cells [64]. It is located on chromosome 19q13.3 as a receptor [61]. CD33 plays a vital role in AD formation. One reason is that it is enriched with microglia, which cause Aβ inhibition due to the lacking of exon 2. Another crucial fact of CD33 is that it makes clearance of Aβ through inflammatory pathways of microglia [65].

3.4.8. CLU and SORL1

CLU is associated with complement regulation, apoptosis, lipid transport, membrane protection, and cell-cell interactions [66]. It is an apolipoprotein located on chromosome 8p21.1 [67]. CLU is highly expressed in the brains of patients with AD [68]. It influences Amyloid deposition and neuritic toxicity as well as Aβ clearances [69]. CLU expresses an amyloid agent, which could affect the AD pathogenesis because it causes neuroinflammation, a hallmark of Alzheimer's disease. Also, PICALM and CLU are linked with expressing AD symptoms [70].

SORL1 is characterized as a mosaic protein containing a domain structure. It is a member of the vacuolar protein sorting-10 domain-carrying receptor family and the low-density lipoprotein receptor family [71]. Its complete form is Sortilin-related receptor L located on

chromosome 11q23.2 [72]. From the cell surface to the golgi-endoplasmic reticulum, it also connects to vesicle trafficking, a risk factor of AD [73]. It has been found that SNP polymorphism (rs 11218343) of SORL1 is related to reducing AD risk [61].

All these genetic factors are associated with neural inflammation and oxidative stress, which is also called the hallmark of AD. However, the most critical biomarkers are three APP, APOE4, Tau protein, and Aβ, which have the predominant connections with nutrition and physiological activities.

3.4.9. Changing the research focus from secondary to primary prevention

Primary Prevention of AD means preventing the disease or lowering the disturbance of everyday work in daily life, which are the results of AD—by making people aware of AD eating healthy, and doing some easy but effective physical and mental exercise. On the other hand, secondary prevention means curing or minimizing the harmful effects of AD with medicine that targets the genetics and pathological factors of AD. The research on secondary prevention has not given any significant cure for this disease after spending over a hundred years researching this side of AD. Meanwhile, researchers who searched the primary prevention got massive significant results. For this reason, the focus of effective AD treatment is diet and exercise are emphasized.

A network analysis was done with 1646 papers from the Scopus database using Vos viewer. We used keywords that have come 150 to more times. The search was conducted in MeSh methods using the words "Alzheimer's", "APoE4", "Tau protein", "APP", "Amyloid precursor protein", "Beta-Amyloid", "Aβ", "Mediterranean Diet", "MD", "DASH diet", "MIND diet". It uses filters of Open-access and gold journal and English language. To see the most focused point in AD research from previously till now.

In Figure-1, we can see that the research is more focused on a cure by studying the genetic and pathological factors for decades. All the genetics and pathological factors are at the top. While from primary prevention, only diet and Mediterranean diet (MD) came because MD is the oldest in the diet group introduced in AD risk and prevention. The result is different if we change the search topic with the preventions term in AD. Another search and network analysis was done with 864 papers from the Scopus database. We took the top 43 words, which have come in 100 or more times (see Fig. 2).

Switching the topic to Alzheimer's disease (AD) prevention resulted in a significant shift in focus. The focus turned predominantly toward primary prevention factors, particularly dietary patterns. Here the bar showed how the focus keeps changing and from 2019 the focus went extremely toward diets than genetic or pathological factors in regards to the prevention of AD. Among genetic factors, research mostly focuses on tau protein (2015–2021).

3.4.10. Primary prevention

The data showed how the focus on AD prevention has changed currently to diets. Among the approaches for AD risk prevention, three distinct diets emerge: Mediterranean Diet (MD), Dietary Approaches to Stop Hypertension (DASH), and Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND).

3.4.11. Mediterranean Diet (MD)

Mediterranean diet, which has been practised in human life for centuries. From the Roman to the Greek empire, it has been practiced in the countries around the Mediterranean Sea [81]. Major countries using MD are Albania, Algeria, Bosnia and Herzegovina, Croatia, Cyprus, Egypt, France, Greece, Israel, Italy, Lebanon, Libya, Malta, Monaco, Montenegro, Morocco, Slovenia, Spain, Syria, Tunisia, and Turkey [82, 83].

A Mediterranean diet is more fresh fruit and vegetable-based and less carbohydrate-containing. Vegetables, fruits, legumes, cereals, fish, a moderate intake of red wine during meals, and mainly extra virgin olive oil [84]. Though there is no specific food, it has a great acceptance in the health sector. Many studies have shown that it has a massive role in reducing the mortality rate by decreasing the rate of cardiovascular diseases, strokes, insulin disorders, obesity, and neurodegenerative diseases at the older age [85,86]. In 2008 a study by Sofi et al. took place where 1574299 participants were enrolled for 18 years from 7 countries and the result showed that MD reduces the cardiovascular mortality rate

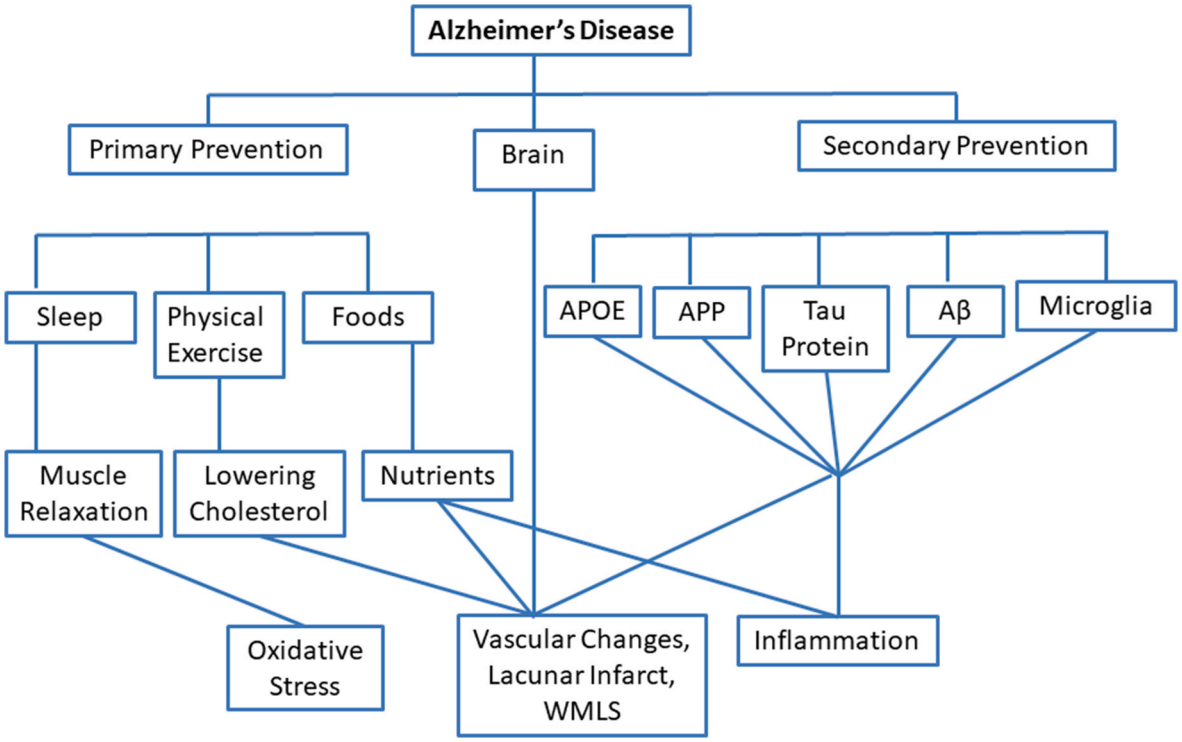

Fig. 1. Relationship among primary and secondary prevention factors of AD.

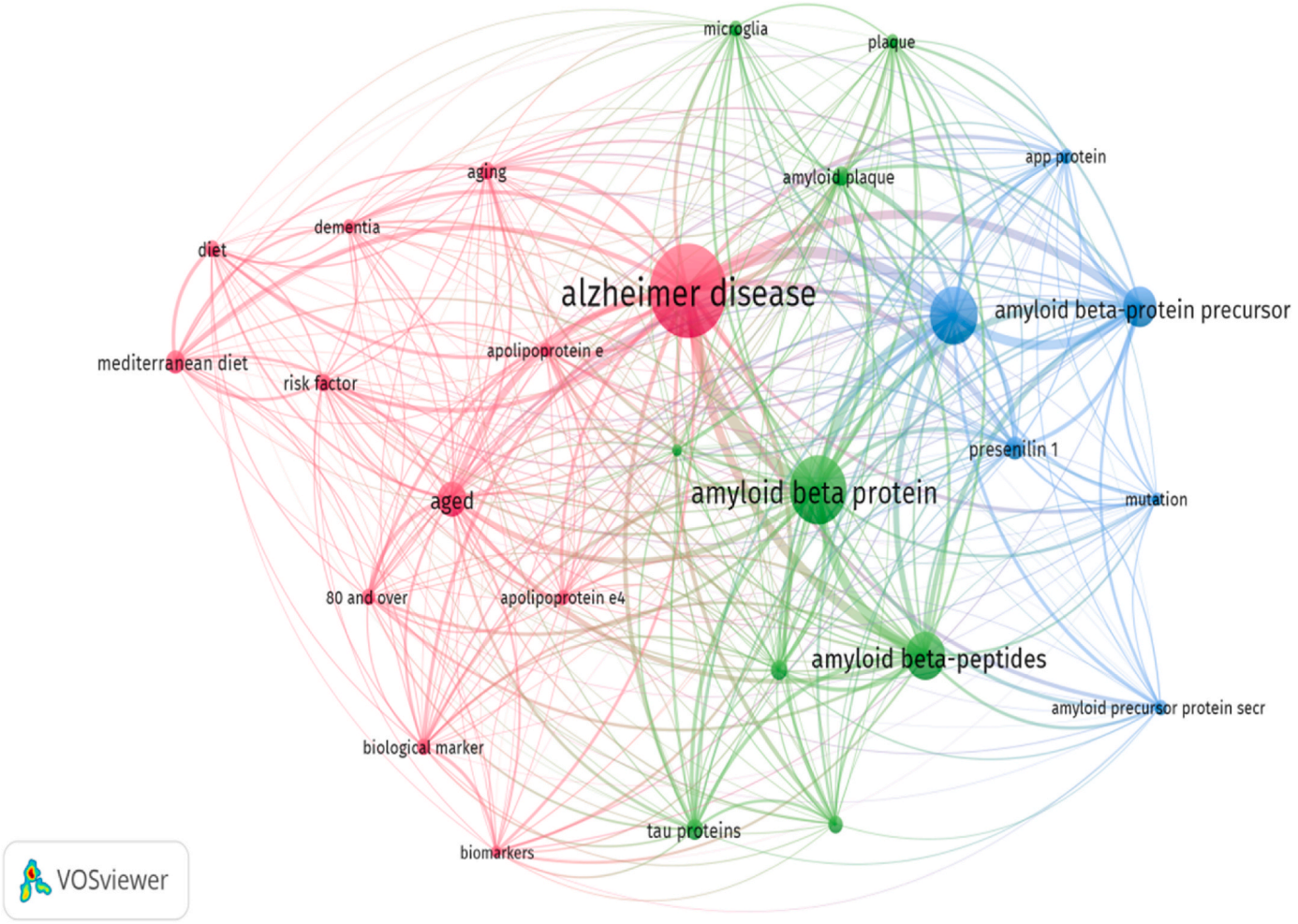

Fig. 2. Network analysis to see the most focused point in AD research from previous research till 2022.

by 9%, cancer by 6% and Parkinson's disease and Alzheimer's disease by 13% [87]. Another study was conducted in 2011 by Scarmeas and Brickman, where 707 participants were enrolled for 5.8 years, and showed that a higher MD score was associated with a lower burden of brain infarction [88]. MD also reduces the risk of stroke (RR = 0.71, 95% CI: 0.57–0.89), depression (RR = 0.68, 95% CI: 0.54–0.86), and cognitive impairment (RR = 0.60, 95% CI: 0.43–0.83). It was also found that moderate taking of MD has effectively lowered the stroke rate in males, predominantly [89]. Obesity which as well as also counts as a pandemic itself because it is the key to initiating many other diseases in the human body and causes a reduction in the mortality rate. Even to prevent obesity, a fat tax on unhealthy food rich in saturated fat has been implied recently [90]. ≈40% of energy from carbohydrates and ≈40% from fat in MD have been shown to reduce weight and waist circumference when energy-restricted [91]. Overall, from the beginning till the present MD does show either positive results or neutral in every research done.

3.4.12. *DASH diet*

Western and Asian diets are full of sodium, sugar, and saturated fat, with all the components causing chronic and cardiovascular diseases [92] whereas they have an inadequate amount of fish, fresh vegetables, whole grain foods, unsaturated fats, n-3 and n-6 fatty acids, which have a beneficial role on lowering mortality rate [93]. Researchers assumed that there might be some relationship between excessive hypertension and a western diet. To find that and to see the food effects on hypertension, dietary approaches to stop hypertension (DASH) diet originated worldwide in 1990. After that, in 1992 NIH started looking for a diet model which could be useful for hypertension and resulted with only food intervention, which was able to decrease the systolic blood pressure by 2.1 mm Hg in the control diet and by 1.3 mmHg by DASH for both regular and hypertension [94,95].

DASH diet contains low-fat dairy products, lean meat products, nuts and seeds, carbohydrates, fruits, and fresh Vegetables [96], as the DASH diet was designed to be effective against hypertension. That is why foods contain potassium, magnesium, and calcium to prevent endothelial dysfunction and muscle relaxation. Fruits such as bananas, oranges, and spinach are rich in calcium and potassium. In contrast, whole-grain foods are rich in magnesium [97,98].

3.4.13. *MIND diet*

After searching and taking knowledge on the dietary benefit of AD, Martha Clare Morris and her colleagues from RUSH Institute developed a new dietary pattern. It is a combined diet developed by 54% of the Mediterranean and 39% of DASH. The study showed that people who follow the MIND diet accurately lower AD risk to 53%, and 35% for people who follow it moderately [99]. The MIND diet has a principle to take 10 types of food (green leafy vegetables, other vegetables, nuts, berries, legumes, whole grains, seafood, poultry, olive oil, and wine) and refuse 5 types of food such as fried or fast food, red meats, cheeses, butter and stick margarine, pastries, and sweets [100,101]. This diet plan is also very effective in depression, and anxiety [102,103]. A vast study also showed that components from these diets are helpful in anti-inflammatory properties and anti-oxidant activity [104,105]. Neural inflammation and oxidative stress are the key markers in

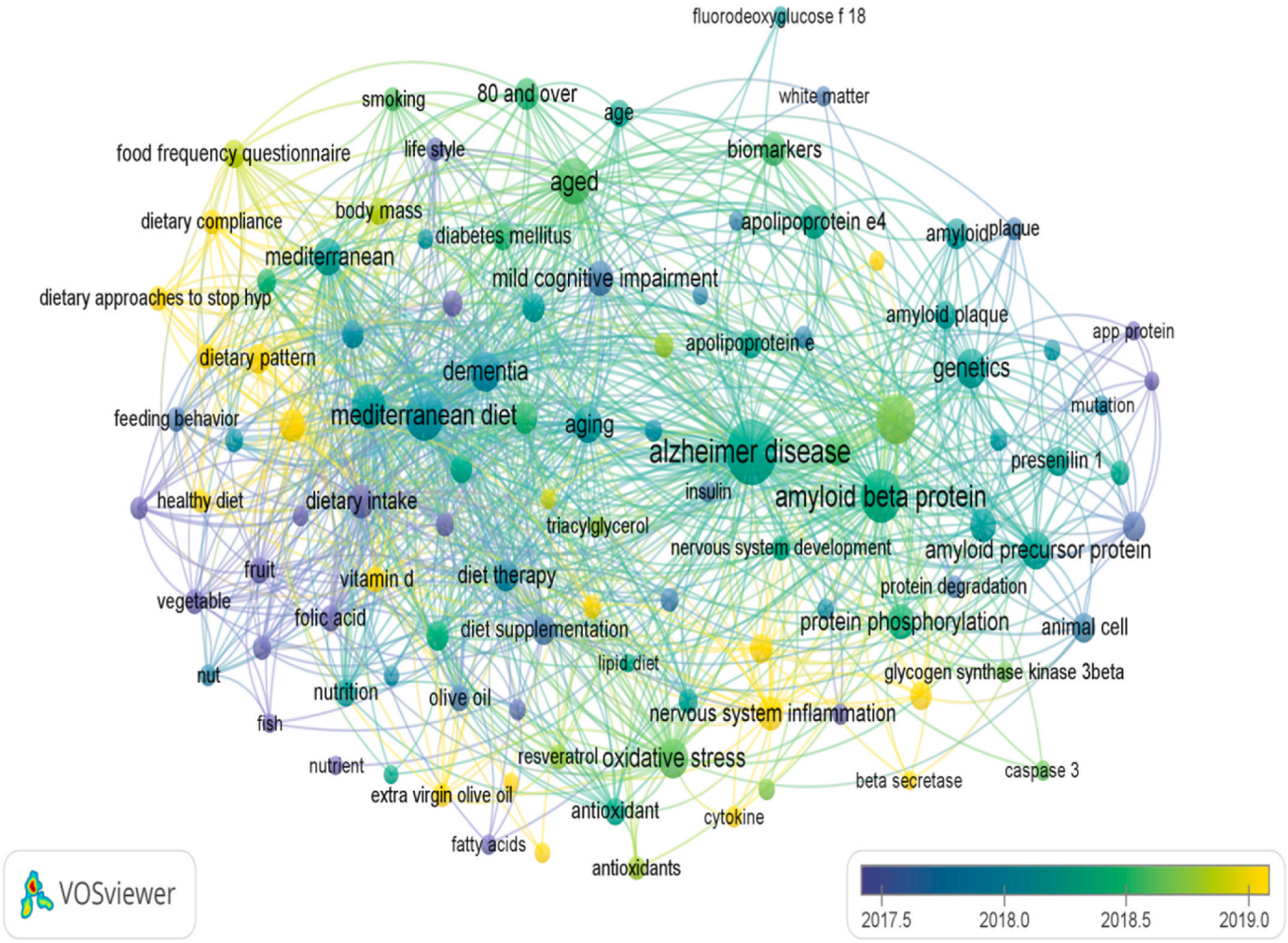

Fig. 3. Network analysis to see the most focused factors in AD prevention from 2015 to 2022.

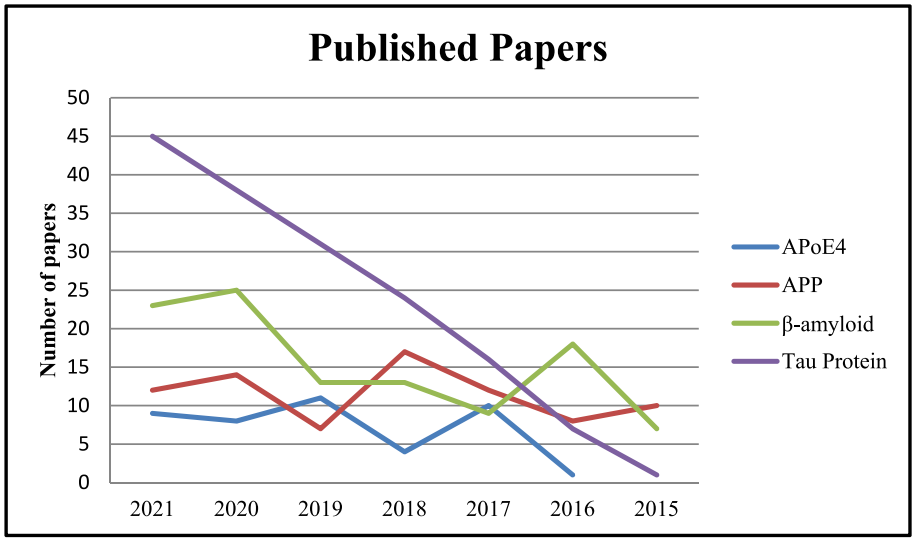

Fig. 4. Published papers in the Scopus database on APoE4, Tau protein, APP, and Beta-amyloid focusing AD cure.

Alzheimer's disease, dementia, and mild cognitive impairment (MCI). Implementing components of the MIND diet can help to manage these symptoms effectively [106]. Also, a considerable number of studies have shown that it plays a significant role in reducing stroke, cardiovascular disease, depression, hypertension, and diabetes-2 [107]. Overall, although the MIND diet is comparatively new to MD and DASH diets, many studies have shown that it is more effective in AD risk prevention than the other two dietary patterns.

In many studies, they named many foods for each diet while mentioning that these foods are criteria rather than specific. Within those criteria, any food can be consumed. From (Table 4), some vegetables, nuts, oil, and alcohol can be found in every diet. These foods contain some essential components for preventing neural inflammations.

3.5. Effect of foods in reducing the risk of AD

3.5.1. Fruits and vegetables

One of the most common fruits is tomato which is high in antioxidants (vitamin C, carotenoids, flavonoids, and hydroxycinnamic acids) and works for anti-inflammation in the brain. However, the most critical antioxidant found in tomatoes is lycopene. It reduces the risk of hypertension and cardiovascular diseases by protecting the skin from harmful sun rays and several chronic diseases [117,118]. Broccoli and Cabbages have indole-3-carbinol, identified as a preventer of different types of cancer [113].

3.5.2. Fish

Fish are high in polyunsaturated fats such as PUFA and MUFA. It has a high level of antioxidants. Fatty acids surround one-fifth of the dry component of the brain, where 20% FA is in the form of n-3 DHA, which has anti-inflammatory properties protecting against AD [115]. In addition, fatty fish intake more than twice a week is associated with a reduced risk of AD by 41% compared with eating fish less than once a month [119]. For this reason, oily fish have excellent benefits in reducing AD and cardiovascular diseases by their omega-3 polyunsaturated fat [120,121].

3.5.3. Olive oil

Olive oil always stays in all diet patterns as a healthy carbohydrate source. It is beneficial for the heart and lowers diabetic diseases by reducing LDL-cholesterol [122]. It also enriches with MUFA and VOD, which are beneficial as an antithrombotic and antihypertensive vasodilator effect and decrease plasma levels of thromboxane B2 [123].

3.5.4. Nuts

Nuts are enriched with arginine, which plays an important role in maintaining the low CRO levels. MUFA, PUFA helps to reduce cardiovascular risk and decrease inflammatory molecules in hypercholesterolemia [124]. Finally, yet importantly α-linoleic acids are present here that work for an excellent cardio health [125].

3.5.5. Wine

Polyphenols, vitamin E, and flavonoids are three nutritional components in wine, which are the possible anti-atherosclerotic agents in the MD [116,121]. Wine can protect the vascular walls, inflammation, platelet aggregation, and thrombus formation upon oxidation. Resveratrol, a chemical mostly found in wine, may act at multiple levels, such as cellular signalling, enzymatic pathways, apoptosis, and gene expression [126].

3.5.6. Physical exercise and sleep

Physical exercise and moderate sleep are two very effective factors in AD risk prevention. A study by Scarmeas N. in 2009 with 1880 participants has shown the effect of physical exercise and sleep in AD risk prevention. Participants who only followed diets lowered their risk by 29% while people with diets and physical exercise did lower their risk of AD by 9% [127]. Also, a daily 40–60 mins short nap at noon or after noon effectively reduces the prevalence of several cardiovascular risk factors and measures of subclinical atherosclerosis [128].

3.6. Alzheimer, obesity, exercise and ketogenic diet in a thread

Alzheimer's disease (AD) is related to cognitive impairment and before the transition to AD, mild cognitive impairment happens because of decreasing cerebral blood flow in different regions of the brain such as the precuneus, hippocampus, and posterior cingulate gyrus. This decrease in blood flow can be reduced or improved by aerobic exercise [143].

In AD, physical exercise helps in the downregulation of ApoE4 protein and Amyloid-β by producing the irisin hormone while reducing obesity, oxidative stress, and neuroinflammation by browning white fats in aerobic exercise [144,145].

Studies show that regular exercise or physical activity (PA) has a positive effect on preventing hippocampal volumetric decreases over time with aging [146]. More or less than 98% of AD development happens due to aging which is associated with obesity and diabetics where obesity increases AD risk 3.5 times higher [147]. Free fatty acids, caused by obesity help in stimulating the assembly of both amyloid and tau filaments, saturated fatty acids directly influence glial activation to cross BBB (brain-blood barrier) and stimulate microglial cells activations and cause neuroinflammation by which obesity plays a role in cognitive dysfunctions [148].

Diabetes also has comorbidity of obesity which cause insulin resistance. IDE (insulin degradation enzyme) insulation is caused by insulin resistance which is the key event for Aβ degradation and clearance causing its aggregation [149].

Deposition of adipose tissue is a major event in obesity and insulin resistance. Irisin is a myokine that correlates with adiposity, Glucose, and lipid homeostasis balance [150]. In study on obesity and diabetes, it was observed that maintaining a balance in glucose and lipid levels plays a role in preventing diabetes and obesity. This is achieved through three main mechanisms:

1. Increasing Irisin levels leads to improved glucose uptake and metabolism.
2. Higher Irisin levels reduce the formation of fat cells, fat production, and fat buildup.
3. The process of breaking down fats and turning white fat into brown fat (which burns more energy) gets enhanced when Irisin is present in the bloodstream [151].

Irisin helps in controlling obesity by maintaining glucose homeostasis, and browning adipose tissue and thus helps in the prevention of amyloid plaque, hyperphosphorylated tau protein in intracellular as neurofibrillary tangles forming and neuroinflammation thus preventing narrowing down (hippocampal blood volume) CBF in the hippocampus [151].

On the other hand, epilepsy is among the early signs of Alzheimer's disease as people age. The positive effects of ketogenic diets (KD), which induce ketone body production through ketosis, have been observed in this scenario [152]. Through ketogenic diets, the body's metabolism shifts from using glucose to rely on fatty acids (FA) for energy. Due to limited glucose availability, adipose tissues adapt by producing FA as an energy source. However, since the brain cannot effectively use FA, it turns to ketone bodies from adipose tissues via the bloodstream for energy production. This process is a result of glucose restriction in the diet [153].

KD and VLCKD (very low-calorie keto diet) also show anti-inflammatory characteristics via activating microglia just as PA or Irisin. Ketogenic diets also possess antioxidant properties that help in reducing oxidative stress and mitigating mitochondrial dysfunction, contributing to the reduction of obesity [154,155].

This explains why obesity is often associated with several key features of Alzheimer's disease, notably diabetes, oxidative stress, and neuroinflammation. By controlling obesity during the aging process, there is potentials to effectively lower the risk of Alzheimer's disease development.

3.7. Which diet pattern is appropriate for AD prevention?

As diet patterns contain foods, foods contain a component that works in AD and neural impairment. All three of the diets can be used for AD prevention. We cannot say that any specific one is better for AD risk prevention. Nevertheless, if we look into the rate of research works on these three diets, we may find an idea. MD diet follows generations of people living by the Mediterranean Sea. DASH was developed to prevent hypertension, and MIND was developed especially for AD prevention. By looking at the graph of published papers in the Scopus database on preventive facts about the three diets, we can see the fall of DASH and MD from 2020, and just after developing in 2015, the MIND diets are getting double focus every year. From this view, it reminds us that MIND was patterned for AD risk prevention. We can say it might be the best, but more research has to be done (See Fig. 5).

3.8. Effect of socioeconomic status and education on AD prevention

MD, DASH, and MIND, three of these diets, are very effective in AD prevention. Nevertheless, this will not be much effective in the world-wide health sector by 2050 because, in developing or low-income countries, the rate of dementia and AD is higher than in the higher income or developed countries [156]. While lower-income countries' diet is mainly carbohydrate based. They have low MUFA, n-3 PUFA, and fiber intake, and high intake of saturated fats and *trans*-fatty acids [157], which causes inflammation in the brain, oxidative stress, hypertension, diabetes, and heart disease more than developing one. SES or Socio-economic status plays a massive role here. Educations and household incomes are the two AD-increasing factors. If the low household incomes continue generation by generation, they cannot get any higher education because by being trapped in poverty, they had to come to the work field at a very early age [157]. For this, they have to do low-income jobs mostly with the ignorance of a healthy lifestyle. In low-income countries, a healthier diet costs 69% more, but food choices greatly affect this estimate [158].

Vegetables such as spinach, and lettuces which are a must in all three diets, have the highest range of SD among all foods. Unhealthy foods such as oil, fats, and sugar are in the lowest price range. Whereas, in low-income regions like South Asian countries, the components of these three diets are notably expensive.

Though lentils are still in all three diets pattern in low-income countries, they will go to an unhealthy food unless they stop taking it as a sub dishes besides rice and bread. Rice and bread are carbohydrate-based food so do lentils [159]. In three low-economic countries of South Asia, Bangladesh, India, and Pakistan, people have lentils with rice and bread as a main dish. By this, the amount of carbohydrates increases in their diet because of the high rate and less protein-based foods than carbohydrate-based food. They were also having less knowledge about food nutrition; in low-income countries, people choose cheap foods that last longer [156,160]. Even from the Table 7 price list, it is explicit that how expensive healthy foods can be; olive oil is one of the most essential foods in diets. People can buy 5 liters of soybean oil with 1 L of olive oil, which will last longer.

Additionally, to see if these concepts work, a short study with ten people, including two families with three members each for four days, was performed from December 31st, 2021, to 3rd January 2022.

Participants, gender, age	Serving foods
Group-1	
Family-1 Male-68 years old Female-1 (59 years old) Female-2 (23 years old)	1 Overcooked leafy vegetables in soybean oil 2 Rice 3 Lentils 4 Chicken/fish
Family-2 Male-1 (37 years old) Female-1 (35 years old) Male-2 (6 years old)	1 Overcooked leafy vegetables in soybean oil 2 Rice 3 Lentils 4 Chicken/fish
Group-2	
Female-1 (25 years old) Female-2 (23 years old) Female-3 (24 years old) Female-4 (24 years old)	1 Tomato 2 Carrot 3 Cucumber 4 Eggs 5 Lettuce

For Group-1, the food has been served 3 meals a day for 4 days by dividing 1 kg lentils into 1/4th per day and 1 kg rice 1/4th per day. And different types of leafy vegetables every day. During the 4 days, Group-2 followed a healthy diet that proved to be almost three times more costly compared to the diet of Group-1.

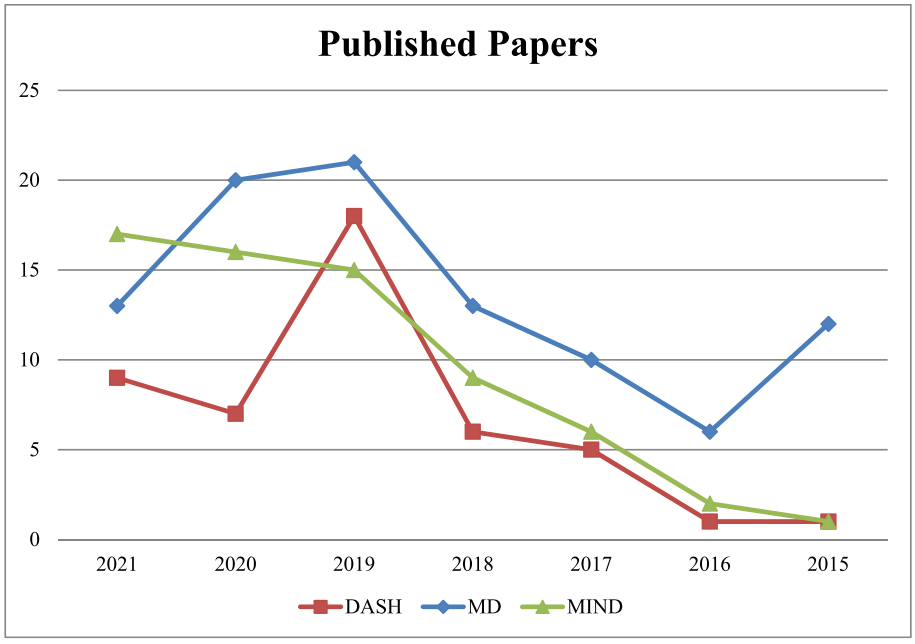

Fig. 5. Published papers in the Scopus database on preventive facts about the three diets.

3.9. Description of tables

Based on exclusion and inclusion screening methods and focusing on preventing AD through 3 dietary patterns, we prepared a total of 8 tables, 2 network analyses, and 2 graphs in this study. Tables 1 and 2, and Table 3 describe the relationships among AD and its biomarkers, consisting of 18 papers out of 55. Table 4 describes the information on Food groups and their serving times in all three effective diets in AD. Table 5 indicates the information about nutrition of the food from the 3 dietary patterns which help prevent AD. Table 6 provides sample and study characteristics of 18 studies where most of the studies (N = 16) were performed in the USA. Among them, 3 were from Boston, two are associated with Greece, Italy, and Switzerland, 1 from Finland, and 1 from Sweeden. Table 7 and Table 8 provide a comparison of prices between healthy and unhealthy foods in different countries, helping to determine the viability of the prevention plan based on the affordability of these food options.

4. Results

4.1. Description of the study

78 out of 165 included articles in this study have shown a promising relationship in improving AD through three selective diets. However, there are other underlying factors, such as sleep, rest, physical exercise, race, education, and mostly social economic status. This review hashish as consisted of previous studies that have found a relationship between diets, socioeconomic status, and AD which are inconsistent with several meta-analyses and reviews that have not found a relationship between diet, and AD. It contains 8 tables and 4 figures. Among 4 figures, two of them showed the network analysis and two of them are graphical illustrations of how the research focuses on AD prevention have been changed from 2009 to 2021 from a single cure to primary prevention through diets.

Table 1 shows the relations and differences between Dementia, MCI, and Alzheimer's. 9 papers were included, where 2 papers are from the USA, 2 from the UK, one from China, one from India, one from Japan, one from Canada, and one from Malaysia. In the UK, one paper was published in London and another in Nottingham.

Table 2 talks about the genetics and pathological causes of AD and gene impacts on them.

Table 3 talks about the biomarkers of AD APOE, Aβ, Tau, Microglia, App and nutritional molecules DHA, Vitamin E, Unsaturated FA, n-3, n-6, PUFA, EPA, MUFA and their effects on developing and preventing these biomarkers.

Table 4 discusses the 10 major groups of foods and food items and their serving times and amount in the three main diet patterns in AD prevention treatment.

Next, Table 5 then talks about the specific macromolecules the food items contain in themselves, which does have a major impact on preventing AD development [113–119].

Table 2
Genetics factors of AD and their physiological factors.

Gene Functions	Gene Name	Pathology	Gene name
APP metabolism	APP, PSEN1, PSEN2	Amyloid	APP, PSEN1, PSEN2, APOE4, ABCA7, INPP3D, PICALM, CLU
Cholesterol metabolism	APOE4, ABCA7, CLU	Tau	BIN1
Immune response	TERM2, CR1, CD33, INPP3D, EMPHA1	Unknown	TERM2, CR1, CD33, NME6, EMPHA1, ZCWPW1
Endocytosis	PICALM, BIN1		
Cytoskeleton	NME6		
Epigenetic	ZCWPW1		

Table 3
Showing multiple positive effects of food nutrients on AD genetics factors.

Biomarkers	Nutritional molecules	Effects
APOE	DHA, Vitamin E, Unsaturated FA, n-3, n-6, PUFA	- e4 carrier declined faster with Vitamin E association [74]
Aβ	DHA, EPA, Unsaturated FA, n-3, D1	- Clearance of Aβ [75] - n-3 FA increases Aβ phagocytosis [76] - D1 inhibits induced fibrillar Aβ apoptosis [77]
APP	EPA, DHA	- Increase non-amyloidogenic processing of APP [78]
Tau	DHA, n-6	- Improve behavioral motor function and survival by expressing tau [79]
Microglia	n-6, PUFA	-Reduce microglia activities [80]

Table 6 contains 18 results of meta-analyses, clinical trials, cohort studies, and cross-country studies where it shows and talks about how the foods in the diets and their chemical molecules does make impacts on cognitive health [88,92,132–142,159–161].

Tables 7 and 8 show the price differences between healthy and unhealthy foods in different countries to show if the prevention plan is going to work based on how affordable these foods are.

4.2. Description of sample

Ranges of sample size observed in the included studies are from 42 to 1,574,299 (M = 70, SD = 10.94), resulting in a total of 143,943.26 participants. Mean sample ages ranged from (38–90) total SD of 10.94.

4.3. Description of dietary pattern

55 studies have been included here, where 42 show the relations between diets and A. Three dietary patterns were evaluated here as the most effective and preventive for AD. Among them, (N = 16) were included about MeDi diets, (N = 17) on DASH diets and (N = 8) papers on MIND diets were included among 55 of included articles. Eight of the studies evaluated the intake of DHA, 10 PUFA and omega-3, and omega-6 [77–82,88,114,115,118,134,140,141,162], EPA [78,118,142,161,162], vitamin E [77,119], vitamin B and D [80,88,137] antioxidant [113,116,119], vegetables, fish, fruits, meat, nuts, dairy products, oil, cereals (whole grain), alcohol, legumes are also included. Finally, among 3 dietary patterns study could not specify a single dietary pattern, but MIND was specifically developed for AD patients and the number of studies on it is getting doubled in Numbers every year since it was introduced in 2015.

4.4. Relations to AD

Of all 55 studies, 42 have shown a relationship between AD, and diets. Thirty-three have specifically shown a relation among MD, DASH, MIND, and AD. Where 18 for MD, 7 for DASH, and 8 for MIND. Only 13 studies have not shown any association between AD and diets. Among them, 2 were from the USA, 2 from the UK, one was from Canada, one was from Malaysia, one was from Finland and one was from India. A total of 42 studies showed the reduction of AD biomarkers from developing and betterment from AD. Among 18 MD studies, 5 of them showed how it helps maintaining the cortical thickness and inflammations. DASH diets are relatively associated with maintaining hypertension and high blood pressure, which can cause neuroinflammation and strokes. The MIND diet is a combined diet developed by 54% of the Mediterranean and 39% of the DASH diet. A study showed that people who follow the MIND diet accurately lower AD risk by 53%, and 35% for people who follow it moderately [99].

MIND scores had a statistically significant reduction in AD rate compared to those in the lowest tertial (53% and 35% reduction,

Table 4
Food and their serving time of three categorized diets in AD risk prevention.

Food Group	Food name (MD)	Serving time [108]	Food name (DASH)	Serving time [109]	Food name (MIND)	Serving time
Vegetables	Tomatoes, broccoli, kale, spinach, onions, cauliflower, carrots, brussels sprouts, cucumbers, potatoes, sweet potatoes, turnips	(≥2 s/ every main meal	Kale, broccoli, spinach, collards, mustards, tomatoes, carrots, broccoli, and spinach	≥4 servings/ day	All kinds of fresh vegetables	Green leafy vegetable ≥6 servings/wk Other vegetables≥1 serving/day
Fruits	Apples, bananas, oranges, pears, strawberries, grapes, dates, figs, melons, peaches	1–2 s/every main meal	Apple, orange, banana, peach, pear, nectarine, plum, kiwi, cherries, berries, mango, pineapple, kiwi, grapes, melon, Low glycemic index fruit	≥4 servings/ day	Berries	≥2 servings/wk
Dairy products	Cheese, yogurt, milk, egg	(2 s/every day	Cheese, yogurt, milk	≥2 servings/ day		<1 serving/wk
Meat	chicken, duck, turkey	<2 servings/ wk	Chicken, duck, turkey	≤2 servings/ day	Chicken, duck, turkey	<4 meals/wk
Nuts	Almonds, walnuts, macadamia nuts, hazelnuts, cashews, sunflower seeds, pumpkin seeds, almond butter, peanut butter	1–2 s/every day	Almonds, walnuts, macadamia nuts, hazelnuts, cashews, sunflower seeds, pumpkin seeds, almond butter, peanut butter	≥4 servings/ week	Almonds, walnuts, macadamia nuts, hazelnuts, cashews, sunflower seeds, pumpkin seeds, almond butter, peanut butter	≥5 servings/wk
Oil	Olive oil	With every meal	Olive oil	Moderate amount	Olive oil	Moderate amount
Cereals (whole grain)	Brown rice, rye, barley, corn, buckwheat, whole wheat bread and pasta, oats,	1–2 s every main meal	Cracked wheat, millet, oats	≥2 servings/ day		≥3 servings/d
Sweets	Pastries, ice cream, and cookies	≤2 servings/ day	Pudding, sorbet, Jam	≤5 servings/ week	Pastries & Sweets	<5 servings/wk
Alcohol	Red wine	1 glass a day	no	no	Wine	1 glass/d
Legumes	Beans, peas, lentils, pulses, peanuts, chickpeas	(≥2 s/week	Beans	≥4 servings/ week	Beans	>3 meals/wk
Fish	All kinds of fish	≥2 s/week	All kinds of fish	≤2 servings/ day	All kinds of fish	≥1 meal/wk

Table 5
Foods and their components effective to cognitive impairment.

Foods	Nutritional component
Tomatoes	1. antioxidants (vitamin C, carotenoids, flavonoids, and hydroxycinnamic acids) 2. significant tomato benefits ingestion are, though, related to the antioxidant lycopene [110]
Nuts	1. PUFA, MuFA 2. ariginine 3. omega-3 [111,112]
Brassica vegetables, cabbages, kale, broccoli, Brussels sprouts, and cauliflower,	1. glucosinolates 2. indole-3-carbinol, 3. polyphenols, flavonoids [113]
Olive oil	1. antioxidant potential as well as its high content in MUFA 2. carotenes, phenolics compounds, and chlorophyll [114]
Fish	1. PUFA, MUFA, DHA 2. Omega-3 3. eicosapentaenoic acid (EPA,C20:5,n3) [115]
Wine	1. Polyphenols and vitamin E 2. flavonoids [116]

respectively). Subjects with the highest adherence to the MD and DASH had a 54% and 39% lower risk of developing AD, respectively, compared to those in the lowest tertial (HR = 0.46, 95% CI 0.26, 0.79) [142].

Furthermore, macronutrients in the food specifically do act strongly in preventing AD. Nutrients like omega-3, omega-6, PUFA, and MUFA found in nuts, and fish can play most roles in the clearance of Aβ, increase Aβ [75], phagocytosis [76], improve behavioral motor function and survival, expression to tau [79], reduce microglia activities [80]. vitamin D inhibits induced fibrillar Aβ apoptosis [77], and vitamin E, APOe4 carrier declined faster with vitamin E association [74]. EPA and DHA increase the non-amyloidogenic processing of APP [78]. EPA + DHA in red blood cells, especially the omega-3 index, has no connection with ischemic lesion volume (represented by both diffused small-vessel disease and white matter hyperintensities) [140]. Here, 10 studies showed the relationship of DHA with AD, 12 with n-3, n-6, PUFA, and MUFA, 5 with EPA, 3 with antioxidants, 2 with Vitamin E, 3 with vitamin B and D, where 1 only with vitamin D.

5. Discussion

The rapidly increasing rate of Alzheimer's, Dementia, and MCI have raised significant concerns among healthcare professionals worldwide. Researchers have highlighted the substantial social and economic impact, with AD prevalence projected to worsen, potentially costing around $2.8 trillion annually by 2050 if current rates continue that is a new patient every 3.2 s [162]. In 2010 alone, the global socioeconomic cost of dementia was $604 billion, surpassing the combined costs of cardiovascular disease and cancer, which are well-known as some of the most expensive treatments.

Despite knowing about the consequences, healthcare professionals do not have any choice but to alarm people about diagnosing it at an early stage, do's and don'ts, the pros and cons of the disease, and the consequences it will bring with it since there is no single cure for it.

Table 6
Meta-analyses and clinical studies performed on the effects of foods and its nutritional quality in cognitive impairment.

Author name	Subjects	Nutrition/ Diet/Food	Benefits	Ref.
Sofi F., Cesari F., Abbate R., Gensini G.F. Casini A.	n = 1,574,299 8 years	MUFA + PUFA: SFA, High n-3,n-6	Reduce Parkinson's disease and Alzheimer's disease rates by 13%, cardiovascular by 9%, and cancer by 6%	[87]
Psaltopoulou T., Sergentanis T.N., Panagiotakos D. B., Sergentanis I. N., Kosti R., Scarmeas N.	22 cohort study	MD	Reduced risk for ischemic stroke, mild cognitive impairment, dementia and particularly Alzheimer's disease But it seems more effective on males for depression, and AD	[89]
Jae H Kang, Alberto Ascherio, Francine Grodstein	n = 13,388 women, aged 70 years and over	Only vegetables, not fruits	High consumption of vegetable associated with less cognitive decline among older women	[129]
Lori A Daiello, Ronald A Cohen, Brian R Ott	n = 819 55–90 years	Fish oil	Fish oil use is associated with lower of both the whole brain (for normal controls and MCI participants) and the hippocampus (for normal controls and AD patients), and less cognitive decline but only among APOE4 non-carriers	[130]
G L Bowman, L C Silbert, D Howieson, H H Dodge, M G Traber	n = 42 age 87 years	n-3 PUFA	Higher plasma long-chain n-3 PUFA associated with lower white matter hyper intensities volume	[131]
Sara C Staubo, Jeremiah A Aakre, Prashanthi Vemuri, Jeremy A Syrjanen, Michelle M Mielke, Yonas E Geda, Walter K Kremers	n = 672 age 79 years	MD	Mediterranean diet score is related with larger cortical thickness in many regions (exceptionally high legume and fish and low carbohydrate and sugar), with no significant rule with an AD signature cortical thickness	[132]
M C Morris, D A Evans, C C Tangney, J L Bienias, R S Wilson	n = 3718 aged 65 years and older	Vegetable	High vegetable, but not fruit, consumption was associated with slower rate of cognitive decline with older age	[133]
Lisa Mosconi, John Murray, Michelle Davies, Schantel Williams, Elizabeth Pirraglia, Nicole Spector, Wai H Tsui, Yi Li, Tracy Butler, Ricardo S Osorio, Lidia Glodzik, Shankar Vallabhajosula, Pauline McHugh, Charles R Marmar, Mony J de Leon	n = 49 54 years old	Vitamin-B12, D,n-3 PUFA	Higher intake of vitamin B12, vitamin D, n-3 PUFA from food sources associated with lower amyloid load in AD regions at C-Pittsburgh Compound B (PIB)-PET	[134]
V Berti, J Murray, M Davies, N Spector, W H Tsui	n = 54 54 years	Vitamin B12, D, zinc	A nutrient intake pattern characterized by higher intakes of vitamin B12, vitamin D and Zinc associated with lower amyloid load	[135]
Hussein N Yassine 1, Qingru, Ida Azizkhanian, Katherine Castor, Alfred N Fonteh, Michael G Harrington, Ling Zheng, Bruce R Reed	n = 61 age (68–88)	DHA	Serum DHA inversely related to amyloid load using 11C PIB-PET	[136]
Scarmeas N, Luchsinger JA, Stern Y, Gu Y, He J, DeCarli C, Brown T, Brickman AM.	n = 707 age 80.03	MD	Higher MD score associated with reduced burden of brain infarcts	[88]
J K Virtanen, D S Siscovick, W T Longstreth Jr, L H Kuller, D Mozaffarian	n = 4128 age 65 years	Fish	Intake fish ≥3 times/week related to lower subclinical infarcts (ischemic lesions)	[137]
J K Virtanen, D S Siscovick, W T Longstreth Jr, L H Kuller, D Mozaffarian	n = 2293 age 65 years	Plasma Phospholipid n-3 PUFA	Plasma phospholipid long-chain n-3 PUFA (EPA + DPA + DHA) associated with lower prevalence of subclinical infarcts	[138]
Z S Tan, W S Harris, A S Beiser, R Au, J J Himali, S Debette, A Pikula	n = 1575 age 67	EPA and DHA	DHA level has a link with lower white matter hyper intensities volume only after adjustment for the complete set of potential confounders; and no connection with	[139]

(*continued on next page*)

Table 6 (*continued*)

Author name	Subjects	Nutrition/ Diet/Food	Benefits	Ref.
			silent cerebral brain infarcts	
James V Pottala, Kristine Yaffe, Jennifer G Robinson, Mark A Espeland, Robert Wallace, William S Harris	n = 1111 age (65–80)	EPA and DHA	EPA + DHA in red blood cells especially the omega-3 index has no connection with ischemic lesion volume (represented by both diffuse small-vessel disease and white matter hyper intensities)	[140]
Sara C Staubo, Jeremiah A Aakre, Prashanthi Vemuri, Jeremy A Syrjanen, Michelle M Mielke, Yonas E Geda, Walter K Kremers	n = 672; 79.8 years	MD	Higher adherence to an MD was noticeably related to a lower risk for AD. Introduction of the high-sensitivity C reactive protein, fasting insulin, adiponectin or combinations of them into the COX model did not change the magnitude of the relation between MD and incident AD	[132]
K Mehlig, I Skoog, X Guo, M Schütze, D Gustafson, M Waern, S Ostling, C Björkelund, L Lissner	n = 1462 age 38-60	Alcohol	The wine was effective for dementia; The relation was strong among women who consumed wine only. consumption of spirits at baseline was associated with a slightly increased risk of dementia	[141]
Morris MC, Tangney CC, Wang Y, Sacks FM, Barnes LL, Bennett DA, Aggarwal NT	n = 960	MIND	The middle and the highest tertiles of MIND scores had a statistically significant reduction in AD rate compared to those in the lowest tertile (53% and 35% reduction, respectively). Subjects with the highest adherence to the MD and DASH had a 54% and 39% lower risk of developing AD, respectively, compared to those in the lowest tertile (HR = 0 46, 95% CI 0.26, 0.79)	[142]

Alzheimer's or dementia still does not have a single cure, but it has been kept voicing from researchers around the word about preventing it than curing it. They established that AD could be prevented by physical and mental exercise, and the best result is in taking healthy foods and maintaining some diet patterns regularly.

The majority of the studies included in the present review (42/55) revealed a statistically significant association between diet and AD. However, because it is particularly difficult to distinguish the exact contributing effect of dietary variables, the fundamental mechanisms behind this connection remain unknown and unclear. For example, individuals who maintain a healthy food pattern are more prone to participate in other health habits, such as physical activity.

Furthermore, the variety of dietary patterns investigated contributes to the confusion in the International Journal of Neuroscience field. For example, many studies have examined the role of dietary patterns such as MD, DASH, and MIND, while others have focused on foods and macronutrients, such as fish, olive oil, Omega-3, Omega-6, DHA, EPA, PUFA, and MUFA. For example, a recent study involving 22 cohort studies on the relation between MD and AD has shown that MD reduced the risk for ischemic stroke, mild cognitive impairment, dementia, and, in particular, Alzheimer's disease. However, its effectiveness appears to be greater in males with depression and AD [89]. Also, a study by Staubo et al. for 8 years period, n = 672, age 79, found that higher adherence to an MD was noticeably related to lower risk for AD. The introduction of the high-sensitivity C reactive protein, fasting insulin, adiponectin, or combinations of them into the COX model did not change the magnitude of the relation between MD and incident AD [132]. However, many studies have shown that it has a massive role in mortality rate by reducing the rate of cardiovascular diseases, strokes, insulin disorders, obesity, and neurodegenerative diseases at an older age which all are known as AD-developing risk factors [85,86].

In 2008, a study by Sofi f et al. took place where for 18 years 1 574 299 participants from 7 countries participated and the result was that MD reduced the cardiovascular mortality rate by 9%, cancer by 6%, and Parkinson's disease and Alzheimer's by 13% [87]. Another study in 2011 by Scarmeas and Brickman, for 5.8 years with 707 participants, showed that higher MD scores with lower brain burden infarct [88]. MD also reduces the risk of stroke (RR = 0.71, 95% CI: 0.57–0.89), depression (RR = 0.68, 95%CI: 0.54–0.86), and cognitive impairment (RR = 0.60, 95%CI: 0.43–0.83). It also showed that moderate taking of MD has been effective in lowering stroke rates in males [89]. Our study finds that MD does not have a good health impact on overall brain health, but it plays a better role if someone has a genetic AD family history and has a very possibility of developing AD in later life to maintain this diet helps to prevent the onset stage of AD.

The DASH diet was developed and is useful for hypertension and results with only food 94, but it does have good effects on the primary stage of AD because this diet contains low-fat dairy products, lean meat products, nuts and seeds, carbohydrates, fruits and fresh vegetables [96] as the DASH diet was designed to be effective on hypertension. That is why foods contain potassium, magnesium, and calcium to prevent endothelial dysfunction and muscle relaxation. Fruits such as bananas, oranges, and spinach are rich in calcium and potassium. In contrast, whole grain foods are rich in magnesium [97,98], which are also almost the same foods as MD.

The MIND diet was developed by Martha Clare Morris and her colleagues from RUSH Institute developed a new dietary pattern focusing on reducing AD development. It is a combined diet developed by 54% of the Mediterranean and 39% of DASH. A study showed that people who follow the MIND diet accurately lower AD risk to 53%, and 35% for people who follow it moderately [99]. A recent study showed that late-life AD patients have less mortality rate [157]. It has a principle to take 10 types of food (green leafy vegetables, other vegetables, nuts, berries, legumes, whole grains, seafood, poultry, olive oil, and wine) and refuse 5 types of food fried or fast food, red meats, cheeses, butter and stick margarine, Pastries, and sweets [100,101]. These are mostly with

Table 7
Differences in the price range of foods among different countries (Number represents standard deviation).

Country name	High income	Europe Central Asia	South America	Central America	Small Island	Middle East, North Africa	East Asia	South Asia	East Africa	South Africa
Number of Country	44	16	7	10	28	9	10	5	6	11
Legumes	1.2	1.7	2.9	2.6	2.3	1.9	3.1	2.2	4.6	4.5
Fruits	1.7	1.8	1.6	1.3	3.1	2.5	3.8	3.0	2.0	4.2
Vegetables	3.3	3.1	8.4	6.0	9.9	4.1	9.6	6.2	6.9	12.9
Fish	4.3	5.2	3.4	3.8	9.4	4.8	4.7	5.4	6.2	5.5
White meat	2.0	2.7	3.2	2.5	3.6	4.2	5.2	7.0	9.8	7.7
Red meat	3.5	4.1	5.3	4.1	6.1	9.9	6.6	8.4	5.0	7.3
Dairy	2.0	2.7	2.9	2.5	2.2	2.5	3.7	4.1	4.9	6.0
DGL vegetables	9.0	11.4	6.2	5.6	15.3	5.9	8.1	7.3	5.1	11.0
Oil	0.4	0.6	0.7	0.7	0.8	0.7	0.8	0.9	1.3	1.6
Sugar	0.5	0.8	1.0	0.7	1.1	1.0	1.4	1.5	1.6	1.8

[Standard deviation (SD) of price comparison of different healthy foods according to the International Comparison Program (ICP) 2011 database and Hardey et al. 2019 [159], which are all included in these three diets of different countries].

Table 8
Price comparison among some healthy food and unhealthy foods in a low-income country.

Healthy food	Unhealthy food
Tomatoes 1 kg (298tk)	Lentils1kg (112tk)
Spinach 100p (150tk)	Rice 1 kg (60tk)
Lettuce 1 kg (450tk)	White Bread 1 kg (160tk)
Carrot 1 kg,8–9p (90tk)	Flour 1 kg (55tk)
Brown sugar 1 kg (195tk)	Refined sugar 1 kg (120tk)
Olive oil 1lt (965tk)	Soybean oil 5lt (873tk)

Note: Data were taken from Bangladesh's most significant online grocery shopping sites, Chaldal.com and othoba.com, on 11 August 2023 *with the lowest price of every product.*

MD but have dissimilarity with serving times, amounts, and reduction of sweets and meats. Even if all three groups have dissimilarities in their food items, they have similarities among the food groups and the nutrient molecules.

MIND scores had a statistically significant reduction in AD rate compared to those in the lowest tertile (53% and 35% reduction, respectively). Subjects with the highest adherence to the MD and DASH had a 54% and 39% lower risk of developing AD [157]. Even after promising to reduce the rate of AD through foods and dietary patterns, a question remains if the assumed preventative rate worldwide is going to work as a primary prevention because of the high food price rate of these diets. A recent study has shown that early preventive interventions based on marker data could reduce more than 40% of AD cases [158].

Studies have shown that Alzheimer's develops more in females than males. Also, more Afro-Americans than the Hispanic race, and if we look a little dipper than that. Today's women aged 65 and above at this age, are at high-risk levels for developing Alzheimer's. Most of these women weren't much educated, thus they had not come in much closure to any cognitive exercise at an early age, and their knowledge about foods or disease was less preferable than men. Also, the African race had low education, less connectivity with convictive exercise, and lower education caused them difficulty getting a good job, resulting in low economic status and poor health. Like women, these were key factors for developing Alzheimer's [163–165].

With this low economic status, it gets really hard for them to maintain any specific healthy diets with expensive foods and they are the majority in number to get developed AD where the questions remain if the prevention strategy will be able to reduce the economic burden, family crisis and more unless diets get developed with low-cost foods but with the same nutrient molecules.

Nonetheless, the current exploratory review has many advantages over previous reviews. First, to the best of our knowledge, it presents the most comprehensive and up-to-date assessment of this issue, including newer studies. The most recent reviews and meta-analyses investigated the role of specific nutrients or foods in the growth of Alzheimer's disease, such as omega-3, omega-6, antioxidant, zinc, alcohol, vitamin supplements, DHA, EPA, olive oil, vegetables, legumes, lean meat. Furthermore, the current study has focused more on recent studies on AD prevention through foods, specifically food nutrients, and their effects on the biomarkers of AD and a slight insight into the socioeconomic status.

6. Conclusion

In conclusion, MD, DASH, and MIND diets can reduce the risk of AD development or the symptoms of AD. The current review supports a link between diet and Alzheimer's disease; however, provided with many unanswered questions, definitive clinical recommendations are not warranted. It should be remarked that innumerable studies on the impact of diet on AD have been conducted on animals, particularly mice. This evidence cannot be easily applied to living beings due to the complexity and multifaceted relationships between human lifestyle modifications and AD.

Notwithstanding the methodological differences at the review and field levels, the current findings can help researchers develop future studies on AD and dietary patterns or factors. As a result, future AD and diet studies must include, but are not limited to, specific foods all around the world but should develop with the same nutritional molecules but with low pricing foods.

Despite the methodological limitations, our finding that 42 out of 55 reviewed studies (3 out of 3 dietary patterns, especially MIND) established an association between diet and AD incidence suggests that diet will be a primary prevention factor for AD. The effectiveness of diets in preventing AD poses a data limitation. The idea of preventing AD through Diets started strongly agreeing since in 2015 according to the publication's numbers. Also, given that AD has a long prodromal period before the presentation of symptoms and decline, the average age of the samples limits the ability to determine the impact of food on AD. More research is required to see if nutrition is a risk or a protective factor for Alzheimer's disease to encourage research to be translated into therapeutic practice and to clarify nutritional advice.

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Author contributions

NZB, MKH conceptualized the manuscript; NZB, MKH, and ZM wrote the manuscript; AR, ZM, MSH, and MKH reviewed and edited the manuscript; MKH completed the administration of the study.

Declaration of competing interest

All authors declare no conflicts of interest, financial or otherwise.

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