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Systematic Review Article

A 5-Year Systematic Review (2018 to 2022) on The Effectiveness of Mediterranean Diet in Preventing Alzheimer's Disease

Nur Khairina Binte Azan[1,2], Ariel SY Ng[1,2], Farij Bin Samsudi[1,2], Muhammad Rusydi Bin Mazlan[1,2], Yuan Kai Loh[1,2] and Maurice HT Ling[1,2,3,4]*

[1]*School of Life Sciences, Management Development Institute of Singapore, Singapore*

[2]*Department of Life Sciences, University of Roehampton, United Kingdom*

[3]*School of Data Sciences, Perdana University, Malaysia*

[4]*HOHY PTE LTD, Singapore*

***Corresponding Author:** Maurice HT Ling, School of Life Sciences, Management Development Institute of Singapore, Singapore.

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Abstract

Alzheimer's disease (AD) is an age-related neuronal disorder characterized by abnormal levels of proteins, beta amyloid (Aβ) and tau, resulting in gradual loss of cognitive functions due to impaired network of neurons in the brain. Past literature has proposed dietary interventions through administration of Mediterranean Diet (MD) as a solution to prevent AD development. A systematic review on the effectiveness of MD in preventing AD is executed up to July 3, 2022, using PubMed as source database within the last 5 years between 2018 to 2022. 131 articles were identified, and 26 articles were included in this review. After analysing the articles, 5 themes were identified to examine the effectiveness of MD: namely, (a) MD adherence and AD risk (b) MD and AD pathological development, (c) MD and cognitive health (d) Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet, and (e) Diet-microbe interaction. MD adherence is a vital factor in achieving successful dietary intervention. Various covariates and demographics affect adherence level. Differing evidence from literature discuss MD's efficacy in preventing AD. MD is concluded to be effective to a certain extent in preventing Alzheimer's disease due to various factors such as adherence levels, demographics etc and further longitudinal and randomised control trials (RCT) are warranted.

Keywords: Randomised Control Trials (RCT); Alzheimer's Disease (AD); Mediterranean Diet

Introduction

Rapid rise in ageing population around the world results in the increasing trend of [1] age related diseases such as Alzheimer's disease (AD), the most common type of dementia [1]. It is estimated that by 2030, 65 million people will be living with dementia worldwide [2] making AD a public health priority [3,4]. Various factors; such as, genetics, age, diet, health and socioeconomic status; contributes to an AD patient's life expectancy. Most dementia develops gradually over several years through subtle cognitive and behavioural deficits, known as mild cognitive impairment (MCI) [5], before emergence of clinical symptoms.

AD is a neurodegenerative disease categorised by two main hallmark pathologies - the accumulation of abnormal proteins, β-amyloid (Aβ), forming plaques [6], and protein tau phosphorylation causing neurofibrillary tangles in brain. These lead to pathological alterations contributing to the physio-

pathological process triggered during AD [7,8]. Aβ accumulation and neurofibrillary tangles disrupt the synaptic communication between neurons; thus, affecting cognition. The five main cognitive domains that are affected are memory, language, attention-speed, executive functioning, visuospatial perception [1]. Further progression of AD could eventually lead to brain atrophy, defined as neuronal loss of connections; leading to structural shrinkage of different parts of the brain, causing further cognitive deterioration.

As aetiology of AD is not known with no effective pharmacological methods to reduce the progression or symptoms in AD, studies are increasingly turning into modifiable risk factors, such as diet. Dietary intervention is widely researched as a prevention of various diseases [9]. This is essential as longer life expectancies worldwide makes AD a recurring problem. Increasing evidence suggest Mediterranean Diet (MD) as a potential dietary pattern in promoting cognitive health and prevention from AD development [1,4,10]. MD is a diet high in fruits, vegetables, nuts, olive oil and moderate intake of proteins, such as fish, and low intake of saturated fats, red meat and poultry [11,12]. MD plays a role in reducing AD's pathologic biomarkers, Aβ and tau while simultaneously promoting cognitive performance. MD is widely known to have health benefits but specific mechanisms behind MD's effectiveness have not been elucidated. Some predicted protective mechanisms against AD include anti-inflammatory and antioxidant properties of various foods in MD [7,8,11,13,14]. Varying adherence among different covariates are evaluated in an array of studies to examine correlation between adherence and AD development and risk factors. Different demographics are identified to be a potential factor for different adherence levels [8,10,11,14-17].

Hybrid of MD together with Dietary Approaches to Stop Hypertension (DASH) diet to form MIND diet and ketogenic diet to form MMKD. MIND and MMKD are actively being discussed as sub-sets/combination dietary pattern which could possibly prevent AD through specific modifications [2,3,5,18]. DASH diet is typically administered to patients with hypertension. MIND diet combines nutrition and science to formulate a diet consisting of specified type and quantity of food items. Literature shows promising results of MIND's efficacy in prevention of neurological disorders like AD through mechanisms such as activation of the transcription factor Nuclear factor-erythroid factor 2-related factor 2 (Nfr2) in green leafy vegetables and berries. MMKD speculates to be an effective diet in preventing mild cognitive disorder (MCI) in its prodromal stages before progressing to AD. MMKD demonstrates possible involvement in AD prevention through diet-microbe interaction.

Gut microbiota is vital for peripheral and central immune homeostasis. Gut microbiota is involved in the production of large amounts of metabolites that may directly or indirectly affect brain functions through the connection of the gut-microbiome-brain axis. Specifically, short chain fatty acids (SCFAs) which includes acetate, propionate and butyrate have the potential of modulating the peripheral and central nervous systems. Amongst these SCFAs, acetate diffuses the blood brain barrier (BBB) to modulate brain signals in food regulation. Acetate also has the ability to reduce blood brain barrier permeability through interactions with microglial cells [5]. As a person ages, the integrity of the gut barrier function decreases. This decrease in the gut barrier function gives rise to the entrance of unfamiliar bacteria that are not common in the gut. Amongst these unfamiliar bacteria that enters the gut in increasing numbers are pro-inflammatory bacterial groups. A distinguished pro-inflammatory bacterium is liposaccharide (LPS) which has the potential to trigger systemic inflammation through increased systemic immune response. This systemic inflammation also triggers amyloid accumulation, leading to AD progression.

The current literature discusses MD's general benefits without much in-depth explanation on the specific mechanisms involved in the protection against AD development. Furthermore, there is a lack of comparison between age groups with regards to the stage at which MD is best administered in order for optimal efficacy in preventing AD. In addition, MD adherence is generally low amongst various covariates in the different studies in which the reasons for non-adherence were not discussed nor debated.

The aim of this review is to discuss on the various issues regarding MD adherence and the importance of timely administration of MD to effectively prevent AD through prevention of its risk factors and triggers AD development. The hypothesis of this review is that MD can be effective in preventing AD when administered with proper follow-up by healthcare professionals as well as providing substantial information with regards to preparation of MD meals to increase adherence levels.

Methodology

Search strategy

Literature search was done on July 3, 2022, to gather articles in PubMed. The search term included keywords "Alzheimer" and "Mediterranean Diet". All articles are narrowed down to include both words, Alzheimer and Mediterranean diet to be either in the title or the abstract of the articles. Filters were applied to include articles within the last five years from 2018 to 2022 only.

Inclusion and exclusion criteria

The exclusion criteria were (A) articles without a full text were excluded; (B) articles that are not published in English were excluded; (C) Duplicates of articles were excluded; (D) articles that did not include Mediterranean diet or components in Mediterranean diet as the main study were excluded; (E) articles that do not include Alzheimer's Disease as the main study is excluded; (F) articles which conducted studies other than on human subjects were excluded; (G) articles other than original studies were excluded.

Data extraction strategy and synthesis strategy

Data extraction via qualitative studies was conducted. A summarised review table was used. Data extracted from studies includes title, authors, journal, Mediterranean diet, Alzheimer's disease, Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND), Modified Mediterranean Ketogenic Diet (MMKD), demographics, methods, results, strengths and limitation of studies. A progression from data extraction to narrative synthesis was conducted.

Results and Discussion

Analysis of search results

There was a total of 131 articles from PubMed search. Of which, 117 has full articles (Exclusion Criterion A), all articles are published in English language (Exclusion Criterion B) and have non-duplicates (Exclusion Criterion C). From these 117 full articles, 107 articles mentioned "Mediterranean diet" (Exclusion Criterion D) and 102 articles mentioned "Alzheimer" (Exclusion Criterion E) within the content of the text itself. 89 articles were human studies (Exclusion Criterion F) and 30 articles were original studies. Within the 30 articles, 4 articles were excluded as they did not explicitly discuss on how Mediterranean diet prevents Alzheimer's disease even though they mention the keywords "Mediterranean diet" and "Alzheimer" within the text. After all the exclusion criteria were carried out, 26 articles will be used in this review.

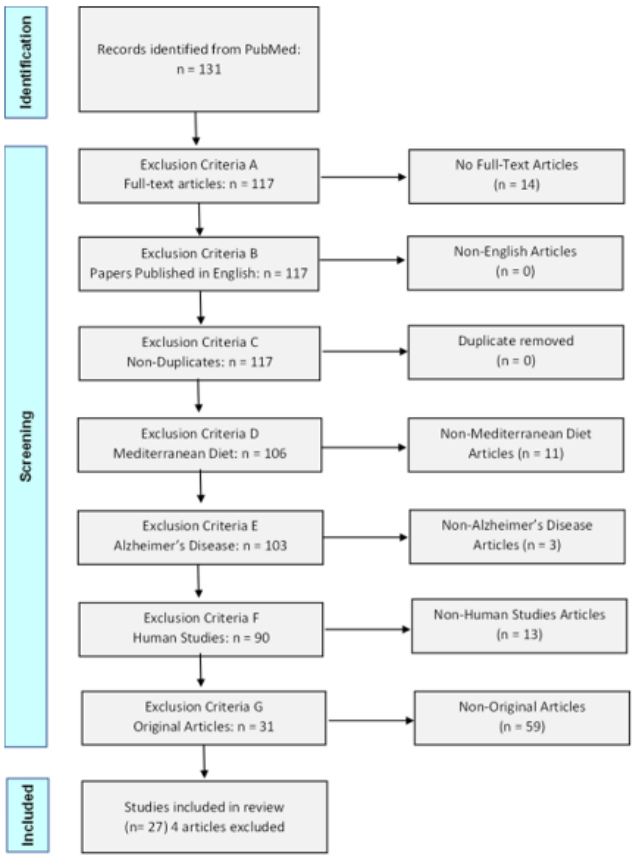

Figure 1: Flow of Hits Through Exclusion Criteria.

[1]https://pubmed.ncbi.nlm.nih.gov/?term=alzheimer[tiab]+AND+"mediterranean+diet"[tiab]&filter=simsearch3.fft&filter=years.2018-2022

Applications	Number of articles	References
Adherence to Mediterranean Diet (MD)	8	[8-11,14-17]
MD and pathological mechanisms of AD	10	[3,6-8,15,19-23]
MD and cognitive health	14	[1,4,6-8,11-15,19,20,22,24]
Mediterranean diet with the Dietary Approaches to Stop Hypertension (DASH) diet (MIND)	6	[2,4,5,10,18,25]
Diet-microbe interaction	3	[2,5,13]

Table 1: Thematic Classification of MD and AD Studies

Applications	Limitations	Potential solutions
Adherence to MD	Exclusion criteria bias	Exclusion criteria needs to be more specific to provide reliable source of eating habits for all participants to achieve a more holistic and reliable study [8]
	Inaccurate Dietary intake method	Change to 1 month diet record instead of two-day diet history for a more accurate reflection of usual intake [17]
MD and pathological mechanisms of AD	Screening Criteria bias	Implement a longer time frame between dietary and brain imaging assessments [15]
	Measurement errors	Evaluate confounders such as lifestyle variables at follow-up [7]
MD and cognitive health	Misreporting dietary intake	Self-reported food frequency questionnaire (FFQ) needs to be validated by healthcare professionals [14,22,24]
	Inaccuracy of short-term studies	Carry out longitudinal studies for stronger and more evident correlations [12]
	Inability to generalise findings to a larger population	Use community-based setting for more generalisation [6,13]
Mediterranean diet with the DASH diet (MIND)	Inaccurate correlation due to practice effects	Limit number of cognitive assessments carried out [18]
Diet-microbe interaction	Small-scaled pilot study	Conduct larger longitudinal studies including pre-symptomatic stages to strengthen findings [5]

Table 2: Limitations and Potential Solutions.

Theme 1: MD adherence and AD risk

A measure of success for diet intervention is through adherence from individuals. Studies recorded varying adherence levels from study populations possibly caused by covariates as a contributing factor. Differences in covariates of participants in different studies might incur inconsistencies in adherence levels. Covariates that differ include gender, age, education, and health status. Another possible difference in adherence levels between studies could result from various demographics of the individual population studies that vary due to dietary habits and economics [8].

Adherence level using Relative Mediterranean Diet (rMED score) shows that there is higher adherence among women compared to men [11]. Similarly, Karstens., *et al*. [14] found that in an equal gender sample, women have a greater MD adherence of 62% compared to men with 59%. Comparison of rMED score discovered that there is a 20% lower risk of AD for those with a higher MD adherence and an additional 8% lower risk of AD per 2-point increment in continuous rMED score [11]. Greater adherence in women is speculated to reflect their longevity compared to men

and an awareness to follow the diet to prevent further morbidities in their longer lifespan.

Age of MD administration is speculated to affect adherence levels. Martin., *et al*. [16] analysed that that there is an inverse correlation between age and MD adherence; i.e., MD adherence decreases as a person age. Taylor., *et al*. [17] analysed that mean MD adherence score of elderly aged 70-74.9 years had higher scores 5.7 out of 18 compared to those aged 80 years and above with 5.0 out of 18 points. In contrast, in younger participants ranging from 30 to 60 years, the mean MD adherence score was 5 [15]. Nevertheless, a low average MD adherence score was observed among different age range of study participants. A possible reason for non-adherence amongst older adults could be due to difficulties preparing meals, having swallowing problems or poor food absorption. This could result in weight loss in the elderly as their appetite decreases with age. A healthy weight is important as a protective factor against AD as weight loss and malnutrition increases AD risk. MD ensures a balanced nutritional status while maintaining a healthy weight [8,9]. As a person ages, metabolic risk factors might develop, increasing the risk of AD. Thus, MD administered early at a younger age such as mid-life could increase familiarity with MD diet, increasing their continued adherence in their lifespan [17].

Varying health status of study participants might affect adherence levels between studies. MD adherence was observed to be slightly higher in overweight individuals. Although not statistically significant, adherence of MD is higher in percentage for overweight individuals (BMI ≥ 27) with 55.9% as compared to normal weight individuals (BMI < 27) with 44.1% [16]. Healthy participants without cognitive impairment showed highest scores for adherence to Mediterranean Diet (MD). There is a correlation between Mediterranean Diet Score (MDS) and change in Mini Mental State Examination (MMSE) score between the baseline assessment and the 18-month follow up of healthy subjects [8]. This suggest that factors such as ability to make food choices to adhere to MD is affected by cognitive health of study participants.

Another covariate, education, shows limited impact on MD adherence as similar data were obtained from all education levels. However, there was a noticeable increase in MD adherence for individuals with college degree or above. Different education qualifications might impact a person's income. In relation to varying income, an inverse correlation between MD adherence and household income is noticeable. An individual's income status affects food choices as some ingredients, for example, extra virgin olive oil (EVOO) and salmon consumed in MD are costly. Data analysed that those with a poverty ratio >2 had slightly higher MedD scores of 5.4 out of 18 points than those reporting a ratio of 1-2 with 5.2 or <1 with 5.0 points [17].

Differing adherence levels are observed in different populations due to dietary preferences. In the US, low adherence to MD might be caused by their high consumption of fast food. Data revealed that older adults does not meet recommendation of wholegrain cereals as their main source of cereals came from refined grains, with a mean score slightly greater than zero out of 18 points for MD adherence. Additionally, studies also indicated that MD is difficult to adhere to even in Mediterranean countries as people are exposed to various international cuisines [8]. Therefore, healthcare professionals can play a role in advising older adults to continue making small changes in their diet to gradually adhere to MD. It is demonstrated by various studies that MD adherence, especially when administered in mid-life reaps potential protective effects against AD development [10,15]. This is because in mid-life, a person has not developed diet-related diseases such as hypertension and diabetes which are risk factors for increased inflammation triggering AD. Hence, the benefits of MD in weight and glucose management can also be utilised for a longer period of time as well as making MD into a dietary lifestyle.

Theme 2: MD and AD pathological development

Hallmarks of AD are determined by abnormal levels of beta amyloid (Aβ) and tau proteins in some individuals as they age [26]. Abnormal levels of Aβ clumps into plaques between neurons, accumulate disrupting cell functions such as cognition [27], which would be discussed further in Theme 3 (MD and cognitive health). MD adherence is investigated at a large scale to associate MD adherence and possible alterations to reduce pathological alterations leading to AD.

Multiple factors advance AD development such as amyloid plaque accumulation, insulin sensitivity and neurofibrillary tangles caused by tau protein phosphorylation [8,21]. Pittsburgh compound B (PiB) is used in positron emission tomography (PET) scans to image Aβ plaques in neuronal tissue. The data

demonstrates higher rates of PiB accumulation in participants with low MD adherence, indicating increased Aβ deposition [15]. Similarly, study by Ballarini., *et al*. [19] states that Higher MD adherence is inversely correlated with less amyloid (Aβ42/40 ratio), p = 0.008 and Phosphorylated tau 181 (pTau181), p = 0.004. Hence, greater MD adherence is associated to reduction in pathologic biomarkers for AD [19]. Increased levels of brain pathologies, such as amyloid-β and neurofibrillary tangles, triggers a sequel of events leading to neuronal damage and cognitive deterioration [3].

A study involving Australian older adults with average age of 71.1 years associates MD adherence with brain health maintenance, providing protection against cerebral AD pathology by reducing Aβ accumulation halting AD development [22]. In contrary, a study on healthy women aged 45 to 55 years suggests that there is no association between MD adherence and Aβ deposition. Results demonstrate that MD is not statistically significant to Aβ accumulation (p = 0.742) and with all covariates included; i.e., age and education, body mass index (BMI) and cognition [20]. This contradiction could manifest due to the different age group of sample participants. Age is a possible confounder and studies with older age group. Rainey-Smith., *et al*. [22] showing correlation between MD and AD biomarker changes. Another possibility is that Aβ amyloid take years to accumulate for the changes to demonstrate a statistically significant association.

Aβ deposition is speculated to be an age dependent phenomenon, supported by Mosconi., *et al*. [6] which reveals that cognitively healthy (CN) individuals aged 45-49 years tested 0% but increases to up to 6% Aβ deposition positivity in older CN individuals. Nevertheless, more research needs to be executed to determine the relation between MD and Aβ amyloid accumulation across various age group [15]. AD pathology develops over many years prior to symptoms, making prevention essential in reducing AD risk and delaying the onset of cognitive decline [6].

Another increasing interest is the association between insulin sensitivity and its influence on the expression of AD biomarkers [6]. High insulin sensitivity is needed for effective use of blood glucose and to reduce blood sugar levels in the body. MD adherence is associated to reducing levels of fasting insulin which in turn increases levels of active insulin-degrading enzyme (IDE). IDE is an Aβ-degrading protease which can potentially reduce Aβ accumulation in the brain [22]. Soluble fibre such as legumes, oatmeal, and flaxseed as well as fruits and vegetables which forms part of MD is associated to increase insulin sensitivity [6,7]. In support, longitudinal follow up suggest that participants with a low MD adherence presents with greater cerebral metabolic rates of glucose (CMRglc) decline compared to those with higher MD adherence [15]. Reduction in CMRglc in AD-vulnerable areas increases risk for developing AD.

To further examine the glucose metabolism in the brain, fluorodeoxyglucose (*FDG*)-positron emission tomography (FDG-PET) was used [1]. Inverse correlation was observed as lower MD adherence relates to reduction in FDG in posterior cingulate cortex (PCC), indicating decline in cerebral glucose utilisation. PCC hypometabolic changes in FDG could trigger Aβ accumulation in the long run. PCC metabolism could indicate progression from Mild Cognitive Impairment (MCI) to AD [23]. Cross sectional research revealed that cognitively healthy elderly with lower MD inversely correlates to increased glucose hypometabolism and brain AD pathology as compared to elderly with higher MD. Implementation of MD is vital during the preclinical stage/ prodromal stage in AD as prevention from progression is more effective [15]. This finding suggests MD's protective role against AD pathologies. However, longitudinal studies are needed to further examine the effects of MD on AD progression as well as causation factors.

Specific mechanisms behind MD's protective role in preventing AD pathology are still undergoing rigorous research. However, some of the identified food components that associates to reduction in AD development; including olive oil, nuts, fruits and vegetables. Olive oil, a main fat consumed in MD contains monounsaturated fats (MUFA). An increased ratio of MUFA compared to saturated fats is significantly associated with increased levels of Aβ42/40 and decrease in pTau181 [19]. Higher Aβ42/Aβ40 ratio and lower pTau181 serves as a protection against AD development [28]. Furthermore, adherence to MD by CN individuals with increased intake of olive oil or mixed nuts shows cognitive improvement compared to control group who experience age-related cognitive decline [22]. Higher MD adherence, specifically high fruit consumption is related to less Aβ accumulation. Results suggest that long term MD adherence associates with reduced cerebral AD pathology accumulation. Fruits such as oranges and grapefruits are rich in vitamin C and phenolic contents. These might be potential mechanisms associated with lesser Aβ accumulation and delaying AD development [22] but further studies are needed.

Theme 3: MD and cognitive health

AD results in a progressive memory loss and ability to function independently [4]. Preventive strategies through dietary changes by adhering to MD is necessary in ensuring cognitive health. Hallmark of AD neuropathology involves prolonged Aβ accumulation in different parts of the brain such as hippocampus and cerebral cortex resulting in changes in cognitive domain [4,20]. Aβ accumulation destructs neurons and their connections, affecting areas in the cerebral cortex responsible for language, reasoning, and social behaviour [29]. Increasing research associated MD adherence with protection against cognitive decline and AD risk [22]. The cognitive domains assessed are memory, language, attention-speed, executive functioning, visuospatial perception and a global cognitive score [1].

A large sample study of 1046 non-dementia individuals aged 64 were analysed for cognitive domain changes with MD intervention. Generalized Estimating Equations (GEE) models were used in finding association of MeDi score with differential rates of cognitive change. GEE models adjusted for confounders revealed that each additional unit of MD score was associated with 0.6% of a standard deviation less decline per year in the attention-speed domain, 0.3% of a standard deviation in the global cognitive score, 0.3% in the executive function domain, 0.2% in the language domain. However, other domains of memory and visuospatial showed no associations with MD score [1]. In contrast, another study of 169 participants combines cognitively healthy and individuals with higher risk of AD; i.e., with Mild Cognitive Impairment (MCI) or Subjective Cognitive Function (SCF). After adjusting for confounders, this study revealed an significant association between MD and both memory and language only with a p value of 0.001. No significance was found in other cognitive domains. A one-point increase in MD was also associated with -1 year of age [19]. Hence, differences in cognitive domain changes with MD administration was seen between studies adjusted for confounders. Specifically, differences in original cognitive health of participants at the start of study impacts the results after MD administration wherein no association was detected in study with cognitively healthy individuals.

Age is a possible non-modifiable factor to cause varying changes in cognitive domain. Comparison between younger participants aged 30 to 60 years and older participants aged 55 to 80 years revealed a 25% reduction in the progression of AD biomarkers across 3 and 4 years respectively with MD adherence [15]. This indicates a possibility that MD's role in AD prevention takes a shorter efficacy period as seen by a 1-year difference to gain the same reduction in AD biomarker. Hence, it is important that MD is administered early in middle adulthood to maximise the effectiveness and protect against AD progression. This is also because the body's metabolism decreases with age and the protective mechanism in MD takes a longer efficacy period as age increases.

A distinguished AD feature of neuronal loss is reduction in grey matter volume, a biological substrate of decline in cognitive functions. Studies have identified grey matter abnormalities in AD patients [29]. Voxel based morphometry was used in analysing the relationship between grey matter volume and MD. Analysis observed a positive association between greater MD score and increased brain grey matter volume at the whole-brain level. Specifically, significant correlation of higher MD adherence and increased brain grey matter volume in the hippocampus [15]. This indicates a possibility that high consumption of MD increases grey matter volume. Increase in grey matter volume will in turn repair neuronal damage, decreasing the possibility of AD progression. Contradicting this, one study [30] shows no significant association between high MD adherence and grey matter volume while an others showed association between high meat consumption and decreased grey matter volume but not with high MD diet as a whole. High consumption of meat and dairy products is significantly related to higher SCF scores, where a one quintile increment in meat consumption was associated with a 0.5% higher SCF score [13]. Difference in MD adherence might affect results due to the protective mechanism being fully utilised in greater MD adherence for more significant changes to be apparent. Another potential difference for grey matter volume across studies is the varying standards of defining high and low MD across studies. According to Karstens., *et al*. [14], high MD adherence group consumed greater non refined grains, fruits, vegetables, legumes and nuts, and olive oil than did the Low MD adherence group which reported greater red meat and processed meat consumption.

MD is rich in antioxidants that could ameliorate age-related decline in cognitive function that precedes the onset of AD. Andreu-

Reinon., *et al*. [11] and Margara-Escudero., *et al*. [7] analysed that a medium or high rMED score is associated with the protective antioxidant compounds such as folate, vitamin E, vitamin C, ß-carotene, and polyphenols provided by the MD components - fruits and vegetables. High in antioxidant rich foods from MD also assist in reducing oxidative stress which in turn have protective effect on AD [13].

MD is associated with increasing the levels of brain-derived neurotrophic factor (BDNF) and neurogenesis; i.e., formation of new neurons in the hippocampus. Increased levels of BDNF is associated to maintenance and growth of neurons [1] and neurogenesis helps to boost memory and brain health [31]. Oily fish intake, such as salmon, was associated with decreased AD-related grey matter volumes in a multi-ethnic cohort of older adults [14]. In addition, Bhushan., *et al*. [13] analysed that omega 3 fatty acids in fish could be one of the mechanisms that mediates the relation between fish consumption and reduced SCF and risk of AD development. Furthermore, Roscapana-Garcia., *et al*. [8] and Mosconi., *et al*. [6] suggest that omega 3 fatty acids in MD plays a role in cerebral structures and cognitive function. Oleuropein which belongs to a group of polyphenols called secoiridoid possesses antioxidant and anti-inflammatory effect that can potentially protect against cognitive decline [32]. A study involving Greek elderly with MCI suggest that high consumption of extra virgin olive oil (EVOO) of more than 250 mg/kg. Phenol molecules in MD is associated with better general cognitive performance; such as global cognition, letter fluency and stability of MCI; after 12 months compared to control group [12]. Consumption of vegetables such as cauliflower and broccoli and wholegrains such as wheat germ contains high levels of polyamine spermidine. Polyamine spermidine is suggested to reduce the risk of neurodegeneration in AD as it consists of strong anti-inflammatory substances. The polyamine spermidine can assist in maintaining brain and cognitive health. As a person ages, the amount of spermidine in the body, including the brain decreases. It is analysed those higher levels of spermidine promotes hippocampal neurogenesis and preserves brain volume, especially in hippocampus. Higher adherence to MD is linked to greater amounts of spermidine, which is suggested to assist in lowering the risk of cognitive decline and AD [24].

Increasingly more studies are discussing on the synergistic effect of food groups in MD [7,13,33]. MD's effect on cognition is not by a single mechanism but modulated by various molecular pathways which synergistically combine action in preventing cognitive decline [33]. Furthermore, nutrients exist in a food matrix acting interactively in MD. MD diet consist of high amounts of dietary fibre from fruits and vegetables. This encourages the stimulation of the hormone leptin which is responsible in reducing appetite in the intestine and decreases the appetite stimulating hormone ghrelin in the brain. These hormones play a role in cognitive processes as they act on hippocampus to promote neuro plasticity i.e., the ability to form synaptic connections between neurons [13].

Theme 4: MD with the Dietary Approaches to Stop Hypertension (DASH) - MIND diet

Dietary Approaches to Stop Hypertension (DASH) diet consist of high intake of fruits, vegetables, whole grains, low-fat dairy products and reduced intake of sodium. Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet is a hybrid of the Mediterranean and DASH diets tailored specifically for brain health which also limits intake of food high in saturated fats [4]. MIND diet comprises of specified quantities of food components which relates to findings on food mechanism and its relation to slower cognitive decline [2,18].

Study by Dhana., *et al*. [18] revealed significant association where one standard deviation increase in the MIND diet score was associated with a slower cognitive decline by 0.012 units per year, independent of AD pathology and age. This independent correlation between MIND diet and AD pathology suggests that adherence to MIND diet protects from some cognitive loss linked with brain pathology and contribute to building cognitive resilience in all ages, especially vital for older adults at increased risk of AD. Furthermore, MIND diet intervention is highly encouraged to be administered in mid adulthood for earlier protection from AD developments. However, cognitive resilience that is still undergoing active research and evidence from a large-scale, randomized controlled trial to test the causal relationship between the MIND diet and protection from cognitive decline is lacking [5].

MIND diet promotes brain health by emphasising intake of fruits such as berries, green leafy vegetables, extra-virgin olive oil, nuts, wholegrains and low animal-based foods and saturated fats. MIND diet assist promoting cognitive health as the foods possess functions; such as antioxidative, anti-inflammatory and neuroprotective [18].

Polyphenols in MIND diet possesses anti-inflammatory properties that may activate the transcription factor Nuclear factor-erythroid factor 2-related factor 2 (Nfr2). Nfr2 is rich in green leafy vegetables; such as kale, and bok choy; and berries; such as blueberries, and cranberries; as consumed in MIND diet. Nfr2 plays a key role in protection against oxidative stress and inflammation [34]. Hence, MIND diet assists in reducing oxidative stress which in turn protects against neurodegeneration in older adult, which could develop into AD [18]. In addition, high consumption of green leafy vegetables, fruits and low consumption of fried foods increases circulating levels of antioxidants lutein and zeaxanthin, serving neuroprotective effect against AD development. The high metabolic activity in the brain makes it vulnerable to free radicals which plays a role in neuronal damage leading to AD. The antioxidants lutein and zeaxanthin have the potential to inhibit free radical formation and protects against oxidative stress. In addition, lutein and zeaxanthin also activates anti-inflammatory pathways reducing neuroinflammation, a factor that contributes to AD's pathogenesis [25]. Furthermore, investigations suggest that individual nutrients such as folate, vitamin E, B vitamins, and n-3 polyunsaturated fatty acids in foods have neuroprotective effects that lower the risk of AD [4]. This further emphasised the potential synergistic effect of a dietary pattern like MIND diet.

Carotenoid is a form of vitamin A which is an antioxidant found in food components in MIND diet. Studies demonstrate that higher levels of carotenoids are associated with a lower risk of cognitive decline among older adults from different regions. The consumption of fruits, nuts and vegetables was positively correlated with higher α-carotene levels in the blood with a p value of 0.05 [25]. Higher plasma levels of α-carotene is associated with improvements in global cognitive performance.

Theme 5: Diet-microbe interaction

In recent years, substantial evidence indicates that imbalances in gut microbiota (GM) can be associated with neurodegeneration [35]. Gut microbiome a distinguish factor that can affect cognitive health and could possibly prevent AD development via gut–microbiome–brain axis. Studies indicate that gut–microbiome–brain axis is an integrated network where microbiome and the central nervous system (CNS) crosstalk via endocrine, immune, and neural signalling pathways [5].

The aging process reduces the gut barrier function which increases gut barrier permeability causing altered gut microbiome signatures that could contribute to AD pathology. In support, Romanenko., *et al*. [36] analysed that in older adulthood after the age of 60 to 65, an individual's gut microbiota diversity generally begins to decrease, while increase in previously non-dominant bacteria such as pro-inflammatory bacterial groups [36]. Evidence suggest that gut microbiome imbalance may contribute to the synthesis and secretion of specific brain-derived neurotrophic factors that are related to cognitive decline and AD [5]. MCI involves cognitive deterioration that precedes clinical symptoms of AD. MCI patients are at risk of progression into AD and interventions are vital [5]. MCI patients have similar gut bacterial signatures which correlates with AD's pathological markers in cerebrospinal fluid (CS), suggesting its role in AD pathogenesis. An altered gut microbiome in MCI patients may increase the pro-inflammatory bacteria, lipopolysaccharide (LPS). LPS is speculated to be able to induce systemic inflammation and amyloid accumulation in the brain, which is an AD biomarker. This suggest that diet-microbe association consist of inter-relationships with other microbes such as fungi (mycobiome) that play a shared role in heath [37]. Hence, ensuring gut microbiota balance is a potential AD prevention [5].

Ketogenic diet (KD) involves a low carbohydrate, moderate protein and high fat diet. KD provides energy from the ketosis process in the body which promotes weight loss and glucose management. Modified Mediterranean Ketogenic Diet (MMKD) is a combination of modifications made in MD and KD. MMKD includes a 50% consumption of calories from fats such as olive oil, 30% proteins from fish, nuts and seeds with reduced consumption of meat and dairy and 20% carbohydrates from fruits and vegetables instead of cereals [38].

MMKD is recently gaining interest as it is speculated to be involved in diet-microbe interaction in the prevention of AD. MMKD is suggested to modulate the mycobiome in association with AD markers and fungal-bacterial co-regulation networks in patients with MCI [5]. MMKD helps to improve profiles of AD biomarkers in cerebrospinal fluid (CSF) in patients with MCI, by modulating the gut bacterial population such as LPS [5]. Supporting this, a study by Nagpal., *et al*. [2] shows that there is a positive correlation between MMKD and AD markers in CSF, demonstrating

an increase in Aβ42 and decreased total tau, suggesting MMKD's possible role in prevention of AD pathology. MD and MMKD food groups of vegetables, whole grains, fish and fruits is beneficial for the gastrointestinal microbiome. This in turn influences the central nervous system by modulation of the hypothalamic pituitary adrenal (HPA) axis, immune system, neurotransmitter pathways, and growth factors [13]. Additionally, MMKD promotes the intestinal short chain fatty acid (SCFAS) production by giving plant-based fermentable fibers through consumption of fruits and vegetables as the main source of carbohydrate to be fermented by the gut bacteria. Increasing the amount of SCFAS [5] improves the gut health by decreasing the intestinal barrier permeability which decreases the amount of pro-inflammatory bacteria. This in turn reduces the inflammation that causes amyloid accumulation in the brain, preventing the risk of AD. As aging results in alteration in the gut microbiome composition, diet such as MMKD plays an important mediating role in maintaining a healthy bacteria biodiversity, preventing AD development through the gut-microbiome-brain-axis.

In contradiction, a six-weeks MMKD intervention in patients with MCI did not demonstrate significant changes in the diversity in the gut microbiota. Nevertheless, this short-term intervention is insufficient to bring about any changes and would need further long-term studies [5]. More research needs to be done to determine the mechanism in specific foods that induce beneficial effect in the gut microbiome related to AD prevention. Furthermore, as gut microbial diversity declines with age, adhering to MD diet in midlife will improve cognitive outcomes greatly.

Principal findings of this review

Effectiveness of MD in preventing AD is heavily dependent on MD adherence in individuals. Different covariates; such as gender, age, education, amd health status; as well as population demographics of studies; such as, dietary preferences, and economics; play a role in adherence levels to MD. Non-adherence from individuals are multi-factorial. However, simplified meal MD meal plans that are quick and easy to cook might benefit older adults who face challenges in preparing their own meals, affecting their adherence. Healthcare professionals could encourage small dietary changes to include MD components as part of their diet for adaptability towards changes and to instil familiarity. This is important as older adults tend to stick with what they prefer and not try new varieties of food such as those in MD if it is unfamiliar to them.

Contradicting views of MD and its effectiveness on AD pathological development and promoting cognitive health are still debated. Greater MD adherence is supported by literature to reduce the main hallmarks of AD development; such as, Aβ plaques accumulation and abnormal protein pTau181. Specific mechanisms behind MD's protective role against AD development are still undergoing research. However, increasing research associating the mechanism of food components in MD and cognitive health promotion shows much efficacy. Food components such as olive oil, fruits and vegetables are suggested to play an anti-inflammatory and antioxidant role in reducing oxidative stress which reduces neuronal loss which in turn reduces AD pathological development.

Effectiveness of hybrid MD diets such as MIND diet and MMKD shows association in reducing the risk of AD. However, longitudinal studies and randomized control trials are needed for determining causal relationships. MIND diet's specified food servings is related to slower cognitive decline and enhancing cognitive resilience while MMKD is associated to improving gut bacterial population specifically in individuals with MCI to prevent progression into AD.

Strengths and weaknesses of this review

The main strength of this review is based on longitudinal studies with a large sample size and long follow up of 20 years is used in showing long-term effect of MD adherence in reducing the risk of AD. Effectiveness of food components in MD was evaluated in detail according to its impact on pathological alterations in AD, cognitive health, gut-microbe interaction as well as a combination with other diets; i.e, DASH and ketogenic diets. This ensures that the different components in MD are discussed based on their different protective mechanisms for different aspects of AD development. Data comparisons made were explicitly chosen to be similar in terms of covariates of study for a more holistic identification of associations. Additionally, specific measurements or models used in data comparison were mentioned for clearer understanding of the methods used to attain the different associations between varying levels of MD adherence. Varying age groups between studies shows the possible effects of MD adherence to identify possible correlations effectively.

However, there are also several weaknesses in these studies. Dietary questionnaire data such as food frequency questionnaire (FFQ) used in studies is self-reporting, which could result in

biasness, affecting the data comparisons made across studies. Furthermore, inaccuracy of MD adherence could be a result of insufficient time frame used in studies through usage of a two-day food intake record. Additionally, different adherence scoring systems were used across different studies although majority uses Relative Mediterranean Diet (rMED score). Nevertheless, other studies used less well-known scoring system such as Mediterranean Diet Adherence Screener (MEDAS). This difference could give rise to inconsistencies when comparing high and low MD adherence based on the scores. Varied sample sizes between studies as well as covariates and demographics affect result interpretation. Comparison across studies that did not explicitly mention about the cognitive health of their study participants could lead to interpretation errors. This is because cognitively healthy and cognitively impaired individuals might reap different results of effectiveness when MD is administered to them.

Conclusion

Review of 26 articles out of 131 (20%) articles on MD and AD revealed 5 themes discussing the effectiveness of MD in preventing AD; namely (a) Adherence to MD (b) MD and pathological developments in AD (c) MD and cognitive health (d) Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet, and (e) Diet-microbe interaction; and found that Mediterranean Diet has potential in preventing Alzheimer's Disease with increased adherence.

Supplementary Materials

Data files for this study can be downloaded at https://bit.ly/MD_AD_SSR.

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