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Emerging Treatment and Prevention Options in Diet Through the Gut-Brain Axis, And Its Impact on Patients with Alzheimer's Disease

Jewel Amrich
jaa2918@rit.edu

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Jewel Amrich, PA-S

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Purpose Statement

Because the number of patients with Alzheimer's disease has drastically increased over many decades and yet there is no cure, this literature review was conducted to analyze the emerging prevention and treatment options for Alzheimer's disease, and how current studies suggest that the gut microbiome, specifically diet, may play a role in preventing and/or reducing Alzheimer's disease.

Abstract

Objectives:

To outline the most recent data regarding diet in the role in moderating prevention and progression of Alzheimer's disease using the relationship between the gut microbiome and central nervous system. In addition, the Mediterranean diet and the components that make up the diet, and those alike will be thoroughly discussed.

Evidence Acquisition:

Using key terms "Alzheimer's Disease" and "Diet", Web of Science searched for papers that were published between 2012 and 2023, which yielded 807 results. Refining the search to "Neurodegenerative Diseases" returned 292 results. Adding "Gut-brain axis", "gut microbiome", and "Mediterranean diet" to separate search inputs yielded 25 sources that were selected for this paper.

Evidence Synthesis:

An analysis of current research reveals a relationship between the central nervous system and the gut-brain axis. The gut microbiome that makes up the gut-brain axis has a variety of inflammatory markers that influence and regulate the health of neurons along the central nervous system and influence the progression of Alzheimer's disease. Several studies have shown that dysregulation of the gut microbiome is linked to neuroinflammation which induces neural degeneration. [1] With this, researchers began investigating how diet could affect and possibly protect neural degeneration by restoring the gut microbiome. The data present that the Mediterranean, Ketogenic, Dietary Approaches to Stop Hypertension (DASH), and combined diets delay cognitive decline and provide neuroprotection in Alzheimer's disease patients. [2]

Conclusion:

The gut microbiome that makes up the Gut-brain axis is essential to neurological health. Dysregulation of the gut microbiome causes neuroinflammation, which results in degeneration and plays a role in the progression of Alzheimer's disease. The newest studies around the treatment and prevention of cognitive decline suggest that the factors that make up the Mediterranean, DASH, MIND, and Ketogenic diets are effective in preventing cognitive decline in Alzheimer's patients. Since these diets and diets alike are rich in antioxidants, and fatty acids, and low in processed ingredients, numerous studies have shown that they are potentially effective in the treatment and have protective measures against the progression of Alzheimer's disease.

Introduction

Alzheimer's disease is the most common type of dementia worldwide, making up 60-80% of dementia cases and one in four people who are over 85 years old, with an expected rise in prevalence over the next few years. [3,5] Several subtypes cause Alzheimer's disease; predominately genetic factors, such as the APOE gene, which increases an individual's risk by 70%. [4] In addition to genetic factors, early-onset Alzheimer's disease causes symptoms to begin earlier in life, around 30-50 years old with genetic and environmental factors playing a part in the inception of this disease. [4] Alzheimer's disease is differentiated from other types of dementia by the presence of amyloid beta plaques and neurofibrillary tangles or tau proteins primarily in the brain's entorhinal cortex and hippocampus regions. [4] Once these proteins accumulate in the brain, they begin to destroy neurons and result in atrophy of the brain. [4] As the disease progresses, the cerebral cortex is affected impacting speech, language, and behavior. [3]

Currently, research shows that there are no routine diagnostic tools to identify Alzheimer's disease in its early stages. [3] Previously, doctors and researchers used fluoroscopy and various brain imaging studies to diagnose or exclude an Alzheimer's diagnosis. [3] However, current diagnostic procedures are limited to strictly identifying individuals at high risk or suspected to have Alzheimer's disease in the advanced stages, when it is essential to recognize its earliest stages to provide the most effective treatment.

New research has identified a relationship between the gut and the brain, known as the "Gut-brain axis", that may contribute to the pathology of Alzheimer's disease. The gut microbiome is composed of thousands of microbes along the intestinal tract that with the brain form the gut-brain axis. [5] Research shows that dysregulation of the gut microbiome that makes up the Gut-brain axis causes systemic inflammation throughout the body and in return causes a

cascade of neuroinflammation, neural injury, and neurodegeneration in the brain. [6] Several studies demonstrated that diet impacts the gut microbiome and gut-brain axis regulation, which is responsible for corresponding with the CNS. Specifically, aspects of diets, such as the Mediterranean, Ketogenic, and Dietary Approaches to Stop Hypertension (DASH) have the potential to play an important role in preventing and treating cognitive decline in Alzheimer's patients.

This literature review will discuss the relationship between the gut-brain axis, through the gut microbiome, and the systemic effects of diet in the development of Alzheimer's disease. Furthermore, the efficacy and validity of specific diets and their components will be thoroughly discussed to offer an evolving theory that diet could not only impact the development of Alzheimer's disease but also be used as a treatment if found in its earlier stages.

Methods

Using key terms “Alzheimer’s Disease” and “Diet”, Web of Science searched for papers that were published between 2012 and 2023, which yielded 807 results. Refining the search to “Neurodegenerative Diseases” returned 292 results. After refining the search further to “review article” 125 results remained. Sources about exercise intervention were omitted since this is not the scope of this literature review; however, articles analyzing gut-brain axis and gut microbiome mechanisms in Alzheimer’s disease were inquired. Moreover, articles incorporating targeted therapy and keywords like “prevention” were analyzed.

Evidence Synthesis

Alzheimer's Disease and the Gut-brain Axis

Research on the gut-brain axis has demonstrated extensive connections throughout the body, affecting numerous systems and impacting disease modulation. [5] The relationship between the gut-brain axis and Alzheimer's disease can be mediated through the gut microbiome, which makes up the gut-brain axis. [5] For instance, the systemic circulation transmits neurotransmitters and neurotoxins produced by the gut microbiome which ultimately regulates activity within neurons. [5] Several studies have shown that dysregulation of the gut microbiome contributes to systemic inflammation throughout the body, leading to neuroinflammation. [5] For example, a meta-analysis conducted by Hung et al. demonstrated evidence that suggests individuals with Alzheimer's disease have decreased diversity in the gut microbiome compared to healthy individuals. [5] Hung et al.'s meta-analysis identified specific bacteria; Proteobacteria Hedges' g = -0.349; 95% CI[-0.604 to -0.095], p= 0.007, Bifidobacterium Hedges' g = -0.608, 95% CI [-0.886 to -0.330], p < 0.001, Phascolarctobacterium Hedges' g = -0.852, 95% CI [-1.348 to -0.357], p = 0.001, and Enterobacteriaceae Hedges' g = -0.460, CI [-0.794, -0.126], p = 0.007 in the gut microbiome that was elevated in those with Alzheimer's disease. [5] This evidence is statistically significant as seen by the p-value less than 0.05 (p= 0.007, p <0.001, p=0.001, and p = 0.007), and suggests that the decrease in diversity observed in individuals with Alzheimer's disease may be indicative of underlying changes in the gut microbiome composition that could be linked to the development and ongoing progression of Alzheimer's disease. [5] Hung et al.'s meta-analysis also detected bacteria in the gut microbiota that was reduced in individuals with Alzheimer's disease. The weakened bacteria included Lachnospiraceae Hedges' g = 0.632; 95% CI [0.402 to 0.862]p<0.001, Clostridiacaeae Hedges' g 1.406; CI [1.001, 1.810], p < 0.001, and

Firmicutes Hedges' g = 0.538; 95% CI [0.224 to 0.853)], p = 0.001. [5] From this analysis, it can be concluded that the data is statistically significant and unlikely due to chance. Moreover, a cohort study conducted by Liu et al. compared the gut microbiota among Alzheimer's disease patients, patients with mild cognitive impairment, and healthy patients. [7] What the authors found agreed with Hung et al.'s research because they had also found a significant reduction in the abundance of Firmicutes 63.84% versus 73.67%; p = 0.008 and an increase in the Proteobacteria 19.48% versus 4.66%; p = 0.024 when compared to the healthy control. [7] Additionally, Liu et al. were able to identify the family Enterobacteriaceae that in addition to having an increased prevalence in patients with Alzheimer's disease when compared to the mild cognitive impaired group 17.66% versus 3.39%; p = 0.038, it was also linked to the severity of Alzheimer's disease as measured by the Clinical Demetria Rating (CDR) $p < 0.05$. [7] Thus, Hung et al.'s meta-analysis when compared to Liu et al.'s cohort study both identified several specific bacteria in the gut microbiome that were analyzed and compared to a healthy control group, and as a result, the authors concluded that there is a relationship between Alzheimer's disease and the alteration of the gut microbiome that makes up the gut-brain axis. Hung et al's systematic review and meta-analysis of the gut microbiome demonstrated an extensive search of the literature and revealed several studies that used thorough methods to affirm the quality and possible biases of the studies presented. The authors disclosed that the studies used various techniques to analyze the gut microbiota, which could have skewed the results correlation. Liu et al.'s study utilized the comparison of several groups with cognitive impairments with healthy controls that identified relevant perspectives on the variations of gut microbiota within the variety of groups studied. A potential study weakness is the small sample size of 43 participants. Furthermore, confounding variables were not identified nor attempted to be prevented, and differences between the study

arms are ambiguous as to whether they are geared specifically toward Alzheimer's disease or general changes in cognition.

The gut microbiome, responsible for the gut-brain axis is linked to Alzheimer's disease through another process caused by the neuroendocrine pathway. The neuroendocrine pathway is made up of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system which is utilized by the gut-brain axis to regulate the immune system by controlling the production of neurotransmitters. [2] Zhong et al. discuss a study conducted by Liu et al. where they found that an imbalance in the gut microbiome led to dysfunction in the neuroendocrine pathway and a reduction in cognition. [2] Research shows that the gut microbiome can impact the immune system through neurotransmitter synthesis. [2] This process is achieved via tryptophan, an important amino acid in the body, and the kynurenine pathway, a regulatory pathway that breaks down tryptophan in the peripheral system and central nervous system. [2] These processes are important in immune activation, and changes in the levels of these structures could contribute to the synthesis of Alzheimer's disease. Furthermore, as individuals age, the immune response and gut microbiome change. [8] To illustrate, the Hordaland Health Study conducted a cohort study on immune activation and the Kynurenine pathway, which revealed that higher levels of kynurenine correlate to increased inflammatory responses in the elderly; Neopterin, a pro-inflammatory marker, and the kynurenine/tryptophan ratio are strongly correlated, $r = 0.47$. [8] Additionally, kynurenines were 20-30% more elevated and tryptophan was 7% lower in the elderly. [8] Therefore, the gut-brain axis contributes to Alzheimer's disease through the neuroendocrine pathway by inciting and reacting to inflammatory processes, which contribute to the progression of the disease. The Hordaland Health study included a large sample population, which allows the results of the study to potentially be relevant and accurate to the public. However, the study only

measured kynurenine and inflammatory markers at a single point in time, which may not accurately demonstrate prolonged levels within the body.

Overall, multiple research studies confirm the relationship between gut microbiota and the development and progression of Alzheimer's disease, demonstrating statistically significant evidence.

Diet and Alzheimer's disease

The nutrients from the food we eat are crucial in maintaining the body's homeostasis; hence, the diet has a significant role in our overall health. According to research, a correlation exists between the composition of the gut microbiome and an individual's dietary habits. Sandhu et al.'s comprehensive review of the literature on the gut-brain axis identifies the role of the gut microbiome in neurodegenerative diseases and how diet can influence the distribution of the gut microbiota, overall affecting brain health and cognitive function. [9] A study conducted by De Filippo et al. identified the gut microbiota in African and European children and found that the children in Africa had a decrease in Enterobacteriaceae $p < 0.05$, an abundance of Bacteroidetes, and a reduction of Firmicutes $p < 0.001$. [10] To clarify, the children in Africa had a more diverse gut microbiome than the European children with bacteria that were beneficial to their health, all from their diet. [10] Furthermore, in a randomized longitudinal parallel study conducted by Fragiadakis et al., a total of 609 participants were divided into five cohorts and randomly assigned either a low-fat, plant-based diet or a low-carbohydrate, animal-based diet for a duration of one year. The study detected significant alterations in the gut microbiota within the initial three months of the intervention. [11] The study findings indicated that changes in both diets and the physiological changes accompanying weight loss were contributing factors to the microbiome modifications. Of note, the study observed an increase in the abundance of

Bacteroidetes [r = -0.089, p < 0/036] relative to the respective diets, and a reduced abundance was noted in individuals with obesity. [11] These discoveries suggest that diet plays a pivotal role in shaping the diversity and composition of the gut microbiome. Therefore, comparing Sandhu et al's review, De Filippo et al's study, and Fragiadakis et al's study reveals that an individual's diet can influence the abundance of the gut microbiome. Sandhu et al. provide a comprehensive review of the literature but lacks perspective on Alzheimer's disease and other neuropsychiatric disorders for comparison. The study by De Filippo et al. provides a thorough comparison between the diet of two cultures but is exclusive to only Africa and Europe, which the ability to generalize the findings. And the study by Fragiadakis et al. utilized a well-designed longitudinal study design to collect data long-term but was limited to obesity and diabetes and could consider a sample that represents the general population. Thus, when it comes to the relationship between gut microbiota and diet, it's important to approach the findings with caution and consider the limitations of the study.

Evolving research indicates that specific diets, including the Mediterranean, Dietary approaches to stop hypertension (DASH), Mediterranean-DASH (MIND), and Ketogenic diets, can impact both the body and the brain through the gut-brain axis. Although the study of the diet's effect on cognition is still emerging, there is evidence to suggest that diets such as the Mediterranean, DASH, MIND, and Ketogenic diets, in addition to their specific components, could have cognitive benefits and even act as preventative measures against Alzheimer's disease.

Mediterranean Diet

It has been widely known that the Mediterranean diet has the potential to be protective against cognitive decline. The Mediterranean diet is composed of a high consumption of vegetables, fruits, legumes, bread, pasta, rice (whole grain), fish, a high intake of olive oil, and a

reduced intake of saturated fat, dairy, and meats. [12] A cohort study conducted by Féart et al. disclosed that a higher Mediterranean diet adherence was related to fewer mistakes on the Mini-Mental State Exam (MMSE) β = -0.006, 95%CI [-0.01 to -0.0003] p = 0.04. In Féart et al.'s prospective cohort study, it was discovered that 66 participants were diagnosed with Alzheimer's disease during the five-year follow-up, but the individuals diagnosed were significantly older 79.4 to 79.1 years versus 75.7 years, p< 0.001. Despite this, the study was statistically significant, as out of the 1410 participants who were 65 years or older, only 66 individuals were diagnosed with Alzheimer's disease. [12] Additionally, a randomized trial conducted by Esposito et al. reported that following the Mediterranean diet had reduced C-reactive protein and Interleukin 6, which are responsible for inflammation within the body, 95% CI [0.5-5.7]. [13] Within the reported diets, they similarly show that reducing the amount of red meat consumed, avoiding processed foods, and increasing the consumption of fruits, vegetables, and fatty fish decreased the rate of cognitive decline. Not only does eating a diet high in fresh produce and fatty fish decrease the rate of cognitive decline, but it also reduces an individual's risk for cardiovascular diseases, cancer, and diabetes. [13] Moreover, a one-year, randomized, parallel trial conducted by Berendsen et al. revealed after one year of adherence to a diet labeled as the NU-AGE diet, which has the Mediterranean diet components, improved mean intake of 13 of 15 NU-AGE dietary components ($p < 0.05$). [14] This suggests that diet ultimately has a fundamental impact on Alzheimer's patients, as it could reduce levels of inflammation in the body and within the brain. Although a potential weakness of Berendsen et al.'s study included self-reported results, which could be inaccurate and biased, utilizing a parallel randomized trial design enabled an explicit comparison between the experiment and control study arms.

Numerous studies have been done on components of the Mediterranean, DASH MIND, and Ketogenic diets, including high intake of omega-3 fatty acids found in fish, consumption of polyphenols, and more to test its effectiveness at reducing or preventing Alzheimer's disease. For instance, the Rotterdam cohort study strictly tested omega-3 intake with higher consumption of fish. Devore et al. did not find sufficient evidence supporting moderate fish and omega-3 intake with participants with risk $p = 0.7$. [15] However, researchers from the Rotterdam study implied that consuming omega-3 fatty acids with other nutrients found in other foods could change the effects of cognitive decline. [15] Moreover, studies show that polyphenols, a naturally occurring compound found in grapes, apples, pears, cherries, berries, tea, coffee, red wine, dried legumes, cereals, and chocolate, are anti-inflammatory, provide neuroprotection, and contain antioxidants [9] A systematic review conducted by Colizzi et al. revealed mixed results regarding the beneficial effects of polyphenols on Alzheimer's disease due to inconsistent types of polyphenols studied. [16] However, the study mentions that of the 24 studies analyzed, 19 had at least one inverse correlation between Alzheimer's disease and one type of polyphenol. [16] To illustrate, consuming fortified fruit juice had improved cognition, $p = 0.009$, and increased consumption of flavonoids produced greater cognitive results [95% CI 0.00 - 0.07]. [16] Authors reveal that the scores for the studies that portrayed an inverse associated have an average of 6.31 out of 10, and this is significant enough to consider the data to be valid, although larger, longer studies should be conducted to verify polyphenols' benefit in reducing cognitive decline. [16]

In short, the Mediterranean diet's components are believed to positively impact cognitive decline in Alzheimer's patients when all components of the diet are combined. However, when studied individually, no significant correlation was found, indicating the need for further studies to confirm their benefits.

DASH MIND Diet

Previously, the Dietary Approaches to Stop Hypertension) (DASH) was utilized to prevent hypertension and the Mediterranean- DASH Intervention for Neurodegenerative Delay) (DASH MIND) was used for its neuroprotective effects by Rush Medical Center. [17] Both of these diets are plant-based and emphasize a high intake of vegetables, fruit, nuts, whole grains, legumes, nuts and seeds, healthy fats, fish, and poultry, but limit meat, sweets, processed foods, and drinks high in sugar. [17] The DASH and DASH MIND diets have the potential to improve modifiable risk factors for Alzheimer's disease in middle-aged individuals, and researchers are currently studying their factors to determine if they contribute to a reduction in cognitive decline. [17] An open cohort study conducted by Morris et al. found that adherence to the MIND diet provided lower rates of Alzheimer's disease HR = 0.65, [95% CI = 0.26, 0.76] but only one-third of the participants in the DASH HR = 0.61, [95% CI = 0.38, 0.97] and Mediterranean diet HR = 0.46 [95% CI = 0.26, 0.79] had lower rates of Alzheimer's disease. [18] Wesselman et al. conducted a multicenter observational longitudinal study and found that high adherence to the Mediterranean diet improved memory, $p = 0.003$, and language, $p = 0.017$. Additionally, high adherence to the MIND diet was associated with better memory, $p= 0.046$, and high adherence to both diets was linked to better memory, $p = 0.004$ and $p = 0.029$ but not as much improvement in language as expected, $p = 0.051$ and $p = 0.053$. [19] The study conducted by Morris et al. enabled data to be collected and analyzed over an extensive period in addition to the comprehensive MIND diet scoring system, but it is important to consider that the data being collected and analyzed were self-reported and subject to unreliable results due to bias. Comparatively, the study conducted by Wesselman et al. also utilized a validated dietary assessment tool but also

relied on self-reported data. Therefore, these two studies provide compelling data to support eating the diet aforementioned but approach each research study with caution, as they also have limitations.

Thus, several studies on the DASH and DASH MIND diets emphasize plant-based foods and limit meat, sweets, and processed foods. These diets have been found to reduce risk factors for Alzheimer's disease and are being studied for their potential to slow cognitive decline. One study found that adherence to the MIND diet was associated with lower rates of Alzheimer's disease, while another study found that high adherence to the Mediterranean diet and the MIND diet improved memory. Even though the improvement in language was not as significant as expected, these studies suggest that these diets may have beneficial effects on cognitive function, but further research is needed.

Ketogenic Diet

A Ketogenic diet is also favored in the prevention of Alzheimer's disease due to the shift from glucose metabolism to fatty acid metabolism, which utilizes ketone bodies for brain fuel, ultimately inhibiting abnormal glucose metabolism in the brain. [20] A systematic review conducted by Bohnen et al. analyzed 10 Alzheimer's disease using ketogenic trials suggesting that there is probable evidence that supports cognitive improvement with a ketogenic diet. [21] To illustrate, one of the studies analyzed was Phillips et al. where a randomized crossover trial utilized the Addenbrookes Cognitive Examination- III (ACE-III) to evaluate cognitive domains such as attention, memory, fluency, language, and visuospatial ability. [22] The authors discovered that individuals who followed a ketogenic diet had a slight increase in the ACE-III score, +2.12 $\pm$ 8.70 points, $p = 0.24$, and an improvement in their Activities of Daily Living Score (ADCS-

ADL) score,+3.37 $\pm$ 5.01 points, p = 0.0067. [22] Phillips et al.'s study utilizes a modified ketogenic diet to reduce cognitive decline, a promising intervention for individuals with Alzheimer's disease. However, the study only contained 20 participants for only six weeks. This limits the ability to generalize the data and identify any long-term effects that the diet might have. While the statistical significance of the Ketogenic diet on individuals with Alzheimer's disease is not strong, the increase in ADL scores is still clinically meaningful for those with Alzheimer's disease which is indicative of reducing the progression of Alzheimer's disease. Additionally, several studies evaluated the ketogenic diet's components that could suggest a cognitive improvement. A randomized, double-blind, placebo-controlled, parallel-group study by Henderson et al. analyzed AC-1202, a medium-chain triglyceride (MCT) that was developed to elevate serum ketone bodies, mimicking a Ketogenic diet. The authors found that consumption of AC-1202 significantly improved cognitive function, p = 0.023. [23] Additionally, a double-blind, randomized, placebo-controlled crossover study conducted by Xu Q et al. analyzed the use of Medium-chain triglycerides (MCT) as an alternative for brain fuel in patients with Alzheimer's disease. The authors found a significant reduction in cognitive impairment when participants took MCT, p <0.01. [24] Overall, the evidence suggests that there is a probable cognitive improvement with a Ketogenic diet and the components that make up the diet.

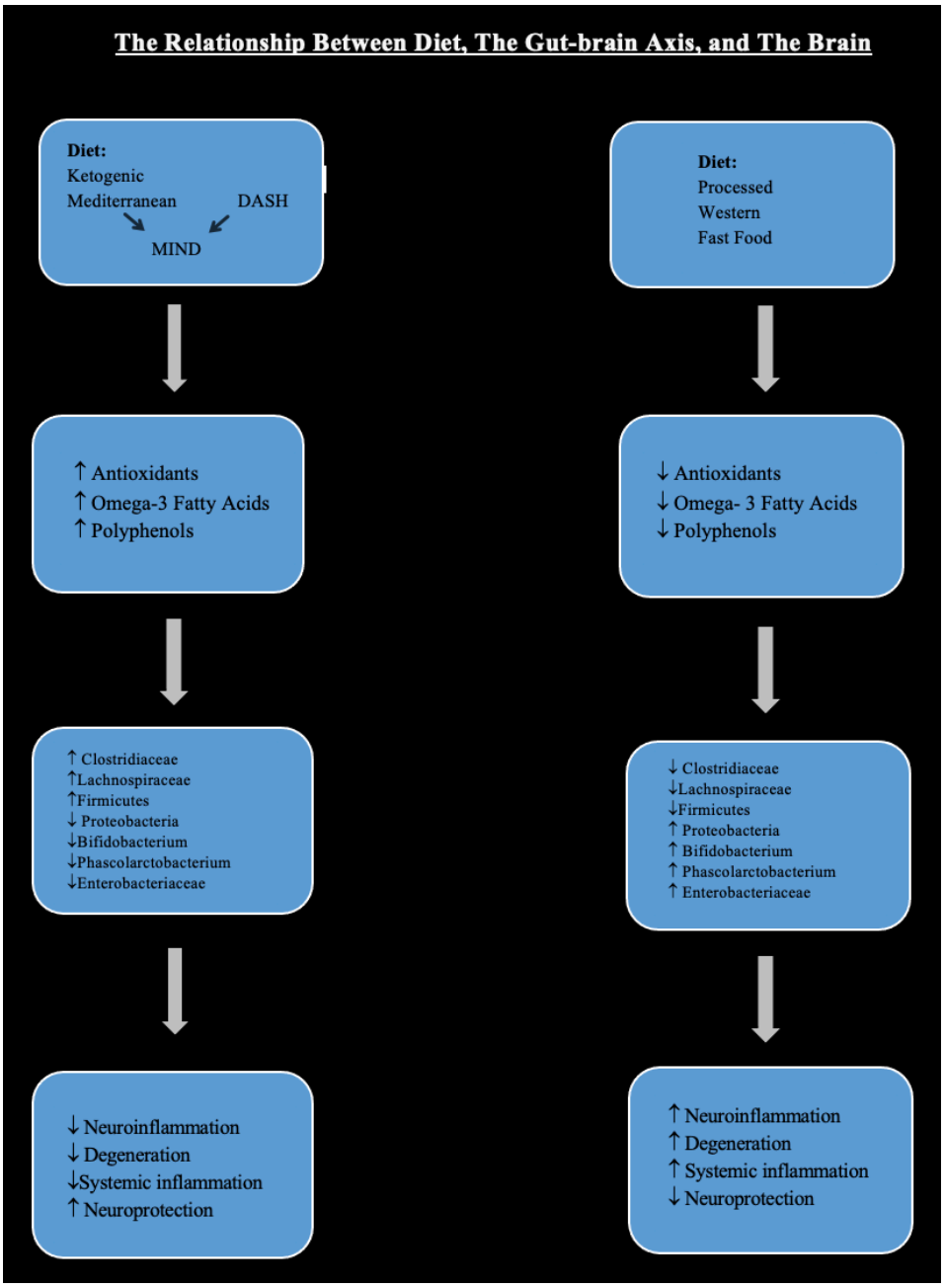

Figure 1. *Relationships between diet, the gut microbiome, the gut-brain axis, and the effects on the brain regarding Alzheimer's disease.*

Conclusion

After extensive analysis of current data regarding the effect of diet on the gut-brain axis and its impact on cognition in Alzheimer's disease, it can be assumed that there is a relationship between types of diets and their effects on the body. The gut microbiome is determined to be influenced by diet, as portrayed through the variations in bacteria within various diets. This impacts the level of the body and the higher-order functions of the brain due to the absorption and systemic effects diet has. There is substantial evidence from various studies that support DASH, Mediterranean, MIND, and Ketogenic diets, and the components that make them up. Increasing intake of these components found in natural fruit, vegetables, wine, and fish has pushed researchers to continue studying their impacts to potentially create a prevention and treatment for Alzheimer's disease. Although the idea has been studied through multiple research studies, there are competing data suggesting that there is no effect of the components of these diets in Alzheimer's patients; however, there are very limited studies, and research suggests that larger studies should be conducted to reflect and confirm the results of the previous studies. Additionally, the diagnosis of Alzheimer's disease is made in advanced stages, and determining a systematic approach to detect early Alzheimer's is key, as the treatment works best at the earliest stages of a disease. Doing so by identifying primary and secondary risk factors could be beneficial in individualizing treatment and determining the best way to approach each patient with Alzheimer's disease. [25] Nevertheless, altering diet is a promising intervention and a step in the right direction to determining a cure for Alzheimer's disease.

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