ETIOLOGY OF BRAIN DISEASES AND THE CURRENT ADVANCEMENTS IN PREVENTION AND SYMPTOM MANAGEMENT

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ABSTRACT

Brain disorders and diseases are a common occurrence and a cause of death in many individuals. There is currently no cure available for many of these conditions and most current treatments aim to manage symptoms through strenuous pharmaceutical treatment. Many problems can arise from this approach, including adverse side effects and financial hardships. Furthermore, people from lower-income households are at a disadvantage when it comes to getting proper care for brain disorders and diseases. An abundance of recent research has focused on potential preventative measures and symptom management approaches that reduce disease burden and increase quality of life. This literary review will discuss dietary and exercise interventions that are reported to have positive effects in patients with four neurological diseases: Alzheimer's disease, schizophrenia, epilepsy, and Parkinson's disease. These four disorders and diseases were chosen for this report because of their increasing prevalence in the world and because there is a substantial amount of evidence available regarding potential interventions. Identifying the right intervention requires an understanding of the mechanisms and genetic components involved in the progression of each disease, as well as the individual needs of each patient. Studies have shown that these accessible interventions can serve to reduce disease risk in the general population and improve the health of those who are already burdened with disease.

PREFACE

In 2016, brain disorders made up 16.5% of total global deaths and were the largest factor impacting disability-adjusted life.[1] My grandfather was 74 when he was diagnosed with Alzheimer's disease (AD) and 80 when he passed away from the illness. Although the signs were clear before the diagnosis, it was something my family did not foresee. I remember the first signs of brain decay that I saw; he would forget simple things like where he put his phone or the fact that he had already gone to the grocery store that day. No other person in our family had ever been diagnosed with a memory-loss disorder. We assumed it was simply old age impairing his memory; little did we know, it was much bigger than that. Over the years, his memory-loss became more noticeable, and he started losing the ability to do familiar things like make breakfast, shower, or even walk on his own. My brother and I watched our once comedic, playful grandfather struggle to form a sentence during our visits. He was taking strong medications to slow his memory loss, but this deceleration came with its own drawbacks. Although he could somewhat recognize our faces, he constantly appeared tired, irritated, and was unable to communicate his needs. Eventually, we realized we were losing someone we thought would live forever.

In January 2021, he passed peacefully after a lengthy battle with AD. Unfortunately, as the sixth leading cause of death among Americans, death is the typical outcome for patients with AD.[2] With no current cure, approaches to treating patients with neurological disorders usually include intense pharmaceutical treatments and therapy. In my grandfather’s case, he took a hefty regimen of pills and was encouraged by his physician to do physical and mental exercises every day, as a last attempt to slow the progression of his memory loss and declining health.

While my grandfather was fighting his battle, I constantly asked myself questions. Why isn't there more that can be done? Why does he look worse every time I see him, despite all the medications he takes? The doctors did everything they could to increase the length of his life, but I just wanted there to be a way to make him feel better and get him back to his normal, high-spirited self. I chose to research AD and other incurable brain disorders to identify interventions that people at risk can utilize to increase their years of healthy living. Until there is a cure, I hope that there is something we can do to slow the progress of these brain diseases from taking over and affecting someone else's grandparent.

1. INTRODUCTION & BACKGROUND

1.1 Brain Structure and Function

The brain is made of many different components that contribute to its complex structure with their unique functions. The brain functions to communicate with other areas of the body and to control emotions, thoughts, memories, and other essential processes. The brain consists of the forebrain, midbrain, and the hindbrain. In the normal aging process, the brain is subject to shrinkage that results in suppression of many of its functions. Aging is not uniform, and everyone is affected at various stages of their lives. While normal aging is inevitable, neurodegenerative diseases and mental disorders are responsible for speeding up the process of brain deterioration and abnormalities resulting in an increased burden and a shorter life span. The brains of AD patients have been analyzed to show that atrophy occurs at a much faster rate compared to healthy aging brains. More specifically, the temporal lobe is largely affected by AD and the percent change in atrophy is greater after one year (Fig. 1). In a healthy elderly patient, the longitudinal change in atrophy shows an approximate 0.5% change in the temporal and prefrontal areas of the brain (Fig. 1).

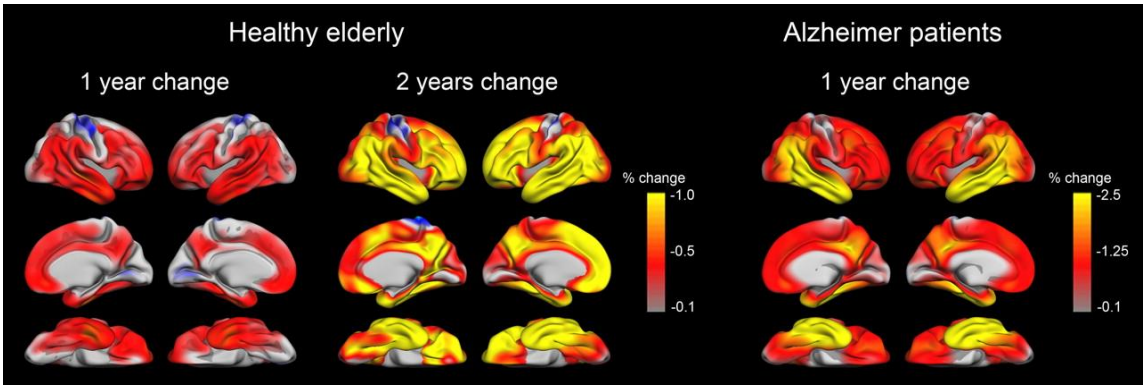

Figure 1. Percent change in atrophy of a healthy elderly brain compared to an AD brain. This figure was included with permission from a previous publication.[65]

The nervous system plays an exceptionally significant role in the body. All communication, memory, learning, and thought processes occur through this body system. The human senses, sleep, breathing, digestion, and many other body functions are regulated here, as well. The nervous system is composed of a complex arrangement of nerves and signals throughout the body to regulate all of these activities. Afferent neurons bring sensory input toward the brain, where sensation is then perceived. Efferent neurons transmit signals from the brain to organs and muscles to effect physiological changes. Therefore, efferent pathways are responsible for executing voluntary movements. There are two subsystems of the nervous system called the central nervous system (CNS) and the peripheral nervous system (PNS).

The CNS of the body consists of the brain and the spinal cord and asks as a processing center. The PNS, which is found everywhere except the brain and spinal cord, relays information between the CNS and the rest of the body. The PNS is further divided into the somatic nervous system and the autonomic nervous system. The autonomic nervous system is involved in subconscious bodily functions. For example, the process of digestion is involuntary and therefore controlled by the autonomic nervous system. On the other hand, the somatic nervous system contributes to conscious, voluntary movements, such as walking.

The integrity of the CNS is negatively impacted by oxidative stress. ATP is produced via oxidative phosphorylation within the mitochondria, and reactive oxygen species (ROS) are also produced in this process. Imbalanced levels of ROS and antioxidants contributes to conditions of oxidative stress. Oxidative stress in the brain is commonly observed in neurodegenerative diseases like AD and Parkinson's disease (PD).[3] There is also evidence that oxidative stress results in mitochondrial dysfunction, which is known to contribute to anxiety and other cognitive deficits.[3]

1.1.1 Memory

The hippocampus of the brain is involved in memory formation and storage. This part of the brain resides in the midbrain and medial temporal lobes as part of the limbic system. Damage to the hippocampus impairs the ability to acquire new knowledge, but does affect factual or long-term episodic memories.[4] Episodic memories learnt more recently are more subject to loss after hippocampal damage compared to episodic memories learnt long ago. This finding supports the idea that, although the hippocampus is involved in episodic memory, it also plays a key role in the formation of memories.

In addition to various regions of the brain that are important for memory, there are neurotropic factors that significantly contribute to both memory and learning. The brain-derived neurotropic factor (BDNF) is important for growth and development of neurons in certain regions of the brain. BDNF is one of the favored ligands for the tyrosine kinase B (TrkB) receptor.[5] In the pathway, once the ligand binds to the extracellular domain of TrkB, it regulates development and function of brain synapses and also influences learning and memory. A previous study showed that BDNF mRNA is most highly expressed in the hippocampal region of an adult mouse brain, but is also very prevalent in the cerebral cortex.[6] This study indicates that BDNF may play a key role in the maintenance and function of neurons in both of these brain regions. As humans age, research shows that BDNF expression changes, and studies have focused on preventing this loss or increasing BDNF expression levels.[7]

1.2 Etiology of Brain Diseases

1.2.1 Alzheimer's disease

AD is the leading cause of dementia, affecting almost 5.8 million Americans as of 2020.[8] It is estimated that disease prevalence will triple within 40 years, with up to 14 million

Americans affected.[8] Age, family history, cardiovascular diseases, down syndrome, and traumatic brain injury are all potential causes for the onset of AD. Evidence also shows that diet, social interaction, sleep, and exercise influence AD development. The symptoms of AD typically begin in people around 60 years of age and progressively worsen over time. The first signs usually observed are minor memory losses. As time progresses, memory loss worsens and other symptoms like confusion, irritation, and anxiety also appear. If diagnosed with early-onset AD, symptoms can be observed as early as age 30 to the mid-60s. The pathological changes seen in patients with AD include extracellular β-amyloid peptide deposition in plaques and an accumulation of microtubules into neurofibrillary tangles (NFT), which cause inflammation in the brain.[9] Studies have also shown that BDNF is reduced in hippocampal tissue of brains affected by AD.[10] The causes and types of AD are broad and are characterized very differently in each case.

Early-onset familial AD (FAD) is an inherited disease that has a more rapid rate of progression and usually begins at less than 65 years of age, but it is only responsible for 1–5% of total AD cases.[8] Previous studies show that mutations in the genes presenilin 1 and presenilin 2 cause cleavage of the β-amyloid precursor protein (APP), which leads to increased accumulation of the β-amyloid plaques in the cerebrum, a common cause of AD.[11,12] Mutations in presenilin have been shown to cause calcium dysregulation in the endoplasmic reticulum. For example, mice expressing mutated presenilin showed increased disruptions in calcium signaling that caused increased calcium release, compared to controls. This supports the hypothesis that a mutation in presenilin results in more free calcium and, therefore, calcium dysregulation, which is another known consequence of AD.[13] This study also showed a relationship between the

increased calcium and β-amyloid plaques, along with their connection to AD. Three genes (APP, Presenilin 1, and Presenilin 2) were identified as diagnostic markers of early-onset AD.

Patients who begin experiencing symptoms in their mid-60s are more likely to have late-onset AD, which is more common. There is a genetic relationship with late-onset AD that can be seen in first-degree relatives at a higher rate than with non-first-degree relatives.[9] Late-onset AD has been associated with the Apolipoprotein E (apoE) ε4 allele. Having one allele of this gene on chromosome 19 has been shown to be a risk factor for AD and lowers the age of onset by 6–7 years. However, the presence of the allele is not sufficient to confirm that the person affected will develop AD, and the absence of the allele does not indicate absence of the disease (NIH). Primary symptoms seen in patients with late-onset AD include declining episodic memory, visuospatial impairment, difficulty with language, and other cognitive abnormalities.[14] AD has affected a broad range of people and it has a large and severe impact on the health of those it affects.

1.2.2 Schizophrenia

Schizophrenia is another neurological disease that impacts many different age groups. For every 300 people in the population, one person is affected by schizophrenia, according to data from 2019.[15] Ongoing research aims to identify a cause, and researchers have narrowed down genetic and environmental factors that could cause schizophrenia. Schizophrenia patients typically present with forms of psychosis that lead to depressive and anxious symptoms. The symptoms of schizophrenia can be distinguished as positive or negative. Positive symptoms are identified as an increase or distortion of normal function, while negative symptoms are defined as a reduction in normal function. Examples of positive symptoms include hallucinations, delusions, and movement disorders; examples of negative symptoms include the inability to feel

pleasure (anhedonia), trouble with their speech, or flattening. Depression and cognitive impairments are included with positive and negative symptoms in schizophrenia patients.

Schizophrenia is known to run in families, but research has not been able to identify a specific gene responsible for this potential inheritance. However, there is a great deal of evidence surrounding the relationship between the environment and physical factors that can cause schizophrenia. Elevated levels of stress lead to high cortisol levels, and studies have shown that this is associated with more severe cases of schizophrenia and cognitive decline.[16] Serotonin and dopamine dysregulation are also thought to play a role in the progression of schizophrenia. Dopamine, a neurotransmitter formed in the substantia nigra, is shown to be hyperactive in the brains of people with schizophrenia.[17] A study also found that symptoms of schizophrenia were significantly improved when patients were given Lumaterperone, a serotonin and dopamine modulator.[18] This finding demonstrates that serotonin and dopamine are dysregulated in schizophrenia patients.

1.2.3 Epilepsy

Epilepsy is another type of brain disorder caused by brain dysregulation. Unlike AD or Parkinson's disease, epilepsy is not an age-related condition and is commonly diagnosed in children. Symptoms of epilepsy vary, and diagnosis (aside from imaging) requires two unprovoked seizures at least 24 hours apart, one unprovoked seizure with a recurrence risk of at least 60%, and epilepsy syndrome.[19] Epilepsy syndrome and epilepsy differ in that epilepsy syndrome characterizes most cases of benign symptoms, in which seizures may not occur at all but abnormal spikes in brain activity may occur. Epilepsy is characterized by frequent seizure episodes, often with no identifiable cause. When a cause is detectable, it is usually related to head trauma, an abnormality within the brain, infection, prenatal injury, developmental disorders,

or genetic causes. Epilepsy disorder includes many distinct types and subtypes with disparate effects on the body.

Epilepsy includes focal seizures and generalized seizures. Focal seizures occur when abnormal activity in a certain region of the brain causes the episodes. Some patients experience simple partial seizures, with maintained consciousness but altered senses and spontaneous jerking. Others experience complex partial seizures, which involve a loss of consciousness and awareness. There are many subtypes of generalized seizures that involve various regions of the brain. The types of generalized seizures are absence, tonic, atonic, clonic, myoclonic, tonic-clonic, and febrile.

There are four subtypes of epilepsy: idiopathic, symptomatic, provoked, and cryptogenic. Idiopathic epilepsy is caused by single gene disorders and is an inherited or genetic form of the disease. Some examples of idiopathic epilepsy include childhood absence epilepsy, juvenile myoclonic epilepsy, juvenile absence epilepsy, and generalized tonic-clonic seizures. Symptomatic epilepsies are known as childhood epilepsy syndromes and are a result of brain malfunction or injury. Provoked epilepsy is caused by environmental factors such as a fever, menstrual cycle, drugs, or alcohol, among others. Cryptogenic epilepsies currently have no known cause and are responsible for more than 40% of adult cases of epilepsy.[20]

1.2.4 Parkinson's disease

Parkinson's disease (PD) is the second most common neurodegenerative disease after AD. The risk of PD increases with age, although genetic factors can be associated with early-onset PD that is diagnosed in patients younger than 50 years of age. It is estimated that the prevalence of PD may reach around 12 million people affected by 2040.[21] This disease is

responsible for impacting the peripheral, central, and enteric nervous system. PD is characterized by resting tremors, bradykinesia, rigidity, and instable posture.[22]

Pathological identification of PD is associated with a loss of dopaminergic projection cells in the substantia nigra and an accumulation of alpha-synuclein in Lewy bodies.[23] The PARK1, PARK2, and PARK3 loci are three of eight loci identified in autosomal dominant and recessive cases of PD. The aggregation of α-synuclein in Lewy bodies is the common pathological identification of the autosomal dominant form of PD, while the presence of the parkin gene on the PARK2 loci is present in half of children with the inherited form of PD as well as 5% of young adults with early-onset AD.[24,25] A mutation in the parkin gene causes degeneration in the substantia nigra without the formation of Lewy bodies[26] and causes autosomal recessive juvenile parkinsonism, which is a rare form of PD diagnosed in people under the age of 40.

2. METHODS

2.1 Data Collection & Analysis

PubMed and Google Scholar were used as the data source. Key words that I included in my searches were: *neurodegenerative disorders*, *Alzheimer's disease etiology, schizophrenia etiology*, *epilepsy etiology, Parkinson's disease etiology*, *neurodegenerative prevention, Alzheimer's disease prevention, schizophrenia intervention, epilepsy intervention*, and *Parkinson's disease intervention*. I found additional studies throughout the cited literature section within the papers. I originally limited the range of publication dates to 2000 until the present, although I ultimately choose to reference a few publications written before 2000. For further analysis, I sorted each publication into categories: background information, etiology, and interventions. The etiology and intervention categories were further subdivided into the four

types of brain diseases discussed in this paper. The interventions category was further subdivided by type of intervention (diet or exercise).

2.2 Classification of Exercise Types

2.2.1 Aerobic exercise

Aerobic exercise is a broad term used to describe physical activity that conditions the cardiovascular system, giving it the alternative name ‘cardio.’ With aerobic exercise, heart rate and respiratory rate are significantly increased because of the increased demand for oxygen for energy production. Cardio can consist of a broad range of exercises, but the ones frequently discussed in brain disease symptom management and intervention are treadmilling, swimming, dancing, boxing, and circuit training. Each of these interventions requires increased oxygen demand for an extended period of time, and can be identified as an aerobic physical exercise.

2.2.2 Anaerobic exercise

Anaerobic exercises are those that do not require oxygen for energy production and instead utilize the breakdown of glucose for energy. Pilates and yoga are two types of anaerobic exercises that have been shown to be beneficial to patients with brain diseases. A systematic review of 119 scientific papers related to Pilates defines the exercise as a mind-body experience that focuses on posture, breathing, and muscle control.[27] The form of exercise developed by Joseph Pilates uses specialized equipment and machines such as the Balanced Body to complete exercises, but these can also be completed on floor mats. Originating in India, yoga involves a combination of breathing exercises, mediation, and relaxation that can be implemented as an exercise for mind and body healing. Both of these exercises are anaerobic in nature and have an overall shorter and quicker duration.

2.3 Classification of Diet Types

2.3.1 Ketogenic diet

Founded in the 1920s, the ketogenic diet involves the increased consumption of fatty foods and the decreased consumption of carbohydrates, with the recommended ratio being 3:1 or 4:1, fat to carbs.[28,29] The mechanism behind the diet is switching the breakdown of food for energy from glucose metabolism to the metabolism of ketone bodies. When a person has consumed less than 20 grams of carbohydrates per day for around 3 days, they will enter a state of ketosis.[30] To be in ketosis means the body has run out of a sufficient amount of glucose to metabolize and is now turning to an alternative energy source which consists of ketone bodies synthesized form acetyl-CoA in the fatty acid oxidation cycle, which is upregulated in this state of being.[31] The diet was originally created as a method of treating epileptic patients by preventing seizures, but recent studies have found it to be beneficial in other neurodegenerative diseases, like AD.

2.3.2 The Atkins diet

The Modified Atkins Diet (MAD) was created by professionals at Johns Hopkins Medical Center to create a less restrictive version of the ketogenic diet. MAD, like the ketogenic diet, induces a state of ketosis. The MAD diet is composed of a 0.9:1 ratio of fats to carbohydrates and proteins; this includes less caloric fat compared to the ketogenic diet, but still has more fat than a typical diet.[32] This type of diet can sound much more appealing because it is much less restrictive than the ketogenic diet and allows for the consumption of more protein and carbohydrates.

2.3.3 Inadequate diets in lower class populations

According to the World Health Organization, a healthy diet consists of a combination of fruits, vegetables, nuts, and whole grains.[33] It is important to maintain this healthy balance to

avoid acquiring life-threatening diseases. Social and economic factors play a significant role in the access and abundance of foods that make up this healthy balance. People in low socioeconomic regions are at a large disadvantage when it comes to acquiring necessary ingredients.[34] There is evidence that the risk of AD and neurological disorders is increased in residents of the most disadvantaged neighborhoods.[35]Education and financial support for these communities is a necessary addition that can improve the quality of life of many people living with neurological and other diseases.

2.3.4 Homocysteine, iron, and vitamin D

Supplements and vitamins that come from certain foods or the environment also impact diseases of the brain. Nutritional deprivation is a worldwide problem that leads to many life-threatening diseases, including schizophrenia. Previous studies have identified an association between the insufficiency of three key nutrients (vitamin D, folic acid, and iron) with the development of schizophrenia.[34] Each study measured the effects of nutrient deprivation during pregnancy on offspring. The study concluded that a deficiency in vitamin D, folic acid, or ion may be a risk factor for the development of schizophrenia.

3. RESULTS

3.1. Alzheimer's Disease

3.1.1 Exercise intervention

With the high prevalence of AD, a great deal of current studies aim to investigate AD prevention and symptom management. In reviewing these studies, it became apparent how well-studied AD is and how many diverse types of physical activities have been proposed as interventions. With many key pathological features of Alzheimer's disease known, such as the accumulation of β-amyloid plaques and inflammation, researchers have investigated how

exercise affects each pathological feature. The studies done on physical exercise and AD range from prenatal mouse model studies to analysis of brain tissue.

There is evidence that prenatal Alzheimer's disease prevention is possible through physical exercise throughout pregnancy in transgenic mouse models carrying the APP 695 transgene. The offspring of transgenic (TG) mothers that were in running wheel (RW) cages showed significantly decreased levels of β-amyloid plaque buildup compared to offspring of TG mothers were in standard (ST) cages.[36] Interestingly, the authors discovered that the levels of *Mme*, a β-amyloid peptide-degrading enzyme, were upregulated in offspring of wild-type (WT) mothers in the RW cages, but offspring of TG mothers from the same environment showed no significant changes in *Mme* levels.[36] In WT offspring, this increase resulted in a larger breakdown of β-amyloid and less inflammation in the cerebrum.[36] This study also showed that levels of microglia were significantly reduced in offspring of physically active TG mothers to a level that matched WT mice[36]. Therefore, in mice with the APP transgene that are predisposed to higher microglia levels, physical exercise maintains microglia at normal levels. Furthermore, this same study identified a significant increase in vessel branching and angiogenesis in offspring of physically active TG mothers.[36] This is an important finding because pro-angiogenic properties are important for transmission of brain supply necessities and β-amyloid transporter regulation. The study concluded that exercise during pregnancy significantly improved AD pathology in the offspring of mouse model of AD. These findings provide novel insight to potential preventative measures that females could take while pregnant to reduce the risk of their child developing AD.

Other studies have shown that AD symptoms can be managed using physical activity. One study identified swimming as a potential activity for improving cognition and behavior in Alzheimer's patients. Interestingly, after induction of the disease via injection of streptozotocin

(STZ) and before exercise, no changes in BDNF levels within the hippocampus of the mice were seen.[37] During the exercise phase of the experiment, the mice participated in a 4-week program, while non-exercise mice were placed in an environment with no water for the same length of time. After a 4-week exercise program, swimming was found to significantly increase BDNF levels and decrease anxiety-related behaviors as well as glutamate levels in STZ-treated mice.[37] Additionally, no significant changes in β-amyloid levels or inflammatory cytokine levels were observed in STZ-treated mice.[37] The researchers suggested that the decrease in glutamate levels may have been responsible for the decrease in anxiety and AD-like behavioral symptoms.[37] The increased levels of BDNF after swimming suggests improved neuronal survival, growth, and differentiation in these mice compared to the STZ-treated mice who did not swim. These findings support the idea that physical exercise is beneficial for symptom management in patients who have already been diagnosed with AD.

3.1.2 Diet intervention

Diet is essential for metabolic balance within the CNS. Therefore, metabolic processes of the CNS must be carefully maintained, and any imbalance will alter the functionality of the brain.[38] The study references AD by its nickname, ‘type 3 diabetes,’ because AD patients often have an inability to utilize glucose as an energy source and develop a resistance to insulin. This results in the use of ketone bodies, similar to type 2 diabetes. The primary source of energy for the brain is glucose; therefore, a solution for prevention would be to intake less glucose and initiate the utilization of ketones, which help the brain maintain normal functionality. A low carb, ketogenic diet is useful in maintaining ideal levels of glucose for the brain to handle. In a low carb diet, as if often prescribed to patients with diabetes, less glucose intake allows for better energy maintenance and reduced need for insulin.

Several studies in mice have shown that the ketogenic diet is associated with reduced levels of β-amyloid in the hippocampus. In one study, this conclusion was made after comparing hippocampal β-amyloid levels in mice that were fed a fat-rich diet versus a carbohydrate-rich diet. The ketogenic diet was found to be far more beneficial than a carbohydrate-rich diet for reducing the pathological changes caused by AD.[39] Another study on the effects of the ketogenic diet found that, in mice with an APP mutation, β-amyloid levels were significantly reduced by almost 25% in the group given a fat-rich, low carbohydrate diet compared to the group given a standard high-carbohydrate, low-fat diet.[40] The authors concluded that diets high in fat reduced β-amyloid levels. The results of both studies identify a diet-based intervention to potentially lessen disease progression in patients suffering from AD.

However, not all studies have identified an association between high-fat diets and a decline in β-amyloid accumulation. In fact, one study found no evidence of a change in β-amyloid levels in mice fed a normal diet or a high-fat diet but did identify significantly increased learning and memory deficits in a Y-maze test in the high-fat diet group after 14 weeks.[41] In another study, normal mice were compared to mice with an APP gene mutation and each group was given either a 'Western diet' (high fat) or a normal diet. No significant changes were observed in β-amyloid levels between the groups, but pericyte integrity was significantly reduced in mice fed a Western-diet.[42] Pericyte integrity is important for the proper functioning of the blood-brain barrier, and therefore is an essential factor in brain functionality and the prevention of neurological conditions.[43] The study concluded that a high-fat diet worsened AD pathology in mice. Both of these studies reported unchanged levels of β-amyloid plaques following a high-fat diet, and reported other cognitive deficits that resulted from this type of diet.

A study by Van der Auwera et al.[40] further considered these contrasting results. The study concluded that the association between improved AD pathology and the ketogenic diet was due to the interaction between a high-fat diet and a low-carbohydrate diet. The authors made this conclusion because high-carbohydrate diets have been proven to play a key role in the development of AD and in impaired insulin signaling. Therefore, it is essential to include the low-carb aspect to ensure a proper observation of the effects of the ketogenic diet. The report also discussed that when negative impacts were observed related to a high-fat diet, these studies again failed to include a low-carbohydrate component. In using ketogenic diets as a method of intervention in AD patients, it will be crucial to signify the importance of the exact definition of the diet to ensure proper reduction in disease progression without added health complications.

3.2 Schizophrenia

3.2.1 Exercise intervention

Interventions for maintaining or improving the symptoms of schizophrenia entail plenty of exercise and an overall healthy lifestyle, similar to interventions for many other neurological diseases. These tasks are important for managing the overall severity of the symptoms. Exercise interventions that have been studied in detail include aerobic exercises, yoga training, and Pilates. These forms of exercise have been shown to reduce certain symptoms of the disease and improve quality of life for patients. Although not an extensive list of interventions, these forms of physical activity can be utilized in future medical approaches to help patients dealing with the burden of schizophrenia.

Yoga has been studied as a potential adjuvant therapeutic for patients with schizophrenia. After 1-hour long sessions, 6 days per week, for 21 days, yoga training was found to significantly improve face memory performance and attention in schizophrenia patients.[44] The

study also found that attention was improved to a greater degree in patients who completed yoga training compared to a physical exercise control group.[44] These findings suggest that yoga may be useful as a possible therapeutic to reduce the symptoms of schizophrenia and improve the quality of life for those diagnosed with the disease.

A study in Germany examined the effects of aerobic exercise in patients with schizophrenia and major depressive disorder. The study aimed to determine how the speed of processing, working memory, verbal learning, visual learning, and other factors were affected after boxing and circuit exercise with cognition training compared to relaxation with cognition training. Although there was no change in pre- and post-testing of the positive symptoms of schizophrenia, there was a significant decrease in negative symptoms during post-testing.[45] The results of the study showed enhancements in speed of processing and visual learning in patients with schizophrenia after the physical training intervention.[45] These findings suggest that a combination of cognitive and physical exercise improves schizophrenia symptoms.

In another study on the effects of aerobic exercise in schizophrenia patients, treadmilling was used as intervention. The study found that aerobic capacity (VO_2 max) was significantly lower in patients with schizophrenia, due to an overall lack of exercise and physical activity.[46] In using treadmilling as an intervention, the study aimed to determine if it would be possible to reverse the effects of the lack of exercise and increase the VO_2 max in these patients. After follow-up, there was a significant decrease in the exercise group for Positive and Negative Syndrome Scale (PANSS) overall and for PANSS general psychopathology scores compared to the control group.[46] The study also reported a significant increase in the VO_2 max of patients in the exercise group after 12 weeks of the intervention.[46] The study suggests that exercise is important to the overall health of patients with schizophrenia and should be prescribed as an

intervention, and more specifically highlights the importance of treadmill exercises in managing the health of schizophrenia patients.

In the improvement of the mental health of patients with schizophrenia, Pilates has been shown to encourage significant improvements in many symptoms of schizophrenia, including postural stability.[47] After 6 weeks of training, the results showed that the Brief Psychiatric Rating Scale (BPRS) and Scale for the Assessment of Positive Symptoms (SAPS) scores of the patients are significantly improved in the Pilates group.[48] The results also showed no significant differences in the Calgary depression scale or Scale for the Assessment of Negative Symptoms (SANS) scores for the Pilates group.[48] Taken together, these data show that Pilates can serve as a therapeutic for patients with schizophrenia, with clear improvements to some symptoms.

3.2.2 Diet intervention

In the discussion of diet with respect to schizophrenia patients, it is important to note that there is no current treatment to prevent disease progression in patients who have already been diagnosed with schizophrenia. Current research is centered around prenatal disease prevention as well as interventions that lessen positive and negative symptoms in schizophrenia patients. Researchers have studied the eating habits of schizophrenia patients and have identified common trends in this population compared to the general population. Studies have found that increasing the consumption of essential vitamins, nutrients, and healthy foods is important in managing symptoms and for prenatal prevention. Studies on schizophrenia intervention are important for educating pregnant women to prevent the disease in their children and for improved maintenance of symptoms in schizophrenia patients.

In a Scottish study, McCreadie et al.[49] identified differences in eating habits of patients with schizophrenia compared to the general population and those without schizophrenia in the

social class with the poorest diet (social class V). The purpose for conducting this research was to determine why patients with schizophrenia were more likely to pass away from cardiovascular diseases, and to provide additional insight to the needs of these patients.

Men with schizophrenia are significantly less likely to consume cooked green vegetables, root vegetables, and rice five times per week or more; raw vegetables, salad, and pulses twice per week or more; and potatoes and pasta compared to the general population and social class V.[49] Compared to the general population, male consumption of breakfast cereal once per day or more is significantly higher than the general population.[49] Females with schizophrenia are significantly less likely to consume raw vegetables, salad, and pulses twice or more per week; skimmed or semi-skimmed milk; and potatoes, pasta, or rice five times per week compared to the general population.[49] Only the consumption of potatoes, pasta, or rice five times per week or more and pulses twice per week or more were significantly reduced in females with schizophrenia compared to females in social class V.[49] The study identifies that, in schizophrenia patients, the intake portions of vegetables and fruits was much lower than the recommended intake and diets included more fatty foods than the rest of the population.[49] The included study subjects were mostly unemployed and deprived of essential nutrients, although they still showed less nutritional intake than social class V.

Taken together, the data from this study indicates that people with schizophrenia are subject to poorer diets, possibly due to negative schizophrenia symptoms inhibiting their desire for healthy foods. Nonetheless, this is a large factor in the reason that patients with schizophrenia die from cardiovascular and other health related issues. The author's discussion of these results highlights the need for nutritional education and free or more affordable healthy foods for future intervention approaches for schizophrenia.

The importance of Vitamin D in pregnant women was highlighted by a study examining the outcome of rats deprived of vitamin D. A study used a Developmental Vitamin D (DVD) model, which included the investigation of schizophrenia risk in offspring after the mother was deprived of the nutrient. Deprived rats showed an increase in locomotive activity and spontaneous locomotion when given the noncompetitive N-methyl-D-aspartate antagonist, MK-801.[50] The results showed that 0.1 mg/kg of the dopamine receptor (DA2) blocking agent, haloperidol, resulted in a significant decrease in locomotive activity in MK-801-treated and DV-depleted animals compared to the controls.[50] The study also found that haloperidol was an effective therapeutic for reducing observed locomotion, indicating that DA signaling was altered when vitamin D was lacking and that the animal models were sensitive to this drug.[50] The researchers acknowledged the need for further testing on this relationship, but their findings signify the importance of vitamin D in the diet for prenatal prevention of schizophrenia. Mothers can eat a variety of foods with Vitamin D (Table 1) or safely increase their exposure to sunlight to correct minor Vitamin D deficiency.

Homocysteine is a type of amino acid used to make proteins in the body. Folic acid, among other vitamins, breaks down this amino acid in the bloodstream to other important substances. This breakdown of homocysteine to methionine occurs when folic acid donates a methyl group to homocysteine. Normally, the breakdown of homocysteine should leave small levels of the amino acid in the blood. A study analyzing the effects of low folic acid in pregnant women during each trimester found that elevated maternal homocysteine levels, specifically in the third trimester, showed a significant increase in the risk of schizophrenia in adult offspring.[51] This finding confirms that elevated levels of homocysteine during pregnancy can be a risk factor for schizophrenia. This is possibly due to folic acid deficiencies, since women have been shown

to have significantly higher levels of folate catabolism during pregnancy.[52] Table 1 shows some foods with folate that pregnant women can consume to avoid this deficiency.

Iron is an important nutrient for the body and, according to the World Health Organization[53], iron deficiency is the most common nutritional deficiency in the world. Pregnant women are reported to be most susceptible to the deficiency due to an increase in the need for iron to maintain an enlarged blood volume during pregnancy, as well as a growing blood supply for the fetus. Regarding brain function, iron is an appropriate coenzyme in dopamine synthesis. A previous study identified iron deficiency in pregnant patients by measuring hemoglobin levels, and then measured the development of schizophrenia spectrum disorders (SSD) in offspring two to three decades after the initial measurements. After adjusting for ethnicity and education, the study identified a five-fold increase in SSDs in offspring whose mothers were diagnosed with clinical anemia (hemoglobin levels of 10 g/dl or less) compared to offspring whose mothers were not.[54] No difference in the rate of SSD in non-anemic mothers was observed when the rate ratio was not adjusted for potential cofounders of the study.[54] This study highlights the importance of maintaining adequate iron levels during pregnancy to avoid a higher risk of schizophrenia in offspring. Iron levels can be restored with over-the-counter iron supplements or with the foods identified in Table 1.

Table. 1 Prenatal Diet Interventions for Schizophrenia

Nutrient	**Deficiency Impact**	**Foods with these nutrients**
Vitamin D[50]	Increased locomotion	Salmon, sardines, egg yolks, mushrooms
Folic acid[51]	Increased homocysteine levels in blood	Peanuts, whole grains, eggs, lettuce, spinach
Iron[54]	Unregulated dopamine levels	Red meat, beans, pumpkin seeds, spinach

The data from these studies identify the importance of selecting nutrients that are essential for the normal function of the brain and its components. Each study highlights the significance that diet has on maintaining a healthy lifestyle with schizophrenia and identifies measures that women can take to lower the risk of schizophrenia in their offspring. These articles characterize the potential consequences of nutritional deficiencies in mothers and the importance of maintaining a healthy diet to lower the risk of mortality in patients who are already burdened with schizophrenia. These results are critical in identifying possible preventative measures for declining the prevalence of the disease and for continued research to champion the needs of people suffering from schizophrenia.

3.3 Epilepsy

3.3.1 Exercise intervention

In people with epilepsy, exercise has been shown to significantly reduce seizure frequency. Research on this topic is limited due to initial uncertainties of the safety of exercise in epileptic patients from the 1960s to the 1990s.[55] Finally, in 1997, it was determined that scuba diving and skydiving are the only physical activities that should be prohibited in epileptic patients.[56] In patients with epilepsy, water sports bear the risk of drowning and falls, while other injuries are also common if a seizure occurs during exercise. There is no research on the effects of contact sports and head trauma with respect to potential worsening of epileptic symptoms.[55] Despite the limitations of how exercise should be implemented in patients with epilepsy, previous studies have identified positive effects of aerobic exercise on symptom management in epileptic patients.

A study done on 14 women with epilepsy found that aerobic exercise, such as dancing, could be used as a potential therapeutic for slowing disease progression. The 15-week exercise

program improved physical fitness and significantly reduced the number of seizures (2.9 seizures per week prior to the intervention; 1.7 seizures per week during the exercise sessions).[57] Although exercise was shown to help decrease seizure frequency on average, there were some patients whose seizures increased in frequency after 15 weeks.[57] The study also found that physical exercise must be maintained beyond the 15-week period to observe continuation of the positive effects in epileptic women[57]. The authors concluded that this intervention should not be recommended for all epileptic individuals, but patients should be encouraged to try it and, if it works for them, to continue exercising to maintain symptom control. Therefore, physical exercise can be recommended to patients with epilepsy to reduce seizure frequency.

To determine whether treadmill exercises reduce seizure frequency, physical activity was applied in female mice. Mice were subjected to either forced training for 4 weeks, with 5 sessions per week, or volunteer training that lasted for 30 days with free access to the running wheel. Interestingly, physical exercise was found to decrease seizure frequency significantly, but in only the voluntary group.[58] It is likely that mice in the forced exercise group experienced stress, and this may have blocked the effects of exercise on seizure frequency. Therefore, when applying these findings to humans, it would be important to ensure that patients are not experiencing any signs of stress or unwillingness to exercise since this stress may interfere with the beneficial effects of exercise.

3.3.2 Diet intervention

The ketogenic diet was founded in the 1920s with the sole purpose of treating epilepsy. As discussed previously, it is also being studied in the context of other neurological diseases like AD and PD, but its effects on patients suffering from epilepsy are more widely studied. A study from 1998 evaluated seizure control after 6 months on a ketogenic diet and found that 51% of

patients had greater than 50% response.[59] The researchers concluded that the ketogenic diet had a significant impact on seizure control and reduction, and should be implemented in the treatment of patients with epilepsy. The study reported some adverse events, such as kidney stones, which are common in ketogenic diets.[59] This led to alternative studies on modifications of the diet that result in the increased intake of essential food groups to prevent these adverse events. While many previous studies have characterized the ketogenic diet as an effective intervention in epileptic patients, there are still drawbacks from the diet that should be considered on an individual basis, and the diet should be altered to encourage the most beneficial outcome.

Although the ketogenic diet has been shown to work very well for patients with epilepsy, the characteristics of the diet can result in a shortage of the essential nutrients required to live a healthy lifestyle. One study used an alternative MAD diet on pediatric epilepsy patients to determine if the effects were compared to the ketogenic diet. A total of 70% of patients showed a greater than 50% reduction in seizures after 1 month on the MAD diet and 65% of patients had a greater than 50% reduction in seizures after 6 months.[60] They also found that the average seizure frequency decreased from 163 seizures per week to 40 seizures per week after 6 months of the trial.[60] The authors concluded that MAD produced comparable results to the Freeman et al.[59] study on ketogenic diet efficacy and therefore would be a better alternative diet for pediatric epileptic patients, as it allows greater flexibility to consume more essential food groups. In patients with epilepsy, the MAD diet has been shown to improve quality of life and reduce seizures. The MAD diet has also been used as an alternative diet to increase nutritional intake in epileptic individuals.

3.4 Parkinson's Disease

3.4.1 Exercise intervention

Aquatic therapy in PD patients is proven to have positive effects on functionality. In a randomized clinical trial, a group of patients with PD were instructed to perform aquatic ai chi or dry land therapy. Aquatic ai chi involved the movement of the upper and lower limbs in a coordinated manner, while standing at shoulder level in a pool of water. Dry land training involved the participation of strength training and aerobic exercises in a gymnasium. The study found that water-based physical activity resulted in a more positive effect on functionality and gait in people with PD.[61] Therefore, aquatic physical activity can be used as an intervention in patients with PD to help improve their symptoms and make living with the disease more bearable.

In a phase 2 randomized clinical trial, the effects of high-intensity treadmill exercises were analyzed in patients with PD. For 4 days per week for 26 weeks, participants exercised on a treadmill for 30 minutes at a level of either high intensity (80–85% maximum heart rate) or moderate intensity (60–65% maximum heart rate). The Unified Parkinson's Disease Rating Scale (UPDRS) was used as a measurement tool in the analysis of the results to determine whether treadmill exercise was efficient in reducing the symptoms of PD, and the high-intensity exercise was found to provide significant improvement in PD motor symptoms.[62] Although a phase 3 clinical trial needs to be completed for efficacy results, high intensity treadmilling looks to be a practical and safe way to manage PD motor symptoms.

3.4.2 Diet intervention

PD symptoms have been observed to improve significantly with nutritional interventions. Similar to schizophrenia, a lack of essential nutrients and food groups leads to progression of PD symptoms and can be managed through interventions that increase the consumption of healthy foods. Similar to AD and epilepsy, diets that allow for increased fat consumption are beneficial

for symptom management. However, diets low in fat have also been shown to improve the quality of life in people with PD.

There is evidence that PD symptom progression is associated with malnourishment in people with lower quality of life. A study measured nutritional status with a Patient-Generated Subjective Global Assessment (PG-SGA) and also used a Parkinson's Disease Questionnaire (PDQ-39) to measure quality of life in people suffering with PD. After analysis, patients were assigned to a standard care group, which provided patients with nutritional education, and an intervention group, which involved dietary advice and weekly follow-ups. Initial measurements indicated that those reporting lower nutritional status also had higher PDQ-39 scores, signifying a poorer quality of life.[63] They also found that both treatment groups had statistically significant positive changes in both their PG-SGA and PDQ-39 scores, but the intervention group showed greater improvements overall.[63] These results indicate that PD and malnourishment are associated, and that nutritional intervention can result in improvements in these patients.

A study looked at the effects of a low-fat diet and a high-fat, ketogenic diet on people with PD. For 8 weeks, subjects were administered a diet and blood glucose, ketone levels, and MDS-UPDRS scores are analyzed frequently. At the end of the study, blood glucose levels and ketone levels were significantly different between groups, a suspected result of the different diets.[64] Both diets resulted in a greater improvement in motor and non-motor symptoms in people with PD.[64] The ketogenic diet also resulted in a statistically significant greater improvement in non-motor function for patients with PD.[64] The study attempted to speculate that the ketogenic diet improves CNS and PNS function and that the low-fat diet increases dopamine levels in the substantial nigra, but these claims were not supported by the study. A separate study in rats supports the hypothesis that the ketogenic diet protects dopamine from degeneration by 6-

hydroxydopamine (6-OHDA).[65] This analysis of the ketogenic diet and low-fat diet indicates that increased or decreased fat consumption with maintained protein levels is associated with improvements in PD symptoms.

Table 2. Suggested Exercise Interventions for Brain Disease				
Disease	**Exercise method**	**Duration**	**Frequency**	**Intensity**
Alzheimer's Disease	Treadmill[36]	120 days	7 days/week	0.63 ± 0.08 km/day
	Swimming[37]	4 weeks	7 days/week	20–30 mins/day
Schizophrenia	Yoga[44]	21 days	7 days/week	60 mins/day
	Pilates[48]	6 weeks	2 days/week	50 mins/day
	Boxing/Circuit training[45]	4 weeks	3 days/week	45 mins/day
	Treadmill[46]	12 weeks	4 days/week	45 mins/day
Epilepsy	Dancing[57]	15 weeks	2 days/week	60 mins/day
	Treadmill[58]	30 days	free access	free access
Parkinson's Disease	Aquatic therapy[61]	10 weeks	2 days/week	35 mins/day
	Treadmill[62]	26 weeks	4 days/week	30 mins/day

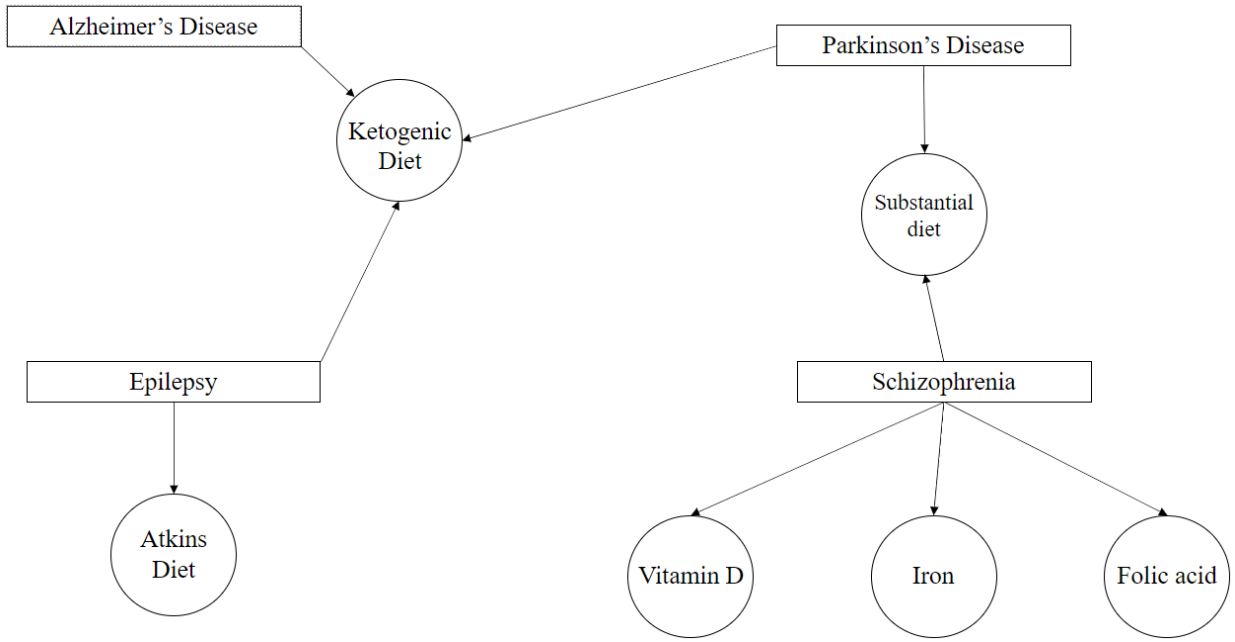

Figure 2. Map of Common and Unique Associations of Brain Diseases and Dietary Interventions

Each brain disease discussed in this review shares a common intervention with each other or has a distinctive diet intervention. This diagram shows how the interventions are connected.

4. DISCUSSION

There is substantial evidence that interventional methods do exist for reducing risk and/or managing symptoms of diseases like AD, schizophrenia, epilepsy, and PD. In focusing on exercise and diet interventions, the goal of this review was to highlight simple and healthy ways to intervene. For people with AD, it is important that aerobic exercises like treadmilling and swimming be practiced to reduce the risk of disease. Schizophrenia patients can practice aerobic exercises as well as anaerobic exercises like yoga and Pilates, which will lessen the extent of anxiety, depression, and other major symptoms of the disease. People suffering from epilepsy are encouraged to practice exercises like treadmilling and dancing, since these will not induce seizures and may reduce seizure frequency. Finally, PD patients have experienced symptom improvement when they practice aerobic exercises like aquatic therapy and treadmilling.

Interventions to reduce disease risk or improve symptom management can also be achieved through changes in diet. A healthy diet is important in many aspects, but current research has identified its specific impact on neurological diseases like AD, PD, epilepsy, and schizophrenia. There is significant evidence that the ketogenic diet plays a powerful role in symptom management. This forced change in the bodily metabolic processing has been shown to decline the intensity of symptoms in AD, PD, and epilepsy. Studies on schizophrenia show that the risk of the disease can be reduced before birth if the mother continues to maintain healthy folic acid, vitamin D, and iron levels, and pregnant women are at greater risk for deficiency of these nutrients. Maintaining a healthy and substantial diet while suffering from schizophrenia and PD is also important for managing the symptoms of these diseases. There are many studies

showing that dietary interventions can serve to prevent or slow these deadly neurological diseases.

Future research on this topic should look more closely at the long-term effects of these interventions. Future studies should also specify an ideal exercise and diet regimen for each disease to properly communicate this to the health care providers who are treating patients suffering from brain diseases. For now, affected patients can focus on maintaining healthy lifestyles and incorporating some of these interventions into their daily routine with the guidance of a healthcare professional. This literary review summarizes potential preventative and interventional methods for managing the unbearable symptoms of only a few of many neurological diseases.

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