

**Alzheimer's Disease and the Role of Beta-Amyloid: A Literature Review**

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### **Abstract**

Alzheimer's disease is a devastating form of dementia which is eventually fatal. Beta-amyloid and neurofibrillary tangles are the two main hypothesis associated with this neurological disorder. The more supported and accepted theory involves the accumulation of beta-amyloid into plaques. Topics such as pathophysiology, risk factors, and intervention are included within this review while maintaining a focus on beta-amyloid peptides. Great advancements have been made in this field of research; however, much remains unknown.

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## **Chapter 1: Introduction**

When the most complex organ of the human body becomes diseased, the impacts are drastic. The brain is the most powerful and significant part of our bodies. Not only does this organ control all of our movements, sensations, and physiological functions, but it also allows us to have thoughts and emotions, interact with other people, have a sense of self, and attach meaning to the life it enables. With such an extensive array of capabilities, the brain is bound to be extremely complex. This complexity allows us to do so much, but also poses a great challenge when trying to understand and treat the brain itself.

While there are many neurological diseases present among our population, one in particular stands out as it has been labeled as the seventh leading cause of death in the United States (CDC, 2022). This is Alzheimer's disease: one of the most common and devastating conditions affecting the brain that we face today. An article published in 2021 stated, "it was estimated 6.5 million Americans aged 65 plus live with the disease with a significant projected increase year over year" (Stellick, 2021). Although this neurological disorder has long been studied since its identification in 1906, researchers still struggle to close the gaps that exist within our comprehension of the disease. With that being said, much progress has been and continues to be made in efforts to extend our knowledge of Alzheimer's disease in all aspects.

### **Study Overview**

This research will take the form of a literature review and is intended to build an understanding of what is occurring within the brain from a physiological standpoint as the disease initiates and progresses, with a focus on the beta-amyloid hypothesis. The results will also cover, although more briefly, the clinical categories of Alzheimer's disease and the role of

genetics in early-onset cases. Additionally, the review will conclude with research on risk factors, lifestyle recommendations, and recent strides made in diagnosis and treatment trials.

## **Research Questions**

Main question:

- What role do beta-amyloid plaques play in the progression of Alzheimer's disease?

Secondary questions:

- What are neurofibrillary tangles, and what role do they have in this disease?
- What is oxidative stress and neuroinflammation?
- How are beta-amyloid plaques formed, and what causes an accumulation?
- Where do we currently stand in terms of the development of effective diagnosis and treatment strategies?
- What are some ways we can alter our lifestyles to reduce the risk of developing Alzheimer's disease later in life?

## **Background**

The search for answers concerning Alzheimer's disease has been a task for several decades now and continues to be highly researched as experts work towards developing accurate, evidence-based conclusions. This is necessary as there is still no clear cause for this neurological disorder, nor a cure.

To better understand the terms used, it is important to acknowledge that Alzheimer's disease is one of the many subtypes of dementia. The term *dementia* is very commonly used as it is a way to broadly refer to this form of neurological decline without having to specify the exact kind. Examples of other forms are vascular, mixed, and frontotemporal dementia. When people

first hear the words ‘dementia’ or ‘Alzheimer’s,’ many may automatically think of memory loss. While this is true, these neurological disorders also present various other symptoms that together, result in a stronger, more detrimental impact.

As mentioned, Alzheimer’s disease was identified in 1907. It was Alois Alzheimer who made this discovery after studying his patient, Auguste Deter. She presented various severe symptoms that affected her behavior, language, and perceptions. Her diagnosis took place at the age of fifty-one, meaning she would have been classified as an early-onset case (Valdez-Gaxiola, 2024). According to Valdez-Gaxiola, “after Auguste Deter’s death in 1906, Alois Alzheimer analyzed her brain and identified “neuritic” plaques and neurofibrillary tangles, which he linked to the patient’s condition (Valdez-Gaxiola, 2024). This discovery has proved to be a massive contribution to the field and continues to stand as the basis of all AD research today.

### **Significance**

This research is important to the general public because Alzheimer’s disease affects multitudes of people, so even if a person may not get this disease, it is likely someone they know, or love will. This review provides specific scientific information about pathophysiology, beta-amyloid hypothesis, and genetic contributions that may appeal to those interested in neuroscience or biological sciences. The last section of results may hold the most personal significance for the audience as diagnosis and treatment issues are discussed, as well as various risk factors and lifestyle contributors. This is important as this information can be utilized by the reader in their daily lives to help reduce their likelihood of developing this disease as they age. Additionally, sharing the results of this research may help to spread awareness for Alzheimer’s disease.

## Definitions

- Alzheimer's disease: "an incurable neurodegenerative disease characterized by progressive decline of cognitive abilities" (Veerabhadrapa, 2020).
- Dementia: "any disorder in which a significant decline in a person's previous level of cognition affects their ability to perform occupational, domestic, or social activities" (Valdez-Gaxiola, 2024).
- Early-onset Alzheimer's disease (EOAD): "Alzheimer's disease onset before 65 years of age" (Valdez-Gaxiola, 2024).

## Abbreviations

- NFT: Neurofibrillary tangles
- ROS: Reactive oxygen species
- A $\beta$ : Beta-amyloid peptides
- AD: Alzheimer's disease
- APP: Amyloid precursor protein

## Limitations

There were several limiting factors affecting the process and outcome of this research. The main challenge faced was the time frame in which the research and final thesis must be completed within. Only fifteen weeks were granted as this process had to align with the duration of a single semester. It is important to note that this thesis was completed alongside a regular course load, making it difficult to dedicate a large amount of time. Another limitation is the complexity of the processes described in the reviewed literature. Many of these topics were fairly advanced and unfamiliar to me, resulting in more time spent on each academic article or study. The final limitation is that the field of neuroscience still lacks a complete understanding of

Alzheimer's disease, specifically surrounding its cause. The absence of a definitive cause leads to slightly more open-ended research in some areas and fewer answers regarding diagnosis, treatments, and a cure.

## Chapter 2: Methodology

This thesis will take the form of a literature review. It will be based on reliable primary sources selected from certain databases accessed through the Mondor-Eagan Library at Anna Maria College. The databases that have been utilized in the process of gathering articles for research are as follows: CINAHL Plus, PubMed Central, Gale OneFile Health and Medicine, and Google Scholar. Within these databases, the terms “Alzheimer’s disease,” “pathophysiology,” “beta amyloid,” “prevention,” “lifestyle,” “intervention,” “treatment,” “history,” and “dementia” were used to generate articles that would exhibit relevancy to the various subtopics of this thesis (See Appendix Figure 1: PRISMA Flowchart).

In order to include important articles while still keeping the information timely and relevant, I chose to only review articles that have been published within the last fifteen years. This specific date range allows for the new findings and advancements to be included in the research but does not exclude the slightly older articles that may help build a strong foundation for this thesis. Since this is such a significant and heavily researched topic within the field of neuroscience currently, thousands of articles match even a refined and advanced search. The amount of data available on this topic is beneficial and detrimental when gathering the sources. While abundant information is available, it can be difficult to identify which articles to use. This has led to only the first ten pages of links presented by a given database to be regarded following a search. This is another crucial aspect of the criteria for inclusion. Additionally, all articles included in this literature review must be available in full text, peer-reviewed, and written in English. Lastly, it is important to note that the timeline of this thesis was limited to only one semester, meaning some areas of research may be less extensive due to the constraint on time.

## Chapter 3: Results

### Introduction

Experts have long been working towards accurately understanding the physiological processes of Alzheimer's disease, and although much headway has been made, many questions remain unanswered. This review primarily focuses on what we do comprehend about the mechanisms of this disease thus far.

In order to appreciate the complexity and severity of AD, it is worthwhile to dive into its means of emergence and progression with emphasis on the beta-amyloid hypothesis. Additionally, factors that affect one's risk of having the disease will be discussed, as well as diagnostic and treatment efforts.

### Pathophysiology

Typically, our brains contain eighty-six billion neurons, which are in constant communication, sending and receiving signals. This occurs due to an unimaginably rapid sequence of events that creates a synapse. To start, an action potential travels down the neuron's axon, and neurotransmitters are then released from the presynaptic terminals into the synaptic cleft. From here, those neurotransmitters bind to the receptors of the neighboring neuron, and that information is passed on. The disruption of these synapses or transmission of signals is a major characteristic of Alzheimer's disease, as this prevents neuronal function (Kalat, 2019).

The inhibition of neural connectivity is accompanied by neuronal death. Both processes are far from simple and likely a result of numerous factors. Scientists view beta-amyloid plaques and neurofibrillary tangles as the main biomarkers of Alzheimer's disease. Beta-amyloid plaques are the result of these specific protein fragments accumulating (Kalat, 2019). The plaques are largely present in extracellular spaces around neurons, which is how communication between

two given neurons may be interfered with. In an article published in *Aging and Disease*, Deng states that these beta-amyloid plaques are insoluble and cause damage to the mitochondria, synaptic dysfunction, oxidative stress, neuroinflammation, neuronal loss, and learning and memory impairment (Deng, 2024). In addition, the development of tau pathology in AD is accelerated as a result of the activation of tau protein kinase by accumulated beta-amyloid proteins (Deng, 2024). The function of beta-amyloid in healthy individuals is unclear; however, the purpose of tau is understood. Normally, tau protein is associated with microtubules and remains attached, providing stabilization, structure, and nutrient transportation for the cell. Pathological changes in an instance, such as AD, result in the hyperphosphorylation and eventual detachment of Tau proteins from a microtubule. The now-isolated proteins pair and alter in shape, which causes neurofibrillary tangles to form (Deng, 2024). Since these tangles of Tau proteins are located within the cell, its ability to carry out its intended functions is impeded due to its physical presence.

Interesting pathological connections between  $A\beta$  and Tau are coming to light. An article reviewed in this research suggested that three key pathways demonstrate NFT formation as a result of internalized beta-amyloid buildup. This article by Sadigh-Eteghad explains that first,  $A\beta$  activates tau kinases which leads to tau hyperphosphorylation, causing the formation of NFT (Sadigh-Eteghad, 2014). Next,  $A\beta$  promotes the dysfunction of proteasome, decreasing the degradation of tau and finally,  $A\beta$  causes NFT formation through the activation of caspase-3 as tau truncation and aggregation occur (Sadigh-Eteghad, 2014). These pathways all stem from beta-amyloid within the cell, which is brought in by the cell membrane receptors (Sadigh-Eteghad, 2014). These links between beta-amyloid and neurofibrillary tangles differ, as most of

what we know about beta-amyloid functions occurs in extracellular space. These examples demonstrate ways in which A $\beta$  may affect Tau proteins to promote pathogenesis.

The presence of beta-amyloid plaques in the brain is associated with other processes that encourage neurodegeneration. An example of this is oxidative stress, which is more abundant in people with AD (Fanlo-Ucar, 2024). It is characterized by an increased amount of reactive oxygen species compared to the number of antioxidants in the brain (Fanlo-Ucar, 2024). The majority of ROS are free radicals, which are unstable, reactive molecules due to the fact that an electron is unpaired. When the antioxidants in the brain are outnumbered by these free radicals, those antioxidants are unable to effectively combat them. The reactive oxygen species are then able to cause damage to other molecules and cells. According to an extensive review article on the role of A $\beta$  in inflammation and oxidative stress, “The brain is particularly susceptible to oxidative damage due to its high oxygen consumption, abundant lipid content, and relatively low antioxidant defenses” (Fanlo-Ucar, 2024). It is known that one of the major origins of free radical production is the mitochondria which is the organelle utilizing these large amounts of oxygen. The mitochondria are responsible for creating energy for the cell’s use, but it is during this process, especially the final stage called the electron transport chain, that ROS are released. Oxidative stress is especially relevant to Alzheimer’s disease as it “contributes to the production and aggregation of A $\beta$ . Furthermore, A $\beta$  itself can generate ROS, creating a vicious cycle of oxidative damage and A $\beta$  production” (Fanlo-Ucar, 2024).

Another pathological event associated with Alzheimer’s disease is neuroinflammation. Within the brain, “the accumulation of A $\beta$  triggers an inflammatory response, leading to neuronal loss and synaptic dysfunction that contribute to the cognitive deficits observed in AD patients (Fanlo-Ucar, 2024). When thinking of inflammation responses, we typically think of a

wound healing or fighting a cold; however, the outcomes of an inflammatory response are not always as beneficial as we may think. An example is the inflammatory response of glial cells associated with Alzheimer's disease. In the early stages of this neurodegenerative disease, microglia and astrocytes become activated by the presence of beta-amyloid aggregation and tau (Deng, 2024). At this time, these cells are classified as M2 and A2 phenotypes, meaning they have anti-inflammatory properties and work to protect the neurons by attempting to clear these accumulations via phagocytosis and cytokine release (Deng, 2024). Despite the cell's attempt to clear abnormal A $\beta$  and tau, they typically fail to fight effectively enough against the advancement of AD, and a person's case progresses to a later stage. In an article focused specifically on microglia and astrocytes, Deng explains that as the disease progresses, microglia polarize from M2 phenotypes to M1 and AD pathology is then exacerbated because microglia release reactive oxygen species and pro-inflammatory factors (i.e., IL-1 $\beta$ , IL-6, TNF- $\alpha$ , and IL-18) (Deng, 2024). A similar phenomenon occurs with astrocytes. Not only is this the main source of neuroinflammation in AD patients, but the release of reactive oxygen species from M1 cells further contributes to the amount of oxidative stress in the brain. Ultimately, neuroinflammation and oxidative stress are thought to be two significant factors in the progression of Alzheimer's disease.

A known specific order of these events or path of progression is not necessarily followed in each case of AD. While cases may have multiple shared pathological changes, this disease is far from linear, and its course will vary from person to person (Valdez-Gaxiola, 2024). Overall, as more beta-amyloid and tau proteins aggregate, more function is observably lost. Something we do know is that without the ability to function, the specialized nerve cells will eventually die, and this usually happens in certain areas first. Short-term memory is typically the first ability

lost. According to Sadigh-Eteghad and others, deposition of A $\beta$  and NFT are present in the hippocampus, neocortex, and other subcortical structures associated with cognition years before the clinical signs of Alzheimer's disease appear (Sadigh-Eteghad, 2014). This would explain why memory is typically one of the first signs of Alzheimer's disease, as the hippocampus is responsible for this cognitive function.

While the previously discussed theories of the pathophysiology of Alzheimer's disease may hold significance, the beta-amyloid hypothesis is ultimately the most evident and specific to this disorder. A neurotherapeutic review states, "amyloid plaques composed primarily of aggregated A $\beta$  and neurofibrillary tangles composed of microtubule-associated protein tau are neuropathological diagnostic criteria for AD. But, in contrast to amyloid plaques, neurofibrillary tangles are less specific for AD and are seen in a greater variety of neurodegenerative diseases, such as progressive supranuclear palsy, corticobasal degeneration, and subtypes of frontotemporal dementia" (Gunnar, 2015). For this reason, we turn our attention to the production, effects, and clearance of beta-amyloid plaques.

### **Beta-Amyloid Hypothesis**

Now that the significance and applications of the beta-amyloid hypothesis have been reviewed, it is important to go into further detail to understand the specifics of the amino acid peptide, A $\beta$ , such as its generation. Beta amyloid peptides originate from a much larger protein known as the amyloid precursor protein. A recent review states "The amyloid precursor protein (APP) is an integral type I transmembrane glycoprotein present in most human cells" (Fanlo-Ucar, 2024). Beta-amyloid proteins come from this precursor protein through the process of cleavage carried out by certain enzymes. In this procedure, there are two pathways: non-

amyloidogenic or amyloidogenic. In the non-amyloidogenic pathway, the APP is divided by  $\alpha$ -secretases and then  $\gamma$ -secretase, which creates the peptide P3, lacking the tendency to form plaques. In the amyloidogenic pathway, amyloid precursor protein is cleaved by  $\beta$ -secretase, then  $\gamma$ -secretase, which produces the beta-amyloid peptide (Valdez-Gaxiola, 2024). This specific pathway is responsible for the generation of beta-amyloid and, therefore, the plaques that these peptides may end up creating (See Appendix Figure 2: A $\beta$  Formation).

As previously mentioned, A $\beta$  can exist within the brain without causing degeneration to the neurons, although their normal function is still not understood. So, what causes an excess amount of these peptides to be produced and consequently accumulate? There are many proposed answers to this question. In the previous section of this review, oxidative stress and neuroinflammation were looked at, both of which pertain to this question.

Another suggested cause for the formation of A $\beta$  plaques is connected back to the amyloidogenic pathway. Two main variations of the amino acid created are A $\beta$ <sub>40</sub> and A $\beta$ <sub>42</sub>. As mentioned by Murphy and LeVine, “The slightly longer forms of A $\beta$ , particularly A $\beta$ <sub>42</sub>, are more hydrophobic and fibrillogenic, and are the principal species deposited in the brain” (Murphy, 2010). The fact that A $\beta$ <sub>42</sub> accounts for a majority of the A $\beta$  found in plaques may be as important as an increased ratio of A $\beta$ <sub>42</sub> to A $\beta$ <sub>40</sub> can suggest the onset or increased likelihood of Alzheimer’s disease. Within an article reviewed, a study was mentioned that found “higher neurotoxicity has been reported with samples of higher A $\beta$ <sub>42</sub>/A $\beta$ <sub>40</sub> ratios” (Gu, 2013).

Another highly supported answer lies within our genetic makeup. Early-onset cases of Alzheimer’s disease are generally due to mutated genes, whereas late-onset cases typically do not arise solely from genetic factors (Valdez-Gaxiola, 2024). According to a recent article, “In EOAD, the presence of pathogenic variants in the *APP* gene can trigger an excessive production

of A $\beta$  protein, and variants in *PSEN1* and *PSEN2* may precipitate a reduction in  $\gamma$ -cleavage, fostering the production of longer and more toxic forms of A $\beta$ , contributing to the onset of AD” (Valdez-Gaxiola, 2024). This statement shows that certain mutations in the gene amyloid precursor protein have the ability to cause unusually high amounts of A $\beta$  to be released in the brain. This is alarming as we know that elevated levels of beta-amyloid peptides increase the likelihood of plaques forming, which ultimately leads to synaptic dysfunction and neuronal death. The article above by Valdez-Gaxiola and others, mentioned that PSEN1 and PSEN2 cause the  $\gamma$ -cleavage to be altered in the amyloidogenic pathway, causing longer forms of beta-amyloid peptides to be produced. This can also be interpreted as a disruption of the ratio between A $\beta$ <sub>42</sub> and A $\beta$ <sub>40</sub>. The form, A $\beta$ <sub>42</sub> has two additional amino acids and is liable for the majority of A $\beta$  plaque composition. The genetic factors associated with late-onset cases are far less significant to the direct generation of beta-amyloid. The article states that “alternatively, in LOAD, the mechanisms underlying the accumulation of A $\beta$  are more complex. While individuals carrying the *APOE $\epsilon$ 4* allele face an elevated risk of LOAD, it does not directly initiate the overproduction of A $\beta$ ” (Valdez-Gaxiola, 2024). There are far more factors involved in the onset of this clinical category of AD, and the exact causes have yet to be determined.

The final factor in A $\beta$  accumulation to be reviewed is the inhibition of A $\beta$  clearance within the brain. This is a fairly complicated aspect; however, there is simplicity in the fact that the amount of A $\beta$  can be regulated by the rate at which it is created and cleared. When the rate of A $\beta$  clearance is hindered, more will be present in the brain. A $\beta$  may be removed from the brain in several different ways; some involve enzymes, while other mechanisms do not. According to an article by Yoon and Jo, “nonenzymatic pathway includes interstitial fluid drainage, uptake by microglial phagocytosis, and transport across the blood vessel walls into the circulation. Multiple

A $\beta$ -degrading enzymes (ADE) implicated in the clearance process have been identified, which include neprilysin, insulin-degrading enzyme, matrix metalloproteinase-9, glutamate carboxypeptidase II and others” (Yoon, 2012). To reduce the neurotoxicity of A $\beta$ , these enzymes may cleave the A $\beta$  peptide into smaller pieces. These smaller pieces would not contribute to the progression of the disease. When any of these mechanisms are prevented, AD becomes more likely.

Although we lack definitive answers as to what causes an increase of A $\beta$  in the brain, research has suggested that some combination of these events may be to blame. It is important to note that due to the extensive number of theories researched, not all have been included. These beta-amyloid plaques are the most distinctive feature of Alzheimer’s disease that has been established to date.

### **Risk Factors, Lifestyle, Diagnosis, and Treatment**

It is troubling to see such a devastating disease with increasing prevalence still lacking a concrete solution or way of definite prevention. With that being said, we are headed in the right direction. Lifestyle changes, methods for diagnosis, and effective treatment drugs are all areas that efforts have been directed to, and progress has been made. All three of these avenues are important to the end goal of reducing the occurrence and fatalistic outcomes of AD.

Understanding the preventable risks associated with this disease is the first step in reducing one’s likelihood of having a late-onset case. Because EOAD is primarily a result of our genetic makeup, LOAD is the focus when discussing lifestyle changes and prevention. Lifestyle and environmental factors may still play a role in the risk of EOAD; however, these factors have a much greater effect on the chance of LOAD onset. Although age is said to be the biggest risk

factor of AD, aging is inevitable, so the factors that are discussed in this section are those that we are able to influence (See Appendix Figure 3: LOAD and EOAD Risk Factors).

Prolonged hypertension, type 2 diabetes, obesity, high cholesterol, and other cardiovascular problems have all been associated with a heightened risk of Alzheimer's disease (Valdez-Gaxiola, 2024). The connection between cardiac and general brain health has long been accepted. Understanding that these health issues have the potential to contribute to the pathology of this fatal disease is concerning, especially with how common diabetes and cardiovascular problems are. Reducing these health conditions in our communities would also lead to a decrease in AD cases. It is very important that we aim to lower these risks in a timely manner as AD cases are projected to continue increasing. Fortunately, we can make choices in our day-to-day lives that reduce or prevent these conditions. One habit that is known to cause many dangerous health issues, including type 2 diabetes, high blood pressure, bad cholesterol, and cardiovascular disease, is smoking cigarettes. According to an article written just months ago, "Smoking is a significant risk factor for LOAD, and it is a factor that individuals can actively change. It is thought to promote oxidative stress and inflammation, processes that may exacerbate neurodegeneration" (Valdez-Gaxiola, 2024).

We can make additional lifestyle changes to better protect our brains against Alzheimer's disease. One key change is diet. It is clear to most that the foods we choose to consume have a direct impact on our health; however, these foods have much more of an effect on us than we tend to realize. Diet can alter people's chances of having many serious diseases and disorders throughout their lifetime, including Alzheimer's. As per an article published in the *Journal of the Council on Nutrition*, "presently, dietary recommendations for AD patients include fruits, vegetables, lean meats, omega-3 sources such as salmon, whole grains and low-fat dairy

products, basically with increase of fresh produce and decrease of processed refined foods” (Alzate, 2018). These recommendations closely align with the guidelines of the Mediterranean diet. In a preventative effort, this diet should be followed throughout earlier years as well, not only after onset. This diet is high in vitamins and nutrients, which help supply the brain with antioxidants that fight to reduce oxidative stress and inflammation. Lidia Alzate states, “In a study involving 1880 non-AD elderly in New York City related the combination of Mediterranean diet and regular physical activity with significant reduction of AD risk (Alzate, 2018). While we can receive the proper nutrients and vitamins for our brain through the foods we ingest, evidence has shown that supplements are an effective way to supply your brain with vitamins essential for brain health that one may be lacking through their diet. Many different vitamins and minerals are necessary for the functions of our brain; however, some in particular stand out in relation to AD. In an article reviewed, “a strong association between low blood folate and brain atrophy was described. Decreased levels of folic acid and B12 vitamin along with increasing levels of homocysteine are associated with AD and vascular dementia” (Alzate, 2018). Vitamins such as these work to decrease the amount of homocysteine in the brain. This is crucial as homocysteine is an amino acid that may cause inflammation and damage if its levels are heightened. Overall, while making these dietary choices will not completely prevent AD from occurring, it does provide the body with the necessary nutrients and antioxidants needed to work against AD. This occurs both directly in the brain but also through the prevention of health conditions such as hypertension and obesity.

Another aspect of Alzheimer’s disease that continues to be explored is the diagnosis of the disease. Unfortunately, AD cannot be diagnosed with full certainty until the patient is deceased, and according to a 2018 article, “Accuracy in diagnosis require examination of tissue

remains of the brain; however, diagnosis can be done by a combination of clinical assessment and modern radiologic methods with about 80-90% of certainty in diagnosis” (Alzate, 2018). A positron emission tomography (PET) scan may be done in order to identify the presence of beta-amyloid plaques in the brain (Alzate, 2018). It may be difficult for a patient to receive such imaging as it is quite costly. Also, symptoms of this neurological disorder can be confused with other conditions or subtypes of dementia and may lack severity until later stages.

An alternative method of diagnosis for AD exists. This involves the detection of beta-amyloid peptides within the bodily fluids of those suspected of having this disease. A review article focused on diagnosis states that “quantification of Ab peptides can be informative for pre-clinical AD, even before amyloid deposition rises to a level that is visible by PET (positron-emission tomography) imaging” (Veerabhadrapa, 2020). Being able to diagnose patients at an early stage is incredibly helpful as it allows medical professionals to intervene with strategies to potentially slow the disease progression. This method is primarily done using cerebrospinal fluid; however, blood and saliva are other fluids that continue to be explored as sample sources. Cerebrospinal fluid is the chief fluid used in the process, as beta-amyloid peptides are more highly concentrated in comparison to other fluids. Within the cerebrospinal fluid, tau and  $A\beta$  are biomarkers. On a more specific level, Veerabhadrapa and the other authors suggest “ $A\beta_{1-40}$ , and in particular, the ratio of  $A\beta_{1-42}/A\beta_{1-40}$ , have been shown to improve the routine diagnostic work up of AD and to provide an increase in both sensitivity and specificity compared with  $A\beta_{1-42}$  alone” (Veerabhadrapa, 2020). While this cerebrospinal fluid detection appears to be sufficient, it is invasive and much less convenient than the other fluids being explored. Ideally, blood or saliva will be a reliable and accessible option for early diagnosis of AD in the near future.

As mentioned earlier in this review, there is no definite cure for this disease. A large amount of research has been delegated to the task of eventually reaching a form of treatment, and much progress has been made. Currently, there are multiple drugs being developed and tested that seem promising. One, in particular, is Donanemab. This is an immunotherapy drug that targets and reduces beta-amyloid plaques in the brain. An article from 2023 states, “There was a favorable reduction in amyloid plaque levels which depended on baseline amyloid levels such that patients with lower amyloid plaque levels were found to have complete amyloid clearance. Other favorable outcomes were a reduction in the accumulation of overall tau levels and relatively lower functional/cognitive decline with Donanemab” (Rashad, 2023). These outcomes show that this drug may be effective for cases of Alzheimer’s disease that are in the earlier stages of progression. Since this article was released, the United States Food and Drug Administration has approved the use of Donanemab via injection for those who have a mild form of Alzheimer’s disease (FDA, 2024). This is a great accomplishment and is the first approval of many to come. More research and trials continue to be done as experts work towards a definitive cure for all affected by this devastating disease.

## Chapter 4: Discussion

### Summary

The brain is an amazingly complex organ that is the basis of everything we do. Every movement, emotion, sensation, and memory come down to the brain. This all happens as a result of the sending and receiving of information involving specialized brain cells called neurons. This communication, in other words, a synapse, is disturbed by the characteristics of Alzheimer's disease: beta-amyloid plaques and neurofibrillary tangles. NFTs are composed of tau proteins that are present within the neuron and inhibit its normal functions. While this is important, A $\beta$  plaques are a much more reliable hallmark of this disease and stand as the focus.

Throughout this review, the beta-amyloid hypothesis has been researched in order to develop an in-depth understanding pertaining to the involvement it has in the physiological processes of Alzheimer's disease. Additionally, the generation of A $\beta$  plaques was researched, as well as risk factors, diagnosis, and treatment advancements.

### Conclusion

Through this literary research, the importance of beta-amyloid peptides has become increasingly clear. A $\beta$  occurs in normal amounts within a healthy brain without causing harm. Problems arise when these peptides exist in large numbers and accumulate into plaques. When many A $\beta$  peptides aggregate to form a plaque in the extracellular space surrounding neurons, the connections between these neighboring cells may be inhibited. This causes a lack of synaptic activity and, eventually, neuronal death. Many processes contribute to this toxicity in the brain; however, A $\beta$  is involved in a large majority.

Oxidative stress and neuroinflammation are two of the main processes discussed within the pathophysiology section of this review. It has been found that oxidative stress encourages the accumulation of beta-amyloid within the brain, which initiates a harmful cycle as  $A\beta$  can release reactive oxygen species, which results in further oxidative stress taking place (Fanlo-Ucar, 2024). Also linked to this sequence of events is neuroinflammation. This research has shown that an increased presence of  $A\beta$  in the brain causes glial cells to activate and eventually polarize into pro-inflammatory phenotypes. These M1 cells not only cause neuroinflammation, but also have the ability to contribute more ROS to the situation. This increases oxidative stress once again, which ultimately leads to more  $A\beta$  accumulation, buying into this cycle.

The role of  $A\beta$  in Alzheimer's disease was further understood by looking at its generation and clearance. Beta-amyloid peptides are created through an amyloidogenic pathway. The cleavage of the peptide is not always consistent, resulting in different forms. It was found that  $A\beta_{42}$  was much more pathogenic than  $A\beta_{40}$ , so an unfavorable ratio may indicate AD. This research has shown that this ratio may be detrimentally altered due to genetic variations, resulting in more amyloid plaques being created. The clearance is equally, if not more important to the progression of AD. The rate at which  $A\beta$  is cleared must compare well to the rate at which it is generated. Inhibition of clearance may result in an increased risk of onset. The damage  $A\beta$  does to the brain is a result of its presence, in both amount and placement. If plaques have not formed, functions are likely to continue.

Through researching the risk factors, diagnosis, and treatment developments, a few conclusions were drawn. Multiple preventable health conditions are linked to an increased risk of developing Alzheimer's disease, such as type two diabetes, hypertension, and obesity. It is suggested that one follow a Mediterranean diet, refrain from smoking, and remain active both

mentally and physically. These preventative measures reduce oxidative stress within the brain, helping to combat A $\beta$  accumulation.

Next, diagnosis and treatment advancements were researched. Although early diagnosis has proved to be difficult, the detection of biomarkers through body fluids appeared to be promising. It is a method that mainly detects A $\beta$  peptides within the cerebrospinal fluid, but there are hopes to eventually have the capabilities of using blood or saliva in order to conveniently diagnose people. The main forms of treatment being developed are immunotherapy drugs. In this research, Donanemab is mentioned. It was found to have been approved by the FDA to treat cases of early Alzheimer's stages. It does this by reducing the A $\beta$  plaques within the brain.

Lastly, it is necessary to conclude that this research supports the fact that there are many aspects of the disease that are still not understood. Despite the vast amount of time and resources committed by experts worldwide, a complete comprehension of Alzheimer's disease does not exist.

Through this research, it is evident that A $\beta$  remains a key factor in all processes and findings, proving its relevance in every Alzheimer's disease aspect examined within this review.

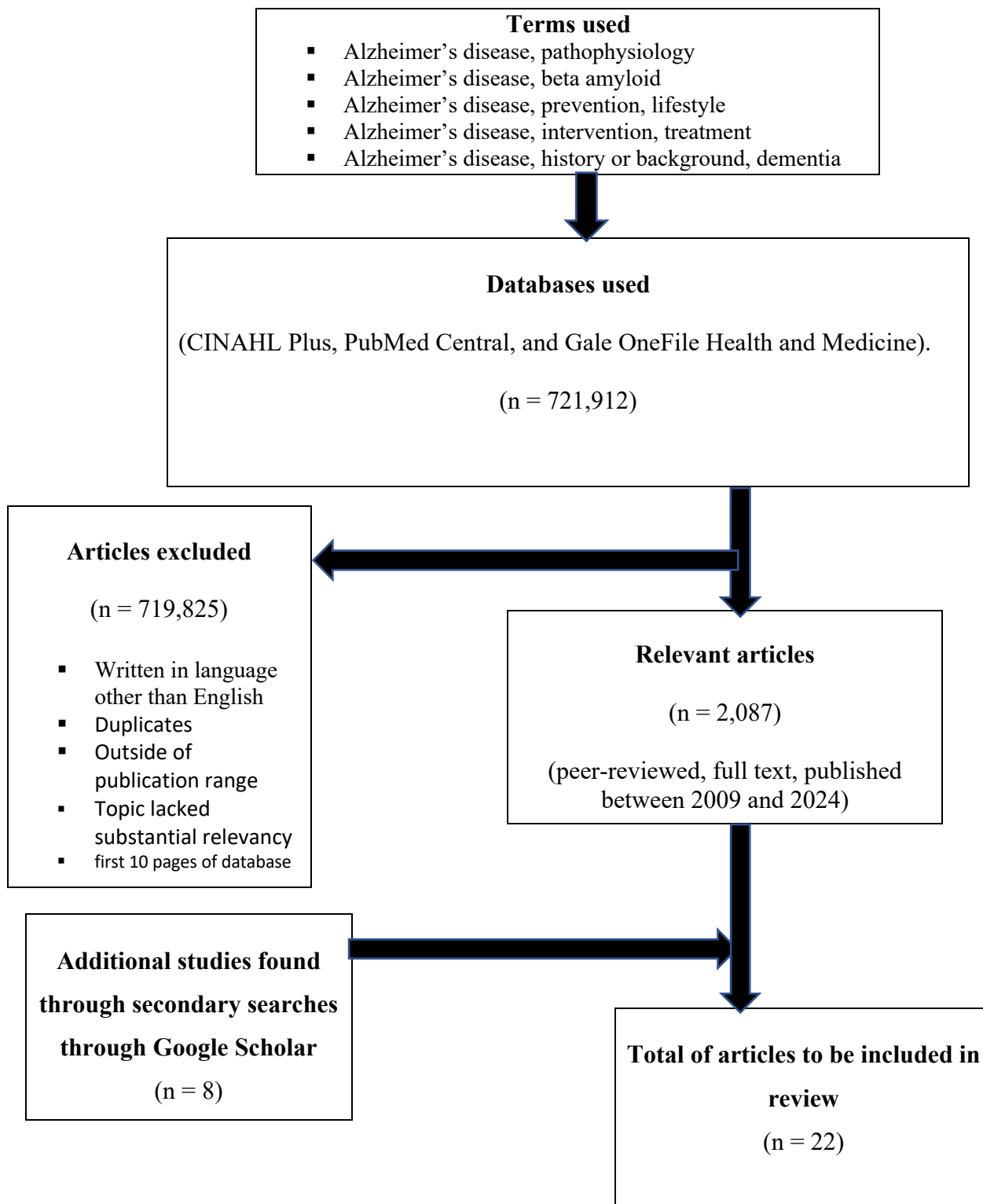
### **Recommendations for Further Research**

Alzheimer's disease is already a very heavily researched topic, and for good reason. With a disease as common and misunderstood as this one, an abundance of research is needed. I would like to see more research geared towards creating effective early diagnosis methods that could be easily accessible to the public upon first signs. With treatments becoming available, but only for mild cases, there must be an emphasis on early detection in order to treat these patients before their condition progresses past the point of treatment. I also recommend further research be done

on the risks associated with certain habits. Sharing this information with the public is incredibly important as our unhealthy habits put us at further risk for this fatal neurological disease. The incidence of AD is projected to continue to increase, and many people remain unaware that their brain health is being jeopardized by some of their daily choices.

## Appendix

**Figure 1: PRISMA Flowchart**



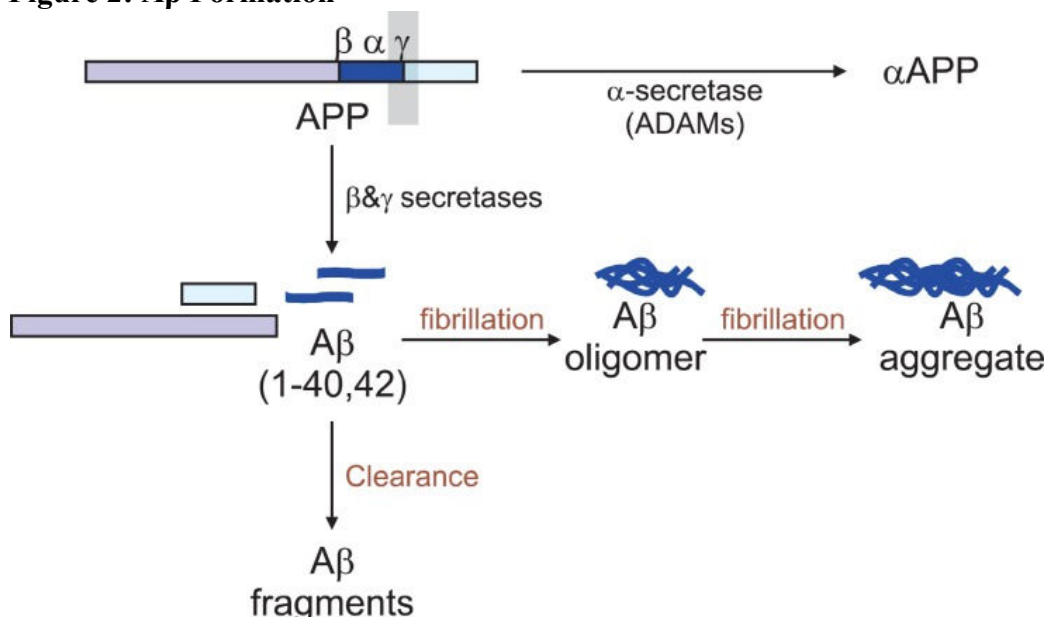
**Figure 2: A $\beta$  Formation**

Figure 2. (Yoon, 2012). Shown is the process in which amyloid precursor protein is cleaved by certain enzymes to produce beta-amyloid peptides which form plaques through fibrillation.

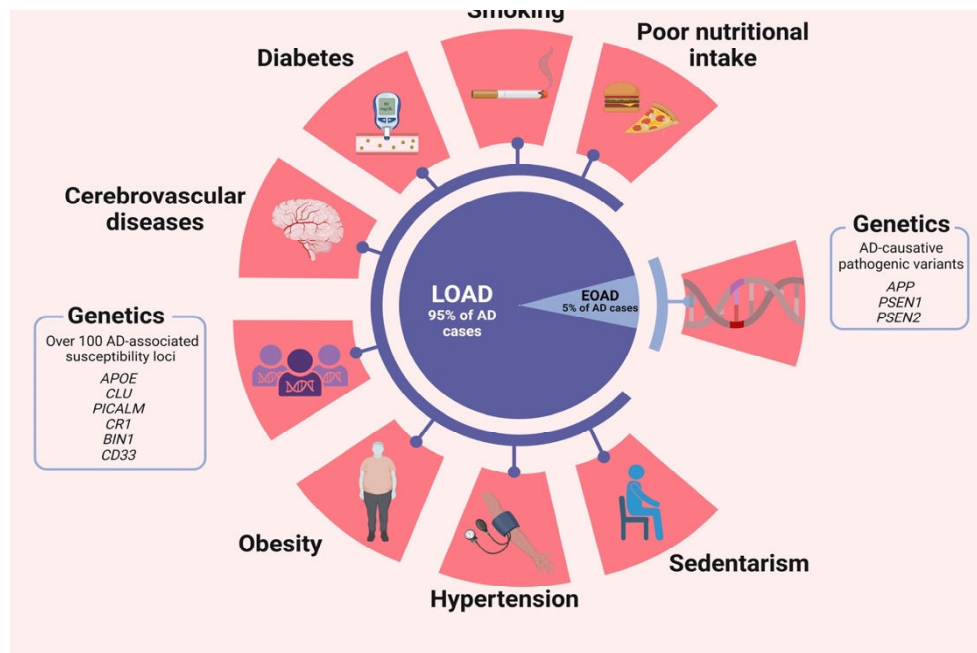
**Figure 3: LOAD and EOAD Risk Factors**

Figure 3. (Valdez-Gaxiola, 2024). This image depicts the risks associated with late-onset and early-onset cases. It is important to note that these factors do not all pose equal risks as this varies with the person.

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