

# The Gut Microbiome and Alzheimer's Disease: Can the Gut Be Used to Prevent or Treat Dementia?

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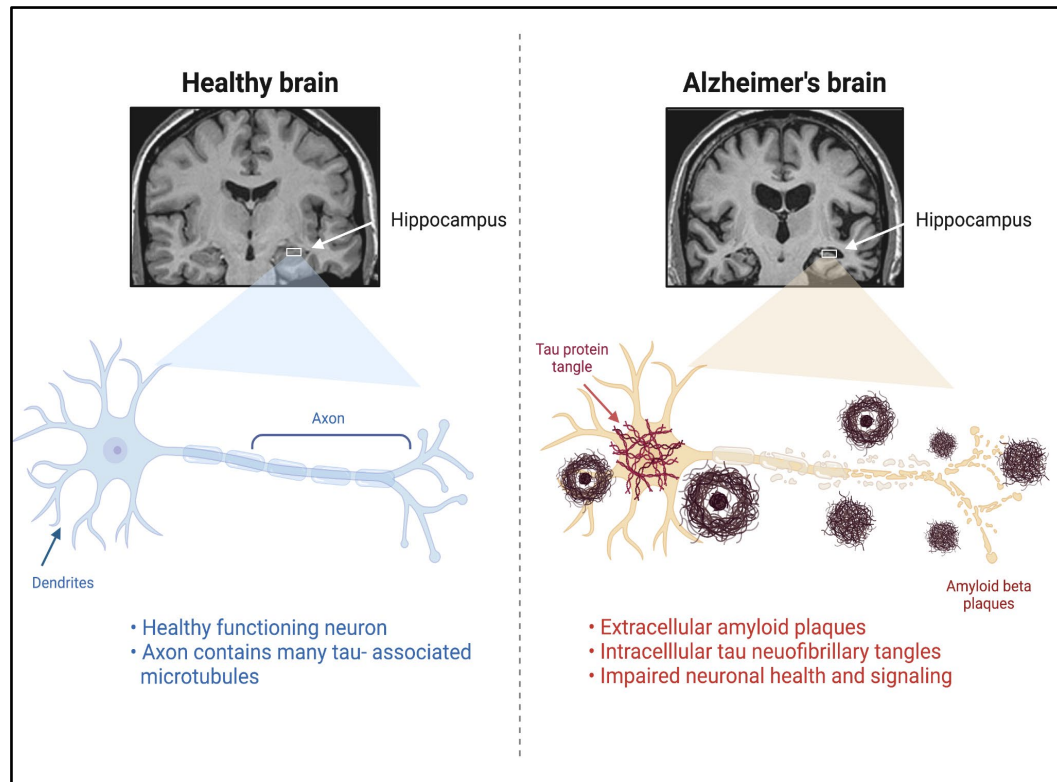
## ABSTRACT

Alzheimer's disease (AD) is a neurodegenerative disease and the most common cause of dementia<sup>1</sup>. There are currently no effective therapies for AD and its etiology remains poorly understood. Recent research has suggested that the gut microbiome may modulate risk for AD, as well as the disease process itself. This paper reviews the current knowledge surrounding AD and the gut microbiome, and aims to explore how this relationship may be used to advance our clinical understanding of the disease; including whether the gut microbiome could be a novel drug target or even serve as a potential biomarker for AD. Although this relationship between AD and the microbiome has not yet been fully elucidated, the gut microbiome is known to dynamically respond to lifestyle factors including sleep, exercise, and nutrition, all of which impact AD-risk. This body of evidence suggests that there may be a relationship between microbiome health and AD. Early studies are investigating whether the microbiome is changed in individuals with AD, and whether any metabolites or bacterial signatures unique in AD populations could be used as a biomarker for early detection of the disease. This review will discuss these points and reflect on how the clinical landscape for AD may be improved by assaying the microbiome and implementing lifestyle factors that both improve microbiome health and reduce AD risk.

## Alzheimer's Disease

Alzheimer's disease (AD) is a progressive, age-related neurodegenerative disease and is the most common cause of dementia<sup>1</sup>. AD can take over a decade to progress and is associated with severe amnesia, or memory loss, and cognitive decline. Individuals with AD can initially present with minute memory problems such as the inability to find common objects or trouble finding their way home. As the disease progresses, they develop dementia and worsening cognitive function. As they lose their memories, they lose their social connections and their personal identity. At the final stages of the disease, those with AD are rendered completely dependent and are unable to perform any activities of daily living alone. In this way, AD is an extremely taxing disease on those afflicted, their families, and their caretakers. In the end, death is an inevitable outcome of the disease.

While a small percentage of AD cases are inherited genetically (early-onset AD), most cases of AD are sporadic and occur after the age of 65; this is known as late-onset AD<sup>1</sup>. The cause of sporadic AD remains elusive. However, it is well established that one of the primary risk factors for the disease is age<sup>2</sup>. AD is associated with the hallmark pathologies of amyloid plaques and neurofibrillary tangles, which accumulate in the brain and impair neuronal health<sup>1,3</sup>.



**Figure 1.** Neuropathology of Alzheimer's disease (AD). Compared to a healthy brain, hippocampal volume is decreased in AD, amyloid plaques accumulate extracellularly, and neurofibrillary tangles composed of hyperphosphorylated tau proteins form inside the neurons. These signature AD pathologies are accompanied by neuronal death.

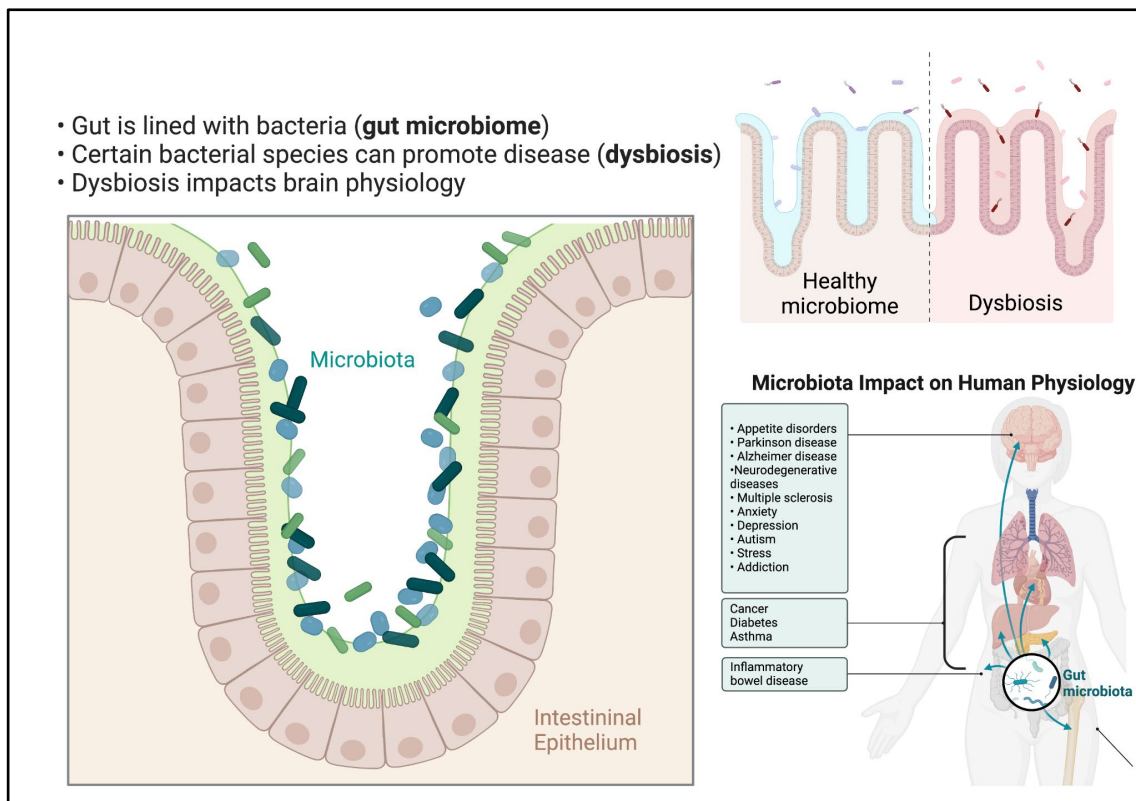
Amyloid plaques are large extracellular clumps of amyloid beta ( $A\beta$ ) protein that aggregate together between neurons<sup>4</sup>. Neurofibrillary tangles, made up of hyperphosphorylated tau protein, typically form later on in the progression of AD following the formation of amyloid plaques<sup>3,5,6</sup>. These tangles are protein aggregates that form inside of neurons themselves. These hallmark AD pathologies first appear in the hippocampus where memories are formed, and then progress globally throughout the brain. The progressive spread of these misfolded proteins is accompanied by large-scale neuronal dysfunction and death. As neurons die off, the brain atrophies or shrinks, causing cognitive decline and dementia.

Currently, there is no treatment available for AD that can alter the progression of the disease. As AD is the leading cause of dementia and among the leading causes of death in the US, there is a deep clinical need for effective therapeutics<sup>7</sup>. This article examines new scientific developments that suggest that the microbiome may modulate AD risk as well as AD pathologies in the brain. Microbiome bacterial and metabolic signatures have also been suggested as possible biomarkers to help in early diagnosis of the disease<sup>8-12</sup>.

## Gut Microbiome

The human microbiome is a collection of diverse microorganisms, including fungi, bacteria, protozoa, archaea, and viruses<sup>13,14,15</sup>. These microorganisms live all over the human body including in the gut. It is estimated that there are 10-100 trillion bacterial cells in our body<sup>16,17</sup>. This estimation does not provide an absolute count as the number of viruses and microbes in our body is still unknown. Other estimations, however, suggest that there

are ten microbes in our body for every one human cell<sup>18</sup>. The majority of these microorganisms are not harmful to humans, but are very beneficial and play an essential role in human health. They contribute to shaping our immune system and participate in nutrition as they help digest food and release important metabolites<sup>19-23</sup>. A healthy microbiome can be characterized as being diverse<sup>14,15,24-30</sup>. An unhealthy microbiome would lack diversity and may contain a higher proportion of bacterial species associated with disease<sup>31-33</sup>. This imbalance is known as dysbiosis. Dysbiosis has been associated with various diseases such as inflammatory bowel disease, asthma, diabetes, allergies, cancer, and even autism<sup>34-40</sup>.



**Figure 2.** Gut microbiome and impact on human physiology. The gut microbiome is composed of microbiota lining the intestinal lumen. Microbial species can promote health, or in cases of dysbiosis can promote disease.

The microbiome can be heavily influenced by an individual's environment and lifestyle. One of the primary modulators of the microbiome is diet; different dietary patterns have been associated with different microbial signatures, some of which have been linked to diseases such as Chron's disease<sup>33</sup>. In addition to diet, the microbiome can also be altered through sleep. Sleep efficiency and gut microbiome diversity have been shown to be positively correlated, while gut microbiome diversity and the time it takes for people to wake from sleep are negatively correlated<sup>41</sup>. These findings suggest that sleep quality and gut microbiome health are closely related, but it is unclear which process is the driver of this effect, or whether this relationship is bidirectional. Interestingly, many of the factors which influence the microbiome also influence AD risk<sup>42-44</sup>. Indeed, studies have demonstrated a correlation between human microbiome signatures and AD<sup>8,10,12,45</sup>.

## Relationship Between Microbiome and Brain

The connection between the gut and the brain is poorly understood. The bidirectional relationship wherein the gut and the brain influence each other is a relatively new concept, termed the gut-brain axis<sup>46-48</sup>. Communication along the gut-brain axis links the cognitive and emotional centers of the brain with peripheral intestinal functions<sup>48</sup>.

The gut microbiome is a key participant in the gut-brain axis, which interacts with the brain through the vagus nerve, which can directly influence the central nervous system (CNS) and behavior<sup>48-55</sup>. A healthy microbiome also regulates the immune system by promoting anti-inflammatory activity, in part through the release of short-chain fatty acids<sup>19,56-60</sup>. Anti-inflammatory activity is important because inflammation can negatively impact behavior and can even contribute to depression<sup>61</sup>. There are many other diseases that have been associated with altered activity of the gut-brain axis, such as obesity, Schizophrenia, and autism<sup>62-65,66</sup>.

The dysbiosis of the gut has also been linked with impaired cognitive function and the ability to form memories<sup>47</sup>. One study which aimed to observe the effects of infection and dysbiosis on cognitive function in mice demonstrated that when mice were exposed to stress, the germ-free mice which lack a microbiome displayed obvious memory impairment<sup>67</sup>. However, the administration of probiotics alleviated this impairment<sup>67</sup>. This study demonstrates the link between the intestinal microbiome and memory function. Since AD is also characterized by impaired memory, perhaps there is a similar level of dysbiosis in AD as well, which could be resolved with a therapeutic method such as use of probiotics.

## **Gut Microbiome and Alzheimer's Disease Risk**

Currently, there are studies that link the gut microbiome to AD risk<sup>8,10-12,68</sup>. Investigating whether there are specific gut microbial signatures associated with AD cases may provide a potential early detection method or biomarker for the disease. Additionally, understanding the relationship between the gut microbiome and AD pathogenesis may open a door to developing new therapeutic approaches.

Some studies have begun to clarify the relationship between the gut microbiome and AD pathology in the brain. Administration of amyloid-beta oligomers into the GI tract has been demonstrated to impact levels of amyloid pathology in the CNS in mice<sup>9</sup>. These results suggest that accumulation of amyloid pathology in late-onset AD may initially be triggered in the GI tract before progressing to the brain. Gut microbial populations and intestinal inflammation may also influence AD progression. Mice with AD pathology were found to have different gut microbial signatures than wild-type mice, and also presented with inflammation and degeneration of the intestinal lining<sup>12</sup>. Fecal transplants from wild-type mice into these AD mice reduced A $\beta$  plaques and neurofibrillary tangles in the brain, rescued cognitive impairment, and reversed the abnormalities found in the gut lining<sup>12</sup>. Clarifying a role for GI involvement early on in AD is important because it offers a potential method for early detection and may lead to microbiota-targeted therapies. If these findings can be replicated in humans, fecal transplantation may present a therapeutic approach to modulate intestinal health, cognition, and AD pathology.

Since AD is a human disease, it is important to understand whether microbial signatures are altered in AD patients compared to healthy individuals. One study concluded that the microbiomes of patients with mild cognitive impairment (MCI) were different from those with AD dementia<sup>8</sup>. Additionally, investigating the gut microbial metabolites of healthy individuals, people with MCI, and people with AD further confirmed that there are microbial signatures uniquely associated with AD<sup>8</sup>. These specific microbial signatures could aid in early detection of AD.

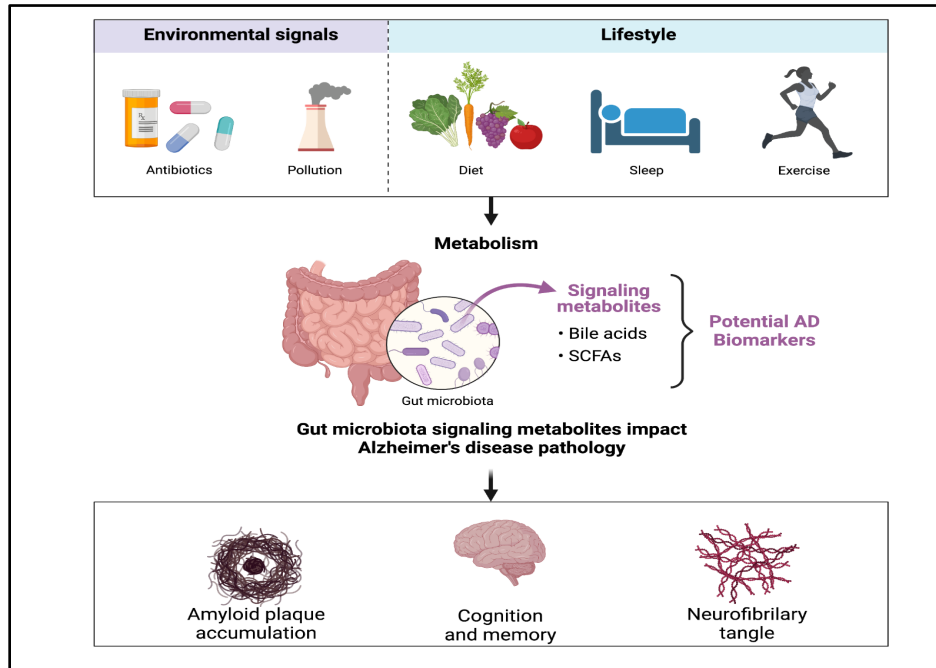
## **Can the Microbiome Be Used as a Biomarker?**

Biomarkers are minimally invasive, easily measured biological signatures that are often used to assist with diagnosis and drug development. Novel methods of early detection for AD are of the utmost importance, as they may provide a therapeutic window to help slow down or even prevent the progression of the disease. The current biomarkers for sporadic AD include monitoring the cerebrospinal fluid (CSF) and imaging the brain with PET scans to determine the progression of amyloid and tau accumulation in the brain<sup>69,70</sup>. However, as spinal taps are painful and invasive and PET scans are expensive, there is a clinical need for new, inexpensive, and non-invasive biomarkers for AD.

Currently, research is being conducted for easier methods to measure microbiome activity as a biomarker for AD. Bile acid (BA) metabolites are produced by gut bacteria and can be measured in the blood. One study examined BA metabolites as a way to indirectly assess the metabolic activity of the microbiome, and found that several BA metabolite signatures correlated with AD biomarker signatures<sup>71</sup>. In addition to BA metabolites, short-chain fatty acids and lipopolysaccharides produced by the gut microbiome may be other blood biomarkers that can inform us about AD progression. In fact, studies have shown that high levels of short-chain fatty acids and lipopolysaccharides correlated with amyloid deposits in the brain<sup>11</sup>. These studies suggest that there is a link between AD and the microbiome, and also that observing the blood for BA metabolites, short-chain fatty acids, and lipopolysaccharides could serve as a way to detect the onset of AD pathology. In this way, examining microbiome-activity through metabolites in the blood may provide a new and easy biomarker for AD, and is much more efficient than assessing the microbiome through sequencing fecal samples.

## **How Do Diet and Lifestyle Affect Disease-Associated Microbiome Signatures?**

Many of the environmental and lifestyle factors that influence the microbiome can also alter risk for developing AD. As discussed earlier, diet strongly influences the diversity of the microbiome<sup>33</sup>. Since many Western diets are dominated by hyper-processed foods, the microbiome composition of individuals who consume these diets must be less diverse compared to the composition of individuals who consume more traditional or Eastern diets which consist of a variety of fruits, vegetables, grains, and fibers. It is plausible that since there is a link between the health of the microbiome and AD risk and pathogenesis, individuals who consume a Western-style diet that is less healthy for the microbiome may be at a higher risk for AD. Individuals who consume a diet that promotes a more diverse microbiome may have reduced AD risk. When the microbiomes of adults with normal brain function and those with MCI were examined, unique microbial signatures were identified in those with MCI, which were modifiable through dietary intervention<sup>10</sup>. These microbial signatures also correlated with AD CSF biomarkers, which also responded to the dietary intervention<sup>10</sup>. These findings suggest that eating a healthier diet can lead to a more diverse microbiome and serve as a preventative measure for AD.



**Figure 3.** Environmental and lifestyle impacts on microbiota and Alzheimer’s disease (AD) pathology. Environmental signals and lifestyle factors alter the composition of the gut microbiome and metabolites released from these bacterial species can impact AD pathology. These metabolites can serve as potential biomarkers for AD.

There are also studies that correlate sleep with AD risk; repetitive patterns of disturbed sleep are associated with developing AD<sup>72-74</sup>. Fewer hours of sleep each night has been correlated with increased amyloid pathology in the brain<sup>44,72-74</sup>. A lack of sleep quality has also been associated with reduced diversity of the gut microbiota<sup>41</sup>. This suggests that perhaps engaging in a lifestyle that promotes a more diverse gut microbiome can improve sleep, which in turn may result in a lower deposition of amyloid in the brain.

Exercise can also positively impact the gut microbiome and is inversely associated with risk for dementia<sup>43,75-79</sup>. More exercise can not only decrease AD risk, but can also increase gut microbiome diversity, as the microbiomes of professional athletes have been found to have higher diversity than those of healthy, non-athletic individuals<sup>80</sup>. These findings suggest that maintaining an active lifestyle can help prevent dysbiosis as well as lower AD risk.

Lifestyle factors such as such as an individual’s surrounding environment may also impact the microbiome and AD. In fact, data suggests that living in an urban or a rural area has been shown to differentially affect microbiome composition<sup>81,82</sup>. For example, the gut microbiome composition of people living in rural areas of North India were found to be more diverse compared to those who lived in urban areas<sup>82</sup>. Urban environments tend to have more air pollution, and studies have found that persistent exposure to particulate matter from polluted-air led to gut dysbiosis in mice<sup>83</sup>. Perhaps dysbiosis may similarly occur in humans with repetitive exposure to air pollutants. Importantly, air pollution is also thought to be associated with increased AD risk<sup>84,85</sup>. It is possible that dysbiosis triggered by air pollution may underlie this increased AD risk in humans with high exposure to air pollution, such as in urban environments.

## Conclusion

Several studies have suggested a strong link between the microbiome and AD risk. As observed in mouse models and human studies, examining the gut microbiome for signature alterations could serve as an indicator

for onset of AD pathogenesis. The discovery of microbial signatures uniquely associated with AD may lead to novel approaches for AD prevention, diagnosis, and treatment. Further research in this area may provide a pathway for therapeutic measures for AD which target the microbiome through probiotics or fecal transplants. Currently, no effective treatments exist for AD, and preventative measures are of the utmost importance. The health and diversity of the gut microbiome can be improved by healthy lifestyle factors such as improving sleep quality, consuming a better diet, getting more exercise, minimizing exposure to air pollution, and perhaps using probiotics. These lifestyle factors can also be implemented as preventative measures to lower AD risk. Looking at alterations of gut microbiota through blood or stool samples could provide more accessible biomarkers to measure AD progression. Finally, as fecal transplants minimized the formation of A $\beta$  plaques and neurofibrillary tangles in the brains of AD mice, they may one day be a promising therapy for AD in humans. Our current understanding of the role of the gut microbiome in AD-risk suggests that this intersection is an exciting and promising direction for the field to explore, both in terms of improving clinical treatments as well as diagnosing the disease.

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