

Exploring the link between the gut microbiome and Alzheimer's disease

Alzheimer's disease is a progressive neurodegenerative disorder that affects memory, thinking and behaviour. While its exact causes remain unclear, emerging research suggests a connection between the gut microbiome – the trillions of microbes in our intestine – and brain health. **Professor Barbara Bendlin** and PhD candidate **Darby Peter**, both from the **University of Wisconsin-Madison** in the US, are investigating this link through the **Microbiome and Alzheimer's Risk Study (MARS)**. Their research explores how gut bacteria may influence brain function and whether imbalances in the microbiome contribute to Alzheimer's.



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The gut and brain may seem like two entirely separate systems, but research suggests they are closely linked. The gut microbiome – the trillions of microbes living in our intestine – not only supports digestion and immune function but also plays a crucial role in brain health. Some scientists believe that

... Talk like a ...

neuroscientist

Alzheimer's disease — a progressive neurodegenerative disorder that affects memory, thinking and behaviour; it is the most common cause of dementia

Calprotectin — a protein found in faecal stool that acts as a marker for intestinal inflammation

Cerebrospinal fluid — a clear fluid that surrounds the brain and spinal cord, helping protect them from injury and transporting nutrients

Dementia — a general term for memory, thinking and behaviour challenges that affect a person's ability to perform daily tasks

Metagenomic sequencing — a method used to study the genetic material of all microorganisms in a sample

Neurodegenerative diseases — a group of diseases (such as Alzheimer's and Parkinson's) that involve the progressive degeneration of the nervous system

imbalances in gut bacteria could contribute to neurological diseases, including Alzheimer's.

Professor Barbara Bendlin, a neuroscientist at the University of Wisconsin-Madison, and Darby Peter, a PhD candidate working in her laboratory, are investigating this connection through the Microbiome and Alzheimer's Risk Study (MARS). Their research explores how gut bacteria influence brain function and whether changes in the microbiome could increase the risk of Alzheimer's.

Gut bacteria and the brain

Scientists have long suspected that the gut microbiome plays a role in brain health, and growing research supports this idea. Studies suggest that gut bacteria help regulate inflammation, produce essential nutrients, and even influence brain function. Some researchers believe that imbalances in gut microbes may contribute to neurodegenerative diseases. However, many questions remain unanswered, particularly about whether changes in gut bacteria are a cause or consequence of Alzheimer's.

“Through MARS, we hope to establish a better understanding of the relationship between the gut and the brain, how they influence each other, and potentially find methods to change the gut to improve brain health,” explains Darby.

Who is participating in the study?

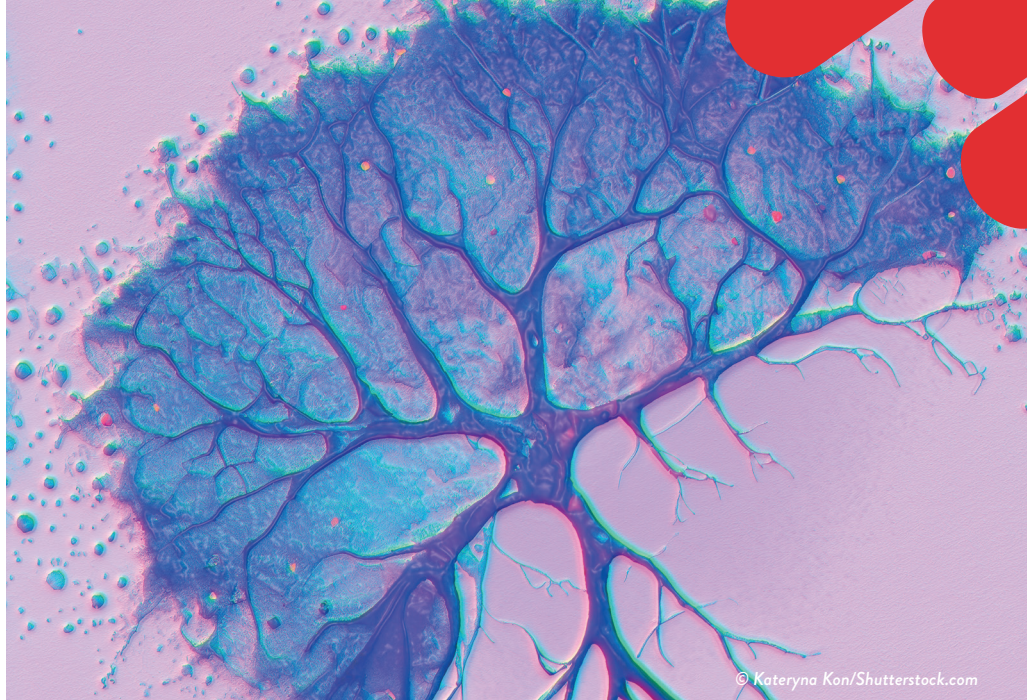
MARS recruits participants from two major dementia research programmes at the University of Wisconsin-Madison: the Wisconsin Alzheimer’s Disease Research Center (ADRC) and the Wisconsin Registry for Alzheimer’s Prevention (WRAP). “To be eligible for MARS, participants must be enrolled in either the Wisconsin ADRC or WRAP, at least 40 years of age, in good health (other than dementia or mild cognitive impairment), and willing to provide a faecal stool sample,” says Barbara. Since the study began in 2016, over 500 participants have contributed samples and completed questionnaires.

How do scientists study gut microbiomes?

To analyse gut bacteria, MARS participants first collect stool samples at home and complete questionnaires about their health and lifestyle. They then send their samples to the research team, where they are frozen until metagenomic sequencing begins. “Metagenomic sequencing involves the extraction of genetic material (DNA) from each sample, followed by DNA sequencing,” explains Barbara. With the help of advanced computational tools, researchers can determine not only which bacteria are present but also what functions they might perform, such as breaking down food or producing important nutrients. These insights could help us understand how gut microbes influence brain health and Alzheimer’s risk.

What has MARS discovered so far?

MARS is one of the first studies to thoroughly examine how the gut microbiome differs in people with Alzheimer’s compared to those without cognitive impairment. The team has found that certain types of gut bacteria are more or less abundant in individuals with Alzheimer’s, suggesting a potential link between microbial imbalances and the disease.



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“We have also expanded on this work by exploring relationships between the gut microbiome and biomarkers of Alzheimer’s disease pathology, including indicators of the abnormal accumulation of proteins beta-amyloid and tau,” says Barbara. Some gut bacteria also appear to influence metabolic by-products found in cerebrospinal fluid, which may play a role in disease progression.

What is the role of intestinal inflammation?

“While there are several potential mechanisms linking changes in the gut microbiome to changes in brain health, including the development of Alzheimer’s, mounting evidence points to inflammation as a key link,” says Barbara. More specifically, researchers suspect that an imbalance in gut bacteria, known as ‘gut dysbiosis,’ may trigger inflammation that weakens the gut barrier. When this barrier is compromised, harmful molecules can enter the bloodstream, potentially causing widespread inflammation – including in the brain.

To investigate this, three graduate students worked to measure levels of calprotectin, a marker of intestinal inflammation, in stool samples from MARS participants. Their findings suggest a connection between gut inflammation and Alzheimer’s-related brain changes. However, more research is needed to determine whether inflammation contributes to the disease or is simply a side effect of its progression.

What insights do questionnaires provide?

“The questionnaires collected from MARS participants are designed to gain insight into additional health and lifestyle factors that

may be influencing the gut microbiome, such as diet, medication use, and gastrointestinal illness,” explains Darby.

Diet is a key focus. Participants fill out food frequency questionnaires, which provide insight into their eating habits and nutrient intake. Previous research has shown that certain diets can shape the gut microbiome and may even impact cognitive function and Alzheimer’s risk. By analysing these responses, the MARS team hopes to uncover how dietary patterns relate to gut bacteria and whether nutrition could play a role in protecting brain health.

What does the future hold?

“Our findings suggest that people with Alzheimer’s disease show significant differences in gut microbial composition, and increased intestinal inflammation,” says Barbara. “Our findings also suggest that the gut microbiome is linked with Alzheimer’s pathology in the brain, as well as cognitive function, even in early stages of disease.” While these results are promising, it remains unclear whether these changes are a cause of the disease or a consequence of it.

The team is now conducting experiments using mouse models of Alzheimer’s, which will provide more insight into potential cause-and-effect relationships. Additionally, MARS is expanding its research by collecting blood samples from participants to analyse proteins and molecules associated with Alzheimer’s. A new sub-study is examining intestinal permeability, or ‘leaky gut’, by tracking how different sugars move through the digestive system. These ongoing efforts could pave the way for interventions that improve gut health and help reduce Alzheimer’s risk.

About *neuroscience*

Neuroscience is the scientific study of the nervous system, including the brain, spinal cord, and networks of sensory and motor neurons. The field combines biology, psychology, chemistry and computer science to better understand how the brain functions and how it affects behaviour, emotions and cognition. Neuroscientists investigate topics ranging from the molecular and cellular processes of individual neurons to complex functions like decision-making and consciousness.

One of the most exciting aspects of neuroscience is its potential to improve lives. “Working in the field of ‘Alzheimer’s Disease and Related Dementias’ research is rewarding in several different ways,” says Darby. “As is the case for many, one of the first things that drew me to this field was the opportunity to contribute to the fight against a condition that has

such profound impacts on individuals, families and caregivers.”

Interdisciplinary collaboration is at the heart of neuroscience research. Experts in genetics, data science, pharmacology and artificial intelligence work together to tackle complex questions about brain function and disease. “Research in the Microbiome and Alzheimer’s Risk Study (MARS) is led by three faculty investigators, Dr Bendlin from the Wisconsin ADRC and Department of Medicine, Dr Federico Rey in the Department of Bacteriology, and Dr Tyler Ulland in the Department of Pathology and Laboratory Medicine,” explains Darby. “Additionally, we work with collaborators across a variety of research institutions with expertise in microbial sequencing and analysis, biomarkers for brain changes associated with Alzheimer’s and related dementias, and those

with expertise in nutrition and the influence of dietary patterns on gut microbiome and cognitive functioning, among others.” This integration of different scientific fields is the key to making new discoveries.

The future of neuroscience is full of possibilities. Advances in technology, such as brain-computer interfaces and artificial intelligence, are opening up new ways to study the brain and develop treatments. “Recently, there have been several exciting advancements in the development of fluid biomarkers for Alzheimer’s pathology and other biological factors that can influence brain health,” says Darby. “Continued work in this area will help us better understand how Alzheimer’s disease and related dementias develop and progress over time, and identify novel therapeutic approaches to slow or prevent cognitive decline.”

Pathway from school to *neuroscience*

“I would recommend seeking a strong foundation in biology, biochemistry and psychology,” says Darby. “At the university level, many undergraduate programmes offer the opportunity to major in neuroscience, specifically.”

“While many biological/health science programmes include some level of statistical methodology training, gaining additional experience in statistical methodology, computer science and bioinformatics would provide an added benefit for you to work in neuroscience,” adds Barbara.



Meet Darby

Having lived with type 1 diabetes for over two decades, I have had the opportunity to benefit first-hand from translational research. This has resulted in a desire to ‘give back’ and contribute to research myself. My early interest in neuroscience was driven by the impact that neurodegenerative conditions have on people, as well as the interdisciplinary nature of the field.

There have been a number of experiences that have shaped my research and career trajectory, but many of them centre on the power of ‘team science’, and the importance of positive mentor/mentee relationships. I would not be where I am today without the powerful team of mentors and collaborators that I have had the honour of working with along the way.

Although each student is bound to face a series of unique challenges over the course of their graduate studies, some common challenges can include work-life balance and imposter syndrome. To maintain a healthy work-life balance in a fast-paced research environment, I have found it helpful to maintain a detailed schedule – both personally and professionally – that includes allotted periods of rest and quality time with friends and family. To combat feelings of imposter syndrome and build confidence in myself and my work, I find it helpful to celebrate ‘small wins’ in addition to the larger milestones!

Some of my proudest career achievements have come from my experiences mentoring students. This stems from my early experiences as an undergraduate research assistant myself, when I was able to form fantastic relationships with my research mentors that have had lasting impacts on my career trajectory and development as a neuroscientist. These early experiences have led to my current motivation to foster meaningful and productive relationships with each student I mentor. Celebrating the growth of my mentees and helping them reach the next stages of their education and career have been some of the most rewarding moments.

As I move forward in my doctoral work and future career, I hope to take advantage of opportunities that allow me to combine my love for research with my passion for sharing science with others in a way that is engaging and relevant to their lives. In my work, I want to make sure that scientific discoveries aren’t remaining in the lab or scientific community from which they originate. I hope to promote effective communication of scientific discoveries to a wide range of audiences.

Explore careers in neuroscience

Gaining experience in the field early on can be incredibly valuable. Many universities offer summer research internships, where high school and undergraduate students can work alongside neuroscientists, receive mentorship, and gain practical lab experience.

Reaching out to local universities is a great way to learn about available programmes, lab openings, and networking events. Attending neuroscience-related talks, workshops and open days can also provide insight into career options within the field.

“To explore a variety of career paths, visit websites like the Wisconsin Healthcare Careers website (wihealthcarecareers.com) and the Health Professions Toolkit (shpep.org/resource/health-professions-toolkit) provided by the Summer Health Professions Education Program,” says Darby. “Through the use of other online resources (such as Datacamp.com and r4ds.hadley.nz), you have the opportunity to build both theoretical and technical expertise in data management and analysis at your own pace.”

Darby’s top tips

1. Never be afraid to ask questions!
2. Take advantage of networking and professional development opportunities at every stage of your career.
3. Have patience when plans change, or when things go unexpectedly.