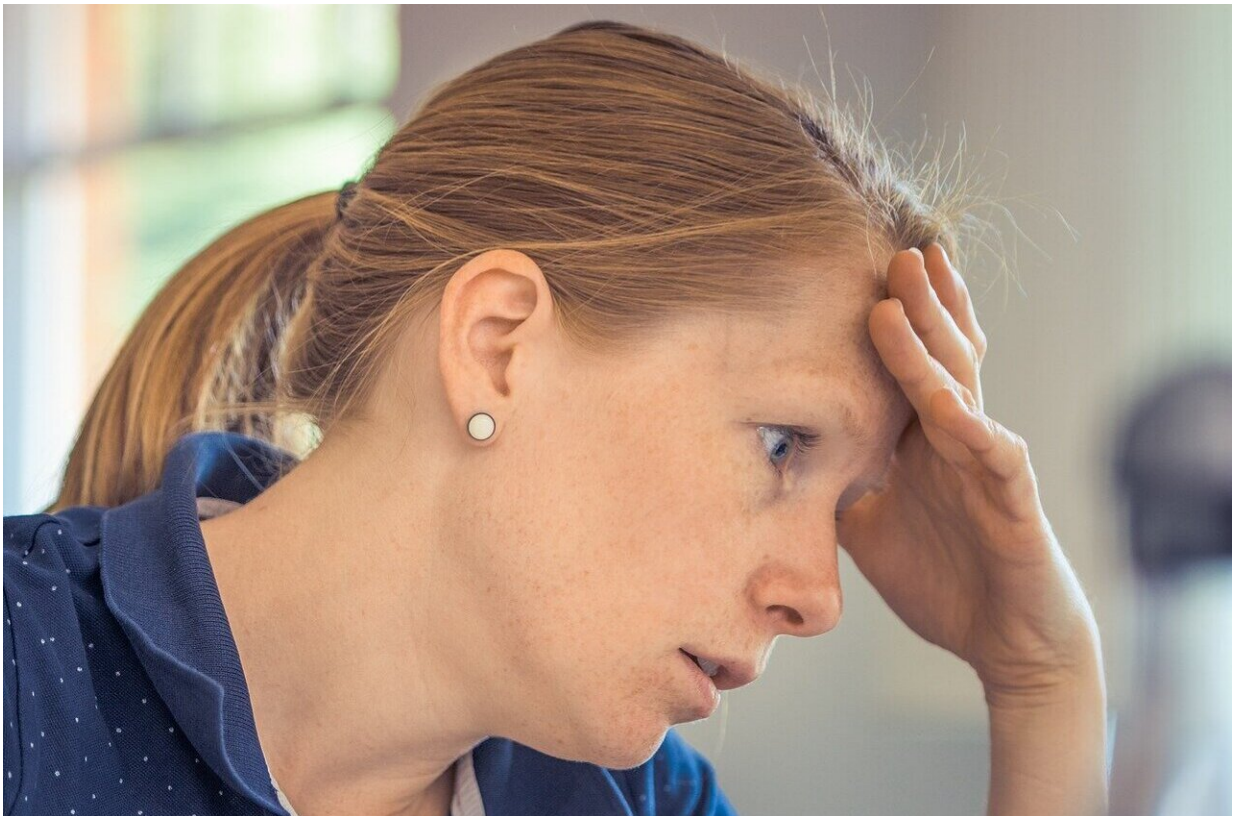


Stress increases Alzheimer's risk in female mice but not males

May 2 2023, by Tamara Bhandari



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Women are about twice as likely as men to be diagnosed with Alzheimer's disease. Some of that is age; in the U.S., women outlive men by five to six years, and advanced age is the strongest risk factor for

Alzheimer's. But there's more to it than that, so Alzheimer's researchers continue to look for other reasons why women have an elevated risk of the deadly neurodegenerative disease.

Stress may be one such reason. A study by researchers at Washington University School of Medicine in St. Louis shows that the effect stress has on the brain differs by sex, at least in mice. In [stressful situations](#), levels of the Alzheimer's [protein amyloid](#) beta rises sharply in the brains of females but not males. In addition, the researchers identified a molecular pathway that is active in brain cells from [female mice](#) but not male mice, and showed that it accounts for the divergent responses to stress.

The findings, published May 2 in *Brain*, add to a growing collection of evidence that sex matters in health and disease. From cancer to [heart disease](#) to arthritis, scientists have found differences between males and females that could potentially affect how men and women respond to efforts to prevent or treat chronic diseases.

"How women respond to stress versus how men respond to stress is an important area of research that has implications for not just Alzheimer's disease but other conditions, too," said co-corresponding author Carla M. Yuede, Ph.D., an associate professor of psychiatry. "In recent years, the National Institutes of Health (NIH) has prioritized understanding sex differences in medicine. Stress is one area in which you can clearly see a difference between males and females. This study shows that reducing stress may be more beneficial for women than men, in terms of lowering the risk of Alzheimer's disease."

Stress falls into the category of socioeconomic risk factors, along with factors such as depression and social isolation, that together account for an estimated 8% of the risk of developing Alzheimer's. That risk calculation, however, doesn't take gender into account. Women

consistently report higher levels of stress than men, and stress affects women's bodies differently than men's in many ways, such as cardiovascular health, immune responses and other issues.

Corresponding author John Cirrito, Ph.D., an associate professor of neurology; Yuede; and first author Hannah Edwards, a graduate student in Cirrito's lab, reasoned that stress also may affect women's brains differently than men's, and these differences may help explain the sex imbalance in Alzheimer's disease.

To find out, they measured levels of amyloid beta—a key Alzheimer's protein—in the brains of mice every hour for 22 hours, beginning eight hours before the mice experienced stress. The experience was equally stressful for male and female mice, as measured by the levels of stress hormones in their blood. But the responses in their brains were not the same.

In female mice, amyloid beta levels rose significantly within the first two hours and stayed elevated through the end of the monitoring period. In [male mice](#), brain amyloid levels did not change overall, although about 20% of them did show a delayed and weak rise in amyloid levels.

Further experiments revealed that the difference comes down to a cellular stress response pathway in [brain cells](#). Stress causes the release of a hormone known as corticotropin releasing factor. Neurons from female rodents take up the stress hormone, triggering a cascade of events that results in increasing levels of amyloid beta in the brain. In contrast, neurons from male rodents lack the ability to take up the stress hormone. It is not known whether there are similar sex differences in how human neurons take up stress hormones.

"There's a fundamental biological difference between males and females in how they respond to stress at the cellular level, in both mice and

people," Cirrito said. "We don't think that stress is the sole factor driving the sex difference in Alzheimer's disease. There are many other differences between men and women—in hormones, lifestyle, other diseases they have—that undoubtedly contribute in some way. But that [stress](#) is driving one aspect of this sex difference I think is very likely."

More information: Hannah M Edwards et al, Sex-dependent effects of acute stress on amyloid- β in male and female mice, *Brain* (2023).
[DOI: 10.1093/brain/awad052](https://doi.org/10.1093/brain/awad052)

Provided by Washington University School of Medicine in St. Louis

Citation: Stress increases Alzheimer's risk in female mice but not males (2023, May 2) retrieved 5 May 2023 from
<https://medicalxpress.com/news/2023-05-stress-alzheimer-female-mice-males.html>

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