

Sex-based Disparities in Alzheimer's Disease

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Abstract

Sex-based disparities in Alzheimer's disease are increasingly recognized as a factor in understanding the prevalence, progression, and treatment outcomes of the disease. Women account for nearly two-thirds of Alzheimer's cases in the U.S., a disparity long attributed to their longer lifespans. However, recent research reveals deeper biological and sociocultural contributors. Hormonal changes during menopause, particularly the decline in estrogen, appear to increase vulnerability to neuroinflammation and stroke—both of which accelerate cognitive decline. Genetic factors, such as the APOE ϵ 4 variant and differences in X chromosome expression, may also play a role. Women often experience faster disease progression and face longer, more complex diagnostic pathways than men. Recognizing sex as a variable in neurodegenerative diseases is foundational for advancing Alzheimer's disease research and improving patient care.

Some men spend a lifetime in an attempt to comprehend the complexities of women. Others preoccupy themselves with somewhat simpler tasks, such as understanding the theory of relativity!

~Albert Einstein

Globally, Alzheimer's disease (AD) is the most common form of dementia with a new diagnosis occurring every 3.2 seconds.¹ AD typically affects individuals over age 65 and is characterized by a progressive decline in cognitive functioning, including memory, reasoning, and activities of daily living (ADL). Currently, more than 57 million individuals worldwide are living with AD and other dementias, and this number is expected to triple as the global population ages over the next few decades.² A major hurdle to successful treatment AD is the failure to diagnose it in its early stages.³ Understanding the risk factors for AD can support strategies aimed at reducing risk or delaying onset, thereby improving opportunities for early intervention.

Who develops AD, And Why Are Some People More Susceptible Than Others?

AD primarily affects individuals over age 65, but it's not a normal part of aging. Factors such as genetics, family

history, education, and lifestyle choices (e.g., high blood pressure, obesity, excessive alcohol consumption) can increase susceptibility, but advancing age remains the strongest non-modifiable risk factor for AD. Interestingly, women are twice as likely to be unpaid caregivers⁴ and twice as likely to develop AD.⁵

Age, APOE ϵ 4 genetic status, and being female (XX)* are recognized as the primary risk factors for AD, often referred to collectively as the risk triad.⁶ Most individuals diagnosed with AD are over 65 years old, and those who carry at least one ϵ 4 allele of the apolipoprotein E (APOE) gene face a significantly elevated risk. Interestingly, women are disproportionately affected, representing nearly two-thirds of all AD cases, a difference partly explained by longevity but also by biological and sociocultural factors.^{4,5,7} And while women do tend to live longer than men—on average, 5 years longer⁸—this time difference alone is insufficient to account for a disease that takes decades to fully develop.⁹ Over the course of their lives, women are more likely than men to develop AD, and this imbalance also appears in how the disease physically alters the brain, particularly in patterns of brain atrophy across the AD spectrum.

Recent studies suggest that MRI analyses of amyloid-positive individuals with AD show distinct brain atrophy trajectories influenced by sex,¹⁰ though more replication is needed. Women exhibited more rapid atrophy in brain regions typically affected by AD, such as the hippocampus,

compared with men at the same disease stage, though cognitive decline trajectories vary by study.

A meta-analysis conducted by Ferreira et al.¹¹ systematically reviewed and categorized biological subtypes of AD, which were identified using structural MRI data collected at a single time point. They found four recurring subtypes, each presenting a specific brain atrophy profile and associated clinical symptoms. However, a major challenge with this approach is that using only cross-sectional data may lead to misinterpretation of disease progression as separate subtypes. To mitigate this, Poulakis et al.¹² developed a method that incorporates longitudinal imaging data, allowing for more accurate tracking of how atrophy evolves from the point of clinical diagnosis. This technique, applied across multiple international datasets, revealed five distinct atrophy progression pathways, characterized by mediotemporal or cortical degeneration patterns.

Notably, Poulakis et al.'s study also revealed that the distribution of men and women varied across the identified subtypes. Women were more likely to fall into the limbic-predominant subtype, which involves greater atrophy in medial temporal areas, whereas men were more frequently associated with the hippocampal-sparing subtype, marked by broader cortical involvement. These findings suggest that sex assigned at birth significantly influences the biological diversity of AD, shaping both the trajectory of brain degeneration and clinical manifestations throughout the disease course.

Hua et al.¹³ significantly contributed to the understanding of sex-specific differences in AD progression by showing that women exhibited brain atrophy at a rate substantially faster, varying by brain region and cohort—sometimes up to 50% faster than their male counterparts in medial temporal areas. Despite this accelerated structural decline, other studies have noted that women tend to experience a more gradual decline in cognitive function during the early phases of AD.¹⁴ More recently, Emrani and Sundermann noted that men and women often perform differently on neuropsychological tests used to detect early AD, indicating that sex may influence not only the disease trajectory but also how it is assessed clinically.¹⁵

How Do Men and Women Differ in AD Presentation?

The reasons behind sex-specific trends in AD aren't completely understood. While a woman's longer lifespan is a part of the puzzle, other potential factors being investigated include hormones, genetics, protein

accumulation in the brain, and external factors.

A recent study by Lusk et al.¹⁶ based on almost 6 million Medicare patients showed that men had "higher mortality and hospitalization rates than women after a dementia diagnosis."¹⁷ So, while more women develop dementia, men progress faster and die sooner.

Women Are Not an Anomaly

About half of the world's population is women, yet women have historically been excluded from medical research. For many diseases, women's symptoms may be different from men's, and differences in presentation for women across disease states may portend worse clinical outcomes. For example, women are considered to have "atypical" heart attack symptoms, simply meaning that their symptoms are different from those seen in men.¹⁸ And as a result, a heart attack diagnosis is missed more frequently in women than in men.¹⁹ Similarly, even though women are more likely to have strokes than men, their sex-specific symptoms (including migraine, nausea, and confusion) are not considered "normal" symptoms, making them less likely to be registered.^{20,21}

Similarly, understanding sex and gender differences in AD is important for identifying specific risk factors and mechanisms helpful for treatment and prevention that may differ between men and women—for example, hormonal changes that may influence the onset and progression of AD. Recognizing differences can lead to more personalized and effective treatment strategies tailored to the patient and ultimately improve outcomes and quality of life.²²

As with heart disease and stroke, the symptoms of AD in women may be different from those in men, particularly in the early stages of disease progression. While early symptoms of AD, such as memory loss, may appear similar in both men and women, the progression and specific behavioral and affective symptoms may differ. For example, women tend to experience faster decline in some domains (e.g., memory and independence) compared with men after a diagnosis.²³ Women may also experience more difficulties with language and communication³ aggravating social interactions and decision-making. Emerging evidence suggests that women experience a faster rate of cognitive decline as they progress from mild cognitive impairment (MCI) to AD. However, women generally have a stronger verbal memory than men,²⁴ which may mask underlying brain pathology and confound the early diagnosis of dementia.^{24,25}

Mental Health

Women are twice as likely to have depression compared with men.^{7,26} Women with AD have a higher prevalence and greater severity of depressive symptoms, aberrant motor behavior, and psychotic symptoms than their male counterparts, but males are more likely to be apathetic.^{27,28} Interestingly, there is a strong link between depression and memory. Depression can impair memory, and in some cases, memory loss can be a symptom of depression. Depression has also been shown to exacerbate memory decline in older adults.^{28–32}

While many neuropsychiatric symptoms of AD are similar between men and women in later-stage disease (loss of inhibitions, rude behaviors, socially inappropriate comments, hallucinations, sexual disinhibition, etc.),²⁸ in mild-AD patients, women experience more neuropsychiatric symptoms such as hallucinations, depression, anxiety, apathy, and aberrant motor behaviors than men.^{16,17,27,33} Men, on the other hand, may display more aggressive and combative behaviors as the disease progresses, making them more challenging to care for in the home.^{27,33,34} In more advanced disease, female AD patients showed higher rates of euphoria in some cohorts, though this is inconsistently reported.

Hormones

Hormones, particularly estrogen, play a significant role in AD, with declining estrogen levels during menopause potentially increasing the risk for women.

Estrogen's neuroprotective effects include promoting brain cell growth and synaptogenesis, reducing neuroinflammation, and improving memory functions like working memory and verbal learning.³⁵ Estrogen may improve cognitive function, including memory, by enhancing communication between brain cells and promoting the formation of longer-lasting memories. It may help reduce amyloid- β (A β) toxicity—buildup of A β in the brain during AD. Hormone therapy (HT) has been studied as a possible modifier of AD risk, but the findings are inconsistent. The menstrual cycle, pregnancy, and menopause all involve intricate hormonal fluctuations that can affect various aspects of a woman's physical and mental health. These shifts can affect mood, energy, sleep, and possibly AD risk, though mechanisms remain unclear.^{6,32}

The age at which a woman experiences her first menstrual period (menarche) and the age at menopause have also been shown to influence her risk of developing AD. Research indicates that women who begin

menstruating at age 12 or younger have a decreased risk of dementia, including AD; conversely, those who start their periods at age 15 or later have a higher risk.³⁶ This is thought to primarily be due to the neuroprotective effects of estrogen, which play a crucial role in brain health. Evidence is mixed; some studies show associations between reproductive span and AD risk, but causality is uncertain.

17 β -estradiol (E2), the primary female sex hormone and a potent estrogen, influences the way neurotransmitters like serotonin, acetylcholine, and dopamine are used to send signals throughout the brain, impacting various brain functions and behaviors.³⁷ It promotes serotonin and dopamine synthesis and decreases their degradation and reuptake—suggesting a role in mood regulation, memory systems, and motivation in both sexes.^{7,37}

Childbearing also seems to play a significant role in the risk of developing AD in women. Women who have children tend to have a lower risk of Alzheimer's compared with those who do not.^{36,38} The protective effects may be due to increases in estrogen during pregnancy or modifications in the immune system leading to lower levels of inflammation.³⁸ However, findings conflict regarding parity: some studies suggest more pregnancies increase risk, while others suggest cumulative months of pregnancy reduce risk. Park et al. suggest that having more than three children may actually increase the risk of dementia,³⁶ while Fox et al. suggest that “women with more cumulative months pregnant” have a lower risk of developing AD.³⁸ Later age at first birth may also decrease risk of dementia, although the results are not conclusive and may be associated with external factors including education and income.³⁹ Pregnancy complications may also factor into dementia risk. For example, hypertensive disorders of pregnancy (HDP) have been shown to involve an exaggerated inflammatory response, which may predispose women to other chronic conditions and may be involved with an increase in brain atrophy and cognitive decline many years after the pregnancy.^{7,40,41}

Estrogen plays a complex role in AD, with its decline after menopause potentially contributing to increased neuroinflammation and higher risk in women. Estrogen modulates neuroinflammation by inhibiting activation of microglia and reducing production of free radicals and pro-inflammatory cytokines.^{42–44} It also protects the blood-brain barrier from inflammation-induced disruption and enhances neuronal survival.^{42,45}

The interaction between age at menopause and synaptic health can influence cognitive decline and AD pathology.

Women who experience menopause at an older age tend to have a lower risk of developing AD.³⁶ This is because a longer reproductive period means prolonged exposure to estrogen. Due to the earlier depletion of estrogen and concomitant rise in gonadotropin hormones such as follicle-stimulating hormone (FSH), which may have neurotoxic effects, early menopause is associated with a higher risk of AD.^{46,35}

One study by Park et al. suggests that because a longer reproductive span means more years of estrogen exposure, it is linked to a reduced risk of AD.³⁶

Conversely, a shorter reproductive span, resulting from either late menarche or early menopause, increases the risk.^{36,47}

While HT has shown some promise in potentially reducing the risk of AD in some women, research also suggests that the timing of HT initiation is crucial, with older women potentially experiencing harmful effects.⁴⁸ HT can be a beneficial option to help decrease symptoms of menopause and osteoporosis. However, long-term use of these artificial hormones comes with potential risks, including increased risk of breast cancer, blood clots, and stroke. And the relationship between HT and AD is complex.

Verghese et al. and Jacobs et al. showed verbal memory improved in post-menopausal women (surgically and age-related, respectively) receiving HRT.^{49,50} However, the Women's Health Initiative Memory Study determined that HRT (in the form of conjugated equine estrogens) "does not protect against dementia or cognitive decline, but substantially increases the risk of dementia of any cause and cognitive decline" in a study of ~7,500 women over the age of 65.⁵¹ Similarly, Kang et al. showed a "significant yet modest adverse association between HT use and decline over 4 years in general cognitive performance"⁵²—including verbal memory and attention.

A recent study suggests that it's not HT itself, but the formulation and timing of the therapy that's important.⁴⁷ For example, Song et al. reported that estrogen HRT alone may have a protective effect, but a combination of estrogen and progesterone (needed to decrease the risk of uterine cancer) or tibolone (a synthetic steroid used to both treat symptoms of menopause and prevent osteoporosis) may actually increase the risk of AD.⁴⁷

More research is needed to fully understand the role of estrogen in preventing AD, including the best formulations and dosages of therapy and the specific mechanisms by which it exerts its protective or deleterious effects.

Genetics and APOE ε4

The apolipoprotein E (APOE) ε4 allele is the strongest genetic risk factor for late-onset AD for both males and females, with those carrying two copies of the allele having an ~8–12-fold increased risk in population-based studies; higher ranges of disease incidence (up to ~20-fold) have been reported in clinic-based cohorts but vary by ancestry and methodology. There are three main genetic alleles for APOE—ε2, ε3, and ε4. Unlike APOE ε4, APOE ε2 provides some protection against AD. APOE ε3, the most common variant, neither protects nor makes one more susceptible to developing AD. (There are other variants, such as the Christchurch mutation, a rare mutation of APOE ε3, that may also provide protection against AD.)

The risk of developing AD as an APOE ε4 carrier differs between males and females. Heterozygous APOE ε4 females are at a higher risk of AD than heterozygous APOE ε4 males, perhaps because of the impact of cardiovascular changes on cortical tau deposition,^{53,54} changes in brain metabolism and atrophy,⁵⁵ or lipid handling (see below).

APOE is primarily expressed by astrocytes and microglia in the brain; some peripheral immune involvement has been reported, but neutrophil expression remains debated.^{56,57} A 2024 study by Rosenzweig et al. identified a new subset of neutrophils that exhibit increased levels of interleukin (IL)-17 and IL-1, inflammatory cytokines linked to cognitive decline.⁵⁸ These neutrophils may be modulated by APOE genotype in sex-dependent ways, infiltrating the brain, interacting with the microglia, and exacerbating cognitive decline.⁵⁶ Their findings underscore the importance of considering sex-specific mechanisms in AD research and treatment.

Tau Levels

Higher levels of tau biomarkers are more strongly associated with clinical Alzheimer's, cognitive decline, and neurodegeneration. Compared with their male counterparts, women carry a greater tau burden at an equivalent level of Aβ, and they experience faster cognitive decline at similar levels of Aβ and tau.⁴⁶ Studies indicate that women accumulate tau aggregates faster, particularly in the temporal lobe.⁹

Tau is involved in the normal function of neurons—maintaining structural integrity of nerve cells, stabilizing microtubules, and regulating axonal transport for neuronal communication. In a healthy neuron, excess tau is marked for degradation by ubiquitinases, prompting degradation of tau by proteasomes or autophagy pathways.^{59,60} Other proteins, called deubiquitinases, remove the ubiquitin tag,

stopping recycling. One deubiquitinase, USP11, has been shown to remove the degradation tags from tau and enhance tau acetylation and aggregation.⁶⁰

Individuals with AD have higher USP11 levels than controls, though quantification varies by study. How does this relate to females? USP11 is encoded on the X chromosome, meaning that females have two copies. Usually, one of the two X chromosomes is inactivated, which ensures that X-linked genes are expressed at similar levels in both males and females. However, USP11 escapes X-chromosome inactivation, giving a double dose of USP11 to females and potentially contributing to sex differences in tau pathology.⁶⁰ Studies targeting USP11 to increase tau ubiquitination are underway.⁵⁹

A recent meta-analysis suggested that, while there were no or only minor differences in biofluid concentrations of various biomarkers between biological sexes, there are sex-specific associations that may influence the interpretation of specific biomarkers in CSF and plasma.⁶¹ These results suggest that sex-specific guidelines may be needed for AD biomarkers.

Matrix Metalloproteinase-9

Matrix metalloproteinase-9 (MMP-9), a proinflammatory,⁶² zinc-dependent metalloproteinase, plays a role in degradation of the extracellular matrix, tissue remodeling, inflammation, cell migration, and regulation of various physiological and pathological processes.^{63,64} There is some evidence that in addition to its role in degrading A β peptides (contributing to the breakdown of amyloid plaques),⁶⁵ and MMP-9 has been shown to increase the rate of tau oligomerization and breakdown of the blood-brain barrier.⁶² It may also be involved with faster cognitive decline and hippocampal volume loss in those with mild cognitive impairment (MCI) and AD.^{66,67} In AD, elevated levels of MMP-9 are associated with the APOE ϵ 4 allele, and this association may be more pronounced in women. In female APOE ϵ 4 carriers, MMP-9 activity may be more detrimental to AD-related pathology, particularly concerning tau protein levels.

Proteins and Lipids

A recent study by Coughlan et al. suggests that women tend to accumulate tau protein faster than men in specific brain regions that are vulnerable to AD—the inferior temporal, temporal fusiform, and lateral occipital regions—and that female APOE ϵ 4 carriers have faster inferior temporal tau accumulation.⁶⁸ Similarly, women show more tau pathology than men with a comparable

amyloid burden, and female APOE ϵ 4 carriers with MCI showed higher levels of CSF tau than male carriers.^{69,70} However, in men, NFL levels are consistently higher—both in those with dementia and those without.⁷⁰

Similarly, abnormal lipid handling may also contribute to AD in a sex-specific manner. As mentioned above, women are more susceptible than men to the impact of APOE ϵ 4. APOE is abundant in the brain. It is involved in maintaining lipid homeostasis and neuronal health and aids in the transport of cholesterol and other lipids. It acts as a ligand for various cell surface receptors, including the low-density lipoprotein receptor, facilitating delivery of lipids like cholesterol and triglycerides to cells.⁷¹ Dysregulated lipid metabolism and aberrant lipid accumulation have been noted in the post-mortem brains of individuals with late-onset dementias,^{72,73} with the buildup contributing to the characteristic plaques and tangles of AD.

A recent study⁷⁴ comparing the lipid profiles of women with and without AD, reported lower unsaturated and higher saturated lipid levels in women with AD compared with controls. This difference was not seen in men.⁷⁴ However, both men and women can benefit from cholesterol-lowering diets rich in omega fatty acids and fruits and vegetables.⁷⁵

Cultural and Societal Factors

Poverty is strongly linked to an increased risk of dementia, regardless of genetic factors,⁷⁶ and those experiencing socioeconomic deprivation are significantly more likely to develop dementia compared with those with higher socioeconomic status. Interestingly, this connection is seen across several dimensions of poverty, including education, health, and finances. And women are far more likely to be poor than men, with lower wages, lack of access to decent work, unpaid care work, and longer workdays.⁷⁷

Over the past 100 years, it was more unusual for women to have higher education and jobs outside the home.⁷ “Women who participated in the paid labor force between early adulthood and middle age experienced slower memory decline in late life, building on previous research that associates work and education with higher levels of cognitive engagement.”⁷⁸

Clearly, biological factors are involved in the increased prevalence of AD in women, but socioeconomic risk factors, including lower income, lower education, and higher stress and caregiving burden are all associated with an increased risk of AD.^{58,79}

Conclusions

Sex differences in AD may help to identify preclinical factors and diagnostic biomarkers to aid in lowering disease risk and improving disease identification, progression, and treatment response. Emerging research continues to show that biological sex influences not only prevalence but also resilience mechanisms (including genetics, lifestyle, and environmental factors) and responses to therapy. Nuanced patterns—such as faster progression in women with mild AD—highlight the importance of sex-aware clinical assessment, care planning, and medication, and studying these differences can enhance our understanding of the disease's underlying biology.

For clinicians, these findings underscore the need to integrate sex-specific risk profiles into diagnostic and therapeutic strategies. Hormonal transitions, particularly menopause, may accelerate neurodegenerative processes in women, while men may present with distinct comorbidities such as vascular disease or sleep apnea that influence disease trajectory. These insights highlight the importance of developing personalized treatment plans that account for sex as a biological variable.

For researchers, the path forward involves refining methodologies to better capture sex-based differences, such as disaggregated data by sex, investigations of genetic and epigenetic factors involved in disease progression, explorations of hormone involvement in disease progression, and responses to treatment. Precision medicine in AD must account for sex as a biological variable. As research continues to uncover the complex interplay between genetics, hormones, and environmental factors, a more equitable and effective approach to Alzheimer's care becomes possible—one that recognizes and responds to the unique vulnerabilities and strengths of both women and men.

Addressing sex disparities in AD research can help promote equity in healthcare. Medical research has often overlooked these differences, leading to gaps in knowledge and treatment efficacy. By prioritizing sex and gender in AD studies, researchers can ensure that findings apply able to diverse populations, improving healthcare outcomes. Ultimately, advancing sex-aware research and clinical practice will improve diagnostic accuracy, therapeutic efficacy, and patient outcomes. By embracing sex as a fundamental variable in AD, clinicians and researchers can move toward a more precise, equitable, and effective model of care.

References

1. Alzheimer's Disease International (ADI). Dementia statistics. Accessed February 26, 2025. <https://www.alzint.org/about/dementia-facts-figures/dementia-statistics/>
2. GBD 2019 Dementia Forecasting Collaborators. Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. *Lancet Public Health*. 2022;7(2):e105-e125. doi:10.1016/S2468-2667(21)00249-8
3. Aggarwal NT, Mielke MM. Sex differences in alzheimer's disease. *Neurol Clin*. 2023;41(2):343-358. doi:10.1016/j.ncl.2023.01.001
4. Alzheimer's Association, Gaugler J, Bryan J, et al. 2025 *Alzheimer's Disease Facts and Figures: American Perspectives on Early Detection of Alzheimer's Disease in the Era of Treatment*. Alzheimer's Association; 2025.
5. Moutinho S. Women twice as likely to develop Alzheimer's disease as men — but scientists do not know why. *Nat Med*. March 14, 2025. doi:10.1038/s41591-025-03564-3
6. Riedel BC, Thompson PM, Brinton RD. Age, APOE and sex: Triad of risk of Alzheimer's disease. *J Steroid Biochem Mol Biol*. 2016;160:134-147. doi:10.1016/j.jsbmb.2016.03.012
7. Mielke MM. Sex and gender differences in alzheimer's disease dementia. *Psychiatr Times*. 2018;35(11):14-17.
8. Dattani S, Rodés-Guirao L. Why do women live longer than men? *Our World in Data*. November 27, 2023.
9. Wang Y-T, Theriault J, Servaes S, et al. Sex-specific modulation of amyloid- β on tau phosphorylation underlies faster tangle accumulation in females. *Brain*. 2024;147(4):1497-1510. doi:10.1093/brain/awad397
10. Inguanzo A, Poulakis K, Oltra J, et al. Atrophy trajectories in Alzheimer's disease: how sex matters. *Alzheimers Res Ther*. 2025;17(1):79. doi:10.1186/s13195-025-01713-x
11. Ferreira PCL, Zhang Y, Snitz B, et al. Plasma biomarkers identify older adults at risk of Alzheimer's disease and related dementias in a real-world population-based cohort. *Alzheimers Dement*. 2023;19(10):4507-4519. doi:10.1002/alz.12986
12. Poulakis K, Ferreira D, Pereira JB, Smedby Ö, Vemuri P, Westman E. Fully bayesian longitudinal unsupervised learning for the assessment and visualization of AD heterogeneity and progression. *Aging (Albany NY)*. 2020;12(13):12622-12647. doi:10.18632/aging.103623
13. Hua X, Hibar DP, Lee S, et al. Sex and age differences in atrophic rates: an ADNI study with n=1368 MRI scans. *Neurobiol Aging*. 2010;31(8):1463-1480. doi:10.1016/j.neurobiolaging.2010.04.033
14. Ferretti MT, Uccheddu MB, Flanagan R, Leroi I, Moro E. Inclusion in neurological research: empowering people living with neurological diseases. *Nat Rev Neurol*. January 7, 2025. doi:10.1038/s41582-024-01047-6
15. Emrani S, Sundermann EE. Sex/gender differences in the clinical trajectory of Alzheimer's disease: Insights into diagnosis and cognitive reserve. *Front Neuroendocrinol*. 2025;77:101184. doi:10.1016/j.yfrne.2025.101184
16. Lusk JB, Ford CB, Soneji S, et al. Sex differences in mortality and health care utilization after dementia diagnosis. *JAMA Neurol*. August 11, 2025. doi:10.1001/jamaneurol.2025.2236
17. Dementia Follows a Different Course in Men—Men had higher mortality than women after diagnosis. MedPageToday. August 12, 2025. Accessed August 18, 2025. https://www.medpagetoday.com/neurology/dementia/116964?utm_source=Sailthru&utm_medium=email&utm_campaign=Automated%20Specialty%20Update%20Neurology%20BiWeekly%20FRIDAY%202025-08-15&utm_term=NL_Spec_Neurology_Update_Active

18. Joseph NM, Ramamoorthy L, Satheesh S. Atypical Manifestations of Women Presenting with Myocardial Infarction at Tertiary Health Care Center: An Analytical Study. *J Midlife Health*. 2021;12(3):219-224. doi:10.4103/jmh.JMH_20_20
19. Januzzi JL. IMPLEMENTATION OF NEW TROPONIN TESTS AIDS DIAGNOSIS OF MI. *Advances in Motion | Massachusetts General Hospital*. Published online June 5, 2018. Accessed May 14, 2024. <https://advances.massgeneral.org/cardiovascular/article.aspx?id=1040>
20. Ali M, van Os HJA, van der Weerd N, et al. Sex Differences in Presentation of Stroke: A Systematic Review and Meta-Analysis. *Stroke*. 2022;53(2):345-354. doi:10.1161/STROKEAHA.120.034040
21. Xu Y, Harris K, Pouncey AL, et al. Sex differences in risk factors for incident peripheral artery disease hospitalisation or death: Cohort study of UK Biobank participants. *PLoS ONE*. 2023;18(10):e0292083. doi:10.1371/journal.pone.0292083
22. Mielke M. Sex and Gender Differences in Alzheimer's Disease and Alzheimer's Disease Related Dementias. *National Academies of Sciences, Engineering, and Medicine Commissioned Paper*. 2024.
23. Bourzac K. Why women experience Alzheimer's disease differently from men. *Nature*. 2025;640(8059):S14-S17. doi:10.1038/d41586-025-01106-y
24. Hirnstein M, Stuebs J, Moè A, Hausmann M. Sex/Gender Differences in Verbal Fluency and Verbal-Episodic Memory: A Meta-Analysis. *Perspect Psychol Sci*. 2023;18(1):67-90. doi:10.1177/17456916221082116
25. Sundermann EE, Biegon A, Rubin LH, et al. Does the Female Advantage in Verbal Memory Contribute to Underestimating Alzheimer's Disease Pathology in Women versus Men? *J Alzheimers Dis*. 2017;56(3):947-957. doi:10.3233/JAD-160716
26. Tang J, Zhang T. Causes of the male-female ratio of depression based on the psychosocial factors. *Front Psychol*. 2022;13:1052702. doi:10.3389/fpsyg.2022.1052702
27. Eikelboom WS, Pan M, Ossenkoppele R, et al. Sex differences in neuropsychiatric symptoms in Alzheimer's disease dementia: a meta-analysis. *Alzheimers Res Ther*. 2022;14(1):48. doi:10.1186/s13195-022-00991-z
28. Pless A, Ware D, Saggu S, Rehman H, Morgan J, Wang Q. Understanding neuropsychiatric symptoms in Alzheimer's disease: challenges and advances in diagnosis and treatment. *Front Neurosci*. 2023;17:1263771. doi:10.3389/fnins.2023.1263771
29. van Harten AC, Mielke MM, Swenson-Dravis DM, et al. Subjective cognitive decline and risk of MCI: The Mayo Clinic Study of Aging. *Neurology*. 2018;91(4):e300-e312. doi:10.1212/WNL.00000000000005863
30. Lyketsos CG, Steele C, Galik E, et al. Physical aggression in dementia patients and its relationship to depression. *Am J Psychiatry*. 1999;156(1):66-71. doi:10.1176/ajp.156.1.66
31. Ng A, Tam WW, Zhang MW, et al. IL-1 β , IL-6, TNF- α and CRP in Elderly Patients with Depression or Alzheimer's disease: Systematic Review and Meta-Analysis. *Sci Rep*. 2018;8(1):12050. doi:10.1038/s41598-018-30487-6
32. Gottshall JL, Agyemang AA, O'Neil M, et al. Sleep quality: A common thread linking depression, post-traumatic stress, and post-concussive symptoms to biomarkers of neurodegeneration following traumatic brain injury. *Brain Inf*. 2022;36(5):633-643. doi:10.1080/02699052.2022.2037711
33. Colombo D, Caltagirone C, Padovani A, et al. Gender differences in neuropsychiatric symptoms in mild to moderate alzheimer's disease patients undergoing switch of cholinesterase inhibitors: A post hoc analysis of the EVOLUTION study. *J Womens Health (Larchmt)*. 2018;27(11):1368-1377. doi:10.1089/jwh.2017.6420
34. Ellison J. Alzheimer's Disease in Men. Alzheimer's Disease Research. August 31, 2021. Accessed May 7, 2025. <https://www.brightfocus.org/resource/alzheimers-disease-in-men/>
35. Briceno Silva G, Arvelaez Pascucci J, Karim H, et al. Influence of the onset of menopause on the risk of developing alzheimer's disease. *Cureus*. 2024;16(9):e69124. doi:10.7759/cureus.69124
36. Park HK, Marston L, Mukadam N. The effects of estrogen on the risk of developing dementia: A cohort study using the UK biobank data. *Am J Geriatr Psychiatry*. 2024;32(7):792-805. doi:10.1016/j.jagp.2024.01.025
37. Bendis PC, Zimmerman S, Onisiforou A, Zanos P, Georgiou P. The impact of estradiol on serotonin, glutamate, and dopamine systems. *Front Neurosci*. 2024;18:1348551. doi:10.3389/fnins.2024.1348551
38. Fox M, Berzuini C, Knapp LA, Glynn LM. Women's pregnancy life history and alzheimer's risk: can immunoregulation explain the link? *Am J Alzheimers Dis Other Dement*. 2018;33(8):516-526. doi:10.1177/1533317518786447
39. Basit S, Wohlfahrt J, Boyd HA. Associations between parenthood and dementia in men and women: biology or confounding? *BMC Neurol*. 2023;23(1):90. doi:10.1186/s12883-023-03108-7
40. Li Q, Yang X, Xu J, et al. Early prediction of Alzheimer's disease and related dementias using real-world electronic health records. *Alzheimers Dement*. 2023;19(8):3506-3518. doi:10.1002/alz.12967
41. Schliep KC, Shaaban CE, Meeks H, et al. Hypertensive disorders of pregnancy and subsequent risk of Alzheimer's disease and other dementias. *Alzheimers Dement (Amst)*. 2023;15(2):e12443. doi:10.1002/dad2.12443
42. Villa A, Vegeto E, Poletti A, Maggi A. Estrogens, neuroinflammation, and neurodegeneration. *Endocr Rev*. 2016;37(4):372-402. doi:10.1210/er.2016-1007
43. Brann DW, Dhandapani K, Wakade C, Mahesh VB, Khan MM. Neurotrophic and neuroprotective actions of estrogen: basic mechanisms and clinical implications. *Steroids*. 2007;72(5):381-405. doi:10.1016/j.steroids.2007.02.003
44. Yao J, Brinton RD. Estrogen regulation of mitochondrial bioenergetics: implications for prevention of Alzheimer's disease. *Adv Pharmacol*. 2012;64:327-371. doi:10.1016/B978-0-12-394816-8.00010-6
45. Sohrabji F. Guarding the blood-brain barrier: a role for estrogen in the etiology of neurodegenerative disease. *Gene Expr*. 2007;13(6):311-319. doi:10.3727/000000006781510723
46. Wood Alexander M, Honer WG, Saloner R, et al. The interplay between age at menopause and synaptic integrity on Alzheimer's disease risk in women. *Sci Adv*. 2025;11(10):eadt0757. doi:10.1126/sciadv.adt0757
47. Song Q, Wang Q, Wu D, et al. Association between duration, initiation time, routes, and formulations of menopausal hormone therapy use and Alzheimer disease in women: A systematic review and meta-analysis. *J Pharmacol Exp Ther*. 2025;392(5):103554. doi:10.1016/j.jpet.2025.103554
48. Coughlan GT, Rubinstein Z, Klinger H, et al. Associations between hormone therapy use and tau accumulation in brain regions vulnerable to Alzheimer's disease. *Sci Adv*. 2025;11(10):eadt1288. doi:10.1126/sciadv.adt1288
49. Verghese J, Kuslansky G, Katz MJ, et al. Cognitive performance in surgically menopausal women on estrogen. *Neurology*. 2000;55(6):872-874. doi:10.1212/wnl.55.6.872
50. Jacobs DM, Tang MX, Stern Y, et al. Cognitive function in nondemented older women who took estrogen after menopause. *Neurology*. 1998;50(2):368-373. doi:10.1212/wnl.50.2.368
51. Craig MC, Maki PM, Murphy DGM. The Women's Health Initiative Memory Study: findings and implications for treatment. *Lancet Neurol*. 2005;4(3):190-194. doi:10.1016/S1474-4422(05)01016-1
52. Kang JH, Grodstein F. Postmenopausal hormone therapy, timing of initiation, APOE and cognitive decline. *Neurobiol Aging*. 2012;33(7):1129-1137. doi:10.1016/j.neurobiolaging.2010.10.007

53. Tsiknia AA, Reas E, Bangen KJ, et al. Sex and APOE ϵ 4 modify the effect of cardiovascular risk on tau in cognitively normal older adults. *Brain Commun.* 2022;4(1):fcac035. doi:10.1093/braincomms/fcac035
54. Altmann A, Tian L, Henderson VW, Greicius MD, Alzheimer's Disease Neuroimaging Initiative Investigators. Sex modifies the APOE-related risk of developing Alzheimer disease. *Ann Neurol.* 2014;75(4):563-573. doi:10.1002/ana.24135
55. Sampedro F, Vilaplana E, de Leon MJ, et al. APOE-by-sex interactions on brain structure and metabolism in healthy elderly controls. *Oncotarget.* 2015;6(29):26663-26674. doi:10.18632/oncotarget.5185
56. Rosenzweig N, Kleemann KL, Rust T, et al. Sex-dependent APOE4 neutrophil-microglia interactions drive cognitive impairment in Alzheimer's disease. *Nat Med.* 2024;30(10):2990-3003. doi:10.1038/s41591-024-03122-3
57. He Y, Rodrigues RM, Wang X, et al. Neutrophil-to-hepatocyte communication via LDLR-dependent miR-223-enriched extracellular vesicle transfer ameliorates nonalcoholic steatohepatitis. *J Clin Invest.* 2021;131(3). doi:10.1172/JCI141513
58. Li R, Fan W, Li D, Liu X. Correlation of common inflammatory cytokines with cognition impairment, anxiety, and depression in acute ischemic stroke patients. *Braz J Med Biol Res.* 2022;55:e11517. doi:10.1590/1414-431X2021e11517
59. Guo Y, Cai C, Zhang B, et al. Targeting USP11 regulation by a novel lithium-organic coordination compound improves neuropathologies and cognitive functions in Alzheimer transgenic mice. *EMBO Mol Med.* 2024;16(11):2856-2881. doi:10.1038/s44321-024-00146-7
60. Yan Y, Wang X, Chaput D, et al. X-linked ubiquitin-specific peptidase 11 increases tauopathy vulnerability in women. *Cell.* 2022;185(21):3913-3930.e19. doi:10.1016/j.cell.2022.09.002
61. Aksnes M. Sex differences in biofluid biomarkers for alzheimer's disease. *Neurodegener Dis.* May 26, 2025:1-11. doi:10.1159/000545717
62. Tsiknia AA, Sundermann EE, Edland SD, et al. The relationship between plasma matrix metalloproteinase-9 and cerebrospinal fluid biomarkers of tau is sex-dependent. *Alzheimer's & Dementia.* December 20, 2022.
63. Chappell WH, Abrams SL, Lertpiriyapong K, et al. Novel roles of androgen receptor, epidermal growth factor receptor, TP53, regulatory RNAs, NF-kappa-B, chromosomal translocations, neutrophil associated gelatinase, and matrix metalloproteinase-9 in prostate cancer and prostate cancer stem cells. *Adv Biol Regul.* 2016;60:64-87. doi:10.1016/j.jbior.2015.10.001
64. Tsiknia AA, Sundermann EE, Reas ET, et al. Sex differences in Alzheimer's disease: plasma MMP-9 and markers of disease severity. *Alzheimers Res Ther.* 2022;14(1):160. doi:10.1186/s13195-022-01106-4
65. Yan P, Hu X, Song H, et al. Matrix metalloproteinase-9 degrades amyloid-beta fibrils in vitro and compact plaques in situ. *J Biol Chem.* 2006;281(34):24566-24574. doi:10.1074/jbc.M602440200
66. Seitz-Holland J, Alemán-Gómez Y, Cho KIK, et al. Matrix metalloproteinase 9 (MMP-9) activity, hippocampal extracellular free water, and cognitive deficits are associated with each other in early phase psychosis. *Neuropsychopharmacology.* 2024;49(7):1140-1150. doi:10.1038/s41386-024-01814-5
67. Abe K, Chiba Y, Hattori S, et al. Influence of plasma matrix metalloproteinase levels on longitudinal changes in Alzheimer's disease (AD) biomarkers and cognitive function in patients with mild cognitive impairment due to AD registered in the Alzheimer's Disease Neuroimaging Initiative database. *J Neurol Sci.* 2020;416:116989. doi:10.1016/j.jns.2020.116989
68. Coughlan GT, Klinger HM, Boyle R, et al. Sex Differences in Longitudinal Tau-PET in Preclinical Alzheimer Disease: A Meta-Analysis. *JAMA Neurol.* 2025;82(4):364-375. doi:10.1001/jamaneurol.2025.0013
69. Buckley RF, Mormino EC, Rabin JS, et al. Sex differences in the association of global amyloid and regional tau deposition measured by positron emission tomography in clinically normal older adults. *JAMA Neurol.* 2019;76(5):542-551. doi:10.1001/jamaneurol.2018.4693
70. Castro-Aldrete L, Einsiedler M, Novakova Martinkova J, et al. Alzheimer disease seen through the lens of sex and gender. *Nat Rev Neurol.* 2025;21(5):235-249. doi:10.1038/s41582-025-01071-0
71. Huang Y, Mahley RW. Apolipoprotein E: structure and function in lipid metabolism, neurobiology, and Alzheimer's diseases. *Neurobiol Dis.* 2014;72 Pt A:3-12. doi:10.1016/j.nbd.2014.08.025
72. Yang LG, March ZM, Stephenson RA, Narayan PS. Apolipoprotein E in lipid metabolism and neurodegenerative disease. *Trends Endocrinol Metab.* 2023;34(8):430-445. doi:10.1016/j.tem.2023.05.002
73. Estes RE, Lin B, Khera A, Davis MY. Lipid metabolism influence on neurodegenerative disease progression: is the vehicle as important as the cargo? *Front Mol Neurosci.* 2021;14:788695. doi:10.3389/fnmol.2021.788695
74. Wretling A, Xu J, Chen W, et al. Lipid profiling reveals unsaturated lipid reduction in women with Alzheimer's disease. *Alzheimers Dement.* 2025;21(8):e70512. doi:10.1002/alz.70512
75. Agarwal P, Leurgans SE, Agrawal S, et al. Association of Mediterranean-DASH Intervention for Neurodegenerative Delay and Mediterranean Diets With Alzheimer Disease Pathology. *Neurology.* 2023;100(22):e2259-e2268. doi:10.1212/WNL.0000000000207176
76. Klee M, Leist AK, Veldsman M, Ranson JM, Llewellyn DJ. Socioeconomic deprivation, genetic risk, and incident dementia. *Am J Prev Med.* 2023;64(5):621-630. doi:10.1016/j.amepre.2023.01.012
77. Oxfam International. Why the majority of the world's poor are women. Oxfam International | The future is equal. 2025. Accessed May 19, 2025. <https://www.oxfam.org/en/why-majority-worlds-poor-are-women>
78. More Women Get Alzheimer's Than Men. Why? Accessed April 30, 2025. <https://www.alz.org/news/2020/more-women-get-alzheimer-s-than-men-why>
79. Sharp ES, Gatz M. Relationship between education and dementia: an updated systematic review. *Alzheimer Dis Assoc Disord.* 2011;25(4):289-304. doi:10.1097/WAD.0b013e318211c83c

