PERSPECTIVE

WOMEN'S HEALTH

Female Clinical Resilience Despite Pathologic Risk in Alzheimer Disease

Kaitlin B. Casaletto, PhD; Dena B. Dubal, MD, PhD

In every society that records mortality, women live longer than men. A growing body of evidence supports a role for female resilience even beyond longevity, influencing biology and clinical manifestation of brain aging and neurodegenerative diseases, including Alzheimer disease (AD).[1] This emerging view counters the dominant narrative that frames women as uniquely vulnerable to AD because two-thirds of people living with AD today are women. Can women be both resilient and vulnerable? Does female biology—X chromosome expression and sex hormones—shape risk and resilience? Why do women carry a greater pathologic burden and how do they outlive their AD pathology?

Why Study Women's Brain Health?

Unraveling the female-specific epidemiology, neuropathology, clinical expression, and treatment response of AD is a major opportunity for science and medicine, with potential gains for all. Defining and then leveraging female-specific pathways to AD could transform our mechanistic understanding of its pathophysiology, advance diagnostic precision, and even identify novel therapeutic targets for both women and men. Beyond its profound moral imperative, considering the unique biology of the female brain is simply rigorous science, defined by careful consideration of all contributing factors. Although women compose half the population and women's health is not a niche topic, the female brain has been understudied and deeply neglected. The opportunity for discovery is substantial.

Epidemiology and Female Survival Advantage

Women with AD live longer than men with AD.[1] This survival advantage extends across other neurologic diseases and neurodegenerative conditions, including multiple sclerosis, amyotrophic lateral sclerosis, and Parkinson disease. Women live longer and have increased AD incidence after approximately age 80 years,[2] an age range that fewer men reach. Thus, men who survive to very advanced ages represent a particularly robust subgroup, introducing a bias that can obscure true sex differences in risk, pathology, and clinical course. However, before this late-life inflection point, women and men show largely similar age-specific incidence of AD when examined across larger epidemiologic studies and meta-analyses.[2] These data suggest that by simply living into the highest risk years, female resilience in longevity contributes to what appears to be vulnerability: a 2-fold higher lifetime AD risk.[3] Emerging preclinical studies implicate signaling of the second X chromosome as a potential mechanism conferring female longevity in aging and AD.[4,5] We posit that deep inquiry into the X chromosome may hold clues to dementia prevention targets.

Higher Tau Burden yet Higher Clinical Resilience in Women

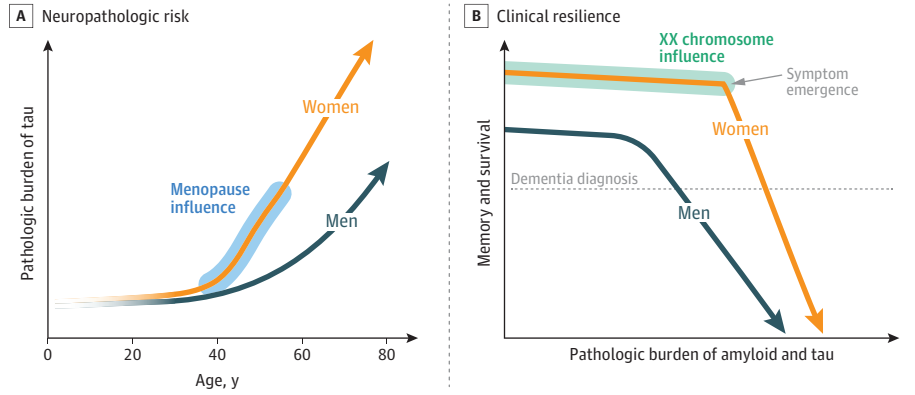
The prevailing scientific narrative has largely emphasized women's biological vulnerability to AD, particularly to tau pathology. Independent of women's longevity, evidence from cerebrospinal fluid, positron emission tomographic imaging, and autopsy studies demonstrates earlier and greater AD pathologic burden in women compared with men, particularly driven by more rapidly accumulating tau for a given level of amyloid.[6] Tau vulnerability may extend beyond amyloid because women with Lewy body disease also show higher tau level for their level of α-synuclein.[7] The increase in AD pathology begins in midlife for women, even among adults without clinical impairments, implicating the menopause transition (mean age in the US, 50-52 years) as a window for AD vulnerability. Other data points that support female-specific risk include *APOE4,* the strongest nonmonogenic risk factor for AD, which confers greater risk in women, as well as faster neurodegeneration (eg, atrophy on magnetic resonance imaging, elevated neurofilament light level) in women with AD biomarkers. Collectively, these findings have shaped an understandably dominant narrative of increased female vulnerability to AD through a lens of heightened neuropathologic risk.

However, this framing is incomplete. A deeper examination of the same evidence reveals that despite carrying a higher burden, in another form of clinical resilience, women show attenuated clinical expression of AD pathology (**Figure**). As in female longevity, both in typical aging and in AD, women demonstrate a well-replicated memory advantage, particularly in the verbal domain. This pattern is observed across test paradigms and languages and spans prepubescent girls to postmenopausal women. In AD, a memory-predominant syndrome, this advantage may manifest as clinical resilience. Thus, at comparable levels of pathology, women demonstrate memory performance and functional outcomes equal to or better than that of men.[8] In other words, for her pathology, a woman appears less clinically affected. Taken together, these findings indicate that women with AD simultaneously exhibit unique vulnerability to neuropathologic burden and more clinical resilience, highlighting a dissociation between pathology and clinical expression that deserves scientific exploration (Figure).

Precipitous Decline Follows Clinical Resilience

The female pattern of outperforming pathology is followed by later more precipitous decline (Figure).[8] Once women begin to manifest AD clinically (eg, mild cognitive impairment), they demonstrate steeper clinical decline than men, effectively catching up to their higher pathologic burden. This trajectory is consistent with cognitive reserve frameworks originally described in adults with higher levels of education. Perhaps women's higher baseline verbal memory and survival reflect a higher starting point with greater potential decline, female-specific protective biology, or both.

Figure. Illustration Showing Female Neuropathologic Risk and Clinical Resilience in Alzheimer Disease



Women show increased pathologic burden of tau (A) alongside increased clinical resilience to Alzheimer disease (longevity and cognition), potentially arising from female-specific biology related to menopause and X chromosomes. These are hypotheses based on existing work, but both menopause and X chromosome biology likely contribute to risk and resilience in women.

Clinical Resilience Beyond AD

Emerging studies suggest that women's clinical resilience may not be unique to AD. Frontotemporal dementia is a young-onset dementia commonly caused by misfolding of TAR DNA-binding protein 43 or frontotemporal lobar degeneration tau and influences empathy and affect processing, domains in which women may also demonstrate a consistent baseline advantage. Women with frontotemporal dementia show steeper increases in biomarkers of neurodegeneration (plasma neurofilament light level or atrophy on magnetic resonance imaging) yet better cognitive and functional outcomes for a given level of neurodegenerative burden, particularly in preclinical and early stages of disease. As in AD, this early clinical resilience is followed by a tipping point marked by steeper clinical decline after mild cognitive impairment diagnosis.[9] Together, these findings suggest a disease-agnostic pattern of vulnerability to neuropathologic burden coupled with early clinical resilience, implicating shared female-specific biology across dementias and maybe across neurologic disease.

We emphasize a critical need to separate pathology from clinical symptomatology and consider age at symptom onset and disease stage when examining sex differences in neurodegenerative diseases. Outstanding questions include the timing of disproportionate neuropathologic accumulation in women, the nature of prolonged asymptomatic phases, and the specificity of these resilience patterns to tauopathies.

Why Does Clinical Resilience Matter?

Female clinical resilience, manifested as longevity and preserved cognition early on despite high pathologic burden, matters. Because mixed proteinopathies are increasingly recognized as the norm in dementia, uncovering the biological drivers that allow a woman to outperform and outlive her pathology offers massive potential for therapeutic discovery relevant for men and women. These mechanisms may overlap with pathways linked to longevity and biologically younger brains, including youthful metabolic and epigenetic signatures enriched in women. Even a 1-year delay in symptom onset could prevent tens of millions of dementia cases worldwide. This resilience, potentially conserved across neurologic conditions, represents an untapped source of high-value biological insight. For example, discovery of aging-induced X chromosome reactivation mechanisms in female mice revealed a target that improved cognition in aged mouse brains of both sexes.[10] What other breakthroughs will emerge when we more fully study the female brain?

Beyond discovery, female clinical resilience in AD in the face of increased neuropathologic disease burden has direct clinical relevance. Women are presenting with more biologically advanced disease at symptom onset, potentially narrowing the therapeutic window for disease-modifying treatments. Consistent with this finding, women showed less than half the clinical benefit to amyloid-lowering drugs in recent trial data. This discovery means we need to recalibrate clinical urgency of reported cognitive changes even when test performance falls within normative ranges, adopt sex-specific biomarker thresholds, and develop sex-informed prognostic and follow-up strategies that account for faster progression after symptom onset in women.

Embracing a framework that integrates the perspective of female resilience, alongside vulnerability, across epidemiologic, clinical, and foundational basic science domains will accelerate discovery, improve care for women, and ultimately advance brain health for all.

ARTICLE INFORMATION

Author Affiliations: Department of Neurology and Weill Institute for Neurosciences, University of California, San Francisco (Casaletto, Dubal); Edward and Pearl Fein Memory and Aging Center, University of California, San Francisco (Casaletto).

Corresponding Author: Dena B. Dubal, MD, PhD, University of California, San Francisco, 1571 24th Ave, San Francisco, CA 94122 (dena.dubal@ucsf.edu).

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