Title

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Journal

Alzheimer's & Dementia, 20(8)

ISSN

1552-5260

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Publication Date

2024-08-01

DOI

10.1002/alz.13844

Peer reviewed

Received: 8 November 2023 | Revised: 8 March 2024 | Accepted: 21 March 2024

DOI: 10.1002/alz.13844

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

REVIEW ARTICLE

Sex and gender differences in cognitive resilience to aging and Alzheimer's disease

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[Correction added on August 01, 2024, after first online publication: The order of the first and last names for the author Prashanthi Vemuri was corrected].

Funding information
Spanish Ministry of Science and Innovation, European Social Fund—State Research Agency, Grant/Award Number: RYC2018-026053-I; Spanish Ministry of Science and Innovation, Grant/Award Number: PID2019-111514RA-I00; Alzheimer's Association, Grant/Award Numbers: AARG2019-AARG-644641, AARG2019-AARG-644641-RAPID; EU Joint Programme-Neurodegenerative Disease Research, Grant/Award Number: JPND2022-138; Research and innovation Program of the Barcelona City Council and Fundació La Caixa, Grant/Award Number:

Abstract

Sex and gender—biological and social constructs—significantly impact the prevalence of protective and risk factors, influencing the burden of Alzheimer's disease (AD; amyloid beta and tau) and other pathologies (e.g., cerebrovascular disease) which ultimately shape cognitive trajectories. Understanding the interplay of these factors is central to understanding resilience and resistance mechanisms explaining maintained cognitive function and reduced pathology accumulation in aging and AD. In this narrative review, the ADDRESS! Special Interest Group (Alzheimer's Association) adopted a multidisciplinary approach to provide the foundations and recommendations for future research into sex- and gender-specific drivers of resilience, including a sex/gender-oriented review of risk factors, genetics, AD and non-AD pathologies, brain structure and function, and animal research. We urge the field to adopt a sex/gender-aware approach to resilience to advance our understanding of the intricate interplay of biological and social determinants and consider sex/gender-specific resilience throughout disease stages.

KEYWORDS
brain maintenance, cardiovascular, cognitive decline, cognitive reserve, education, genetics, inequalities, lifestyle, TDP43

Highlights

- Sex differences in resilience to cognitive decline vary by age and cognitive status.
- Initial evidence supports sex-specific distinctions in brain pathology.

21S0906; National Institute on Aging, Grant/Award Numbers: R01AG072475, R56AG082414; the National Institute of Health, Grant/Award Numbers: T32AG078115, R01-AG059716, F31-AG077791, R00AG066934, R00AG061238, DP2AG082342, R01AG079142, R01AG062167, R01AG077507, U19AG024904, U19AG078109, U19AG073153, R01AG066203, R01AG070028, R01AG027161, RF1AG052324, R01 AG056366, U01 AG006786; NIA-funded Hopkins Economics of Alzheimer's Disease & Services Center; NIA-funded The Science of Alzheimer's Disease and Related Dementias; ICREA Academia 2019 Award; Catalan Government, and the Spanish Ministry of Science and education, Grant/Award Number: PID2022-137234OB-I00; Simons Foundation; Bakar Aging Research Institute Grants, Grant/Award Numbers: AG068325, AG079176

- Findings suggest sex differences in the impact of pathology on cognition.
- There is a sex-specific change in resilience in the transition to clinical stages.
- Gender and sex factors warrant study: modifiable, immune, inflammatory, and vascular.

1 | INTRODUCTION

There is considerable inter-individual variability in the response to Alzheimer's disease (AD) pathology such that some individuals are able to cope better and maintain cognitive function over time. Indeed, ≈ 30% of older adults meet neuropathological criteria for AD at autopsy, yet remain cognitively unimpaired throughout life.[1,2] The concept of resilience aims to explain the disconnect between pathology and cognition, and refers to the brain mechanisms explaining the capacity of the brain to maintain cognitive function with aging and disease.[3–6] The recognition of a long preclinical phase before the appearance of the clinical symptoms in AD and the potential to intervene during this phase[7] has drawn attention to the identification of modifiable factors that may postpone the development of cognitive impairment.

Studies using in vivo AD biomarkers have also demonstrated that some individuals show absence or low burden of pathologies in the context of heightened risk, and suggested that some modifiable factors, such as physical and cognitive activities, are linked with lower burden or slower accumulation of AD pathologies.[4] The concept of resistance to pathologies refers to the notion that, in the context of heightened risk, some individuals show absence or lower-than-expected pathological burden.[4,6]

Recently, there has been increasing awareness of the relevance of studying sex- and gender-specific drivers of resistance and resilience in AD. Women, who make up the majority of AD patients, experience a 2-fold higher lifetime risk and greater mortality compared to men.[8,9] Higher women's life expectancy in aging and AD[10] may contribute to variations in lifetime dementia risk, while incidence differences across genders remain unclear,[11] with conflicting study findings.[12–14] An important factor to consider is that differential risk and resilience may be driven by factors related to sex—referring to an individual's sex chromosome complement (XX vs. XY)—or gender—referring to socially constructed roles, identities, and behaviors—or an intersection of both.[15] However, there is a dearth of literature available focusing explicitly on sex/gender differences in resilience. A sex- and gender-aware resilience framework in AD ought to extend beyond mere description of sex- and gender-related differences and articulate sex and gender to achieve a comprehensive understanding of the sex- and gender-related pathways leading to cognitive decline and dementia or the prevention of it. In line with this, it is essential to highlight that the investigation of factors associated with resilience in AD have mainly been tackled from an individual-level perspective (e.g., the level of educational attainment). An individual-level perspective disregards how societal-level factors and cultural determinants, including gender, race, ethnicity, and their intersections influence individual behaviors,[16] explain differential mechanisms of risk and resilience, and interact with biological risk (e.g., social factors play a role in shaping educational attainment). The scarce available evidence from sex/gender-stratified studies also suggests that widely investigated determinants of reserve such as education and occupation may show differential effects in women and men.[17]

The overall objective of this narrative review is to present the available evidence on sex and gender differences in resilience to AD and establish the foundations for future research. We will first provide a state-of-the-science review and perspective on existing studies formulating testable hypotheses. Then, we will discuss how animal research could aid in the understanding of sex differences in resilience. Finally, we will identify existing research gaps, and provide directions and recommendations to integrate sex and gender into research studies investigating cognitive resilience to aging and AD.

RESEARCH IN CONTEXT

1. **Systematic review**: Through conventional literature sources, we identified sex/gender differences in dementia risk with a gap in understanding specific risk and resilience pathways. In aging and Alzheimer's disease (AD), resilience to cognitive decline may stem from factors linked to diminished pathologies—resistance—or to their limited impact on cognition—resilience—thereby influencing dementia risk.
2. **Interpretation**: Resilience to cognitive decline should be envisaged considering age, cognitive status, and risk factors within a sex/gender-aware framework. Initial evidence supports sex/gender differences in underlying pathologies—women show lower resistance to tau and distinct vulnerabilities to cardiovascular disease compared to men—and in the ability to cope with the effects of amyloid and atrophy—with initially enhanced resilience being lost in women as they transition to clinical stages.
3. **Future directions**: Studies on factors accounting for differential resilience including exposure to risk factors, pathologies, sex, and inflammatory and vascular pathways are warranted.

2 | SEX AND GENDER IN THE RESISTANCE AND RESILIENCE FRAMEWORK: TERMINOLOGY

2.1 | Sex and gender: biological versus social constructs

Sex refers to an individual's sex chromosome complement (XX vs. XY), which is reflected in the reproductive organs.[18] An individual is defined as being male or female according to genetics, anatomy, and physiology. This construct has limitations as growing evidence demonstrates the existence of non-binary and intersex populations.[19] By contrast, gender is a social construct that refers to socially constructed roles, identities, and behaviors.[20] Gender is a multifaceted and fluid construct that is influenced by prior, as well as contemporaneous, social and cultural contexts and environments.

Conventionally, sex has been regarded as a confounding factor (and therefore controlled for) in resilience studies; here, however, we argue that this construct is central to the study of resilience and reserve. The most widely investigated determinants of reserve and resilience, for example, education, are highly gendered. Therefore, the results of studies using gendered determinants of reserve and resilience, such as years of education, need to be interpreted within a broader gender-oriented framework in which women traditionally have had fewer opportunities for higher education. Only this level of understanding of the determinants of resilience will ensure precise approaches to building models of reserve and resilience at an individual, population, and societal level.

There are several limitations when assessing sex and gender (often self-reported) in human research, particularly when attempting to disentangle their specific effects as they are intrinsically linked. Here we will refer to "women" and "men" when discussing human studies without explicit investigation of biological pathways, and "male" and "female" when discussing animal models or referring to potential biological pathways. We will approach gender from a binary perspective, given the very scarce existing literature on other gender identities. Health disparities have been reported in sexual and gender minorities[21] which may in turn have profound effects on individual risk and resilience for cognitive decline. Therefore, we do acknowledge the need for research in sexual and gender minorities as discussed in the Recommendations section.

2.2 | Resilience and resistance to AD

The Collaboratory on Research Definitions for Reserve and Resilience in Cognitive Aging and Dementia[22] established a consensus on the use of *resilience* as an umbrella term[4] encompassing different mechanisms about "the capacity of the brain to maintain cognitive function with aging and disease" including brain reserve, brain maintenance, and cognitive reserve.[23–26] Briefly, these concepts refer to brain mechanisms including greater neurobiological capital to start with, maintenance of brain structure and function over time, or greater adaptability of cognitive strategies.[4]

In the AD field, there has been an increasing consensus on the conceptual separation of the notions of "coping" with AD pathologies versus "avoiding" AD pathologies. We refer to these as resilience (coping) and resistance (avoiding). In the context of AD biomarker studies, this terminology presents with the advantage of separating factors that may help halt the development of AD pathologies (amyloid [A]/tau[T]) ("resistance") versus delay processes downstream to AT, that is, neurodegeneration (N) and the clinical expression of the disease ("resilience").[4,5]

Thus, in AD, resilience refers to the ability to attenuate the detrimental effect of risk (i.e., age, apolipoprotein E [*APOE*] $\varepsilon 4$) and/or pathology (i.e., amyloid beta [Aβ], tau) on cognitive performance. Therefore, a measure of resilience could be the extent to which cognitive performance is better than expected at a given level of risk or pathology.[27] Resilience is also investigated in observational studies in which risk and protective factors are considered to mitigate the associations of risk or pathology with cognitive decline.[4] The brain properties and mechanisms underlying resilience to AD are currently under intense investigation in the field.[28]

In the context of AD, resistance to pathologies refers to the notion that some individuals may show absence or low pathological burden when it is expected (i.e., in the context of heightened risk). It is important to note that the absence of pathology alone does not imply resistance.[4,6] The rationale for this concept is that, while very old age and genetic factors may drive AD-related pathology and cognitive

TABLE 1 Description of the terminology resilience/resistance in the context of AD. The terminology refers to the outcomes (e.g., cognitive or brain measurements) relative to investigated pathology or risk factors. The table provides selected examples for clarity. Lower-than-expected pathologies or better-than-expected outcomes refer to superior results than expected given the level of risk.

Primary outcome	Resistance/resilience	Pathology/risk factor	Meaning
Cognitive (cognition)	Resilience to	Tau	The study investigates factors that attenuate the impact of tau on cognition
Cognitive (cognition)	Resilience	–	The study investigates factors that explain better-than-expected cognition in the context of aging or disease
Cognitive (cognition)	Resilience to	*APOE ε4*	The investigation evaluates factors that attenuate *APOE ε4*'s effects on cognitive outcomes
Brain	Resilience to	Amyloid	The study investigates factors that minimize the effect of amyloid on brain structure and/or function
Brain	Resilience		The study investigates factors that explain better brain outcomes in the context of risk (aging or disease)
	Resistance to	Amyloid	The study investigates factors associated with absence or lower-than-expected amyloid levels
	Resistance to	Tau	The investigation focuses on factors associated with absence or lower-than-expected tau

Abbreviation: AD, Alzheimer's disease; *APOE*, apolipoprotein.

decline, some individuals "avoid" (or mitigate) the effects of risk factors and show none or lower than-expected pathologies.

When using this terminology, it is important to also consider the brain/cognition axis. Cognition theoretically operates at the highest level of abstraction, as it is the result of lifetime exposure to risk and protective factors, brain pathologies, and the ability of the brain to cope with them. Therefore, we considered two broad pathways that may result in maintained cognition in aging and disease: (1) lower presence of pathologies in the context of risk (resistance to pathologies such as amyloid or tau), and (2) more preserved brain structure/function and/or more efficient neural resources to compensate for pathology (brain resilience).[3,20,24] These mechanisms/pathways are determined by a complex interplay of genetic and environmental factors.

To ensure clarity throughout the paper, we will adopt a terminology that refers to the outcome (e.g., cognitive or brain measurements) and pathologies studied as explained in Table 1: for example, "cognitive resilience to tau," "brain resilience to tau," or "resistance to amyloid." The term "cognitive resilience" will be used when talking about studies in the context of aging or risk while not directly addressing brain pathologies or brain mechanisms.

Studies investigating factors and mechanisms associated with maintained cognitive function in aging and disease typically revolve around a framework comprising three components: (1) risk/protective factors, (2) biomarkers of aging or pathologies, and (3) cognitive measurements. Sex and gender may influence the prevalence, level and trajectory of each component, and the relations between them as illustrated in Figure 1.

3 | SEX AND GENDER DIFFERENCES IN COGNITIVE RESILIENCE

In this section, we discuss sex and gender differences in baseline and cognitive trajectories. As supported by the evidence presented below, there is greater consensus on the sex/gender differences in cognitive abilities at baseline than on cognitive trajectories. While one could argue that baseline sex differences will set the stage for higher cognitive resilience and thus a delayed onset of cognitive impairment, the evidence for sex differences in cognitive trajectories is inconsistent. The findings presented in this section suggest that sex differences in cognitive resilience should be envisaged by age period, cognitive status (normal aging vs. disease), and through the consideration of health and sociocultural risk factors.

3.1 | Sex/gender differences in baseline cognition and cognitive trajectories

Cross-sectionally, women generally show better memory, notably, verbal and episodic memory, although better executive functioning in women has also been reported.[29–32] Men tend to show better visuospatial skills, but this is a less consistent finding.[33,34] The memory advantage in women seems to be stable across the lifespan and still present at very old ages. For instance, at > 75 years, women perform better in verbal episodic memory than men.[35,36] Overall, these findings may imply a consistent memory advantage in women as illustrated in Figure 2A. These sex differences have been reported independent

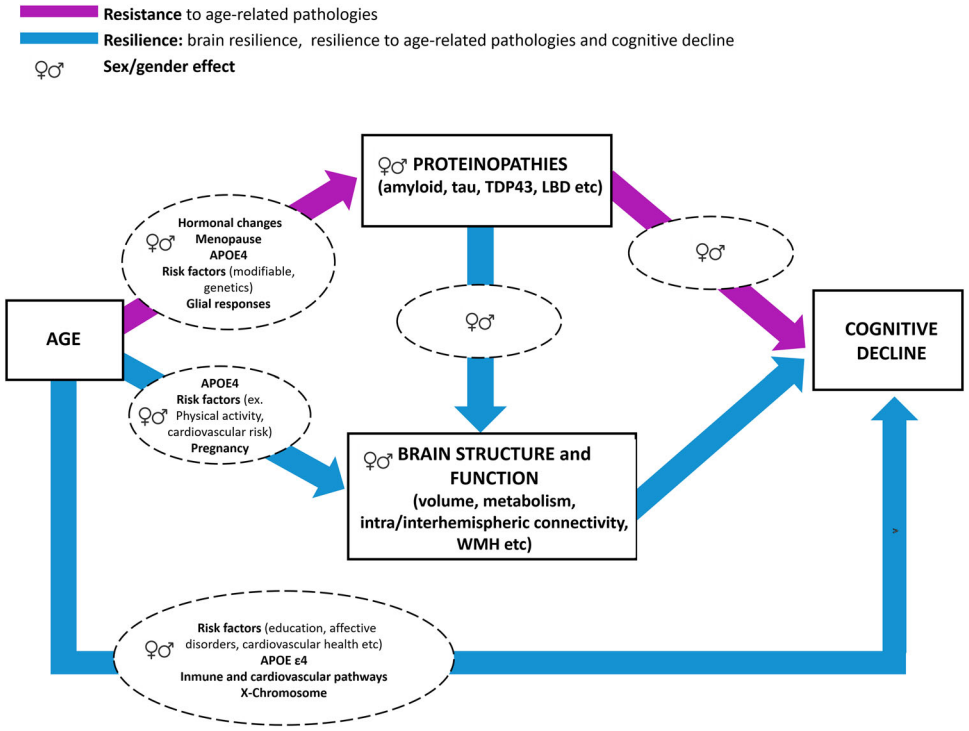

FIGURE 1 Illustration of resilience and resistance frameworks considering sex and gender effects and associated factors. Sex- and gender-related protective factors may act through increasing resistance and resilience to ultimately impact cognitive resilience. We are providing examples of sex- and gender-related factors shown to have an impact on pathologies, brain structure and function, or cognitive decline. *APOE*, apolipoprotein; TDP43, Tar DNA-binding protein; WMH, white matter hyperintensities

of demographics including age, race/ethnicity, education, clinical measurements (i.e., blood pressure), and age-related brain changes,[37,38] suggesting a robust sex-specific advantage across cognitive domains. Recent work with a sociocultural perspective, however, has found interactions of sex/gender with race/ethnicity,[39] implying that the intersection of sociocultural variables and sex/gender requires more attention.

By contrast, results regarding sex differences in rates of cognitive decline are controversial. Longitudinal studies considering the adult lifespan suggest that sex discrepancies in memory performance become particularly salient at[40] or after the age of 40.[37] Slower memory decline in women at the age of 40 and greater decline in women after the age of 60 were reported in the same study.[40] In cognitively unimpaired cohorts with an average age of ≈ 60 years, however, a range of findings have been reported: no sex differences,[41] slower decline in women across cognitive domains or only in perceptuomotor speed, integration, and visuospatial ability.[34] In later life (60s–80s), results seem more consistent, with a meta-analysis reporting no sex differences.[42] Finally, in the oldest old (> 80 years), evidence suggests no sex differences in cognitive trajectories.[36] Figure 2B illustrates sex-specific cognitive trajectories with a lower decline after the age of 40 in women, inconsistent results around the age of 60, and no sex differences at older ages.

Another set of findings suggest that there might be a critical loss of cognitive resilience that women demonstrate as they progress from normal aging to a diagnosis of cognitive impairment and dementia as illustrated in Figure 2C. Hence, in the context of pathological aging, women with mild cognitive impairment (MCI) showed greater cognitive decline than men (as measured by the Alzheimer's Disease Assessment Scale–Cognitive subscale).[43] Further, studies looking at clinical progression have consistently reported that women progressed faster than men to a clinical diagnosis of MCI and dementia.[44–46] Women with AD dementia were outperformed by men in multiple domains including visuospatial, verbal processing, and semantic and episodic memory. This disadvantage was reported independent of age, education level, and dementia severity.[47,48]

Finally, there are interesting and nuanced associations between sex and *APOE* ε4 on cognitive decline and clinical progression. Women *APOE* ε4 carriers show higher incidence rates to dementia than men carriers,[49] although this was more recently limited to the age range between 65 and 75 years.[50] Women carrying the *APOE* ε4 allele have been reported to show worse memory and decline faster than men.[40,50] In MCI patients, female *APOE* ε4 carriers, regardless of zygosity, show poorer delayed memory recall at the cross-section, but only in homozygous men.[51] Finally, one study has suggested that ε 4 may only exacerbate poorer cognition in women relative to men during midlife and not later life, which may arise as a consequence of midlife menopausal changes (discussed in a later section).[52] *APOE* ε4 carriage and menopausal changes should therefore be considered in the context of the controversial

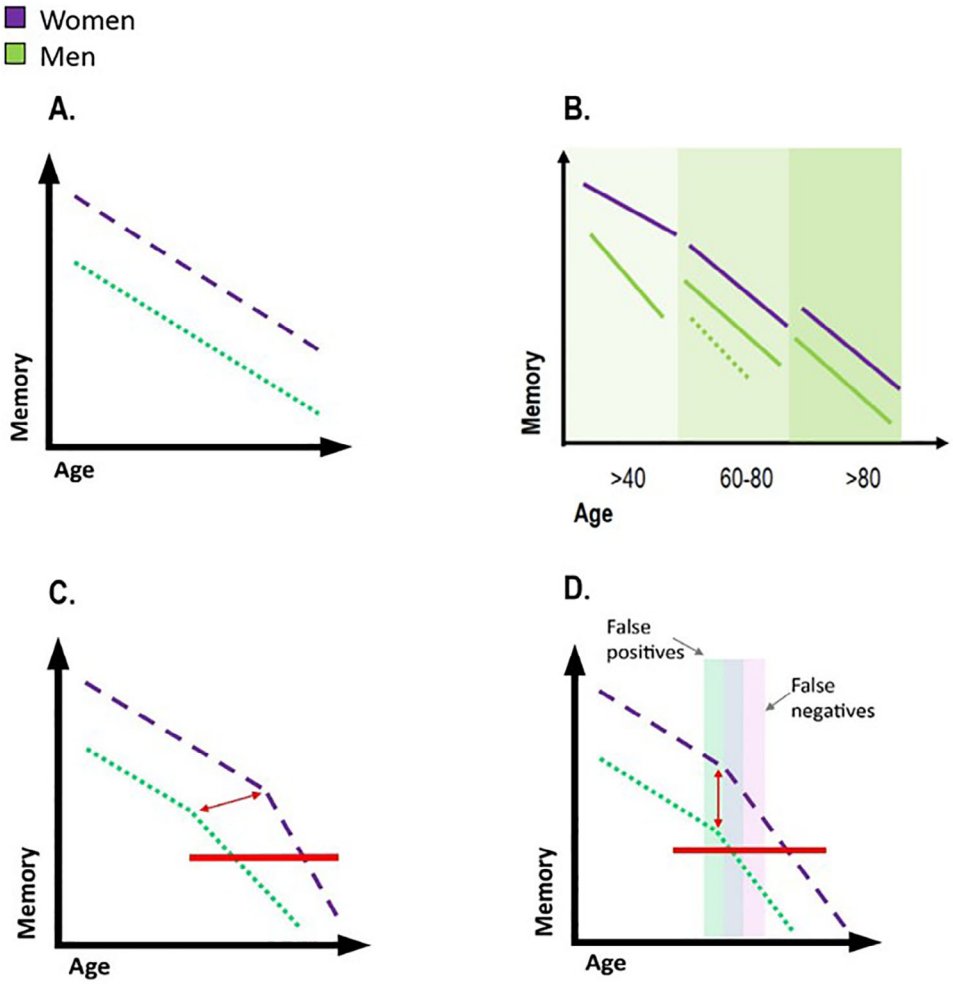

FIGURE 2 Hypothetical models explaining sex differences in memory throughout aging and disease. A, Initial memory advance provides cognitive resilience through aging (differences in level but not slope). B, Sex differences in memory may vary at different stages of the aging process. The discontinuous line in the 60s to 80s period for men illustrates the conflicting findings. C, The initial memory advantage in women diminishes over time: women cope with AD pathology for longer until they experience a faster decline (differences in level and slope). D, Diagnosis bias due to the differences in baseline memory performance. The red line in C and D illustrates the onset of AD pathology.

results regarding sex differences in cognitive decline around the age of 60.

Discrepant results on cognitive trajectories as well as on the moderating effect of *APOE* ε4 on the association between sex and cognitive performance may arise because of different sampling frames and adjustment for different variables that may interact with sex. For example, as discussed below, the differential prevalence and incidence of risk factors across samples and age periods in men and women may differentially influence cognitive trajectories,[40] further, sociocultural factors may also interact with sex and gender.[39] Overall, studies focusing on the resilience frameworks should shift the focus from merely describing sex differences in cognition toward comprehending the underlying factors (*APOE* ε4, menopause, sociocultural factors) and related mechanisms that contribute to these differences.

3.2 | Are sex differences in cognitive resilience the result of lower AD pathologies or preserved brain integrity?

As suggested in the previous section, there might be a critical loss of cognitive resilience in women along the transition from normal to pathological aging. Maintained cognitive performance across normal and pathological aging may be the result of lower pathologies or preserved/enhanced brain structure and function despite the presence of pathologies. Here, we address whether brain resilience to AD pathologies (i.e., differential impact of AD pathological burden on brain structure and function) or lower pathological burden (resistance to pathologies) explains the above-mentioned differences in cognitive resilience in women versus men.

At the cross-section, cognitively unimpaired women outperform men independent of baseline amyloid levels and hippocampal volume, though the hippocampal volume results are less consistent.[53–56] Indeed, women with amnestic MCI seem to outperform men in immediate and delayed recall tasks given equal levels of moderate hippocampal atrophy, but this advantage was only observed at moderate but not higher levels of hippocampal atrophy.[53] Longitudinally, women diagnosed with amnestic MCI or AD dementia demonstrate increased brain atrophy rates of up to 1.5% per year relative to men with the same diagnostic status.[57] Therefore, while women initially show greater cognitive resilience to hippocampal volume loss, it appears to diminish over time, particularly after a diagnosis of cognitive impairment, and probably at advanced levels of AD or neurodegenerative biomarkers.[58]

Research also suggests lower cognitive resilience to AD pathologies in women compared to men. At the cross-section, women's memory performance appears to be robust to the effects of amyloid pathology.[58] However, at comparable levels of cerebrospinal fluid (CSF) amyloid, cognitively unimpaired women decline more rapidly than men in a composite score combining episodic memory, executive function, and global cognition.[54] Similarly, greater cognitive decline in verbal memory and executive functions was observed in women with higher CSF amyloid and total tau levels and unimpaired cognition, MCI, and AD dementia, although the most pronounced sex difference was observed at the MCI stage.[58] Indeed, while there is no association between PET-amyloid positivity and cross-sectional memory scores in women, the effect of amyloid positivity on memory is observable at subjective cognitive decline (SCD)[55] or at MCI stages.[59] In contrast, in men with unimpaired cognition and MCI, amyloid positivity had a less significant impact compared to women, or not at all. Furthermore, women with AD dementia, including those with positive AD biomarkers, exhibit greater cognitive impairment and decline compared to men.[58,60]

Finally, at the brain level, there might a differential impact of AD pathologies on brain structure in women versus men (sex differences in brain resilience to AD pathologies). While cross-sectionally women may have greater brain resilience to the effects of tau,[61] women with lower CSF $A\beta_{42}$ and increased CSF tau showed more rapid hippocampal atrophy, suggesting lower brain resilience to the effects of AD pathologies over time in women.[58] In AD patients, the same clinical severity of dementia was associated with greater reduction in cerebral metabolism in men than in women, which was interpreted as greater ability to cope in men.[62] Overall, these results are consistent with the notion that women show an advantage followed by a loss of compensatory mechanisms resulting in faster decline (see Figure 2B).

An alternative hypothesis is that the verbal memory advantage in women may result in delayed detection of observable cognitive decline by informants and caregivers and therefore missed diagnosis in women (see Figure 2D). In this regard, evidence suggests that sex-adjusted norm/cut scores identify 10% of missed amnestic MCI cases among women and 10% of false positive cases among men.[53] As such, it is possible that women are diagnosed with more advanced pathology and/or more advanced cognitive decline. Because advantages in sex-specific cognitive performances exist, models of cognitive resilience stratified by sex are warranted in future studies.

Figure 3 illustrates the changes in cognitive and brain resilience to specific brain pathologies in women versus men and aligns with the hypothesis of an initial memory advance in women.

4 | MODIFIABLE AND BIOLOGICAL FACTORS: A SEX/GENDER AWARE FRAMEWORK

A key and shared component within theoretical frameworks to study resilience in aging and AD is the recognition that both modifiable (e.g., education or lifestyle) and biological (e.g., genetic risk) factors play roles in enhancing resilience and resistance along with the associated neural mechanisms. Modifiable risk factors, such as education, physical activity, cardiovascular health, and mood disorders, account for up to 40% of dementia cases.[63] Further, chromosomal, reproductive health, and hormonal differences are biological pathways that may also explain differences in cognitive resilience. Biological risk and modifiable factors, including social determinants of health, may independently drive differential resilience or interact with each other to increase resilience or vulnerability. In this section, we consider modifiable and genetic factors as determinants of resilience.

4.1 | A sex/gender perspective on modifiable factors

Almost all the currently identified modifiable risk and protective factors for cognitive decline and dementia demonstrate sex/gender differences in rate and/or risk expression,[64,65] as reviewed in this section. Life course exposures and behaviors systematically differ by sex/gender due to both biological (e.g., pregnancy) and or/social (e.g., education) causes.[19] A detailed description of sex-specific risk and protective factors for cognitive decline and dementia can be found in previous works.[64–66]

4.1.1 | Years of education

Years of education is among the most commonly used proxies of resilience and reserve in the AD field.[67] Higher education is associated with higher levels of global cognition and delayed onset of symptoms[68,69] and might mitigate the adverse effects of sexuality-minority status on cognitive aging.[70] However, it is a poor reflection of the value of educational reflection among minoritized ethnic groups and its contribution to cognitive decline and resilience among racial/ethnic groups deserves further consideration.[71,72] Despite advances in gender equality, education and occupation levels are highly gendered as societal expectations of gender roles have historically manifested in reduced access to higher education for women.[73] While we could expect education to contribute to lower cognitive resilience

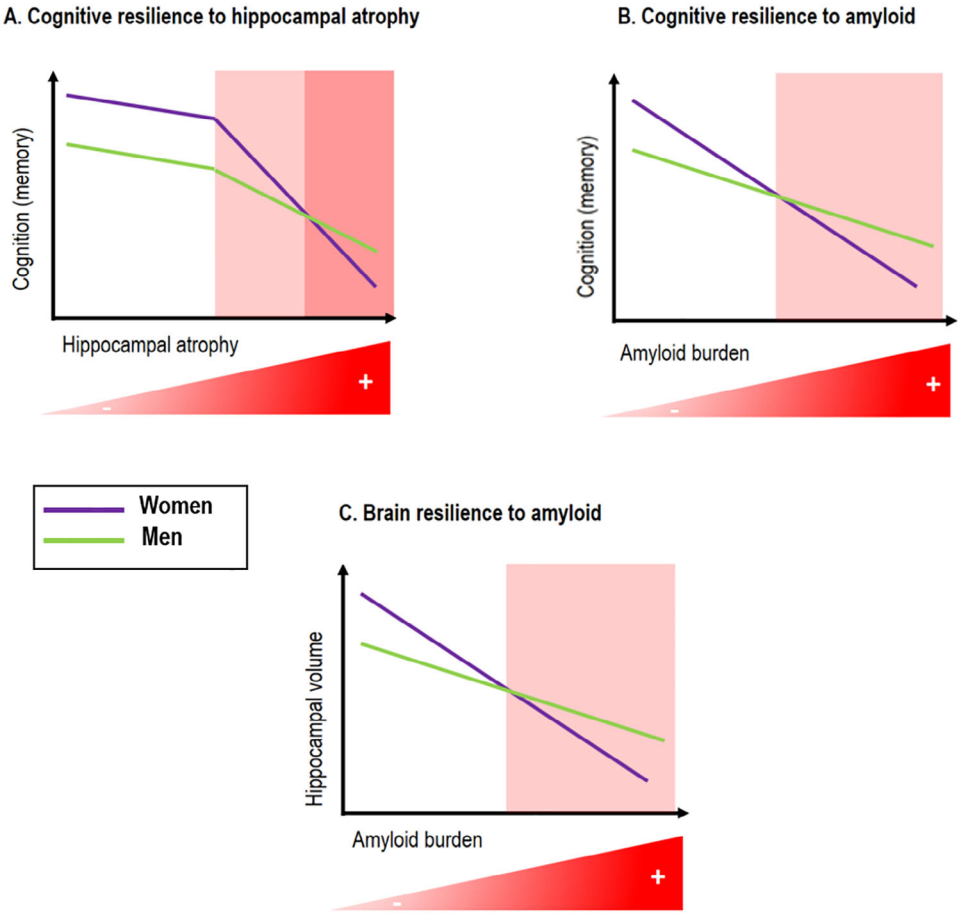

FIGURE 3 Illustration of the hypothesized sex differences in cognitive and brain resilience to amyloid burden and brain atrophy. A, Cognitive resilience to hippocampal atrophy: women show better memory function and maintained memory performance despite hippocampal atrophy, until a certain threshold is reached, beyond which women show accelerated cognitive decline compared to men. B, Cognitive resilience to amyloid: women show greater cognitive resilience to initial amyloid accumulation evidenced by superior memory performance compared to men at similar levels of amyloid deposition. However, this advantage fades away at higher amyloid levels leading to faster cognitive decline in women. C, There is greater brain resilience to amyloid burden in women evidenced by a smaller effect of amyloid on hippocampal volume compared to men at lower levels of amyloid. This trend reverses at higher levels of amyloid burden, leading to a greater effect on hippocampal volume in women. The red background in the despicted scatterplots indicates higher levels of hippocampal atrophy or amyloid burden.

in women, older women show better cognitive function than men,[35] suggesting an interplay between biological and social factors. Further, despite having overall lower levels of education, women show disproportionately larger benefits of education on both mood and cognitive outcomes compared to men.[74]

Recent findings from the United Kingdom suggest that reduced disparities in education levels—due to secular increases in educational opportunities in later birth cohorts—could attenuate sex differences in dementia risk and increase cognitive resilience and reserve at the population level.[75] In Europe, a study reported that the magnitude of sex differences in three separate cognitive domains varied systematically by birth cohort and region, and was confounded by gender-specific changes in living conditions and levels of cognitive enrichment.[76] Sex differences have also been reported in cognitive trajectories across samples from diverse ethno-cultural groups and geographical regions with rates of cognitive decline varying across cohorts but consistent associations with education and *APOE* genotype.[77] As expected, older women show relatively better cognitive performances in countries characterized by more equal gender-role attitudes, and this effect was partially mediated by education and labor-force participation.[78] Therefore, only studies across birth cohorts and considering international differences will shed light on whether and how gender disparities may shape cognitive aging trajectories and cognitive resilience.

4.1.2 | Affective disorders

Higher rates of affective disorders and social marginalization are observed in women compared to men, [74,79–82] which are in turn associated with cognitive decline and/or dementia risk.[83–86] Thus, mood disorders are twice as common in women than men[87] and are associated with an almost 2-fold increased risk of incident dementia.[63] Affective disorders are increasingly being studied in the context of resilience studies,[88,89] while they could also be a prodromal sign of demen-

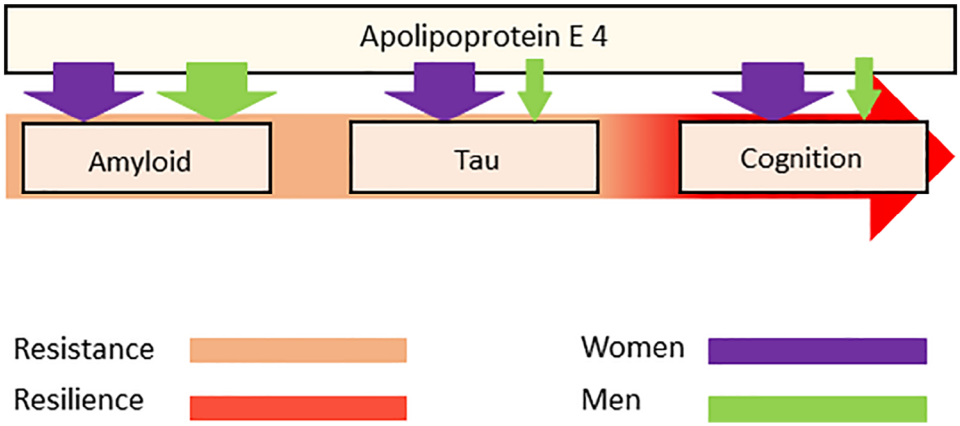

FIGURE 4 Illustration of the effects of *APOE* ε4 on the amyloid cascade. Sex effects are observed downstream amyloid. Illustration of the available evidence showing no sex-specific genetic drivers of amyloidosis but different effects of *APOE* ε4 in tau (lowering resistance in women) and cognition (lowering cognitive resilience in women compared to men). The magnitudes of the arrows are indicative of effect sizes, with larger arrows representing larger effects. *APOE*: apolipoprotein E

tia. Women show stronger immune responses to pathogens, faster wound healing (e.g., including shorter recovery time from traumatic brain injury), greater antibody production, and a higher predilection for autoimmune diseases.[90] These intrinsic immunologic differences may be a common pathway directly impacting mood and cognitive resilience. Another hypothesis is that discrimination and other social standards present since birth that have systematically marginalized women contribute to women's vulnerability to mood disorders and may further impact immune system development.

4.1.3 | Cardiovascular and health behaviors

Men have a higher prevalence of certain risk behaviors (e.g., traumatic brain injury, smoking, and substance use)[91–93] and also cardiovascular disease events (e.g., myocardial infarction, stroke) particularly at younger ages.[94–99] The larger cardiovascular advantage in women may be partially related to high estrogen exposure throughout early to midlife.[100,101] Precipitous decline in estrogens (> 90%) during menopause transition is associated with a shift such that women begin to show disproportionately increased vascular risk compared to men.[102,103] Women who are older than 60 demonstrate increased arterial stiffening, a higher prevalence and mortality from type 2 diabetes, and a stronger association between hemoglobin A1c and brain volume.[97,103,104] A recent study found that differences in stroke and hypertension between men and women contributed to differences in memory decline.[105]

4.1.4 | Physical activity

Sedentary behavior and physical activity, which are among the most strongly linked behaviors with dementia risk, also demonstrate gender differences. Women exercise less than men across the lifespan, which is partially related to the gender roles but also to the lack of encouragement of physical activity for women historically.[106] Nevertheless, meta-analyses suggest that women benefit more from the effects of exercise than men[107] although the directionality is not clear across studies.[96,98,107–112]

Overall, although there are differences in the prevalence of risk factors based on sex and gender it is important to underscore that an over- or under-representation of a particular risk or protective factor in one gender does not automatically result in a more significant or lesser impact on health outcomes.

4.2 | Sex-specific genetic influences on cognitive resilience

Besides modifiable factors, an important biological determinant of resilience is genetics. While, as discussed below, robust evidence exists of genetic contributions to resilience, there has been less work on the degree to which genetic drivers of resilience differ by sex and gender. Nevertheless, initial evidence presented in this section suggests that immune, inflammatory, cardiovascular, and sex hormone pathways drive differences in resilience. This section will cover the current literature of sex-specific genetic drivers of resilience and protection to AD pathology.

4.2.1 | *APOE* associations with AD risk differ by sex

The studies on *APOE* suggest that the genetic architecture of amyloidosis is largely shared across sexes and is driven primarily by *APOE* with only minor sex-specific genetic effects on amyloidosis outside of *APOE*. By contrast, the genetic architecture downstream of amyloidosis seems to include substantial sex differences on tau biomarkers,[113] cognitive decline,[114] and clinical AD[50] (see Figure 4), including several biological pathways of resilience that could serve as precision targets for intervention,[115] some of which will be described below.

4.2.2 | Sex differences in the genetic architecture of resilience: immune, inflammatory, and cardiovascular pathways

Current evidence suggests that genetic drivers of sex hormone signaling, X-chromosome function, immune/inflammatory signaling, and vascular hemodynamics may drive resilience to AD pathology in a sex-specific manner.

A genome-wide association study on CSF Aβ_{42} levels identified a genetic locus with a sex interaction. The top variant in the region was an expression quantitative trait locus (eQTL) for the *SERPIN* gene family, which is implicated in inflammatory processes.[116] A recent study revealed that female cis-eQTLs, but not male cis-eQTLs, colocalized with immune traits.[117] Furthermore, sex-aware genetic correlation analyses on cognitive resilience (against amyloid) demonstrated sex-specific associations with autoimmune traits, such as multiple sclerosis. That is, greater resilience in women was associated with lower genetic susceptibility but higher genetic susceptibility in men.[118] Autoimmune trait prevalence is higher in females, and autoimmune traits and AD have shared biology,[119,120] making the crosstalk between immune/inflammatory pathways and resilience pathways an exciting future direction for sex and gender research.

In the same set of sex-aware genetic correlation analyses, resilience and heart rate variability were shown to share sex-specific genetic architecture: more resilient males had a higher genetic susceptibility for more favorable heart rate, while no association was seen in females.[118] Previous studies have shown that heart rate variability is a good marker of heart health, lowers with aging, and has sex-dependent effects, whereby older males decline in heart rate variability faster than older females.[121–123] As such, findings suggest sex-specific genetic etiology of resilience may partially be explained by immune pathways in females and cardiovascular pathways in males.

4.2.3 | Sex chromosomes and hormones contribute to sex differences in resilience

In addition, sex chromosomes and hormone pathways may contribute to the sex-specific genetic etiology of resilience. A recent meta-analysis on resilience identified shared genetic architecture between resilience and hormone-related traits.[115] Sex-biased gene expression has been linked to enrichment of hormone-related transcription factors.[117] Importantly, loss of circulating estrogen and lifetime estrogen exposure have an established relationship with cognitive decline,[124–126] making the convergence of sex hormones and resilience an important future direction for genetic studies. Additionally, the X chromosome has been implicated in sex-specific genetic pathways of vulnerability to AD. The X chromosome is enriched in brain-related genes, and shows a reduced ploidy during typical aging in females.[127] Specifically, X-chromosome aneuploidy is enriched in the hippocampus and cerebrum, both regions disrupted in AD.[127,128] To date, few genomic studies have been conducted on the X chromosome, despite its role in aging and AD, due to added complexities from dosage differences between sexes. Future X-wide association studies on AD protective endophenotypes are needed to further elucidate the X chromosome's exact role in resilience to AD pathology in each biological sex. Taken together, resilience is a highly heritable trait with genetic contributions, and genetic factors of resilience may relate to pathways of protection to AD in a sex-specific manner. Future sex-aware genomic studies with large sample sizes are necessary to fully elucidate the genetic etiology of resilience to AD pathology.

5 | SEX DIFFERENCES IN BRAIN RESILIENCE: BRAIN STRUCTURE AND FUNCTION

Maintained or enhanced brain structure and function[3,24,28] throughout aging and disease have been proposed as mechanisms explaining why some individuals are able to cope better with pathologies and maintain function, that is, mechanisms underlying resilience. However, measurements of brain structure and function may reflect both pathological processes as well as the protective effect of several risk and protective factors throughout the lifespan leading to brain resilience.[5]

In this section, we first review sex/gender differences in brain structure and function as they may set the stage for further differences in brain resilience throughout aging and disease. Second, we review the scarce literature available suggesting sex/gender as modifier of the association between modifiable factors and brain structure/function. As presented below, the evidence suggesting sexual dimorphism in brain structure and function are consistent across studies, while the evidence for sex-specific rates of change in structure and function is mixed.

5.1 | Baseline differences in brain structure and function

There are consistent sex differences in brain structure and function.[129–132] Men show, on average, larger brain size[133–136] through larger absolute gray matter (GM) volume, and white matter (WM) volume. [129,137,138] By contrast, women show thicker cortices[129] and larger GM and WM volumes, adjusted by total skull size, than men.[138] With respect to microstructural features of the brain, men exhibit higher global fractional anisotropy and stronger intrahemispheric connectivity, while women have higher fiber dispersion and stronger interhemispheric connectivity.[129,139–142] Overall, these studies suggest sex differences in the anatomy and structural connectivity of the brain that should be considered when investigating sex-specific brain mechanisms of resilience.

Findings regarding functional connectivity seem to suggest a women's advantage. Women demonstrated stronger default mode network (DMN) connectivity,[129,143–145] which some studies have associated with reduced cognitive decline[146] and impairment.[147] Furthermore, greater glucose metabolism in the anterior cingulate cortex, as well as in the anterior temporal pole and medial prefrontal cortex,

has been associated with slower cognitive decline, particularly in older women.[148]

5.2 | Rates of change in brain structure and function: differential impact of aging and disease

Conflicting evidence exists regarding differences between men and women in rates of change in brain structure. Greater age-related decline in WM integrity was reported in women[141,149] but also in men.[150] In addition, increased GM atrophy was observed in women[138,151,152] yet also in men.[129,153–155] Previous work suggested faster cortical thinning in both women[156] but also in men.[157,158] Last, accelerated brain aging (as reflected by increased brain-predicted age difference) was found in women[159,160] but also in men.[161–163] As discussed above, a consistent sex difference across studies is the increased rate of hippocampal atrophy in women compared to men,[152,164,165] which may be exacerbated in the presence of AD pathology in women.[58] Despite the dearth of literature examining sex/gender-specific mechanisms of resilience, studies suggest that women may have higher functional brain maintenance as they have younger metabolic brain-predicted ages[166] and weaker and less widespread age-related changes in glucose metabolism than males.[167] Moreover, women have significantly less pronounced age-related decline in DMN connectivity.[168] Overall, while sex differences in the trajectories of age-related WM and GM atrophy are unclear, women may be more vulnerable to the effects of pathologies in the structure of the medial temporal lobe but also show a metabolic and functional advantage compared to men.

5.3 | Do the effects of risk and protective factors on brain structure and function differ by sex?

Initial or longitudinal sex differences in brain structure and function alone may not explain differences in cognitive decline between men and women. Adding to the complexity is the question of how lifestyle factors, or even sex/gender-related factors (e.g., reproductive health, pregnancy), impact brain structure and function in women versus men.

Research exploring sex/gender differences in the association of lifestyle factors with brain structure and function is very scarce. High levels of objectively measured low-intensity daily walking were associated with larger hippocampal volumes only among women.[169] Another study reported an association of maintaining physical activity over 10 years with larger hippocampal volumes in men but larger dorsolateral prefrontal cortex volumes in women, as well as sex-specific benefits on cognitive domains.[170] Higher cardiovascular risk scores have been associated with lower GM volumes and worse memory among men only.[171]

Finally, considering sex-related factors, it is known that pregnancy is associated with reductions in cerebral GM volume, lasting for at least 2 years post partum[172] and it has been reported that hypertensive pregnancy disorders are associated with smaller brain volumes and worse performance on processing speed cognitive tests, compared to normotensive pregnancies.[173]

6 | RESISTANCE TO PRIMARY AD PATHOLOGIES

In this section, we review sex/gender differences in primary AD pathologies. Understanding these differences will set the stage to identify sex/gender-specific vulnerabilities and resiliencies as well as the factors associated to them, as discussed at the end of the section.

6.1 | Resistance to Aβ

The majority of studies examining levels of Aβ have not found differences between men and women, including in amyloid positron emission tomography (PET),[37,54] CSF Aβ42[174,175] or Aβ42/Aβ40 ratio,[176–178] and blood Aβ42/40 ratio.[179,180] However, a few studies found that women showed a trend toward higher levels of amyloid in *post mortem* neuropathological data.[181,182] Further, some studies suggest that higher levels of Aβ may appear during the age of menopause relative to age-matched males, suggesting lower resistance to amyloid in women.[183,184]

6.2 | Resistance to tau

By contrast, several studies showed higher levels of tau pathology in women, as evidenced by PET imaging,[185–189] and *post mortem* data[181,182,189] implying that women may have lower resistance to tau pathology. Interestingly, PET findings suggest that sex differences in tau deposition occur across multiple cortical regions outside the temporal lobe,[185,186–188,190] even in clinically normal older adults.[191] Although few studies have reported a main effect of sex on levels of CSF markers of p-tau,[177,192] there are consistent sex by *APOE* ε4 interaction effects. That is, higher levels of both total tau and p-tau exist in women *APOE* ε4 carriers relative to men carriers and all non-carriers, particularly if they have a diagnosis of MCI or dementia.[113,174,175,193]

Most studies to date investigating blood-based biomarkers have not specifically examined sex differences. In the few that did, conflicting findings have been reported. In one study, levels of p-tau181 or 217 and markers of neurofibrillary tangle pathology did not differ between men and women.[178] By contrast, a study showed that higher plasma p-tau181 was associated with greater amyloid and entorhinal cortex tau accumulation, lower brain glucose metabolism, and faster cognitive decline in women, relative to men.[194] Moreover, in a longitudinal sample of individuals with subjective cognitive concerns,[195] women exhibited faster rates of change in plasma total tau concentration than men. Some recent reports suggest that past hormone therapy use might also be associated with lower tau deposition in women.[186] As such, the area of sex differences in tau markers in plasma is an evolving area of the literature.

6.3 | Do differences in resistance to AD pathologies result in poorer neurodegenerative outcomes?

While there seem to be vulnerabilities to tau deposition in women, it remains somewhat unclear at what point this may result in poorer neurodegenerative outcomes. Studies examining sex differences in CSF markers of neurodegeneration showed higher neurofilament chain light (NfL) levels in males compared to females.[196,197] In apparent disagreement with these findings, women exhibited greater tau-mediated brain glucose hypometabolism than men.[198] Similarly, a recent study in autosomal dominant AD, showed that as disease progresses, women Presenilin-1 E280A carriers have a greater plasma NfL increase than men carriers.[199]

6.4 | Glial cells and resistance to AD pathologies: microglia, astrocytes, and oligodendrocytes

Microglia activation has a stronger mediation effect between Aβ and tau burden in women.[200] As for oligodendrocytes, their global transcriptional activation is positively associated with increased AD pathology in males, whereas not in females.[201] Astrocyte sex differences are less explored, but in animal models, females present a higher astrocyte density in some regions, such as the cortex and hippocampus.[202–204] The hippocampus shows an increase in hypertrophic astrocytes near Aβ plaques in the female brain.[205] Few studies have investigated sex-specific changes in glial cells, including microglia, astrocytes, and oligodendrocytes.[206–209] Some studies have shown that microglia density and phenotype vary between women and men.[210–213] In AD, microglia density increases in both men and women in the parietal cortex.[211] However, male AD individuals present significantly higher density and a more amoeboid microglial morphology compared to females.[211] Microglia from women are more glycolytic and ramified, indicating the presence of different microglial states in male and female brains in the AD continuum.[211,214] The role of glial cells in sex-specific resistance to AD pathologies should be further explored.

6.5 | Impact of sex- and gender-related factors on AD pathologies

There is a lack of studies exploring sex differences in the association of lifestyle risk factors with Aβ and tau. Most existing studies have been unable to explore interactions or stratify analyses by sex due to small sample sizes (particularly men). Studies exploring the association of sleep duration[215] and body mass index (BMI)[216] with Aβ burden have not observed sex differences among cognitively normal participants. A recent cross-sectional study, however, reported that among cognitively intact *APOE* ε4 carriers, higher cardiovascular risk scores are associated with higher levels of tau among women, but not among men, suggesting that women with at least one *APOE* ε4 allele may be particularly vulnerable to the effects of cardiovascular factors on tau deposition.[217] Due to the lack of studies, evidence is inconclusive, and future research is needed to explore possible sex differences in the association between lifestyle risk factors and AD pathology.

7 | SEX DIFFERENCES IN NON-AD PATHOLOGIES

Mixed or comorbid pathologies are common in older adults and are major contributors to cognitive decline and dementia. AD pathologies only account for ≈ 50% of the observed age-related cognitive loss, varying greatly at the individual level.[218,219] Hence, additional non-AD pathologies contribute to lower the threshold for clinical diagnosis of AD dementia[220] and therefore contribute to lower cognitive resilience. Further, non-AD pathologies add significant variation to the mapping between AD pathology and cognition, and are therefore important factors to study in the context of cognitive resilience to AD. Consequently, in this section, we review sex/gender differences in non-AD pathologies.

It is important to note that even when accounting for a wide array of neuropathologies, a large proportion of the variation in late-life cognitive decline remains unexplained.[219] Figure 5 shows a framework in which AD pathologies, risk/protective factors (reviewed above), and non-AD pathologies are associated with cognitive resilience through their association with brain structure and function (brain resilience). Cognitive and brain resilience, therefore, are the result of the interplay of pathologies and exposure to risk and protective factors throughout the lifespan.

As shown in Figure 5, the most common non-AD pathologies are cerebrovascular disease (CVD; infarcts, atherosclerosis, arteriosclerosis, cerebral amyloid angiopathy), Lewy body disease (LBD), TAR DNA-binding protein 43 (TDP-43), and hippocampal sclerosis (HS).[221,222] There are several examples in the literature supporting the need to account for multiple pathologies in resilience studies. For example, in a previous neuropathologic study in the oldest old, less CVD, less cortical aging-related tau astrogliopathy (ARTAG), less TDP-43, less Lewy pathology, and no HS were observed in the cognitively resilient group compared to the AD dementia group, suggesting that reduced non-AD pathological burden explained cognitive resilience.[198] In addition, a recent study suggested that cognitive resilience to AD pathologies may be partially explained by resistance to TDP-43.[223]

Despite the same amount of AD pathology burden in women and men, the difference in these pathologies may impact their cognitive resilience, thus, sex/gender differences are reviewed below.

7.1 | Sex/gender differences in CVD

Approximately 78% of all AD dementia cases have CVD and there is a growing body of evidence showing significant differences in CVD burden between men and women.[224] The most frequently reported difference is in white matter hyperintensities (WMH), which are more likely seen in women compared to men,[225–227] particularly

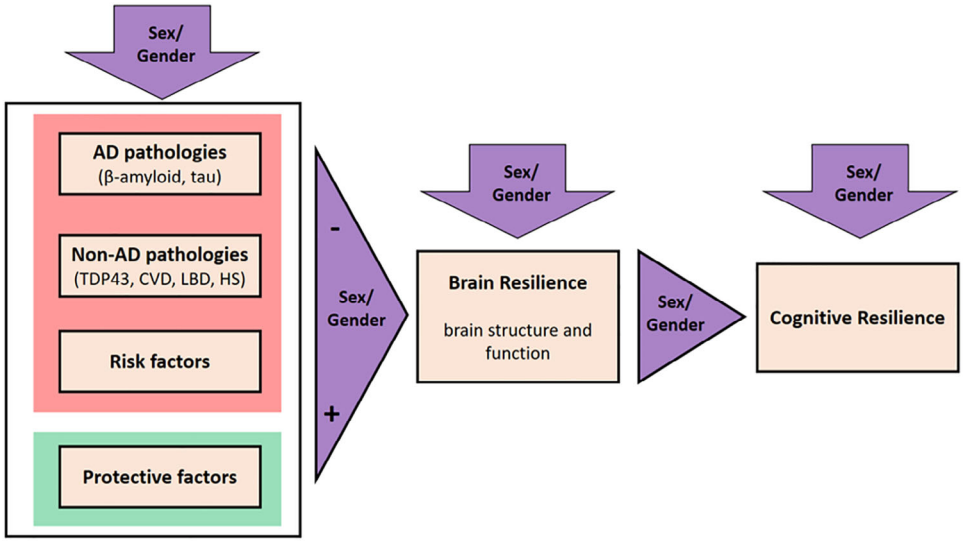

FIGURE 5 Illustration of how non-AD pathologies may diminish brain resilience. Non-AD pathologies are considered together with AD pathologies and risk factors (left box, red) as variables that may have a negative impact on brain resilience, while protective factors may have a positive effect (left box, green). The figure considers that sex/gender may have an effect on each box and in the relation between them. AD, Alzheimer's disease; CVD, cardiovascular disease; HS, hippocampal sclerosis; LBD, Lewy body disease; TDP43, Tar DNA-binding protein 43

post-menopause.[228] These differences are suggested to be driven by factors such as hypertension and BMI that influence WM integrity in women[229,230] and increase vulnerability of WM structures in women.[231,232] Severe atherosclerosis is also more likely in women.[182] By contrast, higher rates of cerebral microbleeds[233,234] and enlarged perivascular spaces[235] are observed in men relative to women. Both these changes are associated with poor cognitive performance.[236,237] Additionally, the risk of stroke is higher in women compared to men and highly dependent on age.[238] Women demonstrate poorer functional outcomes post-stroke, particularly post-menopause.[239,240] These sex-specific differences in stroke outcomes are also mediated by worse WM integrity in women.[240,241] Silent strokes on magnetic resonance imaging are common in the population[242] and are found to be different between men and women with differences in infarct location.[226,233,243]

7.2 | Sex differences in LBD and TDP-43/hippocampal sclerosis

LBD is significantly more common in men than women;[224,244] however, the mixed pathology cases of AD with LBD are more common in women.[224,245,246] Severity of the clinical manifestation of LBD is also sex specific, with a more aggressive clinical disease course evident in women with dementia with LBD compared to men,[245] suggesting lower cognitive resilience to LBD in women. Neuropathology data also provide evidence of greater AD with TDP-43/hippocampal sclerosis disease burden in women relative to men.[224] Finally, women showed greater associations between neocortical type Lewy bodies and limbic-predominant age-related TDP-43 encephalopathy neuropathologic change (LATE-NC). These co-pathologies contribute to worse cognition in women and greater risk of AD dementia,[247] suggesting that investigating regional associations between pathologies may be important to understand sex/gender-specific cognitive resilience.

8 | INPUTS ON SEX-SPECIFIC COGNITIVE RESILIENCE FROM ANIMAL MODELS

The study of sex-specific resilience to AD, and its therapeutic implications, can be informed by the study of animal models. Animal models are required for the elucidation of molecular mechanisms and identification of therapeutic pathways that could improve the human condition. However, a model is only useful if the discoveries generated truly inform us about human disease. Thus, attention to aspects of AD mouse models that recapitulate clinical manifestations of human AD—such as cognition, pathology, survival, and their underlying substrates—is essential. Because there are major limitations to modeling AD, the field has historically used many models and approaches including mouse primary neurons, human amyloid precursor protein (hAPP) mice, human brains, and human cognition and included several AD-related measures to increase the potential relevance of our findings in sex-specific resilience against AD.

Being male or female, defined here as harboring a different sex chromosome complement (XY vs. XX), is a primary and understudied biologic variable in AD that is beginning to be explored in models. In the models studied, there are striking parallels with the human condition. Like women with AD that live to advanced ages worldwide,[10,248,249] contributing to increased female prevalence, female hAPP mice (line J20 on two different genetic backgrounds) live longer than male hAPP mice.[10] Furthermore, after hormonal depletion, female hAPP mice show less cognitive and behavioral deficits than hormone-depleted male hAPP mice.[10] These findings in mice are congruent to human

observations in aging and preclinical AD prior to the age of 85 years when women show better cognition,[54] less cognitive decline, [37,250,251] and decreased measures of neurodegeneration,[252] despite similar deposition of amyloid and tau,[37,253] pathological hallmarks of AD. This could underlie lower prevalence[254] and later onset of MCI in women compared to men in some populations, [255] although cognitive decline is steeper for women later in the course of AD, as pointed out above.[66]

8.1 | X chromosome modulates resilience against pathology in AD models

Using genetic models of sex biology combined with AD models, it has been found that the X chromosome impacts AD-related vulnerability in hAPP mice—including survival and cognition. XX-hAPP mice genetically modified to develop testicles or ovaries showed better survival and less deficits than XY-hAPP mice with either gonad, indicating a sex chromosome effect.[10] After varying sex chromosome dosage, mice with two X's showed increased survival and fewer deficits than those with one.[54] Thus, adding a second X conferred resilience to survival and cognition of both XY males and XO females. The X-mediated resilience extended to male and female primary neurons exposed to AD-related toxicities.

A second X chromosome conferred resilience, in part, through lysine-specific demethylase 6a (*Kdm6a)*, a gene that escapes X-chromosome inactivation in XX females.[10] In humans, genetic variation in *KDM6A* is associated with less cognitive decline over a decade in a population enriched for individuals with MCI[10] and X-chromosome gene expression with cognitive resilience in women.[256] Collectively, the mouse, primary neuronal, and human studies support a role for the X chromosome in modulating resilience against AD.

Many factors influencing brain function are enriched on the X chromosome,[257] which represents 5% of the genome in both women and men. The X influence on human mental function is highlighted by X-linked intellectual disability suffered primarily and more severely by males in the absence of compensatory functions from a second X chromosome. Two X chromosomes, compared to one, potentially confers an advantage in sex-specific resilience against AD in many ways, including diversity of X gene expression from mixed parental origin of the active X—-and increased X dose from baseline escape of the inactive X. Further study of the sex chromosomes and their contribution to sex-specific resilience in AD may lead to novel therapeutic pathways that can benefit both sexes.

Indeed, a recent study of humans supports a role for the X chromosome in sex-specific cognitive change and tau pathology in aging and AD.[256] Differential gene expression profiling of the X chromosome in brains from the Religious Orders Study/Memory Aging Project joint cohorts showed that X expression associated with cognitive change in women, but not men. In the majority of these changes, higher X gene expression associated with slower cognitive decline, suggesting a role for the X in female resilience. In contrast with cognition, X expression associated with neuropathological tau burden in men but not women. These findings in humans suggest that specific X factors could contribute risk or resilience to biologic pathways of AD in each sex.

9 | CONCLUSIONS AND KNOWLEDGE GAPS

The general conclusions of the evidence reviewed in this work are provided below accompanied by the knowledge gaps.

1. **Sex/gender differences in cognitive resilience might be decreasing as a function of reductions in gender inequalities, due to more opportunities for women in education, workforce participation, and improvements in their economic status and living conditions.** There is a need to further understand how gender and sex disparities and inequalities relate to brain health. Notably, to mechanisms underlying cognitive resilience including brain resilience and resistance to pathologies. Education is widely acknowledged as a pivotal factor in building resilience. However, access and distribution to education have historically been gender skewed. Considering education as a gendered proxy helps prevent the missatribution of observe differences in cognitive resilience to inherent biological traits linked to sex.
2. **The examination of sex and gender differences in cognitive trajectories is a subject of controversy, necessitating evaluation across age periods, cognitive status, and considering health and sociocultural risk factors**. Factors conferring differential resilience to cognitive decline in men and women require more attention. For instance, the intersection of sociocultural variables and sex/gender variables may explain some of the inconsistent results. Similarly, mid- and late-adulthood sex differences in cognitive trajectories should be investigated as a function of *APOE* ε4 status as well as hormonal changes.
3. **Sex differences in coping with the effects of amyloid and brain atrophy on cognition are plausible: women may exhibit enhanced initial cognitive resilience that may fade away as they advance toward a clinical diagnosis of MCI and AD.** Longitudinally, cognitively unimpaired women show lower cognitive resilience to amyloid pathology. Nevertheless, the impact of amyloid pathology on the hippocampus is mitigated in women, indicating heightened brain resilience to amyloid. Similarly, the influence of initial levels of hippocampal atrophy on cognition is minimized, suggesting higher cognitive resilience to the initial effects of atrophy. Research investigating AD pathologies, medial temporal structures, and cognition is essential to pinpoint the specific phases in the pathological cascade in which sex/gender differences may manifest. Sex differences in co-pathologies may also explain differential cognitive trajectories.
4. **Almost all the modifiable risk factors for cognitive decline and dementia, considered determinants of resilience, demonstrate sex/gender differences in rate and/or risk ratio.** An over- or under-representation of a particular risk or protective factor in one gender does not automatically result in a modified impact on brain and cognitive outcomes. Knowledge of these sex/gender-

biased risk factors should be considered when explaining cognitive trajectories.

5. **The differential impact of modifiable factors by sex and gender on cognition, pathologies, and brain structure remains understudied.** Additional focus on the differential impact of modifiable factors will inform whether a specific factor has a greater impact on cognitive or brain resilience in men or women. A recent sex-specific analysis of the FINGER trial demonstrated that, despite differential risks by sex, intensive lifestyle modification, including physical activity, diet, and vascular risk management, showed comparable cognitive benefits in men and women.[93] Therefore, these sex-specific vulnerabilities and resilience factors can be leveraged to inform risk stratification, as well as highlight individual-specific pathways of disease genesis.
6. **Sex hormone signaling, X chromosome function, immune/inflammatory signaling, and vascular hemodynamics may drive resilience to AD pathology in a sex-specific manner.** Findings suggest sex-specific genetic etiology of resilience may partially be explained by immune pathways in females and cardiovascular pathways in men. Resilience is a trait with a significant heritable component, influenced by genetic factors that may contribute to pathways of protection against AD in a sex-specific manner. Subsequent genomic studies, attuned to sex considerations and conducted on a substantial scale, are essential to comprehensively unravel the genetics underpinnings of resilience to AD pathology.
7. **Initial sex differences in brain structure may present opportunities for exploration as potential moderators or mediators between pathology and cognition.** There are sex/gender differences in brain structure that seem to be dependent on total intracranial volume/brain size. Because brain size is a variable studied in the context of brain resilience and reserve, it will be important to understand the role of brain size, total volumes, and regional volumes in minimizing the effects of pathology on cognition by sex/gender. Functional and structural connectivity differences could be considered candidate mechanisms explaining the differential resilience to pathologies in men and women including fractional anisotropy, intra and inter-hemispheric connectivity, and fiber dispersion.
8. **Growing evidence suggests a differential sex effect on resistance to AD pathologies, alongside potential biological determinants**. While generally no differences in Aβ accumulation have been reported, some studies suggest great tau accumulation in women. A better understanding of the factors driving these differences whether sex or gender related (e.g., menopause, lifestyle or cardiovascular factors) is needed. Early reports suggest biological mechanisms that may be at play via microglial activation, although further investigation is needed. An intersection between sex and genetics seems clear when considering resistance; for instance, women tend to show stronger effects of *APOE* ε4 downstream amyloid. However, longitudinal studies are needed as it remains unclear whether women show greater-than-expected accumulation of AD pathology as disease progresses relative to men.
9. **Studies with a sex/gender aware framework are lacking**. While sex and gender differences in resilience and resistance to pathologies are starting to be described in the field, an articulation of a sex/gender framework will imply considering sex/gender differences in the study design, research hypothesis, and interpretation of the results to better understand the associated sex and gender differences and underlying mechanisms.

10 | RECOMMENDATIONS

Conflicting results exist regarding sex and gender differences in the different outcomes reviewed in the article that require clarification in future studies. We make the following recommendations to pursue a more nuanced, accurate, and comprehensive grasp of how sex and gender influence cognitive resilience to aging and AD:

1. **Shift the focus from merely describing to comprehending**. Sex/gender-aware studies of resilience should articulate a conceptual frame motivated by sex or gender differences in health, risk factors, pathologies, and brain structure and function. There are many demographic, genetic, social, cultural, and clinical differences that contribute to dementia risk. Each of these facets can include an important intersection with sex and gender, and which can vary markedly by geographic region. There is a need to comprehend the interconnecting contribution of sex- and gender-related factors across cultures and ethnicities.[258]
2. **Publishing negative results to avoid bias**. There is a risk of overestimating sex/gender differences, with a bias toward positive results. Given the conflicting results existing for some of the brain and cognitive outcomes, we recommend that all studies include results disaggregated by sex, as well as studies that are directly investigating sex/gender with neutral or negative results be published and included in systematic reviews and meta-analyses. These include preprints, posters, and conference abstracts.
3. **Consideration of sex/gender in a non-binary manner and resilience research in LGTBQIA+**. Emerging scientific advances suggest that sex and gender should be considered over a continuum.[259,260] Thus, at the individual level, both sex and gender and their interactions with other factors can have differential impact on health and disease outcomes.[261,262] However, sex and gender have historically been binarily characterized and labeled as indicator representing chromosome XX or XY in research. Biological sex, gender, and sexual orientation are distinct concepts and represent heterogeneous groups, therefore, they should not be interchangeably used in research. We acknowledge the limitation of the present review and call for research that combines sociocultural, demographic factors combined with intersectional disparities of sex and gender. Sex and gender minoritized populations are underrepresented in clinical research and are

vulnerable to a greater disease burden of chronic conditions and diseases of aging such as AD and dementia. [19,72,263]

4. **Cross-talk between animal models and human studies**. Animal models support the role of hormones on resistance to AD neuropathology and provide evidence on likely biological mechanisms driving increased survival, brain function, and cognitive resilience associated with X chromosome.[225] Animal models, however, cannot answer some important issues on sex/gender differences that should be further addressed, for example, the complexity of the brain structure and cognitive changes related to aging in humans, the role of sociocultural variables or of menopause, as animal models of menopause can be difficult to reproduce. We recommend more model systems for human translational work and more interdisciplinary collaboration.
5. **Gender inequalities and cognitive resilience: a contextual framework**. Studies on cognitive resilience that consider education or other gendered factors must be deeply contextualized. Researchers should be equipped with historical, sociocultural, and economic frameworks to robustly interpret their findings. It is vital to incorporate other gendered proxies that might influence cognitive resilience, like occupation, social engagements, and even domestic roles. Historically influenced by gender, investigations of these variables can offer a broader understanding of their dynamic interplay to moderate levels of cognitive resilience.
6. **Statistical power to test interaction and moderation effects**. Statistical power is a critical consideration when examining sex differences. Sex differences that are apparent in large sample sizes may not be detected in smaller samples due to reduced statistical power.[264,265] This is particularly important when examining the interaction effect of sex and brain structure/pathology on cognition in cognitively unimpaired cohorts. For instance, a restricted dynamic range of the predictor variable (i.e., brain structure or pathology) can substantially reduce statistical power to detect an interaction effect. The effect size of a moderating effect may also be constrained by the fact that neuroimaging variables account for a relatively small amount of variance in the cognitive function of cognitively unimpaired older adults.[266,267] To account for these statistical issues, researchers could attempt to increase statistical power by using large harmonized cognitive datasets,[268,269] or a meta-analysis approach, or they could increase the likelihood of detecting a moderation effect by oversampling individuals with very low or high values on measures of cognitive function and brain structure or pathology.[270] If these approaches are not possible and a null effect is detected in a smaller sample, researchers should, at a minimum, clarify whether they had sufficient statistical power to detect a sex-based interaction effect.[271,272]
7. **Inclusion of gender measurements in resilience studies**. Better measurements of gender will allow for advances in the field. Unless gender is measured, we cannot estimate the extent to which it confounds the effect of sex in the interpretation of research on cognitive resilience. However, there are no currently agreed methods for measuring gender in the field of cognitive decline and dementia. The pervasiveness of potential gender effects means that many core variables routinely included in statistical models may interact with gender (e.g., education is strongly gendered both in terms of content, type, and quantity of education). A recent framework for measuring sex and gender in cohort studies has been proposed by the "Gender Outcomes International Group: to Further Well-being Development (GOING-FWD)." This involves five steps to assess domains that are identified as influencing gender including identification of gender-related variables, definitions of outcomes, building up feasible final variable lists, harmonization of data, and definition of data structure.
8. **Vigilance in interpretation**. It is crucial to approach gender-based results with caution, particularly when gendered proxies like education come into play. Researchers must differentiate between actual biological characteristics and factors that might be influenced by sociocultural biases. This differentiation ensures that observed differences in resilience are not misattributed to sex when they might be more related to gender-based societal constructs. Our recommendation is to acknowledge potential confounds in their interpretation of findings to ensure that the reader is appropriately educated on the context.

11 | GENERAL CONCLUSION

We urge the field to adopt a sex/gender-aware approach to resilience to advance our understanding of the intricate interplay of biological and social determinants and consider sex/gender-specific resilience throughout aging and disease.

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ACKNOWLEDGMENTS

This manuscript was facilitated by the Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment (ISTAART), through the *ADDRESS!* Special Interest Group which was founded to foster international research collaborations to study cognitive reserve and resilience across sex, gender, race, and ethnic diverse populations. The present work is a joint effort of the *ADDRESS!* Special Interest Group made up of members from the Reserve, Resilience and Protective Factors Professional Interest Area (PIA) and the Sex and Gender Differences in Alzheimer's Disease PIAs. The views and opinions expressed by authors in this publication represent those of the authors and do not necessarily reflect those of the PIA membership, ISTAART, or the Alzheimer's Association. We would like to express our sincere gratitude to Prof. Yaakov Stern for his feedback regarding the conceptual framework of the manuscript. E.M.A.-U. is supported by the Spanish Ministry of Science and Innovation—State Research Agency, and the European Social Fund (ESF) (RYC2018-026053-I), the Spanish Ministry of Science and Innovation (PID2019-111514RA-I00), the Alzheimer's Association (AARG2019-AARG-644641, AARG2019-AARG-644641-RAPID), the EU Joint Programme-Neurodegenerative Disease Research (JPND2022-138), and the Research and innovation Program of the Barcelona City Council and Fundació La Caixa (21S0906). K.C. is supported by the National Institute on Aging (R01AG072475 and R56AG082414). E.P. is supported by the Spanish Ministry of Science and Innovation (PRE2020-095827). C.V.C. is supported by the National Institute on Aging (K99AG073452) A.C. is supported by the National Institute of Health (T32AG078115). T.J.H. is supported by the National Institute on Aging (R01-AG059716). J.E. is supported by The National Institute on Aging (F31-AG077791). J.M.J.V. is supported by the National Institutes of Health (R00AG066934). R.F.B. is supported by R00AG061238, DP2AG082342, R01AG079142. O.O. is employed by University of Wisconsin School of Medicine & Public Health and has received support from the following grants, paid to his institution: R01AG062167, R01AG077507, U19AG024904, U19AG078109, U19AG073153, R01AG066203, R01AG070028, R01AG027161, RF1AG052324. P.V. is supported by the National Institutes of Health (R01 AG056366 and U01 AG006786). P.Z. received travel scholarships from the Alzheimer's Association, the NIA-funded Hopkins Economics of Alzheimer's Disease & Services Center, and the NIA-funded The Science of Alzheimer's Disease and Related Dementias (AD/ADRD) for Social Scientists Program at the University of Southern California. D.B.-F. was funded by an ICREA Academia 2019 Award from the Catalan Government, and the Spanish Ministry of Science and education (PID2022-137234OB-I00). D.B.D. is funded by the Simons Foundation; Bakar Aging Research Institute Grants; the National Institute on Aging at the National Institutes of Health under R01 grants AG068325 and AG079176; and philanthropy.

CONFLICT OF INTEREST STATEMENT

E.M.A.U. has nothing to disclose. R.B has nothing to disclose. K.C. has nothing to disclose. M.A. has nothing to disclose. E.P. has nothing to disclose. M.E. has nothing to disclose. C.V.-C. has nothing to disclose. M.W. has nothing to disclose. L.M. has nothing to disclose. J.M.J.V. has nothing to disclose. S.K. has nothing to disclose. T.K.S.N. has nothing to disclose. J.M.E. has nothing to disclose. H.S. has nothing to disclose. P.V. has nothing to disclose. S.T. has nothing to disclose. L.S.Z. has nothing to disclose. K.A. received honorarium from Roche for a lecture and funding from the National Health and Medical Research Council and the Australian Research Council. T.J.H. sits on the scientific advisory board for Vivid Genomics and is a senior associate editor for *Alzheimer's & Dementia*. O.O. has received consulting fees from Mayo Clinic Rochester and IUPUI and holds a fiduciary role in the International Neuropsychological Society (Board Member). S.L. has received honorarium from Otsuka and Lundbeck. D.B.-F. serves as a member of the Scientific Advisory Council for Linus Health. D.B.D. is an associate editor *for JAMA Neurology*, serves on the Board of the Glenn Foundation for Medical Research, and has consulted for Unity Biotechnology and SV Health Investors. H.Sohrabi is a non-executive Director of SMarT Minds WA, Australia. He has been or is receiving personal reimbursements or research support from the Australian Alzheimer's Research Foundation and Pharmaceutical and Nutraceutical companies including Alector, Alnylam Pharmaceuticals, CWEK PTY LTD (WA, Australia), and Biogen pharmaceuticals. Author disclosures are available in the supporting information.

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How to cite this article: Arenaza-Urquijo EM, Boyle R, Casaletto K, et al. Sex and gender differences in cognitive resilience to aging and Alzheimer's disease. *Alzheimer's Dement*. 2024;20:5695–5719. https://doi.org/10.1002/alz.13844