Title

Sex/gender differences in the clinical trajectory of Alzheimer's disease: Insights into diagnosis and cognitive reserve

Authors

Emrani, Sheina

Sundermann, Erin E

Publication Date

2025-04-01

DOI

10.1016/j.yfrne.2025.101184

Sex/Gender Differences in the Clinical Trajectory of Alzheimer's Disease: Insights into Diagnosis and Cognitive Reserve

Sheina Emrani, Ph.D.[1] and Erin E. Sundermann, Ph.D.[2]

[1]Department of Neurology, University of Pennsylvania, Dulles 3rd Floor, 3400 Spruce Street, Philadelphia, PA 19104

[2]Department of Psychiatry, University of California, San Diego, UCSD ACTRI building, office 2W517 9452 Medical Center Dr. (MC 0875), La Jolla, CA., 92037, USA, esundermann@health.ucsd.edu.

Address Correspondence to: Erin E Sundermann, PhD, UCSD Altman Clinical and Translational Research Institute, office 2W517, 9452 Medical Center Dr. (MC 0875), La Jolla, CA., USA, 92037 USA. Phone: (312) 502-0531 Email: esundermann@health.ucsd.edu.

Key terms: Sex/gender, Alzheimer's disease, Mild Cognitive Impairment, clinical presentation, diagnostic accuracy, cognitive reserve, verbal memory

Funding: This work was supported by the National Institutes of Health [grant numbers R01AG074221] and National Institute on Aging [grant number T32AG076411]

S. Emrani reports no competing interests relevant to the manuscript. E. Sundermann reports no disclosures relevant to the manuscript.

Abstract

The two-times higher prevalence of Alzheimer's disease (AD) in females versus males is well-known; however, there are also sex/gender differences in clinical presentation and diagnostic accuracy that are less examined but equally important to understand in terms of improving early detection, intervention and disease tracking in each sex/gender. This review explores how these disparities in clinical presentation manifest across the AD continuum, with a focus on the earlier stages of preclinical AD and mild cognitive impairment (MCI). We summarize evidence indicating that female's verbal memory advantage may mask early cognitive decline, leading to delayed MCI diagnosis and limiting opportunities for early intervention. Conversely, females demonstrate steeper cognitive decline at later disease stages compared to males. These patterns align with the cognitive reserve theory, suggesting female's verbal memory strength may act as a domain-specific resilience factor. Lastly, this review emphasizes the need for sex-sensitive diagnostic tools to improve early detection accuracy and equity in clinical practice.

Introduction

Alzheimer's disease (AD) and Alzheimer's disease related dementias (ADRD) are multifactorial disorders and a global epidemic. With the rising rates of older adults due to increased longevity, the prevalence of ADRD is projected to reach 153 million cases globally by 2050, compared to roughly 57 million in 2019 (Nichols et al., 2022). AD is the most prevalent form of dementia and ADRD, comprising 60 to 80% of dementia cases (Organization, 2023) and will encompass the focus of this review due to the extent literature and well-established findings of the influence of sex/gender in AD. AD progresses along a continuum that can be divided into three stages: preclinical, mild cognitive impairment (MCI) and AD dementia. Preclinical AD is defined by the international working group revision as requiring the absence of clinical signs and symptoms of AD but the presence of at least one biomarker of AD pathology, including the AD pathological hallmarks of amyloid-beta (Aβ) plaques and neurofibrillary tangles (Dubois et al., 2016). MCI is a prodromal stage of dementia, where individuals experience mild cognitive deficits but are able to maintain everyday responsibilities independently. MCI due to AD is typically characterized by mild episodic memory deficits and often referred to as the amnestic MCI subtype (aMCI), although early-stage AD can often include executive function and language deficits in addition to memory.

As this paper focuses on sex/gender differences in AD, it is important to explain our terminology choices and the rationale behind these choices. Many disease aspects likely have both biological and sociocultural underpinnings that are difficult to disentangle. Thus, we often refer to the joint "sex/gender" term. As most of the findings discussed herein are believed to be more biological in nature, we often refer to "males/females" when detailing sex/gender comparisons; however, this does not discount the potential influence of sociocultural factors. We refer to "women/men" when discussing differences more clearly socioculturally-based (e.g., education and occupation). A limitation of these

classifications is its binary nature that fails to capture the fluidity and diversity that can occur for both sex and gender within and among individuals.

Biological and sociocultural contributions to sex/gender AD disparities

Sex/gender differences in AD serve as a window into disease etiology and suggest that sex/gender disparate factors are at play in AD. These sex/gender disparate factors likely include a mix of more sex-based, biological factors such as sex hormones and genetic factors associated with the X and Y chromosome as well as gender-based sociocultural factors such as fewer opportunities for women to obtain higher degrees or greater occupational attainment compared to men in older generations. Many of our well-established AD risk/protective factors (e.g., vascular dysfunction, apolipoprotein E ε4 allele [APOE4], diet, exercise) show sex/gender disparities and differentially reflect sex- versus gender-based contributions. AD risk/protective factors can differentially affect risk by sex/gender by either having a stronger effect in females such as with the adverse effects of the APOE4 allele (Altmann et al., 2014; Farrer et al., 1997; Neu et al., 2017; Payami et al., 1994; Poirier et al., 1993) or having a higher prevalence in women such as lower access to education and occupational attainment (McDowell et al., 2007; Pankratz et al., 2015; Teipel et al., 2009), or being restricted to female sex such as early or surgical menopause (Georgakis et al., 2019; Gervais et al., 2020; Phung et al., 2010; Rocca et al., 2011). More comprehensive reviews of sex/gender disparities in AD risk factors can be found elsewhere (Arenaza-Urquijo et al., 2024; Mielke et al., 2022; Nebel et al., 2018).

Sex/gender differences in rates of AD

There are multiple aspects of AD that are known to differ by sex/gender but the most well-known sex/gender difference is the higher prevalence rate in females. In fact, female sex is the strongest risk factor for AD after age (Better, 2024; Farrer et al., 1997). Although the sex/gender disparity in the prevalence of AD dementia is clear, findings regarding sex/gender differences in age-specific AD incidence rates are inconsistent. Historically, it has been suggested that the longer average lifespan in females versus males is the reason for a higher risk of the disease. Multiple large-scale, epidemiological studies have found a higher age-specific incidence rate of AD in females versus males, particularly at older ages (Andersen et al., 1999; Chêne et al., 2015; Gao et al., 1998; Letenneur et al., 1999; Miech et al., 2002; Ott et al., 1998), suggesting that the higher prevalence of AD in females goes beyond their longevity. However, other studies in the US and globally have reported no sex/gender difference in AD incidence at any given age (Fiest et al., 2016; Hebert et al., 2001; Katz et al., 2012; Kawas et al., 2000; Mielke et al., 2014; Tom et al., 2015) or even a reverse sex/gender difference (higher AD risk in males versus females) (Matthews et al., 2016) making this view controversial and perhaps dependent on the age distribution of the sample, birthing cohort, and the geographic region of the study.

Sex/gender differences in rates of MCI

Although sex/gender differences in MCI/aMCI rates are less examined than AD dementia, evidence suggest a paradox whereby, multiple studies in older cohorts have reported a higher prevalence of amnestic MCI among males despite their lower rates of AD dementia (Brodaty et al., 2013; Koivisto et al., 1995; Nebel et al., 2018; Roberts et al., 2012). It should be noted that there have been inconsistencies with some studies reporting no sex/gender differences in MCI/aMCI rates; however, to our knowledge, only one study in China reported higher rates of MCI in females versus males based

solely on the Mini Mental State Examination (MMSE) (Liu et al., 2022). One plausible explanation for the paradoxical higher MCI rates in males despite lower AD dementia rates is that more males die during the MCI stage due to higher mortality rates from factors like cardiovascular disease, and, therefore, more females survive to the dementia phase (Mooldijk et al., 2022; Vassilaki et al., 2015). However, evidence from studies discussed in this review suggest that mortality rates likely do not fully explain these differences. Rather, there are other possible contributors including sex/gender disparities in the sensitivity of our clinical diagnostic tools to detect MCI, which we will discuss in more detail. Of course, with the emergence of in vivo measures of AD-related pathology and other neurodegenerative diseases, it will be important to re-examine the incidence and prevalence of various MCI subtypes by sex/gender using new diagnostic criteria that incorporate these newer in vivo measures and allow for better discrimination among dementia types. Additionally, with the new diagnostic criteria of limbic-predominant age-related TDP-43 encephalopathy (LATE) (Wolk et al., 2025), where the main clinical feature is a dense amnestic profile, it will be important to disentangle amnestic profiles due to AD versus LATE.

Overview of sex/gender differences in AD clinical trajectory

Sex/gender differences in the clinical trajectory of AD (i.e., preclinical AD versus MCI due to AD versus AD dementia) are less examined than AD dementia prevalence and incidence rates but equally important to understand in terms of improving early detection, intervention and disease tracking. Historically, the clinical and biological markers and diagnostic tools used to detect and track AD were developed with a "one size fits all" mentality that failed to consider sex/gender disparities (Mielke, 2020). Evidence suggests that, among those on the AD continuum, there are sex/gender differences in clinical presentation that depend on disease stage. Despite prominent AD risk factors being either more

prevalent (e.g., low educational/occupational attainment) or more harmful (APOE4 allele) in females/women or female-specific (e.g., early/surgical menopause), the extant literature suggest that in early stages of AD (preclinical to early MCI phase), females have a cognitive advantage over males (Caldwell et al., 2017; Caldwell et al., 2019; Sundermann et al., 2021; Sundermann et al., 2017; Sundermann, Biegon, et al., 2016; Sundermann, Maki, et al., 2016), especially in verbal memory, which is memory for any verbally presented information. This female cognitive advantage has also been found with global cognitive screening tasks (e.g., MMSE), which is commonly used in clinics to determine cognitive status (Sundermann, Maki, et al., 2020); however, it is unclear how much of this is driven by verbal memory components of the task. On the other hand, studies among individuals with MCI indicate more rapid decline in females versus males during and after the MCI phase (Fernández et al., 2024; Holland et al., 2013; Lin et al., 2015). This pattern suggests that females are better able to stave off higher levels of neuropathology and maintain normal cognitive function than males in early stages of AD. However, there is a tipping point in AD pathology burden whereby females can no longer compensate, resulting in a more rapid cognitive decline (Figure 1).

The female advantage in verbal memory and its influence on AD clinical trajectory

When interpreting sex/gender differences in the AD clinical trajectory, it is important to consider how healthy females and males tend to differ in terms of their natural cognitive strengths and weaknesses. It is well-established that sex/gender differences in cognitive abilities exist across the lifespan. Mainly, females have advantages in tasks that involve verbal skills (language and memory), fine motor skills, and processing speed, while males are more adept in visuospatial abilities, mathematical skills and gross motor functions (Halari et al., 2005; Kramer et al., 1988; Mann et al., 1990; Mous et al., 2017; Snow & Weinstock, 1990; Van der Elst et al., 2005). The female advantage in

verbal memory is relevant to AD given that memory is one of the earliest cognitive skills to show impairment in AD and verbal memory tests are typically a key component of MCI and AD diagnostic criteria (Weintraub et al., 2012). Most clinical tests of episodic memory are verbal memory tests. These often include a list learning task where individuals learn and immediately recall a random list of words over typically 3-5 trials and then are asked to remember that random list of words after about 20-30 minutes (delayed recall) or paragraph recall tasks in which a one paragraph story is read to the individual and similarly are asked to remember the story as best they can immediately and after about a 20-30 minute delay. Ironically, female's superior performance on these verbal memory tasks may become a disadvantage in late life in terms of early-stage AD detection. Despite known sex/gender differences in verbal memory, most normative data for our clinical tests of verbal memory do not adjust for sex/gender differences, as they do for age and education, although this has been gradually changing in the last few years. Thus, female's superior performance on verbal memory tasks may allow them to "mask" the cognitive effects of early-stage brain pathology by sustaining "normal" memory performance, as defined by our clinical cut-points. This would lead to a delayed diagnosis of MCI, thereby limiting opportunities to intervene at an early stage when our currently available interventions are more likely to alter disease course.

Evidence of sex/gender differences in AD clinical trajectory by disease stage

Evidence that sex/gender differences in the clinical presentation of AD varies by disease stage stems from a mix of cross-sectional studies examining sex differences in cognition at different diagnostic stages or pathology levels (mild, moderate and severe Aβ and/or tau pathology) and longitudinal studies of cognitive decline by diagnostic group. The cross-sectional studies have generally found that females show significantly better memory performance than males among those diagnosed as cognitively normal

or MCI or among those with mild to moderate AD pathology biomarkers (Caldwell et al., 2019; Digma et al., 2020; Sundermann et al., 2017; Sundermann, Biegon, et al., 2016; Sundermann, Maki, et al., 2016). Studies specifically probing the preclinical AD stage, have found little to no difference in verbal memory performance between cognitively normal females who are biomarker negative versus biomarker positive (i.e., preclinical AD), whereas verbal memory performance was significantly worse in cognitively normal males who were biomarker positive versus biomarker negative (Caldwell et al., 2017; Caldwell et al., 2019). These results suggest that, in the preclinical phase, females not only show better verbal memory performance than males, but their performance is more resilient to the adverse effects of early-stage AD pathogenesis, resulting in less decline at this stage.

Among the cross-sectional studies showing the female memory advantage in early clinical or pathological AD stages, this sex difference was absent among patients with AD dementia or when biomarker burden was severe (Caldwell et al., 2019; Cieri et al., 2022; Digma et al., 2020; Sundermann et al., 2017; Sundermann, Biegon, et al., 2016; Sundermann, Maki, et al., 2020). This pattern of results has been found across multiple AD biomarkers including hippocampal volume (Sundermann, Biegon, et al., 2016), Aβ (Caldwell et al., 2019; Sundermann et al., 2017), tau (Caldwell et al., 2019; Digma et al., 2020), and brain glucose metabolism (Caldwell et al., 2019; Sundermann et al., 2017; Sundermann, Maki, et al., 2016) and is suggestive of a steeper memory decline in females versus males when advancing from moderate to severe pathology burden. Longitudinal studies have supported the steeper decline in females at later disease stages as measured by clinical diagnosis or advancing pathology. Among 149 cognitively normal older adults from the University of California, San Francisco Memory and Aging Center, Lindbergh and colleagues found that, despite females showing better episodic memory performance than males at baseline (driven by verbal compared to visual memory performance), they demonstrated a steeper episodic memory decline as positron emission tomography

(PET)-measured amyloid burden increased over five years (Lindbergh et al., 2020). Among 398 Alzheimer's Disease Neuroimaging Initiative (ADNI) participants with MCI followed up to eight years, Lin and colleagues found two times faster decline in females versus males on the Alzheimer's Disease Assessment Scale–Cognitive (ADAS-Cog) Subscale and the Clinical Dementia Rating-Sum of Boxes (CDR-SOB) (Lin et al., 2015). In 688 ADNI participants, Holland et al. (2013) compared sex/gender differences in cognitive and brain volume decline among cognitively normal, MCI and AD dementia groups. They found that, despite females showing steeper declines in hippocampus, entorhinal cortex and amygdala volumes in the cognitively normal group, steeper cognitive decline (ADAS-Cog and CDR-SOB performance) in females was only found in the MCI and AD dementia groups (Holland et al., 2013). In line with evidence of a more adverse effect of the APOE4 allele on AD risk in females versus males, all longitudinal studies cited above found that the steeper cognitive decline in females versus males was stronger among APOE4 carriers (Holland et al., 2013; Lin et al., 2015; Lindbergh et al., 2020).

The steeper decline in females versus males in later stages of the AD trajectory is likely due to a combination of factors. For one, females have further to fall given their higher baseline performance. Secondly, female's ability to delay onset of clinically-significant decline implies that the MCI stage in females occurs at a more advanced pathological state compared to males, leading to more intense and concentrated decline in the MCI to dementia progression. Lastly, multiple studies across tau biomarkers have reported greater levels of pathological tau in females versus males who are MCI, amyloid-positive, or APOE4 carriers (Altmann et al., 2014; Banks et al., 2021; Buckley et al., 2019; Hohman et al., 2018; Oveisgharan et al., 2018; Sundermann, Panizzon, et al., 2020). Given that tau is the hallmark AD pathology most closely tethered to cognitive change (Lowe et al., 2018; Ossenkoppele et al., 2016), the greater tau burden in females may also contribute to their steeper decline once accelerated decline

begins. Supportively, the association between tau and verbal memory performance has been found to be stronger in females versus males among those with MCI (Banks et al., 2021) or with neuroimaging evidence of more advanced pattern of AD-associated tau deposition (Buckley et al., 2020). Longitudinal studies that track males and females across the full AD spectrum and, ideally, even from mid-life, are essential to truly interrogate the influence of sex on temporal relationships between AD pathology and cognitive decline.

With the evidence of a cognitive advantage in females at early AD stages followed by steeper decline, it follows that a larger gap in memory performance has been found between healthy females and females with dementia versus healthy males and males with dementia despite similar scores in females and males with dementia on the dementia rating scale and MMSE (Chapman et al., 2011; Gale et al., 2016). Chapman et al. even reported poorer verbal memory performance in females with AD dementia versus males with AD dementia despite female's higher performance in the cognitively normal group suggesting that the female advantage in verbal memory not only disappears but reverses in the AD dementia stage (Chapman et al., 2011). Similarly, others have found poorer performance on verbal memory tests as well as global cognitive screeners (i.e., MMSE) in females versus males with AD dementia (Buckwalter et al., 1993; McPherson et al., 1999).

Sex/gender differences in clinical trajectory aligns with the cognitive reserve theory

In 2023, the Collaboratory on Research Definitions for Reserve and Resilience in Cognitive Aging and Dementia developed a consensus on nomenclature of resilience, defined as a general term that subsumes any concept related to the capacity of the brain to maintain cognition and function with aging and disease (Stern et al., 2023). The three mechanisms that underlie resilience includes cognitive reserve, brain maintenance and brain reserve. Here, we will briefly describe cognitive reserve and its

relation to sex/gender differences. Cognitive reserve is defined as a "property of the brain (e.g., molecular, cellular, and network levels) that allows for cognitive performance that is better than expected given the degree of life-course related brain changes and brain injury or disease" (Stern et al., 2023). The sex/gender differences that we have discussed thus far with respect to the AD clinical trajectory is reminiscent of the cognitive reserve theory. As part of this theory, people with higher reserve, due to multiple factors including education, intelligence quotient, physical activity, social support, and occupational attainment, typically show better memory performance compared to those with lower reserve at baseline (Subramaniapillai et al., 2021). On average, these individuals have a delayed onset of memory decline until a greater pathology burden emerges, after which the decline becomes more accelerated due to advancement of disease. The limited educational opportunities and occupational attainment that women have historically endured has put them at a disadvantage for cognitive reserve. However, one's cognitive reserve reflects a balancing act with various advantageous and disadvantageous factors weighing in. The female verbal memory advantage may represent one form of cognitive reserve that weighs in specifically to the verbal memory domain resulting in better maintenance of verbal memory performance in females versus males in early AD stages. In fact, the female verbal memory advantage likely weighs more heavily than educational and occupational attainment given that it persists despite the lower rates of educational and occupational attainment in women of the current older generation and the effect of sex on verbal memory performance is stronger than that of education (Van der Elst et al., 2005; van Hooren et al., 2007).

The factors behind the sex/gender differences in the AD clinical trajectory are unclear but likely multi-factorial. Besides the psychometric reason of a greater drop in verbal memory performance needed to detect impairment in females, there may be biological mechanisms that support the female cognitive advantage in earlier disease stages and contribute to the steeper decline thereafter. For instance, greater

brain metabolism in females versus males that is sustained at early, but not later, AD stages, could potentially provide greater resilience against early AD-related brain changes (Andreason et al., 1994; Araque Caballero et al., 2015; Goyal et al., 2019; Hu et al., 2013; Perneczky et al., 2007; Sundermann, Maki, et al., 2020) and sex/gender differences in the use of compensatory strategies in the face of early cognitive decline (Dixon et al., 2001).

Implications for the ability to capture females early in disease trajectory

As the female advantage in verbal memory may obscure early decline, it may put females at a disadvantage in terms of detecting and intervening upon AD in its earliest stage. Accordingly, evidence suggests that females are more advanced in the disease when they are diagnosed with MCI compared to males. Based on linear regression models from cross-sectional data in ADNI, Sundermann and colleagues found that, at the cut-score for impairment on the Rey Auditory Verbal Learning Test - Delayed Recall, females demonstrated more advanced AD pathology on average (i.e., smaller hippocampal volume, lower brain glucose metabolism and greater amyloid plaque burden) compared to males (Sundermann et al., 2017; Sundermann, Biegon, et al., 2016; Sundermann, Maki, et al., 2016). In a hospital-based clinical sample of 349 older adults diagnosed with MCI, Karstens et al. found that females showed worse performance in non-memory domains (language and executive functioning/information processing speed) compared to males despite their comparable performance on global cognitive screening tasks and meeting clinical thresholds for MCI diagnosis (Karstens et al., 2023). In the Baltimore Longitudinal Study of Aging, Joynes et al. found that the time between estimated onset of amyloid positivity to MCI or dementia diagnosis was longer in females (median=15.95 years; IQR: 8.35, 21.1) versus males (median=14.85 years; IQR: 6.78, 20.17) suggestive of more time for advancing disease in females prior to MCI diagnosis (Joynes et al., 2024). The clinical

implications of a delayed MCI diagnosis due to imprecise evaluation of memory impairment in females are weighty as it limits the opportunity for early diagnosis and intervention when our currently available pharmaceutical and non-pharmaceutical interventions have the greatest potential of altering the disease course and advanced care planning is better communicated and implemented. In the phase three clinical trial of an anti-amyloid therapy, lecanemab, inclusion criteria included age 50-90, Aβ positivity and a diagnosis of MCI or mild AD dementia with objective memory impairment defined as ≥ 1 standard deviation below the age-adjusted mean in the verbal memory test, the Wechsler Memory Scale IV–Logical Memory II. It is indeed telling that results demonstrated, on average, beneficial effects of the drug in slowing cognitive decline in males but not females (van Dyck et al., 2023). As pharmaceutical drugs such as lecanemab are likely more effective when administered early in the course of disease, it is possible that females were less responsive to the drug because the non-sex-adjusted diagnostic criteria may have identified female participants further along in the disease process compared to male participants.

Our typical methods of detecting early cognitive change may not be serving females as well as they are serving males. Research is warranted into potential strategies that may improve our ability of detecting early cognitive change in females. Related to the emerging focus on precision medicine approaches, it is possible that different tests are more sensitive to early-stage AD in males versus females. One potential strategy is to identify cognitive tests that may be more sensitive to early cognitive change in females. For example, although verbal memory tests are more commonly used clinically, it is possible that performance on visual memory tests, that have less of a sex/gender bias (Brunet et al., 2020), may be more sensitive to early brain changes in females. Intriguingly, Bonner-Jackson and colleagues found that, among individuals with MCI from a memory clinic (57% female), bilateral hippocampal volume more strongly related to visual (Brief Visuospatial Memory Test-Revised) versus

verbal memory (Hopkins Verbal Learning Test-Revised), although sex-stratified analyses were not conducted (Bonner-Jackson et al., 2015).

Another strategy that could be applied to the conventional verbal memory tests is the development and use of sex-adjusted normative data. Sundermann and colleagues developed sex-specific normative data for certain verbal memory tests from which sex-specific cut-scores for impairment were derived and incorporated into aMCI diagnostic criteria in ADNI and The Rush University Memory and Aging Project. They found that when re-diagnosing participants using sex-specific versus conventional criteria, about 10% of females changed from a cognitively unimpaired to aMCI classification (labelled as "false negative" cases), and about 10% of males changed from aMCI to a cognitively normal classification (labelled as "false positive" cases) (Sundermann et al., 2021; Sundermann et al., 2019). The comparison of AD biomarkers and rates of progression to dementia in these false negative and positive cases to true positive and negative cases suggested that the new diagnostic classifications derived from sex-specific norms are more accurate. Overall, findings were illuminating by suggesting that sex-specific norms benefitted both females and males in terms of aMCI diagnostic accuracy and avoids diagnostic errors in about 20% overall. Specifically, sex-specific or sex-adjusted norms can help to identify early aMCI cases in females while also avoiding false aMCI diagnoses and the resulting undue stress and unneeded medications in a subset of males. Findings were also illuminating in terms of the paradoxical higher rates of aMCI in males versus females. Consistent with other studies (Brodaty et al., 2013; Ganguli et al., 2004; Koivisto et al., 1995; Roberts et al., 2012), the prevalence of aMCI was higher in males versus females when using the conventional MCI diagnostic criteria, but this difference was either eliminated or reversed when using sex-specific diagnostic criteria (Sundermann et al., 2021; Sundermann et al., 2019). These results suggest that prior reports of higher MCI rates in males versus females may be an artifact of the use of non-sex-adjusted norms in MCI criteria.

Research into the harmful consequences of non-sex-adjusted norms has begun to motivate change in normative data development. For example, in addition to established age and education norms, the third version of the California Verbal Learning Test (CVLT-3) released in 2017 added a normative adjustment for sex (Delis et al., 2017). The Mayo's Older Americans Normative Studies (MOANS) recently revised their norms for the commonly-used Rey Auditory Verbal Learning Test (RAVLT) by including sex adjustment. Similar to Sundermann et al. (2019, 2021), when they compared diagnoses resulting from age-adjusted only versus the new age- and sex-adjusted norms, they found that the age- and sex-adjusted criteria resulted in more impaired cases in females and less impaired cases in males (Stricker et al., 2021). Researchers from the Mayo Clinic also recently updated age-, sex- and education-adjusted RAVLT norms from the Mayo Normative Studies by limiting the normative sample to cognitively healthy adults without elevated amyloid or neurodegeneration. They found that these new norms with a more conservative approach to identifying a cognitively healthy normative sample show some benefits in diagnostic accuracy over conventional norms, especially for females (Stricker et al., 2024).

Conclusions

There are sex/gender differences not only in the rates of AD but also in diagnostic accuracy and the clinical trajectory of the disease, which has critical implications for our ability to target our interventions to males and females who are at high risk of AD dementia and to do so as early as possible. The sex/gender differences in clinical presentation depends on disease stage. In the preclinical phase, studies suggest that females have a cognitive advantage over males, particularly in the domain of verbal memory; however, in the MCI stage, females show more rapid decline than males. This pattern underscores the importance of accounting for disease stage when examining sex/gender differences in AD, particularly in cross-sectional studies, in which sex/gender difference findings may be masked when

examined across preclinical, MCI and AD dementia stages. The reasons for the sex/gender differences in clinical trajectory are likely multi-factorial but one critical factor is the life-long female advantage in verbal memory given that verbal memory is one of the earliest and most prominent cognitive deficits observed in AD and, therefore, a key component of MCI and AD diagnostic criteria. Our diagnostic approaches often do not account for this sex difference, which can lead to missed MCI diagnoses in females as mild declines in verbal memory performance can still fall in the cognitively normal range. Diagnostic approaches that account for the baseline sex difference in verbal memory suggest an improvement in MCI diagnostic accuracy in 20% across sexes. Considering and accounting for sex/gender differences in the AD clinical trajectory can have both research and clinical benefits. If our clinical trials for AD drugs have false MCI cases and are missing a subset of females with MCI, then we are not able to effectively test our treatments. By reducing sex-related heterogeneity in cohort studies, we may advance our understanding of AD etiology, improve power for more cost-effective clinical trials and develop treatments that serve both sexes.

Future Directions

There is still much to learn about the influence of sex/gender on our ability to detect and intervene upon early AD cases. Longitudinal studies with more sophisticated statistical techniques such as testing non-linear effects or change point or spine modeling are needed to model the change in sex/gender differences across the AD continuum and identify sex-specific pathological tipping points. The incorporation of sex-adjusted normative data for clinical verbal memory tests, such as with the MOANS or CVLT-3 data, needs to become more widespread. Additionally, research is needed to address cognitive assessments that may be more sensitive to early cognitive change in females and, thus, improve our ability of detecting early AD risk in females. For example, subjective cognitive decline is

known to be a prognostic indicator of MCI or dementia risk; however, subjective cognitive decline may have different clinical meanings in females versus males in terms of the prognosis of AD. Females likely perceive a decline in their own verbal memory performance before a clinical test captures this impairment, and thus, clinicians may want to weigh subjective cognitive decline, alongside objective testing, more heavily in females. Indeed, some research suggests that subjective memory decline is more strongly associated with objective memory performance among females versus males with amnestic MCI (Sundermann et al., 2018) and with incident dementia among non-demented older females versus males followed over 15 years (Pérès et al., 2011); however, far more work is needed in this space. Further, this information also needs to be considered in the context of other medical conditions that can impact thinking and cognition and, thus, obfuscate the clinical picture, like menopause transition or conditions that become more common in females in the post-menopause such as new-onset obstructive sleep apnea. Along these lines, we also need to improve our understanding of the biological mechanisms underlying sex differences in cognitive reserve and how these might change throughout the AD trajectory. Relatedly, our knowledge about how combinations of multiple pathologies influence sex differences in the AD trajectory is nominal but critical given that AD pathology typically does not occur alone but alongside other types of ADRD neuropathologies. Lastly, the majority of the studies referenced in this review are from cohorts of mostly white and well-educated adults, which is a major limitation. It is imperative to ask all these questions in more diverse samples that better reflect the U.S. population and understand how social determinants of health influence sex/gender differences in AD.

References

Altmann, A., Tian, L., Henderson, V. W., & Greicius, M. D. (2014). Sex modifies the APOE-related risk of developing Alzheimer disease. Annals of Neurology, 75(4), 563–573. https://doi.org/10.1002/ana.24135

Altmann, A., Tian, L., Henderson, V. W., & Greicius, M. D. (2014). Sex modifies the APOE-related risk of developing Alzheimer disease. *Ann Neurol*, *75*(4), 563-573. https://doi.org/10.1002/ana.24135

Andersen, K., Launer, L. J., Dewey, M. E., Letenneur, L., Ott, A., Copeland, J., Dartigues, J.-F., Kragh–Sorensen, P., Baldereschi, M., & Brayne, C. (1999). Gender differences in the incidence of AD and vascular dementia: The EURODEM Studies. *Neurology*, *53*(9), 1992-1992.

Andreason, P. J., Zametkin, A. J., Guo, A. C., Baldwin, P., & Cohen, R. M. (1994). Gender-related differences in regional cerebral glucose metabolism in normal volunteers. *Psychiatry Res*, *51*(2), 175-183. https://doi.org/10.1016/0165-1781(94)90037-x

Araque Caballero, M., Brendel, M., Delker, A., Ren, J., Rominger, A., Bartenstein, P., Dichgans, M., Weiner, M. W., & Ewers, M. (2015). Mapping 3-year changes in gray matter and metabolism in Aβ-positive nondemented subjects. *Neurobiol Aging*, *36*(11), 2913-2924. https://doi.org/10.1016/j.neurobiolaging.2015.08.007

Arenaza-Urquijo, E. M., Boyle, R., Casaletto, K., Anstey, K. J., Vila-Castelar, C., Colverson, A., Palpatzis, E., Eissman, J. M., Kheng Siang Ng, T., Raghavan, S., Akinci, M., Vonk, J. M. J., Machado, L. S., Zanwar, P. P., Shrestha, H. L., Wagner, M., Tamburin, S., Sohrabi, H. R., Loi, S., . . . Group, t. A. S. I. (2024). Sex and gender differences in cognitive resilience to aging and Alzheimer's disease. *Alzheimer's & Dementia*, *20*(8), 5695-5719. https://doi.org/https://doi.org/10.1002/alz.13844

Banks, S. J., Andrews, M. J., Digma, L., Madsen, J., Reas, E. T., Caldwell, J. Z. K., McEvoy, L. K., Fan, C. C., Dale, A. M., & Brewer, J. B. (2021). Sex differences in Alzheimer's disease: do differences in tau explain the verbal memory gap? *Neurobiol Aging*, *107*, 70-77. https://doi.org/10.1016/j.neurobiolaging.2021.05.013

Better, M. A. (2024). Alzheimer's disease facts and figures. *Alzheimer's Dement*, *20*, 3708-3821.

Bonner-Jackson, A., Mahmoud, S., Miller, J., & Banks, S. J. (2015). Verbal and non-verbal memory and hippocampal volumes in a memory clinic population. *Alzheimers Res Ther*, *7*(1), 61. https://doi.org/10.1186/s13195-015-0147-9

Brodaty, H., Heffernan, M., Kochan, N. A., Draper, B., Trollor, J. N., Reppermund, S., Slavin, M. J., & Sachdev, P. S. (2013). Mild cognitive impairment in a community sample: the Sydney Memory and Ageing Study. *Alzheimers Dement*, *9*(3), 310-317.e311. https://doi.org/10.1016/j.jalz.2011.11.010

Brunet, H. E., Caldwell, J. Z. K., Brandt, J., & Miller, J. B. (2020). Influence of sex differences in interpreting learning and memory within a clinical sample of older adults. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn*, *27*(1), 18-39. https://doi.org/10.1080/13825585.2019.1566433

Buckley, R. F., Mormino, E. C., Rabin, J. S., Hohman, T. J., Landau, S., Hanseeuw, B. J., Jacobs, H. I. L., Papp, K. V., Amariglio, R. E., Properzi, M. J., Schultz, A. P., Kirn, D., Scott, M. R., Hedden, T., Farrell, M., Price, J., Chhatwal, J., Rentz, D. M., Villemagne, V. L., . . . Sperling, R. A. (2019). Sex Differences in the Association of Global Amyloid and Regional Tau Deposition Measured by Positron Emission Tomography in Clinically Normal Older Adults. *JAMA Neurol*, *76*(5), 542-551. https://doi.org/10.1001/jamaneurol.2018.4693

Buckley, R. F., Scott, M. R., Jacobs, H. I. L., Schultz, A. P., Properzi, M. J., Amariglio, R. E., Hohman, T. J., Mayblyum, D. V., Rubinstein, Z. B., Manning, L., Hanseeuw, B. J., Mormino, E. C., Rentz, D. M., Johnson, K. A., & Sperling, R. A. (2020). Sex Mediates Relationships Between Regional Tau Pathology and Cognitive Decline. *Ann Neurol*, *88*(5), 921-932. https://doi.org/10.1002/ana.25878

Buckwalter, J. G., Sobel, E., Dunn, M. E., Diz, M. M., & Henderson, V. W. (1993). Gender differences on a brief measure of cognitive functioning in Alzheimer's disease. *Arch Neurol*, *50*(7), 757-760. https://doi.org/10.1001/archneur.1993.00540070069018

Caldwell, J. Z. K., Berg, J. L., Cummings, J. L., & Banks, S. J. (2017). Moderating effects of sex on the impact of diagnosis and amyloid positivity on verbal memory and hippocampal volume. *Alzheimers Res Ther*, *9*(1), 72. https://doi.org/10.1186/s13195-017-0300-8

Caldwell, J. Z. K., Cummings, J. L., Banks, S. J., Palmqvist, S., & Hansson, O. (2019). Cognitively normal women with Alzheimer's disease proteinopathy show relative preservation of memory but not of hippocampal volume. *Alzheimers Res Ther*, *11*(1), 109. https://doi.org/10.1186/s13195-019-0565-1

Chapman, R. M., Mapstone, M., Gardner, M. N., Sandoval, T. C., McCrary, J. W., Guillily, M. D., Reilly, L. A., & DeGrush, E. (2011). Women have farther to fall: gender differences between normal elderly and Alzheimer's disease in verbal memory engender better detection of Alzheimer's disease in women. *J Int Neuropsychol Soc*, *17*(4), 654-662. https://doi.org/10.1017/s1355617711000452

Chêne, G., Beiser, A., Au, R., Preis, S. R., Wolf, P. A., Dufouil, C., & Seshadri, S. (2015). Gender and incidence of dementia in the Framingham Heart Study from mid-adult life. *Alzheimers Dement*, *11*(3), 310-320. https://doi.org/10.1016/j.jalz.2013.10.005

Cieri, F., Zhuang, X., Cordes, D., Kaplan, N., Cummings, J., & Caldwell, J. (2022). Relationship of sex differences in cortical thickness and memory among cognitively healthy subjects and individuals with mild cognitive impairment and Alzheimer disease. *Alzheimers Res Ther*, *14*(1), 36. https://doi.org/10.1186/s13195-022-00973-1

Delis, D. C., Kramer, J., Kaplan, E., & Ober, B. A. (2017). *CVLT3 California verbal learning test third edition: manual*. NCS Pearson.

Digma, L. A., Madsen, J. R., Rissman, R. A., Jacobs, D. M., Brewer, J. B., & Banks, S. J. (2020). Women can bear a bigger burden: ante- and post-mortem evidence for reserve in the face of tau. *Brain Commun*, *2*(1), fcaa025. https://doi.org/10.1093/braincomms/fcaa025

Dixon, R. A., de Frias, C. M., & Bäckman, L. (2001). Characteristics of self-reported memory compensation in older adults. *J Clin Exp Neuropsychol*, *23*(5), 650-661. https://doi.org/10.1076/jcen.23.5.650.1242

Dubois, B., Hampel, H., Feldman, H. H., Scheltens, P., Aisen, P., Andrieu, S., Bakardjian, H., Benali, H., Bertram, L., Blennow, K., Broich, K., Cavedo, E., Crutch, S., Dartigues, J. F., Duyckaerts, C., Epelbaum, S., Frisoni, G. B., Gauthier, S., Genthon, R., . . . Jack, C. R., Jr. (2016). Preclinical Alzheimer's disease: Definition, natural history, and diagnostic criteria. *Alzheimers Dement*, *12*(3), 292-323. https://doi.org/10.1016/j.jalz.2016.02.002

Farrer, L. A., Cupples, L. A., Haines, J. L., Hyman, B., Kukull, W. A., Mayeux, R., Myers, R. H., Pericak-Vance, M. A., Risch, N., & van Duijn, C. M. (1997). Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. *JAMA*, *278*(16), 1349-1356.

Fernández, A., Cuesta, P., Marcos, A., Montenegro-Peña, M., Yus, M., Rodríguez-Rojo, I. C., Bruña, R., Maestú, F., & López, M. E. (2024). Sex differences in the progression to Alzheimer's disease: a combination of functional and structural markers. *Geroscience*, *46*(2), 2619-2640. https://doi.org/10.1007/s11357-023-01020-z

Fiest, K. M., Jetté, N., Roberts, J. I., Maxwell, C. J., Smith, E. E., Black, S. E., Blaikie, L., Cohen, A., Day, L., Holroyd-Leduc, J., Kirk, A., Pearson, D., Pringsheim, T., Venegas-Torres, A., & Hogan, D. B. (2016). The Prevalence and Incidence of Dementia: a Systematic Review and Meta-analysis. *Can J Neurol Sci*, *43 Suppl 1*, S3-s50. https://doi.org/10.1017/cjn.2016.18

Gale, S. D., Baxter, L., & Thompson, J. (2016). Greater memory impairment in dementing females than males relative to sex-matched healthy controls. *J Clin Exp Neuropsychol*, *38*(5), 527-533. https://doi.org/10.1080/13803395.2015.1132298

Ganguli, M., Dodge, H. H., Shen, C., & DeKosky, S. T. (2004). Mild cognitive impairment, amnestic type. *Neurology*, *63*(1), 115-121. https://doi.org/doi:10.1212/01.WNL.0000132523.27540.81

Gao, S., Hendrie, H. C., Hall, K. S., & Hui, S. (1998). The relationships between age, sex, and the incidence of dementia and Alzheimer disease: a meta-analysis. *Arch Gen Psychiatry*, *55*(9), 809-815. https://doi.org/10.1001/archpsyc.55.9.809

Goyal, M. S., Blazey, T. M., Su, Y., Couture, L. E., Durbin, T. J., Bateman, R. J., Benzinger, T. L., Morris, J. C., Raichle, M. E., & Vlassenko, A. G. (2019). Persistent metabolic youth in the aging female brain. *Proc Natl Acad Sci U S A*, *116*(8), 3251-3255. https://doi.org/10.1073/pnas.1815917116

Halari, R., Hines, M., Kumari, V., Mehrotra, R., Wheeler, M., Ng, V., & Sharma, T. (2005). Sex differences and individual differences in cognitive performance and their relationship to endogenous gonadal hormones and gonadotropins. *Behav Neurosci*, *119*(1), 104-117. https://doi.org/10.1037/0735-7044.119.1.104

Hebert, L. E., Scherr, P. A., McCann, J. J., Beckett, L. A., & Evans, D. A. (2001). Is the risk of developing Alzheimer's disease greater for women than for men? *Am J Epidemiol*, *153*(2), 132-136. https://doi.org/10.1093/aje/153.2.132

Hohman, T. J., Dumitrescu, L., Barnes, L. L., Thambisetty, M., Beecham, G., Kunkle, B., Gifford, K. A., Bush, W. S., Chibnik, L. B., & Mukherjee, S. (2018). Sex-specific association of apolipoprotein E with cerebrospinal fluid levels of tau. *JAMA Neurology*, *75*(8), 989-998.

Holland, D., Desikan, R. S., Dale, A. M., & McEvoy, L. K. (2013). Higher rates of decline for women and apolipoprotein E epsilon4 carriers. *AJNR Am J Neuroradiol*, *34*(12), 2287-2293. https://doi.org/10.3174/ajnr.A3601

Hu, Y., Xu, Q., Li, K., Zhu, H., Qi, R., Zhang, Z., & Lu, G. (2013). Gender differences of brain glucose metabolic networks revealed by FDG-PET: evidence from a large cohort of 400 young adults. *PLoS One*, *8*(12), e83821. https://doi.org/10.1371/journal.pone.0083821

Joynes, C. M., Bilgel, M., An, Y., Moghekar, A. R., Ashton, N. J., Kac, P. R., Karikari, T. K., Blennow, K., Zetterberg, H., & Thambisetty, M. (2024). Sex differences in the trajectories of plasma biomarkers, brain atrophy, and cognitive decline relative to amyloid onset. *medRxiv*, 2024.2009.2003.24312664.

Karstens, A. J., Maynard, T. R., & Tremont, G. (2023). Sex-specific differences in neuropsychological profiles of mild cognitive impairment in a hospital-based clinical sample. *J Int Neuropsychol Soc*, *29*(9), 821-830. https://doi.org/10.1017/s1355617723000085

Katz, M. J., Lipton, R. B., Hall, C. B., Zimmerman, M. E., Sanders, A. E., Verghese, J., Dickson, D. W., & Derby, C. A. (2012). Age-specific and sex-specific prevalence and incidence of mild cognitive

impairment, dementia, and Alzheimer dementia in blacks and whites: a report from the Einstein Aging Study. *Alzheimer Dis Assoc Disord*, *26*(4), 335-343. https://doi.org/10.1097/WAD.0b013e31823dbcfc

Kawas, C., Gray, S., Brookmeyer, R., Fozard, J., & Zonderman, A. (2000). Age-specific incidence rates of Alzheimer's disease: the Baltimore Longitudinal Study of Aging. *Neurology*, *54*(11), 2072-2077. https://doi.org/10.1212/wnl.54.11.2072

Koivisto, K., Reinikainen, K. J., Hänninen, T., Vanhanen, M., Helkala, E. L., Mykkänen, L., Laakso, M., Pyörälä, K., & Riekkinen, P. J., Sr. (1995). Prevalence of age-associated memory impairment in a randomly selected population from eastern Finland. *Neurology*, *45*(4), 741-747. https://doi.org/10.1212/wnl.45.4.741

Kramer, J. H., Delis, D. C., & Daniel, M. (1988). Sex differences in verbal learning. *Journal of Clinical Psychology*, *44*(6), 907-915. https://doi.org/https://doi.org/10.1002/1097-4679(198811)44:6<907::AID-JCLP2270440610>3.0.CO;2-8

Letenneur, L., Gilleron, V., Commenges, D., Helmer, C., Orgogozo, J.-M., & Dartigues, J.-F. (1999). Are sex and educational level independent predictors of dementia and Alzheimer's disease? Incidence data from the PAQUID project. *Journal of Neurology, Neurosurgery & Psychiatry*, *66*(2), 177-183.

Lin, K. A., Choudhury, K. R., Rathakrishnan, B. G., Marks, D. M., Petrella, J. R., & Doraiswamy, P. M. (2015). Marked gender differences in progression of mild cognitive impairment over 8 years. *Alzheimers Dement (N Y)*, *1*(2), 103-110. https://doi.org/10.1016/j.trci.2015.07.001

Lindbergh, C. A., Casaletto, K. B., Staffaroni, A. M., La Joie, R., Iaccarino, L., Edwards, L., Tsoy, E., Elahi, F., Walters, S. M., Cotter, D., You, M., Apple, A. C., Asken, B., Neuhaus, J., Rexach, J. E., Wojta, K. J., Rabinovici, G., & Kramer, J. H. (2020). Sex-related differences in the relationship between β-amyloid and cognitive trajectories in older adults. *Neuropsychology*, *34*(8), 835-850. https://doi.org/10.1037/neu0000696

Liu, Y., Yu, X., Han, P., Chen, X., Wang, F., Lian, X., Li, J., Li, R., Wang, B., Xu, C., Li, J., Zheng, Y., Zhang, Z., Li, M., Yu, Y., & Guo, Q. (2022). Gender-specific prevalence and risk factors of mild cognitive impairment among older adults in Chongming, Shanghai, China. *Front Aging Neurosci*, *14*, 900523. https://doi.org/10.3389/fnagi.2022.900523

Lowe, V. J., Wiste, H. J., Senjem, M. L., Weigand, S. D., Therneau, T. M., Boeve, B. F., Josephs, K. A., Fang, P., Pandey, M. K., Murray, M. E., Kantarci, K., Jones, D. T., Vemuri, P., Graff-Radford, J., Schwarz, C. G., Machulda, M. M., Mielke, M. M., Roberts, R. O., Knopman, D. S., . . . Jack, C. R., Jr. (2018). Widespread brain tau and its association with ageing, Braak stage and Alzheimer's dementia. *Brain*, *141*(1), 271-287. https://doi.org/10.1093/brain/awx320

Mann, V. A., Sasanuma, S., Sakuma, N., & Masaki, S. (1990). Sex differences in cognitive abilities: A cross-cultural perspective. *Neuropsychologia*, *28*(10), 1063-1077. https://doi.org/https://doi.org/10.1016/0028-3932(90)90141-A

Matthews, F. E., Stephan, B. C., Robinson, L., Jagger, C., Barnes, L. E., Arthur, A., & Brayne, C. (2016). A two decade dementia incidence comparison from the Cognitive Function and Ageing Studies I and II. *Nat Commun*, *7*, 11398. https://doi.org/10.1038/ncomms11398

McDowell, I., Xi, G., Lindsay, J., & Tierney, M. (2007). Mapping the connections between education and dementia. *J Clin Exp Neuropsychol*, *29*(2), 127-141. https://doi.org/10.1080/13803390600582420

McPherson, S., Back, C., Buckwalter, J. G., & Cummings, J. L. (1999). Gender-related cognitive deficits in Alzheimer's disease. *Int Psychogeriatr*, *11*(2), 117-122. https://doi.org/10.1017/s1041610299005670

Miech, R., Breitner, J., Zandi, P., Khachaturian, A., Anthony, J., & Mayer, L. (2002). Incidence of AD may decline in the early 90s for men, later for women: The Cache County study. *Neurology*, *58*(2), 209-218.

Mielke, M. M. (2020). Consideration of Sex Differences in the Measurement and Interpretation of Alzheimer Disease-Related Biofluid-Based Biomarkers. *J Appl Lab Med*, *5*(1), 158-169. https://doi.org/10.1373/jalm.2019.030023

Mielke, M. M., Aggarwal, N. T., Vila-Castelar, C., Agarwal, P., Arenaza-Urquijo, E. M., Brett, B., Brugulat-Serrat, A., DuBose, L. E., Eikelboom, W. S., Flatt, J., Foldi, N. S., Franzen, S., Gilsanz, P., Li, W., McManus, A. J., van Lent, D. M., Milani, S. A., Shaaban, C. E., Stites, S. D., . . . Babulal, G. M. (2022). Consideration of sex and gender in Alzheimer's disease and related disorders from a global perspective. *Alzheimers Dement*, *18*(12), 2707-2724. https://doi.org/10.1002/alz.12662

Mielke, M. M., Vemuri, P., & Rocca, W. A. (2014). Clinical epidemiology of Alzheimer's disease: assessing sex and gender differences. *Clin Epidemiol*, *6*, 37-48. https://doi.org/10.2147/clep.S37929

Mooldijk, S. S., Yaqub, A., Wolters, F. J., Licher, S., Koudstaal, P. J., Ikram, M. K., & Ikram, M. A. (2022). Life expectancy with and without dementia in persons with mild cognitive impairment in the community. *J Am Geriatr Soc*, *70*(2), 481-489. https://doi.org/10.1111/jgs.17520

Mous, S. E., Schoemaker, N. K., Blanken, L. M. E., Thijssen, S., van der Ende, J., Polderman, T. J. C., Jaddoe, V. W. V., Hofman, A., Verhulst, F. C., Tiemeier, H., & White, T. (2017). The association of gender, age, and intelligence with neuropsychological functioning in young typically developing children: The Generation R study. *Applied Neuropsychology: Child*, *6*(1), 22-40. https://doi.org/10.1080/21622965.2015.1067214

Nebel, R. A., Aggarwal, N. T., Barnes, L. L., Gallagher, A., Goldstein, J. M., Kantarci, K., Mallampalli, M. P., Mormino, E. C., Scott, L., Yu, W. H., Maki, P. M., & Mielke, M. M. (2018). Understanding the impact of sex and gender in Alzheimer's disease: A call to action. *Alzheimer's & Dementia*, *14*(9), 1171-1183. https://doi.org/https://doi.org/10.1016/j.jalz.2018.04.008

Nichols, E., Steinmetz, J. D., Vollset, S. E., Fukutaki, K., Chalek, J., Abd-Allah, F., Abdoli, A., Abualhasan, A., Abu-Gharbieh, E., Akram, T. T., Al Hamad, H., Alahdab, F., Alanezi, F. M., Alipour, V., Almustanyir, S., Amu, H., Ansari, I., Arabloo, J., Ashraf, T., . . . Vos, T. (2022). Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. *The Lancet Public Health*, *7*(2), e105-e125. https://doi.org/10.1016/S2468-2667(21)00249-8

Organization, W. H. (2023). *Dementia: Key facts*. Retrieved October 25, 2024 from https://www.who.int/news-room/fact-sheets/detail/dementia

Ossenkoppele, R., Schonhaut, D. R., Schöll, M., Lockhart, S. N., Ayakta, N., Baker, S. L., O'Neil, J. P., Janabi, M., Lazaris, A., Cantwell, A., Vogel, J., Santos, M., Miller, Z. A., Bettcher, B. M., Vossel, K. A., Kramer, J. H., Gorno-Tempini, M. L., Miller, B. L., Jagust, W. J., & Rabinovici, G. D. (2016). Tau PET patterns mirror clinical and neuroanatomical variability in Alzheimer's disease. *Brain*, *139*(Pt 5), 1551-1567. https://doi.org/10.1093/brain/aww027

Ott, A., Breteler, M. M., van Harskamp, F., Stijnen, T., & Hofman, A. (1998). Incidence and risk of dementia. The Rotterdam Study. *Am J Epidemiol*, *147*(6), 574-580. https://doi.org/10.1093/oxfordjournals.aje.a009489

Oveisgharan, S., Arvanitakis, Z., Yu, L., Farfel, J., Schneider, J. A., & Bennett, D. A. (2018). Sex differences in Alzheimer's disease and common neuropathologies of aging. *Acta Neuropathol*, *136*(6), 887-900. https://doi.org/10.1007/s00401-018-1920-1

Pankratz, V. S., Roberts, R. O., Mielke, M. M., Knopman, D. S., Jack, C. R., Jr., Geda, Y. E., Rocca, W. A., & Petersen, R. C. (2015). Predicting the risk of mild cognitive impairment in the Mayo Clinic Study of Aging. *Neurology*, *84*(14), 1433-1442. https://doi.org/10.1212/wnl.0000000000001437

Pérès, K., Helmer, C., Amieva, H., Matharan, F., Carcaillon, L., Jacqmin-Gadda, H., Auriacombe, S., Orgogozo, J. M., Barberger-Gateau, P., & Dartigues, J. F. (2011). Gender differences in the prodromal signs of dementia: memory complaint and IADL-restriction. a prospective population-based cohort. *J Alzheimers Dis*, *27*(1), 39-47. https://doi.org/10.3233/jad-2011-110428

Perneczky, R., Drzezga, A., Diehl-Schmid, J., Li, Y., & Kurz, A. (2007). Gender differences in brain reserve : an (18)F-FDG PET study in Alzheimer's disease. *J Neurol*, *254*(10), 1395-1400. https://doi.org/10.1007/s00415-007-0558-z

Roberts, R. O., Geda, Y. E., Knopman, D. S., Cha, R. H., Pankratz, V. S., Boeve, B. F., Tangalos, E. G., Ivnik, R. J., Rocca, W. A., & Petersen, R. C. (2012). The incidence of MCI differs by subtype and is higher in men: the Mayo Clinic Study of Aging. *Neurology*, *78*(5), 342-351. https://doi.org/10.1212/WNL.0b013e3182452862

Snow, W. G., & Weinstock, J. (1990). Sex differences among non-brain-damaged adults on the Wechsler Adult Intelligence Scales: a review of the literature. *J Clin Exp Neuropsychol*, *12*(6), 873-886. https://doi.org/10.1080/01688639008401028

Stern, Y., Albert, M., Barnes, C. A., Cabeza, R., Pascual-Leone, A., & Rapp, P. R. (2023). A framework for concepts of reserve and resilience in aging. *Neurobiol Aging*, *124*, 100-103. https://doi.org/10.1016/j.neurobiolaging.2022.10.015

Stricker, N. H., Christianson, T. J., Lundt, E. S., Alden, E. C., Machulda, M. M., Fields, J. A., Kremers, W. K., Jack, C. R., Knopman, D. S., Mielke, M. M., & Petersen, R. C. (2021). Mayo Normative Studies: Regression-Based Normative Data for the Auditory Verbal Learning Test for Ages 30-91 Years and the Importance of Adjusting for Sex. *J Int Neuropsychol Soc*, *27*(3), 211-226. https://doi.org/10.1017/s1355617720000752

Stricker, N. H., Christianson, T. J., Pudumjee, S. B., Polsinelli, A. J., Lundt, E. S., Frank, R. D., Kremers, W. K., Machulda, M. M., Fields, J. A., Jack, C. R., Knopman, D. S., Graff-Radford, J., Vemuri, P., Mielke, M. M., & Petersen, R. C. (2024). Mayo Normative Studies: Amyloid and Neurodegeneration Negative Normative Data for the Auditory Verbal Learning Test and Sex-Specific Sensitivity to Mild Cognitive Impairment/Dementia. *J Alzheimers Dis*, *100*(3), 879-897. https://doi.org/10.3233/jad-240081

Subramaniapillai, S., Almey, A., Natasha Rajah, M., & Einstein, G. (2021). Sex and gender differences in cognitive and brain reserve: Implications for Alzheimer's disease in women. *Frontiers in Neuroendocrinology*, *60*, 100879. https://doi.org/https://doi.org/10.1016/j.yfrne.2020.100879

Sundermann, E. E., Barnes, L. L., Bondi, M. W., Bennett, D. A., Salmon, D. P., & Maki, P. M. (2021). Improving Detection of Amnestic Mild Cognitive Impairment with Sex-Specific Cognitive Norms. *J Alzheimers Dis*, *84*(4), 1763-1770. https://doi.org/10.3233/jad-215260

Sundermann, E. E., Biegon, A., Rubin, L. H., Lipton, R. B., Landau, S., & Maki, P. M. (2017). Does the Female Advantage in Verbal Memory Contribute to Underestimating Alzheimer's Disease

Pathology in Women versus Men? *J Alzheimers Dis*, *56*(3), 947-957. https://doi.org/10.3233/jad-160716

Sundermann, E. E., Biegon, A., Rubin, L. H., Lipton, R. B., Mowrey, W., Landau, S., & Maki, P. M. (2016). Better verbal memory in women than men in MCI despite similar levels of hippocampal atrophy. *Neurology*, *86*(15), 1368-1376. https://doi.org/10.1212/wnl.0000000000002570

Sundermann, E. E., Edmonds, E. C., Delano-Wood, L., Galasko, D. R., Salmon, D. P., Rubin, L. H., & Bondi, M. W. (2018). Sex Influences the Accuracy of Subjective Memory Complaint Reporting in Older Adults. *J Alzheimers Dis*, *61*(3), 1163-1178. https://doi.org/10.3233/jad-170425

Sundermann, E. E., Maki, P., Biegon, A., Lipton, R. B., Mielke, M. M., Machulda, M., & Bondi, M. W. (2019). Sex-specific norms for verbal memory tests may improve diagnostic accuracy of amnestic MCI. *Neurology*, *93*(20), e1881-e1889. https://doi.org/10.1212/wnl.0000000000008467

Sundermann, E. E., Maki, P. M., Reddy, S., Bondi, M. W., & Biegon, A. (2020). Women's higher brain metabolic rate compensates for early Alzheimer's pathology. *Alzheimers Dement (Amst)*, *12*(1), e12121. https://doi.org/10.1002/dad2.12121

Sundermann, E. E., Maki, P. M., Rubin, L. H., Lipton, R. B., Landau, S., & Biegon, A. (2016). Female advantage in verbal memory: Evidence of sex-specific cognitive reserve. *Neurology*, *87*(18), 1916-1924. https://doi.org/10.1212/wnl.0000000000003288

Sundermann, E. E., Panizzon, M. S., Chen, X., Andrews, M., Galasko, D., & Banks, S. J. (2020). Sex differences in Alzheimer's-related Tau biomarkers and a mediating effect of testosterone. *Biol Sex Differ*, *11*(1), 33. https://doi.org/10.1186/s13293-020-00310-x

Teipel, S. J., Meindl, T., Wagner, M., Kohl, T., Bürger, K., Reiser, M. F., Herpertz, S., Möller, H. J., & Hampel, H. (2009). White matter microstructure in relation to education in aging and Alzheimer's disease. *J Alzheimers Dis*, *17*(3), 571-583. https://doi.org/10.3233/jad-2009-1077

Tom, S. E., Hubbard, R. A., Crane, P. K., Haneuse, S. J., Bowen, J., McCormick, W. C., McCurry, S., & Larson, E. B. (2015). Characterization of dementia and Alzheimer's disease in an older population: updated incidence and life expectancy with and without dementia. *Am J Public Health*, *105*(2), 408-413. https://doi.org/10.2105/ajph.2014.301935

Van der Elst, W., van Boxtel, M. P., van Breukelen, G. J., & Jolles, J. (2005). Rey's verbal learning test: normative data for 1855 healthy participants aged 24-81 years and the influence of age, sex, education, and mode of presentation. *J Int Neuropsychol Soc*, *11*(3), 290-302. https://doi.org/10.1017/s1355617705050344

van Dyck, C. H., Swanson, C. J., Aisen, P., Bateman, R. J., Chen, C., Gee, M., Kanekiyo, M., Li, D., Reyderman, L., Cohen, S., Froelich, L., Katayama, S., Sabbagh, M., Vellas, B., Watson, D., Dhadda, S., Irizarry, M., Kramer, L. D., & Iwatsubo, T. (2023). Lecanemab in Early Alzheimer's Disease. *N Engl J Med*, *388*(1), 9-21. https://doi.org/10.1056/NEJMoa2212948

van Hooren, S. A., Valentijn, A. M., Bosma, H., Ponds, R. W., van Boxtel, M. P., & Jolles, J. (2007). Cognitive functioning in healthy older adults aged 64-81: a cohort study into the effects of age, sex, and education. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn*, *14*(1), 40-54. https://doi.org/10.1080/138255890969483

Vassilaki, M., Cha, R. H., Aakre, J. A., Therneau, T. M., Geda, Y. E., Mielke, M. M., Knopman, D. S., Petersen, R. C., & Roberts, R. O. (2015). Mortality in mild cognitive impairment varies by subtype, sex, and lifestyle factors: the Mayo Clinic Study of Aging. *J Alzheimers Dis*, *45*(4), 1237-1245. https://doi.org/10.3233/jad-143078

Weintraub, S., Wicklund, A. H., & Salmon, D. P. (2012). The neuropsychological profile of Alzheimer disease. *Cold Spring Harb Perspect Med*, *2*(4), a006171. https://doi.org/10.1101/cshperspect.a006171

Wolk, D. A., Nelson, P. T., Apostolova, L., Arfanakis, K., Boyle, P. A., Carlsson, C. M., Corriveau-Lecavalier, N., Dacks, P., Dickerson, B. C., Domoto-Reilly, K., Dugger, B. N., Edelmayer, R., Fardo, D. W., Grothe, M. J., Hohman, T. J., Irwin, D. J., Jicha, G. A., Jones, D. T., Kawas, C. H., . . . Schneider, J. A. (2025). Clinical criteria for limbic-predominant age-related TDP-43 encephalopathy. *Alzheimer's & Dementia*, *n/a*(n/a), e14202. https://doi.org/https://doi.org/10.1002/alz.14202

Figure Captions

Figure 1. Visual depiction of hypothesized sex/gender differences in the clinical trajectory of Alzheimer's disease. Evidence suggests that females are better able than males to sustain normal cognitive performance, particularly verbal memory, in the presence of early-stage Alzheimer's disease pathogenesis. However, once pathology burden reaches a tipping point at moderate stages, females can no longer compensate and their cognitive function begins to decline more rapidly compared to males until the dementia stage.