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Sexual Dimorphism in Predisposition to Alzheimer's Disease

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Abstract:

Clinical studies indicate that Alzheimer's disease (AD) disproportionately affects women in both disease prevalence and rate of symptom progression, but the mechanisms underlying this sexual divergence are unknown. Though some have suggested this difference in risk is a reflection of the known differences in longevity between men and women, mounting clinical and preclinical evidence supports women also having intrinsic susceptibilities towards the disease. While a number of potential risk factors have been hypothesized to mediate these differences, none have been definitively verified. In this review, we first summarize the epidemiological studies of prevalence and incidence of AD amongst the sexes. Next, we discuss the most likely risk factors to date that interact with biological sex, including 1) genetic factors, 2) sex hormones 3) deviations in brain structure, 4) inflammation and microglia, 5) and psychosocial stress responses. Overall, though differences in lifespan are likely to account for part of the divide between the sexes in AD prevalence, the abundance of preclinical and clinical evidence presented here suggests an increase in intrinsic AD risk for women. Therefore, future studies focusing on the underlying biological mechanisms for this phenomenon are needed to better understand AD pathogenesis in both sexes, with the eventual goal of sex-specific prevention and treatment strategies.

Keywords:

Sex difference; Cognition, APOE, Brain Structure; Hormones; Stress; Alzheimer's disease

1. Introduction:

Alzheimer's disease (AD) is a progressive neurodegenerative disease that affects 5.4 million Americans aged 65 or older and is the fifth leading cause of death in the US. Of these 5.4 million patients, 3.3 million (nearly 70%) were women (Alzheimer's Association 2015, Hebert, et al., 2013), but the biological basis of the sex-based differences in AD onset and progression remain elusive (Hua, et al., 2010).

While a definitive cause has yet to be proven, scientists and physicians have developed both epidemiological and biological explanations for this apparent increase in risk (Lin and Doraiswamy, 2014, Mielke, et al., 2014, Riedel, et al., 2016a). Clinicians and researchers have noted that in most populations around the world, women tend to outlive men so that the gap between the number of men and women in a population widens with advancing age (Brookmeyer, et al., 1998, Hebert, et al., 2001, Plassman, et al., 2007, Seshadri, et al., 1997). Though prevalence and incidence are rates, and so the frequency of women or men would normally not impact these measures, advancing age is the strongest risk factor for AD, and so the increased frequency of women at the highest age groups increases the likelihood of AD being diagnosed. Thus, the greater frequency of women of the oldest ages also impacts women's risk profiles, since AD diagnoses double roughly every 5 years (Walter 2002). Combined with hypotheses integrating the improved cardiovascular health profiles of men who live to greatly advanced ages (i.e. 85 years or older) (Carmelli, et al., 1998), many experts have concluded that the apparent differences in AD prevalence between men and women are due to the indirect consequences of greater female longevity.

While this view still remains widely held, many recent studies have demonstrated that there are age- and risk factor-matched increases in the incidence of developing AD in women, though previous results have been inconsistent (Fiest, et al., 2016, Bachman, et al., 1993, Edland, et al., 2002, Hebert, et al., 2001, Rocca, et al., 1998). These recent clinical (human) and pre-clinical studies (animal models) have led to some new hypotheses predicting a female-specific increase in AD risk based on intrinsic biological differences, including sex-specific genetic interactions (Altmann, et al., 2014, Janicki, et al., 2014, Ungar, et al., 2014), hormones and associated endocrinological changes with age (Morrison, et al., 2006, Rocca, et al., 2011), sexual dimorphism in brain structures (Elbejjani, et al., 2015, Mielke, et al., 2014, Sampedro,

et al., 2015), heightened inflammatory responses in women (Hanamsagar and Bilbo, 2016), and sex by stress interactions (Bangasser, et al., 2016). Still, the collection of evidence necessary to validate one or more of these hypotheses is in its infancy, and so the perspectives of individual experts on this subject remain varied.

In this review, we summarize and evaluate both the epidemiological and biological evidence explaining the sex-difference in AD risk in order to better inform both researchers and clinicians on the issue. After reviewing the available evidence, we believe this review will demonstrate that while some of the sex differences observed in AD prevalence are due to differences in longevity, it is very plausible that other distinct biological mechanisms increase the risk and disease progression of AD in women. We hope to present the most recent data shaping expert perspectives, inspiring researchers to go in new directions, and driving development of future diagnostic tools and treatments for AD.

2. Epidemiological Perspective

Age remains the greatest risk factor for AD, and the prevalence of AD in populations 85 and older is vastly increased when compared to other age ranges (Riedel, et al., 2016b), with multiple studies showing that the incidence of AD rises exponentially after the sixth decade of life (Kukull, et al., 2002, Masters, et al., 2015). Similar to this increase in disease diagnoses, there are more women aged 85 or older than men in most global subpopulations (Fratiglioni, et al., 2000), meaning there are more women at greatest risk based on age. In addition, women outlive men by an average of 4.5 years (World Population Ageing 2015). So while the prevalence of AD is often reported to be higher for women compared to men due to the increase in risk by greater age, the relative increase in women living to more advanced ages makes it difficult to assess whether women also have an increased *aged-matched* risk of the disease (Brookmeyer, et al., 1998, Hebert, et al., 2001, Plassman, et al., 2007, Seshadri, et al., 1997). Reflecting this, the literature examining incidence has also yielded conflicting results, as some studies report higher age-adjusted numbers for women (Irvine, et al., 2012, Seshadri, et al., 1997). In addition, some evidence suggests that disease progression is accelerated in women, such as imaging studies indicating that women with mild cognitive impairment (MCI) and AD show greater memory impairment

compared to males with the same diagnoses (Gale, et al., 2016, Lin, et al., 2015). Still, other studies fail to find an association between incidence, progression, and sex (Bachman, et al., 1993, Edland, et al., 2002, Hebert, et al., 2001, Rocca, et al., 1998) or remain inconclusive (Fiest, et al., 2016).

The inconsistent findings between studies may be explained by many factors, such as 1) type of study (i.e prospective cohort, retrospective cohort, cross-sectional analysis), 2) cultural differences affecting diet, exercise, and stress response strategies, 3) differences in inclusion/exclusion criteria, especially for co-morbid diseases, 4) sample size and statistical power, and 5) differing methods of classifying and confirming AD diagnoses. This last factor is of particular importance as many different criteria have been used across studies. According to the NINCDS-ADRDA diagnostic criteria, which a majority of current AD studies use, a definitive diagnosis of AD can only be made post-mortem while probable AD is routinely diagnosed clinically through the presentation of certain symptoms, such as memory loss, and the exclusion of other possible diagnoses, including vascular dementia, other neurodegenerative diseases, other neuropsychiatric diseases, or acute causes of dementia such as traumatic injury or stroke (Trojanowski, et al., 2007). While the diagnoses of AD are verified with autopsies in some studies (Gustafson, 1987) (Zandi, et al., 2002), (Miech, et al.), (Matyi, et al.)), many others (Barnes 2003, Herbert 2001, Galasko, et al., 1998) use a clinical diagnosis, which may categorize other dementia presentations incorrectly as being AD. In addition, the pre-AD diagnosis of MCI can complicate the timing of when the later diagnosis of AD is made, making the process of defining the age-of-onset for AD more variable. Further, aging women without dementia and with early MCI and sex-matched quantities of A β seem to have better verbal recall memory than their respective age-matched male counterparts, and as the diagnosis of later stage MCI and AD are partially dependent on this cognitive process, women receive the diagnosis of AD later than men and may not be classified as having MCI as readily; (Sundermann, et al., 2017, Sundermann, et al., 2016). Finally, one would think that a higher age-specific incidence of AD dementia among women would translate to a higher incidence of MCI and subclinical AD. Yet some data have found the opposite (Roberts, 2012), and while this may be explained by the increased verbal memory reserve in women, possibly leading to later MCI diagnoses (Sundermann 2016, 2017), this paradox deserves careful investigation.

The culmination of these classification difficulties is apparent in a study looking at subjects from two longitudinal assessments on community dwelling elderly patients by Schneider and colleagues (Schneider, et al., 2009). When comparing autopsy results of 483 participants with a diagnosis of either probable AD, MCI, or no cognitive impairment, they found that only 41.8% of patients had pathology consistent with an AD-only diagnosis. Of the remaining patients, 45.8% had mixed pathology with AD and vascular dementia or FTD-like findings, 6.2% were misclassified, and 6.2% had no pathological markers of any of the studied dementias. Likewise, 29.4% of patients without cognitive impairment had signs of AD pathology, 8.8% had signs of mixed pathology with AD, 16.5% had infarcts or Lewy-Bodies, while only 45.3% had no significant pathological findings (Schneider, et al., 2009). The findings in the cognitively unimpaired patients are generally concerning for our understanding of AD pathogenesis, but the results suggesting that a large portion of clinical diagnoses are not corroborated by pathology makes quantifying the actual incidence and prevalence of AD even more challenging. It is also interesting to note that the most often-cited study reporting statistically significant differences in incidence between men and women, the Cache County Memory Study, verified many of their probable AD diagnoses with autopsy (Zandi, et al., 2002, Miech, et al., Matyi, et al.).

Further supporting classification bias as an issue in determining the real incidence of AD in men and women, many studies have shown that vascular dementia, as well as Lewy Body Dementia, is more common in men (Whitmer, et al., 2005, Ferencz 2015), and because of the high occurrence of mixed pathology in clinical AD diagnoses, it could be suggested that more men with dementia are being incorrectly classified as having AD as the precipitating factor for their cognitive decline, thus overestimating the total population of men with AD, especially at younger ages where the sex difference in prevalence is not as apparent. Indeed, it has been suggested that one aspect of the enlarged gap in AD prevalence between sexes in patients over 85 years old is because men with vascular complications tend to die earlier, so that the remaining healthy males have reduced cardiovascular risk factors for AD (Whitmer, et al., 2005). In addition, it has been reported that men have better overall health at older ages than their female counterparts in terms of morbidity but not mortality (Graves, et al., 2006). Though these differences have been shown reproducibly, this argument for improved male health with older age is a

double-edged sword, as it becomes unclear if AD diagnoses are overestimated in younger men due to increasing adverse cardiovascular events and possible misclassification of the resultant dementia.

For all these stated reasons, it is unsurprising that there remain large differences in the reported incidence of AD between men and women across studies. Perhaps the single most pertinent example of this discrepancy was found in a recent meta-analysis, where inclusion of 22 studies on sex differences revealed that “all estimates of incidence and prevalence were higher for females compared to males, though the differences were not statistically different” (Fiest, et al., 2016). Still, the relative narrowing of the incidence rates compared to prevalence in studies that have found a difference, such as the Cache County Memory Study, suggest that longevity remains an important reason why there are more women with AD than men. The complications in estimating incidence and the increasing body of clinical and pre-clinical evidence supporting sex-specific biological mechanisms in diverging AD risk remain an important adjunct explanation to the epidemiological perspective and should be investigated more closely in future studies.

Table 1 summarizes most representative studies investigating sex differences in humans collected from 2000 to date.

3. Biological Perspective

It is interesting to note that women tend to develop diseases associated with senescence – defined as reduced function due to aging – at earlier ages than men, especially for diseases that are notorious for resulting in increased morbidity but rarely lead directly to mortality (Graves, et al., 2006). In addition, women consistently have a higher age-specific prevalence of disability globally (Jagger, et al., 2016, Buttery, et al., 2016, Freedman, et al., 2016; Crimmins, et al., 2011, Wahrendorf, et al., 2013, Whiteford, et al., 2015). It is therefore very likely that similar trajectories are present for the development of cognitive deficits due to diseases with low or late stage mortality. The potential for a real increase in AD incidence among women may be part of this trend towards rapid senescence and disability, and many of the biological mechanisms proposed to explain this global, age-related reduction in functionality also extend to the development of AD. In the following sections, we review some of the prevailing biological

mechanisms that may explain the increased incidence of AD in women reported in some studies, drawing on both clinical and pre-clinical studies from the literature.

3-1. Sex and Genetics Interaction in AD: Focus on ApoE and BDNF

ApoE

As more genomic studies uncover risk genes for various diseases, there have been more instances of differing risk profiles for a particular genomic variant between sexes (Gatz, et al., 2006, Riedel, et al., 2016b). In line with this, recent epidemiologic studies demonstrated that the *APOE* allele confers different AD risk profiles based on sex. These studies indicate that women with *APOE-ε4* are at greater risk for developing AD than age-matched men, especially when comparing heterozygous individuals carrying the *APOE-ε4* allele (Damoiseaux, et al., 2012, Altmann, et al., 2014). In a large meta-analysis (Farrer, et al., 1997) and in a large population study of AD (Bremner, 1999), women who were heterozygous for the *APOE-ε4* allele had AD diagnosed five years earlier than heterozygous men (Poirier, et al., 1993). Similarly, the odds ratio for AD in women with one copy of the *APOE-ε4* allele is 4-fold greater than in men (Altmann, et al., 2014, Farrer, et al., 1997, Payami, et al., 1994). In addition, women carrying *ε3/ε4* often show faster age-related decline and greater cognitive deterioration than age-matched *ε3/ε4* men (Beydoun, et al., 2012, Farrer, et al., 1997). However, one study found that the association between the *APOE* genotype and cognitive decline is significant only in women over the age of 70 (Mortensen and Høgh, 2001) while a recent meta-analysis suggested women with one copy of *APOE-ε4* only had higher risk in 65-75 year old age range (Neu, et al., 2017), and so more research is needed to determine the impact of this sex-by-gene interaction.

In support of these clinical findings, preclinical investigations of AD mouse models have revealed similar sex-by-*APOE* interactions for AD-like pathology and cognitive deficits. Notably, one study demonstrated that female 3xTg-AD mice with neural expression of the human *APOE-ε4* showed increased spatial memory deficits compared to *APOE-ε4* male mice or *APOE-ε3* males and females starting at 6 months of age (Raber, et al., 1998).

Paradoxically, men homozygous for *APOE-ε4* are reported to be at greater risk for MCI and AD in some studies than homozygous women, with men in these studies demonstrating a shift to lower episodic

memory scores (Farrer, et al., 1997, Lehmann, et al., 2006). In conjunction, one report noted that men who are *APOE*- ϵ 4 homozygotes with MCI have smaller hippocampal volumes than homozygous women (Fleisher, et al., 2005). These discrepancies between sexes for AD risk in the homozygous and heterozygous states complicate the interpretation of the sex-by-gene interactions concerning the *APOE*- ϵ 4 allele.

APOE's influence on AD pathogenesis is multifaceted and likely includes regulation of A β clearance, tau phosphorylation, cerebrovascular permeability, blood-brain-barrier integrity, inflammatory responses, and synaptic maintenance (G. Bu, 2009, Tai, et al., 2016). It is tempting to speculate that the heterozygotes may suffer more from abnormal A β production and clearance while the homozygotes have increased dementia pathogenesis from impaired cardiovascular function (Liu, et al., 2013) and, thus, may affect men and women differently. However, a more detailed understanding of *APOE*'s role in AD pathogenesis is essential to discovering why such divergent risk profiles by sex are apparent in *APOE*- ϵ 4 carriers.

BDNF

The neurotrophin BDNF is an important factor controlling synaptic plasticity in the CNS (Kowianski 2017), and many neuropsychiatric diseases have demonstrated changes in BDNF in their pathogenesis or treatment, especially mood disorders (Yeh, et al., 2015). Recently, certain *BDNF* polymorphisms in humans have been shown to affect the risk of AD development and cognitive decline (G.-D. Li, et al., 2017, Chen, et al., 2014, Noriko Fukumoto, et al., 2010, Matyi, et al., 2017, Lim, et al., 2015), and AD patients have been reported to have decreased BDNF in post-mortem brain samples (G. Li, et al., 2017) and peripherally in blood (Qin, et al., 2017). Similar to *APOE*, many of these association studies discovered increased risk of AD for women over men. For instance, the *BDNF* Val66Met polymorphism has been shown to increase AD risk only in women but not men (G.-D. Li, et al., 2017, N. Fukumoto, et al., 2010, Chen, et al., 2014) while similar findings of increased risk in only women were found for two other SNPs, rs2072446 and rs56164415 (Matyi, et al., 2017). In addition, one of these studies reported that while BDNF was decreased in many cortical areas in both sexes, only females demonstrated BDNF downregulation in the entorhinal cortex, a main input and output area of the hippocampus (G.-D. Li, et al., 2017). Preclinically, it is interesting to note that in a prominent AD mouse model, APPsw/PS1dE9,

female mice had higher levels of soluble A β and mature BDNF (mBDNF) at baseline but saw a precipitous drop in mBDNF and the mBDNF/proBDNF ratio with stress. In contrast, the male counterparts had an increase in mBDNF with chronic stress, suggesting that female mice may suffer more from a stress-by-genotype interaction in terms of BDNF loss than males.

In addition, both genetic and biochemical studies have demonstrated a link between *APOE* and *BDNF* in AD pathogenesis (Ward, et al., 2014, Lim, et al., 2015, Sen, et al., 2015, Sen, et al., 2017)). Multiple studies have suggested that in the presence of A β , *APOE- ϵ 4* and *BDNF* Val66Met worsen cognitive decline more than either allele in isolation, especially for episodic memory (Ward, et al., 2014, Lim, et al., 2015). Mechanistically, it has been suggested that *APOE* directly regulates *BDNF* expression and secretion (Sen, et al., 2015, Sen, et al., 2017). It has also been shown that the *APOE- ϵ 4* causes HDAC4 and HDAC6 to translocate into the nucleus, where these deacetylases reduce *BDNF* expression through transcriptional repression (Sen, et al., 2015), leading to decreased *BDNF* creation and secretion (Sen, et al., 2017). In contrast, *APOE- ϵ 3* has little or no effect on *BDNF* levels (Sen, et al., 2015). Given the increasing evidence that *APOE* status can affect *BDNF*, and that certain *APOE* and *BDNF* alleles may predispose women to develop AD more easily than men, a sexually divergent interaction between these AD effectors is quite possible. In general, it is also interesting to note that estrogen can influence the expression of *BDNF* and that many of the pathways supported by *BDNF* signaling are also influenced by estrogen (Scharfman and MacLusky, 2006). However, whether estrogen plays a mechanistic role in the cross-talk between *APOE* and *BDNF* remains to be seen.

While evidence demonstrating *BDNF*'s role in AD pathogenesis continues to build, it remains unclear how *BDNF* alone or combined with *APOE* influences AD. As *BDNF* is a dynamic regulator of neuronal survival and synaptic plasticity (Kowiański, et al., 2017), a simple hypothesis may suggest that loss of *BDNF* makes neurons more susceptible to AD-related toxicity. In addition, it is possible that *BDNF* directly acts on AD-causing intermediates, as *BDNF* has been shown to reduce A β -42 in primary neurons from AD mice through the SORLA-MEK/ERK pathway (Rohe, et al., 2009), another pathway regulated by *APOE* (Guojun Bu, 2009). Though progress has been made, future investigations will be needed to define this mechanism more clearly. Because of the ample evidence suggesting greater AD

susceptibility for women with *BDNF* mutations, investigating sex differences should be an important part of these investigations.

3-2. Sex-specific Brain Structure Changes and Biomarkers in AD

One explanation for the sexual dimorphism in AD risk and severity centers on the divergent changes in brain structures that men and women have in response to disease or disease-causing insults. It is posited that women may be more sensitive to pathological agents for AD and experience more rapid structural loss when compared to their male counterparts, who are posited to have a larger cognitive reserve based on increased brain volume (Mielke, et al., 2014). Many examples of this are apparent in the literature.

As part of the Alzheimer's Disease Neuroimaging Initiative (ADNI), a study examined 1-year atrophy rates using 3D-tensor based MRI morphometry in 1368 MRI scans (144 subjects with AD, 338 subjects with MCI, and 202 controls), it was discovered that annual atrophy rates were faster in women (Hua, et al., 2010). A follow-up study further showed that women with MCI had greater atrophy in numerous brain regions and a steeper decline in certain cognitive tasks compared to men, as well as greater atrophy in numerous regions once an AD diagnosis had been made (Holland, et al., 2013). In the Minimal Interval Resonance Imaging in AD (MIRIAD) study, women with probable AD demonstrated significantly faster rates of hippocampal atrophy than their male counterparts (Ardekani, et al., 2016). On a molecular level, another study used discovery driven quantitative proteomics to detect modulation of several redox proteins in the temporal lobe of patients with combined AD and cerebrovascular disease (AD + CVD subjects) and observed sex-specific alterations in the white matter and mitochondrial proteomes in women. Female patients also displayed downregulation of certain ATP synthase and cytochrome oxidase subunits, suggesting increased severity of mitochondrial impairment in women with AD + CVD (Gallart-Palau, et al., 2016). These studies suggest that when degeneration begins, it may affect women more rapidly than men, resulting in the observed increase in pathophysiology.

In concert, a clinical-pathological study observed a large sex difference in the association of AD pathology with the odds of AD dementia in men and women. Specifically, it was reported that each additional unit of AD pathology was associated with a nearly 3-fold increase in the odds of AD dementia

in men compared with a more than 22-fold increase in the odds of AD dementia in women (Barnes, et al., 2005), again suggesting that women might possibly be more sensitive to the pathological agents that cause AD. In agreement, a recent study reported that women with higher CSF A β -42 and total Tau levels, indicative of worse pathological changes, showed more rapid hippocampal atrophy and cognitive decline than men, furthering the notion that divergent responses in structural integrity to pathological insults are based on sex in AD (Koran, et al., 2016).

While the current studies seem to be in agreement in regards to divergent structural responses to pro-AD agents, it is difficult to conclude whether the observed sex difference is driven by differences in the etiology and pathophysiology of the AD cascade or the late-life risk factors of poor brain aging. Further, while these structural changes are readily observed, the underlying molecular mechanism leading to this divergence is still far from clear.

3-3. Impact of Differing Sex Hormones in AD

Changes in sex steroid hormones (i.e. estrogen and progesterone in females and testosterone in males) have been associated with AD onset and progression, representing an endocrinological explanation for AD risk (Grimm, et al., 2016). Among these sex hormones, estrogen has received the most attention in clinical and preclinical investigations. While much of the body's estrogen is synthesized in the ovaries, a significant amount is also produced in the CNS, where one of the three isoforms of estrogen, E2 and its receptor (ER), has been observed in high levels in limbic system regions, such as the hypothalamus and hippocampus (Cui, et al., 2013). E2 has been shown to mediate sex-specific behaviors, regulate synaptic plasticity, and promote neural survival in a number of studies (Green and Simpkins, 2000). Due to its neuroprotective role, the rapid decrease in endogenous estrogen levels during menopause has been proposed as a trigger for the development of AD in females (Paganini-Hill and Henderson, 1994).

However, only a few studies have shown a direct link between estrogen and AD. One clinical study from the Mayo Clinic, the Cohort Study of Oophorectomy and Aging, showed an almost two-fold increase in dementia risk in women who underwent bilateral oophorectomy before menopause (Rocca WA 2007). In the Cache County Memory Study, women who used hormone replacement therapy in the perimenopausal period had fewer cases of AD later on life (Zandi, et al., 2002). Another study found that

surgical menopause was associated with a faster rate of cognitive decline and more pHF-tau pathology (Bove, et al., 2014). In support of this, one preclinical study demonstrated that in young APP^{swe} mice with ovariectomies, absolute A β levels remain similar to controls, but the A β /sAPP α ratio significantly increases due to decreased APP. However, supplemental estrogen administered to these mice paradoxically reduced A β levels but did not alter the total levels of APP. These results suggest that estrogen might enhance α -secretase activity leading to increased formation of sAPP α , though the uncoupling between APP and A β metabolism with ovariectomy and subsequent estrogen replacement complicates this conclusion (Levin-Allerhand and Smith, 2002). Another study showed that ovariectomies in APP transgenic mice (Tg2576) increased the levels of A β levels in the brain and that estrogen replacement therapy blocked this effect (Zheng, et al., 2002). However, the same experiments in Tg2576+PS1 double mutant mice demonstrated a much smaller effect, suggesting that differences in transgenes or strains might mediate the relative impact of estrogen in these models (Wang, et al., 2003). The downstream mechanisms of estrogen's effect on AD neuropathology are still poorly understood, and hypotheses centering on transcriptional regulation and downstream kinase cascades have both been presented (Hwang, et al., 2016, Sarkar, et al., 2015). One probable mechanism whereby estrogen is neuroprotective in AD is through shifting APP processing towards the non-amyloidogenic pathway via α -secretase through activation of extracellular-regulated kinase 1 and 2 (ERK1 and 2) and protein kinase C (PKC) (Cordey, et al., 2003, Wang, et al., 2016). Further, estrogen may act through activation of the MARK/ERK pathway to reduce A β levels, potentially through BACE1 inhibition and increased A β clearance (Tamagno, et al., 2009).

But while the pre-clinical evidence seems to suggest a protective role for estrogen in AD pathogenesis, clinical trials concerning estrogen replacement therapy (ERT) have resulted in inconclusive data, with some even showing decreased cognitive function with estrogen-only therapies (Asthana et al., 2001, Tang et al., 1996, Wang et al., 2000, Mulnard et al., 2000, Henderson et al., 2000, Shumaker et al., 2003). The results of these studies are surprising, though it is possible that ERT confers other risks that interact with AD pathogenesis to worsen cognition, such as those regarding cardiovascular health. Further, it remains unclear if estrogen + progesterone or progesterone alone may have different

neuroprotective properties in post-menopausal women compared to those who took ERT. Finally, some preclinical studies have suggested that estrogen may be an important factor in preventing AD during certain “critical windows,” which is supported by association data in the Cache County Memory Study (Zandi, et al., 2002). One preclinical study suggested that ERT had a higher likelihood of being neuroprotective in the perimenopausal but not postmenopausal period (Christensen 2017). Intriguingly, another study noticed an increase in A β and poorer working memory in female AD mice compared to males that could be reversed by supplementing neonatal females with testosterone propionate, resulting in brain masculinization (Carroll, et al., 2011) and suggesting that early exposure to sex hormones during development may have a large impact on later life AD risk. Still, whatever the reason for the disconnect between pre-clinical and clinical studies, the role of estrogen in AD pathogenesis is likely to be more complex than originally perceived.

Interestingly, studies in human patients and animal models suggest that androgen deprivation may also represent a risk factor for AD pathogenesis in males (Pike, et al., 2009, Rosario, et al., 2010, Verdile, et al., 2014). One study demonstrated that brain testosterone levels were inversely correlated to soluble A β concentration in men (Rosario, et al., 2011). Another preclinical study indicated that increased testosterone in aged male 3xTg-AD mice was correlated with reduced A β plaque pathology (Overk, et al., 2013), suggesting a role for testosterone in amyloid processing or clearance. These data were supported by findings where testosterone altered APP processing (Goodenough, et al., 2000). Despite these interesting data points, there still remains only a few studies to date that have investigated androgens’ role in AD pathogenesis, and so closer investigations are likely warranted.

In summary, while an endocrinological basis of AD risk is likely to exist, the significance of these declining sex hormones with age is relatively unclear. For instance, though estrogen seems to be neuroprotective in rodent models, ERT in humans was unable to improve cognition or delay AD onset. Regardless of the impact of sex hormones on AD, it is very likely that subtle second messenger system alterations between sexes underlie and likely unify many of the observed increases in AD risk for women when viewed at the genetic (*APOE*, *BDNF*), structural, or hormonal levels. In agreement with this, it has been observed that sexually-dimorphic second messenger signaling is evident for certain GPCRs and

may increase AD risk in a sex-specific manner (Bangasser, et al., 2016). One of the most salient examples of this is discussed in section 3-5.

3-4. Sexual dimorphism in immune function and the link with AD

While A β and hyperphosphorylated-tau are considered to be the pathogenic intermediates underlying AD, their interaction with the immune system has garnered a lot of attention. Recently, many immune function genes that are expressed in microglia have been identified in GWAS studies investigating genetic causes of AD risk, including TREM2 (Guerreiro, et al., 2013, Wang, et al., 2015), CR1 (Lambert, et al., 2009) CLU (Lambert, et al., 2009, Harold, et al., 2009), and CD33 (Bradshaw, et al., 2013, Griciuc, et al., 2013). In addition, a recent gene-network analysis implicated immune and microglial dysfunction as the leading perturbed pathway in AD in human patients, a result which was specific to AD and not found in other neurodegenerative disorders, such as Huntington's Disease (Zhang, et al., 2013). In line with this, it has been found that elevation of certain cytokines in plasma are correlated with dementia development or conversion from MCI to AD, and imaging studies have found that increased microglial activation is a better predictor of cognitive decline than A β load (Engelhart, et al., 2004, Laurin, et al., 2009, Buchhave, et al., 2010, Cagnin, et al., 2001, Edison, et al., 2008, Holmes, et al., 2009, Jin, et al., 2008, Patel, et al., 2005).

Microglia play an active role in both A β regulation and immunological response (Heneka, et al., 2015). As evidence accumulates showing that persistent immune dysregulation affects AD development, numerous studies have demonstrated specific mechanisms whereby microglia may mediate neural degeneration and cognitive dysfunction (Ji, et al., 2013, Hong, et al., 2016, Lenz and McCarthy, 2015). Of these mechanisms, microglial regulation of synapses may be the most important for AD. It has been shown that the degree of synaptic degeneration is a much better predictor of cognitive decline in AD than A β levels, as degeneration of these synaptic structures syncs up more closely with symptom development and precedes neuronal loss (DeKosky and Scheff, 1990, Terry, et al., 1991, Mucke and Selkoe, 2012, Lue, et al., 1996, Hong, et al., 2016). These findings are in line with the hypothesis that chronic A β toxicity primes microglia, causing them to respond more readily to local environmental changes with

cytokine release and enhanced pruning of synapses (Heneka, et al., 2015, Perry and Holmes, 2014, Holmes, 2013).

Given the role for the immune system in AD development, it is important to note that females have a propensity towards greater immune reactions than men. First, males tend to develop infections more readily than females (Klein, 2000), and females tend to have a more robust immune response in the form of greater antibody production and a greater propensity towards TH1 responses ((Amadori, et al., 1995, Kovacs, et al., 2002) (Hanamsagar and Bilbo, 2016, Kivity and Ehrenfeld, 2010). In addition, estrogen generally enhances the immune system at low doses while androgens tend to be more immunosuppressive (McClelland and Smith, 2011, Hanamsagar and Bilbo, 2016). At the level of the brain, males tend to have more microglia early in development while females tend to have many more microglia from early adulthood onwards (Schwarz, et al., 2012, Lenz and McCarthy, 2015)).

Perhaps most interestingly, however, is the fact that about 80% of patients with autoimmune disorders are women (Cooper and Stroehla, 2003, Gleicher and Barad, 2007, Kivity and Ehrenfeld, 2010), (Hanamsagar and Bilbo, 2016)), suggesting that women may have more primed immune systems and thus more readily exhibit heightened immune responses. In support of this, one study found that while children of women with autoimmune disorders often developed autoimmune diseases, they were rarely the same disease exhibited by the mother (Gleicher and Barad, 2007). This is an important point, as it may explain why AD is not necessarily associated with other autoimmune diseases, since AD patients may manifest disease due to common immunological priming while expressing divergent pathophysiology to specific insults.

Finally, the interaction between stress and the immune system is different between men and women. Specifically, it was shown that while glucocorticoid signaling, which is a main mediator of the vertebrate stress response, induced apoptotic pathway upregulation in male hepatic cells, female hepatic cells tended to upregulate IL-6 related pathways, which are pro-inflammatory (Deak, et al., 2015). Further, glucocorticoid signaling tends to be higher in females at baseline, and estrogen has been shown to increase glucocorticoid release while androgens decrease it (Gaillard and Spinedi, 1998). Interestingly, when challenged with a lethal dose of the immunogen LPS, the corticosteroid dexamethasone was able

to prevent death in male rats at low doses while much higher doses were needed for females (Deak, et al., 2015), demonstrating that the female immunosuppressive response to glucocorticoids is less potent than males.

Still, while AD is likely to be affected by immune system function, and while ample evidence suggests very different inflammatory responses between sexes, whether these divergent responses leads to a difference in AD susceptibility is unclear. For one, even the role of sex in autoimmune disease pathogenesis is unknown, with hypotheses describing differences in sex hormones, X-inactivation patterns and gene dosing, and microchimerism all having evidence supporting and diminishing their likelihood as being the underlying mechanism (Selmi, 2008, Gleicher and Barad, 2007, Kivity and Ehrenfeld, 2010). Future studies demonstrating an immune system and sex interaction in AD pathogenesis would be needed, and rigorous hypothesis based testing would be essential to confirm if any of the mechanisms potentially leading to increased autoimmunity also lead to increased AD risk in women.

3-5. Stress and sex-specific CRF signaling in AD

Clinical evidence has suggested a link between psychosocial stress and AD going back at least two decades. Stress-related increases in plasma cortisol levels (Swanwick, et al., 1998),(Rehman, 2002) (Umegaki, et al., 2000) and correlations between increased cortisol levels and the severity of cognitive decline (Csernansky, et al., 2006, Pedersen, et al., 2001) have been reported in AD. These changes in the Hypothalamus-Pituitary-Adrenal (HPA) axis do not appear to be secondary to MDD, as AD patients with and without MDD have higher cerebrospinal fluid cortisol levels compared to controls (Hoogendijk, et al., 2006). In support of this, the centrally active stress response receptor Corticotropin Releasing Factor 1 (CRF1) is also increased in the hippocampi of AD patients (Behan, et al., 1995),(De Souza, 1995), and HPA axis changes have been associated with hippocampal atrophy (O'Brien, et al., 1996). Further, many abnormal behaviors, termed Behavioral and Psychosocial Symptoms in Dementia (BPSD), occur at an alarmingly high rate in AD patients, and at least some of these abnormal behaviors can be attributed to alterations in stress hormone signaling (Reisberg, et al., 1987). In line with these human studies, transgenic mouse models have recapitulated at least some of the neuropathological and

behavioral changes associated with AD and thus provide an opportunity to investigate how the different biochemical markers underlying the psychosocial stress response and AD pathogenesis interact *in vivo* (Dong, et al., 2004, Jeong, et al., 2006, Cuadrado-Tejedor, et al., 2012, Green, et al., 2006, Kang, et al., 2007, Campbell, et al., 2015, Carroll, et al., 2011, Dong, et al., 2008, Rissman, et al., 2012).

Women are more susceptible to stress-influenced diseases, and it is possible that sexually dimorphic stress responses could greatly influence the difference between men and women in the rate of AD conversion and progression. While clinical evidence demonstrating an interaction between sex and stress in AD development remains scarce, an intriguing study demonstrated that women with mild to moderate AD have significantly increased levels of cortisol production compared to their male counterparts (Rasmuson, et al., 2011), though these data could not establish causation.

Though studies in humans are limited, preclinical studies have also shown a sex-specific difference in AD pathogenesis under psychosocial stress (Sierksma, et al., 2012). For instance, 5-day restraint stress (6 h/day) in 5XFAD transgenic mice leads to increased levels of neurotoxic A β 42 peptides, β -secretase-cleaved C-terminal fragment (C99), and plaque burden in the hippocampus of female but not male mice at a time point before severe AD-like behavioral deficits are observed. Moreover, sex- and brain region-specific accelerations in β -amyloidosis is accompanied by elevations in BACE1, APP, and phosphorylated EIF2 α in response to psychosocial stress (Devi, et al., 2010). Also, environmental stress preferentially triggers memory impairments in female but not male P301L-Tau mice (Sotiropoulos, et al., 2015). Furthermore in this model, stress-related increases in caspase-3-truncated Tau and insoluble Tau have been found to aggregate exclusively in the female hippocampus (Sotiropoulos, et al., 2015). Potentially driving this effect, expression of the molecular chaperones Hsp90, Hsp70, and Hsp105 were altered to favor accumulation of tau aggregates (Sotiropoulos, et al., 2015). Though some ambiguity exists between these studies regarding the interaction between stress and sex, it seems likely that both are impacting disease pathogenesis.

As mentioned, the exact stress-response molecules that mediate increased AD pathogenesis are still unknown, though data confirming an important hypothesis implicating central CRF1 signaling in this process is emerging. Increased CRF1 signaling has been associated with multiple stages of APP

proteolysis, regulation of A β generation, and A β -mediated toxicity (Thathiah and De Strooper, 2011); (Thathiah, et al., 2013), and GPCR signaling in general has been suggested as a novel target for AD drug development (Femminella, et al., 2013, Wolfe, 2013). Importantly, CRF overexpression in the forebrain can lead to accumulation of A β and Tau phosphorylation through CRF1-Gs-PKA signaling, consistent with Gs-PKA signaling's role in influencing the amyloid production cascade through modulation of α -, β - and γ -secretases (Park, et al., 2015, Robert, et al., 2001, Thathiah and De Strooper, 2011, Thathiah, et al., 2013, Xu, et al., 1996). Specifically, while transient activation of these signaling cascades shifts APP metabolism towards the α -secretase-mediated pathway that results in non-pathogenic amyloids, chronic activation shifts APP metabolism to the β -, γ -, and perhaps also the η -secretase mediated pathways that results in increased pathogenic A β generation (APP-CTF99, A-beta 40 and A-beta 42). (da Cruz e Silva, et al., 2009) (Willem, et al., 2015). Additionally, PKA signaling is associated with tau phosphorylation, another molecular pathway that is highly implicated in AD pathogenesis (Blanchard, et al., 1994, Sanchez-Mut, et al., 2014). Thus, there is much evidence implicating CRF1 signaling as the causative pathway facilitating psychosocial stress's detrimental effects on AD pathogenesis.

When taken together with the evidence that prolonged CRF signaling through CRF1 results in sexually dimorphic second messenger activation, a potential mechanism begins to take shape: Because Gs-PKA signaling is central to the formation of AD-causative amyloids and phospho-tau, and there exists a bias towards CRF1-Gs-PKA signaling in females, this signaling pathway may provide a functional link between these two processes and begins to create a unified, biologically driven explanation for why women develop AD more readily than men. Still, this hypothesis is based on evidence from a combination of isolated experiments that only suggest this mechanism, but rigorous and direct testing of this hypothesis will need to be specifically undertaken to assess whether it is a suitable explanation for what is observed in AD patients. In addition, how CRF1 signaling and peripheral glucocorticoid signaling interact is still unknown in terms of increased AD risk, and experiments specifically targeting one or the other are needed to see if an interaction between the two is necessary for the increased risk of AD.

Table 2 summarizes the studies on sex difference in AD with animal models, collected from 2000 to date.

4. Conclusion

An explanation for the apparent difference in the rate of AD diagnoses between men and women remains elusive, but more and more evidence is beginning to suggest that a true increase in risk is complementing the epidemiological explanations describing the increased female prevalence for the disease. Importantly, biological mechanisms that are intrinsic to women are increasingly prominent in the literature. Specifically, those involving age-related changes in sex hormone signaling, sexual dimorphism in neural structures, gene-by-sex interactions, female-specific increases in immune responses, and the interaction between sex and stress have been gaining traction as important determinants of AD. Still, much remains to be described before adopting any of these potential explanations as drivers of disease, and certainly a greater understanding of the biology underlying these mechanisms is warranted before therapeutic development should be undertaken. The ERT trials stand as a sobering testament to that fact. It seems clear that more detailed studies using pre-clinical animal models to explore these molecular explanations will begin to unravel the mystery concerning the increased risk of AD in women, and the promise of future therapeutics through this line of investigation remains high.

One of the most important outstanding questions – and perhaps the largest “elephant in the room” – is why so many studies have suggested the presence of female-specific, biological risk factors and why so few studies have uncovered a difference in incidence between sexes. As described in length previously, difficulties in correct classification of AD remain one potential source of ambiguity, but this alone is unlikely to be the sole source of bias. What remains a possibility is that prospective cohort studies and meta-analyses have been insufficiently powered to detect a difference, as seen in the Fiest 2016 meta-analysis which consistently detected higher prevalence and incidence rates for women without reaching statistical significance. Though a significant undertaking, a large, prospective cohort study with post-mortem confirmation of AD would be immensely helpful in resolving this issue.

Finally, as we move towards “personalized medicine,” improving our understanding of sex-specific disease mechanisms will be one of the first areas to yield substantial improvements in prevention and treatment outcomes across all branches of medicine. But it is important to note that investigations of sex-

specific risk are just as likely to reveal central mechanisms of disease pathogenesis that are independent of sex. By careful comparison and inclusion of both sexes in preclinical and clinical research, upstream and downstream pathways that converge in both sexes will point the way towards shared mechanisms resulting in disease pathogenesis and severity. Exploiting these commonalities is more likely to lead to successful interventions and treatments than ignoring sex as a potential risk factor, as careful consideration of disease pathogenesis by sex will reduce sex-specific motifs that are mistaken as being causative but are in truth epiphenomenal. So while improving our understanding of underlying sexual dimorphism in AD risk will be critical for developing treatments that are especially effective in women, this line of research also has the potential to reveal new targets for the treatment of AD and other neurodegenerative disorders in both sexes.

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	Author (s)	Year	Journal	Control		MIC		AD		Study Design	Length of Follow-Up or Study Period	Diagnostic Criteria for AD	Main Result/Conclusion
				M	F	M	F	M	F				
d	Matyi et al.	2017	J Gerontology: Biological Sciences					1476	2023	Prospective Cohort	12 years	NINCDS-ADRDA	Female carriers of the minor T allele for rs56164415 had a 60% and 93% higher risk of AD, respectively, than male non-carriers of the T allele of rs2072624. This was not seen in male carriers of the T allele of rs2072624 than male non-carriers at trend-level significance.
e	Li et al.	2017	Neurobiology of Aging	113/121 (A/G)	262/314 (A/G)			164/182 (A/G)	208/188 (A/G)	Association Studies and meta-analysis	Variable	NINCDS-ADRDA	Genetic association between BDNF and AD in males. BDNF mRNA was significantly higher in AD patients, especially in females. BDNF SNP rs6265 on AD endophenotype.
	Neu et. al.	2017	JAMA Neurology	Variable depending on comparison group (31,430 total analyzed patients out of 57,979 potential patients identified)						Meta-analysis	Variable	Not stated	Women heterozygous for <i>ApoE-ε4</i> had a higher risk of AD than men at ages 65-75 year old
s	Ardekani et al.	2016	J Alzheimer's Disease					18	25	Prospective Cohort	1 year	NINCDS-ADRDA	In patients with probable AD, the hippocampal volume decreased significantly faster rate in women compared to men.
	Koran et al.	2016	Brain Imaging Behav.	164	184	327	238	100	85	Prospective Cohort	2.5 years	NINCDS-ADRDA	Women with Aβ-42 and total tau levels above the pathological changes showed more rapid cognitive decline and cognitive decline
	Ronquillo et al.	2016	J Women & aging			4110	4028	7423	8709	Retrospective Analysis of three longitudinal studies (ADNI, CAMD, NACC)	Variable	NINCDS-ADRDA	Females were 1.5 times more likely than males to have a documented diagnosis of probable Alzheimer's disease.
n y	Shinohara et al.	2016	Acta Neuropathologica	68	103			114	143	Post-mortem pathological assessment	N/A	NINCDS-ADRDA; Definitive AD only	The associations between <i>APOE4</i> and AD were statistically significant in females but not males.
n	Gallart-Palau et al.	2016	Mol Brain					7	10	Post-mortem Proteomic Study	N/A	NINCDS-ADRDA; Definitive AD only	Hyper-citrullination and hyper-deamidation of proteins were more prevalent in female patients with AD.
t d	Gale et al.	2016	J Clin Exp Neuropsychol.	64	113	46	30	63	38	Cross-Sectional Analysis	N/A	Clinical Dementia Rating Scores	Performance gap between healthy and AD groups was consistently larger than the gap between healthy and AD men for both MCI and AD groups.
	Xing et al.	2015	Behav Neurol.			74	84	65	92	Cross-Sectional Analysis of AD patients	N/A	NINCDS-ADRDA	Female patients with at least one copy of the <i>APOE4</i> allele were significantly more likely to have some AD symptoms in moderate to severe AD, compared to males with irritability.

	Ferencz and Gerritsen	2015	Comprehensive Psychiatry			101	193			Prospective Cohort	3 years	NINCDS-ADRDA	In men, the significant risk factors for were severe periventricular white matter poorer global cognitive function. In women older age, clinically significant depression and positive <i>APOE</i> $\epsilon 4$ alleles.
	Lin et al.	2015	Alzheimers Dement (NY)			257	141			Prospective Cohort	8 years	N/A; MCI diagnostic criteria	Women with MCI had greater longitudinal functional decline than men.
n y	Sampedro et al.	2015	Oncotarget					78 (MRI) 166 (FED-PET) 136(CSF)	90 (MRI) 162 (FED-PET) 138 (CSF)	Cross-Sectional Analysis	N/A	N/A: Healthy non-demented patients	Female <i>APOE-$\epsilon 4$</i> carriers show greater and atrophy than male carriers.
	Altmann et al.	2014	Ann Neurol.	1844	3652	1331	1275			Retrospective Cohort	8 years	NINCDS-ADRDA	<i>APOE-$\epsilon 4$</i> conferred greater AD risk in suggest that increased <i>ApoE</i> -related risk associated with tau pathology.
	Holland et al.	2013	American Journal of Neuroradiology	$\epsilon 4$ - 70 $\epsilon 4$ + 26	$\epsilon 4$ - 67 $\epsilon 4$ + 25	$\epsilon 4$ - 74 $\epsilon 4$ +102	$\epsilon 4$ - 42 $\epsilon 4$ + 55	$\epsilon 4$ - 36 $\epsilon 4$ + 87	$\epsilon 4$ - 25 $\epsilon 4$ + 67	Prospective Cohort	3 years	NINCDS-ADRDA	<i>APOE-$\epsilon 4$</i> significantly accelerated rate regional specific atrophy and clinical cohorts had higher rates of decline than
E l	Damoiseaux et al.	2012	J Neurosci.	$\epsilon 3$ + 66 $\epsilon 4$ + 33	$\epsilon 3$ + 85 $\epsilon 4$ + 26					Cross-Sectional Analysis	N/A	N/A; Healthy non-demented patients	Higher prevalence of the <i>APOEE-$\epsilon 4$</i> and AD and interaction between <i>ApoE</i> genotype detectable in the preclinical period
n	Rosario et al.	2011	Neurobiology of Aging	17	12	17		33	32	Post-mortem pathological assessment	N/A	NINCDS-ADRDA; Definitive AD only	Within defined age ranges, AD in women estrogens whereas AD in men is associated
	Hua et al.	2010	Neurobiology of Aging	202		338		144		Prospective Cohort	1 year	NINCDS-ADRDA	Brain atrophy rates were faster in women
F n O	Fukumoto et al.	2010	American Journal of Medical Genetics	220	305			230	427	Case-Control study and meta-analysis	N/A	NINCDS-ADRDA	Significant allelic association between the Val66Met polymorphism Japanese women but not in men
s	Pirskanen et al.	2005	European Journal of Human Genetics	185	282			116	271	Case-Control	N/A	NINCDS-ADRDA	Women carrying two T alleles were more to develop AD when compared to subjects SNP2 or SNP3 loci of the <i>ESR2</i> but not
al t	Barnes et al.	2005	Archives of General Psychiatry	28	25	13	18	23	34	Prospective Cohort with pathological follow-up	Variable (yearly follow-up until death)	NINCDS-ADRDA	AD pathology was more likely to be associated dementia in women than in men.

n	Fleisher et al.	2005	Arch Neurol.			107	86			Cross-sectional Analysis	N/A	N/A; MCI diagnostic criteria	The <i>APOE-ε4</i> genotype status had a greater gross hippocampal pathology and more women than in men.
e r	Miech et al.	2002	Neurology	1384	1924			62	123	Prospective Cohort	3 years	NINCDS-ADRDA with 83.3% PPV of consensus AD diagnosis by autopsy	A statistical interaction of sex and age of AD in women than in men after age
	Zandi et al.	2002	JAMA	1352	1901			35	88	Prospective Cohort	3 years	NINCDS-ADRDA	AD risk was more common in women in women with previous hormone replacement compared to those without
	Rasmuson et al.	2001	Biol Psychiatry		7				10	Case-Control	N/A	NINCDS-ADRDA	Increased daily glucocorticoid production metabolism in women in the early stage
	Mortensen and Høgh	2001	Neurology	79	84					Prospective Cohort	30 years	N/A; Healthy non-demented patients	The <i>APOE-ε4</i> allele is associated with in cognitive functions in women only.
	Fiest et al	2016	Canadian Journal of Neurological Sciences	Not described for meta-regression by sex						Meta-analysis and Systemic Review	Variable	Predominantly NINCDS-ADRDA	Meta-regression of 22 studies determined prevalence of AD found that “All estimated prevalence were higher for females compared to the differences were not statistically different
	Barnes et al.	2003	Neurology	271	577					Prospective Cohort	8 years	NINCDS-ADRDA	The results suggest that patterns of cognitive incidence of AD are similar in older men
	Hebert et al.	2001	Am J Epidemiol.	280	362			28	57	Prospective Cohort	11 years	NINCDS-ADRDA	These findings suggest that the excess of AD is due to the longer life expectancy specific risk factors for the disease.
	Ghebremedhin et al.	2001	Neurology					359	370	Post-mortem pathological assessment	N/A	N/A; no clinical assessment	An association between the $\epsilon 4$ allele and women was found at ages 60 to 79 years ≥ 80 years of age ($p = 0.063$). By comparison, association in both age categories ($p =$

Table1. Representative articles on human studies collected from 2000 to date. The articles in black color indicate studies supporting women more vulnerable to neuropathogenesis of AD and those in blue color oppose those findings.

Article	Author(s)	Year	Journal	Genotype/ Strain	Age (months)	Measurements	Main Results/Conclusion
Sex Dimorphism Profile of Alzheimer's Disease-Type Pathologies in an APP/PS1 Mouse Model	Jiao et al.	2016	Neurotox Res.	APP/PS1 mice	12	Neuropathology	Female APP/PS1 mice had more severe cerebral amyloid angiopathy, subsequent microhemorrhage, higher levels of phosphorylated tau, proinflammatory cytokines, more severe astrogliosis and microgliosis, and greater neuronal and synaptic degenerations than male counterparts.
A TgCRND8 Mouse Model of Alzheimer's Disease Exhibits Sexual Dimorphisms in Behavioral Indices of Cognitive Reserve.	Granger et al.	2016	J Alzheimers Dis.	TgCRND8 mice	2, 4, 6, 8	Neuropathology	A β PP females and males exhibit comparable A β burden at all ages, yet Tg females show enhanced vulnerability to A β pathology and A β -associated stereotypy, phenocover in the MWM maze earlier, and exhibit fewer behavioral indices of cognitive reserve than males.
Sex differences between APPswePS1dE9 mice in A-beta accumulation and pancreatic islet function during the development of Alzheimer's disease.	Li et al.	2016	Lab Anim.	APP/PS1mice	4, 6, 9	Neuropathology Memory function pancreatic islet function	A β levels and plaques, in the female mice were significantly higher than in the males. Cognitive function of female APP/PS1 mice was attenuated earlier than in the males. Impairment of glucose tolerance and insulin tolerance occurred earlier in male APP/PS1 mice than in female mice.
Peripheral amyloid levels present gender differences associated with aging in A β PP/PS1 mice.	Ordonez-Gutierrez et al.	2015	J Alzheimers Dis.	APP/PS1 mice	3, 15	Amyloid levels in plasma	After 9 months of age, there is an increase in amyloid levels in plasma among females and a decrease among males.
Cognitive and emotional profiles of aged Alzheimer's disease (3 \times TgAD) mice: effects of environmental enrichment and sexual dimorphism.	Blazquez et al.	2014	Behav Brain Res.	3 \times TgAD mice	12-15	Behaviors Neuropathology	3 \times TgAD mice show increased cognitive deficits in females and increased levels of novelty-induced behavioral inhibition in males.
Cumulative effects of the ApoE genotype and gender on the synaptic proteome and oxidative stress in the mouse brain.	Shi et al.	2014	Int J Neuropsychopharmacol.	Human-ApoE4 mice	N/A	Isolated synaptosomes Label-free quantitative proteomics	The lack of estrogen-mediated protection regulated by the <i>ApoE</i> genotype led to synaptic mitochondrial dysfunction and increased oxidative stress.
Effects of prenatal stress exposure on soluble A β and brain-derived neurotrophic factor signaling in male and female APPswe/PS1dE9 mice.	Sierksma et al.	2012	Neurochem Int.	APP/PS1 mouse	Prenatal, 8	Stress Neuropathology	Female APPswe/PS1dE9 mice have higher levels of hippocampal proBDNF and soluble A β as compared to their male littermates.
Gender-dependent transthyretin modulation of brain amyloid- β levels: evidence from a mouse model of Alzheimer's disease.	Oliveira et al.	2011	J Alzheimers Dis.	A β PPswe/PS1A246E/TT-/- A β PPswe/PS1A246E/TTR+/- A β PPswe/PS1A246E/TTR+/+	3,6,10	Neuropathology Brain levels of testosterone and 17 β -estradiol	Reduced levels of brain testosterone and 17 β -estradiol in female mice with TTR genetic reduction might be associated with increased AD-like neuropathology.
Sex differences in β -amyloid accumulation in 3xTg-AD mice: Role of neonatal sex steroid hormone exposure	Carroll 2010	2010	Brain Res.	3xTg-AD mice		Sex steroid hormone	Male 3xTg-AD mice demasculinized during early development exhibit significantly increased A β accumulation in adulthood. In contrast, female mice defeminized during early development exhibit a more

							male-like pattern of A β pathology in adulthood.
Sex- and brain region-specific acceleration of β -amyloidogenesis following behavioral stress in a mouse model of Alzheimer's disease	Devi et al.	2010	Mol Brain.	5XFAD mice	3	Stress, Neuropathology	Exposure to the relatively brief behavioral stress increased levels of neurotoxic A β 42 peptides, the β -secretase-cleaved C-terminal fragment (C99) and plaque burden in the hippocampus of female 5XFAD mice but not in that of male 5XFAD mice.
Females exhibit more extensive amyloid, but not tau, pathology in an Alzheimer transgenic model.	Hirata-Fukae et al.	2008	Brain Res.	3xTg-AD transgenic mice	3, 6, 9, 12, 16, 20, 23	Amyloid, Tau	Increase in beta-secretase activity and a reduction of neprilysin but not tau in female mice compared to males
Age-dependent sexual dimorphism in cognition and stress response in the 3xTg-AD mice	Clinton et al.	2007	Neurobiol Dis.	3xTg-AD mice	4, 12	Stress Cognition Neuropathology	3xTg-AD females performed worse than males at 4 month of age, which correlated with the enhanced corticosterone response of the stressful tasks.
Progesterone and Estrogen Regulate Alzheimer-Like Neuropathology in Female 3xTg-AD Mice	Carroll et al.	2007	J Neurosci.	3xTg-AD mice	3, 12	Progesterone and Estrogen intervention Neuropathology	Ovariectomy-induced depletion of sex steroid hormones in adult female 3xTg-AD mice significantly increased Abeta accumulation and worsened memory performance. Treatment of ovariectomized 3xTg-AD mice with estrogen, but not progesterone, prevented these effects.
Gender differences in the amount and deposition of amyloidbeta in APPswe and PS1 double transgenic mice	Wang et al.	2003	Neurobiol Dis.	APP+PS1 mice	4, 12, 17	Neuropathology	Female APP/PS1 mice accumulate amyloid at an earlier age and develop more amyloid deposits in the hippocampus than age-matched male mice
Modulation of A(beta) peptides by estrogen in mouse models	Zheng et al.	2002	J Neurochem.	Tg2576 mice	4-7	Ovariectomy and estradiol supplementation	A(beta) levels were higher in estrogen-deprived mice than intact mice, and this effect could be reversed through the administration of estradiol.
Effects of BACE1 haploinsufficiency on APP processing and A β concentrations in male and female 5XFAD Alzheimer mice at different disease stages.	Devi and Ohno	2015	Neuroscience	BACE1(+/-) BACE1(+/-)·5XFAD mice	6-7 12-14	Neuropathology	BACE1 haploinsufficiency rescues memory deficits in 5XFAD mice irrespective of sex but only in the younger age group.
Olfactory delayed matching to sample performance in mice: sex differences in the 5XFAD mouse model of Alzheimer's disease.	Roddick et al.	2014	Behav Brain Res.	5XFAD mice	6-7	Olfactory delayed matching-to-sample	5XFAD female mice showed higher levels of performance on the delayed matching-to-sample task than males, indicative of better working memory.
Sex differences in β -amyloid accumulation in 3xTg-AD mice: Role of neonatal sex steroid hormone exposure	Carroll et al.	2010	Brain Res.	3xTg-AD mice		Sex steroid hormone	Male 3xTg-AD mice demasculinized during early development exhibit significantly increased A β accumulation in adulthood. In contrast, female mice defeminized during early development exhibit a more male-like pattern of A β pathology in adulthood.
Testosterone regulation of Alzheimer-like neuropathology in male 3xTg-AD mice involves both estrogen and androgen pathways	Rosario et al.	2010	Brain Res.	3xTg-AD mice	3-7	Androgen and estrogen	Testosterone regulated A β pathology through androgen and estrogen pathways and reduced tau pathology largely through estrogen pathways.
Androgens Regulate the Development of Neuropathology in	Rosario et al.	2006	J Neurosci.	3xTg-AD mice	3, 7, 13	Gonadectomized (GDX)	Androgen depletion accelerates the development of AD-like neuropathology

a Triple Transgenic Mouse Model of Alzheimer's Disease						androgen	
Testosterone stimulates rapid secretory amyloid precursor protein release from rat hypothalamic cells via the activation of the mitogen-activated protein kinase pathway.	Goodenough et al.	2000	Neurosci Lett.	immortalized rat hypothalamic cell line (GT1-7)	N/A	Androgens	Testosterone was found to increase the amount of APP secretion rapidly after treatment without effecting the overall amount of cellular APP. The species of APP secreted was found to be predominantly the product of the non-amyloidogenic alpha-secretory pathway. Further, this event is regulated via aromatase-mediated conversion of testosterone to estrogen and the mitogen-activated protein kinase (MAP kinase) signalling pathway.

Table1. Representative articles on animal models collected from 2000 to date. The articles in black color indicate studies supporting females more vulnerable to neuropathogenesis of AD and those in blue color oppose those findings.

Highlights

- 1) Intrinsic susceptibilities of women to Alzheimer's disease (AD) are beginning to be reported.
- 2) Potential mechanisms include female-specific inflammatory and stress responses.
- 3) Discussion of future studies on the underlying mechanisms for sex differences in risk of AD.