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Sex Differences in Alzheimer's Disease: Understanding the Molecular Impact

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Abstract

Alzheimer's disease (AD) is a common neurodegenerative disorder that presents with cognitive impairment and behavioral disturbance. Approximately 5.5 million people in the United States live with AD, most of whom are over the age of 65 with two-thirds being woman. There have been major advancements over the last decade or so in the understanding of AD neuropathological changes and genetic involvement. However, studies of sex impact in AD have not been adequately integrated into the investigation of disease development and progression. It becomes indispensable to acknowledge in both basic science and clinical research studies the importance of understanding sex-specific differences in AD pathophysiology and pathogenesis, which could guide future effort in the discovery of novel targets for AD. Here, we review the latest and most relevant literature on this topic, highlighting the importance of understanding sex dimorphism from a molecular perspective and its association to clinical trial design and development in AD research field.

Keywords

Alzheimer's Disease; Risk Factors; Pathogenesis; Sex Differences; Molecular Impact

1 Introduction

Neurodegeneration involves a progressive functional and structural loss of both neurons and glia that ultimately contribute to massive cell death within the central nervous system. Advances in precision medicine approaches have been instrumental in studying mechanisms

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underlying neurodegenerative processes. Different mechanisms have been implicated including aggregation of misfolded proteins, impairment in degradation pathways, defective axonal transportation, DNA and membrane damage, mitochondrial dysfunction, and programmed cell death (Gitler and Tsuiji, 2016). On the other hand, sex and gender differences have been increasingly recognized for their impacts on etiology, incidence, severity, progression and treatment outcomes of several neurodegenerative disorders. Sex refers to the physiological and biological disparities between men and women with chromosomal variations and gonadal hormones as the primary contributors of these differences at cellular and systemic levels. Gender alludes to a combination of influences (i.e. social, cultural, and environmental) that affect biological factors within men and women. In other words, gender is implanted by biology but molded by experience and environment (Roselli, 2018).

While major progresses have made in understanding Alzheimer's disease (AD) pathogenesis (Podcasy and Epperson, 2016), there has been lack of attention until recently on sex differences in AD. A growing amount of evidence suggests that sex and gender differences may play important roles in the heterogeneities of AD prevalence, clinical manifestations such as behavior and cognitive performance, disease course and prognosis, as well as pathology (Heun, 2002; Jack et al., 2013; Pini et al., 2016). For example, women have increased risks of developing AD than men (Nebel, 2018). Sex differences have also been observed in treatment responses of patients in clinical trials (Kim et al., 2015). It has been increasingly recognized that sex- and gender-related differences cannot be completely explained by longer lifespans of women (Nebel et al., 2018). Furthermore, sex differences in AD are stratified by many factors. Therefore, a greater understanding of sex and gender differences from a molecular to a clinical point of view could greatly improve symptom awareness, risk modification and prevention, as well as clinical management of AD. In the present review, we provide updates about current understanding of sex and gender differences in brain aging and AD-related pathological processes, emphasizing on how developmental, genetic, comorbid and environmental factors impact on sex dimorphism in AD.

2 Sex Differences during Nervous System Development and Aging

2.1 Development of Nervous System and Neural Network

Sex dimorphism starts at early stage of brain development and continues its dynamic molding throughout the entire human lifespan. There are many structural and functional differences between men and women during the development of nervous system and neural network. For example, males have higher brain volumes with relatively higher white matter content whereas females have lower volumes of brain and cerebrospinal fluid (CSF) with relatively higher gray matter content (Allen et al., 2002; Cosgrove et al., 2007). In consistent with these observations, neuroimaging analysis demonstrated that males have more myelinated fibers than females at the start of puberty (Herting et al., 2012). Functional magnetic resonance imaging studies indicated that cognitively healthy adult males present with higher within-hemispheric connectivity, whereas females showed higher degrees of network efficiency and cortical connectivity (Ingalhalikar et al., 2014; Kanaan et al., 2012).

Moreover, brain regional differences were noted in blood flow of males and females, with higher blood flow in parietal cortex of women and in motor and visual cortex of men (Gur et al., 1995; Hsieh et al., 2012). It has been suggested that regional effects of sex hormones with specific expression profiles of sex hormone receptors could at least partially explain sex dimorphism in brain development, as well as sex differences in structural and functional network connectivity (Giedd et al., 1999; Li and Singh, 2014; Tomasi and Volkow, 2012).

2.2 Aging processes

It should be noted that sex dimorphism may extend beyond the development and adolescent stages. Some neuroimaging studies in normal aging subjects have shown that men present greater age-related cortical volume loss than women (Jack et al., 2015; Jack et al., 2017). There are significantly more cortical atrophy and glucose metabolic deficits in males than in females during aging (Murphy et al., 1996). Another study reported that men present a greater degree of white matter microstructural damage than female healthy older participants, suggesting a greater degree of brain reserve in men to maintain cognitive performances at similar levels of women despite more severe structural damage (O'Dwyer et al., 2012).

Many mechanisms have been proposed for sex differences in longevity such as sex asymmetries in the X chromosome and mitochondrial genome inheritance (Frank and Hurst, 1996; Tower, 2006) and sex-specific selection (Maklakov et al., 2009; Maklakov and Lummaa, 2013). Studies also suggest that the changes in biological sex and sex hormone mediated memory circuitry have become evidence in midlife (Pudas et al., 2018). This time-period in women transitioning through menopause may play an important role in cognitive decline during aging (Jacobs and Goldstein, 2018). For example, low estradiol levels correlated with poor performance on memory retrieval task and changes in hippocampal connectivity (Jacobs et al., 2016). In addition, postmenopausal women demonstrated different hippocampal responses during verbal memory tasks when compared to premenopausal women (Jacobs et al., 2016; Jacobs et al., 2017). It has been suggested that reduction in estrogen levels during aging and menopausal periods are associated with heightened oxidative stress and mitochondrial dysfunction (Beckman and Ames, 1998), exacerbated pro-inflammatory responses (Berchtold et al., 2008), and reduced synaptic plasticity (Baudry et al., 2013). For example, female cells were found less vulnerable to oxidative insults than males (Ide et al., 2002; Matarrese et al., 2011). In addition, female animals had lower levels of reactive oxygen species (Vina et al., 2003) and reduced mitochondrial DNA damage than male counterparts (Borras et al., 2003). One interesting study that assessed cognitive resilience in healthy older adults with AD risk genes including apolipoprotein E4 (ApoE4) in a 9-year follow-up period indicated sex-specific predictors of memory resilience, e.g. pet ownership and history of depression in men, whereas marital status, subjective health, mobility and current alcohol use in women (McDermott et al., 2017), indicating sex-specific modifiable factors for healthy aging. A recent study using system biology approaches to analyze large sets of microarray data from hippocampal brain regions of normal aging individuals, identified the effects mediated by sex-aging interaction that lead to changes in functions of mitochondria, autophagy, and miRNA expression. This

information may elucidate important pathways and mechanisms underlying sex dimorphism in aging brain (Guebel and Torres, 2016).

3 Sex Differences in Alzheimer's disease

Unlike healthy aging population, several lines of data strongly indicate that female AD subjects are more affected by disease processes than male patients are (Filon et al., 2016; Malpetti et al., 2017). AD women showed a greater decline in essentially all cognitive domains than AD men (Laws et al., 2018). Irvine et al. reported significant male advantages over female in five cognitive domains (Irvine et al., 2012). Consistently, two independent studies concluded statistically significant worsening of verbal and visuospatial performance in female mild cognitive impairment (MCI) and AD subjects than male counterparts, regardless of apolipoprotein E4 (ApoE4) genotype status (Gale et al., 2016; Tensil et al., 2018). Data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) study suggest the rate of cognitive decline in women is twice as fast as that of men even after corrected for the ApoE genotypes (Lin et al., 2015). Furthermore, there have been sex differences in behavioral symptoms observed of AD subjects despite the relatively small sample sizes in these studies, such as an increased likelihood of agitation (Mega et al., 1996) and socially inappropriate behaviors (Kitamura et al., 2012; Ott et al., 1996; Ott et al., 2000) in AD men, and an increased likelihood of depressive symptoms (Teri et al., 1989) and delusions (Karttunen et al., 2011) in AD female subjects.

The biomarker studies indicate no clear sex differences in brain amyloid or neurofibrillary tangle burden of AD subjects as determined by postmortem neuropathological analysis (Barnes et al., 2005; Shinohara et al., 2016), or by measurement of cerebrospinal fluid amyloid-β ($A\beta_{42}$) and tau levels (Mattsson et al., 2017). Consistently, no sex differences are present in amyloid positivity or tau accumulation between male and female MCI subjects as determine by PET imaging studies (Jack et al., 2017; Jansen et al., 2015; Johnson et al., 2016). On the other hand, sex differences in brain atrophy rates have been observed in many brain regions of normal aging, MCI, and AD subjects (Hua et al., 2010; Skup et al., 2011). In MCI and AD women, the atrophy rates are 1–1.5% faster than those in men (Ardekani et al., 2016; Hua et al., 2010). Surprisingly, female MCI subjects with positive biomarker studies such as increased amyloid plaque and neurofibrillary tangle burden (Barnes et al., 2005) or CSF biomarker changes (Koran et al., 2017) had significantly higher chances of developing dementia or neurodegeneration than male counterparts, suggesting a potential interaction between sex and AD biomarkers in the disease prognosis. Several animal models have been used to determine the molecular mechanisms underlying sex-specific differences in AD. A clear sex-specific effect in amyloid load and cognitive deficits have been characterized in AD transgenic mouse models such as 3xTg, APP/PS1 and Tg2576 lines (Dubal et al., 2012), as well as human ApoE4 mouse models such as ApoE4 KI (Bour et al., 2008; Reverte et al., 2012) and EFAD lines (Tai et al., 2017). The sex effects on tau hyper-phosphorylation are rather controversial (Yue et al., 2011).

One possible mechanism is related to differences in γ–secretase activities between females and males as suggested in mouse model studies (Placanica et al., 2009). More importantly, sex hormones contribute to sex dimorphism in AD-related pathological processes. Sex

steroid hormones are important risk factors in AD development because they are fundamental determinants of sex differences in brain function and cognition. The mechanisms of action of sex hormones are mediated by binding of specific steroid hormones with their specific receptors which are also nuclear transcription factors, followed by modulation of transcriptional activities after binding (DeMayo et al., 2002). The incidence of AD is higher in postmenopausal women, which has been linked to abrupt reduction of estrogens and progesterone (Geerlings et al., 2001). Studies have demonstrated significant decrease in verbal memory related to alterations in the hippocampal function during menopausal transition due to declines in estradiol levels (Jacobs et al., 2016; Rentz et al., 2017). The peri-menopausal cognitive decline is believed to be temporary with evidence indicated recovery during postmenopausal stages by some researchers (Greendale et al., 2009), whereas others showed persistent cognitive decline (Jacobs et al., 2016; Rentz et al., 2017).

The decrease of circulating estrogen and progesterone with age has served as the foundation to test whether estrogen intervention may help protect against AD progression. Several early clinical studies in women with AD undergoing hormone therapy suggested that estrogen preserves cognitive function (Doraiswamy et al., 1997a; Doraiswamy et al., 1997b; Henderson et al., 1994). Another recent study reported a significant lower risk of developing AD in women with estrogen therapy in comparison with individuals who had placebo (Manson et al., 2017). However, many studies have found that hormone treatment in older aged women (≥65) led to a two-fold increase in risks of developing dementia (Shumaker et al., 2003; Shumaker et al., 2004). These studies suggested that starting hormone therapy at older ages may have adverse consequences. Overall, the current thinking is that women who initiated hormone therapy early during menopausal transition may lower the risks of developing AD compared to women received treatment at later stages (Henderson et al., 2005; Whitmer et al., 2011).

A possible mechanism by which estrogens exert anti-neurodegenerative effects in the brain is through the modulation of Aβ generation (Xu et al., 1998). Estrogen is shown to reduce Aβ production in neurons, revealing a neuroprotective mechanism against AD progression. Other possible protective mechanisms include the regulation of basal forebrain activities (Luine, 1985), synaptic plasticity (Woolley et al., 1997), neurotrophin signaling (Toran-Allerand, 1996), and reduction of free radical induced oxidative stress (Behl et al., 1995). Moreover, estrogen has been shown to regulate vesicle formation from late secretory pathway (Scammell et al., 1986), and vesicle trafficking from the trans-Golgi-network (TGN) to the plasma membrane (Platt et al., 1991). Specifically, estrogen stimulates biogenesis of APP-containing vesicles from the TGN, promotes APP delivery to cell surfaces, and thereby significantly decreases Aβ production (Greenfield et al., 2002).

Decreased testosterone during aging constitutes a risk factor for AD in men. Studies on AD-like transgenic mouse model have shown that depletion of androgen exacerbates AD-related neuropathological changes, which is rescued by treatment with androgen (Pike et al., 2009). Testosterone mediates most of its effects, including the regulation of Aβ neuropathology, through both androgen and estrogen pathways, since it is metabolized in the brain into androgen dihydrotestosterone (DHT) and estrogen 17β-estradiol (E2). In contrast, the

regulation of tau hyper-phosphorylation by testosterone may be mainly regulated by estrogen pathways, as neuronal tangle burden is reduced by testosterone and E2 but not DHT (Rosario, 2010).

It should be noted that the effects of hormones on brain aging and neurodegenerative processes are important contributors of sex differences. However, they are not he only sex-based influences. Many factors contribute to sex differences in cognition, behavior and neural processes. In the following section, we will discuss the impact of genetic risk factors, comorbid and environmental factors contributing to sex differences in AD pathogenesis.

4.1 The Impact of Genetic Risk Factors on Sex Differences in AD

4.1.1 ApoE

ApoE serves as an important lipid binding protein that facilitates the transport of phospholipids and cholesterol in a myriad of different tissue types through receptor mediated interactions at cell surfaces (Bu, 2009; Verghese et al., 2013). There are 3 genetic variants of ApoE: *APOE*2, *APOE*3 and *APOE*4, where the *APOE*4 allele confers the strongest genetic risk factor for AD development (Saunders et al., 1993; Strittmatter et al., 1993). ApoE4 has direct effects on Aβ aggregation and clearance (Kim et al., 2009; Ossenkoppele et al., 2015; Verghese et al., 2013). Moreover, ApoE4 isoform is susceptible to proteolytic cleavage, resulting in the release of neurotoxic fragments (Mahley and Huang, 2012). Evidence further suggests that ApoE affects tau pathogenesis independent of Aβ pathology, and ApoE4 exhibits a gain of toxic effect on tau pathologies (Shi et al., 2017). A recent study has also shown that ApoE4 contributes to elevation of hyper-phosphorylated tau levels after traumatic brain injury (TBI) exposure that could subsequently induce neurodegeneration and neuro-inflammation (Cao et al., 2017).

While the AD risk posed by ApoE4 is observed in both males and females, females with at least one copy ApoE4 often exhibit faster cognitive decline and deterioration than males with at least one copy of ApoE4 (Farrer et al., 1997). A recent study showed that carriers of ApoE3/4 genotype between age of 65 and 75 had risks of developing AD when compared to ApoE4 non-carriers (odd ratios 4.37 ApoE4 women and 3.14 in ApoE4 men). Moreover, ApoE3/4 female carriers of age 55 to 70 had increased risks of cognitive impairment than male carriers (Neu et al., 2017). Consistently, other studies also demonstrated that female ApoE4 carriers have a higher risk of converting into AD (Corder et al., 2004) and a faster decline of cognitive function when compared to non-ApoE4 carrier women or men with any *APOE* genotype (Beydoun et al., 2012). It is interesting to note that the gender effect is most pronounced among ApoE3 and ApoE4 heterozygotes (Farrer et al., 1997), and that these disparities are most apparent in women with menopause (Burger et al., 2002). It is suggested that alterations in estrogen levels may account for increased risks of developing AD among menopausal women compared to men.

Since estrogen level decline stemming from menopause is implicated in AD related cognitive vulnerabilities, estrogen therapy was first implemented to ameliorate AD related cognitive deficits. Interestingly, there was a notably trend in which women with ApoE4 receiving estrogen therapy exhibited more cognitive decline than ApoE4 women without

estrogen treatment. This contrasts with ApoE2 and ApoE3 women carriers who demonstrated cognitive improvement from estrogen therapy (Burger et al., 2002). One possible explanation is the interplay between estrogen receptor alpha (ERα) and estrogen receptor beta (ERβ). Both ERα and ERβ can regulate the expression of ApoE lipoprotein as demonstrated *in vitro* in HT-22 cells and hippocampal neurons, and *in vivo* in mice (Wang et al., 2006). Upon stimulating ERα with either 17β-estradiol (E2) or propylpyrazole triol, an ERα-selective ligand, ApoE protein expression was up-regulated. In contrast, subjecting ERβ to an ERβ-selective ligand such as diarylpropionitrile down-regulated ApoE gene expression and protein levels (Wang et al., 2006). It is possible that ApoE4 carriers receiving estrogen therapy suffered an exacerbated ApoE4 overexpression stemming from ERα stimulation while the ApoE2 and ApoE3 carriers on estrogen therapy benefited from the protective effects of ApoE2 and ApoE3 over-expressions, which could account for the complex impact that estrogen therapy has on postmenopausal AD individuals that are ApoE3 and ApoE2 carriers versus ApoE4 carriers (Yaffe et al., 2000). From a therapeutic standpoint, this highlights not only ERα and ERβ as potential drug targets for AD treatment but also the need for a more personalized therapeutic approach; what works for ApoE2 and ApoE3 carriers might not benefit and may in fact be detrimental to ApoE4 carriers.

In addition to gene expression, estrogen also serves to regulate various pertinent metabolic pathways in the brain such as glycolysis and the Krebs cycle within the mitochondria (12). Studies with ovariectomy mice models that mimic postmenopausal hormonal conditions demonstrated a shift in bioenergetics that diminished glucogenic pathways via shunting of glucose transport in the brain and upregulated ketogenic compensatory pathways (Yao et al., 2012). This clearly suggests that estrogen promotes glucogenic metabolic pathways and lessens the need for ketogenic pathways for adenosine triphosphate (ATP) generation in female brains. Previous studies pertaining to AD have also implicated metabolic shift from one that is glucogenic to a more ketogenic system that relies on utilizing white matter for fuel in ApoE4 carriers (Reiman et al., 2005). This seems to suggest that ApoE4 brains heavily rely on a dual metabolic pathway consisting of both glucose and keto bodies. For ApoE4 carriers, estrogen therapy that suppresses ketogenic pathways may compromise ATP production because the brain of ApoE4 carriers may be less acclimated to an exclusive glucogenic pathway. Conversely, promoting glucogenic metabolic pathways while simultaneously mitigating ketogenic pathway in brains that are more tune to using glucose as the primary metabolic pathway, as is the case with ApoE2 and ApoE3 carriers, may confer a more positive and conducive bioenergetic profile for generating ATP. This may offer another contributing factor and explanation for why estrogen therapy disproportionally benefits ApoE2, and ApoE3 carriers but harms ApoE4 individuals. Ultimately, the effects observed from estrogen therapy may be a culmination of mechanisms that amalgamates that what is observed in the clinical setting.

Lastly, in addition to influencing energy profiles, ApoE4 may also influence expression of β-site APP cleavage enzyme (BACE1), a key enzyme in the amyloidogenic pathways responsible for generating amyloid-beta (Vassar, 2004). In AD mice models expressing APP^{Swe} and tau^{P301L} (3xTg) with various ApoE genetic profiles, ApoE4 female carriers were disproportionally overexpressing BACE1 compared to male ApoE4 and other ApoE genetic counterparts (Hou et al., 2015). These results confirm what is currently established

in AD research; females with ApoE4 carry the highest risk for developing AD (Payami et al., 1994). While the exact mechanism for this phenomenon is uncertain, there may be two possible explanations. The first possibility is the relationship between ApoE and cholesterol. ApoE4 has been shown to increase cholesterol concentration in both CSF and blood (Notkola et al., 1998; Papassotiropoulos et al., 2002). Elevated cholesterol levels have also been implicated to stimulated BACE1 activity (Runz et al., 2002). Therefore, ApoE4 females accelerate BACE1 by indirectly modulating cholesterol quantities. A second possibility is increased APP recycling by ApoE4, which in turn increases for APP exposure to BACE1 for cleavage (Yang et al., 2003).

Nevertheless, several AD clinical trials studies have demonstrated the role of ApoE as an important determinant for treatment responses, indicating major differences between ApoE4 carriers and non-carriers and between males and females (Hanson et al., 2015; Salloway et al., 2014). For example, hormone therapy may exhibit beneficial effects on cognition, but only seen in non-ApoE4 carriers (Kunzler et al, 2014). On the other hand, hormone therapy reduced AD risks in ApoE4 carriers more so than in non-ApoE4 carriers (Tang et al., 1996). Further research is needed to address molecular mechanisms underlying sex-specific impact on AD pathogenesis in ApoE4 carriers and non-carriers over the life span. In addition, the effects of ApoE4 genotype and its correlation with sex differences should be taken into considerations when evaluating the efficacy of AD clinical trials.

4.1.2 Other AD genes:

Presenilin 1 (*PS1*) gene is an important AD gene. PS1 protein, along with its genetic counterpart, presenilin 2 (*PS2*) protein encompasses a key component of the γ-secretase complex and its catalytic core, which cleave amyloid precursor protein (APP) to generate Aβ (Wolfe, 2006). Mutations in PS1 and PS2 could result in faulty cleavage of APP, leading to elevated Aβ generation and altered $A\beta_{42}/A\beta_{40}$ ratio (Hutton and Hardy, 1997). There are some experimental evidence suggesting that the effects of PS1 on AD pathogenesis might differ based on genders. It was shown that Aβ levels were increased with aging in APP/PS1 transgenic mouse models. Additionally, female cohorts consistently demonstrated greater Aβ burden compared to males at the same age (Wang et al., 2003). A separate study conducted by Piscopo et al found that neocortical and hippocampal PS1 expression was much higher in female wildtype mice than in males. However, these differences in PS1 expression were attenuated after brain maturation (Thakur and Ghosh, 2007). Nevertheless, these results support that sex dimorphic differences in PS1 expression might play a role in differential brain development, and that male and female brain might have different mechanisms for regulating PS1 expression (Ghosh and Thakur, 2008a; Ghosh and Thakur, 2008b; Thakur and Ghosh, 2007).

Interestingly, PS1 expression may be modulated by gonadal sex hormones. It has been shown that PS1 expression in cerebral cortex was down-regulated by 17β-estradiol and testosterone in both male and female mouse models (Ghosh and Thakur, 2008a). Therefore, the reduction in estrogen levels after menopause may contribute to increased PS1 expression leading to amyloid plaque buildup. Males on the other hand experience a less dramatic hormone loss compared to females. Additionally, males may also convert testosterone into

estradiol (Wu et al., 2009), which confers more protection against PS1-mediated AD pathology. Clearly, sex hormones regulate PS1 expression, and more research is need in this area to fully elucidate AD gender differences pertaining to PS1.

Besides PS1/PS2, brain-derived neurotrophic factor (BDNF) plays an important role in memory formation (Kemppainen et al., 2012; Rabbitts et al., 1985). It also protects neurons against Aβ-induced toxicities (Doi et al., 2013; Rohe et al., 2009). The association of BDNF polymorphism with AD was controversial (Li et al., 2017b). Several studies identified female-specific association between BNDF polymorphism and AD. A meta-analysis identified the BDNF Val66Met polymorphism increased AD risks in females (Chen et al., 2014a). These studies were supported by others (Fukumoto et al., 2010; Li et al., 2017a; Li et al., 2017b). Matyi et al also found two additional single nucleotide polymorphisms (SNPs) of BDNF highly associated with AD women (Matyi et al., 2017). On the other hand, the expression of BDNF was reduced in AD patients (Connor et al., 1997; Hock et al., 2000; Li et al., 2017a; Peng et al., 2005; Qin et al., 2017), and in AD mouse models (Francis et al., 2012; Naert and Rivest, 2012). In APP/PS1 mouse models, female mice presented with a dramatic drop of BDNF levels upon stress, whereas males had an increase in BDNF levels after exposure to chronic stress (Autry et al., 2009). In addition, ApoE4 reduces BDNF levels through epigenetic regulation of histone deacetylase (HDAC) activities (Sen et al., 2015; Sen et al., 2017). Future studies are necessary to characterize molecular mechanisms underlying sex dimorphism of AD susceptibility in the presence of risk genes, and to investigate how they interact with each other to affect AD pathogenesis.

4.2 The Interaction between Sex and Comorbid Risk Factors in AD Pathogenesis

A number of studies have identified cardio-metabolic risk factors such as obesity, type 2 diabetes (T2DM), and metabolic syndrome associated with AD (Barnes and Yaffe, 2011). However, only a few studies analyzed how sex differences influence these factors during the progression of AD (Kautzky-Willer et al., 2016).

4.2.1 Vascular risk factors

It is known that vasculature system in men is significantly different from that of women. While microvascular disease is a major contributor to cardiovascular disease in women, obstructive coronary artery disease is a main contributor in men (Bairey Merz et al., 2006). Women also present with an increased risk of diabetic complications including myocardial infarction and depression, both of which are AD risk factors (Kautzky-Willer et al., 2016). Recent studies examined the association between the risks of developing dementia and various cardiovascular risk factors like coronary artery disease (CAD), atrial fibrillation, myocardial infarct, hypertension and heart failure, as well as sex-specific effects (Kim et al., 2018). For example, men have a much higher incidence of CAD than women in all ages (Kivipelto et al., 2001a; Kivipelto et al., 2001b), which is believed to be due to protective effects of estrogen against atherosclerosis, oxidative stress and inflammation in women (Mendelsohn and Karas, 2005). CAD is associated with cognitive decline (Roberts et al., 2010) with brain microvascular lesions as proposed mechanisms (Rosano et al., 2005).

Studies have shown that microvascular lesions reduced intracranial blood flow, impaired blood-brain barrier (BBB) integrity and reduced Aβ clearance through BBB leading to brain damage (Bell and Zlokovic, 2009; Kovacic et al., 2011a; Kovacic et al., 2011b).

In fact, BBB failure is one of the central mechanisms underlying development of cerebral small vessel diseases and dementia. It contributes to neurodegeneration and rapid progression from vascular defects to major neurological diseases (Sweeney, 2019; Sweeney, 2019b). The genetic mutations of AD genes PS1 and PS2 have been associated with the BBB malfunction and higher risks for AD (Sweeney, 2019b) (Basun, 2008; Cohen, 2009). Genome-wide association studies have identified AD risk loci on genes like PICALM, CLU and SORL1 that are well-known to regulate BBB transport and clearance function (Carrasquillo, 2010; Corneveaux, 2010; Harold, 2009; Lambert, 2009; Rogaeva, 2007). A connection between PICALM polymorphisms and AD has been identified, and lower levels of PICALM may increase AD risks (Harold, 2009; Lambert, 2009). The amino terminal tail of PICALM contains a PIP_2-binding domain which allows PICALM to sense membrane curvature and modulates the size of clathrin-coated vesicles (CCV). PICALM also has a key role in the internalization and intracellular traffic via the SNARE-mediated fusion of CCV to endosomes (Miller, 2011). These functions play important roles in tau clearance from autophagy pathway (Moreau, 2014) and Aβ clearance across the BBB (Zhao, 2015). CLU is another important AD risk gene (Carrasquillo, 2010; Corneveaux, 2010), which encodes for APOJ and regulates lipid transport and membrane recycling (Calero, 1999; Nuutien, 2009). In the brain, astrocytes secrete APOJ that binds to soluble Aβ (Nuutien, 2009), and APOJ regulates Aβ clearance by promoting $Aβ_{42}$ efflux though the BBB (Tanzi, 2012). Currently there is no reported literature regarding the sex-specific effects on the function of these genes in AD.

Similarly, the incidence of atrial fibrillation, MI and heart failure is much higher in men than in women with limited studies examining their association with dementia (Kim et al., 2018). Hypertension is known to increase risk for cerebrovascular disorders but whether it directly affects the risk of developing dementia remains controversial (Kim et al., 2018). A recent study demonstrated an association between diastolic blood pressure and Aβ levels (Shah et al., 2012). Interestingly, middle age hypertension is highly associated with increased risks of dementia in females but not in males (Gilsanz et al., 2017). Future studies are needed to understand the sex-specific effects of cardiovascular risk factors on AD progression, specifically on how they vary by different types of disorders and by age.

Some studies have found that stroke prevalence in men is significantly higher than in women and that men develop strokes at much earlier ages (mean age 68.6 year old versus 72.9 year old in women) (Appelros et al., 2009). In contrast, others have shown that women possess a higher risk of developing stroke given their longer life expectancy (Seshadri et al., 2006) and the increased likelihood of developing comorbid conditions such as thrombosis and diabetes (Cheng and Kong, 2016). Several lines of studies support the important role of insulin-like growth factor-1 (IGF-1) in acute ischemic stroke. For example, lower serum IGF-1 levels are correlated with an increased risk of stroke, whereas higher levels associated with better outcomes post stroke (De Smedt et al., 2011; Dong et al., 2014; Tang et al., 2014). Similar findings have been related to AD, where low IGF-1 levels are associated with an increased

risk of AD progression, and higher levels with larger brain volumes, even in normal individuals without history of stroke or dementia (Westwood et al., 2014). Furthermore, data suggested that levels of IGF-1 were reduced during aging (Rosario, 2010), and much more so in males than in females (Waters et al., 2003).

The proposed mechanisms for IGF-1's protective effects against neurodegeneration include anti-inflammation, anti-thrombotic and survival-promoting effects (Jin et al., 2013; Li et al., 2010; Patel et al., 2014). Studies in animal models have identified neuroprotective effects of IGF-1 against ischemic strokes in both males and females, at young and old ages (Sohrabji, 2017). The IGF-1 replacement treatment post-stroke was found to rescue neurotoxicity, ameliorate stroke-associated brain damage and motor impairment, reduce neuro-inflammation and BBB disruption in middle-aged ovariectomized or estrogen deficient female rats (Bake et al., 2014; Selvamani and Sohrabji; Selvamani and Sohrabji). Moreover, modulating IGF-1 levels by miRNA manipulations demonstrated significant sex differences in treatment effectiveness, with effects only seen in females but not in males or estrogen deficient females (ovariectomized animals), suggesting that the IGF-1 treatment may be strongly influenced by hormonal environment (Selvamani et al.).

New evidence suggests a sexual dimorphism in the cellular death pathways during ischemic stroke (Gibson; Liu et al., 2011). Poly-ADP ribose (PAR) is important molecule inducing programmed cell death (Strosznajder et al., 2012). Poly (ADP-ribose) polymerase-1 (PARP-1) is a key enzyme regulating PAR levels with important roles in transcriptional regulation and long-term potentiation (Hernandez et al., 2009). In AD patients, pathological activation of PARP-1 led to PAR accumulation in the brains (Cozzi et al., 2006). In addition, PARP-1 polymorphisms are identified in AD (Liu et al., 2010). PARP-1 was found to be activated in AD with an increased Aβ generation (Martire et al., 2013). Moreover, Aβ activates PARP-1 resulting in PAR-modulated mitochondrial release of apoptosis-inducing factor (AIF), ultimately causing cell death (Yu et al., 2006). PARP-1 activation plays a major role in cardiovascular diseases (Song et al., 2013; Sun et al., 2015). The downstream effectors of PARP-1 including AIF and PAR have been shown to induce cell death after ischemic insults only in male mice (Yuan et al., 2009). Recent animal studies have further demonstrated sexually dimorphic neuroprotective effects through the inhibition of PARP-1 that is seen only in male mice, but not in females (Lang and McCullough; Li and McCullough; Liu et al., 2011).

Another type of vascular risk factors unique to females is known as hypertensive pregnancy disorders, which affects more than 10% of all pregnancies. These disorders include preeclampsia, eclampsia, and chronic and gestational hypertension (Mielke et al., 2016; Postma et al., 2014). There has been direct association among these conditions with impaired cognition as well as multiple brain lesions (Aukes et al., 2007; Mielke et al., 2016; Postma et al., 2014). However, most of published studies were limited by small sample sizes and short time periods of cognitive function assessment (less than a decade after development of hypertensive pregnancy disorders). A recent large cohort study of multiethnic women around 60 years of age found that females with prior history of hypertensive pregnancy disorders had greater degrees of brain atrophies decades after their pregnancies when compared to normotensive pregnancies (Mielke et al., 2016). It remains

unclear whether there is a shared mechanism that increases the risk of developing hypertensive pregnancy disorders and cognitive impairment after pregnancy, or if hypertensive pregnancy disorders directly increase the risk of developing cognitive impairment. The current research suggests that alterations in serum levels of angiogenic factors contribute to the pathogenesis of hypertensive pregnancy disorders (Hod et al., 2015). Angiogenesis is closely regulated by angiogenic factors to maintain optimal microenvironment for blood vessels. Reduced levels of angiogenic factors such as vascular endothelial growth factor (VEGF) and transforming growth factor beta led to endothelial dysfunction and clinical manifestations of pregnancy hypertensive disorders (Romero and Chaiworapongsa, 2013; Venkatesha et al., 2006). Therefore, it becomes critical to better predict or prevent hypertensive pregnancies, and more importantly to understand the mechanisms by which angiogenic factors contribute to hypertensive pregnancy disorders and their associated cognitive deficits.

4.2.2 Sleep

Sleep plays a critical role in the maintenance of health and modulates behavioral and physiological functions. Sex-related differences in risks of developing sleep disorders are well established. While studies show that young healthy adult women tend to have better sleep quality than men (Goel et al., 2005), most studies in patients of all ages indicate that women present more sleep problems including insomnia and inadequate sleep compared to men (Bixler et al., 2002; Zhang and Wing, 2006). Women are more prone to present clinical symptoms from inadequate sleep, and they may also be more inclined to report symptoms. In general, there is a correlation between a decline in slow-wave sleep and aging processes (Carrier et al., 2001). Sleep disorders increase with age, reaching a peak for women during menopause (Bixler et al., 2001). Impaired circadian rhythm and sleep disorders are frequently seen among individuals with AD, which influence the development and progression of AD pathology (Ju et al., 2014). For example, the production and clearance of Aβ are correlated with the wake/sleep cycles. While wakefulness is associated with Aβ production, clearance of Aβ occurs mainly during the sleep stage (Cedernaes et al., 2017). Shorter sleep duration and poorer sleep quality are associated with increased Aβ accumulation and risks of developing AD in older adults (Lim et al., 2012; Spira et al., 2013).

It has been reported that brain has its own lymphatic-like clearance system named the glymphatic system which operates via a network of perivascular clearing mechanisms (Kress et al., 2014). The glymphatic system is suggested to function exclusively during sleep (Xie et al., 2013). Moreover, animal studies have characterized a clearance system in the brain that involves bulk flow of interstitial fluid and water-channel protein, aquoporin-4 (AQP4) localized throughout astrocytic processes (Lundgaard et al., 2017). AQP4 function has been directly linked to Aβ clearance, most likely through the glymphatic system as suggested by the AQP4 knockdown mice (Yang et al., 2012). It is hypothesized that poor-quality sleep is associated with reduced Aβ clearance and increased Aβ accumulation in the brain due to impaired AQP4 function (Rainey-Smith et al., 2018). A recent study proposed a synaptic homeostasis hypothesis, where sleep is suggested to selectively attenuate synaptic strength between neurons (Tononi and Cirelli, 2014). With electrophysiological, molecular, and

behavioral studies, this report suggested that during wakefulness, demand of synaptic strengthening is high and requires more energy. Conversely, sleep promotes synaptic weakening of neurons, decreases cellular stress, and allows the reestablishment of energy reserves in the brain. This and other studies suggest that sleep has an important role in re-sculpting synaptic landscape and restoring brain energy reserves. Future research is needed to understand in depth the association between sleep and the risk of developing neurodegenerative diseases, especially AD, and whether the risk changes within different sex.

4.2.3 Psychiatric comorbidity

Depression is another well-known risk factor for AD in older adults (Ownby et al., 2006). It has been reported that women have two-fold increase of risk developing depression than men, which peaks during menopause (Bromberger et al., 2011). Clinically significant depressive symptoms in women were associated with an increased risk of developing cognitive impairment (Goveas et al., 2011). In contrast, another study indicated that men with depressive symptoms have a significantly higher risk of developing AD compared to women counterparts (Dal Forno et al., 2005). A possible explanation for the discrepancies between these two studies is that male subjects were more likely to present with severe depression upon evaluation since men were less willing to admit depression symptoms, which could post a higher risk of developing AD when compared to their female counterparts.

Hormonal changes may be key factors underlying sex-specific differences in depression. The biggest indicator is that the increased prevalence of depression seems to correlate well with hormonal changes in women most notably during puberty and menopause (Soares and Zitek, 2008). This is bolstered by the protective effects of estrogen against depression in post-menopausal women (Gordon and Girdler, 2014). However, men have a lower rate of depression even without estrogen. One possible explanation is the ability of male brains to convert circulating testosterone into 17β-estradiol, and to maintain a more consistent 17β-estradiol reservoir for protection against depression without having drastic androgen spikes (Wu et al., 2009).

The sexual dimorphic brain activities in depression may also be observed at the transcriptional level. Labonté B et al analyzed the extent of transcriptional expression differences across six regions of postmortem human brains of male and female depression and control subjects. They demonstrated an upregulation in transcription signatures across all six brain regions of male and female depression subjects when compared to controls, but with few overlaps in transcriptional signatures between the two genders, suggesting a gender based dimorphic transcriptional signatures in patients who had depression (Labonte et al., 2017). These transcriptional expression differences were also found in C57BL/6 mice subjected to chronic variable stress (Labonte et al., 2017). One specific genetic expression of interest is DUSP6, which can modulate synaptic signaling activity via ERK1/2 phosphorylation (Mazzucchelli et al., 2002; Muda et al., 1996). Specifically, DUSP6 down-regulation in pyramidal neurons of ventromedial prefrontal cortex in female C57BL/6 mice induced an increase in frequency of spontaneous excitatory postsynaptic currents compared

to control. Conversely, male showed no such distinction in DUSP6 down-regulation (Labonte et al., 2017). This is one of the examples how different transcriptional expression profiles exist between males and females, which could be responsible for brain dimorphism between the two genders.

Stress has also been linked to AD and increased cortisol levels during stress have been associated with cognitive impairment (Csernansky et al., 2006; Pedersen et al., 2001). Changes in stress hormone signaling have been found in AD patients (Reisberg et al., 1987). For example, the levels of corticotrophin releasing factor 1 (CRF1) were found much higher in hippocampal brain regions of AD patients (De Souza, 1995). The signaling changes in hypothalamus-pituitary-adrenal axis are associated with hippocampal atrophy (O'Brien et al., 1996). Sex dimorphic responses to stress have been reported with women being more vulnerable to stress-related disorders. One study reported that levels of cortisol in female mild-to-moderate AD patients were much higher compared to males (Rasmuson et al., 2011). Several studies using AD mouse models further supported sex-specific differences in response to stress challenges (Devi et al., 2010; Sierksma et al., 2012; Sierksma et al., 2013; Sotiropoulos et al., 2015). It is hypothesized that heightened CRF1 signaling is associated with increased AD pathologies including elevated Aβ and pTau generation, as well as worsened Aβ toxicity, and that the sex dimorphic activation of CRF1 and GRCR-PKA signaling may contribute to sex dimorphism in AD pathogenesis (Fisher et al., 2018).

4.2.4 Diabetes Mellitus

The relationship between type 2 diabetic mellitus (T2DM) and AD has been well studied with high prevalence of both diseases among the aging population. Growing epidemiological research suggests that there is a strong comorbid association between both diseases (Cha et al., 2014), possibly because T2DM and AD have similar underlying pathophysiological processes (Moreira, 2012). Previous research spanning over the last decade implicates insulin insensitivity to AD pathology from *in vitro* experiments, clinical observations, and animal models (Chen et al., 2014b; Craft, 2006; Schioth et al., 2012). It has been found that chronic hyperglycemia in the brain is associated with chronic hyperinsulinemia, leading to brain insulin resistance manifested as impaired insulin signaling and disrupted BBB integrity leading to cognitive impairment and neurodegeneration (Neth and Craft, 2017; Yoo et al., 2016). Abnormal insulin signaling also increased Aβ accumulation and tau hyper-phosphorylation (Cao et al., 2007; Currais et al., 2012; Devi et al., 2012; Ho et al., 2004; Mehla et al., 2014; Vandal et al., 2014), as well as inhibited APP degradation leading to increased Aβ production (Yang et al., 2013). Interestingly, the association between AD prevalence and insulin insensitivity is stronger among female patients than in males (Ekblad et al., 2015). Additionally, clinical trials using intranasal insulin administration showed memory enhancement particularly among women and non-ApoE4 carriers, which further supports the role of insulin in AD pathology progression (Benedict et al., 2008; Reger et al., 2006).

A possible explanation of increased insulin insensitivity among women that leads to AD progression is the loss of estrogen after menopause (Asthana, 2003). It is well established that estrogen confers protection against weight gain and insulin insensitivity via estradiol-

induced up-regulation of heat shock protein HSP72 and diminished inflammatory response (Chung et al., 2008). This result is also corroborated in two separate studies using animal models treated with high fat diet (HFD). In the first study, a greater increased in insulin insensitivity and glucose intolerance was found in male mice treated with HFD than in female mice (Estrany et al., 2013), suggesting sex hormones at play. While testosterone does confer some protection against weight gain and insulin insensitivity (Zitzmann, 2009), it seems that estrogen is more protective than testosterone as seen in the HFD mouse model studies (Estrany et al., 2013). In the second study, estrogen receptor knockout mice treated with HFD presented with increased insulin resistance and glucose intolerance (Riant et al., 2009). These results are consistent with the fact that males accentuate a consistent but slow decrease in testosterone levels through aging while females experience a sudden drop in estrogen during menopause and hence why females are more afflicted by comorbidities later in life that can be modulated by sex hormones as exemplified by insulin insensitivity in this case. This is bolstered by a separate study where protection against obesity is lost in post-menopausal women (Meyer et al., 2011).

4.2.5 Thyroid dysfunction

Hypo- and hyperthyroidism are implicated as AD risk factors in the elderly population (de Jong et al.; Kalmijn et al., 2000). A large cohort study reported an association between changed levels of thyroid-stimulating hormone (TSH) and dementia exclusively among women (Tan et al., 2008). Suggested mechanisms include alterations on Aβ and tau deposition, neuronal survival, and indirect mediation through vascular risk factors (de Jong et al., 2009; Tan et al., 2008).

Reduced levels of TSH before any memory decline may predict the conversion of MCI to AD (Annerbo et al., 2006). Several studies indicated that thyroid hormones regulate APP expression, and modulate APP processing and secretion (Belandia et al., 1998; Latasa et al., 1998). For example, low levels of thyroid hormones increased APP expression and Aβ levels leading to AD. On the other hand, studies implicate that lower TSH levels could be a consequence of AD rather than the cause. The AD-associated neurodegenerative processes may reduce secretion of TSH-releasing hormone (TRH) and blunt pituitary responses to TRH, manifested as reduced TSH and thyroxine (T4) levels (Shi et al., 1993). TRH depletion itself can also induce AD progression by promoting tau hyper-phosphorylation (Luo et al., 2002). In rodents, treatments with TRH analogues increased acetylcholine synthesis and release (Ogasawara et al., 1996). Hyperthyroidism with increased T4 levels has been found in sub-clinical dementia patients. It is believed that hippocampal atrophy occurred during early stages of AD generates less feedback regulation on the hypothalamus-pituitary-thyroid axis, resulting in higher levels of free T4 (den Heijer et al., 2006). On the other hand, hyperthyroidism patients are found to have increased oxidative stress and lower antioxidant metabolite levels (Bianchi et al., 1999), which could potentially increase AD risks through inflammation.

Overall, comorbidity factors are important contributors to cognitive and functional decline during AD progression. They bring considerable implications for both patients and healthcare providers since more expertise, service, and requirements are needed compared to

when dealing with only one condition. Clinical patients would benefit greatly from improving multidisciplinary in-depth studies to understand the underlying mechanisms, emphasizing on the pathological time-course and sex difference implications. A major challenge in comorbidity studies is that most research relies upon statistical analysis of clinical readouts. To fully understand the mechanistic link between comorbid conditions and AD pathogenesis, and how they differ between sexes, an integration of molecular information available among diseases and how they altered by sex are needed.

4.3 The Interaction between Environmental Risk Factors and Sex in AD Pathogenesis

Many environmental factors such as lifestyle (e.g. diet and exercise), inflammation and immune responses, prior exposure to traumatic brain injury and stress may interact with sex to impact the development and/or progression of AD.

4.3.1 Lifestyle risk factors

Numerous studies have suggested obesity as an AD risk factor (Feart et al., 2009; Grant, 1999). Fat consumption and caloric intake are among the most significant dietary risk factors for AD, both contributing to oxidative stress either directly or indirectly. Studies have shown that high fat diet accelerated cognitive decline and AD-related neuropathology in human and animal models (Barron et al., 2013; Elias et al., 2003). The sex-specific differences have been implicated in obesity, adiposity, insulin resistance and metabolic syndromes in both experimental animal models and human studies (Franconi et al., 2008; Regitz-Zagrosek et al., 2006). It is speculated that cognitive decline and AD-related neuropathology after exposure to high fat diet might be different between males and females. Recently, studies in animal models and human subjects have demonstrated that long-term exposure to high fat diet exerted more profound impairments in cognitive function or synaptic plasticity in males than in females (Elias et al., 2003; Hwang et al., 2010). Higher insulin resistance was observed in obese male cohorts suggesting male vulnerability in this regard. Conversely, the Mediterranean diet, rich in fruits, vegetables, fish and olive oil, has been studied for AD prevention trials and is considered highly beneficial (Feart et al., 2009; Morris et al., 2015a; Morris et al., 2015b). It is important to determine any possible sex-specific differences in response to AD preventive trials like healthy diet treatment. The sex dimorphic effects of obesity are manifested in the degrees of BBB disruption, oxidative stress, and inflammation. Overweight and obese women have increased BBB disruption while obese men have significantly more gray matter loss (Gustafson et al., 2007; Taki et al., 2008). Obesity and inflammation are linked through involvement of oxidative stress and free radical production. It has been found that obesity induces a much greater inflammatory response with an increased likelihood of developing metabolic disturbances in women (Ahonen et al., 2012; Khera et al., 2009; Thorand et al., 2007).

Sex differences have been suggested in response to physical exercise as well. Studies have shown that physical exercise improved cognitive performance in AD transgenic mice and ameliorated AD-related white matter changes in early stage of diseases (Nichol et al., 2009; Yuede et al., 2009; Zhou et al., 2018). It was found that female AD mice have lower volume

of white matter and less myelinated fibers. However, after running exercise, a greater improvement of axonal diameter of myelinated fibers was observed in the white matter of the female AD mice, suggesting that exercise may improve cognitive function more effectively in female AD transgenic mice (Zhou et al., 2018). Studies have also indicated greater benefits in cognition from aerobic training (AT) in females than in males (Baker et al., 2010; Colcombe and Kramer, 2003). Higher levels of physical activity lower dementia risks more so in women than in men (Laurin et al., 2001; Middleton et al., 2008). Studies led by Varma et indicated older females but not males who underwent greater amounts of walking activities over one week measured objectively presented with larger hippocampal volumes (Varma et al., 2015; Varma et al., 2016). At the molecular level, Cotman et al. (2007) proposed induction of neurotrophic factors such as BDNF, IGF-1 and VEGF as a possible mechanism underlying that beneficial effects of AT (Cotman et al., 2007). Animal studies further strengthen the concept that brain BDNF mediates beneficial effects of AT by showing that inhibition of hippocampal BDNF signaling blocks the effects of AT on cognitive function (Maass et al., 2016; Vaynman et al., 2004a; Vaynman et al., 2004b). Interestingly, the AT-induced increase in brain BDNF levels may be sex-dependent (Chan and Ye, 2017; Szuhany et al., 2015; Venezia et al., 2016), with greater effects observed in females than in males both from animal studies (Barha et al., 2017b) and human studies (Barha et al., 2017a).

4.3.2 Inflammation and neuro-immune responses

Several lines of evidence support the importance of inflammation in AD. Recent genetic studies identified polymorphisms of genes involved in immune responses such as CD33 (Bertram et al., 2008), TREM2 (Kleinberger et al., 2014) and CR1 (Lambert et al., 2009). Environmental factors that increase inflammation such as obesity and TBI are associated with increased risks of AD (Breunig et al., 2013; Moser and Pike, 2016). The inflammatory response is also a common effect following viral infection (Brothers et al., 2018; Kumar et al., 2016; Van Lenten et al., 2001). In AD, activated microglia surrounding amyloid plaques produce higher levels of pro-inflammatory cytokines and accelerate Aβ accumulation (Glass et al., 2010; Sastre et al., 2008; Sheng et al., 2003). A study performed on a group of individuals over the age of 55 found that individuals taking non-steroidal anti-inflammatory drugs (NSAIDs) for two years presented with a lower risk of AD progression than individuals not taking NSAIDs (in t' Veld et al., 2001).

Sex-specific differences have been observed in immune system including neuro-immune modulation of memory and cognitive function (Tronson and Collette, 2017). For example, greater immune activities are seen in females than in males with different pathways and cells triggered after stimulation (Klein et al., 2015; Moxley et al., 2002). These differences correlate with higher susceptibility to infections in men, and higher incidence of autoimmune disorders in women (Fairweather et al., 2008). It is suggested that sex hormones and sex chromosomes contribute to sex-specific differences in immune system (Tronson and Collette, 2017). Similarly, sex differences are also seen in the neuro-immune system with unique immune-neuron interaction, cytokine responses and signaling in males and females (Sorge et al., 2011). The interactions between neurons and microglia via chemokine CX3CL1 are critical for memory formation, and immune challenges modify

memory through activation of microglia (Sheridan and Murphy, 2013). Following immune stimuli, males and females demonstrated different cytokine activation. For example, after systemic LPS injection, males show a stronger and sustained hippocampal activation of cytokines than females (Hudson et al., 2014; Pyter et al., 2013). Dysregulation of microglia and astrocyte-mediated neuro-immune responses has been strongly implicated in AD and TBI (Dzamba et al., 2016; Sajja et al., 2016). However, how the function of these cells affected in sex-specific manners remains unaddressed. It is also important to identify sex-specific cellular and signaling mechanisms in neuro-immune activation which could provide critical information for developing sex-specific AD therapies.

4.3.3 TBI

TBI is also one of the most studied environmental risk factors for AD, increasing the chance of developing the pathology nearly four-fold (DeKosky et al., 2010; Schofield et al., 1997). Epidemiological studies following TBI and its association to neurodegeneration have suggested that genetic risk factors such as *ApoE*4 can modulate the effect of the impact (Cao et al., 2017; Hayes et al., 2017). The risk magnitude for AD may increase with TBI frequency, age of when the injury took place, and sex differences among the population. While males account for the majority TBI patients and have been overly represented in preclinical and clinical studies, TBI in females still a major contributor to morbidity and mortality among children and elderly subjects (Colantonio et al., 2010; Scott et al., 2015). One review by Berry et al. demonstrated that moderate-to-severe TBI female subjects at peri-menopausal and post-menopausal stages had lower risks of mortality than males, but this advantage was not seen in pre-menopausal female patients (Berry et al., 2009). In addition, female patients after moderate-to-severe TBI exposure had few complications and shorter hospital stay than males (Berry et al., 2009).

TBI is often associated with higher risks of developing mental health comorbid conditions. Data suggest that female TBI patients are more prone to develop or report symptoms of depression, anxiety, headache and impaired memory when compared to men (Colantonio et al., 2010; Farace and Alves, 2000; Scott et al., 2015). Similarly, studies of veterans with TBI found that female veterans with a history of TBI are more likely to develop depression and anxiety whereas male TBI veterans are more likely to have alcohol use disorder and post-traumatic stress disorder (PTSD) (Epstein et al., 2019). In animal model studies, female mice performed worse in spatial working memory tasks than males post-TBI exposure (Tucker et al., 2016).

Mechanisms such as sex hormone regulation, sex differences in cerebral blood flow autoregulation as well sex-specific microglial responses in TBI have been proposed (Caplan et al., 2017). For example, male mice after cortical compact injury (CCI) presented with more profound pro-inflammatory microglial phenotypes and astrogliosis when compared to females. Subsequently, cytokine profiles associated with increased neuronal cell death and brain lesion were identified in male mice post CCI (Villapol et al., 2017). A greater density of microglia around lesion site was also reported in male mice post cortical stab lesions when compared to females (Acaz-Fonseca et al., 2015). A recent report shows that expression patterns of brain cannabinoid receptors (CB1 and CB2) are differentially

modified in female and male rats after repeated stress challenges, suggesting a potential mechanism underlying sex-related differences after TBI exposure and TBI/PTSD development (Xing et al., 2014). Together, the sex dimorphism in TBI have been reported in animal models but more studies are needed in human clinical studies. It becomes essential for future investigations to determine the mechanisms of developing post-TBI neurodegeneration and cognitive decline based on sex, age, and other factors that may modify the risk or protection.

It should be noted that comorbid diseases share some common mechanisms. Hence, one therapy used to treat one condition could also be a risk for initiating or accelerating the progression of another disorder (Bohlega and Al-Foghom, 2013; Shin and Chung, 2012). Interestingly, most studies have been focusing on specific biological pathways without considering how dysregulated effectors can modulate the comorbid association among diseases (i.e. SNPs, epigenetic modifications, miRNA, genes and proteins). Therefore, there is an urgent need to create a comprehensive model that takes into considerations of molecular mechanisms involved in comorbidities of AD in time-dependent and sex-specific manners.

5 Sex-specific treatment responses in AD

The stratification of sex when evaluating drug efficacies and safety profiles has made significant impact in clinical practice such as aspirin and warfarin in stroke (Berger et al., 2006; Cordonnier et al., 2017). On the other hand, the studies of sex differences in AD treatment are rather limited. Systematic reviews of currently available results from randomized clinical trials regarding efficacy and safety of cholinesterase inhibitors and memantine in total 20,688 patients found very limited data studying sex differences in these regards (Canevelli et al., 2017; Mehta et al., 2017). Similarly, limited data are available on sex stratified effects of drugs tested in recent AD clinical trials such as phase III studies of γ–secretase inhibitor semagacestat (Henley et al., 2009), anti-Aβ antibody solanezumab (Doody et al., 2014) and bapineuzumab (Salloway et al., 2014), or BACE inhibitor verubecestat (Egan et al., 2018). Several preventive trials such as FINGER and MAPT are yet to release any data for assessing sex specific effects on lifestyle stratification (Ferretti et al., 2018). One interesting study of a phase II clinical trial of intranasal insulin in amnestic MCI subjects reported greater effects on delayed story recall in males than in females, whereas greater benefits on activities of daily living in women than in men (Claxton et al., 2013). The effects were further stratified by ApoE genotypes, with worsened cognitive performance seen in ApoE4 females but improved performance in ApoE4 males. The interaction of sex and ApoE was also seen in some clinical studies of hormone replacement therapy (HRT) with ApoE4 women benefitting the least (Burkhardt et al., 2004; Ryan et al., 2009; Yaffe et al., 2000). The clinical benefits of HRT remain controversial and require more future long-term follow up studies in early HRT treatment (Ferretti et al., 2018). Together, the importance of tailoring sex-specific diagnosis, prognosis, prevention and treatment strategies of AD patients is increasingly recognized.

6 Future perspectives for understanding sex-specific differences in AD

High-throughput and bioinformatics technologies have helped us tremendously in understanding molecular and genetic basis of sex dimorphism in aging and AD. A new study analyzed genome wide transcriptome datasets from various brain regions of AD men and women using system biology network approaches (Sun et al., 2019). They have identified pathways and genes associated with AD in males and revealed that female molecular networks were more conserved than male ones across different brain regions at various disease stages. An ongoing research effort utilizing systems biology approaches including multiscale network analysis has identified several key molecular pathways and regulators that are specific in AD females and males, further classified by ApoE genotypes (Lei et al., *manuscript in preparation*). Together, these findings will contribute to a deeper understanding of sex differences in individuals with AD and could help greatly in the development of personalized and effective strategies for both AD diagnosis and treatment.

Prior studies have unveiled several important aspects of sex differences in AD as we discussed in this paper. However, in the era of precision medicine, a more comprehensive understanding of molecular mechanisms underlying sex dimorphism in AD is urgently needed for better development of diagnostic markers and target-driven therapies for AD (Mielke et al., 2014; Miller et al., 2013). New research should not only focus on the biological sex, but also focus on factors that contribute to male and female disparity. It is important to understand the interaction between sex and other risk factors of AD such as genetic and environmental factors. As the field is moving toward early detection and preventive strategies, future AD research should always evaluate sex differences, particularly when designing clinical trial studies.

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Abbreviations

Aβ	Amyloid-β
AD	Alzheimer’s disease
ApoE	Apolipoprotein E
ApoE2	Apolipoprotein E2
ApoE	Apolipoprotein E3
ApoE	Apolipoprotein E4
AIF	Apoptosis-Inducing Factor
APP	Amyloid precursor protein

AQP4	Aquoporin-4
AT	Aerobic Training
ATP	Adenosine Triphosphate
BBB	Blood Brain Barrier
CAD	Coronary Artery Disease
BACE1	β-site APP cleavage enzyme
BDNF	Brain-Derived Neurotrophic Factor
CCI	Cortical Compact Injury
CCV	Clathrin-Coated Vesicles
CRF1	Corticotrophin Releasing Factor 1
CSF	Cerebral Spinal Fluid
DHT	Dihydrotestosterone
E2	Estrogen 17β-Estradiol
ERα	Estrogen Receptor Alpha
ERβ	Estrogen Receptor Beta
HFD	High Fat Diet
HRT	Hormone Replacement Therapy
HT	Hormone therapy
IGF-1	Insulin-Like Growth Factor-1
LDLR	Low-density lipoprotein receptor
MCI	Mild Cognitive Impairments
NDs	Neurodegenerative diseases
NFTs	Neurofibrillary tangles
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
PAR	Poly-ADP ribose
PARP-1	Poly (ADP-ribose) polymerase-1
PS1	Presenilin 1
PS2	Presenilin 2
SNPs	Single Nucleotide Polymorphisms

T2DM	Type 2 diabetes mellitus
T3	Triiodothyronine
T4	Thyroxine
TBI	Traumatic brain injury
TRH	TSH-releasing hormone
TSH	Thyroid-stimulating hormone
VEGF	Vascular Endothelial Growth Factor

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Highlights

- Sex differences in Alzheimer's disease (AD) play a pivotal role in the prevalence, clinical course, responses to treatment during clinical trials, prognosis, and severity of pathological changes.
- A greater understanding of sex differences in AD from a molecular to a clinical point of view may improve symptom awareness, risk factor prevention, and clinical outcomes.
- Our review on recent and relevant literature about sex differences in AD highlights its impact on how development, aging, genetic, comorbidity, and environmental factors contribute to disease pathogenesis.