Sex differences in cognitive reserve: implications for Alzheimer's Disease in women

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Abstract

Women represent $\frac{3}{4}$ of the cases of Alzheimer's disease (AD). Current research has focused on differential risks to explain higher rates of AD in women. However, factors that reduce risk for AD, like cognitive reserve, are less well explored. We asked: what is known about sex differences in how cognitive reserve mitigates risk for AD? To address this, we conducted a narrative review of the literature. Keywords were: "sex/gender differences", "cognitive/brain reserve", "Alzheimer's Disease", and the following cognitive reserve contributors: "education", "IQ", "occupation", "cognitive stimulation", "bilingualism", "socioeconomic status", "physical activity", "social support". Fifteen papers disaggregated their data by sex. Those papers observed sex differences in cognitive reserve contributors. There is also evidence that a subset of women may have greater resistance to AD, possibly due to greater cognitive reserve. We discuss how traditional cognitive reserve contributors are gendered and may not capture factors that support cognition in aging women.

Keywords: cognitive reserve, brain reserve, sex, gender, Alzheimer's disease, resistance, resilience

1. Introduction

Currently, over 65% of people with late-onset Alzheimer's Disease (AD) are women (Association, 2019; Bailly et al., 2019; Mielke et al., 2014; Nebel et al., 2018; Schmidt et al., 2008). In fact, after age, sex is one of the strongest risk factors for developing AD (Table 1). It has also been hypothesized that the higher rate of AD in women compared to men may be because women are more negatively affected by some of the known risk factors for AD, than men (Table 1). For example, having an apolipoprotein E ϵ 4 allele (+APOE4) places women at a higher risk of developing AD, compared to men). Indeed, women in their sixties carrying one or two APOE4 alleles have a greater risk of developing AD compared to their male counterparts (Bretsky et al., 1999b; Farrer et al., 1997). Importantly, female-specific hormonal transitions including puberty, parity and menopause can help in our understanding of why women are more likely to be diagnosed with AD (see Table 2). Earlier onset of menopause, either surgical (ovarian removal) or spontaneous (gradual cessation of menses at ~51yrs), is associated with increased AD/dementia risk (Bove et al., 2014; Fox et al., 2013a; Gilsanz et al., 2019; Rocca et al., 2007). Total reproductive years (age at menarche to age at menopause) has repeatedly been shown to be negatively correlated with the rate of AD diagnosis, indicating that duration of ovarian hormone exposure protects against AD (Fox et al., 2013a; Gilsanz et al., 2019). In fact, there is evidence that the 17 β -estradiol (E2) decline at menopause may contribute to cognitive decline in women at late midlife, and that estrogen replacement initiated shortly after menopause reduces the incidence of AD (Kawas et al., 1997; Merlo et al., 2017; Shao et al., 2012; Tang et al., 1996; Whitmer et al., 2011). While estrogen replacement following menopause has been shown to promote resistance (i.e., the ability to delay AD onset, discussed below), many women who do not take estrogen therapy do not get AD, so factors beyond ovarian hormones contribute to the sex difference in AD.

Although significant consideration has been placed on sex as a risk factor for AD, little is known about the role of gender¹. Interestingly, although risk factors for AD overlap for women and men, there are sex

¹ "Sex refers to the biological attributes that distinguish organisms as male, female, or intersex...gender refers to psychological, social and cultural factors that shape attitudes, behaviours, stereotypes, technologies and knowledge. Gender includes three related dimensions. Gender norms refer to spoken and unspoken rules in the family, workplace, institution or global culture that influence individuals. Gender identity refers to how individuals and groups perceive and present themselves within specific cultures. Gender relations refer to power relations between individuals with different gender roles and identities." (Tannenbaum et al., 2019).

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differences in the effect of these risk factors. There are also general health moderators, such as mental health, sleep, and cardiovascular fitness (Table 3), which can interact with AD risk factors to increase susceptibility to AD in both sexes. It is possible that these health moderators have sex-specific effects. For example, women are more commonly diagnosed with mood disorders, which include major depressive disorder, generalized anxiety disorder, social anxiety disorders, and post-traumatic stress disorder (Kessler, 2003; Kessler et al., 2005, 1993; Parker and Brotchie, 2010; Weissman and Klerman, 1977). Differences in how women and men perceive, respond, and react to stress may contribute to women's elevated response to stressors and increased stress-related pathology like depression and anxiety diagnoses (Bangasser and Valentino, 2014; Bangasser and Wicks, 2017; Bangasser and Wiersielis, 2018). It is not possible to quantify how these health moderators specifically interact with AD risk factors in women, compared to men, but one possibility is that higher rates of mood disorders and perceived stress may contribute to the elevated levels of AD in women (for review see Mielke et al., 2014; Nebel et al., 2018; Podcasy and Epperson, 2016). Since gender interacts with many of these health moderators and AD-specific risk factors, it may also play a role in the differential frequency of AD in men and women.

It is critical to better understand what factors prevent or delay AD in women and men, since this would allow for sex-specific interventions that could stave off AD. The accumulation of reserve across the lifespan is one such factor (Stern, 2002). Reserve has been operationalized as the gradual accumulation of neural resources across the lifespan which can preserve cognitive function by reducing the effects of age- and AD-related neuropathology (Barulli and Stern, 2013; Cabeza et al., 2018). Importantly, these neural resources can be reflected in terms of brain reserve and/or cognitive reserve.

Brain reserve is a quantitative measure of neural capacity (e.g., overall brain size, number of neurons/synapses) that supports cognitive performance (Barulli and Stern, 2013). Cognitive reserve is a more dynamic measure of reserve and can be reflected in terms of greater neural efficiency (i.e., lower activity required for equivalent performance) and/or higher compensation (i.e., recruitment of alternative regions or networks to support performance, not typically recruited for that task). Factors thought to contribute to reserve (sometimes called proxies but referred to here as contributors) are education level, occupational complexity, Intelligence Quotient (IQ), cognitively stimulating activities, bilingualism, socioeconomic status (SES), physical activity, and social support. Greater reserve capacity, resulting from an increased lifetime engagement in these contributors is hypothesized to protect against cognitive decline, accumulation of neuropathology, and onset of AD (Baldivia et al., 2008; Barulli and Stern, 2013; Calvo et al., 2016; Stern, 2012,

2002). In the domain of AD research, it has been hypothesized that individuals with high reserve will show: 1) later cognitive declines in the face of AD pathology (Fig 1 point of inflection; called resistance); 2) later clinical diagnosis of AD in the face of worse pathology; 3) worse AD pathology at any level of cognitive performance; and 4) faster clinical AD progression once diagnosed with AD (i.e. after point of inflection in Fig 1, called resilience; Stern, 2009).

An individual with higher reserve is predicted to have greater resistance, but less resilience, to AD than an individual with lower reserve. Resistance is defined as an individual's ability to withstand AD-related brain pathology and remain cognitively normal, particularly in relation to a greater risk of developing AD (e.g., older age, presence of APOE4 allele; Montine et al., 2019). Resilience refers to one's ability to sustain cognitive performance in the presence of substantial AD-related pathology (Montine et al., 2019). Evidence indicates that individuals with greater reserve capacity resist diagnosis of AD for longer, maintaining cognitive function despite presence of AD pathology (e.g., Boots et al., 2015; Stern, 2002). Once individuals with higher reserve, and thus greater resistance, succumb to AD there is evidence that the disease progresses more rapidly reflecting lower resilience (Barulli and Stern, 2013; Stern, 2002). To date, little is known of whether there are sex or gender differences in cognitive reserve, resistance, or resilience.

We conducted a literature review in order to determine what is known about women's cognitive reserve throughout the lifespan, and how this may affect women's resistance and resilience to AD. We hypothesized that women accumulate less cognitive reserve across the lifespan according to traditional measures of reserve, but that mitigating factors including gender might suggest other possible contributors to reserve.

2. Method

We searched the literature for sex or gender differences in the accumulation of reserve and its effect on the progression of AD using the following databases: *Medline*, *EMBASE*, *PsycInfo*, *PubMed*, and *Web of Science*. In addition, we performed a manual search of the reference lists on *Google Scholar* for relevant articles not included in those databases. Keywords for our initial search were: "sex differences", "gender differences", "cognitive reserve", "brain reserve", "reserve", "Alzheimer's Disease", "Alzheimer", "AD". In order to perform a more thorough search of reserve factors, we conducted separate searches to include common contributors to reserve including: IQ, education, occupation, cognitively stimulating activities, bilingualism, SES, physical activity, and social support. We completed these additional searches by replacing

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the reserve key terms (i.e. “cognitive reserve”, “brain reserve”, and “reserve”) with each contributor to reserve that we considered in the review: 1) “IQ” or “intelligence quotient”; 2) “education”; 3) “occupational complexity” OR “occupation”; 4) “cognitively stimulating activities” OR “cognitive stimulation” OR “cognitive activity” OR “cognitive activities”; 5) “bilingualism” OR “multilingualism”; 6) “socioeconomic status” OR “SES”; 7) “physical activity” OR “exercise”; 8) “social support” OR “socialization” OR “marital status”.

We did not restrict our search based on the year of publication but did restrict it based on the articles being in English. We removed duplicate entries and using the title and abstract, screened articles to identify eligible studies that considered sex and/or gender differences in reserve or contributors to reserve, and their effect on AD. Articles were included for full text screening if the title or abstract explicitly mentioned sex and/or gender differences in reserve or reserve contributors. If reserve or its contributors were mentioned in the title or abstract but consideration of sex and/or gender were not, we included the article for full text screening to check for any post-hoc analyses of sex/gender. We excluded any articles that covaried for the effects of sex and/or gender or reserve (e.g., years of education) since that would essentially remove those contributors from the analysis.

Articles that remained were read in full to assess inclusion. We included studies in our final analysis if they explicitly used sex and/or gender in their analyses by: 1) stratifying the sample by sex or gender, running the analyses separately for women and men; 2) testing sex and/or gender using interaction terms; or 3) using higher modelling techniques to test the significance of sex and/or gender (Figure 2).

3. Results

Based on the above criteria, our search returned 15 studies, which we review below. Two studies directly investigated sex differences in reserve, and 13 studies used the six contributors to reserve: education ($n = 8$), IQ ($n = 2$), and occupational complexity ($n = 3$; Table 4). We found no papers that investigated sex differences in the reserve contributors of SES, social support, or physical activity in the risk for AD, nor any papers that investigated gender differences in cognitive reserve.

3.1. Sex differences in direct measurement of cognitive/brain reserve

Three studies explicitly stated that the goal was to investigate sex differences in cognitive/brain reserve (Malpetti et al., 2017; Perneczky et al., 2007b; Sundermann et al., 2016b). One study shows that women and men with AD have similar performance on a cognitive battery testing verbal fluency, memory, and

visuospatial skills despite men's greater deficits in cerebral metabolism, suggesting that men have greater resilience than women (Pernecky et al., 2007). A second study shows the opposite: in women and men with MCI, women had better verbal memory performance despite equivalent cerebral hypometabolism suggesting that women may have greater resistance in the verbal domain, although this relationship was not observed in healthy older adults or those diagnosed with AD (Sundermann et al., 2016b). It should be noted that despite discussing sex differences in reserve in the context of cerebral metabolism, both Pernecky (2007) and Sundermann (2016b) controlled for years of education in their analyses, suggesting that variability in the data from cognitive reserve accumulated via education was statistically removed. Sex differences in cognitive performance or cerebral glucose metabolism might have been correlated with level of education, which would imply sex differences in reserve accumulation based on education, but this cannot be determined from these studies since education was used as a covariate. One study examined sex differences in cognitive reserve, which was operationalized as education and occupation, on cerebral glucose metabolism. Women and men diagnosed with AD demonstrated positive correlations between years of education and occupational attainment and cerebral glucose metabolism; this was observed in frontal and limbic regions in women but parietotemporal regions in men (Malpetti et al., 2017). Thus, both sexes benefit from higher reserve as measured by cerebral glucose metabolism, but the brain regions affected by reserve differed between women and men. These results also suggest that early reserve accumulation (via education) benefits women more while mid-life reserve accumulation (via occupation) benefits men more. Taken together, these studies point to sex specific life periods and types of contributors that differentially build functional reserve in women and men.

3.2. Sex Differences in contributors to cognitive reserve

Thirteen studies investigated sex differences in the factors thought to contribute to reserve on cognition and/or AD pathology.

3.2.1. Education

Years or level of education is the most commonly studied contributor to reserve (Stern, 2006). Studies that explored the effect of education on cognitive ability in adults with AD or with risk factors of AD, but did not take sex into account, found that higher level of education was consistently associated with lower prevalence and incidence of AD (for review see Meng and D'Arcy, 2012). We found eight studies that

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examined sex differences in the effect of education on cognitive reserve in AD. Two studies found that although more years of education was associated with reduced prevalence or incidence of AD, the effect of education did not differ between the sexes in either study suggesting that education confers similar reserve capacity to women and men (Fratiglioni et al., 1991; Letenneur et al., 1999, respectively). Similarly, fewer years of education correlated with cerebral hypometabolism in women and men but there were sex differences in the brain regions demonstrating hypometabolism (Malpetti et al., 2017). These studies suggest that education contributes to reserve in both sexes, although underlying neural circuits may differ.

In contrast, other studies indicated that increased education provided greater protection against AD in women but not men. Specifically, women with high education had reduced risk of developing AD compared to women with low/moderate education, a relationship that was not observed in men (Launer et al., 1999; Letenneur et al., 2000). Furthermore, in individuals who did not carry the APOE4 allele, more years of education was associated with slower declines in Mini Mental Status Exam (MMSE) score with age in women but not men (Oliveira et al., 2016). In APOE4 carriers, more years of education was associated with slower cognitive decline, measured by the Cognitive Dementia Rating Scale, in women but not men (Oliveira et al., 2016). Lastly, CSF levels of amyloid beta at baseline predicted more rapid decline in executive function in women compared to men (Koran et al., 2017). These effects were most pronounced in women with fewer years of education suggesting that education allows women to maintain executive function in the face of AD pathology. Additionally, although Fratiglioni et al. (1991) did not observe a sex difference in the effect of education on AD prevalence in their sample, when participants with vascular dementia and AD were grouped together lower level of education significantly increased dementia risk in women but not men. Similarly, Letenneur et al. (1999) did not observe sex differences in education and incidence of AD, but when they augmented their sample using other European test sites, they found that lower education predicted AD in women but not men (Lettenneur et al., 2000). Taken together, these results indicate that higher education may be more critical to women's cognitive reserve than to men's and that higher education for women may help decrease the risk for AD.

Only one study observed that education conferred greater protection against AD in men than women. Men with AD had significantly better performance on the MMSE than women of the same age with the same level of education (Pradier et al., 2014). Differences in sample characteristics, sample sizes or other reserve factors that are associated with education (i.e. occupational complexity and SES) may contribute to these studies not matching other research on sex differences in how education modifies risk of AD diagnosis.

When these results are considered together, they suggest that education may affect reserve capacity in women more than men since higher education confers greater protection against developing AD and cognitive decline in old age, even in the face of AD pathology. However, there are contradictory findings so more research on this is warranted. In spite of the fact that in all the papers where sex differences in years or level of education were assessed, men had higher rates of education than women (Letenneur et al. 1999; Letenneur et al. 2000; Malpetti et al., 2017), women still benefitted more from higher levels of education suggesting that education level is critical to women's resistance.

It should be noted that although education as a reserve factor is often measured from early life (i.e. high school and undergraduate programs are completed in young adulthood), in men, training in the workforce later in life can compensate for an initial low level of education resulting in equivalent cognitive performance to individuals with high levels of education (Wight et al., 2002). We are not aware of any studies that have explored this with respect to sex differences or in women.

3.2.2. Intelligence Quotient (I.Q.)

IQ aims to measure crystallized general intelligence and is frequently used as a contributor to cognitive reserve. IQ is measured using a wide range of standardized tests (i.e., Wechsler Adult Intelligence Scale, Wide Range Achievement Test, National Adult Reading Test). Depending on the test used, IQ can be derived from calculating participants' ability to read (e.g., pronounce a list of words ranging in difficulty), understand sentences, spell, reason abstractly, and/or solve math problems. In studies of AD patients that do not consider sex, higher estimates of premorbid IQ have been linked to reduced dementia severity (Maddrey et al., 1996), better MMSE performance (Osone et al., 2015), higher cerebral glucose metabolism (Alexander et al., 1997), and larger hippocampal volume (Lo et al., 2013; Osone et al., 2015). In all of these studies, premorbid IQ was estimated using verbal reading tests after patients were diagnosed with AD (e.g., Wide Range Achievement Test, National Adult Reading Test). Although reading tests have been established as reliable measures of premorbid IQ (Bright and van der Linde, 2020), many studies also account for the effect of dementia severity in their analyses (e.g., Alexander et al., 1997; Osone et al., 2015).

We found two studies that looked at sex differences in the relationship of IQ to episodic memory performance in a sample of MCI and AD patients. Higher composite IQ scores and greater academic achievement during adolescence (i.e., high school) predicted lower incidence of AD in both women and men; the odds ratios were almost identical indicating that IQ benefits the sexes equally (Huang et al., 2018).

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However, the situation is more complicated when premorbid IQ is estimated in AD patients using the German vocabulary test (Wortschatztest, WST). In a sample of AD patients split into four groups based on sex and IQ (low <100 vs. high >100), all four groups performed similarly on a verbal episodic memory task, but men in both IQ groups performed better on the delayed component of a visuospatial episodic memory task than women (Beinhoff et al., 2009). Specifically, high IQ women had elevated CSF tau compared to high IQ men, possibly suggesting greater preservation of brain reserve in regions mediating visuospatial episodic memory task in men which may be compromised in women. However, in the low IQ groups the CSF tau levels were similar for women and men but women had worse visuospatial memory suggesting that IQ benefits cognitive reserve for visuospatial episodic memory function more in men. Interestingly women in the high IQ group performed better on the visuospatial task than women in the low IQ group suggesting IQ does benefit cognitive reserve in women, but possibly less than in men. The results of these studies are mixed indicating that higher adolescent IQ reduces AD risk equally in men and women, but that measures of premorbid IQ in AD patients indicate that IQ may benefit reserve more in men than women.

3.2.3. Occupational Attainment

Occupational attainment is thought to reflect occupational complexity, another contributor to cognitive reserve (e.g., Boots et al., 2015). In addition to collecting data about the participant's occupation, occupation complexity can be coded in terms of work with data, people, and/or things (Sörman et al., 2019). In studies that did not disaggregate their analyses by sex, different components of occupational complexity, such as decision latitude (autonomy to make decisions at your job instead of deferring to a supervisor), interactions with people, and data management were associated with reduced risk of developing late onset AD (Dekhtyar et al., 2016; Smart et al., 2014; Wang et al., 2017). Higher occupational complexity in interpersonal and data management realms was also associated with higher scores of general cognitive ability, memory, and processing speed (Boots et al., 2015; Smart et al., 2014), suggesting that occupation may help delay AD onset. In a traditional sense of work outside the home, men have held more complex occupations than women (Mielke et al., 2014). In the few recent studies that have examined this, evidence from both Swedish and Scottish cohorts of older adults demonstrates that in work outside the home, men still have access to higher occupational complexity than women (Finkel et al., 2009), particularly in fields working with data. Although there are exceptions, the benefits of occupational complexity may accrue primarily to men.

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We found three studies that stratified their analysis of occupation by sex. The general findings of these papers were mixed. In one study, the age and sex adjusted primary analysis revealed that manual work (presumably lower complexity) was significantly associated with greater risk of developing AD, compared to non-manual work (Qiu et al., 2003). However, the authors found sex differences in the type of manual work (i.e., manual work in general, manual work involving goods production or service production) and its risk for AD. In men, there was no significant association between general or manual work involving goods production and the risk of developing AD. In contrast, in women manual work involving goods production was associated with a higher risk of developing AD. There was also a lower risk of developing AD and manual work involving goods production across both sexes in the higher education (>8 years) vs. the lower education group (<8 years) and in the older age group (≥ 85 years) compared to the 'younger-old' age group (75-84 years). Interestingly, the authors suggested that environmental circumstances may have contributed to the elevated risk of AD diagnosis associated with manual work involving goods production. They note that industrial changes that occurred after the 1950s could have resulted in an increased exposure to industrial pollutants related to increased AD, which may have affected the younger-old individuals when baseline examination was performed (1987-89). In addition, many of the jobs that fall under the category of manual work involving goods production (e.g., mechanical technicians, welders, metal workers) generally involve exposure to multi-toxins, which may have contributed to the elevated likelihood of AD diagnosis. Lastly, the authors speculated that manual work is related to low income, which may be associated with poorer living conditions (e.g., in housing, nutrition, and social environment) and engaging in unhealthy behaviours (e.g., excessive smoking, alcohol intake) contributing to elevated AD pathology (Dartigues et al., 1992; Engelhart et al., 2002; Fratiglioni et al., 2000, 1993; Merchant et al., 1999; Moceri et al., 2000; Morris et al., 2002; Ott et al., 1998; Scarmeas et al., 2001). Thus, this study suggests that complexity of work may reflect the conditions rather than the mental challenges and that it is more likely the conditions of the work that contribute to cognitive decline.

In the second study, Helmer et al (2001) found that although the global effect of occupational categories did not confer protection in mixed sex analyses, when they stratified by sex women exhibited greater resistance than men to developing AD if they were crafts workers and shopkeepers. In men these occupational categories increased risk of developing AD (Helmer et al., 2001). These authors also suggest that differences in health behaviour and exposure to environmental factors, which may be linked to the type of occupation, may contribute to elevated risk of dementia generally. Thus, investigating the relationship

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between occupational attainment and risk of developing AD is complicated by the conditions of the work environment as well as the different health behaviors of women and men.

A last study challenged the idea that occupation had to be 'outside the home.' In a large sample of women and men (n = 1722 men; 2161 women), Santabarbara and colleagues (2019) found that for women and men, being a farmer conferred greater AD protection than other occupation categories (white-collar, blue-collar, homemaker). In women, being a farmer was more protective against developing AD than being a homemaker. Being a homemaker, in turn, was related to greater likelihood of living alone, having depression, hypertension and obesity (i.e., general health moderators associated with greater likelihood of AD diagnosis) than any other occupation category. All individuals from the homemaker category (n = 1407) in this study were women. The authors theorized that being a farmer conferred greater protection, in part, because of the environmental circumstances in which the participants were born. Their Spanish cohort was born at the start of the 20th century and lived through the Spanish Civil War and post-war years. The war-related stress and nutritional deficits may have had a greater impact to city inhabitants (who were usually blue-collar workers) as opposed to farmers' families, who had better access to nutrition during the war compared to urban dwellers. Thus, occupational attainment in the studies explicitly disaggregating their data by sex suggest that 1) jobs thought to be just manual labor (farming) may have very complex attributes and 2) the conditions of work, as well as complexity, contribute to cognitive reserve.

3.2.4. Cognitively Stimulating Activities

In cohorts that don't distinguish between women and men, cognitively stimulating leisure activities in old age (i.e. skill based games and crossword puzzles, and social activities) also contribute to reduced risk of developing AD, suggesting that reserve can be accumulated or at least maintained into old age in individuals engaging in those activities (Boots et al., 2015; Smart et al., 2014; Wang et al., 2017). In a sample of AD patients from the *Cache County Study on Memory in Aging*, a higher number of cognitively stimulating activities per week predicted slower cognitive decline measured by the MMSE over a one-year period (Treiber et al., 2011). They noted that men participated in significantly more cognitively stimulating activities than women. However, they covaried sex in their analyses without reporting whether sex affected their model, so it is unclear whether cognitive activities had different effects in women and men. The beneficial effect of cognitive stimulation was strongest in those with the shortest duration of AD, indicating that it is important to engage in these activities as early as possible (Treiber et al., 2011).

We found no studies examining sex differences in the beneficial effects of cognitively stimulating activities. Further research is needed to determine whether cognitive activity in midlife and old age benefit reserve differently in women and men.

3.2.5. Bilingualism

Studies that do not disaggregate their data by sex reveal that bilingualism has the potential to increase resistance, delaying AD onset by 4-5 years (Bialystok et al., 2007; Perani and Abutalebi, 2015). Bialystok and colleagues used sex as a covariate in their primary analysis to determine if bilingualism delayed AD onset (Bialystok et al., 2007), but subsequent analyses to determine if there was a difference in monolinguals seeking medical attention longer than bilinguals. The authors found that generally, men delayed clinic visits longer than women, and monolingual males were slower to seek medical attention than any other group (Bialystok et al., 2007). Thus, although bilingualism may delay AD onset, it was difficult to determine whether there was a sex difference in bilingualism and reserve.

We found no studies that looked at sex differences in the effects of bilingualism on cognitive reserve in AD. One study, however, did investigate sex differences in the role of bilingualism on preventing any kind of dementia onset (Alladi et al., 2013). The cohort consisted of 424 men and 224 women with dementia (37% AD) from Hyderabad, India. There was no significant interaction between sex and bilingualism on the age of onset for dementia. However, this sample had significantly more men than women and participants were diagnosed with various forms of dementia which makes it difficult to determine how sex differences in bilingualism affect AD onset specifically. Another study of mixed sex found that multilinguals who spoke four or more languages were diagnosed with AD at a later age than those who spoke fewer than four languages. Sex was used as a covariate in primary analyses eliminating any effects of sex. However, women were more represented in the monolingual group and thus the trend for men to be diagnosed at a later age than women supports the idea that multilingualism delays AD (Chertkow et al., 2010).

3.2.6. Socioeconomic Status (SES)

Low socioeconomic status (SES), often assessed as a combination of education, occupation, and income (Darin-Mattsson et al., 2017), is linked to poorer health leading to earlier mortality (Matthews and Gallo, 2010) and increased risk of AD (Karp et al., 2004). It is hypothesized that low SES increases stress

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because of greater financial strain, exposure to physical strain from living in areas with elevated chemical and noise pollution, and unavailability of a nutritious diet (Cohen et al., 2010; Evans and Kim, 2010).

We found no studies that looked at whether SES affected cognitive reserve to impact risk of AD differently in men and women. However, one study investigated sex differences in the ability of SES (measured by education and occupation) to mitigate risk for dementia in people carrying the APOE4 allele (Hasselgren et al., 2019). In a sample of 580 women and men from *the H70 Birth Cohort Study* and the *Prospective Population Study on Women*, high SES (a white-collar occupation and higher educational attainment) delayed dementia onset even in men carrying an APOE4 allele. However, women with high SES (white-collar occupation) carrying the APOE4 allele developed dementia earlier than women with high SES who did not carry an APOE4, at a similar age to women with low SES (blue-collar occupation). AD onset in women with low SES (blue collar women) was unaffected by the APOE4 allele. Higher educational attainment did not seem to particularly benefit women: both women with the highest (i.e., secondary/university) and lowest levels (i.e., primary) of education had shorter time to disease onset than women with lower-secondary education. Thus, the one study that investigated sex differences in the SES-dementia relationship showed clear advantages of SES in delaying dementia in men, but not in women (Hasselgren et al., 2019). One limitation is that SES in this study was largely defined as the participants' education and occupation, so other measures indicative of SES (e.g., income, characteristics surrounding their living situation, etc.) were not considered.

Another study on SES and general dementia highlights the complexity of proxies for SES. While there was no association between low neighbourhood SES (measured via neighbourhood composition, e.g., affluent vs. disadvantaged) and dementia in men, there was for women. Women with lower neighbourhood SES (i.e., highest unemployment rate, greater proportion of tenant occupancy) had higher risk of dementia. In this sample, women were more often widowed than men, had lower education, lower income, and lived alone more than men (Letellier et al., 2018). Thus, 'low SES' for women was associated with negative health factors and lower access to reserve contributors than 'low SES' for men. It is important that future work consider the different factors that enter into SES for women and men since it is important to disentangle the effect of differential contributors to reserve, education and occupation.

3.2.7. Physical Activity

In mixed sex studies, increased physical activity is associated with better cognitive performance for both women and men (Guiney and Machado, 2013). For example, frequency of weekly physical activity is positively correlated with motor reaction time and attention (measured by the Eriksen Flanker Task) in both younger and older adults, and accuracy in older adults (Hillman et al., 2006). Although exercise benefits cognition across the lifespan it seems to be particularly beneficial for older adults (Barha and Liu-Ambrose, 2018). Higher levels of physical activity are linked to decreased pathology associated with aging and AD (Brown et al., 2019). Specifically, physical activity is associated with increased cerebral blood flow (Guiney et al., 2015), increased anterior hippocampal volume (Erickson et al., 2011), decreased cortical tau burden (Brown et al., 2018), and less age-related decrease in cerebral glucose metabolism and increase in cortical β -amyloid deposition (Okonkwo et al., 2014). However, none of these studies stratify their data by sex.

We found no studies that investigated whether physical activity affected the risk of developing AD differently in women and men. However, two meta analyses of intervention trials with healthy older adults demonstrate that cohorts with higher percentages of women consistently have a larger effect size, suggesting that women's reserve benefits more from exercise than men's (Barha et al., 2017; Colcombe and Kramer, 2003). The same is the case in studies of MCI; aerobic exercise training programs improve performance on more measures of executive function in women compared to men (Baker et al., 2010). They also improve attention and memory performance in women while only improving memory in men (Van Uffelen et al., 2008). Thus, women's reserve seems to benefit more from physical exercise whether this is through resistance or resilience remains to be determined. Unfortunately, women in middle to old age have lower levels of physical activity than men internationally (Canadian cohorts: Kaplan et al., 2001; US cohorts: Lee, 2005; and Korean cohorts: Lee et al., 2017). This suggests that ultimately physical activity will play a lesser role in women's cognitive reserve than men's because women are less physically active. This could be viewed as a gendered effect on reserve as gender norms have dictated that women exercise less. Less exercise in women may also raise their rates of obesity which, in itself, is a risk factor for AD (Table 3).

3.2.8. Social Support

In general, social support is thought to contribute to cognitive reserve because it reduces feelings of loneliness that are associated with an increased risk for dementia (Holwerda et al., 2014). In this same vein,

unmarried or single people are at greater risk of developing AD than married individuals (Helmer et al., 1999; Sundström et al., 2016).

We found no studies that compared the effect of social support in women and men on the likelihood of developing AD. One study with 600 AD patients (214 men; 386 women) that disaggregated their data by sex noted that women reached greater than 50% loss of autonomy (but not in need of 24-hour care or institutionalization) more quickly than men (Sinforiani et al., 2010). The authors speculated that this may partly be because more women in their cohort lived alone, but this was not tested directly. While women may enjoy more social support than their male peers in youth and middle age, this earlier social support does not seem sufficient to stave off earlier dependence in women. In studies that look at dementia in general, divorced men are at greater risk of developing dementia than divorced women (Sundström et al., 2016) and never married or widowed men have a greater risk of developing dementia compared to women (Pankratz et al., 2015).

Two gender norms, social support and caregiving, may intersect to protect women against the toll of caregiving. Several studies have found that being a caregiver for someone with dementia compromises caregiver health and well-being (Brodaty and Donkin, 2009; Richardson et al., 2013). When data are disaggregated by sex, husbands who are caregivers are at greater risk for developing dementia than caregiving wives, suggesting that women may effectively find protection in other social ties or an earlier history of social support, while men may not find such ties outside of their marriage (e.g., Dykstra & Gierveld, 2014). Theoretically, since women are more likely to seek social support than men (Billings and Moos, 1981; Folkman and Lazarus, 1980; Hamilton and Fagot, 1988; Stone and Neale, 1984) one would think that social support would be a larger contributor to women's cognitive reserve (Evans et al., 2018). However, based on the dearth of studies in women, further research examining sex differences in social support are required to understand how different kinds of social support would mitigate against AD pathology. It is possible that, because women spend greater time caring for loved ones than men, women experience a greater toll of caregiving for women. This reinforces the necessity to look at how different contributors to cognitive reserve intersect and how gender norms influence these reserve contributors to affect each sex differently.

4. Discussion

We reviewed the literature on sex differences in factors that contribute to cognitive reserve. Out of 63 articles that met the screening criteria, only 15 met screening criteria, including an analysis of women or sex

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differences. The elevated rate of AD diagnosis in women and their more rapid cognitive decline once diagnosed with AD in concert with hormone deprivation at menopause – known to worsen general health moderators (i.e. mood disorders, sleep, inflammation) – may reduce reserve capacity as they enter older adulthood (Irvine et al., 2012; Laws et al., 2018). However, despite the cognitive reserve literature having the potential to contribute to an understanding of sex differences in the risk for AD, there is very limited research examining sex differences in reserve or reserve in women. Further, we found no studies that specifically investigated gender differences in reserve, although some of the contributors to reserve may be gendered. This suggests that while reserve contributors have been assumed to apply to both sexes, we really do not know that they do or, whether they affect both sexes to the same extent.

Of the three studies that directly examined sex differences in *cognitive* reserve at the functional level, those using cerebral glucose metabolism as an indicator of reserve have complicated results, suggesting that one size does not fit all. Men with AD exhibit similar performance on a cognitive battery compared to women with AD despite having greater hypometabolism, suggesting men have more resilience than women (Pernecky et al., 2007). However, in specific cognitive domains (e.g., verbal), although there were no sex differences in verbal ability in the AD sample, in the MCI sample: women perform better than men despite having similar levels of hypometabolism, suggesting women have more resistance than men (Sundermann et al., 2016b). When the direct effect of reserve contributors (i.e. education and occupation) on cerebral glucose metabolism were assessed, they suggested that different brain circuits may underly reserve (Malpetti et al., 2017). Due to the lack of studies, we could not draw conclusions about sex differences in reserve from contributors including bilingualism, physical activity, cognitively stimulating activities, SES, and social support. However, except for social support, the historical accessibility and social acceptance of these other reserve factors has been far greater for men than in women. In domains where women's reserve seems to benefit more – education and physical activity – gender norms seem to mitigate their engagement in these activities and consequently, women have less opportunity to accumulate reserve from these. However, if women had the same opportunities to engage in these factors, extant literature suggests they would benefit women's reserve possibly more than men's.

Our review suggests that when women have higher contributors to reserve, women gain more resistance to AD onset, compared to men. However, these factors do not seem to contribute to resilience in women following AD diagnosis. For example, generally higher education provides greater resistance in women than in men (Launer et al., 1999; Letenneur et al., 2000). However, once diagnosed with AD, men have greater

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resilience than women despite similar levels of education (Pernecky et al., 2007; Pradier et al., 2014; but see Malpetti et al., 2017). In terms of IQ, although we found no studies that examined sex differences in resistance, one study demonstrated that higher IQ provides men greater resilience than women on the visuospatial episodic memory task (Beinhoff et al., 2009). Finally, 'higher occupational attainment' did not necessarily confer greater resistance or resilience in either sex. Instead, the type of occupation had to be considered in the context in which the occupation was held (e.g., availability to nutrition, resources, presence of war, exposure to toxins). Extant studies suggest that having certain jobs with healthy working conditions (e.g., crafts worker, shopkeeper, farmer) confers greater resistance in women than men, particularly in comparison to other jobs that women held (e.g., homemaker; Helmer et al., 2001; Santabarbara et al., 2019; but see Qiu et al., 2003). Finally, although higher SES (measured by occupation type) was dementia-protective to men independent of APOE4 status, higher SES provided less protection to women if they carried the APOE4 allele (Hasselgren et al., 2019). This suggests that contributors to reserve need to be considered in the context of AD risk factors, biological sex, gender, and their intersections.

Our review reveals that social support may contribute to more resistance in women than men because women engage in more social factors, such as seeking greater social support and more regular medical attention (Billings and Moos, 1981; Dykstra and Gierveld, 2014; Hamilton and Fagot, 1988; Shye et al., 1995), which may increase reserve. Men have a greater risk of developing dementia compared to women if they have never married or are widowed (Pankratz et al., 2015) and although women are more likely to be caregivers than men, male caregivers are at 3x higher risk of developing dementia than women (Norton et al., 2010). These data suggest that a lack of spousal support and caregiving stress increases the likelihood of AD diagnosis in men more than women, possibly due to lack of other social supports. In one study, all 1407 participants in their 'homemaker' occupation category were women; these women were more likely to live alone and have depression than participants from any of the other occupation types (Santabarbara et al., 2019). These findings highlight the importance of also considering social support in the context of one's occupation type and how that might also protect against AD. Just as risk factors and general health moderators compound in complex ways, reserve factors can also work in multiplicative ways to increase reserve and hence, resistance to AD.

In spite of the paucity of sex difference studies in cognitive reserve, some findings from this review suggest that although the rate of AD is higher in women than men, there may be a subgroup of women that have high resistance to AD than men, potentially because of increased accumulation of reserve.

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Supporting this is research that indicates sex differences in the incidence of AD are specific to the cohort's age (Andersen et al., 1999; Brayne et al., 1995; Fratiglioni et al., 1997; Letenneur et al., 1999; Miech et al., 2002; Ott et al., 1998; Ruitenberg et al., 2001). For example, once diagnosed with MCI, the rate of progression to AD at 70-79 years is greater in men than women but at >80 years, higher in women than men (Roberts et al., 2012). By segregating individuals according to whether they are older or younger than 80 years, the findings reveal a survival bias in the older women, with later age of onset suggesting they may be resistant to AD.

This survival bias within women is further supported by the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort of women and men with MCI. Measuring CSF tau/A β levels to divide women and men according to whether they had "high" or "low likelihood" of progressing to AD led to the finding that "high likelihood" women had significantly faster cognitive decline than "low likelihood" women, while high and low likelihood men did not differ in the rate of their cognitive decline (Sohn et al., 2018). Importantly, these studies demonstrate that there are two populations of women, one with more resistance to AD. Thus, the resistant group is an important one to study to better understand the factors contributing to their later onset of AD, including those contributing more generally to cognitive reserve in women.

Further evidence suggests that if women can resist cognitive decline during early, older adulthood, this may minimize the effect of AD risk factors that disproportionately affect women, such as carrying an APOE4 gene (Bretsky et al., 1999a; Corder et al., 1993; Gómez-Tortosa et al., 2007). A meta-analysis found that women have an elevated risk of developing AD between the ages of 65 and 75 if they have the APOE-e3/e4 genotype, but that there are no sex differences in APOE4 risk prior to 65yrs or after 75yrs, suggesting a potential critical period in which women could defray their increased risk of AD (Neu et al., 2017). Thus, maintaining health during middle age and across the menopause transition might buffer against cognitive decline during this critical period in a woman's life when there is elevated risk of progressing to AD.

If cognitive decline can be resisted during this critical period, women may fare better than men. In healthy aging, men demonstrate faster rates of cognitive decline in key cognitive domains than women (McCarrey et al., 2016). For example, older women tend to perform better than older men on episodic memory (a domain affected in early stages of AD; Asperholm et al., 2019; Herlitz and Rehnman, 2008; Jack et al., 2015), and have lower age-related declines in brain volume than men (Jack et al., 2015; Pfefferbaum et al., 2013). Again, these suggest that some women have greater resistance to AD than men. More direct support of women's elevated resistance comes from studies observing better performance in women than men on a delayed verbal memory task (Rey Auditory Verbal Learning Test) despite having similar hippocampal atrophy,

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glucose hypometabolism, and β -amyloid accumulation (Sundermann et al., 2016a, 2016b, 2018). This clearly demonstrates that women are able to maintain verbal memory across the lifespan better than men indicating greater resistance to AD. Interestingly, in this series of studies, the men had significantly higher education level than women, suggesting that education may not confer as strong resistance in men as women, as per studies presented earlier (Koran et al., 2017; Launer et al., 1999; Letenneur et al., 2000; Oliveira et al., 2016).

This subgroup of women who are able to resist AD diagnosis until older age (>80yrs) has sometimes been attributed to sex differences in longevity and differential mortality (e.g., Brayne et al., 1995), but it may not be as simple as that. First, the effect is observed in studies that account for sex differences in longevity by adjusting for age in their models (Andersen et al., 1999; Corrada et al., 2008; Ott et al., 1998; Ruitenberg et al., 2001). In addition, although there is a tendency for women to live longer, in many of these studies, there were no sex differences in the participants who were ultimately excluded due to loss of interest or death (Andersen et al., 1999; Corrada et al., 2008; Ruitenberg et al., 2001), meaning there was no longevity bias favouring women.

As noted, many of the contributors to reserve are highly gendered, including education, occupation, physical activity, and social support. The majority of participants in studies on AD were born in the early- to mid-1900s, when, because of gender norms, reserve factors such as education, occupation, and physical activity were pursued by men, but not women. For example, in this review, most cohorts included women and men whose formative years would have been ~1915-1955, generations in which men had higher education than women (Letenneur et al., 2000, 1999; Malpetti et al., 2017; Sundermann et al., 2016b). It would have also been a time when men who were working would have had jobs with higher occupational complexity compared to the jobs of women (Mielke et al., 2014). Critically, modernization has affected many of these gendered factors to potentially allow for greater reserve accumulation in the next generation of aging women. Education has steadily increased for women in many societies over the past 25 years, and currently more women obtain a four-year university degree than men in both the United States (Duffin, 2019) and Canada (Statistics Canada, 2015). This increase in women's education, and thus occupational attainment, should theoretically increase women's accumulation of reserve, and contribute to the decreased magnitude of the sex difference in AD observed in some American studies (Mielke et al., 2014). Therefore, it is important to incorporate such characteristic differences in generations, including changes in economic, political, environmental, and social landscapes that may impact our understanding of sex differences in cognitive

reserve. For example, measuring social progress indicators and/or living conditions may be relevant to incorporate in analyses of sex differences in cognitive reserve (Asperholm et al., 2019).

However, although women have been engaging in more reserve contributors as societies modernize, some gender-typical roles still fall under the responsibility of women to a greater extent than men. For example, women make up 2/3 of caregivers for individuals with AD (Association, 2019). In addition, caregivers for those with dementia are more likely to develop dementia themselves (Norton et al., 2010), requiring that women have yet more reserve to offset this risk. In fulfilling caregiving responsibilities, women are more likely to report negative symptoms of loneliness than caregiving men (Beeson et al., 2000). Coupled with women's susceptibility to depression (Liming Alspaugh et al., 1999; Rose-Rego et al., 1998; Russo et al., 1995; Schulz et al., 1992), this could worsen general health and increase the risk of developing AD for women, perhaps beyond what reserve can mitigate. This could potentially contribute to the subset of women at risk for AD in early, older adulthood.

Further supporting gender norms, many of the contributors to reserve underplay the complexity of tasks involved in more female-typical occupations, such as farm wife. For example, "farm wife" may not adequately capture the complexity of managing the finances and resource planning for the farm, socializing with family members, caregiving for children and elderly parents, and managing daily household tasks. Thus, what might be considered low occupational attainment and hence, complexity, may actually be relatively complex and contribute to accumulation of reserve capacity. In fact, being a farmer contributed to reserve in both women and men (Santabarbara et al., 2019). Thus, to prevent gender bias while investigating reserve, future work should seek to consider less gendered measures of reserve to better capture women's ability to resist AD.

When women do engage in many of these reserve factors, it benefits them substantially, sometimes more than they benefit men. Selective survival may be occurring in this subset of women who engage in reserve factors that increase resistance in women more than men. Although our review did not find studies that considered sex differences in all of the reserve factors considered, studies do demonstrate the importance of education (Letteneur et al., 2000, Oliviera et al., 2016, Koran et al., 2017, Launer et al., 1999), bilingualism (Subramaniapillai et al., 2018), and physical activity (Baker et al., 2010; Barha et al., 2017; Colcombe and Kramer, 2003; Van Uffelen et al., 2008) to women's resistance to age-related cognitive decline.

Importantly, this review reveals that cognitive tasks with known sex differences in performance (visuospatial tasks in men; verbal tasks in women) tend to mark resistance/resilience in the sex they favour.

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Since many of the tasks used to assess memory have a verbal component, on which women typically perform better, they may favour resistance in women. Thus, it is critical that future work consider this differential effect of resistance in women and men based on the specific cognitive task employed and whether women or men may be already advantaged in the faculties that the task assesses. For example, IQ is often assessed by measuring a participant's verbal ability, as per Beinhoff (2009) that assessed IQ via a German vocabulary test (Beinhoff et al., 2009). One might expect that since this requires verbal ability, the test would favor women in that they would perform as well as men with more cognitive reserve. And, indeed, the authors found no sex differences in the effect of IQ on verbal memory. Further, they found that low IQ men outperformed women on visuospatial episodic memory. Thus, future psychometric measures that aim to capture contributors to reserve should consider using non-verbal tasks to assess reserve or using verbal ability/memory as a covariate of interest (Sundermann et al., 2019).

In sum, our review of the literature on sex/gender differences in cognitive reserve in AD reveals that a) the literature is very sparse and b) when analyses are stratified by sex they reveal opportunities for women to increase reserve capacity, possibly reducing their risk for AD. Historically these opportunities have been hampered by social norms of gender, but represent an opportunity for interventions which might reduce sex differences in the rate of AD if women engage with these reserve contributors. This review also highlights the need to look at intersections between different reserve contributors, and their interactions with health moderators, since these can have multiplicative effects. It is critical to understand what contributes to the increased resistance to AD observed in a subset of women, including better understanding of sex differences in cognitive reserve, to maximize healthy aging in women and men.

Conclusions

Given the sparsity of the extant publications on sex differences in reserve in AD, it is important that future research consider both sex and gender in reserve through appropriate analyses. They should report whether or not such analyses were conducted and, even null findings. Sex stratified analyses and gender considerations are critical not only to reveal different AD-related mechanisms in women and men, but also in finding the most efficacious interventions for each sex. In addition to widening the types of activities viewed as contributors to cognitive reserve, it is critical to begin to integrate and welcome into research participants with a diversity of backgrounds including, sexual and gender identities as well as ethnicities and social positions. Wider inclusion of diverse peoples will increase our understanding of the key components

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contributing to cognitive reserve for each group. Integrating sex and gender in our investigations of cognitive reserve, resistance, and resilience to AD could better inform health interventions and social policies that aim to reduce the burden of AD among women and men.

Declarations of interest: None

Acknowledgements:

This work was supported by the Wilfred and Joyce Posluns Chair in Women's Brain Health and Aging (the Women's Brain Health Initiative, Ontario Brain Institute, and the Canadian Institutes of Health Research, awarded to G. Einstein); the Canadian Institute of Health Sciences Project grant PJT 153321 and the Natural Science and Engineering Research Council RGPIN-2018-05761 (awarded to M. N. Rajah); the Alzheimer's Society Postdoctoral Fellowship for the Posluns Chair (awarded to A. Almey); and the Natural Science and Engineering Research Council Graham Bell Canada Graduate Scholarship-Doctoral (awarded to S. Subramaniapillai).

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Tables and Figures

Table 1. Sex differences in risk factors for Alzheimer's disease

Risk Factor	Sex Prevalence Findings	Age	References
Age	<ol style="list-style-type: none"> W>M: Even after controlling for longevity the rate of AD is higher in women. The risk for AD doubles approximately every 5 years after the age of 65 years. 	OA (>65yrs)	<ol style="list-style-type: none"> Alzheimer's Association, 2019. Buckley et al., 2019; Prince et al., 2016.
Biological Sex	<ol style="list-style-type: none"> W>M: Females are at greater risk of developing AD than men. 	OA (>75yrs)	<ol style="list-style-type: none"> Chêne et al., 2015; Bailly et al., 2019; Einstein, 1999.
Family History of AD	<ol style="list-style-type: none"> In offspring with 2 AD parents 20% risk of AD at 70yrs and 60% risk of AD at 80yrs. W>M: Women with first degree relative with AD have greater AD risk. M>W: When more distant relatives included men have greater AD risk. 	OA (>65yrs)	<ol style="list-style-type: none"> Jayadev et al., 2008 Green et al. 2002 Cannon-Albright et al. 2019
Genetic Risk: APOE4	<ol style="list-style-type: none"> APOE4 allele is the strongest genetic predictor for late onset AD. W>M: Pro- and retro- spective studies show higher AD in female APOE4 carriers. W>M: Female APOE4 carriers have greater accumulation of neurofibrillary tangles (tau). W>M: Female APOE4 carriers have greater accumulation of senile plaques (amyloid). 	<ol style="list-style-type: none"> OA (>65yrs) OA (~75yrs) OA (>70yrs) MA+OA, greatest plaque accumulation 55-65yrs. 	<ol style="list-style-type: none"> Harold et al., 2009 Altman et al., 2014 Damoiseaux et al., 2012; Hohman et al., 2018 Corder et al., 2004.
Inflammation	<ol style="list-style-type: none"> Elevated inflammation increases the risk of AD, and extended use of anti-inflammatories reduces AD risk. W>M: Higher prevalence of autoimmune disorders in women (i.e. multiple sclerosis) suggesting elevated immune activation. W>M: Type II Diabetes: earlier onset in males BUT W>M once diagnosed - greater cardiovascular decline in women. 	<ol style="list-style-type: none"> MA+OA YA (~20yrs) MA+OA 	<ol style="list-style-type: none"> Reviewed in McGeer et al., 2016 Bupp et al., 2018 Cho et al., 2018; Kalyani et al., 2014; Kautzky-Willer et al., 2017

Abbreviations: AD=Alzheimer's disease; APOE4=apolipoprotein allele 4; M>W = men more affected than women; MA=middle adulthood; OA=older adulthood; W>M = women more affected than men; W=M no difference; YA=young adulthood.

Note: Articles in the table are not an exhaustive review, but instead represent a selection of research and reviews over the past 20 years.

Table 2. Women's reproductive risk factors for Alzheimer's disease

Female hormone contribution to AD	Participants	Comments	Reference(s)
Parturition and Alzheimer's Risk/Pathology			
<ul style="list-style-type: none"> 1-2 pregnancies = 1.8x increase risk for AD 3 pregnancies = 3.2x increased risk for AD > 3 pregnancies = AD 4yrs earlier 	Total n = 405 (women) AD n = 204, avg 75yrs Controls n = 201, avg 74yrs	<ul style="list-style-type: none"> Statistics did not covary for group differences. HT use reduced risk for AD 	Colucci et al., 2006
<ul style="list-style-type: none"> ≥5 completed pregnancies increase AD 1.7x (Li et al.) ≥2 completed pregnancies worse MMSE (Jang et al.) ≥1 incomplete pregnancy reduced AD risk by half (Li et al.), better performance on MMSE (Jang et al.) 	Total n = 2 737 (women, avg 73yrs – Li et al.) Total n = 3 499 (women, avg 72yrs – Jang et al.)	<ul style="list-style-type: none"> Oral contraceptive and IUD use protect against cognitive impairment (Li et al., 2016) 	Jang et al., 2018 Li et al., 2016
<ul style="list-style-type: none"> Women: # offspring associated with higher total AD pathology and plaques (entorhinal + amygdala) Men: # offspring unrelated to AD pathology 	Total n = 73 Women n = 42 Men n = 31	<ul style="list-style-type: none"> Total AD pathology via plaque and tangle count in multiple ROIs 	Beeri et al., 2009
<ul style="list-style-type: none"> # pregnancies and younger age at menopause associated with decline on MMSE over 12.8yrs 	Total n = 316 (women, avg 64yrs) Menopausal at 3 rd visit	<ul style="list-style-type: none"> Covary for age, education, oral contraceptive, and others 	McLay et al., 2003
<ul style="list-style-type: none"> More months breast feeding = reduced AD risk Larger ratio of months breastfeeding to months pregnant associated with reduced risk of AD First child <21yrs increases risk for AD 	Total n = 81 (>75yrs) Total AD n = 40	<ul style="list-style-type: none"> Breastfeeding counteracts multiparity effect on risk of AD 	Fox et al., 2013b
Spontaneous/Surgical Menopause and Alzheimer's Risk/Pathology			
<ul style="list-style-type: none"> Dementia 2x higher if surgical menopause ≤45yrs Risk higher if younger at surgery (<38yrs) ET post-surgery eliminates increase in dementia risk 	Total surgical meno. n = 1 472; AD n = 150 Total control n = 1 489, AD n = 98	<ul style="list-style-type: none"> Mixed uni- and bi- lateral ovary removal and hysterectomy 	Rocca et al., 2007
<ul style="list-style-type: none"> Surgical menopause: faster decline in episodic and semantic memory, elevated AD pathology HT use within 5yrs of surgery protective Trend toward positive associations: <ul style="list-style-type: none"> a) surgical menopause + AD b) spontaneous menopause age + memory 	Total n = 1884 (women, avg 78yrs at study end) Followed for 18yrs ~1/3 surgical menopause	<ul style="list-style-type: none"> HT = systemic or local estrogen and/or progestin 	Bove et al., 2014
<ul style="list-style-type: none"> Verbal memory decline more in post vs. men Hippocampal and frontal metabolism decline more in peri and post vs. pre and men More β-amyloid accumulation in frontal cortex of peri and post vs. pre and men 	Pre, peri, post menopausal and men (47, 53, 58, 52yrs, respectively) n = ~15 per group Tested 3yrs apart	<ul style="list-style-type: none"> Exclude for surgical menopause, ET, and cancer history. Controlled for age and APOE4 	Mosconi et al., 2018
<ul style="list-style-type: none"> Each month ovarian hormone exposure (menarche-menopause) reduced risk of AD by 0.5% Trend for # menstrual cycles reducing risk for AD 	Total n = 89 (women, 70-100yrs) AD n = 38 Control n = 51	<ul style="list-style-type: none"> Menarche/menopause age, and oral contraceptives not related to risk for AD 	Fox et al., 2013a
Estrogen Therapy and Alzheimer's Risk/Pathology			
<ul style="list-style-type: none"> Risk of AD lower if with ET post-menopause Unrelated to duration of ET or age at menopause 	Total n = 514 (women, avg. 78yrs at study end) ET for ≥1yr n = 231 Control n = 283	<ul style="list-style-type: none"> ET = conjugated equine estrogens or estradiol Mix spontaneous and surgical 	Kawas et al., 1997
<ul style="list-style-type: none"> ET reduced risk of AD AD incidence 5yrs: 2.7% ET, 8.4% non-ET 	Total n = 1124 (women, avg 74yrs) ET n = 156, avg 73yrs	<ul style="list-style-type: none"> ET primarily conjugated equine estrogens Mix spontaneous and surgical menopause 	Tang et al., 1996

Abbreviations: AD=Alzheimer's disease; APOE4=apolipoprotein allele 4; ET= systemic estrogen therapy; HT=hormone therapy of any type; MMSE=Mini-Mental State Exam

Note: Articles in the table are not an exhaustive review, but instead represent a selection of research over the past 25 years.

Table 3. Sex differences in general health moderators that contribute to risk of Alzheimer's disease

General Health Factor	Sex Prevalence Findings	Age	References
Mental Health: Depression Anxiety Stress	<ol style="list-style-type: none"> W>M: Depression more common in women. W>M: Anxiety disorders more common in women. W>M: Elevated psychosocial stress in women contributes to depression/anxiety. 	Begins at YA, persists through MA and OA	<ol style="list-style-type: none"> Reviewed in Kessler et al., 2005 McLean et al., 2011, reviewed in Kessler et al., 2005 Bangasser & Wiersielis, 2018
Cardiovascular Health: Blood Pressure	<ol style="list-style-type: none"> M>W: Higher blood pressure at middle age. W>M: Higher blood pressure post-menopause; shift in cardiovascular risk. 	MA, OA	<ol style="list-style-type: none"> Yanes & Reckelhoff, 2011 Miller et al., 1995; Reckelhoff, 2001
Obesity	<ol style="list-style-type: none"> W>M: Globally, women more overweight and obese than men. 	YA, MA, OA	<ol style="list-style-type: none"> Lovejoy et al., 2009; https://www.worldobesity.org/
Smoking	<ol style="list-style-type: none"> M>W: Men use more tobacco products. W>M: Smoking is a stronger risk factor for coronary heart disease in women. 	YA, MA, OA	<ol style="list-style-type: none"> https://www.drugabuse.gov/publications/research-reports/tobacco-nicotine-e-cigarettes/are-there-gender-differences-in-tobacco-smoking Njølstad et al., 1996
Cardiovascular Disease	<p>Coronary artery disease: M>W in absence of diabetes M=W in presence of diabetes</p> <p>Cardiovascular Disease: W>M - lifetime risk after 40yrs</p> <p>Stroke: W>M - after 20yrs</p> <p>Heart failure: M>W - after 20yrs</p> <p>Coronary Heart Disease: M > F - after 20yrs</p>	YA, MA, OA	Kalyani et al., 2014; Mosca et al., 2011
Sleep	<ol style="list-style-type: none"> W>M: Insomnia more common in women. W>M: Poorer self-reported sleep quality. W>M: More sleep disorders in women during puberty, pregnancy, menopause. 	YA, MA, OA	<ol style="list-style-type: none"> Zhang et al., 2006 Mallampalli et al., 2014 Mallampalli et al., 2014; Lee & Kryger, 2008; Nicholl, Almey, & Gervais, 2020

Abbreviations: M>W = men more affected than women; MA=middle adulthood; OA=older adulthood; W>M = women more affected than men; W=M no difference; YA=young adulthood.

Note: Articles in the table are not an exhaustive review, but instead represent a selection of research over the past 25 years.

Figure 1. Theoretical depiction of how accumulation of reserve may affect the onset and progression of cognitive decline and diagnosis with mild cognitive impairment/Alzheimer's disease. Resistance is greater in individuals with greater reserve accumulation, reflected in a later point of inflection. Resilience is hypothesized to be lower in individuals who resist cognitive decline for longer, reflected in steeper decline in memory performance after the point of inflection (reproduced with permission from Stern, 2009).

Figure 2. PRISMA flow diagram depicting the selection of papers for this review.

Table 4. Sex Differences in contributors to cognitive reserve

Sex Differences in Reserve Contributors	Study Size	Age	Demographics	Reference
Education				
Reserve capacity: F = M <ul style="list-style-type: none"> No Sex*Education interaction on AD risk 	Total n = 2881 AD n = 140 (women n = 98, men n = 42)	> 65yrs	PAQUID Cohort: random selection from electoral rolls in south-west France	Letenneur et al., 1999
Reserve capacity: F > M <ul style="list-style-type: none"> Women: low/moderate education increased risk of AD risk compared to high education. Men: Education did not affect risk of AD 	Total n = 12 954 AD n = 328 (women n = 233, men n = 95)	> 65yrs	EURODEM cohort: selection from Odense (Denmark), PAQUID (France), Rotterdam (Holland), MRC-ALPHA (United Kingdom)	Letenneur et al., 2000
Reserve capacity: M = F <ul style="list-style-type: none"> Education negatively correlated with hypometabolism: <ul style="list-style-type: none"> Women: frontal + med. temporal Men: lat. temporal, parietal, occipital Occupational negatively correlated with hypometabolism: <ul style="list-style-type: none"> Women: inferior temporal cortex Men: precuneus, cingulate, lat. temporal, parietal 	AD n = 282 (women n = 159, men n = 123) Control n = 225 (women n = 110, men n = 115)	> 60yrs	ADNI cohort (United States), NEST-DD cohort (mixed European), and Nuclear Medicine Database (Milan, Italy)	Malpetti et al., 2017
Reserve capacity: M= F <ul style="list-style-type: none"> Education associated with higher MMSE in both men and women 	Total n = 39 451 (women n = 25 643, men n = 13 808)	> 60yrs	BNA cohort: longitudinal database recruiting from memory clinics in France	Pradier et al., 2014
Reserve capacity: F > M <ul style="list-style-type: none"> Education(yrs) negatively correlated with time for MMSE decline in women but not men (no APOE4) Education(yrs) negatively correlated with time for Clinical Dementia Rating decline in women but not men (APOE4) 	AD n = 214 (women n = 146, men n = 68).	> 60yrs	AD patients at Behavioral Neurology Section of Hospital Sao Paulo. Followed up over 44 months	Oliveira et al., 2016
Reserve capacity: W=M <ul style="list-style-type: none"> Education (elementary vs. secondary/university) did not affect risk of AD in women or men AD combined with vascular dementia: <ul style="list-style-type: none"> Women: secondary/university had reduced risk of dementia compared to elementary Men no effect of education on risk of dementia 	Total n = 2368. AD n = 116 (women = 98, men = 18) Dementia n = 216 (women = 177, men = 39)	> 75yrs	Recruited from Kungsholmen parish in Sweden from 1987-88	Fratiglioni et al., 1991
Reserve capacity: W>M <ul style="list-style-type: none"> Women: β-amyloid predicted worse executive function at follow-up compared to men Sex difference most pronounced among individuals with low education 	Total n = 1098. AD n = 185 (women n = 85, men n = 100)	Avg: 74yrs	ADNI cohort: selected if cognitive data and CSF for β -amyloid and Tau	Koran et al., 2017

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Reserve capacity: W>M <ul style="list-style-type: none"> Less education (yrs) increased risk of AD risk in women but not in men. <ul style="list-style-type: none"> Women: <8yrs education, relative risk AD 4.55 Men: <8yrs education, relative risk AD 1 .00 	Total n = 28 768 (women n = 16 498, men n = 12 270) AD n = 352 (women n = 256, men n = 96)	>65yrs	EURODERM cohort: those who developed AD at follow-up (see above for cohort details)	Launer et al., 1999
IQ				
Reserve capacity: M>W <ul style="list-style-type: none"> Low IQ women performed worse than men on delayed visuospatial task despite similar CSF tau Women: low IQ performed worse high IQ Men: IQ did not affect performance 	AD n = 68 male low IQ (n = 20), male high IQ (n = 18), female low IQ (n = 15) female high IQ (n = 15).	Avg: 69.5yrs	Dementia clinics at hospitals in Berlin and Ulm, Germany Post-AD IQ: low>100, high <100	Beinhoff et al., 2009
Reserve capacity: M=W <ul style="list-style-type: none"> Lower high school IQ and academic achievement increased odds ratio for AD in older adulthood Odds identical in men and women 	Total women n = 42 749 AD women n = 1416 Total men n = 43 014 AD men n = 1238	>65yrs	Project Talent cohort: 1960 high school IQ, data linked to medicare in 2016 for AD diagnoses	Huang et al., 2018
Occupational Complexity				
Reserve capacity: M=W <ul style="list-style-type: none"> Women: lower probability AD among farmers than homemakers Men: lower probability AD among farmers and white-collar jobs than other occupations 	Total: women n = 2161, men n = 1722 AD: women n = 90, men = 38	>55yrs	Sample from 1991 census (Zaragoza, Spain) Longitudinal 4-wave study (1994-2006)	Santabàrbara et al., 2019
Reserve capacity: M=W <ul style="list-style-type: none"> Women: manual work involving goods production associated with greater risk of AD Men: no association between general or goods production manual work and risk of AD 	Total n = 913 AD at 6yr follow-up: Women n = 166 Men = n = 31	>75yrs	Recruited from Kungsholmen, Sweden Longitudinal: 2-wave study (1987-1996)	Qiu et al., 2003
Reserve capacity: M=W <ul style="list-style-type: none"> Occupation categories didn't modify risk of AD until sex stratified <ul style="list-style-type: none"> Women: being a craftsman/ shopkeeper was AD protective Men: being a craftsman/ shopkeeper increased AD risk 	Total n = 2950 baseline Total AD n = 251 (Sex differences in AD # not specified) Craftsmen/shopkeeper n = 499 (11.3%W; 16.7%M)	>65yrs	Recruited from Gironde/Dordogne, France Longitudinal 10-year follow-up (1988- 1997)	Helmer et al., 2001

Abbreviations: AD=Alzheimer's disease; APOE4=apolipoprotein allele 4; M>W = men more affected than women; MA=middle adulthood; OA=older adulthood; W>M = women more affected than men; W=M no difference; YA=young adulthood.

Note: Articles in the table met the search criteria for our narrative review.