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"A Biological Determinant in the Pathophysiology and Pharmacology of Neurovascular and Neurodegenerative Diseases: Sex"

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ABSTRACT:

As our population ages, dementia is becoming more widespread. Cerebrovascular and neurodegenerative illnesses are the main causes of dementia. More than 80% of instances of dementia are caused by vascular cognitive impairment (VCI) and Alzheimer disease (AD). For AD and disorders connected to VCI, such as stroke and cerebral amyloid angiopathy (CAA), there aren't many long-term, effective treatments available. This study focuses on three main types of dementia: stroke, which is the most prevalent cause of "vascular" dementia, AD, which is the most common "neurodegenerative" cause of dementia, and CAA, which is a "emerging" cause of dementia. We will go over the literature that is currently accessible on pharmaceutical therapies that show sex differences. By sex differences, we mean any combination of hormonal, chromosomal, gonadal, or anatomical differences that exist between males and females. We will stress how crucial it is to view sex as a biological factor in the planning of preclinical and clinical research on dementia that looks into underlying pathologies or the way the disease responds to medication.

Abbreviations: AD, Alzheimer disease; ADAS-Cog11, Alzheimer's Disease Assessment Scale- Cognitive Subscale; ADNI, Alzheimer's Disease Neuroimaging Initiative; APOE ε4, ε4 allele of the apolipoprotein E; Aβ, amyloid-β; CAA, cerebral amyloid angiopathy; ChEIs, cholinesterase inhibitors; CI, confidence interval; CIMT, carotid intimal-medial thickness; CVD, cardiovascular disease; HMG-CoA, 3-hydroxy-3-methyl-glutaryl-CoA; ICH, intracerebral haemorrhage; MCI, mild cognitive impairment; MHT, menopausal hormone therapy; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; OR, odds ratio; PD, Parkinson disease; UA, uric acid; VaD, vascular dementia; VCI, vascular cognitive impairment.

1. Introduction

As our population ages, the incidence of neurodegenerative and cerebrovascular illnesses keeps rising. One of the most common aging conditions and a significant factor in the expense of healthcare in the US is dementia. Alzheimer's disease (AD) and vascular dementia (VaD) account for roughly 60% and 20% of all dementia cases worldwide, respectively, despite the fact that the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition lists a long list of "Neurocognitive disorders" that can cause dementia (Rizzi, Rosset, & Roriz-Cruz, 2014). This review will concentrate on stroke as the most prevalent cause of "vascular" dementia, AD as the most common "non-vascular" cause of dementia, and cerebral amyloid angiopathy (CAA) as a "emerging" cause of dementia that links AD and stroke. We will also talk about The complexity of the data stems from the fact that all screening techniques and scales used to evaluate dementia severity and response to pharmaceutical treatments rely heavily on secondary data gathered from patients, family members, or caregivers. Over time, a lot of assessment scales have been improved to reduce subjectivity and increase objectivity. After a brief discussion of a few widely used evaluation instruments, the sections on sex differences in dementia generated by AD, CAA, and stroke and the pharmacology of these conditions are presented.

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COMMON DEMENTIA CAUSES

Mixed dementia refers to the majority of dementia patients who exhibit characteristics of both neurodegeneration and cerebrovascular illness, which exacerbates their cognitive impairment (Bennett, 2001). Due to similarities in their pathogenesis, risk factors, and clinical presentations, AD and VaD can be challenging to differentiate. It is rare for a focused stroke to be the exclusive cause of dementia. Hachinski et al.'s seminal study from 1975 categorizes cognitive deterioration due to vascular events as more sudden, gradual, variable, and linked to cerebrovascular risk factors and specific neurological deficit. The term "vascular cognitive impairment" (VCI), which describes how cerebrovascular dysfunction contributes to cognitive impairment, is relatively new in the area. The set of circumstances that result in VCI is diverse and dynamic. Recent thorough analyses of Conditions linked to VCI can be found in the literature (van der Flier et al., 2018).Dementia can result from a number of disorders than AD and VaD. The epidemiology of the majority of these illnesses shows a marked deficiency in reporting tailored to a person's gender. Crucially, the majority of illnesses for which sex-specific epidemiological data are available have sex variations. In a study involving 296 PD patients of all ages, it was discovered that the proportion of men having PD-related dementia was twice that of women (0.10 vs. 0.05 when percentage prevalence was computed; Savica, Grossardt, Rocca, & Bower, 2018). There are no differences in prevalence between the sexes for Huntington's disease, a CAG triplet repeat pathology with an autosomal dominant inheritance (Ghosh & Tabrizi, 2018). Fascinatingly, The amount of the inherited CAG repeat appears to be influenced by the parent's sex, according to mechanistic investigations of triplet repeat expansion and contraction in the etiology of Huntington's disease. According to one study, paternal transmission accounts for practically all substantial expansions (>7 CAG repeats greater than the parent's gene; $P \leq 10-7$), but children of afflicted mothers are more likely to exhibit neither a change in CAG size ($P \leq .01$) nor a contraction ($P \leq .002$; Kremer et al., 1995). Geographical location has an impact on the reports of frontotemporal dementia. For example, in Cambridgeshire, UK, there is a 14:3 ratio for males to females with frontotemporal dementia, whereas in Italy, there is a 1:3 ratio (Onyike & Diehl-Schmid, 2013). Patients with underlying dementias also exhibit gender disparities. endocrine disorders. Higher TSH levels were associated with a lower incidence of thyroid-related dementia (hazard ratio [HR] of 0.67, 95% confidence interval [CI] [0.54, 0.82]; Chaker et al., 2016). Women with poorer cognitive Z scores had higher levels of parathyroid hormone among dementia patients ($P \leq .05$; Kim et al., 2017). Sex-specific epidemiological reporting for dementia patients with normal-pressure hydrocephalus or underlying CNS vasculitis is not easily accessible.

COMMONLY USED SEVERITY SCALES IN DEMENTIA

Subscale 11 of the Cognitive Assessment of Alzheimer's Disease

In moderate cognitive impairment (MCI) and Alzheimer's disease (AD) trials, the 70-point Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog 11) is frequently used to measure the severity of cognitive impairment. Eleven activities make up the ADAS-Cog, which measures orientation, language production and comprehension, constructional and ideational praxis, and learning and memory. Given that the score is determined by the quantity of errors, higher scores correspond to lower performance (Hua et al., 2010). The ADAS-Cog test has a limited clinical relevance due to its 40-minute duration when administered by a skilled interviewer; yet, it is still the most used evaluation tool in dementia medication studies. A 2018 study looked at how sex affects changes in cognition Using the Alzheimer's Disease Neuroimaging Initiative (ADNI) database, researchers found that among AD patients, females experienced a considerably higher mean worsening in their ADAS-Cog11 score than did males (Sohn et al., 2018).

SEX DIFFERENCES IN THE MOST COMMON DEMENTIA PATHOLOGIES

An overview of stroke, AD, and CAA Neurofibrillary tangles, or AD, are caused by the insoluble microtubule-associated protein Tau forming intracellular filamentous aggregations and extracellular aggregations of amyloid-β (Aβ) stacks of pleated β-sheets (also known as "plaques"). The pathology of CAA, an emerging dementia cause, has been connected to stroke and AD. Because abnormal Aβ accumulations underlie both AD and CAA disorders, their pathophysiology's are identical. While Aβ preferentially deposits into the cerebral vasculature's basement membrane in CAA, leading to recurrent hemorrhagic stroke, it primarily accumulates in the brain parenchyma in AD. CAA causes white matter injury, cortical microhemorrhages,

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and lobar intracerebral hemorrhages (ICH), which in turn cause gradual cognitive decline and dementia in the senior citizens. Stroke is a primary global cause of death as well as a significant contributor to permanent disability. When a blood supply to a particular vascular region is cut off, stroke occurs. This causes rapid death of neurons, parenchymal damage, and a variety of other neurological issues, including dementia.

Unfortunately, acute reperfusion therapy (endovascular or intravenous thrombolytic therapies) is the only treatment available for stroke, leaving many stroke patients without any chance of recovery at all. There are also few effective treatments for AD or CAA. Men and women suffering from these incapacitating illnesses differ, according to epidemiological studies (Bushnell et al., 2018). Thus, comprehending the function of sex as a biological variable is essential for the creation of innovative pharmaceutical treatments for the management of dementia brought on by AD, CAA, stroke or other disorders involving the circulation. We will discuss the evidence that suggests sex differences exist in the most common diseases that cause dementia and how those disorders respond to current treatments within the parameters of this review. We will highlight the significant—and frequently fixable—factors that still have a detrimental effect on our present understanding of how sex-dependent patients respond to these medicines.

Disparities in the epidemiology of AD by sex Although women are disproportionately afflicted by AD—3.3 million out of 5.2 million people with AD in the United States who are 65 years of age or older are women—men may have a higher risk of MCI. (Hebert et al., 2013). The incidence data analyzing disparities between men and women continue to be somewhat inconsistent, but the epidemiological data are consistent with a higher prevalence of AD in women. Most research indicates that the incidence of dementia in people between the ages of 70 and 79 is comparable in men and women. However, incidence rates are higher in women than in men after the age of 80, which is likely due to sociocultural detection biases and the longer life expectancy observed in women (Roberts et al., 2014). To clarify these epidemiological variations, data has surfaced about the variation in clinical presentation among dementia patients as a result of social exclusion, financial standing, healthcare accessibility, and various other gender-specific variables (refer to Section 6). But the most recent analysis of the body of data indicates that sex plays a significant role in the dimorphic pace of progression to AD in both men and women, in addition to gender-related variables (Lin et al., 2015). These results imply that age and sex, two independent but connected biological variables in AD pathogenesis, interact.

Variations in the epidemiology of stroke by gender Stroke disproportionately affects women and is a major cause of morbidity and mortality worldwide. Older women are disproportionately affected by stroke-related disability; over 500,000 more women than males have survived strokes in the United States to date. According to Writing Group Members et al. (2016), stroke is now the fifth most common cause of death for males in the US, while it still ranks third for women. Today, there are 3 million men and over 3.8 million women in the US who have survived a stroke (Writing Group Members et al., 2016). As our society ages, these numbers are predicted to rise, underscoring the critical need for a deeper comprehension of sex-specific mechanisms that may result in stroke victims having access to efficient treatment alternatives.

Sex differences in VCI VCI is the second most common cause of dementia but most patients with “VaD” have a combination of other contributing factors such as AD (van der Flier et al., 2018). VCI classification is most often on the basis of prior history of stroke without neuroimaging evidence of cerebrovascular disease. The risk of post-stroke dementia has decreased over the past four decades, most likely because of improved treatment of acute stroke and better management of vascular risk factors (Satizabal et al., 2016). The classification of VCI on the basis of prior stroke may inflate the reported estimates of the vascular contribution to dementia. On the other hand, if individuals with mixed dementia and individuals with white matter hyperintensities on MRI are included under the VCI classification, then vascular conditions contribute to a higher percentage of overall dementia cases (Toledo et al., 2013). Specific diagnostic criteria for VCI and improved characterization of vascular contribution to dementia are continually updated (van der Flier et al., 2018).

A meta-analysis of European studies found that sex differences in prevalence of VaD reversed their trend with advanced age such that VaD was more prevalent in men before age 79, but more prevalent in women after age 85 (Lobo et al., 2000). This finding suggests that caution should be taken when interpreting the prevalence data due to possible survival bias and sex-

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and gender-specific vascular risk factors that may explain epidemiological sexual dimorphisms. Reviews of sex differences in vascular risk factors with potential contribution to VCI are available (Gannon, Robison, Custozzo, & Zuloaga, 2018).To date, few pathological studies have addressed sex difference in AD and contribution of cerebrovascular disease to dementia. This may seem contradictory, as there are clear sex-specific, age-related increases in incidence of cerebrovascular disease, most commonly stroke. Women are disproportionally affected by stroke at older ages and are significantly more likely to suffer from cognitive decline following stroke (Bushnell et al., 2014). This observation may be confounded by age or the higher rate of large cardioembolic strokes seen in females, secondary to atrial fibrillation than males with this condition (Rienstra, McManus, & Benjamin, 2012).Post-mortem examination of 1,453 persons who participated in either the Religious Orders Study or the Rush Memory and Aging Project showed that women had higher levels on a global measure of AD pathology ($P < .001$), Tau tangle density ($P < .001$), and Aβ load ($P \leq .056$; Oveisgharan et al., 2018). Compared to men, women included in this study had more severe arteriosclerosis (odds ratio [OR] = 1.28, 95% CI [1.04, 1.58], $P \leq .018$) but were less likely to have gross infarcts (OR = 0.78, 95% CI [0.61, 0.98], $P < .037$; Oveisgharan et al., 2018). In addition to potential confounders, uncertainties over diagnostic criteria for VCI and lack of generally accepted protocols for post-partum neuropathological assessment of suspected VCI make data analysis even more challenging (Skrobot et al., 2016). With the advancement in non-invasive and minimally invasive techniques for clinical evaluation of patients with cerebrovascular disease, new assessment tools also emerge that can facilitate future studies of sex differences in VCI.

Carotid intimal-medial thickness (CIMT), vascular reactivity, and arterial stiffness are emerging as markers of arterial ageing and may serve as risk markers for VCI. Increasing evidence that assessment of white matter microstructure by diffusion-tensor imaging in patients with AD, CAA, and stroke may be able to differentiate between these diseases and controls, but to date, minimal studies have examined sex differences using these techniques (Auriel et al., 2014). Several clinical and neuro-radiological features have been linked to VCI including CAA, large vessel infarcts, lacunar infarcts, microinfarcts, myelin loss, arteriolosclerosis, and enlarged perivascular spaces, as recently summarized (Skrobot et al., 2016). Although to date, there is only negligible epidemiological data demonstrating sex differences in VCI, there are clear sex differences in many of the underlying processes that contribute to VaD including CAA and stroke, as discussed briefly below.

Sex differences in CAA

CAA is an increasingly recognized dementia subtype that has been linked to both AD and stroke. CAA pathogenesis is similar to AD in that Aβ protein plaque deposition is a central event. In CAA, the toxic Aβ preferentially deposits into the basement membrane of the cerebral vasculature. CAA-associated vasculopathy leads to lobar ICH, cortical microhaemorrhage, cortical superficial siderosis, and ischaemic change in the white matter. Recent advancements in neuroimaging-based diagnostic techniques such as gradient-echo T2 MRI and amyloid-binding PET ligands (e.g., Pittsburgh compound B, “PiB PET”) allow for detection of CAA pathology without a need for brain biopsy (Reijmer et al., 2015). To date, few studies have focused on sex differences in CAA. A population-based neuroimaging study using specified cut-off points for amyloid PET, Tau PET, and cortical thickness by MRI of individuals aged 50–89 years stratified participants into eight groups with respect to normal or abnormal levels of cerebral Aβ, Tau protein, and neurodegeneration. When examining sex differences, the group with the greatest proportion of men was normal-Aβ/normal-Tau/abnormal-neurodegeneration (57%, 95% CI [37, 77]) from age 65 to 75 years and the group with the greatest proportion of women was abnormal-Aβ/normal-Tau/normal-neurodegeneration (78%, 95% CI [64, 93]; Jack et al., 2017). However, the analysis showed that the overall effect of sex on the prevalence of all eight groups was small when using cortical thickness as a measure, but more pronounced when using adjusted hippocampal volume, suggesting that different sex-specific and age-specific pathological processes may contribute to overall prevalence of dementia. A recent study examining the roles of ε4 allele of the apolipoprotein E (APOE ε4) and sex on CAA among AD patients concluded that both factors differentially influenced the presence and severity of CAA in AD. An association of APOE ε4 carrier status with a higher overall CAA score was seen using an autopsy-based histological scoring of CAA severity in 428 confirmed AD cases, which was consistent with earlier studies in AD patients with APOE ε4 allele. However, the effect of sex on CAA pathology

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was not consistent with results seen in AD studies. After correcting for age, Braak neurofibrillary tangle stage, and Thal amyloid phase, the overall CAA scores were higher in males than in females (Shinohara et al., 2016). This suggests factors that contribute to sex differences in CAA may be different from those that contribute to sex differences in AD. In an observational study of 82 CAA-associated ICH patients, serum uric acid (UA) levels, an endogenous neuroprotective molecule involved in sex differences, were significantly lower in those with clinical diagnosis of "possible" CAA when compared to healthy controls. Furthermore, the serum UA levels of those diagnosed with "probable" CAA were significantly lower than those with "possible" CAA (Hu et al., 2014), suggesting that UA may be a molecular mediator in sex differences in CAA severity. Future studies that focus on sex differences may reveal new genetic, metabolic, or environmental risk factors that could aid in early detection or disease-modifying pharmacological interventions for CAA.

Sex differences in animal models of dementia Ageing wild-type mice do not develop AD, CAA, or most other age-related disorders seen in humans, thus transgenic mice models are often used in the laboratory. Sex differences have been reported in several animal models of dementia. The Tg-2576 transgenic model is one of the most widely used AD animal models expressing human APP695 containing the double mutation K670N/M671L under the control of hamster prion protein (Hsiao et al., 1996). This model develops cognitive impairment beginning around 8 months persisting up to 16 months. Preclinical studies of sex differences showed that female Tg-2576 mice develop a more prominent cognitive impairment (wrong choice total) compared to their male littermates at 12, 14, and 16 months. Furthermore, female Tg-2576 mice exhibit increased impairment on memory function testing, when compared to male mice with the same total amount of Aβ in prefrontal cortex. Some animal models of CAA also exhibit sexual dimorphism. For example, transgenic mice carrying human APOE ε4 allele and familial AD gene, known as EFAD mice, show excess of CAA in females by the age of 7 months, a pattern opposite to that of seen in humans with CAA (Finch & Shams, 2016). This observation of opposite pattern of sex differences between animal models and human data warrants careful evaluation of sex differences in animal models of CAA and AD prior to accepting them as "sufficiently accurate" for the purposes of preclinical studies and the basis for designing randomized clinical trials. Reviews of animal models of dementia and model-specific sex differences are available (Yang et al., 2018).

Potential explanations for gender variations in AD and stroke Recent findings point to the interaction of several biological variables as one of the processes underlying the pathophysiology and development of sex differences in AD. The most likely AD risk factors that interact with biological sex are (a) variations in chromosomal and gonadal hormones, (b) variations in neuro-inflammation, immunity, and microglia activation, (c) variations in brain structure, and (d) exposure to psychosocial stressors (see Figures 1 and 2). These findings were reported in a recent comprehensive review (Fisher, Bennett, & Dong, 2018). Aspects of sex differences in AD can be extrapolated to other causes of dementia, such as stroke and CAA, but not all of them. The sex differences in stroke are caused by (a) variations in gonadal and chromosomal hormones, (b) intrinsic modifications in the coagulation cascade (reviewed in Roy-O'Reilly & McCullough, 2014), (c) cellular mechanisms (reviewed in Chauhan, Moser, & McCullough, 2017), (e) other immunomodulatory pathways, and (f) innate immune cells and their response to ischemic injury. Figure 1 summarizes various sets of underlying mechanisms of sex differences in neurodegenerative and neurovascular diseases. Some, but not all, of these possible underlying processes of sex differences will be the subject of this review.

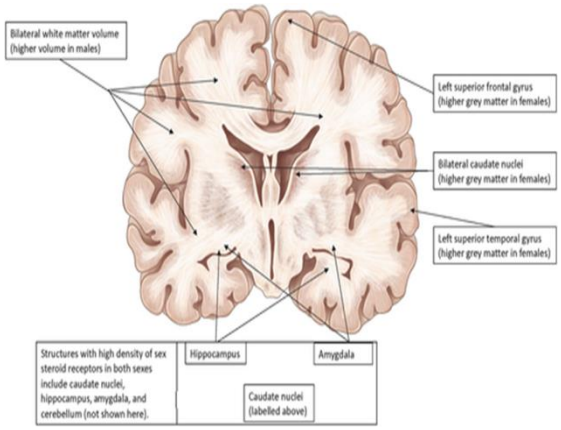

Figure :1 A diagram of a coronal view of the human brain, labelling those anatomical areas with sex differences. Females on average have a higher percentage of grey matter in the caudate nuclei, left superior temporal gyrus, and left superior frontal gyrus while in males, a more rapid increase in white matter volume is seen, which contributes to the overall 10% larger brain volume in men than in women. Areas with

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high density of sex steroid receptors in both sexes are the caudate nuclei, amygdala, hippocampus, and cerebellum.

Addiction risk and sex hormones

The impact of estrogen on the lifetime risk of Alzheimer's disease has been studied and reported in the media. The bulk of clinical studies to date have not been able to capture crucially important components of patients' reproductive histories, despite strong public interest and research evidence to support this claim. Oral contraceptive use, the number of pregnancies, the length of nursing, the regularity of menstrual cycles, post-partum anovulation, abortions, and miscarriages are some of these components. These significant characteristics all have an impact on cumulative exposure to oestrogen, which, in clinical investigations, can be a significant confounding factor if it's not properly controlled and randomized. Furthermore, prevalent pregnancy-related issues that are known to affect dementia and vascular risk, like a history of pre-eclampsia or eclampsia, are frequently overlooked (Basit, Wohlfahrt, & Boyd (2018)).

In the brain and other tissues, estrogens exert a variety of positive effects (Pike, 2017). Some, but not all, studies indicate that lower levels of oestrogen are linked to a higher risk of AD in postmenopausal women, which is consistent with these positive effects. Research indicates that women are more likely to develop dementia if they have more pregnancies, as this lowers their lifetime oestrogen exposure overall (Beeri et al., 2009). Further research revealed that women who experience a natural menopause and have a longer exposure to endogenous oestrogens (measured by the number of reproductive years) do not have a lower risk of dementia (Geerlings et al., 2001). These results suggested that while extended endogenous oestrogen exposure could not have a protective effect, a reduction in endogenous oestrogen exposure might increase the risk of AD. on the risk of AD. Studies revealed that surgically induced menopause (e.g., oophorectomy and/or hysterectomy), when performed prior to natural menopause, significantly increases the risk of dementia (Bove et al., 2014; Rocca, Grossardt, & Shuster, 2011). These findings are consistent with suggested detrimental effects of reduced oestrogens prior to menopause. Dementia risk is not increased by surgical menopause following natural menopause (Imtiaz et al., 2014). When compared to age-matched women without AD, women with AD and mean ages over 80 have significantly lower brain levels of oestrogens, notably estradiol 17β and estrone (Rosario, Chang, Head, Stanczyk, & Pike, 2011). According to Rosario et al. (2011), there is no discernible difference in the amounts of oestrogen in the brains of males with and without AD. 2013 cohort research on the risk of AD in 89 senior women estimated the number of months with oestrogen exposure and the number of months with menstrual cycles using the respondents' comprehensive medical and reproductive histories. The findings indicated that women's risk of AD decreased by 0.5% for each extra month of oestrogen exposure (Fox, Berzuini, & Knapp, 2013). All of these results point to a link between women's increased risk of AD and low oestrogen. Large-scale clinical trials examining the impact of menopausal hormone therapy (MHT) based on estrogen on the risk of dementia have, however, produced mixed findings. Early research found that estrogen therapy dramatically decreased the incidence of AD, suggesting that estrogen may have a protective role (Zandi et al., 2002). But the Women's Health Initiative discovered that estrogen treatment was linked to higher, as opposed to the expected decline in postmenopausal women over 65 years of age in terms of MCI and dementia risk (Shumaker et al., 2004). The concept of a "window of opportunity" for MHT has been introduced by these findings (Maki, 2013). It suggests that the effects of oestrogen on dementia risk vary with age and that there may be a "critical period" for the beneficial effects of oestrogen in lowering dementia risk, which is likely to occur around menopause. Two recent clinical trials that sought to assess the ideal timeframe for MHT were the Early vs Late Intervention Trial with Estradiol (Hodis et al., 2015) and the Kronos Early Estrogen Prevention Study (KEEPS; Wharton, Gleason, Miller, & Asthana, 2013). In a KEEPS follow-up investigation on MHT's impact on Aβ deposition, PiB Transdermal 17-β estradiol treatment was linked to decreased Aβ deposition, especially in APOE ε4 carriers, according to PET imaging results from 68 recently postmenopausal women (ages 52–65) (Kantarci et al., 2016). Researchers discovered that white matter hyperintensities persist beyond the cessation of oral conjugated equine oestrogen in another imaging-based investigation involving KEEPS participants (Kantarci et al., 2018). These results imply that MHT can affect structural alterations linked to cognition as well as molecular biomarkers. KEEPS data, however, indicate that MHT does not affect cognition in recently postmenopausal

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women as measured by the MMSE and other clinical cognitive tests (Gleason et al., 2015). A brief observational neuroimaging study examining sex differences in the endocrine aging process and development, involving forty-two participants aged forty to sixty of AD revealed that, in comparison to asymptomatic perimenopausal women and men, postmenopausal and symptomatic perimenopausal groups had increased AD biomarkers, including hypometabolism, increased Aβ deposition, and reduced grey and white matter volumes in AD-vulnerable regions (P <.001) (Mosconi et al., 2017). Furthermore, compared to all other groups of men and women, postmenopausal APOE ε4 carriers had greater levels of Aβ deposition, as measured by PiB binding seen by PET imaging (Mosconi et al., 2017). The neuroimaging results are consistent with earlier research in that they indicate the preclinical AD phase occurs around the time of the perimenopausal endocrine transition. This suggests that the best time to intervene therapeutically with estrogen in women is during the early stages of endocrine ageing (Mosconi et al., 2017). The proof that MHT should be used for the A comprehensive study has been conducted elsewhere on the prevention of chronic illnesses in postmenopausal women, such as dementia and stroke (Gartlehner et al., 2017). Depletion of sex hormones by ovariectomy (OVX) results in a considerable rise in soluble Aβ levels in the brain of wild-type mice, according to animal research examining the underlying mechanisms of oestrogen in AD pathogenesis (Jayaraman et al., 2012). OVX exacerbates the cognitive phenotype and expedites Aβ pathology in transgenic mouse models of AD (Levin-Allerhand, Lominska, Wang, & Smith, 2002). In contrast, OVX AD transgenic mice treated with 17β-estradiol showed a substantial reduction in Aβ accumulation as compared to OVX mice given with a placebo (Carroll et al., 2007). It is noteworthy that several transgenic models did not exhibit comparable effects of 17β-estradiol on Aβ, suggesting that these findings may be strain-specific (Golub et al., 2008) It's interesting to note that in both transgenic and non-transgenic models of AD, the protective effects of oestrogen may decrease with ageing (Palm et al., 2014). This could be because progesterone has regulatory effects (Carroll, Rosario, Villamagna, & Pike, 2010), which suggests that oestrogen's beneficial effects in AD pathology may be restricted to a critical reproductive period. Men's age-related testosterone decline substantially raises their risk of AD compared to women (Hogervorst, Combrinck, & Smith, 2003). Low endogenous serum total testosterone may manifest as early as 10 years before the clinical diagnosis of dementia, according to a longitudinal research of 574 men followed for an average of 19 years (Moffat et al., 2004). This suggests that testosterone depletion is an early event in the etiology of AD in males. Apart from serum concentrations, In both the early and late stages of AD pathology in men, there is a considerable reduction in brain levels of testosterone (Rosario et al., 2011). According to a study conducted on patients with prostate cancer, those who underwent androgen deprivation therapy had a noticeably increased risk of AD (Nead et al., 2016). According to Lee et al. (2017), a study examining the sex-specific relationship between cerebral Aβ (measured by PiB-PET) and serum sex hormones revealed that higher levels of free testosterone in women were linked to lower levels of cerebral Aβ, while in men, free testosterone was positively correlated with both hippocampal volume and cognitive status. These results imply that testosterone may postpone hippocampus neurodegeneration in men and suppress early stages of Aβ buildup in females.

Research on male rodents also points to a protective function for the role of testosterone in AD development. For instance, non-aromatizable androgen dihydrotestosterone reverses the impact of endogenous testosterone reduction through orchiectomy in male rats, increasing soluble Aβ (Ramsden et al., 2003). Notably, this investigation also revealed that 17β-estradiol was unable to counteract the effects of testosterone deprivation, suggesting that androgens—rather than oestrogens—play a sex-specific function in the regulation of Aβ-related pathologies in male rats. Males may appear to have fewer complex hormones and age-related reproductive processes than females. However, age and gender considerations are still just as vital in studies involving solely men as they are in studies involving women or mixed genders. Future research, both preclinical and clinical, examining the function of sex hormones in age-related diseases including stroke and dementia must take into consideration the interaction of Two independent biological factors are age and sex.

Sexual hormones and stroke risk

Premenopausal women are known to be less likely than men to develop cardiovascular disease (CVD); however, this protection does not last for older patients. After menopause, women's risk increases and by the age of 80,

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it exceeds men's (Benjamin et al., 2018). This implies that women's sex hormones have a protective function. Exogenous oestrogen-based hormone therapy, however, has been linked to an elevated risk of CVD and stroke, according to randomized prospective clinical trials (Manson et al., 2003). The causes of this disparity are yet unknown, although they may have to do with the participants' ages, pre-existing cardiovascular disease, the timing and quantity of their treatment, the particular hormone they were taking, or the diverse ways that it affected different oestrogen receptor subtypes and consequences related to thrombosis and coagulation, the majority of which have already been discussed elsewhere (Rosano, Vitale, & Fini, 2009; Roy-O'Reilly & McCullough, 2014). According to CIMT, women who began using oestrogen-based hormone therapy around menopause saw a decreased rate of atherosclerosis progression than those who received a placebo (Hodis et al., 2016). It is unclear whether the observed CIMT reduction will translate to a lower stroke risk later in life because the women involved in these trials were at low risk for stroke due to their relatively youthful age (50s). When planning clinical trials, it is crucial to collect the vitally significant components of reproductive history in addition to the previously stressed necessity for increased enrollment of women. Anything that can affect the history of vascular disease particular to a given sex or the cumulative exposure to estrogen, such as If appropriately controlled and randomized, pre-eclampsia (Moatti, Gupta, Yadava, & Thamban, 2014) may not be a confounding factor in clinical trials. There has been a review of the underlying mechanisms of oestrogens and oestrogen receptors in stroke pathology (Hara et al., 2016).

Animal studies demonstrate that the neuroprotective effect of estrogen is dependent on when it is administered, just like in women. It has been observed that as female animals age, a proinflammatory milieu forms, which adversely affects the effects of oestrogen (Liu, Benashski, Xu, Siegel, & McCullough, 2012). Less ischemic damage was seen in female mice given an estradiol supplement at 15 months of age, or middle age, and then suffered a stroke at 20 months of age. On the other hand, if replacement was started at 18 months, following a lengthy of gonadal senescence, stroke was inflicted upon mice, and estradiol exacerbated the damage. Remarkably, males benefited from treatment at any time point, indicating a potential interaction between chromosomal sex effects and sex hormones.

Variations BETWEEN GENDER

Biomedical research and clinical practice are influenced by cultural and psychosocial elements in many environments. The majority of preclinical research is conducted on male animals since it is believed that, because of hormonal differences, females are inherently more variable than males. However, this assumption has been called into doubt (Franconi, Rosano, & Campesi, 2015). Furthermore, bias may also exist in the preclinical context because in vitro studies sometimes do not define the sex of cells investigated. Gender variables may influence treatment compliance, care access, housing arrangements, and socioeconomic standing in the setting of clinical research. Even the gender of the caregiver and healthcare professional can influence how differently patients are treated for a variety of conditions, particularly when those conditions have primarily mental elements like dementia Negative outcomes in neurological illnesses, particularly in the elderly population, have been linked to social isolation. A 2018 study found that living alone compared to living with a partner increased the risk of dementia development in people with MCI by 50% (Grande et al., 2018). Notably, women and older age groups were more prevalent among the chosen participants who were living alone. This is in line with current trends in US census data, which show that a growing number of women over 80 live alone. This is likely due to the fact that these women frequently outlive their spouses and other family members. The US Census Bureau's most recent 5-year community survey data shows that, between 2012 and 2016, the statistics of "widowed females" compared to "widowed males" was 2.6% versus 9%. A number of often disregarded factors lead to lower recruitment and participation rates of women in trials: physical immobility; lack of personal transportation; cognitive impairment resulting in incapacity to provide informed consent or appropriately follow study guidelines; and general dearth of social support. It may be culturally appropriate to look into and address this additional potential gender-based component, which has been brought to light by a few recent analysis of sizable patient databases. At all CHA2DS2-VASc score levels, women were substantially less likely than males to obtain OACs among patients with atrial fibrillation, according to an analysis of the PINNACLE National Cardiovascular Data Registry from 2008 to 2014. Women consistently exhibited lower rates of non-vitamin K OAC use despite their use growing at a rapid

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pace. of OAC use over time compared to men, indicating that the way therapeutic guidelines are applied to men and women may differ (Thompson et al., 2017). Research is required to ascertain whether gender-based healthcare practices are linked to distinct clinical outcomes. Should this be the case, increased awareness campaigns and subsequent measures are required to eradicate these practices. The financial burden of mitigating gender-specific factors in costly clinical trials will be high, but in the long run, the cost of ignoring biological differences that are clinically significant in drug development studies will be greater than the incremental cost of offering a workable way to enrol more women. Even though it could be challenging to simulate these gender differences in a lab setting, well thought out studies on the impact of social isolation on of stroke recovery and ischemic injury have been effectively assessed (O'Keefe et al., 2014). Consequently, gender differences and their significance in dementia ethology, development, and pharmacological response to therapy must be taken into consideration as an additional variable in the design of future preclinical and clinical investigations, in addition to the sex differences included in this review.

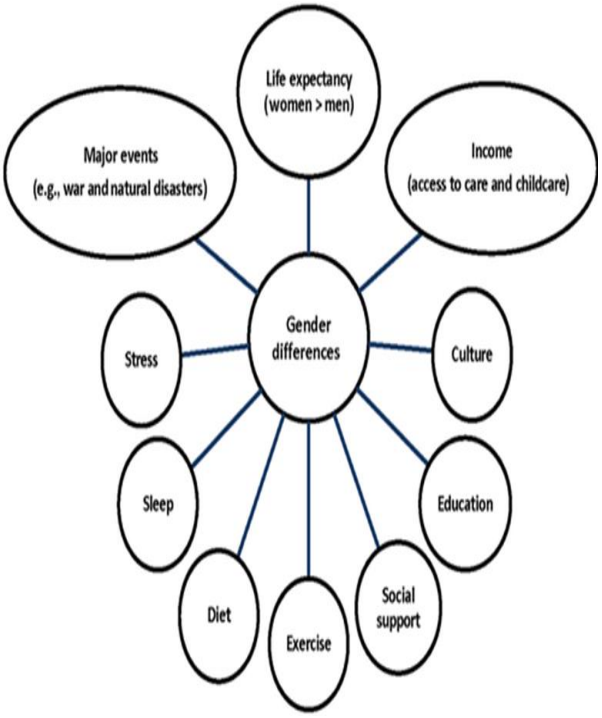

figure : 2 Gender factors that may contribute to differences seen between men and women with dementia. These factors may also contribute to the low rates of recruitment of women in clinical studies.

FINAL SUMMARY

In the field of medicine, gender and sex are two distinct but related characteristics. The aetiology, symptomology, diagnosis, response to treatment, and prognosis of the majority of diseases are influenced by both sex and gender, despite the difficulty in separating the two ideas. Despite this understanding, there is still a dearth of biomedical research and reporting on the roles that gender and sex play in health and disease. In order to better the treatment of both men and women suffering from dementia, stroke, VCI, and other neurological disorders, it will be essential to identify and comprehend the fundamental roles that sex and gender play as two biological variables. Because each disease has a unique mechanism and clinical presentation, accurate experimental models of each disease are required. How crucial it is that Gender and sex differences may be disease specific and may change dramatically with age, which emphasizes the need for well-designed bench and clinical investigations. Successful drug development is still severely hampered by the underreporting of sex-specific drug responses and side effects in preclinical research and clinical trials, as well as by the inadequate recruitment of women in clinical trials. Future research must be planned to either definitely detect or rule out differences in sex and gender that may be disease-, drug-, age-, or any combination of these specifics. Clinically, analyzing the available data is made more difficult by the inevitable yet reducible degree of subjectivity in patient-derived reporting. It is critical to raise awareness of potential sex disparities in current clinical guidelines, or how they are being implemented, should be thoroughly examined and, if necessary, removed. Understanding how sex-dependent responses to pharmacological interventions, as well as differences in the diagnosis and treatment of AD, CAA, and stroke, are influenced by differences in male and female biology has broad implications for many fields of neurobiology and medicine.

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