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The puzzle of sex, gender and Alzheimer's disease: Why are women more often affected than men?

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Abstract

Objective: There are impressive differences in the incidence, prevalence and experience of women and men with Alzheimer's Disease (AD). Notably, two-thirds of those with AD, the most common form of dementia, are women. Our objective was to provide a literature-based framework to understand these sex and gender differences in AD.

Methods: We conducted a narrative review to examine sex and gender influences on AD.

Results: We present a framework to understanding why these sex and gender differences exist in AD. This includes the influence of longevity (women live longer than men), biological differences (hormonal differences, epigenetics and frailty), differences in cognitive performance (women and men tend to perform differently on some cognitive tests), and gendered social roles and opportunities (educational and occupational opportunities, functional roles post-retirement). Our review clearly indicates the complex interaction of these sex and gender differences and variability within each.

Conclusions: Given these important sex and gender differences in AD, we provide recommendations and steps forward describing how both sex and gender should be considered in dementia diagnosis and management and in the design and implementation of dementia research, including studies of caregiving interventions and models of dementia care.

Keywords

Alzheimer's disease, dementia, frailty, gender, sex

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Dementia affects the health and wellbeing of many older adults and is therefore relevant to the functioning and sustainability of our healthcare systems. As populations age, it becomes ever more important to get things right with the way we plan and provide health services to care for people and families living with dementia. As we undertake this essential work, it is important that we learn from dementia epidemiology. Here, an intriguing fact stands out: *women experience more dementia than men, and this difference is not small*. Exact estimates vary by region and study design and also by type of cognitive impairment or dementia.[1] It is important to acknowledge that dementia is a clinical diagnosis, in which an individual experiences decline in cognition that impact function in day-to-day activities. There are many types of dementia, including Alzheimer's disease (AD), vascular dementia, Lewy body dementia, Parkinson's dementia (PD), frontotemporal dementia, and chronic traumatic encephalopathy (CTE). Importantly, it is now becoming understood that in many people, especially at older ages, dementia does not relate to a single type of brain changes (or neuropathology), but rather arises as a mix of several neuropathologies accumulate.[2] Also intriguing is the fact that the presence of neuropathology does not necessarily mean that a person will experience cognitive symptoms or meet criteria for a clinical diagnosis of dementia; the concept of cognitive reserve arises from

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attempts to understand why this is so.[3] While some less common forms of dementia (e.g. PD, CTE) are more often experienced by men, overall women experience a greater burden of dementia. This is largely driven by AD, the most common form of dementia, where estimates suggest that about two-thirds of affected persons are women.[4]

This article aims to outline an approach to why women have a disproportionate experience of AD. Given that differences in *longevity* and *biology* have received the most attention in the literature and are likely to be top of mind for many readers, we address these two categories of contributing factors first. Even so, as we go on to discuss, numerous other factors are likely to be relevant, so we then move to consider the sex and gender gap in relation to *cognitive performance* and *social roles and opportunities*. This is not meant to be an exhaustive list of all possible mechanisms, rather a framework for considering the possible influences. Notably, these categories are not necessarily mutually exclusive; there may be complex interactions between domains that impact diagnosis, care, and planning of health services.

There are several pieces which are likely contributing to this puzzle, relating to both sex (reproduction, sex hormones) and gender (social roles, identities, and opportunities) and the interaction between the two (e.g. epigenetics).[5] Some of the literature referenced comes from fundamental research and animal models, while other evidence is from clinical and epidemiological studies. For clarity, the terms female and male are used when referring to animal studies, while comparisons between women and men refer to human studies.

This article concludes by offering some suggestions regarding how these important sex and gender differences can inform systems of dementia care.

Longevity

Some argue that the sex differences in AD are largely or entirely attributable to the well-known demographic fact that women live longer than men. Since AD incidence and prevalence increase with age, it would logically follow that more women would live long enough to develop dementia. Evidence is mixed as to whether there is truly a greater age-adjusted risk of AD in women than in men, but many studies are finding this to be the case, suggesting that there is more to the story than simple differences in longevity.[1,6–8] At the heart of this debate is to what degree survival bias is a contributing factor, given that sex and gender are associated with dementia but also with mortality, each likely via numerous mechanisms. Survival bias arises when an exposure (here sex and gender) is associated with an outcome of interest (dementia) but is also a risk factor for mortality.[9] Adding to the complexity, some studies from the United States have found no difference in age-adjusted risk of AD, while studies from Europe and Asia have generally found that women have higher risk than men, which has also been supported by a meta-analysis.[1,10] This difference in experience between geographically defined populations may serve to highlight the important inter-relationships between social and biological factors.

Biology

Numerous biological mechanisms are likely at play, including sex differences in hormones, pregnancy, brain structure and function, inflammation, genetics, epigenetics, and frailty.

Hormones

Sex hormones are clearly relevant to biology and health, and this is no different when it comes to brain health and dementia.[11,12] Estrogen has been described as being neuroprotective; this is thought to accrue through various mechanisms, including supporting growth and development of cholinergic neurons, increasing cholinergic activity, antioxidant properties, and alternative metabolism of amyloid. Interestingly, due to conversion pathways from testosterone, older men have higher levels of estrogen than postmenopausal women.[13] The relative concentrations of different types of estrogens also change after menopause, with a shift toward the weaker estrogen estrone from the stronger 17β-estradiol which predominates in pre-menopausal women. There is some evidence that while 17β-estradiol exerts a positive influence on cognition, estrone may have more negative effects.[12] The timing of hormonal changes also appears to make a difference: for many women, estrogen levels may drop rapidly at the time of menopause or following oophrectomy, whereas the reduction in testosterone is more gradual in older men.

Efforts at intervening with hormone replacement therapy (HRT) have yielded conflicting results. Some studies have shown that HRT initiated soon after natural or surgical menopause can have a protective influence in reducing the risk of developing AD, while others have shown the opposite, especially when HRT was initiated too late after what some have described as an early window of opportunity.[1,14,15] The Women's Health Initiative Memory Study identified an increased risk of cognitive impairment and AD in women aged 65+ years who were randomized to receive HRT with Premarin (a conjugated equine, mainly estrone formulation) along with medroxyprogesterone acetate (MPA), a synthetic progestogen if they had not had a hysterectomy; however, this finding was not replicated in women without a uterus who did not receive progesterone. Also, another study showed that women who had memory complaints but normal cognition who were randomized to HRT did not show age-related declines in memory relative to the untreated placebo group.[16] In other

studies, HRT use has been associated with increased risk of vascular events and stroke, which also likely contributes to increases in dementia risk.[17] Overall, there remains uncertainty around the impact of timing, formulation, and dose of HRT in relation to cognition and dementia risk, and the evidence of adverse effects cannot be ignored. Also, clearly, most women transition to menopause and beyond without experiencing cognitive decline and dementia, which reminds us that the picture is complex and demands consideration of additional factors.

Pregnancy

Pregnancy and its complications may also play a role in later life cognitive impairment in women. For example, a history of preeclampsia has been associated with a trend toward increased risk of Mild Cognitive Impairment and dementia in later life.[18] Pregnancy and motherhood are also associated with a myriad of other influences on a woman's life, spanning biological and social, some of which may also influence dementia risk in ways that are yet to be well understood.

Brain structure and function

The brains of women and men are similar in many ways, but different in others. This extends well beyond the now-widespread colloquial (and often flippantly invoked) understanding that "Men are from Mars, Women are from Venus,"[19] impacting brain structure and function on many levels. On a structural level, males tend to have larger brain volumes than females, along with relatively more white matter, while females have relatively more gray matter.[20] On a functional level, blood flow and connectivity may be higher in the parietal association cortex in females, and in the motor and visual cortices among males.[1,21,22] These differences may impact risk of developing clinically significant cognitive decline and dementia, as well as the rate at which these declines occur. For example, if males have a greater brain volume to start with, they may be more resilient to neuropathological changes and neuronal losses, at least to a point. This idea was supported by a brain autopsy study in which females had a higher burden of AD pathology (particularly neurofibrillary tangles), and these neuropathological changes were more likely to be associated with clinically manifest symptoms of dementia in females than in males.[23] Another study, focusing on biomarkers of AD, found that women were more susceptible to atrophy in the hippocampus, an area of the brain which is critical for memory function.[24]

Inflammation and metabolism

There are known sex differences in propensity to develop disorders of inflammation and immune function.[25] Inflammation may also play a role in the pathogenesis of AD and other neurodegenerative conditions. Inflammation and microglial activation have been hypothesized to contribute to AD neuropathology, and there are important sex differences in immune parameters such as microglial number and function (and disruption) and brain responses to inflammatory mediators and markers which may contribute to higher risk of AD among women.[26,27] Mitochondrial function may also be relevant to sex differences in the incidence and prevalence of AD. The mitochondrial hypothesis states that changes in mitochondrial function, notably the handling of energy production and oxidative stress, may contribute to the pathological changes found in AD.[28] Given the matrilineal inheritance of mitochondria and research demonstrating sex differences in mitochondrial function and proteomes, including important sex hormone influences on mitochondrial function in health and disease, changes in mitochondrial function may be an important factor contributing to sex differences in AD.[28,29]

Genetics and epigenetics

Many genes are implicated in causing AD. As another example of how biology may be at play, recent study of the *APOE* gene variant, a known risk factor for AD, has shown that it may be a more important risk factor for women than men.[30] The situation is complex; while some other genetic mutations and polymorphisms exhibit the same influence in both sexes, others such as APOE appear to have differential influence by sex, increasing risk more for women than for men or vice versa.[1,31] Epistasis is an example of how some sex differences may be explained at a basic genetic level, in that a gene or locus in one area of the genome (for example, on an autosomal, or non-sex specific, chromosome) may be modulated by the product of a gene or locus on another chromosome (which could be an allosome or sex-specific chromosome, such that its presence or levels of expression would differ between the sexes) to upregulate or downregulate expression of the first gene.[1,31,32]

Genetic and hormonal influences dovetail in the form of epigenetic influences on brain development. Epigenetics is the study of how life experiences and the environmental milieu can exert influence on gene expression. As such, epigenetics lends a more dynamic understanding to the traditional static influence of Mendelian genetics. DNA methylation and histone modulation of gene expression are key epigenetic mechanisms, and there are sex differences in both, with estrogen exerting important influences.[12] These sex differences have in turn been found to influence neurogenesis and neurodevelopment, contributing to sex differences in brain structure and function. These epigenetic sex differences also appear to play a role in aging and disease expression. Evidence suggests, for example, that epigenetic mechanisms may be at play in differential responses to brain ischemia seen in females versus males and that hormone-mediated influences on

amyloid deposition implicated in AD may be regulated through epigenetic mechanisms.[33]

Frailty

Humans are complex systems, in that their cells, tissues, and organs all need to work together. At this systems level, frailty also seems to play a role in sex differences in AD as well as other forms of dementia. Frailty is a state of increased vulnerability to adverse outcomes compared to others of the same age.[34] Frailty can be defined in many ways, including as an accumulation of deficits (e.g. frailty index),[35] a phenotype (e.g. three or more of weakness, weight loss, slowness, inactivity, and exhaustion),[36] or as a clinical state (e.g. Clinical Frailty Scale).[37] However, it is defined that almost all studies show that women have higher levels of frailty than men, though they have better survival than men at any age and at any level of frailty.[38] For example, in a comparison of seven leading models of frailty, women had higher frailty than men in all seven.[39] Using the phenotypic definition of frailty, women are more likely to be slower, have weaker grip strength and lower muscle mass, have lost weight, have reduced their physical activities, or complain of exhaustion than men.[36] Using the deficit accumulation approach to frailty, at any age, women have more health deficits (health conditions, symptoms, and functional problems) than men do.[35] This is important because having many health problems (even things which are not traditionally seen as risk factors for dementia) appears to be an independent risk factor for AD and dementia, and so, the increased levels of frailty experienced by women may be an important mechanism contributing to women's increased experience of AD.[40,41]

In the bigger picture, this complexity underscores the importance of specifically looking for sex differences in studies of the neurobiology of AD. If we do not look for these differences, we are likely to miss out on potential opportunities to move our understanding forward in meaningful ways. For example, in a recent study highlighting the importance of sex stratification to look for sex-specific effects, mid-life hypertension has been found to be associated with increased risk for dementia in women but not in men.[42]

Cognition

Cognition is a phenotypic expression of numerous complex factors, including many biological, genetic, and epigenetic factors discussed above, along with social factors including living conditions and educational opportunities which are discussed further below.[43] In the case of AD, cognitive decline is both a key symptom and pivotal for diagnosis (in that it must be noted by the diagnosing clinician), so the question of whether there are sex and gender differences in cognition merit specific attention. As an example, estrogen influences new learning and memory through various genomic (e.g. direct influence on gene transcription) and non-genomic (e.g. molecular signaling pathways) mechanisms; the hippocampus, the brain structure most closely associated with memory, is a hotbed of these estrogen actions.[12]

Women and men perform differently on some cognitive tests. Men tend to score higher on visuospatial tasks, whereas women tend to have higher scores on tests of verbal memory.[1,44] Some have suggested that since women tend to have better baseline verbal memory than men, and verbal memory impacts day-to-day interactions more than visuospatial memory, declines in performance are clearer to friends and family members when they occur. This observation that "women have farther to fall" [in verbal memory] may facilitate better detection of dementia in women,[45] although (in keeping with the complexity of this field) findings to the contrary have also been reported, along with the suggestion that these differences in verbal memory might in fact lead to delays in diagnosis and treatment in women.[46] A meta-analysis highlighted differences in cognitive deterioration between men with AD and women with AD, finding that women with AD had worse cognition across all cognitive domains (even verbal memory where women without AD tend to outperform their male counterparts).[44]

Social roles and opportunities

Higher education and income, occupational complexity, and greater physical activity are protective for dementia, and women in today's older cohorts have often had different opportunities in all three than men of a similar age. These factors, among others, are important for considering how sex and gender influence cognitive reserve.[3] Women in older cohorts often had fewer educational opportunities, resulting in less educational attainment.[43] Women in older cohorts may also have had fewer options for participation in the workforce, and when they did so, it was more likely in jobs with lower occupational complexity, and for shorter time periods, compared to men.[47,48] Occupational complexity is an interesting issue in relation to cognition, as one might argue that baseline cognitive ability leads to higher occupational complexity (the "preserved differentiation" hypothesis), though evidence supports the opposite relationship, that higher occupational complexity stimulates better cognitive performance in older age ("the differential preservation" hypothesis).[49] Particularly in older cohorts, but still relevant today, there are important lifestyle factors which may be experienced in gendered ways. For example, historically men were more likely to be smokers, but smoking rates in women have since risen.[50] Lifestyle factors which have positive metabolic effects can also of course be protective. Control of vascular risk factors such as hypertension, diabetes, and obesity are critically important when it comes to promoting brain health and preventing dementia, especially as we understand the role of mixed neuropathology.[51] Exercise and diet, both protective factors for

dementia, may also be gendered to varying degrees. For example, men in older cohorts are more likely to have had opportunities to participate in sports or in physically demanding occupations.[52] The mechanisms through which these protective factors exert their influence on brain health and dementia risk is interesting to ponder; for example, in addition to their known role in vascular brain health, there may be important epigenetic influences (relating back to the above discussion of biological factors).

Gender may also influence clinical diagnosis of dementia. For example, after retirement, women may be more likely than men to engage in a more varied range of functional tasks in running the household. Declines in functional abilities, which is key to making a diagnosis of dementia, may therefore be more readily detected by friends and family in older women than might be the case for a now-retired man whose role was working in outside employment and "never did" much around the house. This gender difference in functional roles may contribute to earlier (and more) diagnoses in women, though there is a paucity of research in the area and it remains a challenging hypothesis to test empirically. However, there is some evidence in support of a protective "functional reserve" influence from continuing to do these daily household chores, which may preserve functional independence for longer even in the face of cognitive declines.[53] All in all, there is a critical need to examine clinical diagnostic practices through a gender lens.

On a related note, women are more often engaged in family and friend caregiving roles, meaning that they bear a greater burden of the dementia experience from this perspective as well.[54] Unfortunately, there is evidence that caregiving itself can be associated with increased risk of cognitive impairment and dementia,[55] although there is also some evidence that among spousal caregivers, husbands may be at higher risk for dementia compared to wives.[56]

Complexity and interactions

Complicating matters, these factors may also interact. For example, the drop in estrogen levels experienced by older women at the time of menopause (be it a cause or a consequence of aging processes) may occur at the same time as other health problems begin to accumulate. Adding caregiving responsibilities and changing social roles to the mix, along with changes in cognitive abilities, may contribute non-linearly to dementia risk. Sex and gender factors may also interact. For example, there are known differences in the kinds of medications prescribed to men and women. Women, including those with dementia, are more likely to be prescribed certain classes of psychotropic medications including sleep aids, which increase the risk of cognitive impairment.[57] Men may be more likely than women to receive treatment with cholinesterase inhibitors, currently the main medication class used in the specific treatment of AD.[58] These prescribing differences may be due to gender differences in the care of women versus men by physicians. However, this possible gender difference in patterns of medication use is complicated by sex differences in drug metabolism,[59,60] and thus, these two together may render women more susceptible than men to cognitive impairment.[57] Also, some medications in current and future use (including some antidepressants and mood stabilizers) have epigenetic mechanisms of action which may differ between the sexes.[33] This may in turn account for sex differences in treatment response which will be missed if drug studies do not specifically include both women and men and target specific investigation of sex differences. Research is ongoing into sex and gender differences in medication use, including in the setting of dementia.[61]

Conclusion

As we have seen, the influences on observed sex and gender differences are complex. The categories of factors in the framework we present here (longevity, biology, cognition, and social roles and opportunities) likely contribute to varying degrees and interact in ways that are known and unknown. All in all, the sex and gender gap in AD and other forms of dementia is an important area for further research. Granting agencies are increasingly recognizing the importance of considering both sex and gender in research across many fields, including brain health.[12] The subject of sex and gender differences in dementia risk and experience has been gaining increasing traction in the literature. Interested readers are also referred to other recent reviews for additional insights.[62–64]

As an example, the focus on sex and gender is one of the unique features of the Canadian Consortium on Neurodegeneration in Aging (CCNA), Canada's coordinated dementia research effort, on the international stage (www.ccna-ccnv.ca). The CCNA has partner support from the Canadian Institutes of Health Research Institute of Gender and Health (http://www.cihr-irsc.gc.ca/e/8673.html) and the Women's Brain Health Initiative (www.womensbrainhealth.org) and has a "Women, sex, gender and dementia cross-cutting program" which brings a sex and gender lens to all of its work.

The sex and gender gap is also clearly clinically relevant when it comes to dementia care and health policy. Although many jurisdictions including several in the United Kingdom and Canada have Dementia Strategies in place or in progress, more could be done to ensure that sex and gender issues are taken into account as we plan programs of care to support women and men living with dementia, their families, and communities.[65] See Box 1 for a summary of recommendations and steps forward. Attention to sex and gender as they relate to dementia remains an important gap to fill from bench to bedside to communities; dementia is a pressing health issue that we cannot afford to get wrong.

Box 1.

Recommendations and steps forward:
- Clinical and pre-clinical research investigations of dementia should include both sexes and should have sufficient numbers of each so that sex differences can be directly examined rather than simply adjusting for sex as a covariate.
- Sex differences in the risk for dementia should be considered systematically in research into causes and contributors to dementia.
- Sex and gender differences contributing to differences and potential bias in dementia diagnosis should be considered in the contexts of clinical practice and clinical service design and in further research.
- Optimal management of dementia may be different for women and men. For example, there may be sex differences in drug effects and response to non-pharmacological interventions, and thus, there is an urgent need to design and implement studies to improve clinical care.
- Sex and gender differences in each of these areas (risk, diagnosis, and management) should be considered in clinical settings and as part of policy initiatives such as Dementia Strategies.
- Caregiving may affect women and men differently; interventions targeted to caregivers should consider gender differences in caregiving experience and support needs.

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