Clinical research

Considering sex and gender in Alzheimer disease and other dementias

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Introduction

Dementia is a pathological, neurodegenerative process leading to progressive decline in cognitive and functional abilities. It has multiple causes, diverse manifestations, and heterogeneity with respect to the impact of sex or gender on prevalence, risk factors, and outcomes (Table I). Alzheimer disease (AD) is the most common form of dementia, comprising up to 80% of cases; however, not all studies distinguish AD from all-cause dementia. The estimated prevalence of all-cause dementia varies from 4.7% in Central Europe to 8.7% in North Africa/Middle East, with North America falling between at 6.4%. Currently, over 46 million individuals live with dementia worldwide and this number is projected to increase to 131.5 million by 2050. The economic impact is enormous. By 2018, dementia is expected to become a trillion dollar disease. To put these costs in more tangible terms, dementia care, if it were a country, would be the world's 18th largest economy. Current treatments for dementia are inadequate in slowing the progression of disease, and there are no

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Clinical research cures, with the possible exception of dementia related to normal pressure hydrocephalus (NPH). Hence, identification of modifiable risk factors (Figure 1) has been a primary focus of much investigation. Unfortunately, the two strongest predictors of dementia—age and sex—do not fall into this category. Moreover, sex and gender factors interact with age across development to alter risk for dementia. Beginning in utero and onward, the brain is acted upon in a sexually dimorphic manner. This promotes risk and resilience with respect to health outcomes across the life span.

This review will examine current knowledge regarding individual and interactive effects of sex and gender as they relate to dementia risk, prevention, and treatment. Briefly, sex refers to the classification of human beings according to their sex chromosomal compliment, with females having two X chromosomes and males having one X and one Y chromosome. Gender refers to a person’s psychosocial and cultural self-identification as being male or female. Past researchers have reviewed sex- and gender-specific risk factors for development of dementia; however, the separation of sex as a biological variable (SABV) and gender as a societal construct/personal identity has not always been clearly defined in dementia research. The waters between sex and gender can indeed be muddy when considering that aspects of gender influence an individual’s biology, and vice versa. Similarly, one’s gender does not always conform to one’s biological sex. Although there is a growing need to consider health outcomes in transgender and intersex communities, this review will focus on sex and gender differences in dementia among individuals who have expected chromosomal compliment for males (XY) and females (XX) and are not utilizing exogenous hormones or surgical procedures to alter their gender or sexual identity.

### Selected abbreviations and acronyms

- **AD**: Alzheimer disease
- **APOE**: apolipoprotein E
- **CI**: confidence interval
- **CJD**: Creutzfeldt-Jakob disease
- **CNS**: central nervous system
- **FTD**: frontotemporal lobe dementia
- **LBD**: Lewy body dementia
- **MCI**: mild cognitive impairment
- **NPH**: normal pressure hydrocephalus
- **PD**: Parkinson disease

### Disorders leading to dementia

**Prevalence/incidence & impact of sex/gender**

| Disorder                                    | Frequency |
|---------------------------------------------|-----------|
| Alzheimer disease                           | Accounts for 60%-80% of dementia cases. | Almost twofold increased risk in women versus men.¹  |
| Vascular disease                            | Accounts for 10%-20% of dementia cases. | Risk factors for vascular or multi-infarct dementia are more common in males, but have greater severity of impact in females.³  |
| Dementia with Levine bodies                 | Extensive overlap with Parkinson disease dementia. | Incidence greater in males than females (4.8 vs 2.2).⁴  |
| Parkinson disease dementia                  | Parkinson disease prevalence higher in males than females.⁵,⁶  | Earlier onset of Parkinson disease dementia in males.⁷  |
| Due to multiple causes (mixed)              | Most often a combination of vascular dementia and Alzheimer disease.⁵,¹⁰  | More common in males than females: 31% vs 25%.¹¹  |
| Normal pressure hydrocephalus               | Prevalence differs greatly depending upon age and study, but is 1.3% according to a recent systematic review.¹²  | Almost twice as common in men than women after age 60, though other studies suggest equal frequency in males and females.¹³  |
| Frontotemporal degeneration                 | Earlier age of onset in those with TBI and LOC. | May be more common in males.¹⁴,¹⁵  |
| Creutzfeldt-Jakob disease                   | Rare: 1.26 cases/million people.¹⁷  | Sex differences in prevalence and clinical course have not been reported.  |

Table I. Prevalence/incidence of disorders leading to dementia and the impact of sex or gender. LOC, loss of consciousness; TBI, traumatic brain injury.
Impact of sex and gender during development: setting the stage

Seminal work conducted by McCarthy and Arnold and others\(^\text{19-21}\) implicates a critical role of testosterone and its aromatization to estradiol in sexing of the human brain, with a greater degree of exposure enhancing masculinization. Variations in hormonal exposures/responses occur throughout the central nervous system (CNS) between brain regions and individual cells, leading to a mosaic of maleness and femaleness in any given brain.\(^\text{22,23}\) After birth, organizational effects of gonadal hormones are thought to be relatively quiescent until puberty when male and female gonads begin to produce sex steroids. However, brain regions (eg, hippocampus and prefrontal cortex) and physiologic processes (eg, cerebral blood flow) that are critical to cognition and brain health are rapidly developing across childhood and adolescence and thus vulnerable to environmental perturbations. Sex differences already present at birth can conceivably modify the individual’s response to medical conditions and environmental insults such as adversity, whereas gender is associated with specific types of traumatic exposures.\(^\text{24}\) Education, intellectual enrichment, and cognitive reserve are additional factors in the risk for dementia that may vary by gender.\(^\text{25,26}\) Although the vast majority of individuals receive some form of education during childhood, there are considerable gender disparities in the level of educational attainment in some countries and cultures. Moreover, education attainment interacts with gonadal steroids in a sex-specific manner. Among older men, low levels of free testosterone increased the risk of dementia to a greater degree in men with a high level of education than in those with a low level of education.\(^\text{27}\) Gender differences in these and other exposures can interact with the biology of the individual in a sex-specific manner, which highlights the complexity of sex and gender when considering adult health outcomes.

Examples of early and developmental sex differences come from the large Philadelphia Neurodevelopmental Cohort in which individuals ages 8 to 22 years underwent brain imaging.\(^\text{28}\) The basic physiologic process of cerebral perfusion is critical for brain metabolism and is diminished in numerous neurological disorders. This differs in magnitude and direction between males and females across development.\(^\text{29-31}\) Again, in the Philadelphia Neurodevelopmental Cohort, amygdala volume increased significantly in adolescent boys, whereas hippocampal volume increased and thinning of cortical gray matter occurred faster in girls.\(^\text{32}\) These sex differences are crucial to consider when interpreting brain-imaging outcomes in normally developing individuals, as well as in those with neuropsychiatric and cognitive disorders. Sex differences in brain development serve as the proverbial stage on which medical conditions and other risk factors associated with dementia act to increase or reveal vulnerability to pathological cognitive aging.

Sex/gender differences in dementia by subtype

Alzheimer disease

AD, the most common cause of dementia, is characterized by β-amyloid plaques, neurofibrillary tangles, and neurodegeneration in areas of the brain associated with

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**Figure 1.** Relationship between males and females and possible risk factors for the development of Alzheimer disease and other dementias. Dementia risk factors, such as smoking, coronary artery disease, and brain injury with loss of consciousness, are more common among men than women. However, other risk factors, such as diabetes, obesity, and hypertension, are also more common among men, but women are disproportionately at risk for dementia when these conditions are present. Most studies of dementia examine risk by age. The longer life spans observed in women does not fully explain the sex bias for Alzheimer disease, but increases the overall prevalence of all-cause dementia in women among the oldest old. Older age, family history of dementia, APOE-ε4 carrier status, and low education are prominent risk factors worldwide in both males and females. APOE, apolipoprotein E; LOC, loss of consciousness.
cognition, such as the cortex and hippocampus. The disruption to critical metabolic processes leads to cell death, neuronal loss, and progressive decline from mild cognitive impairment (MCI) to AD dementia. AD is characterized by interference with everyday activities involving memory, speech and language, reasoning, planning, and other cognitive abilities. Advanced age is the strongest predictor; however, sex and gender differences have been noted in prevalence, clinical manifestation, disease course, and prognosis. Data from the Framingham Study, which enrolled a total of 2611 cognitively intact participants (1550 women and 1061 men) and followed up on many for 20 years, indicated that for a 65-year-old man, remaining lifetime risk of AD was 6.3% (95% confidence interval [CI], 3.9 to 8.7) and remaining lifetime risk of developing any dementing illness was 10.9% (95% CI, 8.0 to 13.8); corresponding risks for a 65-year-old woman were 12% (95% CI, 9.2 to 14.8) and 19% (95% CI, 17.2 to 22.5), almost twice that of men.

Several epidemiologic studies show that neurodegeneration and clinical symptoms occur more rapidly for females once a diagnosis is suspected. Researchers have hypothesized that this is due to longer female life expectancy or sociocultural detection bias; however, there is support that faster progression is due to neurobiological vulnerability in postmenopausal females. Though progression of the disease may be more rapid among elderly women, studies conducted in the United States and United Kingdom suggest that males with AD have a shorter survival time. Women are often diagnosed earlier in the course of illness than men, which could confound determination of postdiagnosis longevity. However, data from a recent systematic review focusing on mortality in AD and all-cause dementia support findings of a shorter life span among males, regardless of age at diagnosis. Among those who have a positive or stable response to cholinesterase inhibitors over 6 months, female sex is a predictor of longer life span.

The importance of considering SABV and gender with other risk factors for dementia such as apolipoprotein E (APOE) genotype, alcohol use, and depression, has become increasingly apparent. The APOE gene encodes a protein that transports cholesterol in the bloodstream. Carriers of the ε4 variant are predisposed to high cholesterol and AD. When examined at autopsy, a greater portion of individuals diagnosed with AD were found to have one or two copies of the APOE ε4 allele. Female allele carriers were twice as likely as noncarriers to have dementia, and allele status predicted progression from MCI to AD in both sexes. The CREDOS study (Clinical Research Center for Dementia of South Korea) of 301 individuals with MCI at enrollment confirmed that APOE ε4 status is a predictor of transition from MCI to AD in both males and females. However, APOE ε4 status affected the rapidity with which women transitioned, as did clinically relevant levels of depression at baseline. For men with MCI, baseline burden of periventricular white matter hyperintensities predicted a more rapid transition from MCI to AD over 3-year follow-up. APOE ε4 allele status has been suggested to interact with degree of alcohol consumption to promote risk or resilience to AD and other dementias. Further research is necessary to define light-to-moderate alcohol consumption by sex, determine effects of different types of alcohol, and consider co-use of alcohol and cigarettes on dementia risk. Finally, several sex and APOE genotype interactions have been described for effectiveness of treatments used to slow progression of cognitive decline in AD. Treatment with intranasal insulin showed a positive impact on cognition in male APOE ε4 carriers versus noncarriers, whereas their female APOE ε4- negative female counterparts experienced worsening cognition during insulin treatment. Impact of APOE ε4 genotype status in men and women with respect to response to cholinesterase inhibitors has been decidedly mixed. Knowledge of these sex differences in risk factors with respect to prevention, treatment, and prognosis highlight the importance of inclusion of SABV in all studies of normal cognitive aging, MCI, and dementia. The relationship between female sex and depression is particularly important given recent evidence that selective serotonin reuptake inhibitor treatment reduces accumulation of β-amyloid plaques in rodents and cerebrospinal levels of β-amyloid in humans.

Results from preclinical and human observational studies of estradiol treatment before a prolonged period of hypogonadism suggest a neuroprotective effect of estradiol. The impact of estradiol on brain structure and function with respect to cognition are profound and beyond the scope of this review. A study by the Women’s Health Initiative (WHI), though important, created some confusion regarding the role of estrogen in preventing cognitive decline. Since the WHI re-
leashed its findings of increased risk for thromboembolic events and cognitive decline in women randomized to conjugated equine estrogen and progestin medroxyprogesterone acetate, both preclinical and clinical researchers have put forth the “healthy cell hypothesis” that estradiol serves as a protectant when neural tissue is healthy.\textsuperscript{56} Administration of estrogen after prolonged periods of hypogonadism, which was the experience of many WHI participants, has shown to diminish the neuroprotective profile of the hormone and enhance markers of neuroinflammation. Cells have essentially become “less healthy” during the period of hypogonadism and aging.\textsuperscript{57,59}

Development of AD at a later age among women has been linked to greater lifetime exposure to estrogens.\textsuperscript{60} Nonetheless, during the late menopause transition, women experience a profound decrease in estradiol levels. Age-matched men either maintain their lifelong levels of gonadal steroids or experience a relatively slow decline in testosterone synthesis.\textsuperscript{54,61} Reductions in estradiol levels during the fifth decade and beyond may be responsible for deficits in brain metabolism and vascular pathologies, primarily among females, as age-matched males would still be aromatizing testosterone to estrogen. “Brain sex,” the degree of feminization and masculinization during development, is likely to moderate neuroprotective effects of estradiol and testosterone.\textsuperscript{61}

Inflammation is another risk factor for AD that varies by sex.\textsuperscript{62} with inflammatory dysregulation being stronger in females.\textsuperscript{63} Preclinical research suggests important sex differences in microglia, the primary immune cell of the CNS, during development and in response to fluctuating gonadal steroids across the life span. Females have been shown to have more microglia than in males, especially during adolescence, a time when female-biased disorders such as depression and anxiety are on the rise. Although causes of AD are unclear, it is possible that this disruption in microglia sets the stage for development of neurodegenerative diseases in older adulthood.\textsuperscript{52,64} Others have reported sexually dimorphic effects of glucocorticoids in brain regions critical to cognition.\textsuperscript{65} In humans, low-grade inflammation is a feature of a number of medical conditions such as diabetes, obesity, and depression, which are risk factors themselves for AD and vary in prevalence and impact on AD risk, as well as that of other dementia subtypes.\textsuperscript{66}

**Vascular dementia**

Vascular dementia results from ischemic or hemorrhagic insults to regions of the brain critical for cognitive functions.\textsuperscript{67} Research conducted worldwide indicates that stroke prevalence, whether ischemic or hemorrhagic, is 44\% higher in men than women. In addition, men experience their first stroke at a younger age, 68.6 years versus 72.9 years.\textsuperscript{3} Findings from the Framingham Study, however, indicate that women have a greater lifetime risk of stroke, perhaps given their longer life expectancy; increasing risk of stroke with age\textsuperscript{68}; and increased risk for thrombosis and stroke with atrial fibrillation and diabetes.\textsuperscript{69} A 2009 systematic review of the literature indicates that strokes tend to be more severe in women, with a 1-month case fatality of 24.7\% in females and 10.7\% in males.\textsuperscript{3}

Dementia is a consequence and a risk factor for stroke and vascular dementia. Many of the risk factors for stroke and multi-infarct dementia, such as atrial fibrillation, heart failure, high blood pressure, atherosclerosis, obesity, and diabetes, are more common among men, but women suffer disproportionate risk for dementia related to many of these risk factors.\textsuperscript{70,71} In a pooled analysis of 2.3 million individuals with over 100,000 cases of dementia, type 2 diabetes increased the risk for developing dementia by 60\%. In this sample, risk for dementia among women with diabetes was 19\% greater than for men.\textsuperscript{71} Female sex, medial temporal lobe atrophy, and family history of dementia, are stronger predictors of pre- than poststroke dementia. Prestroke dementia may be a sign or cause of a primary degenerative pathology that increases the likelihood of vascular events.\textsuperscript{72} Women are more likely than men to experience poststroke depression, another risk factor for dementia.\textsuperscript{73}

**Lewy body dementia**

The pathognomonic pathology in Lewy body dementia (LBD) is an abnormal accumulation of the protein α-synuclein, referred to as a Lewy body. Besides cognitive decline, common symptoms of LBD are visual hallucinations, sleep disturbance, autonomic dysregulation, fluctuating attention, depression, and Parkinson-like symptoms of bradykinesia, rigidity, and tremor. Clinically, LBD is distinguished from PDD by onset of dementia before or within the first year of onset of par-
kinsonism. Autopsy studies suggest that LBD accounts for 15% to 25% of dementia cases, making it the third most common type of dementia.\textsuperscript{74,76} Autopsy registries of individuals who died with known dementia revealed that Lewy bodies were present almost three times more often in males, regardless of age, smoking history, or education.\textsuperscript{7} This sex difference in prevalence is consistent with a recent analysis of LBD and PDD among citizens of Olmsted, Minnesota, diagnosed with parkinsonism between 1991 and 2005. There was an almost fourfold higher incidence rate for LBD among men in this population study.\textsuperscript{77} This male predominance is interesting given one of the risk factors for LBD is having a previous diagnosis of depression or anxiety, conditions more common among women.\textsuperscript{78}

**Frontotemporal dementia**

Unlike previously discussed dementias, frontotemporal dementia (FTD) is most prevalent among those 60 to 69 years of age, with roughly 13% having onset when younger than age 50.\textsuperscript{16} Younger onset may be due in part to heavy genetic loading for FTD, with up to 50% of cases being familial and up to 40% autosomal-dominant in nature.\textsuperscript{8,10} At least five genetic loci are associated with FTD, but none will be discussed herein as there are no data, to our knowledge, regarding potential sex interactions with these genes. Nongenetic risk factors include head trauma and thyroid disease.\textsuperscript{79} Estimated point prevalence documented in several large studies is 15 to 22/100,000 individuals,\textsuperscript{80,81} and there is evidence of a three-to-4.7-fold greater prevalence in males than in females,\textsuperscript{14,15} although this sex distribution has not been supported by all studies.\textsuperscript{82,83} Inconsistency in prevalence with respect to sex differences between studies may be due, in part, to heterogeneity in clinical presentations. Based upon the predominant early features, there is a behavioral variant of FTD both with and without evidence of motor-neuron disease, such as amyotrophic lateral sclerosis (ALS) and atypical parkinsonism. The behavioral variant is characterized by progressive behavioral impairment and decline in executive function; the semantic dementia variant is characterized by loss of object knowledge and anomia; and the progressive nonfluent aphasia (PNFA) variant is characterized by expressive or motor speech deficits.\textsuperscript{84}

Given the midlife onset of FTD, there is a dramatic reduction in life expectancy that does not appear to differ by sex.\textsuperscript{16} Survival partially depends on the variant of FTD and ranges from 2 to 3 years after symptom onset when motor neuron symptoms are prominent and up to 12 years for the semantic dementia variant.\textsuperscript{16}

**Dementia from multiple causes (mixed dementia)**

Mixed dementia refers to cognitive impairment due to multiple CNS pathologies. Most commonly, these pathologies are a combination of AD pathologies—β-amyloid deposits and tau tangles—and vascular compromise, such as that occurring with multiple microbleeds or infarcts.\textsuperscript{85} Autopsy reports suggest that vascular pathology occurs in up to 28% of AD cases.\textsuperscript{9,10,86} Dementia related to Parkinson disease (PD) is frequently accompanied by vascular-related lesions. A recent report from two longitudinal population-based studies, the Nun Study and HAAS (Honolulu-Asia Aging Study), found that neuropathic abnormalities such as Lewy bodies and AD changes were more common among white women in the Nun Study, whereas microinfarcts were more common in Japanese American HAAS men. As expected, cognitive decline was greatest among individuals with multiple types of neuropathologic changes, whether Lewy bodies, AD pathology, or vascular disease.\textsuperscript{87} Cerebrospinal fluid markers of AD found in individuals diagnosed with LBD were associated with a more rapid cognitive decline among those participating in a large European multicenter study of LBD.\textsuperscript{88} It is generally accepted that vascular dementias and mixed dementias occur more frequently in males, with rates of 31% versus 25% in females.\textsuperscript{76,11}

**Parkinson disease dementia**

PD, a movement disorder characterized by bradykinesia, rigidity, tremor at rest, gait disturbance, and difficulty with speech, is more prevalent in males. Loss of midbrain dopaminergic neurons in the substantia nigra pars compacta and consequently loss of dopamine input to the caudate nucleus and putamen (striatum) lead to the motor and nonmotor symptoms of PD. Depression, anxiety, insomnia, and cognitive decline, can impact quality of life for individuals with PD to a degree that rivals that of the motor symptoms.\textsuperscript{89} The prevalence of PD is between 0.3% and 3% of the population worldwide, with a 2 to 1 male to female ratio at any given age.\textsuperscript{5,6} On average, women are diagnosed 2 years later
(53.4 years) than men (51.3 years), perhaps due to a milder disease presentation among women. Women are likelier to present with a mild tremor, which is associated with a slower rate of motor decline. Whereas rigidity is more common among men with PD, dyskinesia and depression are more common among women with PD.

Sex differences in progression to dementia among individuals with PD are unclear. Men with PD have been reported to experience greater deficits in verbal fluency and recognition of facial emotions, whereas women reportedly experience more difficulties in visuospatial cognition. Findings from the NET-PD LS-1 (National Institutes of Health Exploratory Trials in Parkinson’s Disease Long-Term Study-1) suggest that among individuals undergoing treatment during the early stages of PD, women fare better than men with respect to cognitive functioning.

Several additional nonmotor symptoms differ in prevalence and severity by sex. Women with PD are likelier to report fatigue, nervousness, sadness, constipation, and restless legs, whereas men report more difficulties pertaining to daytime sleepiness, dribbling saliva, interest in sex, and problems having sex. Life expectancy and quality of life are diminished among individuals with PD who develop dementia, regardless of sex.

**Normal pressure hydrocephalus**

The classic presentation for normal pressure hydrocephalus (NPH) is the triad of gait or motor disturbance, cognitive impairment, and bladder sphincter dysfunction, but individuals may present with some combination thereof. Cognitive, motor, and behavioral changes associated with NPH occur as normal flow of cerebrospinal fluid within the brain becomes blocked, cerebrospinal fluid builds up, ventricles expand, and cortical tissue is compressed. NPH can be secondary to CNS insults, such as subarachnoid hemorrhage and infection, but cases with no identifiable cause are common and are referred to as idiopathic. The overall prevalence of NPH ranges from 0.02% to up to 5.9%, depending upon age and specific population studied.

Timely diagnosis of NPH is critical, as shunting to drain the cerebrospinal fluid can reduce pressure on the brain and improve prognosis. In a large population study conducted in Spain, where the male to female ratio for individuals 60 years and older was 0.756:1 in the general population, the male-to-female ratio for those with idiopathic NPH (iNPH) was 1.39:1 ($P<0.0001$). The corresponding incidence rate ratio between male and females with iNPH was 1.838 ($P<0.0001$), indicating that iNPH is almost twice as likely to occur in older males than older females.

**Creutzfeldt-Jakob disease**

Creutzfeldt-Jakob disease (CJD) occurs primarily in individuals older than 60 years of age and affects roughly 1 out of a million individuals worldwide. Although much about the pathophysiology of the disease is not known, investigators believe that the disease is caused by a prion, or misfolded protein, which aggregates in the brain and leads to neuronal death. In some variant cases, CJD presents with psychiatric symptoms, but problems with muscular coordination, personality changes, impaired vision, and rapidly progressive dementia are more common presentations. As with many other dementias, confirmation of diagnosis occurs postmortem when, in the case of CJD, spongiform changes in the brain can be directly observed. Premortem electroencephalography (EEG) can identify periodic sharp-wave complexes in approximately two thirds of patients whose diagnosis is later confirmed by pathology. Whether sporadic, inherited, or by contamination, cases of CJD do not appear to vary by sex, nor is survival time of 3.8 months (on average) from diagnosis different in males and females. It is known, however, that cerebrospinal fluid levels of T-tau and P-tau, markers of CJD, were significantly higher in women diagnosed with CJD in Sweden between 2002 and 2012, suggesting that CNS changes related to prions may differ to some degree in females.

**Conclusions**

Dementia prevalence and risk factors vary by and interact with the sex of the individual in some, but not all, types of dementia. Reproductive hormones and environmental factors program the brain in a sexually dimorphic manner across early development. Our understanding of the importance of this window of development with respect to risk and resilience for dementia is an area of increasing interest, as sex differences in brain development set the stage on which lifestyle and health conditions exert an influence. Gender comes into
play when societal factors create opportunities for advanced education and healthy lifestyles.

Behavioral interventions that target risk factors for dementia, such as those that focus on diet and exercise, must consider gender in order to be successful. Prevalence of exercise across the life span, uptake and compliance with recommended exercise plans, and motivation for physical activity vary by sex.\(^{10-12}\) Regrettably, there is a dearth of literature regarding the impact of sex on response to pharmacotherapy, including hormone therapy, in the prevention and treatment of dementia.

We are aware that risk factors interact with sex in several cases, but there is no literature clearly indicating whether sex impacts the effectiveness of strategies to prevent or target these risk factors. For example, we previously discussed the fact that type 2 diabetes exerts a greater risk for dementia among women than men. However, it is not known whether adequate glucose control would reverse this disproportionate risk among women. Similarly, concussion with loss of consciousness is more common among males, and thyroid disease occurs more frequently in women; however, to our knowledge, there is no literature regarding the role of sex in these conditions as it relates to risk for FTD or whether effective treatment of these conditions is preventative.

Given the prevalence of dementia in our society and the vast number of individuals who will be affected in the decades to come, it is critical that we further our understanding of how sex and gender create risk and resilience for dementia. Because sex is not typically modifiable, both it and gender may influence our treatments and the effectiveness in targeting modifiable risk factors.

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