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Invited Commentary

Invited Commentary: Examining Sex/Gender Differences in Risk of Alzheimer Disease and Related Dementias—Challenges and Future Directions

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The majority of people living with Alzheimer disease (AD) and related dementias are women. Longer life expectancy is one factor thought to contribute to this observation, but possible sex-specific biological mechanisms have received considerable attention from the research community. In the current issue of the *Journal*, Buckley et al. (*Am J Epidemiol*. 2019;188(7):1213–1223) use death certificate information on all deaths occurring among adults aged ≥60 years in Australia between 2006 and 2014 to evaluate sex/gender differences in rates of death with dementia (all types), AD dementia, and vascular dementia listed on the death certificate. The paper by Buckley et al. highlights several important methodological challenges for research examining sex/gender differences in risk of AD and related dementias, including challenges in measurement, survival bias and competing risks, and selection bias arising from sample selection. The current evidence on possible sex-specific biological risk factors for AD is intriguing, but there are numerous alternative explanations for differences in AD dementia and AD biomarkers between women and men. Triangulation of evidence from study designs with different strengths and weaknesses and transdisciplinary collaboration will be vital to generating conclusive evidence about sex/gender differences in risk of AD and related dementias.

Alzheimer disease; competing risks; dementia; gender differences; outcome measurement errors; selection bias; sex differences; survival bias

Abbreviations: AD, Alzheimer disease; ADRD, Alzheimer disease and related dementias.

Alzheimer disease and related dementias (ADRD) are a major public health challenge, and women are disproportionally affected: Nearly two-thirds of people living with ADRD in the United States are women, and the majority of caregivers for persons living with ADRD are women (1). Many women will be caregivers for a person living with ADRD (possibly for multiple generations of family members) and eventually develop ADRD themselves. One major factor contributing to the fact that the majority of people living with ADRD are women is that ADRD incidence increases substantially with age (2, 3) and more women than men survive to older ages (4).

Besides differences in longevity, the possibility that there are sex/gender differences in Alzheimer disease (AD) mechanisms and risk factors has received particular attention. If there are sex/gender differences in ADRD risk, identifying the processes that drive these differences could lead to new treatments or interventions to prevent or slow cognitive decline among all older adults. In this research area, it is important to distinguish between sex—a biological construct based on biological characteristics enabling sexual reproduction—and gender, a social construct (5). To date, much of the research on sex/gender differences in ADRD research has used these terms interchangeably, but sex-linked biology and gender roles may be independent or synergistic determinants of ADRD risk, including possible sex-based biological mechanisms for AD pathophysiology and historical gender differences in educational and occupational opportunities. The extant human-subject studies on ADRD cannot rigorously delineate effects of sex and gender. Throughout this commentary, I use the term "sex/gender" to reinforce that any observed differences in ADRD could be due to purely biological mechanisms, purely social mechanisms, or independent or synergistic effects of both.

Epidemiologic evidence about sex/gender differences in ADRD risk is equivocal, with many studies showing no difference in age-specific incidence rates of dementia overall (all-types dementia) or AD dementia (6, 7). Most epidemiologic studies that have reported sex/gender differences have shown higher incidence rates of AD dementia in women only among the oldest-old (i.e., persons aged 85 years or older) (8, 9). However, most of the epidemiologic studies on sex/gender differences in ADRD incidence with long follow-up periods and sample sizes large enough to support precise age-specific incidence rate estimates were published in the 1990s. Findings from some animal studies (10), autopsy studies (11), and biomarker studies (12–14) suggest that sex-specific biological mechanisms could possibly lead to elevated susceptibility of women to AD pathology. Given the equivocal evidence on sex/gender differences in ADRD incidence from epidemiologic studies, the continued interest in studying potential sex/gender differences in ADRD has likely been bolstered by findings from animal, autopsy, and biomarker studies, which report sex/gender differences more consistently than epidemiologic studies, although the evidence from these studies is far from conclusive. As with epidemiologic studies, the extant autopsy studies and biomarker studies may also be prone to conflate potential effects of sex and gender.

In the current issue of the *Journal*, Buckley et al. (15) examined rates of death with dementia based on death certificate information on all deaths occurring among persons aged 60 years or older in Australia between 2006 and 2014. The majority (58%) of deaths with dementia listed on the death certificate were coded as "unspecified" dementia. In age-adjusted models, rates of death with dementia (all types) listed on the death certificate were similar for women and men, rates of death with AD dementia listed on the death certificate were higher for women, and rates of death with vascular dementia listed on the death certificate were higher for men. The paper by Buckley et al. highlights several major methodological challenges for research examining sex/gender differences in risk of ADRD, including challenges in measurement, survival bias and competing risks, and selection bias arising from sample selection.

CHALLENGES IN MEASUREMENT OF ADRD

Measurement is a major challenge in ADRD research. Dementia is a clinical syndrome defined by a decline in memory, language, problem-solving, and other cognitive skills that interferes with activities of daily living (16). AD and vascular pathology are progressive brain diseases that are widely believed to be the main pathologies contributing to most cases of dementia (1), and autopsy studies suggest that most people with dementia have both AD and vascular pathology (17). In addition to the presence of multiple etiologies in most people with dementia, measurement in ADRD research is further complicated by the fact that not everyone with dementia-related pathology develops dementia in their lifetime: In autopsy studies, many older adults who did not have dementia when they were alive had evidence of dementia-related pathology in their brain at death (17, 18). Thus, the clinical syndromes corresponding to a diagnosis of AD dementia or vascular dementia do not have perfect sensitivity or specificity for the (probably complex) underlying pathology. Even all-cause dementia (regardless of subtype diagnosis) may be inconsistently diagnosed among people with the same underlying level of dementia-related pathology.

Measurement challenges in ADRD should be carefully considered in research evaluating sex/gender differences in ADRD incidence. Sex/gender differences in clinical presentation and/or diagnosis of dementia among people with dementia-related pathology (19) could contribute to estimates of sex/gender differences in dementia incidence, even if there are no sex/gender differences in underlying dementia-related pathology. Sex/gender differences in comorbidity could contribute to sex/gender differences in diagnosis of vascular dementia versus AD dementia. People with dementia symptoms and a history of stroke are more likely to be diagnosed with vascular dementia (20). The higher incidence and prevalence of stroke in men (21) means that clinicians may be more likely to attribute identical clinical dementia symptoms to AD dementia in women and to vascular dementia in men, even if there is no true difference in the burden of AD pathology by sex/gender.

Challenges in measurement of ADRD could contribute to the higher observed rates of AD dementia among women and higher rates of vascular dementia among men in the study by Buckley et al. (15) and other studies. As Buckley et al. note in their Discussion, measurement is further complicated in research relying on death certificates (15). More than half (58%) of dementia cases in their data were coded as "unspecified" dementia, 30% were coded as AD dementia, and 12% were coded as vascular dementia. Additionally, in their prior work examining reporting of dementia on death certificates in the Australian Longitudinal Study on Women's Health, 54% of women with a dementia diagnosis in life did not have dementia listed on their death certificate, and 16% of women with dementia listed on their death certificate did not have a dementia diagnosis in life (22). With these multiple sources of misclassification of dementia (all types), AD dementia, and vascular dementia, even slight sex/gender differences in the probability of misclassification might explain the sex/gender differences in AD dementia and vascular dementia observed by Buckley et al. (15) and in other studies examining sex/gender differences in ADRD. Quantitative bias analysis (23, 24) could be a useful tool for quantifying the magnitude of potential bias arising from misclassification in ADRD research and to evaluate whether misclassification could plausibly explain the sex/gender differences in AD dementia and vascular dementia in the study by Buckley et al. (15), as well as other studies examining sex/gender differences in risk of ADRD.

SURVIVAL BIAS AND COMPETING RISKS

ADRD incidence increases dramatically with age, and more women than men survive to late life (4). If incipient (preclinical) ADRD influences mortality or there are common causes of ADRD and mortality, the population of men surviving to older ages will disproportionately include men with lower ADRD risk profiles. This selection process could induce noncausal associations between sex/gender and ADRD (this source of bias is often is often called survival bias (24, 25), a special case of collider-stratification bias (26)), especially among the oldest

old—the age group in which sex/gender differences in ADRD are most commonly observed. That is, the population of men who survive to late life could be more highly selected than the population of women who survive to late life. If this selection process is associated with ADRD risk, this could lead to sex/gender differences in ADRD (including clinical dementia and dementia-related brain pathology), even if biological mechanisms for ADRD are identical for men and women.

In addition to survival bias, death due to other causes can preclude onset of ADRD, so elevated mortality rates in one group of people, especially at ages before ADRD incidence is common, reduces lifetime risk of ADRD in that group. Even in causal structures not consistent with survival bias, the competing risk of death from other causes will result in sex/gender differences in lifetime risk of ADRD (27).

SAMPLE SELECTION

Buckley et al. included all deaths occurring among older adults in Australia during the study period (15), an impressive undertaking. In contrast, many biomarker and autopsy studies, which provide the opportunity for more precise measurement of ADRD pathology and cognitive function, are often conducted in highly selected samples of persons recruited from memory clinics. As noted above, results from some biomarker and autopsy studies have provided support for potential sex-specific biological mechanisms for ADRD (11–14). Sample selection has the potential to result in biased or entirely spurious associations between sex/gender and ADRD pathology biomarkers in the study samples arising from collider-stratification bias (26) if sex/gender (or a social or environmental correlate of sex/gender) and the biomarker (or a correlate of the biomarker, such subjective memory decline) influence selection into the study sample.

CONCLUSIONS

The quest to identify effective strategies to prevent and treat ADRD is hampered by our limited understanding of the causes of this complex group of diseases. Delineating whether there are sex/gender differences in ADRD risk has the potential to expand our understanding of the biological mechanisms underpinning ADRD. Transdisciplinary collaborations including epidemiologists, biostatisticians, neuroscientists, neuropsychologists, neuropathologists, and neurologists have the potential to address the challenges in this important area of research. Triangulation of evidence from different types of studies carried out in diverse settings with different strengths and weaknesses, including empirical research in diverse populations and simulation studies, will be vital to generate clear evidence about potential sex/gender differences in ADRD.

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