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Research Report

Sex Differences in the Risk of Dementia in Older Veterans

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Abstract

Background: Studies have demonstrated women to have a higher prevalence of dementia compared to men. However, sex differences in dementia incidence are controversial with conflicting reports showing women with higher, lower, or similar incidence. Source of difference may be due to clinical setting and lack of consideration of competing risk of death. We examined dementia incidence in a sample of the national Veteran population to determine differences by sex.

Methods: We examined data from the Veterans Health Administration (VHA), the largest integrated health care system in the United States. We studied 947 797 Veterans aged ≥55 years (mean age: 69.9 ± 8.4, 3% female) evaluated in the VHA from October 1, 1999 to September 30, 2019. We estimated age-adjusted incidence rates of dementia (*International Classification of Diseases, 9th and 10th Edition* codes) by sex, and used Fine–Gray proportional hazards models with age as time scale to examine time to diagnosis, accounting for competing risk of death.

Results: During the follow-up (mean 8.4 years), 11.3% (n = 106 977, 11.4% men and 8.0% women) of Veterans developed dementia. Age-adjusted incidence was 12.6/1 000 person-years for men and 12.7/1 000 person-years for women. Compared to male Veterans, risk dementia was slightly higher among females (hazard ratio = 1.15; 95% confidence interval: 1.10–1.20), and on average, female Veterans developed dementia 0.2 years earlier than male Veterans. After additional adjustment for race, education, medical, and psychiatric conditions, results were similar.

Conclusions: Among older Veterans in a national cohort, women had a slightly increased risk for developing dementia compared to men after accounting for competing risk of death.

Keywords: Dementia, Dementia incidence, Dementia prevalence, Gender, Sex, Veterans

Dementia is characterized by cognitive and functional impairment and is one of the leading causes of morbidity and mortality worldwide (1). A number of studies have consistently shown that women experience higher dementia prevalence compared to men (2,3). This has been attributed to lower life expectancy in men and biological differences between the sexes. What remains unclear is if there are differences in dementia incidence by sex. Prior studies are conflicting with some suggesting women have higher incidence, others suggest that men have higher incidence, and still others have found no difference by sex (4–10). This variability is not well understood but may be due to the populations studied and other methodological differences including whether the competing risk of death from causes other than dementia is considered.

Older Veterans are a population within the United States that may have higher risk for dementia. Compared with non-Veterans, Veterans have higher rates of traumatic brain injury (TBI), posttraumatic stress disorder (PTSD), and depression, all risk factors for cognitive impairment and dementia (11–13). Female Veterans exposed to these military risk factors are also at increased risk for dementia diagnosis, yet it is unclear if male and female Veterans differ in their incidence of dementia (14). Studying Veterans who are enrolled in the Veterans Health Administration (VHA), the largest integrated health care system in the United States, provides a unique

opportunity to investigate the role of sex in dementia incidence. The VHA sample is more "real-world" and allows for national representation of all Veterans who receive their care in VHA medical centers.

Method

Study Population

We identified a random sample of all Veterans obtaining care at VHA medical centers, aged 55 and older, from October 1, 1999 to September 30, 2019. For each fiscal year from FY00 through FY19, we selected a 2% random sample from a total sample of 9 499, 811 unique veterans and merged these samples for all years. This resulted in a random sample of 1.1 million Veterans receiving VHA care during that time period.

We obtained demographic information and dementia diagnoses from all inpatient and outpatient visits available from the National Patient Care Databases and mortality status from the Vital Status File database. Participants were required to have at least 1 visit during the 2-year period prior to their baseline, and at least 1 follow-up visit (n = 986 981). We excluded participants with prevalent dementia (n = 24 979) during the 2-year baseline and those with other/unknown race (n = 14 205). Our final analytic cohort was comprised of 947 797 Veterans.

Protocol Approvals

All study procedures were approved by institutional review boards at University of California, San Francisco; San Francisco Veterans Affairs Medical Center; and the U.S. Army Medical Research and Material Command, Office of Research Protections, Human Research Protection Office. Informed consent was waived because the study involved retrospective review of administrative data from the VHA.

Measures

Dementia

We defined prevalent dementia during baseline (for exclusion) and incident dementia over follow-up using the *International Classification of Diseases, 9th Revision and 10th edition* (ICD-9/ICD-10) codes recommended by the Veterans Affairs (VA) Dementia Steering Committee.

Demographics

Demographic data included self-reported age, sex, race/ethnicity, and education. Self-reported race/ethnicity was categorized into 4 groups: non-Hispanic White (hereafter, White), Black, Hispanic, and Asian. Survey data were used to categorize Veterans' residences into educational categories (≤25% or the adult population has earned a bachelor's degree or higher vs >25%).

Comorbid conditions

We identified medical and psychiatric comorbidities using ICD-9 and ICD-10 codes during the 2-year baseline. Comorbidities included hypertension, diabetes, TBI, PTSD, and depression.

Analyses

Baseline characteristics of veterans were compared according to sex using t tests for continuous variables and χ^2 analysis for categorical variables. The practical incidence estimators macro developed by the Framingham Study investigators was used to derive sex differences in dementia incidence rates, person-years, and age-adjusted incidence rates per 1 000 person-years.

Fine–Gray proportional hazards models were then used to estimate sex differences in risk of dementia with age as time scale while accounting for the competing risk of death. Time to event was calculated from the date of the first encounter until dementia diagnosis (whichever occurred first). Veterans who did not die or develop dementia over follow-up were censored at the last medical encounter. Traditional Cox proportional hazards regression considers those who die as censored, which assumes that they would still be "at risk" if additional follow-up had been available. Fine–Gray models treat death as an alternative "competing risk" thereby providing a more conservative estimate of the association. Models were unadjusted and adjusted in steps for demographics (race/ ethnicity) and demographics and comorbid conditions (race/ethnicity, education, hypertension, diabetes, PTSD, TBI, and depression) and reported as hazard ratios (HRs) with 95% confidence intervals (CIs). All p values were 2-sided with significance set at $p < .05$. Analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC).

Results

Of the 947 797 Veterans without dementia at baseline, 3.2% were female (n = 29 895), and the average age was 69.9 (SD 8.4) years. Most Veterans were White (87.5% [n = 829 240]), 10.8% were Black (n = 102 330); the remaining were Hispanic (1.0% [n = 9 722]) or Asian (0.7% [n = 6 505]), consistent with previous reports of the racial/ethnic distribution in older VHA patients. Average follow-up time was 8.4 (SD 5.6) years. Approximately 33% of the sample (n = 307 838) died during follow-up. Table 1 shows the baseline characteristics of the Veterans by sex.

Overall, 106 977 Veterans (11.3%) developed dementia during follow-up (11.4% of men and 8.0% of women). We found that men (12.6/1 000 person-years) and women (12.7/1 000 person-years) had similar age-adjusted dementia incidence rates (Table 2). The risk of dementia in unadjusted models with age as timescale accounting for the competing risk of death was slightly higher among females compared to males (HR = 1.15; 95% CI: 1.10–1.20). After adjustment for race the adjusted risk for dementia was 1.16 (95% CI: 1.11–1.21) for female versus males. Further adjustment for education, medical and psychiatric comorbidities led to similar results (HR = 1.12; 95% CI: 1.08–1.17). The Figure 1 shows that cumulative incidence of dementia based on age as the timescale was higher for female Veterans compared to male Veterans, and indicates that the curves for the sex groups begin to diverge at around age 70. On average, female Veterans developed dementia 0.2 years earlier than male Veterans (7.66 vs 7.82 years, $p < .001$).

Discussion

Our study of >900 000 older Veterans investigated the relationship between sex and dementia incidence in a nationwide sample. We found that female Veterans had a small but significant increased risk for developing dementia compared to male Veterans after accounting for competing risk of death. This finding is important as it provides evidence of higher incidence of dementia in women within a cohort of Veterans enrolled in the largest national, integrated health care system in the United States.

Prior studies on sex difference in dementia incidence have offered contradictory findings and are often restricted to smaller research

Table 1. Baseline Characteristics of Older Veterans by Sex

Characteristic [mean (*SD*) or *N* (%)]	Male (*n* = 917 902)	Female (*n* = 29 895)	*p* Value
Age, years	70.0 (8.3)	67.0 (9.1)	<.001
Race			<.001
White	804 760 (87.7)	24 480 (81.9)	
Black	97 537 (10.6)	4 793 (16.0)	
Hispanic	9 528 (1.0)	194 (0.7)	
Asian	6 077 (0.7)	428 (1.4)	
>25% college-educated ZIP Code*	382 861 (42.4)	13 425 (46.0)	<.001
Hypertension	613 915 (66.9)	15 277 (51.1)	<.001
Diabetes	251 936 (27.4)	5 443 (18.2)	<.001
Traumatic brain injury	3 649 (0.4)	178 (0.6)	<.001
Posttraumatic stress disorder	61 116 (6.7)	2 229 (7.5)	<.001
Depression	117 517 (12.8)	6 589 (22.0)	<.001

Notes: *SD* = standard deviation.
*Education had 15 596 (1.6%) missing values.

Table 2. Dementia Incidence and Risk by Sex Among 947 797 Older Veterans

Sex	No. Event	No. Person-Years	Age-Adjusted Incidence Rate Per 1 000 Person-Years	Hazard Ratio (95% CI)
Men	104 587	8 262 844	12.6	1 [Reference]
Female	2 390	215 926	12.7	1.15 (1.10, 1.20)

Notes: Hazard ratios are from the Fine–Gray model. CI = confidence interval.

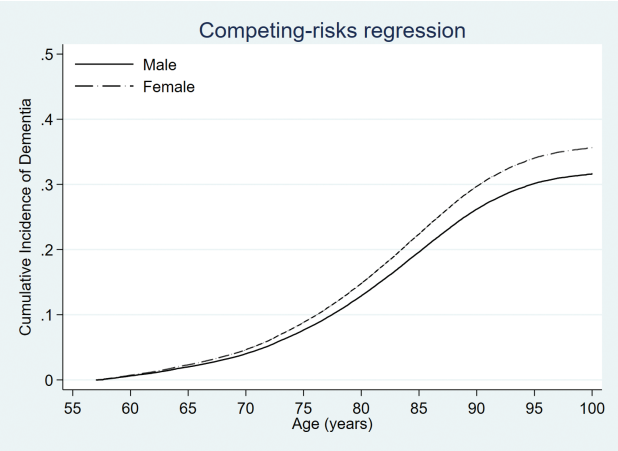

Figure 1. Cumulative incidence curve of dementia for male and female Veterans, accounting for the competing risk of death. Age is used as the timescale. Full color version is available within the online issue.

cohorts who were likely less representative of the national population. For example, in the Framingham Heart Study, the cumulative incidence of dementia was significantly higher among females than among males after the age of 85 years, the Adult Changes in Thought study found no significant sex differences in dementia incidence, and the Monongahela Valley Independent Elders Survey found higher incidence of dementia in men (4–6). Our large cohort study of older Veterans sheds light on the controversy over sex differences in dementia incidence when death from all cause-mortality is a competing risk among patients.

Our results showing sex difference in dementia incidence in a nationwide sample with relatively equal access to health care are consistent with the findings of several prior studies that have shown sex-based differences in dementia incidence among civilians (6–10). The mechanism of this increased risk is not well understood but likely multifaceted. Alzheimer's disease (AD) is the most prevalent form of dementia comprising 60%–70% of all cases, and numerous studies have found women to be more susceptible to AD diagnosis. This may be due to several mechanisms that include: (i) greater risk of dementia from the Apolipoprotein E ε4 allele among women (15); (ii) the loss of neuroprotective effects of estrogen after menopause (16); (iii) neuroanatomical differences between men and women (17); and (iv) social/lifestyle differences between men and women (18). A recent study that examined risk factors for all cause dementia found that the pattern of sex differences in dementia risk factors suggested that higher rates of dementia in women in late life may be due to their having fewer modifiable risk factors over the life course and greater susceptibility to the effect of vascular risk factors (19). Still, other studies have found lower incidence of dementia in women, and there are indications that the X chromosome may contribute to resilience against dementia (14,20).

There are some important limitations to our study which affect the interpretation and generalizability of our results, particularly the use of ICD-9/ICD-10 codes to establish diagnoses. Dementia diagnosis was solely determined though ICD-9/ICD-10 codes, which restricted our study population to Veterans who received a diagnosis of dementia during a VA health care visit. While our cohort of Veterans represents a "real-world" sample of patients, we had limited ability to examine Veterans who did not receive care through the VHA health care system, those who may have been house-bound, and the non-Veteran population, so results may not be broadly generalizable. Administrative diagnostic codes are less sensitive than structured interviews, and it is likely than Veterans with less severe symptoms of dementia did not receive diagnoses. Finally, we were unable to examine dementia diagnosis by subtype which is not well defined in electronic medical records.

This study demonstrates innovation in the use of data from the largest integrated health care system in the United States to explore

the relationship between sex and dementia. Our results suggest that there is a slightly higher risk of dementia among female Veteran population and highlights the need to identify reasons for the sex difference in dementia as the aging female population continues to grow.

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Conflict of Interest

J.E., A.B., E.K., and F.X. report no conflict of interest. K.Y. serves on Data Safety Monitoring Boards for Eli Lilly and several National Institute on Aging-sponsored trials and serves on the board of directors for Alector, Inc.

Author Contributions

Statistical analysis conducted by F.X., MS, MPH, SFVA/NCIRE and A.B., PhD, UCSF/NCIRE.

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