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Differences Between Women and Men in Incidence Rates of Dementia and Alzheimer's Disease

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Abstract

In the following brief report, we examined gender differences in incidence rates of any dementia, Alzheimer's disease (AD) alone, and non-Alzheimer's dementia alone in 16,926 women and men in the Swedish Twin Registry aged 65+. Dementia diagnoses were based on clinical workup and national health registry linkage. Incidence rates of any dementia and AD were greater in women than men, with any dementia rates diverging after age 85 and AD rates diverging around 80. This pattern is consistent with women's survival to older ages compared to men. These findings are similar to incidence rates reported in other Swedish samples.

Keywords

Alzheimer's disease; any dementia; gender differences; incidence; Swedish Twin Registry

INTRODUCTION

Two-thirds of clinically diagnosed cases of dementia and AD are women, according to U.S. [1] and most European reports. The primary reason offered for this gender difference is women's greater longevity [2], as risk of developing dementia increases with age. In spite of this proposed explanation, the extent to which gender differences are primarily a matter of the increasing number of women relative to men at older ages or also of women's having a greater risk than men at the same age remains to be resolved. The extant literature is far from conclusive, consisting mainly of plausible hypotheses about sex-specific biological and gender-specific sociocultural factors that might increase women's vulnerability over men's [3–5]. Ultimately, understanding gender-specific trends in dementia and AD may point to

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SUPPLEMENTARY MATERIAL

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preclinical factors that might lower risk of onset differentially in men and women [6]. In the present study, we examine differences between men and women in risk of any dementia, AD alone, and non-AD dementia (NAD) alone by looking at incidence density rates by age and gender.

The higher number of AD or dementia cases among women is often taken to suggest that women have a higher incidence. Yet, a closer inspection of the literature reveals a more complicated account. First, few studies report statistically significant gender differences in incidence rates [6]. Second, meta-analysis has not clarified similarities and differences in rates across international samples [7]. In European samples, several studies have observed gender differences [8–11] whereas the majority do not [12–16]. Gender differences also are observed in U.S. samples [17–20], although again some do not observe them [21–23] or observe them where they previously did not [24, 25].

Irrespective of statistical significance, many studies descriptively suggest gender differences. Incidence rates in women consistently were higher than men in numerous European and U.S. samples [9, 12, 14, 16, 18, 24, 26–31]. Small samples may explain the lack of significant differences between men and women in these studies [24]. Pooling samples in meta-analyses to increase sample size generally demonstrates significant gender differences in AD incidence [7, 32, 33]. One exception, however, is a recent pooled analysis [34] that concluded no gender differences in AD risk between age 55 and 85.

Where gender differences have been observed, they tend to be observed later in life, with the inflection point at which rates begin to differ between men and women also varying by study. While most studies support a pivot age at approximately 80 years old—in which incidence rates in women either switch position with or climb above men's rates [17–20, 23–25, 35, 36]—there is quite a bit of variability. Previous studies have reported incidence rates that begin to diverge as early as 75–79 years (the Baltimore Longitudinal Study [37]) and as late as 90+ (Kungsholmen Project [8]).

The aim of the current report is to contribute to this literature by tracing annual incidence density rates of older adult participants in the Swedish Twin Registry (STR) to evaluate whether and at what age rates of newly diagnosed cases of dementia are higher in women than men. Using the STR offers several benefits, including a large sample from a single source; the ability to link to administrative records; and the application of uniform methodology to estimate incidence rates for men and women across a broad range of ages. Incidence rates that do not differ by gender would suggest that the greater number of dementia cases in women must be largely a function of their greater longevity, with more women than men surviving long enough to become demented. If incidence rates do differ by gender, survival remains one among many explanations ranging from genetic to environmental causes [17].

METHODS

Sample

The sample was drawn from four different studies of Swedish older adults, all sampled from the STR [38] and all born between 1895 and 1935:1 cross sectional census of all twins in the STR aged 65 and older at the time of study and three longitudinal studies that followed representative sub groups within the STR from the same birth cohort. Some individuals participated in both a longitudinal study and the cross-sectional assessment (described in the Supplementary Material); each was included in the sample only once, but drawing data from both studies combined. In all, 17,349 individual twins were included in the current sample. At first assessment, mean age of men was 71.40 years ($SD = 8.75$) and mean age of women was 72.61 years ($SD = 9.13$), with 16.87% of the sample with a final study age of 85 years or greater ($n = 2,927$). Sample sizes are presented in Table 1 for the total sample and Supplementary Table 1 for individual STR studies.

Dementia assessment

All participants received cognitive screening at each contact. Longitudinal study participants were administered a cognitive test battery including the Mini-Mental State Examination. The cross-sectional census included the TELE cognitive screening measure [39], with an in-person dementia diagnostic workup for those who performed poorly. Additionally, in-person dementia diagnostic assessments were conducted on a control sample who made few screening errors for purposes of validation. For participants who missed a longitudinal wave, telephone cognitive screening was also conducted. For all four studies, a diagnostic consensus board assigned a consensus clinical diagnosis using information from the in-person workup and medical records using DSM-III-R and DSM-IV criteria for dementia, and NINCDS-ADRDA criteria for AD [40]. The same consensus protocols were used across all four studies.

Those not in a longitudinal study or otherwise lost to follow-up were followed by registry linkage, using individual-level data from the Swedish National Patient Register (NPR) and Cause of Death Register (CDR). Registries contained International Classification of Disease (ICD) codes for dementia diagnoses (provided in the Supplementary Material). Of the 3,871 individuals with a dementia diagnosis, 2,325 were diagnosed with AD and 1,546 with another form of dementia (mainly comprising vascular dementia, mixed type, and dementia not otherwise specified). Follow-up continued until 2014, providing a retrospective cohort design.

Participants designated as not having dementia ($n = 13,478$) were those who were determined to be cognitively normal through participation in at least 1 data collection by a longitudinal study or through the cognitive screening of the entire STR. All others were excluded from the current study sample ($n = 423$).

Age at onset

Individuals who were clinically diagnosed with dementia received an age at onset based on information collected during their in-person clinical assessment. For individuals whose

diagnosis came from the NPR, age at onset was inferred by subtracting three years from NPR date of discharge, which is a conservative estimate given that other analyses of the STR data have established that onset typically is five years before diagnoses appear in the NPR [41]. For individuals whose diagnosis came from the CDR, age at onset was designated as three years prior to date of death [41] plus a small amount of normally distributed random “noise” [$N(0,0.66)$] to model natural occurring variability in onset.

Data analysis

Incidence rates for dementia were calculated for all individuals using person-years [36]. Participants were determined to be cognitively intact at baseline based on in person evaluation, assessment age ≥ 60 , or no registry diagnosis of dementia. Crude rates were estimated by dividing the number of newly diagnosed individuals by the total number of person-years at risk for every year from age 60 to age 100. Newly diagnosed cases were based on age at onset. Rates are expressed per 1000 person-years, with number of years lived past age 60 serving as the time scale (i.e., start of the study window). Age 60 was selected as the “point of entry” to capture the 5-year period prior to the phase of risk for late-onset dementia. Person years were calculated for demented individuals (cases) and nondemented individuals (controls). Cases contributed 1 person year for every year lived until age of dementia diagnosis. For cases, we estimated disease onset as the midpoint between the last age they were nondemented and their age of onset. Thus, individuals diagnosed at age 72 contributed 1 person year from age 60 until age 71, but at age 72 contributed only 0.5 person year. Person-years contributed from each nondemented individual was 1 additional year for every year lived until age death. Local polynomial regression fitting (loess) was used to estimate the 95% confidence intervals (CIs). Incidence rates for any dementia, AD alone, and NAD are presented. Where 95% CIs overlap, the results do not support a statistically significant gender difference in incidence rates.

RESULTS

Gender differences in incidence rates of dementia

Table 1 presents the proportion of men and women diagnosed with any dementia, AD alone, and NAD alone. Of the 3,871 individuals with a dementia diagnosis, 2,325 were diagnosed with AD and 1,546 with another form of dementia. Women were more likely than men to be diagnosed with any dementia and AD whereas NAD was more equally prevalent. Incidence rates of any dementia for men and women were nearly equivalent until the early 80s, but diverged thereafter and significantly diverged between 85 and 90 years of age (Fig. 1a). Beyond 90, incidence rates for both men and women declined, most likely because of the sparseness of data in old-old age. For AD alone, significant divergence in rates occurred at approximately 80 years of age. Although divergence is visually more prominent at a somewhat younger age (younger than 75), the confidence intervals of the loess lines still overlap (Fig. 1b). For NAD alone, rates are similar between men and women until greater than 90 years of age, at which point women have significantly higher rates than men despite slight visual differences (Fig. 1c). Patterns were similar when incidence rates were traced only with clinically diagnosed cases of dementia as well as separately in the cross-sectional census alone and combined longitudinal samples.

To draw support for the explanation that longevity plays a role in women's greater incidence rates than men's at older ages, we estimated survival rates of nondemented men and women. Men had lower likelihood of survival beyond age 90 compared to women (Fig. 2), with women's survival nearly double men's and diverging with men's between ages 70–75.

DISCUSSION

Epidemiological studies present a bewildering impression of gender differences in dementia and AD. Careful review of published data suggests that in most studies, gender differences in incidence rates do not emerge until after age 80. European studies have more consistently reported gender differences; yet, lack of consensus between and within American and European study samples illustrates heterogeneity in rates and ages of divergence in male and female rates. In the current study, any dementia rates were relatively similar until after age 80, with women reaching significantly higher rates than men in the late 80s. For AD alone, women had significantly higher rates of AD starting in the early 80s.

The current results fit well with previous findings in a number of U.S. and European samples [8, 10, 28, 33, 35] where women's rates were observed to be consistently higher than men's after age 80, and rates declining in both genders in old-old age. Contrary to previous findings, we found statistically significant differences in AD rates at an earlier age than for any dementia. Women's survival to longer ages may be one explanation for women's higher incidence of dementia and AD, possibly. Other explanations may be etiological differences, selective attrition of men due to early mortality attributable to cardiovascular risk factors with a competing risk of death or dementia, and lower thresholds of disease pathology required to produce symptoms [17]. The current results encourage deeper investigation of biological and environmental mechanisms that put women at greater risk compared to men [6].

The combination of clinical and registry-based diagnoses stabilize incidence rates into the early 90s, offering reasonable resolution of gender differences in risk during this period. These results can be safely generalized to nontwin Swedish populations, as they support and extend reports from the Kungsholmen Project [8], and prior research noted similar prevalence rates in the STR compared to other population-based European and U.S. samples [42].

Non-AD dementia rates primarily reflect vascular dementia, but include other dementias and are therefore confounded by differing genes of pathology. The NAD results are useful in making clear that rates for any dementia mainly represent AD.

The study has several limitations. First, not all dementia diagnoses were made from clinical assessments. However, use of registry-based diagnosis provides reliable identification of dementia and AD cases in the Swedish National Patient Registry [43], with no evidence of gender differences in sensitivity of the registries. Albeit, the registry underestimates true cases and has a sensitivity of about 0.50. Second, secular trends could not be addressed in the current study. Third, a retrospective cohort design was used that included an older population who survived longer to be included in the study, which may have introduced bias

attributed to selective mortality from competing causes of death (e.g., cardiovascular disease) and dementia onset between genders in older age groups [17]. Ideally, all data would have come from longitudinal research designs, with all participants non-demented at baseline. The advantage, however, was an increase in power and representativeness.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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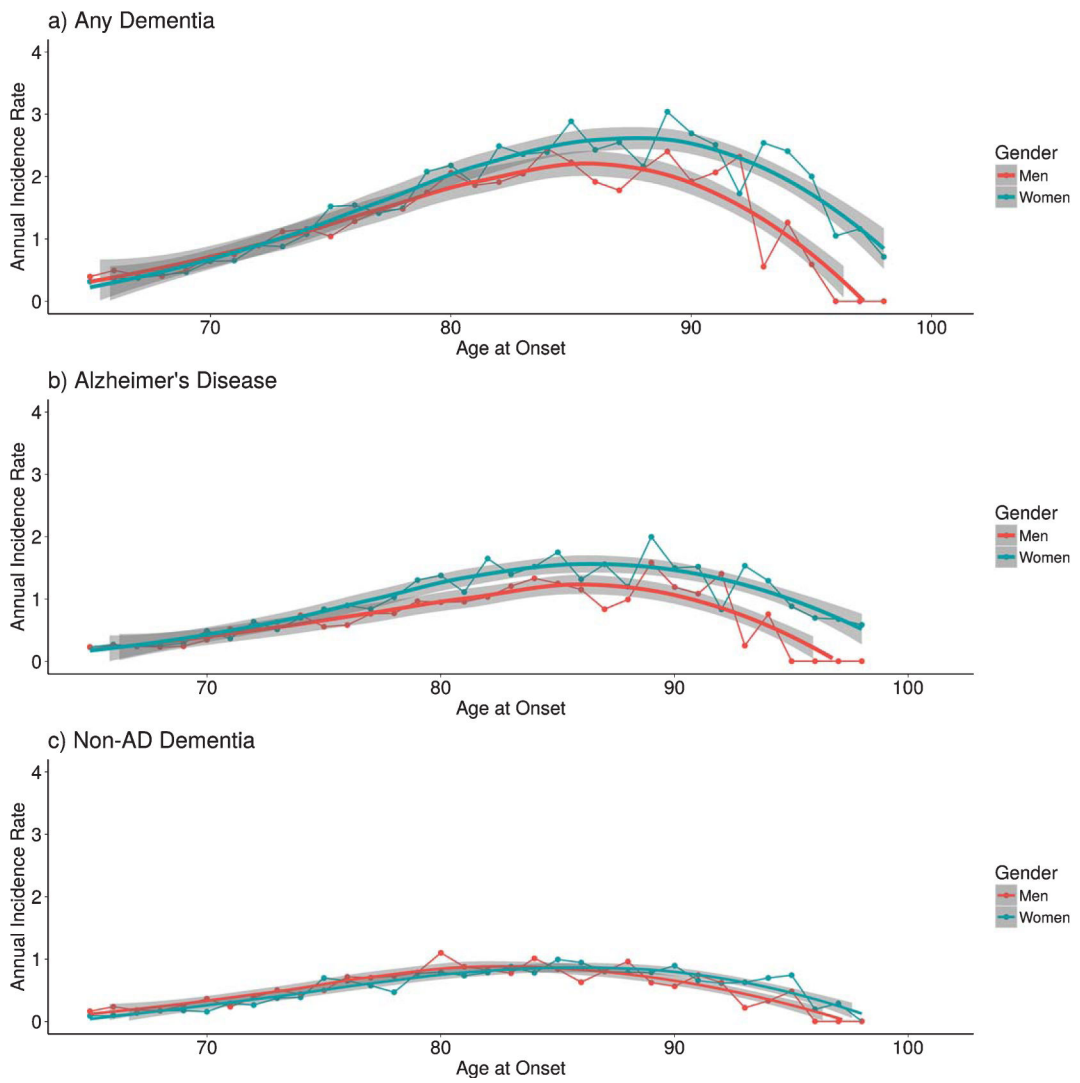


Fig. 1. Incidence density rates of a) any dementia, b) Alzheimer’s disease, and c) non-AD dementia per 1000 person-years in men and women twins across late adulthood. Loess smoothing lines (with 95% confidence interval) were fit using nonparametric local polynomial regression fitting methods.

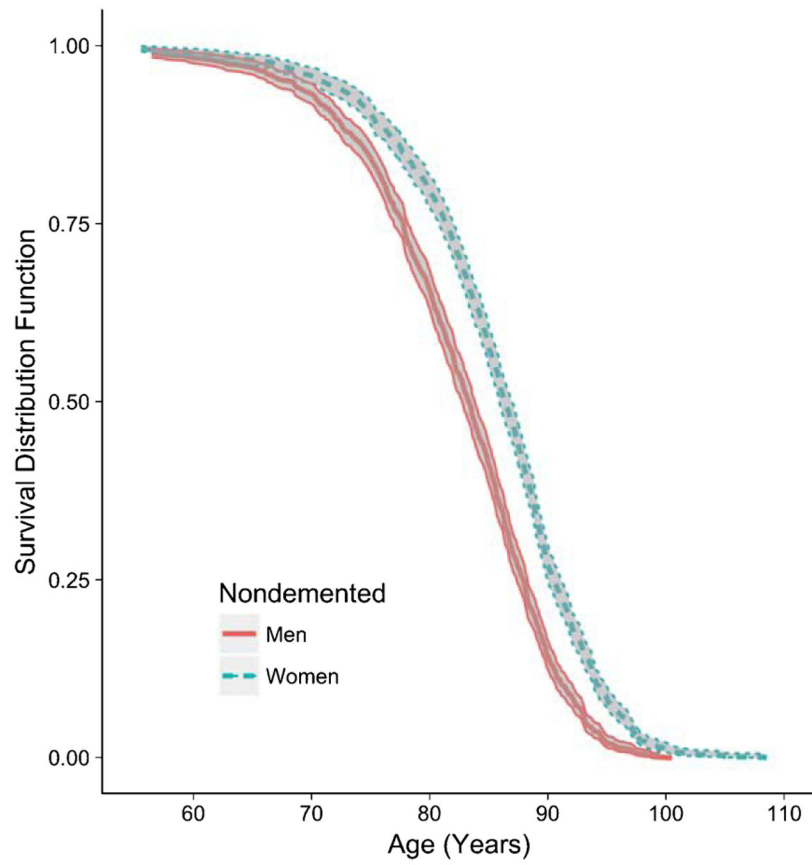


Fig. 2. Kaplan-Meier survival curves of nondemented men and women. The exact probabilities of survival beyond age 90.0 are 0.14 for men and 0.27 for women.

Table 1

Descriptive statistics of any dementia and Alzheimer’s disease for men and women

Sample	Any Dementia		AD Only		Non-AD Dementia		No Dementia Diagnosis		Total	
	N (%)	Age at onset (SD)	N (%)	Age at onset (SD)	N (%)	Age at onset (SD)	N (%)	Age at onset	N	N
Male	1386 (18.54)	79.84 (7.58)	765 (10.24)	80.02 (7.86)	621 (8.31)	79.62 (7.22)	6088 (81.46)	-	7474	
Female	2485 (25.16)	81.47 (7.53)	1560 (15.80)	81.33 (7.71)	925 (9.37)	81.69 (7.21)	7390 (74.84)	-	9875	
Total	3871 (22.31)	80.88 (7.59)	2325 (13.40)	80.90 (7.78)	1546 (8.91)	80.86 (7.28)	13478 (77.69)	-	17349	

Note. Total sample is equal to the sum of the sample sizes of Any Dementia and No Dementia Diagnosis values. Number of individuals diagnosed with AD Only and number of individuals diagnosed with Non-AD Dementia sum to number of individuals diagnosed with Any Dementia.