

## *Guest Editorial*

# Is Female Gender a Risk Factor for Alzheimer's Disease?

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Despite a growing list of potential new risk factors for Alzheimer's disease (AD), one of the oldest remains controversial. Is female gender a risk factor for AD? It is likely that the greatest influence on the gender differential in crude prevalence rates is the increasing incidence of dementia with age (Paykel et al., 1994) combined with the greater longevity of women (Moritz & Ostfeld, 1990). This must be distinguished from the hypothesis that there may also be a gender difference in the age-specific prevalence rates of some dementias such as AD. In turn, this could be due to either a higher incidence of dementia in women, or to longer survival times in women following diagnosis. What is the evidence for these hypotheses?

First, with regard to age-specific prevalence rates, Jorm and colleagues (1987) analyzed 22 dementia prevalence studies carried out between 1945 and 1985. They reported that the overall age-adjusted prevalence of dementia showed no gender difference. When their analysis was adjusted for the specific dementia diagnosis, they found higher rates of AD for women but no difference for multi-infarct dementia. They pointed out that the 22 studies varied widely and that they did not all give age-specific prevalence data, with only 3 studies pro-

viding age-specific data for the gender/diagnosis analysis. Hofman and colleagues (1991) analyzed age- and gender-specific prevalence rates from European studies carried out between 1980 and 1990. They reported a slightly higher rate of dementia in men for subjects under 75 years and a higher prevalence of dementia in women in the 75 years or older age group.

More recently, Skoog and colleagues (1993) and Kirby and coworkers (1997) reported no significant gender difference in prevalence rates for AD or "organic disorders," respectively. However, three recent studies have reported higher rates in women. In a Chinese community sample, Zhang and colleagues (1990) found a higher age-specific prevalence rate in women for dementia as defined by a cutoff on the Mini-Mental State Examination. Consistent with the analysis of Hofman and coworkers (1991), the Framingham study (Bachman et al., 1992) found a higher age-specific prevalence of both dementia and AD in women compared to men in the 75 years or older age group, whereas Saunders and colleagues (1993) reported higher rates of "organic disorder" in women for those over 75 years of age but no significant gender difference in younger age groups.

It must be noted that these prevalence studies examined very different populations. For example, some used samples based on a birth cohort (e.g., Skoog et al., 1993) whereas others used geographically based samples that included (e.g., Bachman et al., 1992) or excluded (e.g., Kirby et al., 1997) persons in residential settings.

Second, population incidence studies for dementia and AD have also been inconsistent. Most have reported no gender difference in incidence rates for dementia and/or AD when rates were adjusted for age (e.g., Aronson et al., 1990; Bachman et al., 1993; Bickel & Cooper, 1994; Hagnell et al., 1992; Hebert et al., 1991; Letenneur et al., 1994). However, a number of these studies showed a trend towards higher incidence rates in women but had sample sizes that were too small to have sufficient power to demonstrate a significant gender effect. In contrast, Fratiglioni and colleagues (1997) reported that incidence rates for both dementia and AD were higher for women than for men in a follow-up study of 987 subjects 75 years of age or older. Incidence studies have recently been the subject of a meta-analytic review that suggested a modest gender difference in incidence rates for AD. The odds ratio for women to develop AD relative to men was 1.56 (95% confidence interval, 1.16 to 2.1) (Gao et al., 1998). Payami and colleagues (1996) proposed that the contrasting incidence data may be due to heterogeneity. They pointed out that studies that have examined the incidence of AD in patient's relatives have found a higher risk or earlier age of onset in women. One possible explanation for these findings is that gender may be a risk factor only in familial AD.

An alternative to differential incidence rates as an explanation for increased

prevalence in women is that survival may be longer in women compared to men. Many studies have addressed this issue with varying results. Some (Becker et al., 1994; Drachman et al., 1990; Walsh et al., 1990) found no gender difference in survival for subjects with AD. Others (Beard et al., 1994; Corder et al., 1995; Galasko et al., 1994; Moritz et al., 1997; Stern et al., 1997) reported increased survival in women with AD but did not give standardized mortality ratios. It is difficult to interpret such studies because among nondemented elderly individuals, survival is greater in women (Moritz & Ostfeld, 1990). Burns and colleagues (1991) found no gender difference in standardized mortality ratios but, when gender was added to a multivariate analysis of survival, female gender was found to be protective. Van Dijk and coworkers (1992) and Heyman and colleagues (1997) reported increased survival in women compared to men with AD who were living in institutions. Again these findings are difficult to interpret because of potential gender interactions between dementia severity, duration of symptoms, and social circumstances and other variables at the time of institutionalization. In contrast to most of the other studies, Jagger and coworkers (1995) controlled for both the gender differential in survival for the nondemented elderly and for the institutionalization. They reported longer survival for women compared to men, with the risk for men increasing over time. They concluded that the longer survival of women may explain the gender differences found in the prevalence of AD without accompanying differences in incidence.

In conclusion, despite methodological problems and differences among studies, there appears to be a degree of

consensus that the age-specific prevalence of AD, and possibly dementia in general, is higher in women. This finding appears to be more robust in the 75 years or older age group. However, the influence of gender on incidence rates remains controversial and there is currently insufficient evidence to explain the increased prevalence rates for women on the basis of similarly higher incidence rates. As supported by the findings of Jagger and colleagues (1995), this points to the conclusion that being female means that you live longer with dementia or that men die earlier. Finally, there is insufficient evidence to support the notion that female gender is a risk factor for AD. This raises serious questions about the role of hormonal influences in the etiology of AD in women, unless similarly powerful male-specific influences can also be proposed.

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