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Commentary

Women and Alzheimer Disease

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The Alzheimer's Association convened the Work Group on Women and Alzheimer's Disease in the fall of 1998 to address three issues: (1) identify new research directions in this area, (2) develop a consensus statement on the currently available scientific evidence, and (3) inform policy development efforts of the Association.²

The following questions were posed to the Work Group. (1) Is there scientific evidence that Alzheimer disease has either a different neuropathologic profile or a mechanism-of-disease process by gender? (2) What is the evidence that the epidemiology of the disease differs by gender? (3) Is there evidence that the natural history and pattern of cognitive impairment and behavioral symptoms differ depending on gender? (4) Is there evidence that the response to currently available pharmacologic treatments differs by gender? (5) What is the evidence that the responsibilities and impact of caregiving for people with Alzheimer disease is differentially distributed by gender? Invitations were sent to scientists around the world asking them to join the Work Group on Women and Alzheimer's Disease and to submit a position paper on one of these questions.

The Alzheimer's Association is a national organization with a mission to reach all people with Alzheimer disease and their families. Therefore, the Advisory Committee to the Work Group on Women and Alzheimer's Disease approached the questions and issues from a public health framework. The primary goal of the Advisory

Committee and the Work Group was to assist the Alzheimer's Association in its program and policy development efforts; therefore, the evidence was reviewed from a population-based, epidemiologic paradigm. The Advisory Committee reached a number of conclusions based on the evidence and arguments presented in the position papers received from the Work Group members.³

NEUROPATHOLOGIC DIFFERENCES OR MECHANISM OF DISEASE DIFFERENCES BY GENDER

There is an "absence of evidence rather than evidence of absence" of relationships. Studies to examine gender relationships in pathogenesis or neuropathology will have to be methodologically rigorous, draw from population-based samples, and be adequately powered to detect small differences.

EPIDEMIOLOGY

Most studies have shown that the prevalence of Alzheimer disease is higher in women. However, prevalence rates are a function of the rate at which new cases occur and the duration of illness, and older women live longer than older men, both in the presence and absence of Alzheimer disease. Incidence studies are required to address gender differences in the occurrence of illness.

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²The Alzheimer's Association Work Groups are developed, convened, and managed by Drs. Zaven S. Khachaturian and Teresa S. Radebaugh. The Work Group on Women and Alzheimer's Disease was supported solely by the Alzheimer's Association.

³The text of the summary document, *Women and Alzheimer's Disease*, can be accessed through the website of the Alzheimer's Association (www.alz.org). The Advisory Committee is extremely grateful to the scientists who joined the Work Group and submitted position papers: Drs. Caleb Finch and Robert Sapolsky; Drs. Carol Miller, Galen Buckwalter, and Victor Henderson; Dr. Haydeh Payami; Dr. C. Dominique Toran-Allerand; Dr. Lindsey Farrer; Dr. Laura Fratiglioni; Dr. Amy Graves; Dr. Walter Kukull; Dr. Ingmar Skoog; Dr. Barry Reisberg; Dr. Kathleen A. Welsh-Bohmer; Dr. Robert Wilson; Dr. Mary Sano; Dr. Leon Thal; Drs. Kathleen C. Buckwalter and Meridean Maas; Ms. Lisa Gwyther; Dr. Kathleen Hall; Dr. Mary Mittelman; and Dr. Richard Schulz.

The evidence of differences in age-specific incidence rates by gender is inconclusive at this time. If the incidence of Alzheimer disease is higher for women than for men, the differences are likely modest. The methodologic problems in control of age, the differential age structure for older men versus older women, the clear differential in life expectancy, secular trends affecting education of women, and variations in race and ethnicity make this an extremely complicated question to answer. Moreover, the data are insufficient.

A major concern for future investigations is that without sound research methods and careful population sampling, the data on the occurrence of Alzheimer disease in men and women will be misleading. A potentially fruitful, but thus far largely unexplored, area is that of gender differences in risk and protective factors for and against Alzheimer disease, including but not limited to estrogen, genetics, other exposures, and co-morbid conditions.

NATURAL HISTORY

Overall, investigators have found relatively small changes or differences in performance on cognitive tests between men and women. Many of these differences have questionable relevance to long-term care of people and are useful for research purposes only. There are some data on gender differences in behavior (i.e., men are more likely to be aggressive, and women are more likely to be depressed), but these differences are hypothesized to relate to stage of illness or to premorbid factors. Two important issues that may differentiate the genders and about which more research is required are gender differences (1) in survival and disease duration and (2) in the rates and severity of functional disability across the course of illness.

RESPONSE TO TREATMENTS

There are few relevant data on the question of response to drug treatments for cognitive symptoms and differences by gender. There is literature on the use of psychotropic medications, their effectiveness, and metabolism by gender. Psychotropic medications for behavioral symptoms are commonly prescribed for people with Alzheimer disease. The applicability of these studies and data to people with Alzheimer disease should be considered.

CAREGIVING

The literature on caregiving concludes that there is a gender difference, in that women are not only more likely to receive care but also to provide care. The literature

also points to gender differences between male and female caregivers in the change of lifestyle and potential health effects of caregiving that accompany their caregiving careers.

Although there is substantial literature on caregiving, there are serious scientific and technical limitations in many of the studies, including the volunteer nature of the study groups and the lack of adequate representation of ethnic and racial minorities. Extending the findings of many of the caregiving studies to larger populations or using the findings as a platform for building programs or developing services should be done with great caution.⁴

CONCLUSIONS

There are many reports in the epidemiologic and clinical literature on genetic risk factors, rates of illness by gender, etc., that hint at differences, but the findings lack consistency. In some ways, the field now faces the task of sorting through this fascinating group of insights and separating out those that are valid and reproducible to understand whether there are important relationships between gender and development, course, and outcomes of Alzheimer disease.

There is stronger evidence supporting social differences by gender than evidence refuting or supporting biological differences by gender. These hypothesized social differences are likely to be further elaborated and differentiated when controlled by race, ethnicity, culture, religion, language, immigration status, socioeconomic status, etc. The evidence thus far is much more striking for psychosocial and cultural differences than for sex differences in the biology of the disease, *per se*. Possible, and promising, exceptions include the roles of and interactions with gender, of genes and estrogen, and responses to drug treatments.

Understanding the relationships between gender and the development and experience of Alzheimer disease will be enhanced by future investigations that

- have an adequate sample size and sufficient statistical power to detect small differences
- control for confounding variables such as age, life expectancy, cohort effects, education, selective exposures, ethnic/social/economic factors, stage of disease and comorbidity
- consider the heterogeneity of the base population and develop studies that address the ethnic and cultural

⁴Dr. Leonard Pearlin, University of Maryland, served as an *ad hoc* member of the Advisory Committee for consideration of the position papers and issues in caregiving research.

diversity of people with Alzheimer disease and their caregivers

- present data derived from clinical or volunteer samples very carefully and note the limitations in extrapolations to diverse population groups.

A major requirement for future research is increased funding. Funding increases will enable investigators to design adequately powered studies of sufficient duration

to answer questions about the relationship between gender and Alzheimer disease. Careful study of the differences and similarities in the biology and risk factors for Alzheimer disease between the genders may lead to novel hypotheses about the disease; fine tuning in the development of pharmaceutical treatments, their dosages, and applications; and new strategies for the support of caregivers and their families. The goal is to eradicate the disease and ease the suffering of both men and women affected by it.