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WOMEN WITH MILD COGNITIVE IMPAIRMENT DECLINE TWICE AS FAST AS MEN WITH THE CONDITION

WOMEN AT SIGNIFICANTLY HIGHER RISK FOR COGNITIVE AND FUNCTIONAL DECLINE AFTER SURGERY/GENERAL ANESTHESIA

WASHINGTON, DC, July 21, 2015 – Women with mild cognitive impairment (MCI) have two times faster decline in cognition than men with MCI, according to new research reported at the Alzheimer's Association International Conference® 2015 (AAIC® 2015) in Washington, D.C. In addition, women decline more dramatically than men in cognition, function and brain size after surgery and general anesthesia, according to another study reported at the conference.

MCI involves a slight but noticeable and measurable decline in cognitive abilities, including memory and thinking skills, but the changes are not severe enough to interfere with daily life or independent function. A person with MCI is at an increased risk of developing Alzheimer's or another dementia.

Women are at the epicenter of the Alzheimer's crisis. According to the Alzheimer's Association *Alzheimer's Disease Facts and Figures* report:

- Almost two-thirds of American seniors living with Alzheimer's disease are women.
- Among those aged 71 and older, 16 percent of women have Alzheimer's and other dementias, compared with 11 percent of men.
- At age 65, women without Alzheimer's have more than a one in six chance of developing Alzheimer's during the remainder of their lives, compared with a one in 11 chance for men.
- Women in their 60s are about twice as likely to develop Alzheimer's disease over the rest of their lives as they are to develop breast cancer.

“Women are disproportionately affected by Alzheimer's, and there is an urgent need to understand if differences in brain structure, disease progression, and biological characteristics contribute to higher prevalence and rates of cognitive decline,” said Maria Carrillo, PhD, Alzheimer's Association Chief Scientific Officer. “To intervene and help reduce the risk of Alzheimer's, it's critical to understand the reasons for these differences. Results presented at AAIC 2015 begin to shed light on this issue, but much more research is needed.”

Toward this goal, the Alzheimer's Association is conducting a campaign – the Women's Alzheimer's Research Initiative – to raise \$5 million; the Association plans to award a series of research grants specific to gender-related issues in Alzheimer's and other dementias. A recent Alzheimer's Association-convened think tank on “Gender Vulnerability Related to Alzheimer's Disease” looked deeply into these issues and plans to develop a manuscript of the meeting proceedings for publication. The focus was on three main topics that may link gender and vulnerability to Alzheimer's disease: biological mechanisms, hormonal factors and lifestyle factors.

Women at Risk for Alzheimer's and Dementia Decline Twice as Fast as At-Risk Men

Katherine Amy Lin, Wrenn Clinical Research Scholar in Alzheimer's disease, Duke University Medical Center, and colleagues used data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) to study how the cognitive abilities of about 400 people with MCI (141 women, 257 men), mostly in their mid-seventies, changed over the course of up to eight years.

They found a clear answer: cognitive abilities of women in the study with MCI declined twice as fast as men's – a result that was statistically significant.

Cognitive abilities were measured using the ADAS-Cog (Alzheimer's Disease Assessment Scale–cognitive subscale), one of the most frequently used tests to measure cognition in clinical trials, which has 11 parts and is scored from 0 to 70. The researchers found that the rate of decline in men was 1.05 points per year, in women it was 2.3 points per year. People of both genders with the ApoE4 Alzheimer's risk gene had a faster rate of decline. After adjusting for age, education, baseline Mini Mental State Examination score, follow up time and ApoE4 status, the effect of gender on ADAS-Cog rate of change was significant ($p=0.005$). The variability of cognitive change was also much greater in women than in men.

“Our findings suggest that men and women at risk for Alzheimer's may be having two very different experiences,” said Lin. “Our analyses show that women with mild memory impairments deteriorate at much faster rates than men in both cognitive and functional abilities. These results point to the possibility of as yet undiscovered gender-specific genetic or environmental risk factors that influence the speed of decline. Uncovering those factors should be a high priority for future research.”

“Because the ADAS-Cog is increasingly used as a cognitive outcome in prevention trials, our findings suggest the need to consider gender in the design and interpretation of such trials,” Lin added.

Women Decline Faster than Men After Surgery/General Anesthesia

General anesthesia during surgery is a carefully monitored process because of its potential impact on the brain. Though the majority of people undergoing surgery have no lasting effects from the anesthesia, research has shown that older adults are at higher risk for long-term cognitive and functional problems following surgery with general anesthesia.

At AAIC 2015, Katie Schenning, MD, MPH and colleagues from the Oregon Health & Science University, Portland OR, reported results from a study that explored whether exposure to general anesthesia would lead to faster deterioration of cognition, function and brain volumes in women than in men. To study this question, the researchers reviewed two different research program databases that are examining cognitive aging – the Oregon Brain Aging Study and the Intelligent Systems for Assessing Aging Changes. Out of 527 total participants, 182 people underwent a total of 331 procedures under general anesthesia. The researchers found that:

- Men exposed to general anesthesia during surgery declined in measures of cognition, functional status, and brain volumes statistically significantly faster than men who did not have surgery.
- Women exposed to general anesthesia during surgery also declined on those measures, and at a significantly faster rate than men. That difference was even more pronounced for women who underwent multiple surgeries with general anesthesia.

“This is one of the first studies to suggest that among older adults, women are at a higher risk for postoperative brain dysfunction than men,” said Schenning. “Our research clearly shows an association between surgery, general anesthesia and cognitive decline in older adults. More studies are needed to confirm this observation and to identify ways to minimize the effects of surgery and general anesthesia on older adults. Future research should focus on whether certain people are more susceptible to postoperative cognitive decline by virtue of sex or genetic risk factors.”

[Note: a third piece of science will be added to this story.]

About AAIC

The Alzheimer's Association International Conference (AAIC) is the world's largest gathering of leading researchers from around the world focused on Alzheimer's and other dementias. As a part of the Alzheimer's Association's research program, AAIC serves as a catalyst for generating new knowledge about dementia and fostering a vital, collegial research community.

AAIC 2015 home page: www.alz.org/aaic/

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About the Alzheimer's Association®

The Alzheimer's Association is the leading voluntary health organization in Alzheimer's care, support and research. Our mission is to eliminate Alzheimer's disease through the advancement of research, to provide and enhance care and support for all affected, and to reduce the risk of dementia through the promotion of brain health. Our vision is a world without Alzheimer's. Visit alz.org or call 800.272.3900.

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- Katherine Lin, et al. Marked Gender Differences in Rate of Cognitive Decline in Subjects at Risk for Alzheimer's Disease. (Funders: Alzheimer's Disease Neuroimaging Initiative (ADNI), Karen L Wrenn Family Trust)
- Katie Schenning, MD, MPH, et al. The Role of Sex in Postoperative Cognitive & Functional Decline. (Funders: Office of Research on Women's Health, Oregon Alzheimer's Disease Center)

Proposal ID: P4-108

Poster, Wednesday, July 22

Topic Selection: Diagnosis & Prognosis: Neuropsychology

Marked Gender Differences in Rate of Cognitive Decline in Subjects at Risk for Alzheimer's Disease

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Background: Women not only make up the majority of caregivers but also make up over two-thirds of Alzheimer's patients. The reasons for the higher prevalence of AD in women are not known but attributed to differences in longevity, hormonal status, education, and other factors.

Methods: We used data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) to examine gender differences in longitudinal rates of change in cognition in 398 subjects with MCI (141 Females, 257 Males). Mean follow up duration was 4.1 (2.5) years with some subjects followed over 7 years.

Results: The rate of decline in ADAS-Cog in men (1.05 points per year) was half that of women (2.3 points per year). ApoE4 was associated with faster rate of decline in both genders. In a mixed effects model, after adjusting for age, education, baseline MMSE, follow up time and ApoE4 status, the effect of gender on ADAS-Cog rate of change was highly significant ($p=0.005$). The variability of cognitive change was also much greater in women than in men.

Conclusions: This analyses of longitudinal data over 4 years finds that women at risk for AD decline at twice the rate as men. Our findings suggest the need for further exploration of gender related differences in AD pathophysiology to explain these findings. Because the ADAS-Cog is increasingly also used as a cognitive outcome in secondary prevention trials, our findings suggest the need to consider gender in the design and interpretation of such trials.

Proposal ID: P1-264

Poster, Tuesday, July 21

Topic Selection: Public Health & Psychosocial: Epidemiology

The Role of Sex in Postoperative Cognitive & Functional Decline

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Background: Older adults receive >1/3 of the over 40 million anesthetics delivered yearly in the US, and these individuals are at the highest risk for deleterious postoperative neurocognitive outcomes. While women have an increased risk of developing AD, the role of sex in postoperative cognitive decline is unknown. We hypothesized that exposure to general anesthesia (GA) and surgery in older adults is associated with an accelerated deterioration of cognition, function, and brain volumes, and that this decline is more pronounced in women.

Methods: We performed a retrospective, cohort analysis in two natural history studies of cognitive aging, the Oregon Brain Aging Study (n=304) and the Intelligent Systems for Assessing Aging Changes (n=223). After controlling for age, years of education, and Cumulative Illness Rating Scale, we used mixed-effects models to assess the relationship between exposure to GA/surgery and longitudinal change in measures of cognition, function, and brain volumes (Table 1). Exposure to GA/surgery was modeled as both a dichotomous categorical factor as well as a continuous variable indicating the number of exposure events to evaluate the role of repeated anesthesia application.

Results: Of the 527 participants, 182 underwent a total of 331 procedures under GA after enrollment in the study (Table 2). While men exposed to surgery/GA experienced a more rapid rate of decline than their unexposed counterparts in Mini-Mental State Examination (MMSE) (p=0.009), Instrumental Activities of Daily Living (IADL, p=0.024), and Clinical Dementia Rating-Sum of Boxes (CDR-SB, p=0.027), women exposed to surgery/GA experienced a significantly more rapid rate of deterioration in the following outcomes: MMSE (p<0.001), CDR (p=0.003), CDR-SB (p<0.001), Activities of Daily Living (ADL, p<0.001), Delayed Logical Memory (p=0.011), and ventricular volume (p=0.005). (Table 3) The sex differences were even more pronounced when considering exposure as a continuous variable indicating the number of exposure events (Table 4).

Conclusions: In this retrospective cohort analysis, exposure to surgery/GA in older women was associated with more rapid rates of decline in measures of cognition, function, and brain volumes than older men.

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