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FROM THE ALZHEIMER'S ASSOCIATION INTERNATIONAL CONFERENCE 2018

PREGNANCY AND REPRODUCTIVE HISTORY MAY IMPACT DEMENTIA RISK

PLUS, THE MOVE TO RE-THINK THE IMPACT OF HORMONE THERAPY ON COGNITION

Plus, Sex-Based Approaches May Improve Diagnostic Accuracy in Alzheimer's

Chicago, July 23, 2018 – Research reported at the Alzheimer's Association International Conference (AAIC) 2018 in Chicago highlighted sex differences associated with dementia and Alzheimer's disease across the life course, including the first ever large-scale study of reproductive history and dementia risk in women.

New results reported at AAIC 2018 suggest:

- Associations between dementia risk and number of children, number of miscarriages, age at first menstrual period, and reproductive period (years between first menstrual period and menopause).
- In a separate study, a correlation between cumulative months of pregnancy and Alzheimer's risk.
- Re-thinking the long held thought that hormone therapy negatively affects cognition.
- A need for sex-based standards for cognitive assessments, to improve early detection in women.

"More women than men have Alzheimer's disease or other dementias; almost two-thirds of Americans with Alzheimer's are women," said Maria Carrillo, PhD, Alzheimer's Association Chief Science Officer. According to Alzheimer's Association *2018 Alzheimer's Disease Facts and Figures*, of the 5.5 million people age 65 or older with Alzheimer's in the United States, 3.4 million are women and 2.0 million are men.

There are a number of potential biological and social reasons why more women than men have Alzheimer's or other dementias. The prevailing view has been that women live longer than men on average, and older age is the greatest risk factor for Alzheimer's. However, some research suggests that the risk for developing Alzheimer's could be greater for women due to biological or genetic variations, or even different life experiences, such as education, occupation or rates of heart disease.

"More research is needed in this area, because having a better understanding of sex-specific risk factors across the lifespan may help us discover — and eventually apply — specific prevention strategies for different populations of people with Alzheimer's and other dementias," Carrillo added.

Link Between Reproductive History and Dementia Risk in Women
(Note: Includes late-breaking analyses generated since the original abstract was submitted in February.)

As reported at AAIC 2018, in the first-ever large-scale epidemiological investigation in the U.S. of various aspects of reproductive history and dementia risk, Paola Gilsanz, ScD, staff scientist, Kaiser Permanente Northern California Division of Research in Oakland, Calif.; Rachel Whitmer PhD, Professor at UC Davis; and colleagues found a correlation between risk of dementia and the number of children, number of miscarriages, age at the time of first menstrual period, age at natural menopause, and reproductive period (the number of years between first menstrual period and menopause). Self-reported data from 14,595 women between the ages of 40-55 in 1964-1973 were evaluated.

"Possible causes of dementia in women, in particular reproductive factors, are not well understood," said Gilsanz. "In our study, we aimed to identify female-specific risks and protective factors impacting brain health, which is critical to diminishing the disproportionate burden of dementia experienced by women."

The researchers found that women in the study with three or more children had a 12 percent lower risk of dementia compared to women with one child. These women continued to be at lower risk of dementia after adjusting for additional mid- and late-life risk factors, such as body mass index and stroke history.

The researchers also asked about miscarriage and menstrual history. They found that each additional report of a miscarriage was associated with a 9 percent increased risk of dementia, compared to those women who reported no miscarriages. On average, women were 13 when they had their first menstrual period and were 47 at natural menopause. Additionally, women who indicated having their first menstrual period at age 16 or older were at 31 percent greater risk than those who reported having their first menstrual period at 13. Compared to women who experience natural menopause after age 45, those who experience natural menopause at 45 or younger were at 28% greater dementia risk adjusting for demographics.

The average length of reproductive period was 34 years. Compared to women with reproductive periods of 38-44 years, women with reproductive periods of 21-30 years were at 33% elevated dementia risk adjusting for demographics. Further research is needed to evaluate the mechanistic pathway between reproductive events and brain health.

Women's Pregnancy History May Influence Alzheimer's Risk
(Note: Includes late-breaking analyses generated since the original abstract was submitted in February.)

In a case-control, cross-sectional study of 133 elderly British women, Molly Fox, PhD, Assistant Professor, Departments of Anthropology and Psychiatry & Biobehavioral Sciences, University of California, Los Angeles, and colleagues collected reproductive history information and measured severity of Alzheimer's disease dementia to evaluate the potential association between pregnancy history and Alzheimer's risk, and to determine whether the relationship could be attributed to immune function.

Study findings suggest that the number of months of pregnancy — especially months spent in the first trimester — is a significant predictor of Alzheimer's risk. The researchers report that, in this study population, a woman who spent 12.5 percent more months pregnant than another otherwise identical woman had approximately 20 percent lower Alzheimer's risk.

"We are intrigued by the possibility that pregnancy may reorganize the mother's body in ways that could protect her against developing Alzheimer's later in life," said Fox. "These results also suggest that the story might not be so simple as being all about estrogen exposure, as previous researchers have suggested."

Investigators hypothesized that persisting beneficial effects on the immune system generated during the early stages of pregnancy may be responsible for the observed risk reduction.

Hormone Therapy May Not Always Be Associated with Cognitive Harm

A new study reported at AAIC 2018 sought to investigate why results from the influential Women's Health Initiative-Memory Study (WHIMS) and WHI-Study of Cognitive Aging (WHISCA) differed from previous findings that suggest a worsening of cognition associated with hormone therapy.

Carey E. Gleason, PhD, Wisconsin Alzheimer's Disease Research Center, University of Wisconsin School of Medicine and Public Health, Madison, and researchers from Hartford Hospital, Hartford and George Washington University, D.C., looked at two separate studies published since WHIMS and WHISCA: the Kronos Early Estrogen Prevention Study-Cognitive and Affective Study (KEEPS-Cogs); and the Early v. Late Intervention Trial with Estradiol-Cognitive Endpoints (ELITE-Cog). The results showed:

- No negative effect on cognition was measured in women who had initiated hormone therapy between ages 50-54. In contrast, those who initiated hormone therapy between ages 65-79 demonstrated reductions in global cognition, working memory and executive functioning.
- Women on hormone therapy with type 2 diabetes also showed a higher risk of cognitive impairment compared to non-diabetic women on hormone therapy and diabetic women who were administered placebo treatment, after controlling for age.

"These findings add to our understanding of the complex effects of hormones on the brain," said Gleason. "These data are sorely needed to guide women's healthcare during and after the menopausal transition and to help women make personalized and informed decisions regarding management of their menopausal symptoms and the prevention of future adverse health outcomes."

Female Advantage in Verbal Memory May Mask Early Stages of Alzheimer's

Pauline Maki, PhD, Professor of Psychiatry and Psychology, Senior Research Director of the Center for Research on Women and Gender, University of Illinois, Chicago, and researchers from the University of California, San Diego, examined data from the Alzheimer's Disease Neuroimaging Initiative that suggest women have an advantage in retaining memory for words and verbal items, not only during normal aging but also during amnestic mild cognitive impairment (aMCI).

As the tests most frequently used to diagnose Alzheimer's disease are related to verbal memory, memory of word lists, stories and other verbal materials, researchers wanted to better understand sex differences in verbal memory and brain aging and how they may be related to sex differences in presentation and clinical course of Alzheimer's disease.

The study found that women appeared to sustain their cognitive performance in early stages of disease, compared to men, despite having moderate levels of Alzheimer's brain pathology — as measured by three brain markers (hippocampal atrophy, brain hypometabolism and cortical beta-amyloid deposition). However, at high levels of disease burden, the female advantage in verbal memory was eliminated.

"These findings may help to explain why women show a more rapid decline across a wide range of cognitive abilities after being diagnosed with Alzheimer's," said Maki. "While the female advantage may be functionally beneficial, it could mask early stages of Alzheimer's, resulting in a more severe burden of disease at the time of diagnosis, with more rapid deterioration thereafter."

When a gender-based diagnostic approach was applied, it resulted in improved diagnostic accuracy in both sexes. This suggests the need for, and value of, alternative approaches — such as sex-specific "cut points" in diagnostic tests — to improve early detection in women.

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- Paola Gilsanz, ScD, Rachel Whitmer, PhD, et al. Women's Reproductive History and Dementia Risk. (Funder: U.S. National Institute on Aging)
- Molly Fox, PhD, et al. Women's Pregnancy History May Influence Alzheimer's Risk through Alterations in Immune Function. (Funder(s): Gates Cambridge Trust)
- Carey Gleason, PhD, et al. Hormonal Contributions to Alzheimer's Disease Risk in Women. (Funder: U.S. National Institute on Aging)
- Pauline Maki, PhD, et al. Hormonal Contributions to Alzheimer's Disease Dementia Risk in Women. (Funder(s): U.S. National Institute on Aging; Alzheimer's Disease Neuroimaging Initiative; U.S. Department of Defense.)

Proposal ID: P3-587

Women's Reproductive History and Dementia Risk

Background: Women have substantially higher prevalence of dementia compared to men but female sex-specific risk factors over the lifecourse are not well understood. There may be female-specific risk and protective factors which impact hormonal milieu and brain health.

Methods: We evaluated 14,595 female members of Kaiser Permanente who were aged 40-55 in 1964-1973 and remained members as of 1/1/96. Between 1964-1973 women reported number of children, miscarriages, and age of menarche and menopause. Education, race, sex, and midlife health indicators (BMI, hypertension, and smoking) were collected between 1972-1973. Dementia diagnoses and late-life health indicators (stroke, heart failure, and diabetes) were abstracted from medical records from 1/1/1996-9/30/2017. Cox proportional hazard models (age as time scale) evaluated associations between aspects of reproductive history and dementia adjusted for sociodemographics and lifecourse health indicators.

Results: 98% reported having ≥1 child. Mean age of menarche was 12.9 (SD=1.5 years) and mean age of menopause was 45.0 (SD=6.1 years). Of the 6,751 women who responded to questions regarding miscarriages, 75% reported ≥1 miscarriage. Compared to women with one child, women with 3 children and those with ≥4 children had a 12% lower risk of dementia (Table). Women with 3 children and those with ≥4 children continued to be at lower risk of dementia in fully adjusted models. Each additional report of a miscarriage was associated with an 8% increased risk of dementia (aHR=1.08; 95% CI: 1.05-1.12). Compared to women reporting no miscarriages, those with ≥3 miscarriages had 47% elevated dementia risk (aHR=1.47; 95% CI: 1.27-1.71). Compared to menarche between ages 10-13 years, menarche at ≥16 was associated with 22% greater risk (aHR=1.22; 95% CI: 1.03-1.44). Menarche at ≤9 was associated with a non-significant 40% increased risk versus menarche at ages 10-13 (aHR=1.40; 95% CI: 0.83-2.37). There was no evidence of an association between age of menopause and dementia risk.

Conclusions: This is the first large-scale epidemiological investigation of various aspects of reproductive history and dementia risk. We found that number of children, miscarriages and age at menarche was associated with dementia; future research should examine mechanistic pathway between reproductive events and brain health.

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Proposal ID: 25107

Women's Pregnancy History May Influence Alzheimer's Risk through Alterations in Immune Function

Background: Pregnancy is associated with improvement in immunoregulation that, potentially, persists into the geriatric phase of life. Women with higher gravidity may experience increased regulatory T-cell frequencies in the long-term. Such an increase in immunosuppressive function might protect against Alzheimer's Disease (AD) pathogenesis, because depleted immunoregulatory mechanisms have been implicated in AD aetiology. We hypothesize that women who spend more cumulative months pregnant may experience reduced risk of AD later in life via improved regulation of inflammation. We aim to investigate the relationship between pregnancy history and AD risk, and determine whether the relationship could be attributed to an immunologic mechanism.

Methods: In a case-control, cross-sectional study of elderly British women (N=133), we collected reproductive history information and measured degree of Alzheimer's-type dementia. Cox's proportional-hazards modelling was used to assess the putative effect of cumulative months pregnant on women's AD risk, and the mutually adjusted effects of the counts of first and third trimesters on AD risk.

Results: Cumulative months pregnant is a significant predictor of AD risk after adjusting for age at first birth, reproductive span, breastfeeding, marriages, and occupation. For each additional month pregnant, women exhibited a 5.5% decrease in AD risk ($p=0.02$), similarly after adjusting for parity (4.7% decrease, $p=0.03$). Cumulative number of first trimesters was associated with a lower risk of AD after adjusting for the number of third trimesters ($p<0.01$), while the latter predictor had no significant effect on AD after adjusting for the former ($p=0.31$).

Conclusions: This is the first study to suggest pregnancy affects Alzheimer's risk through alterations in the immune system. Our observation that more first-trimesters (but not third-trimesters) conferred protection against AD is more consistent with pregnancy's persisting immunological effects, which are driven by early gestational physiology, than the oestrogenic exposures associated with pregnancy, which are greatest in late gestation.

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Proposal ID: F2-01-03

An Update on Menopausal Hormone Therapy Trials

Background: In response to the seminal Women's Health Initiative (WHI) — Memory Study (WHIMS) and WHI — Study of Cognitive Aging (WHISCA), several studies examined the cognitive effects of menopausal hormone therapy (HT), attempting to clarify why WHI results diverged from previous findings suggesting HT was cognitively beneficial.

Methods: We highlight work conducted after publication of WHIMS and WHISCA findings; specifically, studies designed to address remaining controversies.

Results: The Kronos Early Estrogen Prevention Study–Cognitive and Affective Study (KEEPS-Cog) included 662 women, administered HT or placebo for 4 years. Participants were within 3 years of their last menstrual period, and none had undergone a hysterectomy or oophorectomy. Performance across multiple cognitive domains did not differ between women treated with two forms of HT and women on placebo. Women receiving oral CEE demonstrated improved mood with reductions in anxiety and depressive symptoms. Another randomized control trial, the Early vs Late Intervention Trial with Estradiol–Cognitive Endpoints (ELITE-Cog), included women who were either within 6 years of, or 10+ years past menopause. Women received oral estradiol for up to 5 years. Findings suggested no cognitive benefit or harm for either group. Importantly, the women in both groups were on the whole very healthy. Finally, data from the WHI were re-examined. Investigators compared HT's cognitive effects in women enrolled in the WHIMS – Young (WHIMS-Y) to those enrolled in WHIMS. Women in WHIMS-Y were between age 50 and 54 when therapy was started. No cognitive effects were observed with HT for WHIMS-Y women. In contrast, women enrolled in WHIMS (aged 65-79), receiving HT, demonstrated persisting decrements in global cognition, working memory, and executive functioning. WHIMS investigators also found that outcomes differed depending upon the presence of diabetes. Women with type II diabetes randomized to receive CEEs were at elevated risk of cognitive impairment and probable dementia compared to their aged-matched counterparts without diabetes, and women with diabetes randomized to placebo.

Conclusions: Altogether, data suggest that HT is not associated with cognitive harm when 1) therapy is initiated proximal to the menopausal transition, and/or 2) when women are healthy, e.g., non-diabetic. The long-term effects of menopausal HT are yet unknown.

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Proposal ID: F2-01-04

Intersection between Reproductive Aging and Brain Aging

Background: Organizational and activational effects of sex steroid hormones (i.e., estradiol and progesterone) contribute to sex differences in cognition, including verbal episodic memory. For example, prospective cohort studies have demonstrated decreases in verbal memory as women transition from premenopausal to perimenopausal stages of the menopausal transition, even after controlling for age and menopausal symptoms. Neuroimaging studies suggest that estrogen-induced alterations in the hippocampus and prefrontal cortex may contribute to these effects. Recent works shows that these sex differences in cognition and brain aging contribute to sex differences in the presentation and clinical course of Alzheimer's disease (AD). In a series of studies, we examined the implications of these sex differences in the diagnosis of amnestic mild cognitive impairment (aMCI) and AD.

Methods: First, sex differences in cognition and neuroimaging outcomes (hippocampal volume, brain hypometabolism, and cortical amyloid-β (Aβ) plaque burden) were examined in a series of studies drawing on the Alzheimer's Disease Neuroimaging Initiative (ADNI). Second, we applied sex-adjusted cut-scores for verbal memory impairment to determine if they improved the accuracy of aMCI and AD diagnosis when compared to conventional cut-scores. There, diagnostic accuracy was assessed using positivity rates for the cerebrospinal fluid (CSF) phosphorylated tau (p-tau)/Amyloid-β (Aβ) ratio.

Results: For each of three neuroimaging biomarkers, women and men showed similarly moderate levels of disease burden despite better verbal memory performance in women. At high levels of disease burden, the female advantage was eliminated. The application of sex-adjusted cut-scores resulted in improved diagnostic accuracy; positivity rates for the p-tau/Aβ ratio levels were appropriately high for newly classified impaired individuals and appropriately low for newly classified unimpaired individuals. This enhanced diagnostic accuracy in both sexes (i.e., more "true positive" women and fewer "false positive" men).

Conclusions: These findings suggest that the female advantage in verbal memory serves as a form of cognitive reserve that can mask underlying AD pathology in the aMCI stage. The application of sex-adjusted cut-scores for verbal memory may result in earlier detection of memory impairment in women and improved diagnostic accuracy in women and men.

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