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FROM THE ALZHEIMER'S ASSOCIATION INTERNATIONAL CONFERENCE 2017

STRESSFUL LIFE EXPERIENCES AGE THE BRAIN BY FOUR YEARS, AFRICAN AMERICANS MOST AT RISK

- Four studies highlight racial disparities in dementia risk and incidence -

LONDON, July 16, 2017 – A series of studies reported at the 2017 Alzheimer's Association International Conference (AAIC 2017) in London confirm racial inequities in numbers of people with Alzheimer's disease and other dementias - even after age 90 - and also point to growing evidence that early life stress and neighborhood conditions contribute to dementia risk in late life.

One new study in Wisconsin found that a single major stressful event in early life is equal to four years of cognitive aging, and African Americans are most at risk - on average, they experience over 60 percent more of such events than non-Hispanic Whites over their lifetimes. A second study conducted by a health plan in Northern California found that African Americans born in states with the highest levels of infant mortality had 40 percent increased risk of dementia compared to African Americans not from those states, and 80 percent increased risk compared to Whites not from those states. Other studies reported at AAIC 2017 found:

- Racial disparities in the risk for new cases of dementia previously observed in the younger elderly continue into the oldest-old (age 90+), which is the fastest-growing segment of the population. Researchers found oldest-old African Americans and Latinos had the highest incidence rates compared to Asian Americans and Whites - matching the overall patterns of racial/ethnic disparities in dementia seen in younger elderly. This is the first time different ethnicities in this older population group have been studied for risk of incident dementia.
- Neighborhood disadvantage may contribute to observed disparities in prevalence of dementia.

“These studies were done with U.S. data, but they add weight to the global body of evidence around disadvantage and dementia risk, which is an issue governments around the world grapple with, and one that requires coordinated action,” said Maria C. Carrillo, Ph.D., Alzheimer's Association chief science officer. “For a racially diverse nation like the United States, and to address Alzheimer's and dementia on a global scale, these findings support the need for targeted interventions, whether preventive or service-driven, to help address the gaps we know exist - and for more research.”

“In addition to research on Alzheimer's risk factors and biology, the Alzheimer's Association is particularly interested in increasing understanding of stigma and concern related to Alzheimer's and other dementias in diverse communities,” Carrillo said.

Racial disparities in dementia continue into the oldest-old

In younger elderly (65 and older), there are marked differences in rates of dementia by racial/ethnic groups, showing increased rates for African Americans and decreased rates for Asian Americans. The [Alzheimer's Association 2017 Alzheimer's Disease Facts and Figures](#) reported that, for all adults 65 and older, African-Americans are about twice as likely to have Alzheimer's or other dementias as older Whites and Hispanics are about one and one-half times as likely to have Alzheimer's or other dementias as older Whites. However, it is not known if these discrepancies apply to the oldest-old (90 and older).

Rachel Whitmer, PhD, from Kaiser Permanente of Northern California (KPNC), and Maria M. Corrada, Sc.M., Sc.D., of the University of California, Irvine, and colleagues focused on 2,351 members of the KPNC health plan who, in 2010, were older than age 90 (avg. 93.1) with no diagnoses of dementia. Most of the study participants were women; the cohort was 72% White, 16% African American, 4% Latino, and 7% Asian American. The study looked at dementia diagnoses in the group made between 2010 and 2015, abstracted from electronic medical records.

The researchers found oldest-old Asian Americans have the lowest cumulative incidence (21%), followed by Whites (31%), Latinos (35%) and African Americans (39%) - matching the overall patterns of racial/ethnic disparities in dementia seen in younger elderly. In models adjusted for age as the time scale, education, sex, mid-life and late-life vascular comorbidities, oldest-old African Americans had a 28 percent higher risk than oldest-old Whites. Compared to Asian Americans, African Americans had a 30% increased risk of dementia.

“Our results show that racial inequities in rates of dementia at younger ages continue after age 90,” said Whitmer, Senior Scientist at Kaiser Permanente Division of Research and senior author on the scientific abstract. “These are the first estimates of dementia incidence in a diverse cohort of individuals age 90 and older. Given the increasing ethnic diversity in the coming decades, it is imperative to identify what factors contribute to the differences in rates, whether genetic, social, or lifestyle, as some of these factors may be modifiable.”

Lifetime stressful experiences worsen memory and thinking - more strongly in African Americans

Prevalence of Alzheimer's disease and cognitive impairment is rising, and the greatest burden seems to be falling disproportionately on historically disadvantaged communities. Despite substantial evidence for racial disparities in later life cognitive health, specific causes remain unclear and the cognitive impact of lifelong adversity is underexplored.

Megan Zuelsdorff, Ph.D., at the University of Wisconsin School of Medicine and Public Health, and colleagues examined the impact of lifetime stressful experiences on cognition as part of the Wisconsin Registry for Alzheimer's Prevention (WRAP) Study. The study population included a total of 1,320 adults - African American (n=82) and non-Hispanic white (n=1,232); the goal was to understand how stressful experiences - such as being fired from a job, the death of a child, growing up with a parent who abused alcohol or drugs, or experiencing combat - impacted cognition differently in these two groups.

Average age, years of education, and APOEε4 status did not differ by race. Stressful experiences included educational difficulties, interpersonal conflicts, financial insecurity, legal/justice system issues, serious health events and psychosocial/physical trauma. Participants answered a questionnaire about stressful experiences and completed cognitive tests that measured memory and problem-solving abilities. Researchers stratified the sample by race and looked at stress-cognition relationships within African American and white subgroups.

A greater number of stressful events was associated with poorer late-life cognitive function for all study participants. Even within a relatively small, highly educated sample, African Americans experienced over 60 percent more stressful events than non-Hispanic Whites during their lifetimes, and these experiences were linked to poorer memory and thinking skills in older age. The researchers determined that, in African Americans, each stressful experience was equivalent to approximately four years of cognitive aging.

“Among African Americans in our study, adverse events across the lifespan predict cognitive function more strongly than established risk factors including age, education, and the APOE-e4 Alzheimer’s risk gene,” Zuelsdorff said. “Adversity is a clear contributor to racial disparities in cognitive aging, and further study is imperative.”

Early life conditions - such as high infant mortality rates - may contribute to dementia risk in late life

High infant mortality rates are a marker of adverse social and physical conditions, and birth in areas with high infant mortality rates are associated with a variety of poor health outcomes. Yet, it is unknown if birth in states with high infant mortality impacts dementia risk.

Paola Gilsanz, ScD, of the University of California, San Francisco, and Kaiser Permanente Division of Research, and colleagues looked at race specific infant mortality rates in 1928 of the birth states of more than 6,200 members of the Kaiser Permanente Northern California health system. Members born in the 10 states with highest rates of infant mortality for their race were categorized as being born in high infant mortality states. They linked this information with medical records to see if people born in high infant mortality states were at greater risk of dementia. They found that:

- 1928 rates of infant mortality were much higher among African Americans (up to 277 deaths/1,000 live births) compared to Whites (up to 129 deaths/1,000 live births).
- African Americans born in a state with a high infant mortality rate had a 40% higher risk than African Americans born in states without high infant mortality rates, even after taking into account education, high blood pressure in midlife, body mass index, stroke, and diabetes.
- African Americans born in high infant mortality states had almost 80% greater risk of dementia even after accounting for education and health risk factors, compared to Whites born outside high infant mortality states.
- Being born in a high infant mortality state was not associated with dementia risk among Whites.

“This is the first study of place of birth and long-term dementia risk,” Gilsanz said. “African Americans born around 1928 were likely exposed to harsher early life conditions that may have increased their risk of dementia later in life. Our findings suggest that differences in early life conditions may contribute to racial inequalities in dementia rate, and they point to growing evidence that early life conditions contribute to dementia risk in late life.”

Living in a Disadvantaged Neighborhood may increase Alzheimer’s disease risk

Disadvantaged neighborhoods often pose barriers for accessing healthy foods, safe exercise options, toxin-free environments, and other factors that impact health. It is known that living in a disadvantaged neighborhood increases risk of diabetes, cancer, and early death, and that moving to less disadvantaged settings improves health.

Amy Kind, MD, PhD, of the University of Wisconsin School of Medicine and Public Health and colleagues used data from 1,479 people enrolled in WRAP. The scientists found the level of socioeconomic neighborhood disadvantage for each study participant using the Area Deprivation Index (ADI) score, which incorporates indicators of poverty, education, housing, and employment.

The researchers examined whether patterns of cognitive function and protein biomarkers (n=153 with spinal fluid samples) of Alzheimer’s were found more often in certain neighborhoods than would be expected to occur by chance alone. They found that people in the most disadvantaged neighborhoods had markedly worse cognitive performance in all aspects measured (working memory, immediate memory, speed and flexibility of cognition, and verbal learning), even after adjusting for age and education. They also had disproportionately higher levels of one Alzheimer’s disease biomarker in their spinal fluid (phosphorylated tau).

“This study provides evidence to suggest that living in a neighborhood challenged by poverty, low education, unemployment, and/or substandard housing may increase risk of Alzheimer’s disease, and may account for some of the observed differences in Alzheimer’s disease risk among people of different racial backgrounds and income levels,” said Kind.

Kind’s group has quantified ADI scores for more than 50 million neighborhoods across the United States and Puerto Rico; those results could be used to target dementia-focused intervention and research programs to areas of highest need.

While the U.S. Congress has recently provided additional funding for Alzheimer’s research at the National Institutes of Health (NIH), the commitment falls far short of the need. Congress must continue its commitment to the fight against Alzheimer’s and other dementias by increasing funding for Alzheimer’s research by at least an additional \$414 million in fiscal year 2018.

About Alzheimer’s Association International Conference (AAIC)

The Alzheimer’s Association International Conference (AAIC) is the world’s largest gathering of 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 2017 home page: www.alz.org/aaic/

AAIC 2017 newsroom: www.alz.org/aaic/pressroom.asp

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 +1 800.272.3900.

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- Rachel Whitmer, Ph.D., Maria M. Corrada, Sc.M., Sc.D., et al. Racial/Ethnic Differences in Rates of Dementia Incidence Among the Oldest-Old (Funder(s): U.S. National Institute of Aging)
- Megan Zuelsdorff, Ph.D., et al. Lifetime Stressful Experiences, Racial Disparities, and Cognitive Performance: Findings from the Wisconsin Registry for Alzheimer’s Prevention (WRAP) Study. (Funder(s): U.S. National Institute on Aging, U.S. National Institute of Child Health and Human Development, Helen Bader Foundation, Northwestern Mutual Foundation, Extencicare Foundation, U.S. National Institutes of Health National Center for Advancing Translational Sciences)
- Paola Gilsanz, Sc.D., et al. Birth in a High Infant Mortality State, Race, and Risk of Dementia (Funder(s): U.S. National Institute on Aging; UCSF Training for Research on Aging and Chronic Disease)
- Amy J. Kind, M.D., Ph.D., et al. Neighborhood Socioeconomic Contextual Disadvantage, Baseline Cognition and Alzheimer’s Disease Biomarkers in the Wisconsin Registry for Alzheimer’s Prevention (WRAP) Study (Funder(s): U.S. National Institutes of Health; U.S. National Institute on Aging; UW Institute for Clinical and Translational Research; William S Middleton Memorial Veterans Hospital Geriatric Research, Education and Clinical Center; University of Wisconsin Department of Medicine)

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Abstract 19320 / Proposal ID O1-09-01

Public Health and Psychosocial: Epidemiology: Risk Factors for Dementia - A Life Course Approach
Oral (AAIC), Sunday, July 16, 2017: 4:15-5:45 PM

Birth in a High Infant Mortality State, Race, and Risk of Dementia

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Background: Birth in high infant mortality states has been linked to poorer long-term health outcomes yet it is unknown if it impacts brain health in late-life. Adverse early life conditions may partially explain racial inequalities in rates of dementia, but thus far this has never been explored.

Methods: We evaluated 6,284 Kaiser Permanente Northern California health-plan members (17% Black, 83% White) born between 1919-1932 with health survey and clinical exam data collected between 1964-1973.

Clinical measures of midlife hypertension, BMI, and self-reported state of birth, race, and education were collected between 1964-1973. A birth state was categorized as a high infant mortality state (HIMS; yes versus no) if it was one of the 10 states with the highest rate of race-specific infant mortality in 1928. Dementia diagnoses (ICD-9 codes 331.0, 290.4x, 290.0, 290.1x, 290.2x, 290.3, 294.2x, and 294.8), stroke, and diabetes were abstracted from medical records 1/1/1996-10/1/2015. Cox proportional hazard models (age as time scale) evaluated associations of HIMS and dementia adjusted for sociodemographics and lifecourse vascular risk factors. Participants were censored at dementia diagnosis, death, health-plan membership lapse, or end of follow-up.

Results: 1928 rates of infant mortality were much higher among Blacks (median=116 deaths/1,000 live births; range: 65-277) than Whites (median=64 deaths/1,000 live births; range: 45-129). Adjusted for age and sex, HIMS birth was not associated with higher risk of dementia among Whites (adjusted Hazard Ratio (aHR)=1.01, 95% Confidence Interval (CI): 0.83-1.23). However, Blacks born in HIMS had 40% elevated risk (95% CI:1.02-1.91), which persisted after adjusting for education and comorbidities throughout the lifecourse (aHR=1.40, 95% CI:1.01-1.93). Compared to Whites born outside HIMS, Blacks born inside HIMS had almost 80% elevated dementia risk (aHR=1.79; 95% CI:1.31-2.44) adjusting for education and vascular comorbidities.

Conclusions: Infant mortality rates for Blacks in 1928 were much higher than that of Whites. In a cohort of elderly individuals, Blacks born in states with the highest levels of race specific infant mortality rates had 40% increased risk of dementia, though all individuals subsequently moved to California. Early life conditions may contribute to racial inequalities in dementia incidence and needs to be further investigated.

Abstract 14332 / Proposal ID O1-09-04

Public Health and Psychosocial: Title: Epidemiology: Risk Factors for Dementia - A Life Course Approach
Oral (AAIC), Sunday, July 16, 2017: 4:15-5:45 PM

Lifetime Stressful Experiences, Racial Disparities, and Cognitive Performance: Findings from the Wisconsin Registry for Alzheimer's Prevention (WRAP) Study

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Background: Prevalence of Alzheimer's disease and cognitive impairment is rising, and the greatest burden falls upon historically disadvantaged communities. Despite substantial evidence for racial disparities in later life cognitive health, underlying pathways are unclear and the cognitive impact of lifelong adversity remains underexplored. Stressful experiences cluster and accumulate across the life course, potentially fomenting cognitive health disparities. We examined relationships between lifetime stress and cognition among African American and non-Hispanic white adults in the longitudinal Wisconsin Registry for Alzheimer's Prevention (WRAP) study.

Methods: Participants (N=1,320) reported lifetime stressful experiences and completed comprehensive neuropsychological testing. Cognitive outcomes included two executive function factor scores (Speed & Flexibility and Working Memory) and four memory scores (Immediate Memory, Verbal Learning & Memory, Visual Learning & Memory, and Story Recall). The key predictor of interest was a Lifetime Stress index score (sample range=0-17 experiences). Mixed-effects regression models, including socioeconomic and health covariates, were utilized to assess effects of lifetime stress in each cognitive domain. We stratified by race to explore between-group differences in stress-cognition relationships.

Results: Average age (mean=58.1, SD=6.5), years of education (mean=16.2, SD=2.8), and APOEε4 carrier proportion (38.5%) did not differ by race. However, African Americans (n=82) reported significantly more (mean=4.5) stressful experiences during their lifetime than non-Hispanic whites (n=1,232; mean=2.8, p<.001). In fully adjusted models including the full sample, lifetime stress partially attenuated negative relationships between African American race and both domains of executive function. Stratification revealed that cognitive detriment associated with lifetime stress in non-Hispanic whites is significantly potentiated among African Americans, for whom it is the strongest measured predictor of Speed & Flexibility (p=0.002) and Working Memory (p=0.03).

Conclusions: We found that lifetime stress is associated with poorer later-life cognition, particularly executive function, and contributes to racial disparities therein. Even within a small, highly-educated sample, African Americans report experiencing more stressful events and exacerbated stressor-associated cognitive dysfunction, with each reported experience equivalent to more than four years of cognitive aging. Our findings reaffirm the effect of stress on cognitive health and disparities, and emphasize the need to expand within-group, lifecourse-based strategies as we strive to eliminate disparities through targeted interventions.

Racial/Ethnic Differences in Rates of Dementia Incidence Among the Oldest-Old

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Background: By 2060 there will be 9.5 million individuals age 90+ in the United States and over one third will be Non-White. In younger elderly, there are marked differences in rates of dementia by racial/ethnic groups, showing increased rates for Blacks and decreased rates for Asians. However, it is completely unknown if these discrepancies also occur in the oldest-old.

Methods: We established a cohort of 2,351 members of Kaiser Permanente Northern California (KPNC) health-plan who, in 2010, were >age 90, with no diagnoses of dementia. Dementia diagnoses (ICD- 9 codes 331.0, 290.0-290.4x, 294.1, 294.2x, and 294.8) made in primary care, neurology, memory clinics, and psychiatry were abstracted from electronic medical records from 1/1/2010-12/31/2015. We estimated dementia incidence rates standardized to the 2000 US Census 90+ year- old population by race/ethnicity. Cox proportional hazard models (age as time scale) evaluated the association between racial/ethnic groups and dementia risk. Participants were censored at dementia diagnosis, death, >90 day gap in health plan membership, or end of study.

Results: The mean age in 2010 was 93.1 (range: 90-109). The cohort is 65% female, 72% White (N=1,702), 16% Black (N=375), 4% Latino (N=105) and 7% Asian (N=169). 771 members (32.8%) were diagnosed with dementia during the 5-year follow-up period. The mean age of dementia diagnosis was 95.48 (SE=0.10) and was similar across racial and ethnic groups: 95.56 (SE=0.11) for Whites, 95.21 (SE=0.23) for Blacks, 95.71 SE=0.66 for Latinos, 95.28 (SE=0.31) for Asians. The overall age-adjusted incidence rate (aIR) was 100.5 per 1,000 person-years. Asians had the lowest incidence rates (aIR=89.3), followed by Whites (aIR=97.0), Latinos (aIR=105.8), and, lastly, Blacks who had the highest rates (aIR=121.5). In cox proportional hazard models adjusted for age as the time scale, education, sex, midlife and late-life vascular comorbidities, Blacks had significantly higher risk (aHR=1.28; 95%CI: 1.05-1.51), compared to Whites.

Conclusions: These are the first estimates of dementia incidence in a diverse cohort of 90+ individuals. Patterns of racial/ethnic disparities in dementia seen in younger elderly continue after age 90. These estimates provide an important foundation for understanding the burden of racial disparities in dementia in the oldest-old, the fastest growing segment of the population.

Abstract 14725 / Proposal ID O1-04-03

Public Health and Psychosocial: Epidemiology: Social Disadvantage/Inequalities
Oral (AAIC) Sunday, July 16, 2017: 2:00 PM-3:30 PM

Neighborhood Socioeconomic Contextual Disadvantage, Baseline Cognition and Alzheimer's Disease Biomarkers in the Wisconsin Registry for Alzheimer's Prevention (WRAP) Study

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Background: Dementia due to Alzheimer's Disease (AD) disproportionately impacts racial/ethnic minorities and the socioeconomically disadvantaged—populations often exposed to neighborhood disadvantage. Neighborhood disadvantage is associated with education, health behaviors and mortality. Health improves with moving to less disadvantaged neighborhoods (Ludwig, Science 2012). Although studies have linked neighborhood disadvantage to diseases like diabetes and cancer, little is known about its effect on development of dementia. **Objective:** To examine the association between neighborhood disadvantage, baseline cognition, and CSF biomarkers of AD among participants in the WRAP study, comprising a cohort of late-middle-aged adults enriched for parental family history of AD. **Methods:** We created and validated neighborhood-level quantifications of socioeconomic contextual disadvantage for the full US—over 34 million Zip+4 codes—employing the latest American Community Survey and Census data. This metric—the Area Deprivation Index (ADI)—incorporates poverty, education, housing and employment indicators; predicts disparity-related health outcomes; and is employed by Maryland and Medicare through our provision. We used standard techniques to geocode all WRAP subjects with a documented address (N=1479). WRAP participants were ranked into deciles of neighborhood disadvantage, by ADI. Baseline cognitive function (indexed by factor scores) and CSF biomarker outcomes for levels of A β 42 and P-tau181 (n=153 with CSF samples) were examined by neighborhood disadvantage decile. **Results:** Higher levels of neighborhood disadvantage were associated with worse baseline cognitive outcomes, especially within the most disadvantaged neighborhood decile (p<0.0001). After adjustment for age and education, those within the most disadvantaged decile demonstrated worse cognitive performance across all domains (beta [95% confidence interval] and p-value by domain: working memory: -0.45 [-0.62, -0.28], <0.0001; immediate memory: -0.34 [-0.52, -0.17], <0.0001; speed/flexibility: -0.62 [-0.78, -0.45], <0.0001; verbal learning: -0.44 [-0.61, -0.27], <0.0001). Furthermore, subjects within the most disadvantaged neighborhood decile exhibited a mean CSF P-tau 11.61 units higher (p=0.064) than those within less disadvantaged neighborhoods. A β 42 did not differ by neighborhood decile. **Conclusions:** These early data suggest that neighborhood disadvantage may account for some of the observed disparities in prevalence of dementia. Given the urgent need to reduce dementia and AD disparities, the current results suggest that neighborhood disadvantage deserves additional study.