LESSONS LEARNED FROM NONSIGNIFICANT FINDINGS IN EXERCISE WITH INDIVIDUALS WITH DEMENTIA
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The National Institute on Aging recognizes the importance of identifying promising non-pharmacological interventions (NPI) to promote health in individuals with Alzheimer’s disease and related dementias. Several systematic reviews have been completed investigating exercise in this population resulting in mixed evidence regarding efficacy across functional domains. It is critical to investigate the methodological factors from the original interventions for a true understanding of these findings as to not outright dismiss exercise as benefical. One example is Ohio’s replication of Reducing Disability in Alzheimer’s Disease (n=508), which resulted in no significant improvements in physical performance for individuals with dementia (gait speed (p=.81), balance (p=.82), functional reach (p=.58)). In this investigation, along with many others, researchers were not guided by key principles of exercise science leading to critical intervention design and methodological flaws. Thus, exercise interventions for individuals with dementia need to include interpretations of non-findings and report key factors affecting the outcomes.

SESSION 7685 (SYMPOSIUM)

CAUSES AND MECHANISMS UNDERLYING DISPARITIES AND TIME TRENDS IN ALZHEIMER’S DISEASE AND RELATED DEMENTIAS
Chair: Igor Akushevich
Co-Chair: Carl Hill
Discussant: Konstantin Arbeev

The objective of the Symposium is to make progress in understanding the causes and mechanisms of health-related disparities in Alzheimer’s disease, related dementia and other prominent age-related diseases. Topics will cover a range of academic and administrative topics including: i) partitioning analysis of disparities and time trends in Alzheimer’s Disease and Related Dementia; ii) a structural model approach to ethnic disparities in dementia and its assessment; iii) traumatic brain injury and dementia in the Medicare population: differences in genotype and phenotype-related risk between veteran and non-veteran subsets; iv) geographic disparities in county-level prevalence of Alzheimer’s disease across the United States; and v) the role of comorbidities in the geographic disparities of AD/ADRD mortality. A focus will be made on evaluating patterns of race/ethnicity and geographic health disparities as well as changes in time trends in AD/ADRD prevalence and mortality; identifying the causes and describing the mechanisms of these respective processes, and demonstrating how they can be identified in studies using established administrative data resources such as Medicare claims databases; and demonstrating how innovative analytic approaches such as partitioning analyses, structural model approaches, and methods of latent data analyses can be used in conjunction with empirical and regression approaches to uncover previously overlooked or understudied aspects in this area of research. Analyses of such increasingly available large health datasets provides an opportunity to obtain nationally representative results based on individual-level measures that reflect the real care-related and epidemiological processes generating disparities and time trends in AD/ADRD health outcomes.

PARTITIONING ANALYSIS OF DISPARITIES AND TIME TRENDS IN ALZHEIMER’S DISEASE AND RELATED DEMENTIA
Igor Akushevich, Duke University, Durham, North Carolina, United States

This study uses Medicare data to i) identify age patterns, time trends, and race/geography-related disparities in prevalence and mortality of AD/ADRD; ii) apply partitioning methodology to separate out trends in causal components including incidence and survival, and iii) expand the method for analysis of disparities to identify the magnitude and trends in causal components of race-related disparities in AD/ADRD. Analysis shows that the trend in AD/ADRD incidence explains up to 70% of the observed changes in AD prevalence and mortality and is the main contributor to the differences in race-specific prevalence (higher for African Americans (AA)). Differences in race-specific incidence explain up to 80% of the disparity while 20% are due to difference in survival. This indicates that for AAs, incidence is worse but survival is better. This is confirmed by direct evaluations of hazard ratios: AD incidence HR for AA is 1.50(1.46,1.54) and 0.93(0.91,0.96) for survival after AD diagnosis.

A STRUCTURAL MODEL APPROACH TO ETHNIC DISPARITIES IN DEMENTIA AND ITS ASSESSMENT
Donald Royall, UTHSCSA, San Antonio, Texas, United States

Ethnicity complicates the assessment of dementia and its biomarkers in the Texas Alzheimer’s Research and Care Consortium (TARCC). Its effect can be mitigated by the construction of latent variables in a structural equation model (SEM) framework. We have developed a dementia-specific phenotype, i.e. “δ” (for “dementia”) by that approach. δ provides a continuously distributed dementia severity measure that may be resistant to ethnicity effects. We propose to test the impact of Mexican-American (MA) ethnicity in TARCC data [N = 3502; MA = 1313; Non-Hispanic Whites (NHW) = 2189]. Significant structural associations between observed cognitive performance, δ and δ’s serum protein biomarkers will be tested for ethnicity effects by CHISQ differences across ethnicity stratified models. Observed clinical variables can be impacted by demographic effects. Those can lead to presumed disparities in clinical outcomes or biomarkers. Latent variables have potential to mitigate demographic effects, refute some perceived disparities and confirm others.

TRAUMATIC BRAIN INJURY AND DEMENTIA IN MEDICARE POPULATION: DIFFERENCES IN RISK BETWEEN VETERANS AND NON-VETERANS
ArseniY Yashkin, Duke University, Durham, North Carolina, United States
The aim of this study was to assess differences in the effect of traumatic brain injury (TBI) on the onset of Alzheimer’s disease (AD) and other dementias between veteran and non-veteran respondents of the Health and Retirement Study as well as to measure the sensitivity of these differences to the introduction of controls for groups of demographic, medical co-morbidity and polygenic risk scores reflecting AD hallmarks. Using the Fine-Gray proportional hazards model we found that TBI was a strong predictor of dementia in community dwelling residents age 65+: for AD associated risk was 181% [Hazard Ratio (HR): 2.81; CI:2.05-3.86] sample-wide and 142% [HR: 2.42; CI:1.31-2.46] in veteran males. Effect magnitude decreased with the addition of risk-related control variables but remained associated with significantly increased risk. Large differences in risk were observed between veteran and non-veteran males for AD, vascular dementia, senile dementia, and dementia with Lewy Bodies.

GEOGRAPHIC DISPARITIES IN COUNTY-LEVEL PREVALENCE OF ALZHEIMER’S DISEASE ACROSS THE UNITED STATES
Mackenzie Fowler, Michael Crowe, and Richard Kennedy, University of Alabama at Birmingham, Birmingham, Alabama, United States

While national and state estimates of the prevalence and incidence of AD are available, estimates across finer geographic regions offer an opportunity to tailor programs to the needs of the local population. Previously, we estimated prevalence and incidence of AD at the county level across the continental United States and found that estimated prevalence of AD varied more than threefold across counties, predominantly in the Southeastern and Midwestern United States. We also observed “islands” of low AD within regions with high AD, and vice versa. We update these findings by examining changes in projected prevalence of AD over time, and comparing projected prevalence of AD to prevalence of AD diagnoses in Medicare. We also examine regional variation in provider specialty patterns and racial differences across counties as possible explanatory factors. Understanding small-area geographic disparities in prevalence will be critical for addressing practice variation in the prevention and diagnosis of dementia.

GEOGRAPHIC DISPARITIES IN COMORBIDITIES IN MORTALITY OF PATIENTS WITH ALZHEIMER’S DISEASE
Julia Kravchenko, Duke University, Durham, North Carolina, United States

Comorbidity can contribute to the gap in Alzheimer’s disease (AD) mortality between the East and West coast U.S. Using Multiple-Cause-of-Death and 5%-Medicare data, we analyzed age-adjusted (65+) mortality rates from AD in two Health and Human Services (HHS) areas with opposed mortality patterns in 2010-2018: 150.9±0.6/100,000 in HHS2 (NJ,NY) and 363.1±1.5/100,000 in HHS10 (AK,ID,OR,WA). Co-existing diabetes, heart failure, cerebrovascular, digestive, and kidney diseases significantly contributed to this gap, while contribution of heart diseases reduced its magnitude. An unexpectedly strong effect (higher rate in HH10 by a factor of 3-5) was identified for symptoms/signs that are not from identified specific diseases, life-threatening injuries/falls and other external causes that are common among patients with AD. We concluded that although contributions of comorbidities with well-developed treatment guidelines (e.g., heart disease) to geographic disparities in AD mortality were small, the disparities can be generated by unexpected comorbidities including diseases with poorly defined conditions.

SESSION 7690 (SYMPOSIUM)
COMPLEMENTARY AND INTEGRATED STUDIES OF LONGEVITY AND HEALTHY AGING
Chair: Steven Cummings
Co-Chair: Thomas Perls
Discussant: Evan Hadley

Five NIH-funded studies, the Long Life Family Study (LLFS, U19), the Longevity Consortium (LC, U19), Longevity Genomics (U24), and Protective Omics Profiles in Centenarians (UH2) work together to triangulate on mechanisms of extreme longevity and healthy aging with the ultimate goal of discovering predictors and targetable pathways. Linkage analyses by LLFS identified extremely strong genetic linkage peaks for cross-sectional as well as longitudinal trajectory rates-of-change phenotypes. Deep sequencing suggests these peaks are driven by rare, protective variants in selected pedigrees. In cross-species studies (UH2, LC), genomics, metabolomics and proteomics are used to exploit many-fold variances in natural life spans to discover protective mechanisms that explain some of these differences. Proteome analysis reveal several longevity-related proteins such as Cip1/p21, FOXO3, TOP2A, AKT1, RICTOR, INSR and SIRT6 harboring post translational modification sites that preferentially appear in short- versus long-lived species. The U24 effort developed a tool using genetically-mediated gene expression to prioritize genes for longevity translational efforts. We found that BLOC1S1 was associated with longevity and protection from atrial fibrillation and hearing loss without being associated with adverse events. This novel target is undergoing functional characterization. A proteomic assay (4,131 proteins, Somasscan) annotated by genome-wide association study results in a total of 1,797 centenarians and 3,685 controls divided into independent discovery and replication sets, discovered significant and replicated over-expression (thus, pro-longevity) of BIRC2 and under-expression of APOB in carriers of the APOE ε-2 allele. A novel protein signature of rs2184061 (CDKN2a/CDKN2B in chromosome 9) was also associated with slower aging.

THE LONG LIFE FAMILY STUDY: SEQUENCING EXCEPTIONAL PEDIGREES FOR RARE PROTECTIVE VARIANTS
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