

AWARD NUMBER: W81XWH-20-1-0253

TITLE: "EVALUATING EFFECTS IN THE RELATIONSHIP BETWEEN TRAUMATIC BRAIN INJURY AND ALZHEIMER'S DISEASE: EPIDEMIOLOGICAL DETERMINANTS, THEIR HEALTH-RELATED CAUSES, AND THE RESULTING DISPARITIES"

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CONTRACTING ORGANIZATION: DUKE UNIVERSITY

REPORT DATE: July 2021

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**PREPARED FOR: U.S. Army Medical Research and Materiel Command Fort Detrick,
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13. SUPPLEMENTARY NOTES					
14. ABSTRACT In year 1 of the project, we received the Local IRB/IACUC and HRPO/ACURO approvals and completed the process of obtaining RIF DUA approval by CMS. The process has taken much longer time than we expected because of COVID-19 work environment. We concentrated the expanding and finalizing the preliminary results described in the original grant-submission, development of partitioning models for Alzheimer's disease (AD) and related dementia (ADRD) prevalence and mortality, analyses of ADNI DoD data. Specifically, we harmonized the Barell/extended Barell matrixes to account for changes in disease reporting from ICD-9 to ICD-10 standard, found a strong association of TBI and dementia in community dwelling residents and in veteran males age 65+, and developed a partitioning model for time-trends of AD/ADRD prevalence and mortality that allowed us to identify the epidemiological causes of the changes in these measures over time. The primary determinant responsible for declines in prevalence and IBM was the deceleration in the increase and eventual decrease in incidence rates though changes in relative survival began to affect the overall trends in prevalence/IBM in a noticeable manner after 2008. The results were published in one paper and presented in six conference presentations.					
15. SUBJECT TERMS None listed.					
16. SECURITY CLASSIFICATION OF: DOD			17. LIMITATION OF ABSTRACT UU	18. NUMBER OF PAGES 15	19a. NAME OF RESPONSIBLE PERSON USAMRMC
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1. INTRODUCTION:

The objective of this study is to: evaluate epidemiological patterns of Traumatic Brain Injury and Alzheimer's Disease; their associations in veteran and civilian populations; the effects of time-independent, modifiable and genetic risk factors; the roles of these factors on the relationship between Traumatic Brain Injury and Alzheimer's Disease.

2. KEYWORDS:

Traumatic brain injury, Alzheimer's Disease, Alzheimer's Disease related dementia, epidemiology, decomposition analysis, time-trends.

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Specific Aim ¹	Timeline	Status
Epidemiology of traumatic brain injury and Alzheimer's disease		
Major Task 1.1. Epidemiology of TBI and its subtypes	Months	
Subtask 1. TBI Profiles created	1-6	75%, in progress
Subtask 2. Epidemiological studies complete	1-12	20%, in progress
Local IRB/IACUC Approval	3th	100% 03/23/2020
Milestone Achieved: HRPO/ACURO Approval	4th	100%, 08/17/2020
Milestone(s) Achieved: <i>Evaluated TBI profiles and their epidemiologic patterns</i>	12th	50%, in progress
Major Task 1.2. TBI and AD/ADRD associations for veteran and civilian subpopulations	Months	
Subtask 1. Comparative studies complete	1-12	25%, in progress
Milestone(s) Achieved: Estimated associations between TBI and AD, publication of a peer reviewed paper	12th	25%, in progress
Major Task 1.3. Partitioning analysis of racial and veteran/civilian disparities	Months	
Subtask 1. Partitioning analysis of time trends	3-12	25%, in progress

Subtask 2. Partitioning analysis of racial and veteran/civilian disparities	6-18	15%, in progress
Major Task 1.4. Effects of time independent risk factors	Months	
Subtask 1. Study of genetic risk factors	1-6	30%, in progress
Subtask 2. Modeling AD resilience	6-18	10%, in progress
Subtask 3. Comparative studies complete	1-3	25%, in progress
Specific Aim 2 Effects of modifiable risk factors	Timeline	Status
Major Task 2.1. Socioeconomic environment and wellbeing	Months	
Subtask 1. Study of educational factors	6-12	25%, in progress
Major Task 2.2. Modifiable Risk factors	Months	
Subtask 1. Study of behavioral risk factors	6-12	25%, in progress
Major Task 2.3. Effects of comorbid diseases	Months	
Subtask 1. Study of co-morbidity risk factors	6-21	20%, in progress
Major Task 2.6. Multivariable model for predicting and analyzing the disparities	Months	
Subtask 1. Estimate multivariable model	1-6	10%, in progress

What was accomplished under these goals?

Major activities. In year 1 of the project (07/01/2020 – 06/30/2021), we focused on the expanding and finalizing the preliminary results described in the original grant-submission, development of partitioning models for Alzheimer’s disease (AD) and related dementia (ADRD) prevalence and mortality, analyses of ADNI DoD data, and obtaining the DUA for 5%- and HRS-Medicare data. Traumatic brain injury profiles based on the harmonization of the Barell/extended Barell matrixes between disease definitions based on ICD-9 and ICD-10 codes were created as this work did not require direct access to Medicare data.

Specific objectives. In year 1, we received Local IRB/IACUC Approval, protocol Pro00104488 and the HRPO/ACURO Approval E01575.1a. We harmonized the Barell/extended Barell matrixes to account for changes in disease reporting from ICD-9 to ICD-10 standard. Further progress was retarded by delays in obtaining RIF DUA approval by Centers for Medicare and Medicaid Services (CMS). We presented the results of comparative studies on the effects of genetic risk factors and multivariable modeling at the Gerontological Society of America 2020 conference. They were limited to the HRS publicly available data, since the DUA

for use of restricted access data was not finalized during the reporting period. We developed a partitioning model for time-trends of AD/ADRD prevalence and mortality that allowed us to identify the epidemiological causes of the changes in these measures over time.

Significant Results and Key Outcomes. The Medicare-linked data central to this project requires additional safeguards to protect the protected health information (PHI) of Medicare beneficiaries. To this end, we created the organizational infrastructure specific to the aims of the study and compliant with the data provider, institutional and governmental policies. We received Local IRB/IACUC Approval as well as HRPO/ACURO Approval. Since the null version of Duke IRB protocol Pro00104488 v.1.3 approved by Duke IRB Board and USAMRMC HRPO, we submitted two amendments to Duke DUHS IRB to better describe the data used. No changes were made to the protocol in regard to the research summary or unanticipated risks to human subjects. The current version of the IRB protocol Pro00104488 is 1.5. No amendments were submitted to USAMRMC HRPO, since the changes to the protocol Pro00104488 were minor, did not affect risks to the human subjects and were therefore not subject USAMRMC HRPO reporting requirements. The local IRB protocol renewed at Duke in a timely manner, and the according notification submitted to the USAMRMC HRPO on 3/14/2021.

During the first year, we verified 5%- and HRS-Medicare data availability (in terms of specific variables necessary for the project) and submitted necessary paperwork to the CMS through its authorized contractor, Research Data Assistance Center (ResDAC). The application was processed and reviewed at Centers for Medicare and Medicaid Services and, ultimately, was conditionally approved by CMS on 06/01/2021. The formal approval was issued on 07/14/2021 after acknowledgement of payment for the data by CMS for re-use of 5% Medicare files. The Department for Population Health Studies (the host and custodian of the 5% Medicare files at Duke) configured the computing environment for the project and verified the credentials of the designated users of the data. The Data License Agreement for the HRS-linked CMS records is fully executed and the payment order is created by Duke. We would like to note that the University of Michigan's Restricted Data Access (RDA) Reviewing Committee was unusually slow – due to COVID-19 work environment – in processing the application approval which is a necessary requirement for the application for the HRS-linked CMS data. The process that, based on our prior experience, usually takes 2 months has taken 9 months in 2020 for all of our RDA projects. Furthermore, ResDAC has been experiencing high levels of requests during the reported period. Their response time was longer than expected and the application was reviewed over 8 months instead of the projected 6. Our expectations to obtain the RIF DUA approval by May 2021, as reported in the last quarterly report, were overly optimistic. The DoD-ADNI data from LONI and the genetic component of the HRS data from dbGAP are available to us from the second quarter of the project.

We conducted an extension of a preliminary study that assessed the differences in the effect of traumatic brain injury (TBI) on the onset of Alzheimer's disease (AD) and other dementias between veteran and nonveteran 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. We used the results of our preliminary studies to assess the differences in the effect of traumatic brain injury (TBI) on the decline in cognitive status and the risk of Alzheimer's disease and related dementia (AD/ADRD) between veteran and non-veteran respondents of the Health and Retirement Study (HRS) and measured the sensitivity of these differences to the incremental introduction of controls for associated risk factors (Yashkin, 2020; Akushevich et al., 2020a, 2021a). Three groups of AD/ADRD risk-related variables were used: i) demographic/socioeconomic factors, including gender, race, marital status, education, income, and the number of limitations in activities of daily living; ii) comorbidities, including co-existing depression/post-traumatic stress syndrome (PTSD), substance (alcohol, tobacco and/or prescription drug) abuse, diabetes mellitus, stroke, and heart failure; and iii) genetic factors, including the presence of at least one pair of the APOE4 allele and a series of polygenic risk scores associated with AD hallmarks. The dynamics of changes in cognitive impairment in response to TBI, PTSD, and mild cognitive impairment were

validated against respective measures estimated using the Department of Defense Alzheimer's Disease Neuroimaging Initiative (DoD-ADNI) data. The results of the analyses showed that TBI and PTSD were strongly associated with cognitive decline and the risks of AD/ADRD in both veteran and non-veteran subpopulations in HRS data and the difference between them was not statistically significant. Specifically, 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. In addition, the analysis of DoD-ADNI data demonstrated that prevalence of mild cognitive impairment was associated with TBI at baseline in DoD-ADNI data, but no cognitive decline was observed during one year of follow-up.

Then we assessed the effect of traumatic brain injury (TBI) on the onset of Alzheimer's disease, vascular dementia, senile dementia, dementia not otherwise specified (NOS), frontotemporal dementia (FTD), dementia with Lewy Bodies (LBD) as well as a combined measure of any of the above dementia types and measure changes in these effects as groups of demographic, medical co-morbidity and genetic risk-factors are controlled for as well as the differences in risk between veterans and non-veterans. The Fine-Gray proportional hazards model was used to assess the risk of dementia under four increasingly complex models. We found that TBI was a strong predictor of dementia in community dwelling residents age 65+. The risk associated with TBI followed the same general pattern for all forms of dementia for which reliable estimates could be obtained. Large differences in risk were observed between veteran and non-veteran males for AD, vascular dementia, senile dementia, and LBD as well as any dementia type. The APOE4 allele was a strong predictor of AD. However, it was also found to be associated with risk of senile and, NOS dementia – consistent with the presence of multiple dementias. Specifically, the results suggest that more attention should be given to identifying and addressing preventable risk factors of such as TBI to reduce future private and social burden of neurocognitive disorders. Specifically, this study provides further support for TBI as an important risk factor for the onset of neurodegenerative disorders including Alzheimer's disease. The APOE4 *allele* was found to increase the risk of the onset of AD, senile and NOS dementia. Part of this relationship could be due to multi-dementia or the miss-diagnosis of AD for other dementia types. Since the AD is the most common type of dementia in the U.S. and is associated with over \$259 Billion in costs, coupled with increasing lifespans and the general aging of the U.S. population this makes the potential future burden of this and other neurocognitive conditions high. To offset this problem more attention should be given to identifying preventable risk factors such as TBI, the rates of which have been increasing and are expected to continue to increase.

We used partitioning analysis to decompose time trends of age-specific and age-adjusted prevalence and disease-specific mortality in terms of the contributions of four components: i) prevalence at age 65, ii) the probability of relative survival of prevalent individuals at age 65, iii) the incidence rate, and iv) the probability of relative survival after disease diagnosis. We applied this approach to AD/ADRD to explain the origin of time trends of AD/ADRD prevalence and mortality is the result of competing epidemiological processes. We empirically identified age patterns and time trends in prevalence and incidence-based mortality (IBM) of AD/ADRD, and then applied the partitioning methodology to decompose these trends into their causal components such as trends in incidence and survival. We proved that that the effect of AD prevalence at 65 is minor since age is the most important non-genetic risk factor of AD, so the trends are largely determined by the trends in AD/ADRD incidence and survival. This resulted in an improvement in the statistical accuracy of incidence/survival estimates. Analysis specifically showed that the prevalence of AD was increasing between 1992 and 2011 after which it started to decline. IBM of AD increased over the entire study period, although

with a significant slowdown in its rate of growth from 2011 onwards. For ADRD, both prevalence and IBM increased through 2014 prior to taking a downwards turn. The primary determinant responsible for the beneficial trends in prevalence and IBM was the deceleration and eventual decrease in incidence rates, especially for ADRD. The effects of changes in relative survival, were comparatively weak in magnitude and began to affect the overall trends in prevalence/IBM in a noticeable manner only after 2008. The results underline the important role of improvements in the ascertainment of AD to the epidemiological trends of this condition over the 1991-2008/10 period but show that the changes associated with this effect have been exhausted in more recent years.

The partitioning approach requires explicit models for AD/ADRD incidence and survival, i.e., the analysis involves the design and estimation of separate models for i) the incidence rate, ii) relative survival after AD/ADRD diagnosis as well as of individuals prevalent at 65 and/or 1992, iii) prevalence at the age boundary (age 65), iv) prevalence at the time boundary (year 1992), and v) mortality in the general population. The partitioning components are expressed in terms of derivatives of these functions with respect to time. The model for any function contains parameters to describe the function for each year of diagnosis, and the parameters of B-splines (with equidistant knots including 4 inner knots and boundary knots on the year boundaries, the parameters of the boundary knots being equal to those of the closest inner knot) that are used to model the relationships between year-specific model parameters and evaluate the calendar time-dependences of the function. B-splines allow explicit calculation of derivatives without requiring additional simplifying assumptions. The distribution of age (and time after onset for relative survival) is modeled using i) the generalized 4-parameter Armitage-Doll model with additional individual predisposition parameterized by gamma or inverse Gaussian distributions (for incidence), ii) the Weibull model for time after disease onset with the quadratic function of age for the shape and scale parameters (for relative survival). These models are both standard for these outcomes and demonstrated better goodness-of-fit characteristics in respect to the alternatives (specifically, we tested a spectrum of survival models available in literature. The model parameters are estimated using non-linear least squares for age-specific incidence, mortality, and prevalence at boundaries, and the likelihood-based approach for relative survival.

The results of the partitioning analysis were presented at Workshops (Akushevich 2020, 2021, Akushevich et al, 2020b) and published in the Journal of Alzheimer's disease (Akushevich et al. 2021c). Based on the empiric estimates obtained in these analyses we will continue developing a partitioning approach for AD and TBI.

PROTOCOL (1 of 1 total):

Protocol [HRPO Assigned Number]: E01575.1a

Title: Evaluating Effects in the Relationship Between Traumatic Brain Injury and Alzheimer's Disease: Epidemiological Determinants, Their Health-Related Causes, and the Resulting Disparities

Target required for clinical significance: NA

Target approved for clinical significance: NA

SUBMITTED TO AND APPROVED BY:

- **Duke DUHS IRB, approved 03/28/2020**
- **USAMRMC HRPO, approved 08/17/2020**

HRPO Protocol Number	Protocol PI Name	Organization (Site)	# Target	# Enrolled	# Completed	# Screened	# Recruited	Other (Available for secondary data analyses per approved DUA)
E01575.1a	Igor Akushevich	Duke University	37,488 (HRS) 204 (DoD-ADNI) 5,539,467 (5% Medicare)	NA	NA	NA	NA	42,232 (HRS) 204 (DoD-ADNI) 6,042,239 (5% Medicare)

What opportunities for training and professional development has the project provided?

Nothing to Report.

How were the results disseminated to communities of interest?

The PI of the project was among the organizers of the Symposium at the Gerontological Society of America (GSA) 2021 Annual Research Meeting (Akushevich et al., 2020a) and the Duke-NIA-Alzheimer’s Association Workshop “*Leveraging Existing Data and Analytic Methods for Health Disparities Research Related to Aging and Alzheimer’s Disease and Related Dementias*” that focused on methodological aspects and uncovering mechanisms underlying disparities and time trends in AD/ADRD health outcomes. The workshop was broadly advertised by public relations associates at Duke and the Alzheimer’s Association through different channels, including social media such as Twitter and Facebook, multiple electronic newsletters at Duke, Alzheimer’s Association, Alzheimer’s Society, Alzheimer’s Foundation of America, NIH, NIMHD and many more. Personal invites with requests to further disseminate information on the event were distributed by the PI and his collaborators across many U.S. Universities. The audience of the workshop exceeded two hundred participants. Participation in the workshops were open to all, independent of membership to any specific group. The online format of the Workshop together with the lack of a registration fee improved accessibility for individuals of limited financial resources. Among the participants of the workshop, women and minorities were represented according to our plan to recruit women and underrepresented minorities, and to provide accessibility for individuals with disabilities.

What do you plan to do during the next reporting period to accomplish the goals?

We are planning to follow the SOW. Specifically, we are planning to i) complete epidemiological studies using empiric and regression approaches (Major Task 1.1, subtask 2), ii) complete and publish the analysis of TBI and AD/ADRD associations for veteran and civilian subpopulations (Major Task 1.2), iii) develop an approach for partitioning analysis of racial and veteran/civilian disparities (Major Task 1.3), and iv) work on the studies of the effects of time-independent (Major Task 1.4), socioeconomic (Major Task 2.1), and modifiable (Major Task 2.2) risk factors as well trajectories of cognitive impairment (Major Task 2.4).

4. IMPACT:

We completed the analysis of the epidemiologic causes of racial disparities performed based on

partitioning analysis that allowed us to identify and estimate the contributions to AD/ADRD prevalence and related mortality of changes in epidemiological measures such as disease incidence, initial prevalence, and relative survival.

What was the impact on the development of the principal discipline(s) of the project?

The results of partitioning analysis will allow researchers to extract important information on periods of success and failure in AD/ADRD care and prevention contained in time trends in disease prevalence and mortality after AD/ADRD diagnoses.

What was the impact on other disciplines?

Nothing to Report.

What was the impact on technology transfer?

Nothing to Report.

What was the impact on society beyond science and technology?

Nothing to Report.

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

Nothing to Report.

Actual or anticipated problems or delays and actions or plans to resolve them

During the reported period, there was unanticipated delay in obtaining approvals from the data providers described in detail in “Significant Results and Key Outcomes” of the section “ACCOMPLISHMENTS”. We ascribe the delay to the adjustment of institutions to COVID-19 working environment. We would like to note that there was no delay on Duke’s side – all data access requests to counterparties were prepared ahead of the schedule and submitted in accordance to the SOW. However not relevant to the current project, we are planning to contact the data providers in advance to reflect the dates accurately on the SOW of the future projects, if there will be any.

Changes that had a significant impact on expenditures

Due to the delay in access to the data, the effort of the personnel was allocated accordingly. It will be adjusted in the future reporting period.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents:

Significant changes in use or care of human subjects

Nothing to Report.

Significant changes in use or care of vertebrate animals

Not Applicable.

Significant changes in use of biohazards and/or select agents

Not Applicable.

6. PRODUCTS:

- **Publications, conference papers, and presentations**

Akushevich I, Hill C, and Arbeev K, (2020a) Causes and Mechanisms Underlying Disparities and Time Trends in Alzheimer's Disease and Related Dementias. Innovation in Aging, 4(Supplement_1), pp.850-850. Symposium Abstract, Oral presentation

Akushevich I (2020) Partitioning Analysis of Disparities and Time Trends in Alzheimer's Disease and Related Dementia. Innovation in Aging, 4(Supplement_1), The Gerontological Society of America's (GSA) 2020 Annual Scientific Meeting, online, November 4-7 (Oral) pp.850-850.

Akushevich I (2021) Use of analytic methods and Medicare data in the analyses of disparities in AD/ADRD health outcomes. A Talk given at the Duke-NIA-Alzheimer's Association Workshop entitled "Leveraging Existing Data and Analytic Methods for Health Disparities Research Related to Aging and Alzheimer's Disease and Related Dementias". Durham (online, oral), NC, March 9-10, 2021

Akushevich I, Yashkin A, Kolpakov S, and Kravchenko J (2021a) The Effect of Traumatic Brain Injury on Alzheimer's Disease and Cognitive Decline in Veterans and Non-Veterans, Abstract accepted for oral presentation at the Gerontological Society of America's (GSA), 2021 Annual Scientific Meeting. Abstract to be published in Innovation in Aging. Oral presentation.

Akushevich I, Yashkin A, Kravchenko J, Yashin AI (2021b) Partitioning of Historical Time Trends in Prevalence and Mortality of Alzheimer's Disease and Related Dementias and Associated Racial Disparities. The Population Association of America's annual meeting, St. Louis, MO, USA, May 5-8, 2021. Poster presentation

Yashkin, AP (2020) Traumatic Brain Injury and Dementia in Medicare Population: Differences in Risk Between Veterans and Non-Veterans, The Gerontological Society of America's (GSA) 2020 Annual Scientific Meeting, online, November 4-7 (Oral). Innovation in Aging, 4(Suppl 1), 850.

- **Journal publications.**

Akushevich, I., Yashkin, A.P., Kravchenko, J. and Yashin, A.I., (2021c). Analysis of Time Trends in Alzheimer's Disease and Related Dementias Using Partitioning Approach. Journal of Alzheimer's Disease, vol. Pre-press, no. Pre-press, pp. 1-13, 2021, DOI: 10.3233/JAD-210273

- **Books or other non-periodical, one-time publications.**

Nothing to Report.

- **Other publications, conference papers and presentations.**

Nothing to Report.

- **Website(s) or other Internet site(s)**

Nothing to Report.

- **Technologies or techniques**

The partitioning approach for the AD/ADRD is described in detail in 'Significant Results and Key Outcomes' of the 'ACCOMPLISHMENTS' section.

- **Inventions, patent applications, and/or licenses**

Nothing to Report.

- **Other Products**

Nothing to Report.

7. PARTICIPATING & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name: Igor Akushevich, Ph.D.

Project role: PI

Researcher Identifier: 0000000334717846

Nearest person month worked: 1

Contribution to the project: Dr. Akushevich has performed work in the area of partitioning analysis and analysis of ADNI-DOD data.

Name: Arseniy Yashkin, Ph.D.

Project role: Senior Investigator

Researcher Identifier: 000000021185148X

Nearest person month worked: 1

Contribution to the project: Dr. Yashkin created traumatic brain injury profiles and conducted an extension of a preliminary study for association between AD and TBI

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to Report.

What other organizations were involved as partners?

Nothing to Report

8. SPECIAL REPORTING REQUIREMENTS

Not Applicable

9. APPENDICES

Akushevich I, Hill C, and Arbeev K, (2020a) Causes and Mechanisms Underlying Disparities and Time Trends in Alzheimer's Disease and Related Dementias. *Innovation in Aging*, 4(Supplement_1), pp.850-850. Symposium Abstract, Oral presentation

Abstract

The objective of the Symposium is to make progress in understanding the causes and mechanisms of health-related disparities in Alzheimer's disease, related dementias 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.

Akushevich I (2020) Partitioning Analysis of Disparities and Time Trends in Alzheimer's Disease and Related Dementia. *Innovation in Aging*, 4(Supplement_1), The Gerontological Society of America's (GSA) 2020 Annual Scientific Meeting, online, November 4-7 (Oral) pp.850-850.

Abstract

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.

Akushevich I (2021) Use of analytic methods and Medicare data in the analyses of disparities in AD/ADRD health outcomes. A Talk given at the Duke-NIA-Alzheimer's Association Workshop entitled "Leveraging Existing Data and Analytic Methods for Health Disparities Research Related to Aging and Alzheimer's Disease and Related Dementias". Durham (online, oral), NC, March 9-10, 2021

No abstract available. The presentation is published on: <https://sites.duke.edu/adrd/agenda/>

Akushevich I, Yashkin A, Kolpakov S, and Kravchenko J (2021a) The Effect of Traumatic Brain Injury on Alzheimer's Disease and Cognitive Decline in Veterans and Non-Veterans, Abstract accepted for oral presentation at the Gerontological Society of America's (GSA), 2021 Annual Scientific Meeting. Abstract to be published in *Innovation in Aging*. Oral presentation.

Abstract

We assess the differences in the effect of traumatic brain injury (TBI) on the decline in cognitive status and the risk of Alzheimer's disease and related dementia (AD/ADRD) between veteran and non-veteran respondents of the Health and Retirement Study (HRS) and measure the sensitivity of these differences to the incremental introduction of controls for associated risk factors. Three groups of AD/ADRD risk-related variables were used: i) demographic/socioeconomic factors, including gender, race, marital status, education, income, and the number of limitations in activities of daily living; ii) comorbidities, including co-existing depression/post-traumatic stress syndrome (PTSD), substance (alcohol, tobacco and/or prescription drug) abuse, diabetes mellitus, stroke, and heart failure; and iii) genetic factors, including the presence of at least one pair of the APOE4 allele and a series of polygenic risk scores associated with AD hallmarks. The dynamics of changes in cognitive impairment in response to TBI, PTSD, and mild cognitive impairment were validated against respective measures estimated using the Department of Defense Alzheimer's Disease Neuroimaging Initiative (DoD-ADNI) data. The results of the analyses showed that TBI and PTSD were strongly associated with cognitive decline and the risks of AD/ADRD in both veteran and non-veteran subpopulations in HRS data and the difference between them was not statistically significant. Effect magnitude decreased with the

addition of risk-related control variables but remained associated with the increased risks. Prevalence of mild cognitive impairment was associated with TBI at baseline in DoD-ADNI data, but no cognitive decline was observed during one year of follow-up.

Akushevich I, Yashkin A, Kravchenko J, Yashin AI (2021b) Partitioning of Historical Time Trends in Prevalence and Mortality of Alzheimer's Disease and Related Dementias and Associated Racial Disparities. The Population Association of America's annual meeting, St. Louis, MO, USA, May 5-8, 2021. Poster presentation

Abstract

The time trend of Alzheimer's disease (AD) and related dementias (ADRD) prevalence and mortality is the result of competing processes like changes in incidence and relative survival. Our new partitioning approach allows for evaluating the relative contributions of these and other components to prevalence/mortality trends and any racial disparities. Using 5%-Medicare data, we found: i) incidence of AD/ADRD is the most influential factor contributing to trends and disparities in AD/ADRD, ii) increases in prevalence and mortality for AD/ADRD has decelerated and passed the maximum in prevalence, iii) racial disparities in these measures increase slowly and relative fractions of their determinants are stable with time, iv) relative survival and morbidity at 65 are the second leading factors responsible for changes in prevalence/mortality and disparities, respectively. Partitioning approaches provide quantitative information on the causal determinants of time-trends and trend-disparities, and form the basis for both predictive inference and formal forecasting models.

Yashkin, AP (2020) Traumatic Brain Injury and Dementia in Medicare Population: Differences in Risk Between Veterans and Non-Veterans, The Gerontological Society of America's (GSA) 2020 Annual Scientific Meeting, online, November 4-7 (Oral). *Innovation in Aging*, 4(Suppl 1), 850.

Abstract

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