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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, Durham, NC

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6. AUTHOR(S)

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

The primary completed deliverable of this reporting period was the development of partitioning models for Alzheimer's disease (AD) and related dementia (ADRD) prevalence and mortality. We found that the prevalence of AD was increasing between 1992 and 2011 and declining thereafter, while incidence-based mortality (IBM) increased over the study period with a significant slowdown in its rate of growth from 2011 onwards. For ADRD, prevalence and IBM increased through 2014 prior to taking a downwards turn. The primary determinant responsible for declines in prevalence and IBM was the deceleration in the increase and eventual decrease in incidence rates through changes in relative survival begun to affect the overall trends in prevalence/IBM in a noticeable manner after 2008. Other components showed only minor effects. The prevalence and IBM of ADRD is expected to continue to decrease. The directions of these trends for AD are not clear because AD incidence, the main contributing component, is decreasing and at a decreasing rate suggesting a possible reversal. Furthermore, emerging treatments may contribute through their effects on survival. Improving ascertainment of AD played an important role in trends of AD/ADRD over the 1991-2009/10 period but this effect has exhausted itself by 2017.

15. SUBJECT TERMS
None listed.

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
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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 Epidemiology of traumatic brain injury and Alzheimer's disease	Timeline	Status
Major Task 1.1. Epidemiology of TBI and its subtypes	Months	
Subtask 1. TBI Profiles created	1-6	95%, in progress
Subtask 2. Epidemiological studies complete	1-12	40%, in progress
Local IRB/IACUC Approval	3th	100% 03/23/2020
Milestone Achieved: HRPO/ACURO Approval	4th	100%, 08/17/2020
Milestone(s) Achieved: *Evaluated TBI profiles and their epidemiologic patterns*	12th	75%, in progress
Major Task 1.2. TBI and AD/ADRD associations for veteran and civilian subpopulations	Months	
Subtask 1. Comparative studies complete	1-12	35%, in progress
Milestone(s) Achieved: Estimated associations between TBI and AD, publication of a peer reviewed paper	12th	50%, in progress
Major Task 1.3. Partitioning analysis of racial and veteran/civilian disparities	Months	
Subtask 1. Partitioning analysis of time trends	3-12	50%, in progress
Subtask 2. Partitioning analysis of racial and veteran/civilian disparities	6-18	25%, in progress
Major Task 1.4. Effects of time independent risk factors	Months	

Subtask 1. Study of genetic risk factors	1-6	40%, in progress
Subtask 2. Modeling AD resilience	6-18	15%, in progress
Subtask 3. Comparative studies complete	1-3	50%, 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	45%, in progress
Major Task 2.2. Modifiable Risk factors	Months	
Subtask 1. Study of behavioral risk factors	6-12	45%, in progress
Major Task 2.3. Effects of comorbid diseases	Months	
Subtask 1. Study of co-morbidity risk factors	6-21	50%, in progress
Major Task 2.5. Analysis of ADNI DoD data	Months	
Subtask 1. Validation of genetic effects and cognitive decline found for HRS-Medicare data	18-27	30%
Major Task 2.6. Multivariable model for predicting and analyzing the disparities	Months	
Subtask 1. Estimate multivariable model	1-6	40%, in progress

What was accomplished under these goals?

Major activities. In year 2 of the project (07/01/2021 – 06/30/2022), we focused on the evaluating and explaining the role of TBI in the risk of Alzheimer's disease (AD) and related dementia (ADRD) in veteran/non-veteran and White/Black subpopulations, finalizing the analyses of specific profiles based on the Barell/extended Barell matrixes using HRS-Medicare and 5%-Medicare data.

Specific objectives. In year 2, we continue working on the methods of partitioning and decomposition of disparities in AD/ADRD with specific focus on identification of the effects of exposure and vulnerability that are evaluated using the generalized Oaxaca-Blinder approach. We identified the effect of TBI on AD and cognitive decline in veterans and non-veterans using HRS-Medicare data as well as studied and compared short term vs. long term risk of TBI on AD in veterans and non-veterans groups. We also identified mutually exclusive morbidity profiles and identified their time trends and effects of AD/ADRD risks. We presented the results of comparative studies on the effects of genetic risk factors and multivariable modeling at the Annual

Meetings of Population Association of America (2022) and Gerontological Society of America (2021) conferences.

Significant Results and Key Outcomes.

We evaluated (Akushevich et al. 2021a) the associations between TBI and AD that could be attributable to certain confounding (or moderating) factors including among others, comorbidities, behavior, genetics, and education. Specifically, we assessed 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. We found that TBI was strongly associated with AD risk in both veteran and non-veteran subpopulations in the HRS data. In total sample: HR=2.603 (CI: 2.008-3.373), p<.0001 in veterans and HR=2.357 (CI: 2.079-2.672), p<.0001 in non-veterans. In males-only subsample: HR=3.919 (CI: 2.941-5.222), p<.0001 in veterans and HR=2.577 (CI: 1.982-3.352), p<.0001 in non-veterans. TBI was strongly associated with cognitive decline in both veteran and non-veteran subpopulations in HRS data: -0.0071 p<.0001 (total sample) and -0.0084, p=0.0060 (males only). Difference between veterans and non-veterans is not significant in all analyses excepting the model for AD risk in males only: HR=0.664 (0.476-0.926), p=0.0157. Using PTSD instead of TBI results in similar estimates but with lower significance, e.g., AD HR=2.450 (1.099-5.462), p=0.0285 (total sample). Effects of AD and ADRD are similar, e.g., ADRD HR for male veterans and non-veterans are 4.128 (3.181-5.358) and 2.789 (2.200-3.535), respectively. Effect magnitude decreased with the addition of risk-related control variables but remained associated with the increased risks. In total sample: HR=2.376 (2.097-2.691) for the pooled sample (both veterans and non-veterans) becomes 2.374 after adjusting for demographic and socioeconomic (SES) variables and 2.162 after additional adjusting for comorbidity. In the total sample with genetics: HR=2.669 (2.120-3.361) for the pooled sample (both veterans and non-veterans) becomes 2.558 after adjusting for all three groups of cofactors. In the males only subsample: HR=3.939 (3.023-5.133) for the pooled sample (both veterans and non-veterans) becomes 3.801 after adjusting for demographic and SES variables and 3.387 after additional adjusting for comorbidity. In males only subsample with genetics: HR=4.584 (2.827-7.434) for the pooled sample (both veterans and non-veterans) becomes 4.193 after adjusting for all three groups of cofactors. Subsequent analysis of ADNI-DoD data showed that prevalence of mild cognitive impairment was strongly associated with TBI at baseline in DoD-ADNI data, and that no cognitive decline was observed during one year of follow-up.

We continued the study of the Year 1 attempting to find evidence to support TBI as a short term or long-term risk factor by assessing how the effect of TBI changes with time after injury and comparing associated risk between veterans (a subgroup with higher probability of early life TBI) and non-veterans using data drawn from the Health and Retirement Study (HRS) linked to Medicare Administrative claims records for the 1991-2015 period (Yashkin et al., 2022). The study-wide incidence of AD/ADRD was 8.78/10.47% for the entire sample, 7.67/9.38% in veteran males and 6.63/8.33% in non-veteran males. Veteran males were more likely to exit the study due to death, be older, be married, have college education, have high economic status and be a former smoker. Conversely, they were less likely to be non-white, have less than high school education, have low economic status, have hypertension, and have diabetes. Veteran males were in better overall health as measured by the weighted comorbidity index. Incidence of a new episode of TBI after age 70 was found to be associated with increased risk of AD and ADRD. The (unweighted) strength of the effect ranged from (Hazard

Ratio (HR) 3.05; 95% Confidence Interval [2.49-3.75]) for AD in the full sample to 4.00 [2.92-5.47] for ADRD in veteran Males. These exceptionally high HRs are offset by the protective effects associated with each post-TBI year that passed without AD/ADRD onset which were highly consistent across all specifications ranging from 0.90 [0.86-0.95] for ADRD in veteran males to 0.91 [0.89-0.94] for ADRD in the full sample. Veterans, a group with higher probability of early life TBI, did not show a statistically significant difference in risk to non-veterans even after differences in demographics/socioeconomics and morbidity at baseline were accounted for by pseudorandomization. Our results confirm that receipt of a TBI after age 70 increases the risk of both AD and ADRD in the elderly. These associated HR are exceptionally high and consistent across all specifications. However, our results indicate that the risk associated with TBI goes down over time. This is suggested by the significant protective HR for every year past the first documented injury and the fact that veteran status (a subgroup of the population with a higher probability of receiving a TBI in earlier years) does not have a significant effect in any model specification. To offset this problem more attention should be given to preventing TBI in the elderly, including by the prevention of falls – the most common cause of TBI in this subgroup – as well as by improving access to post-TBI care which is often withheld from elderly individuals based on age and cognitive function-related cutoffs.

We tested the effects of TBI and other comorbid diseases on the risk of AD by defining mutually exclusive morbidity profiles and incorporating them to the partitioning models developed in Year 1 (Akushevich et al., 2022a). Since each case of AD can contain a set of risk factor diseases diagnosed prior to AD diagnosis, a unique (mutually exclusive) combination of pre-existing diseases known to be AD risk factors represent the morbidity profile of an individual with separate projection models developed for each such profile. The following approaches are used for this identification: i) Cox model in multivariable analyses in which all diseases are included, ii) exclusion the cases with the disease with highest hazard ratio and evaluation the hazard ratio for remaining diseases, iii) empiric analyses of obtained morbidity profiles that includes their age- and year-specific frequency distributions, and iv) evaluated effects of preliminary-identified exclusive morbidity profiles in Cox model. TBI was identified as primary contribution, and the following five mutually exclusive morbidity profiles were identified: i) profiles with a history of tumor brain injury (TBI) (fraction: 15.40%, AD OR=12.4), ii) profiles with history of cerebrovascular disease including stroke, but without TBI (39.35%, OR=8.7), iii) profiles with history of pneumonia/influenza and without cerebrovascular diseases and TBI (16.87%, OR=6.3), iv) profiles with diabetes or renal disease and without diseases in items i)-iii) (11.98%, OR=4.0), and v) profiles with arterial hypertension and without diseases in items i)-iv) (12.06%, OR=3.7). We found that the morbidity profile associated with cerebrovascular diseases was the only profile whose prevalence declines with time. All other profiles demonstrate an increase in their prevalence. Partitioning analyses demonstrated that in all profiles the resulting patterns come from a trade-off of two disadvantageous processes: increased incidence and disimproved survival. Except for the cerebrovascular disease associated profile trend in incidence overpower respective trends in survival. Time patterns of partitioning components are similar. Deceleration in incidence rates was detected for all profiles, but only two of them did not have periods of increased in incidence rates: profiles associated with TBI and diabetes/renal disease (because of the contribution of renal disease).

We continue developing partitioning and decomposition methods with the focus on disparities in AD/ADRD. Specifically, we developed and applied a new methodological framework based on a series of decomposition approaches which allows researchers to explain heath disparities in terms of health-care-related factors. (Akushevich et al., 2022b,c, Akushevich 2021, Nikitin et al., 2021). To date, we applied a Blinder-Oaxaca algorithm modified for censored data to 5%-Medicare to explain higher incidence levels of AD in Black Americans in terms of differences in higher exposure and vulnerability to morbidity profiles based on 10 major AD-risk-related diseases. We found that the primary contribution to racial disparities in AD risk comes from morbidity profiles that include hypertension with about $1/5^{th}$ of their contribution due to differences in prevalence (exposure effect) and $4/5^{ths}$ to differences in the effects of the morbidity profile on AD risk

(vulnerability effect). We further demonstrated that the vulnerability effect can be further decomposed into parts accounted for by individual socioeconomic variables, and that the exposure effect is determined by racial differences in initial morbidity, i.e., prevalence of arterial hypertension at age 65. We concluded from these analyses that since arterial hypertension is a manageable and potentially preventable condition, mitigation of the role of this disease in engendering higher AD incidence in Black Americans should be a primary concern. Specific attention was paid the effect of TBI on generating the disparities in the risk of AD. The total effect of TBI n the disparities in AD was minor and negative because of exposure effect (higher prevalence of TBI in White) and negligible vulnerability effect (risk of AD in both White and Black subgroups is almost equal).

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., 2021b) 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*", 2022 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.

To ensure broader dissemination, we published the results of the analyses in open access scientific journals.

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) publish epidemiological studies using empiric and regression approaches (Major Task 1.1, subtask 2), ii) publish the analysis of TBI and AD/ADRD associations for veteran and civilian subpopulations (Major Task 1.2), iii) complete and publish the approach for partitioning analysis of racial and veteran/civilian disparities (Major Task 1.3), and iv) complete and publish the study of the effects of time-independent (Major Task 1.4), socioeconomic (Major Task 2.1), and modifiable (Major Task 2.2 and Task 2.3) risk factors as well as trajectories of cognitive impairment (Major Task 2.4); and v) complete analysis of ADNI-DoD data (Task 2.5)

4. IMPACT:

We developed and approach for analyses of health disparities in the risk of AD/ADRD and completed the analysis of the causes of racial disparities performed based on this approach that allowed us to identify the critical role of arterial hypertension in generating racial disparities in AD/ADRD risk as well as identify minor role of TBI in generating such disparities.

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

Given that hypertension is a manageable and potentially preventable condition, mitigating the effects of this disease in engendering higher AD incidence in Black Americans should be a prominent public health concern. Furthermore, interventions focused on Black American communities, especially with high numbers of 75+ individuals, are urgently needed. Improving hypertension management after disease onset would lead to drastic reductions in the Black/White disparity in AD risk since a sizeable proportion of the total disparity is caused by post-onset vulnerability. Emphasis should be placed on the effects of antihypertensive pharmacological therapy as this pathway is most amenable to immediate modification and targets one of the most influential single sources of disparity. This approach will be applied for veteran-non-veteran disparities in the risk of AD/ADRD and evaluating the role of TBI in generating such disparities.

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

Due to the delays in obtaining access to the data related to COVID-19 reported before, some delay observed in completion of the tasks of the project.

Changes that had a significant impact on expenditures

Nothing to Report.

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., 2021. Decomposition of Disparities in Alzheimer's Disease and Related Dementia, *Innovation in Aging*, *5*(Supplement_1), pp.275-275.

Akushevich, I., Yashkin A., Nikitin, S., Kravchenko, J. 2021a. The Effect of Traumatic Brain Injury on Alzheimer's Disease and Cognitive Decline in Veterans and Non-Veterans, *5*(Supplement_1), pp. 305–

306,

Akushevich, I., Hill, C.V. and Arbeev, K., 2021b. Expanding the Scope of Administrative Health Records Through Advanced Statistical Methods. *Innovation in Aging*, *5*(Supplement_1), pp.275-275.

Akushevich I, Yashkin A, Kovtun M, Kravchenko J, Arbeev K, Yashin AI (2022a) Forecasting Prevalence and Mortality of Alzheimer's Disease using the Partitioning Models, *The Population Association of America's annual meeting (oral presentation)*, Atlanta, GA, USA, April 6-9, 2022

Akushevich I, Yashkin A, Kolpakov S, Kravchenko J (2022b) Causes of Racial Disparities in Alzheimer's Disease Risk, *The Population Association of America's annual meeting (oral presentation)*, Atlanta, GA, USA, April 6-9, 2022

Nikitin, S., Yashkin, A., Kravchenko, J. and Akushevich, I., 2021a. Causes of the Racial Disparities in the Risk of Alzheimer's Disease. *Innovation in Aging*, *5*(Suppl 1), pp.59-59.

Yashkin AP, Akushevich I, Gorbunova G, Yashin AI (2022) Traumatic Brain Injury in the Elderly as a Risk Factor for Alzheimer's Disease and Related Dementias: Short Term or Long Term Risk? *The Population Association of America's annual meeting (poster presentation)*, Atlanta, GA, USA, April 6-9, 2022

- **Journal publications.**

Akushevich I, Kolpakov S, Yashkin AP, Kravchenko J. Vulnerability to hypertension is a major determinant of racial disparities in Alzheimer's disease risk. American Journal of Hypertension. 2022c May 17. In press

- **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: 0000-0003-3471-7846
Nearest person month worked: 1.9
Contribution to the project: Dr. Akushevich has developed the decomposition approach for the disparities in AD/ADRD risks and evaluated disease-related causes of the disparities using such an approach.

Name: Arseniy Yashkin, Ph.D.
Project role: Senior Investigator
Researcher Identifier: 0000-0002-1185-148X
Nearest person month worked: 1.9
Contribution to the project: Dr. Yashkin completed the analyses of epidemiological studies using empiric and regression approaches in the analysis of TBI and AD/ADRD associations for veteran and civilian subpopulations

Name: Murali Doraiswamy, Ph.D.
Project role: PI
Researcher Identifier: 0000-0003-0697-3893
Nearest person month worked: 1.4
Contribution to the project: Dr. Doraiswamy contributed to the analysis of associations of TBI and the risk of AD/ADRD.

Name: Larry Tupler, Ph.D.
Project role: PI
Researcher Identifier: 0000-0001-7372-8711
Nearest person month worked: 1.1
Contribution to the project: Dr. Tupler has performed work in the area of TICS trajectory evaluation and analysis of ADNI-DOD data.

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., 2021. Decomposition of Disparities in Alzheimer's Disease and Related Dementia, *Innovation in Aging*, *5*(Supplement_1), pp.275-275.

Abstract: This study uses Medicare data to non-parametrically evaluate race- and place-of-residence-related disparities in AD/ADRD prevalence and incidence-based mortality, separate them out into the epidemiological causal components including race-related disparities in incidence and survival, and finally explain these in terms of health-care-related factors using causal methods of group variable effects (propensity scores and the rank-and-replace method) and regression-based analyses (extended Fairlie's model and generalized Oaxaca-Blinder approach for censoring outcomes). Partitioning analysis showed that the incidence rate is the main predictor for temporal changes and racial disparities in AD/ADRD prevalence and mortality, though survival began to play a role after 2010. Arterial hypertension is the leading predictor responsible for racial disparities in AD/ADRD risks. This study demonstrated that Medicare data has sufficient statistical power and potential for studying disparities in AD/ADRD in three interacting directions: multi-ethnic structure of population, place of residence, and time period.

Akushevich, I., Yashkin A., Nikitin, S., Kravchenko, J. 2021a. The Effect of Traumatic Brain Injury on Alzheimer's Disease and Cognitive Decline in Veterans and Non-Veterans, *5*(Supplement_1), pp. 305–306,

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., Hill, C.V. and Arbeev, K., 2021b. Expanding the Scope of Administrative Health Records Through Advanced Statistical Methods. *Innovation in Aging*, *5*(Supplement_1), pp.275-275.

Abstract: The objective of the Symposium is to expand familiarity of the application of advanced methods of

modern statistical modeling and data management, to administrative health data by combining methodological innovations with practical hands-on demonstrations. Topics will cover a range of methodological and substantive topics including: i) decomposition and partitioning approaches in analysis of disparities and time trends in AD/ADRD; ii) new artificial intelligence technologies that allow us to enrich electronic health record datasets with self-report scores in geriatrics; iii) using administrative data to model adherence to disease management and health-related behavior; iv) the use of longitudinal extension of the average attributable fraction to study health disparities and multimorbidity; and v) the geographic and racial disparities in total and remaining life expectancies after diagnoses of AD/ADRD and other chronic conditions. The increasing availability of large-scale datasets based on electronic health records and administrative claims records provide an unprecedented opportunity for obtaining nationally representative results based on individual-level measures that reflect the real care-related and epidemiological processes. This makes the reduction of barriers to entry to the use of such data of vital importance to the community of geriatrics and health researchers.

Akushevich I, Yashkin A, Kovtun M, Kravchenko J, Arbeev K, Yashin AI (2022a) Forecasting Prevalence and Mortality of Alzheimer's Disease using the Partitioning Models, *The Population Association of America's annual meeting (oral presentation)*, Atlanta, GA, USA, April 6-9, 2022

Abstract: A new forecasting model for prevalence and mortality based on a trend partitioning approach which models trends in age-adjusted prevalence and incidence-based mortality in terms of changes in interpretable epidemiologic quantities such as disease incidence and survival, is developed and applied to generate forecasts of Alzheimer's disease (AD) prevalence and mortality up to 2028 using health data drawn from a 5% sample of the total Medicare population. Forecasts are generated for entire AD population and for unique subgroups characterized by the presence of high-impact health conditions (stroke, traumatic brain injury, pneumonia, hypertension, diabetes) prior to AD diagnosis. Prevalence of AD is predicted to be stable between 2017 and 2028 primarily due to a decline in prevalence of pre-AD-diagnosis stroke. Mortality, on the other hand, is predicted to increase. In all cases the resulting patterns come from a trade-off of two disadvantageous processes: increased incidence and disimproved survival.

Akushevich I, Yashkin A, Kolpakov S, Kravchenko J (2022b) Causes of Racial Disparities in Alzheimer's Disease Risk, *The Population Association of America's annual meeting (oral presentation)*, Atlanta, GA, USA, April 6-9, 2022

Abstract: Higher incidence rates of Alzheimer's disease (AD) in Black Americans are well documented. However, quantitative explanations of these disparities in terms of AD-risk-related diseases acting through well-defined pathways is lacking. We applied a Blinder-Oaxaca algorithm modified for censored data to a 5% random sample of Medicare beneficiaries age 65+ to explain Black/White disparities in AD risk in terms of differences in exposure and vulnerability to morbidity profiles based on 10 major AD-risk-related diseases. The overwhelmingly leading contribution to the racial disparities in AD risk comes from morbidity profiles that included hypertension with about 1/5th of the contribution due to differences in prevalence (exposure effect) and 4/5ths to differences in the effects of the morbidity profile on AD risk (vulnerability effect). Hypertension is a manageable and potentially preventable condition, making mitigation of the role of this disease in engendering higher AD incidence in Black Americans a prominent concern.

Nikitin, S., Yashkin, A., Kravchenko, J. and Akushevich, I., 2021a. Causes of the Racial Disparities in the Risk of Alzheimer's Disease. *Innovation in Aging*, *5*(Suppl 1), pp.59-59.

Abstract: The risk of Alzheimer's disease (AD) is not uniform across race-specific subpopulations: Blacks

face approximately 50% higher risk of AD onset compared to Whites(Hazard Ratio=1.50; 95%CI:1.46-1.54). We used Blinder-Oaxaca decomposition, modified for censored data, to explain the disparities in the risk of AD between these races in Medicare beneficiaries aged 65+. This approach measures the contributions to the total difference in AD risks from the differences in the prevalence and the difference in magnitude of the effects of each potential explanatory variable. We used hypertension, diabetes mellitus, depression, cerebrovascular and renal diseases as the potential causes of the racial disparities in AD risk. We found that the greatest contribution was due to the impact of arterial hypertension, of which 24% of the effect was due to differences in prevalence and 76% due to the differences in effect magnitude. Unexpectedly, the contributions of other studied diseases explained only a small part of the racial disparity in AD risk. The remaining incidence rates, which could not be explained by the contributions of hypertension and other included diseases in the age-specific analysis, were lower for the Black population, although initially, the total age-specific incidence rates of AD were higher for the Blacks when compared to the Whites. Therefore, our results suggest that targeted interventions in the Black subpopulation are urgently needed to mitigate the adverse health effects of hypertension, independent of the possible causes, such as access to hypertension care, or race-related differences in adherence to antihypertensive treatment.

Yashkin AP, Akushevich I, Gorbunova G, Yashin AI (2022) Traumatic Brain Injury in the Elderly as a Risk Factor for Alzheimer's Disease and Related Dementias: Short Term or Long Term Risk? *The Population Association of America's annual meeting (poster presentation)*, Atlanta, GA, USA, April 6-9, 2022

Abstract: Although there is general acceptance of traumatic brain injury (TBI) leading to the development of neurocognitive disorders, there is still much uncertainty as to whether such injuries lead to a life-long increase in risk or if the increased risk declines with time. This study attempts to find evidence to support TBI as a short term and/or a long-term risk factor by assessing how its effect changes with time post-injury and comparing risk between veterans (high probability of early-life TBI) and non-veterans. Results confirm that receipt of a new TBI after age 70 increases the risk of both Alzheimer's Disease and Related Dementias. The associated hazard ratios are exceptionally high (3.05 [2.49-3.75]-4.55 [3.29-6.29]) and consistent across alternative specifications. However, this risk goes down over time (0.86 [0.82-0.91]-0.91 [0.88-0.94]). If validated, these results suggest the need for increased efforts in the prevention of TBI in the elderly and post-injury care.