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

PRINCIPAL INVESTIGATOR: Igor Akushevich

CONTRACTING ORGANIZATION: DUKE UNIVERSITY, DURHAM, NC

REPORT DATE: JULY 2023

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
July 2023	ANNUAL	01July2022-30Jun2023

4. TITLE AND SUBTITLE

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

5a. CONTRACT NUMBER
W81XWH-20-1-0253

5b. GRANT NUMBER
W81XWH-19-PRARP-CSRA

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

Igor Akushevich, Ph.D.

5d. PROJECT NUMBER
AZ190084

5e. TASK NUMBER

5f. WORK UNIT NUMBER
BARU, SSRI, DUKE

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
DUKE UNIVERSITY
2200 W MAIN ST, STE 710
DURHAM, NC 27708-4677

8. PERFORMING ORGANIZATION REPORT NUMBER
N/A

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)
DHA

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT. In year 3 of the project, we completed and published several analyses started in years 1 and 2. The primary deliverable of this reporting period was the analysis of the differences in risk of Alzheimer's disease following later life traumatic brain injury in veteran and civilian populations. We identified associations between incident TBI, post-TBI duration and TBI treatment intensity, with a diagnosis of clinical AD dementia in Medicare beneficiaries age 68+ from the Health and Retirement Study and found that i) later-life TBI was strongly associated with increased AD risk, especially in those requiring high-intensity/duration care, ii) effect magnitude decreased with time following TBI, iii) there are significant differences in AD risk between veterans and nonveterans, and iv) the protective effect associated with veteran status was largely due to differences in demographics, socioeconomics, and morbidity. Other published analyses extended developments of Years 1 and 2, including multivariable models for analyzing the risks and disparities in AD/ADRD, forecasting prevalence and mortality of AD using the partitioning models, and development of a new decomposition technique of disparities in life expectancy. 3rd-year analyses are at the stage of completion. Main ideas and current statuses of these analyses were presented at scientific forums and soon will be submitted for publication.

15. SUBJECT TERMS None listed.

16. SECURITY CLASSIFICATION OF: DOD			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON USAMRDC
a. REPORT	b. ABSTRACT	c. THIS PAGE			19b. TELEPHONE NUMBER *(include area code)*
U	U	U	UU	16	

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

TABLE OF CONTENTS

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	100%
Subtask 2. Epidemiological studies complete	1-12	90%
Local IRB/IACUC Approval	3th	100%
Milestone Achieved: HRPO/ACURO Approval	4th	100%
Milestone(s) Achieved: *Evaluated TBI profiles and their epidemiologic patterns*	12th	100%
Major Task 1.2. TBI and AD/ADRD associations for veteran and civilian subpopulations	Months	
Subtask 1. Comparative studies complete	1-12	75%
Milestone(s) Achieved: Estimated associations between TBI and AD, publication of a peer reviewed paper	12th	100%
Major Task 1.3. Partitioning analysis of racial and veteran/civilian disparities	Months	
Subtask 1. Partitioning analysis of time trends	3-12	75%
Subtask 2. Partitioning analysis of racial and veteran/civilian disparities	6-18	50%

Subtask 3. Partitioning analysis of TBI and AD	12-18	80%
Milestone(s) Achieved: *evaluation of racial and veteran/civilian disparities in PC, their partitioning components, publication of 1-2 peer-reviewed papers*	18th	
Major Task 1.4. Effects of time independent risk factors	Months	
Subtask 1. Study of genetic risk factors	1-6	60%
Subtask 2. Modeling AD resilience	6-18	50%
Subtask 3. Comparative studies complete	1-3	80%
Milestone(s) Achieved: *Estimated associations between TBI and AD, publication of a peer reviewed paper*	18th	
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	80%
Subtask 2. Study of socioeconomic factors	12-18	80%
Milestone(s) Achieved: Estimated effects of the socioeconomic and wellbeing factors	18th	
Major Task 2.2. Modifiable Risk factors	Months	
Subtask 1. Study of behavioral risk factors	6-12	80%
Subtask 2. Study of modifiable factors	12-18	80%
Milestone(s) Achieved: *Estimated effects of the modifiable factors*	18th	
Major Task 2.3. Effects of comorbid diseases	Months	
Subtask 1. Study of co-morbidity risk factors	6-21	90%
Milestone(s) Achieved: *Estimated effects of comorbidity; publication of a peer-reviewed paper summarizing the results of Tasks 2.1-2.3*	21th	
Major Task 2.4. Trajectories of cognitive impairment	Months	75%
Subtask 1. Empiric analysis and modeling of trajectories of TICS and TICS differences in subpopulations and their associations with AD/ADRD rates	12-33	75%
Milestone(s) Achieved: *Evaluated associations of cognitive trajectories and Ad/ADRD risks*	33ht	75%
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	75%
Milestone(s) Achieved: *estimated effects in DoD-ADNI data*	27th	50%
Major Task 2.6. Multivariable model for predicting and analyzing the disparities	Months	
Subtask 1. Estimate multivariable model	1-6	80%
Milestone(s) Achieved: *estimated ranks of the specific factors, publication of one peer-reviewed paper*	27th	80%
Other	Timeline	Status
Major Task 4.1 Data management and integration of updated datasets	1-36	80%
Milestone(s) Achieved:	36th	

What was accomplished under these goals?

Major activities. In year 3 of the project (07/01/2022 – 06/30/2023), we focused on further methodological development and substantive analyses in the area of 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.

Specific objectives. In year 3, specific objectives included: i) the analysis of the differences in risk of Alzheimer's disease following later life traumatic brain injury in veteran and civilian populations, ii) multivariable model for predicting and analyzing the risk of AD/ADRD and estimating related health disparities using 5%-Medicare data, iii) forecasting prevalence and mortality of Alzheimer's disease using the partitioning models developed in Years 1 and 2, iv) development of a new decomposition technique of disparities in life expectancy with applications to administrative health claims and registry data, v) evaluating the effects of Medicare comorbidities including TBI, self-reported factors, and polygenic risk scores on risks of Alzheimer's disease and related dementias, vi) analysis of DoD-ADNI TBI assessed using TICS neuropsychological domains, vii) analyses of distinct TBI-related subtypes reflecting differences in type of injury received using the DoD-ADNI dataset, viii) testing quality of aging in the U.S. Veterans, "healthy soldier" effect lasts >40 years, and ix) examining the allocation of β-amyloid (Aβ) plaques in the brains of Veterans and non-Veterans.

Significant Results and Key Outcomes.

We published the paper on differences in risk of Alzheimer's disease following later life traumatic brain injury in veteran and civilian populations (Yashkin et al., 2023). In this study we found that although incident older-life TBI is strongly associated with clinical AD/ADRD diagnosis, the strength of this effect decreases with time. Fine-Gray models combined with inverse probability weighting were used to identify associations between incident TBI, post-TBI duration and TBI treatment intensity, with a diagnosis of clinical AD dementia in Medicare beneficiaries age 68+ from the Health and Retirement Study. We found that later life TBI was strongly associated with increased clinical AD risk

in the full sample (pseudo-hazard ratio [HR]: 3.22; 95% confidence interval [CI]: 2.57-4.05) and in veteran/non-veteran males (HR: 5.31; CI: 3.42-7.94); especially those requiring high intensity/duration care (HR: 1.58; CI: 1.29-1.91). Effect magnitude decreased with time following TBI (HR: 0.72: CI: 0.68-0.80). We found no differences in the study-wide risk of clinical AD/ADRD between veterans and nonveterans in univariate analysis and that any differences in risk over the course of survival analysis were likely due to differences in demographics, socioeconomics, and morbidity between veterans and nonveterans at baseline rather than a reflection of a characteristic of membership in the veteran group. Our findings suggest that future longitudinal studies incorporating more complete documentation of TBI history are necessary to uncover pathophysiological mechanisms leading to increased risk of clinical AD/ADRD diagnosis. Furthermore, incorporation of diagnostic procedures (e.g., neuroimaging and blood biomarkers) and military documentation (e.g., personnel files, hospital inpatient, and health records) quantifying lifetime TBI events into claims/electronic health record–based analysis will be invaluable in uncovering the pathophysiological mechanisms of closed and penetrating injuries mediating or moderating the development of AD/ADRD presentations.

We published the paper on multivariable model for predicting and analyzing the risk of AD/ADRD and estimating related health disparities using 5%-Medicare data (Akushevich et al., 2022). We included the following AD-risk-related diseases: arterial hypertension, cerebrovascular disease, several other diseases of the circulatory system, diabetes mellitus, renal disease, traumatic brain injury, and depression. Then, we kept 5 diseases with major contributions (arterial hypertension, cerebrovascular disease, diabetes mellitus, renal disease and depression) and constructed and used 32 morbidity-profile indicators of all possible mutually exclusive combinations of them as predictors. The main conclusion from these analyses is that the leading contribution to the difference of AD risks between Black and White subpopulation is due to hypertension: 20% is due to difference in hypertension prevalence and 80% is due to the differences in the effects. Then we extended these analyses using HRS-Medicare data and adding genetic and socioeconomic variables additionally available in HRS-Medicare data. Specifically, we evaluated effects of Medicare comorbidities, self-reported factors, and polygenic risk scores on risks of Alzheimer's disease and related dementias and discussed how conclusions on heath disparities can be made. The results show that i) effects of Medicare diagnoses on AD/ADRD risk were larger than those of self-reported diseases; ii) cerebrovascular and heart diseases, depression, and brain injury had largest effect on AD/ADRD risk; iii) depression, arterial hypertension, and APOE4 proxy SNP rs769449, together, explained approximately half of the population attributable fraction of AD risk. Predictive multivariable models for AD/ADRD risks were constructed. TBI also appeared in the list of 12 risk factors and explained 3% of variance in AD risk and was set in the group of midlife predictors. The effect of TBI is much higher for males, probably because of more severe or more frequent injuries in males. One conclusion was that our study demonstrated that AD/ADRD risk is multifactorial in nature and its variation is tied to multiple demographic, socioeconomic and health-related risk factors.

We published the paper on forecasting prevalence and mortality of Alzheimer's disease using the partitioning models (Akushevich et al., 2023a). This analysis extends the partitioning models for AD/ADRD developed in year 1 of this project. We found that prevalence of AD is predicted to be stable between 2017 and 2028 primarily due to a decline in the prevalence of pre-AD-diagnosis stroke. Mortality, on the other hand, is predicted to increase. We identified five mutually exclusive combinations of pre-existing diseases that contribute to morbidity profiles in AD cases. The morbidity profile associated with a history of traumatic brain injury had the highest AD diagnosis odds ratio. The morbidity profile associated with cerebrovascular diseases had the highest prevalence and the leading contribution to AD risk. In all cases the resulting patterns come from a trade-off of two disadvantageous processes: increased incidence and disimproved survival. Analysis of health interventions demonstrated that the projected burden of AD differs significantly and leads to alternative policy implications. The applications of such models for analyses of interventions would allow for predicting future burden of AD/ADRD conditional on a specific treatment regime.

We published the paper on analyses of geographic and racial disparities in life expectancy at age 65 (Akushevich et al., 2023b). We developed a new decomposition technique of disparities in life expectancy with applications to administrative health claims and registry data. Specifically, we analyzed Pollard's integral, which is exact by construction, and developed exact analytic solutions for both types of data without the need for numerical integration. The solutions are broadly applicable and easily implemented. Applying these solutions, we found that

the largest relative contributions to geographic disparities in life expectancy at 65 were chronic lower respiratory diseases, circulatory diseases, and lung cancer; and, to racial disparities: arterial hypertension, diabetes mellitus, and cerebrovascular diseases. Overall, the increase in LE65 observed over 1998–2005 and 2010–2017 was primarily due to a reduction in the contributions of acute and chronic ischemic diseases; this was partially offset by increased contributions of diseases of the nervous system including dementia and Alzheimer's disease.

We continued studying the effects of comorbid diseases (including TBI) and both modifiable and genetic factors on the risk of AD/ADRD. Although a number of risk factors for AD/ADRD have been identified, there is no consensus about their joint role in risk of this disorder. In this study, we used HRS-Medicare, survey, and genetic data to evaluate and compare the effects of three groups of AD/ADRD risk factors: i) Medicare diagnoses for AD risk-related diseases including TBI, ii) self-reported health, behavior, physical function, education, and socioeconomic status, and iii) genetic markers. We identified most powerful predictors for AD/ADRD risks and evaluated their population attributable fractions. Our results showed comorbid diseases make strong contributions to the risk of AD/ADRD; however, they are not capable of explaining the variability in AD/ADRD risk completely. The effects of genetic factors were reduced to the effects of APOE-related SNPs. Arterial hypertension, depression, and genetics were found to be factors having the highest population attributable fraction in the risk of AD. The attributable population fraction of TBI to the risk of AD was found to be 2%. The manuscript was submitted to the *Journal of Alzheimer's Disease*. Furthermore, an abstract has been accepted for the upcoming Gerontological Society of America (GSA) annual meeting (November, 2023) reporting a greater rate of decline over 3 HRS waves for AD compared with TBI and vascular dementia.

We used the DoD-ADNI dataset to define and identify distinct TBI-related subtypes reflecting differences in type of injury received, and in Task 2.5 to evaluate cognitive decline by fitting neuropsychological test scores measured longitudinally to the HRS analyses. Our analysis of TBI-related subtypes has expanded into four major event classifications as they relate to i) exposure to kinetic conflict versus ii) noncombat military service and iii) prior versus iv) following military service. These divisions, expected to have an impact on TBI and PTSD severity, were abstracted via Access Visual Basic code from the CASPECIF and CACOMM fields of the ADDCOMM table, yielding: explosive-blast injury, military vs. civilian motor-vehicle accidents (MVAs), blunt-impact trauma, falls, sport-related injuries, assaults, combined events (e.g., blast/MVAs), and other categorizations. The issue of blast as a cause of the TBI has constituted a prominent topic in the literature examining Veterans of the Afghanistan and Iraq wars, but was also highly prominent during the Vietnam War. These data will allow an important investigation of the effects of aging on cognitive impairment (CI) from diverse TBI mechanisms with potential implications downstream for this Afghanistan/Iraq military cohort. We have furthermore refined our quantification of TBI severity in accordance with VA/DoD and American Congress of Rehabilitation Medicine criteria rather than the novel, arbitrary boundary of >5 min loss of consciousness applied by DoD-ADNI. We have also transformed an errant and unsystematic dataset holding thousands of participants into a cleaner, better-characterized compilation embodying database integrity and expanded detail/precision. We believe other investigators interested in using this large DoD-ADNI sample of TBI data stand to benefit from broader dissemination of our work.

To further refined the sophistication of our approach to quantifying CI: we examined key psychometric properties of the Telephone Instrument for Cognitive Status (TICS) in the DoD-ADNI dataset. The TICS contains 11 items that evaluate neuropsychological domains of temporal orientation, recent memory, attention/processing speed, language, environmental orientation, and abstraction. Our examination of these domains affords more fine-tuned analysis of the specific impaired component processes of CI that may attend distinct TBI-related subtypes in elderly combat veterans at risk for dementia. We examined psychometric properties of the TICS: SAS statistics revealed raw and standardized Cronbach's alpha with and without inclusion of missing values in the mid-0.70 range of internal-consistency reliability, with a dispersion of 0.55%–99.29% items incorrect. Exploratory factor analysis applying the oblimin rotation yielded results similar to other work with healthy civilians analyzing TICS section totals assigned a priori (e.g., temporal orientation, list learning). However, neuropsychological component processes were more subtly differentiated with our enrichment of analyses with deconstructed individual items,

e.g., a factor structure reflecting primary versus secondary memory and speech-language. An abstract of these findings has been accepted for a paper presentation for the upcoming GSA annual meeting (November, 2023). In future work, participant dates of birth will permit examination of the natural experiment provided by the Selective Service draft, which shifted the racial composition of the Armed Forces toward more random selection, with greater representation of African Americans. With our modifications, improvements, and expansion of the database beyond the neuroimaging subset to include approximately $N = 2{,}750$ in the initial screening subset, $n = 1{,}775$ data points exist with TBI-relevant quantification (e.g., negative vs. positive and severity, if positive) and confidence indices. We have $n = 1{,}950$ zip codes enabling investigation of place-based healthcare disparities. TICS analyses in SAS are ongoing to further describe the relationship between TBI history and longitudinal neurocognitive presentations in these elderly Vietnam War Veterans.

Previously it was shown that the "healthy soldier" effect lasts up to 30 years before being eroded. We aim to show that this effect lasts even more, up to 40 years, when we speak about the generation born between 1930-1940 and confirm the hypothesis that this effect erodes faster for the latest generations (Afghanistan and Iraq war Veterans). Applying the logistic regression to HRS data (HRS RAND file), we compared the attributes of successful aging, socioeconomic environment, and general well-being of the U.S. Veterans after concluding military duties, and citizens who did never exercise service duty and are aged 70+. We consider five aspects of aging: such as living conditions, psychosocial well-being, education, health, morbidity, and depression in five age cohorts, 70-75, 75-80, 80-85, 85-90, and 90+ for the patients included in the HRS RAND study.

We examined the allocation of β-amyloid (Aβ) plaques in the brains of Veterans, long-time survivors of traumatic brain injury (TBI), and those, who did not report brain trauma, and compared it with a spatial distribution of Aβ plaques in the brains of participants of the ADNI program as well as with the pattern of the spatial distribution of Aβ in the brains of participants of ADNI with Alzheimer's disease. This study included 675 community-dwelling male participants from the ADNI and DoD-ADNI databases (137 veterans, 131 cases of TBI, and 123 AD cases) 62 years old or older. We performed regression analysis, using a pseudo-randomization algorithm, and propensity-score inverse-probability weighting to equalize the subsamples for fourteen outcomes, 12 standardized uptake value ratio variables, and 0.79 and 1.11 cutoffs. Race, educational level, geriatric depression score, age when florbetapir-18 (18F) PET scans were performed, APOE genotype, and Modified Hachinski Ischemic Score were used as predictors. The pattern common for AD showed the highest levels of β-amyloid in the cingulate cortex as well as in the frontal, parietal, and temporal lobes. Veterans have shown a statistically significant increase of 18F concentration in the cerebellum gray matter along with a lower concentration of it in the whole cerebrum as well as in neocortical regions than patients, who did not participate in combats. The continuous exposition to micro-TBI events, which does not necessarily necessitate the loss of consciousness or severe contusion likely can explain the high concentration of 18F in cerebellum gray matter in ex-combatants.

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) 2023 Annual Research Meeting 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*", 2023 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 plan to publish the paper "Effects of Medicare Comorbidities, Self-Reported Factors, and Polygenic Risk Scores on Risks of Alzheimer's Disease and Related Dementias" submitted to the Journal of Alzheimer's Disease, and complete the following analyses: i) time trends of TBI using 5%-Medicare data, ii) joint analysis of 5%-Medicare and HRS-Medicare data, iii) analysis of the rate of decline over three waves of the HRS for three disorders: AD, vascular dementia, and TBI, iv) effects of genetic markers on disparities in AD/ADRD, and v) two analyses of ADNI-DoD focused on the examining key psychometric properties of the Telephone Instrument for Cognitive Status (TICS) and the allocation of β-amyloid (Aβ) plaques in the brains of Veterans and non-Veterans. The results of the analyses will be published in open access journals when possible.

4. IMPACT:

We performed several substantive analyses that can be used for better understanding of the role of TBI in pathways to AD/ADRD development and developed several computational techniques that are listed in the 'Technologies or techniques' Section.

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

First, several new results clarified the role of TBI in the development of AD/ADRD (Yashkin et al., 2023). Specifically, our findings suggest that future longitudinal studies incorporating more complete documentation of TBI history are necessary to uncover pathophysiological mechanisms leading to increased risk of clinical AD/ADRD diagnosis. Furthermore, incorporation of diagnostic procedures (e.g., neuroimaging and blood biomarkers) and military documentation (e.g., personnel files, hospital inpatient, and health records) quantifying lifetime TBI events into claims/electronic health record-based analysis will be invaluable in uncovering the pathophysiological mechanisms of closed and penetrating injuries mediating or moderating the development of AD/ADRD presentations.

Second, we confirmed the role of hypertension in generating racial disparities in the risk of AD/ADRD (Akushevich et al., 2022). Since hypertension is a manageable and potentially preventable condition, mitigating the effects of this disease should be a prominent public health concern. Emphasis in health interventions should be placed on the effects of antihypertensive pharmacological therapy as this pathway is the most amenable to immediate modification and targets one of the most influential single sources of disparity.

Third, the forecasting model developed in Akushevich et al. (2023a) is an important building block for the next generation of forecasting approaches that involve rigorous mathematical models and incorporation of the dynamics of important determinative risk factors for AD/ADRD risk. Further model extensions will allow for estimating the future size of AD/ADRD-related burden while simultaneously accounting for multiple time trends in new and established risk factors. The ability of our forecasting models to account for the effects of interaction between TBI and other diseases will allow us to model plausible scenarios of future demographic and epidemiologic changes in AD/ADRD patterns and trends and identify areas with potential for health care interventions in the short-term. The applications of such models for analyses of interventions would allow for evaluating new possibilities that do not require direct investments in clinical trials for testing new medications but use hidden connections among existing diseases with well-established treatment regimens as well as for identifying new factors and mechanisms of disease development responsible for dependence between AD/ADRD and diseases common in older adults and produce new information about how the robustness (incidence rate) and resilience (case fatality rate) characteristics of AD/ADRD depend on the presence or absence of other diseases, as well as on associated genetic and non-genetic factors. The results will produce new insights on aging-related health decline and the role of AD/ADRD in this process.

Fourth, we calculated the disparities in life-expectancies at 65 and identified emerging trends (Akushevich 2023b) that could become a target of future efforts of policymakers and other health professionals. Specifically, we found the increase in life expectancy at 65 observed in 1998–2005 and 2010–2017 was primarily due to a reduction in the contributions of acute and chronic ischemic diseases, although this was partially offset by increased contributions of diseases of the nervous system, including dementia and Alzheimer's disease. In addition, we identified conditions that are responsible for persistent race and geographic disparities in life expectancies. Then we developed a forecasting model of AD/ADRD risks that involves rigorous mathematical models and incorporation of the dynamics of important determinative risk factors for AD/ADRD risk. The applications of such models for analyses of interventions would allow for predicting future burden of AD/ADRD conditional on a specific treatment

regime.

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., Yashkin, A., Kovtun, M., Kravchenko, J., Yashin, A. (2022a) Forecasting prevalence and mortality of Alzheimer's disease and related dementia using partitioning models. Program Abstracts from the Gerontological Society of America 2022 Annual Scientific Meeting "Embracing Our Diversity, Enriching Our Discovery, Reimagining Aging", November 2-6, 2022, Indianapolis, IN. Innovation in Aging, 2022, Vol.6, No.S1, page 472.

Akushevich, I., Yashkin, A., Kravchenko, J. (2022b) Geographic disparities in incidence and mortality of Alzheimer's disease. Program Abstracts from the Gerontological Society of America 2022 Annual Scientific Meeting "Embracing Our Diversity, Enriching Our Discovery, Reimagining Aging", November 2-6, 2022, Indianapolis, IN. Innovation in Aging, 2022, Vol.6, No.S1, page 2.

Akushevich I (2023) Analytic Methods for Health Disparities in Alzheimer's Disease and Related Dementia Risks and Survival. 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, NC, March 15-16, 2023

Akushevich I, Yashkin A, Kovtun M, Arbeev K, Kravchenko J, Yashin AI (2023) An Exact Approach for Decomposing the Population Attributable Fractions. The Population Association of America's annual meeting, New Orleans, LA USA, April 12-15, 2023

Kravchenko J (2023) Exposure to environmental contaminants and Alzheimer's disease risk. 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, NC, March 15-16, 2023

Nikitin SK, Akushevich I. Loci Responsible for Racial Disparity Between White and Black Americans in Alzheimer's Disease. Program Abstracts from the Gerontological Society of America 2022 Annual Scientific Meeting "Embracing Our Diversity, Enriching Our Discovery, Reimagining Aging", November 2-6, 2022, Indianapolis, IN. Innovation in Aging. 2022 Nov;6(Suppl 1):590.

Singh A, Arbeev K, Yashkin Y, Yashin A, Akushevich I (2023) Race and Sex Related Genetic Disparity in Alzheimer's Disease: Evaluating SNPxRACE and SNPxSEX Two-way Interactions. The Population Association of America's annual meeting, New Orleans, LA USA, April 12-15, 2023

Singh, A., Arbeev, K., Yashin, A. and Akushevich, I., 2022. Genetic Architecture of Alzheimer's Disease Risks. Program Abstracts from the Gerontological Society of America 2022 Annual Scientific Meeting "Embracing Our Diversity, Enriching Our Discovery, Reimagining Aging", November 2-6, 2022, Indianapolis, IN. Innovation in Aging, 6(Supplement_1), pp.2-2.

Yashkin A (2023) AD/ADRD disparities in Skilled Nursing Facilities. 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, NC, March 15-16, 2023

Yashkin A, Akushevich I, Yashin A, Gorbunova G, Ukraintseva S. (2022) Fungal Infections, Use of Antifungal Agents, and the Risk of Alzheimer's Disease. Program Abstracts from the Gerontological Society of America 2022 Annual Scientific Meeting "Embracing Our Diversity, Enriching Our Discovery, Reimagining Aging",

November 2-6, 2022, Indianapolis, IN. Innovation in Aging, 2022, Vol.6, No.S1, pages1-2.

- **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. Am J Hypertens. 2022 Aug 1;35(8):745-751.

Akushevich I, Yashkin A, Kovtun M, Kravchenko J, Arbeev K, and Yashin AI. (2023a) Forecasting prevalence and mortality of Alzheimer's disease using the partitioning models. *Experimental Gerontology*, *174*, p.112-133.

Akushevich I, Yashkin A, Kovtun M, Stallard E, Yashin AI, Kravchenko J. (2023b) Decomposition of disparities in life expectancy with applications to administrative health claims and registry data. Theoretical Population Biology, 153: 50-68

Yashkin, A.P., Gorbunova, G.A., Tupler, L., Yashin, A.I., Doraiswamy, M. and Akushevich, I., (2023) Differences in Risk of Alzheimer's Disease Following Later-Life Traumatic Brain Injury in Veteran and Civilian Populations. The Journal of Head Trauma Rehabilitation, pp.10-1097.

We submitted the manuscript "Effects of Medicare Comorbidities, Self-Reported Factors, and Polygenic Risk Scores on Risks of Alzheimer's Disease and Related Dementias.". It is under review by the Journal of Alzheimer's Disease.

- **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 new techniques includes: i) adaptation of the Oaxaca-Blinder approach for analyses of the effects of predictors of disparities for Medicare data, ii) extension of partitioning models for models of forecasting of AD/ADRD prevalence and mortality, and iii) development of a new decomposition technique for disparities in life expectancy with applications to administrative health claims and registry data. More details on these approaches are provided 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: 1.63
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: 1.10.
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: Senior Investigator
Researcher Identifier: 0000-0003-0697-3893
Nearest person month worked: 1.44.
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: Senior Investigator
Researcher Identifier: 0000-0001-7372-8711
Nearest person month worked: 1.32
Contribution to the project: Dr. Tupler has performed work in the area of TICS trajectory evaluation and analysis of ADNI-DOD data.

Name: Masudul Hoque, Ph.D.
Project role: Statistician
Researcher Identifier: 0000-0002-5831-0250
Nearest person month worked: 1.40
Contribution to the project: Dr. Hoque has provided support related to all aspects of statistical analysis on the project.

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

Not Applicable