AWARD NUMBER: W81XWH-18-1-0692

TITLE: Genetic, comorbidities, and ethnicity: Effects of TBI on dementia

PRINCIPAL INVESTIGATOR: Kristine Yaffe, MD

CONTRACTING ORGANIZATION: Northern California Institute for Research and Education
San Francisco, CA 94121

REPORT DATE: October 2019

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**
OCT-2019	Annual	30-SEP-2018 – 29 SEP-2019

4. TITLE AND SUBTITLE

Genetic, comorbidities, and ethnicity: Effects of TBI on dementia

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH‐18‐1‐0692

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

Kristine Yaffe, MD

E-Mail: Kristine.yaffe@ucsf.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Northern California Institute for
Research and Education
4150 Clement Street (151 NC)
San Francisco, CA 94121-1545

8. PERFORMING ORGANIZATION REPORT NUMBER

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)

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

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

Up to 20% of young veterans have had a traumatic brain injury (TBI), with many older veterans having TBI as well. Some epidemiological studies have reported a link between TBI and increased risk of dementia even after years of active life post injury, however, few have examined what factors may increase or decrease the risk of dementia after TBI. In recent decades, as the country has become more racially and ethnically diverse, so has the U.S. military. However, no studies have examined how race and ethnicity may influence the TBI outcomes and risk of developing dementia. Findings have linked TBI with negative socioeconomic, medical and psychiatric consequences. Yet, these factors also have been identified independently as risk factors for cognitive impairment. This new and unique research collaboration will leverage two established epidemiological datasets to investigate factors associated with adverse cognitive outcomes among veterans with head injuries. Our overall hypothesis is that veterans who are non-white, have lower socioeconomic status and education, and those with greater psychiatric and medical comorbidities will have a higher risk of dementia after TBI. Further, we hypothesize that these differences will still be present after accounting for early life exposures and genetics by studying a large cohort of 3000 twin pairs. Finally, we will determine the population attributable risk (PAR) or proportion of dementia attributable to TBI, both among Veterans and non-veterans. This estimate will allow us to compare TBI to other important risk factors in order to design better prevention and intervention strategies and help highlight the public health significance of TBI.

15. SUBJECT TERMS

Dementia, aging, cognitive impairment (CI), Alzheimer's disease (AD), traumatic brain injury (TBI)

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	10	**19b. TELEPHONE NUMBER** *(include area code)*

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

TABLE OF CONTENTS

	Page
1. Introduction	4
2. Keywords	4
3. Accomplishments	4
4. Impact	6
5. Changes/Problems	6
6. Products	6
7. Participants & Other Collaborating Organizations	7
8. Special Reporting Requirements	10
9. Appendices	10

- **INTRODUCTION:** Up to 20% of young veterans have had a traumatic brain injury (TBI), with many older veterans having TBI as well. Some epidemiological studies have reported a link between TBI and increased risk of dementia even after years of active life post injury, however, few have examined what factors may increase or decrease the risk of dementia after TBI. In recent decades, as the country has become more racially and ethnically diverse, so has the U.S. military. However, no studies have examined how race and ethnicity may influence the TBI outcomes and risk of developing dementia. Findings have linked TBI with negative socioeconomic, medical and psychiatric consequences. Yet, these factors also have been identified independently as risk factors for cognitive impairment. This new and unique research collaboration will leverage two established epidemiological datasets to investigate factors associated with adverse cognitive outcomes among veterans with head injuries. Our overall hypothesis is that veterans who are non-white, have lower socioeconomic status and education, and those with greater psychiatric and medical comorbidities will have a higher risk of dementia after TBI. Further, we hypothesize that these differences will still be present after accounting for early life exposures and genetics by studying a large cohort of 3000 twin pairs. Finally, we will determine the population attributable risk (PAR) or proportion of dementia attributable to TBI, both among Veterans and non-veterans. This estimate will allow us to compare TBI to other important risk factors in order to design better prevention and intervention strategies and help highlight the public health significance of TBI.

- **KEYWORDS:** Dementia, aging, cognitive impairment (CI), Alzheimer's disease (AD), traumatic brain injury (TBI)

- **ACCOMPLISHMENTS:**

    - **What were the major goals of the project?**

        - Task 1: Planning and Regulatory Review (Months 1-5)
        - Task 2: Aim 1 - To determine the contribution of sociodemographic factors such as race, ethnicity, education, and socioeconomic status (SES) to the association between TBI and dementia in the VA TBI Cohort. (Months 5-15)
        - Task 3: Aim 2 - Determine the contribution of medical and psychiatric conditions to the association between TBI and dementia in the VA TBI Cohort. (Months 8-24)
        - Task 4: Aim 3 - Capitalizing on the twin design, determine the contribution of sociodemographic factors such as SES and education to the association between TBI and risk of cognitive decline and dementia in the Twin Registry. (Months 6-15)
        - Task 5: Aim 4 - Using the Twin Registry, to determine the contribution of medical and psychiatric conditions to the association between TBI and cognitive decline/dementia. (Months 9-24)
        - Task 6: Aim 5 - Estimate the attributable risk of TBI on dementia among veterans and the portion of that risk attributable to each of the mediating or moderating variables including medical and psychiatric comorbidities. (Months 22-36)

    - **What was accomplished under these goals?**

        - We have made excellent progress developing a partnership between the UCSF and Duke groups over the first year of this project and have completed one poster and one manuscript. In the first several months of the project we submitted and received all the required regulatory approvals at Duke, UCSF, and HRPO.

          Using the VA TBI cohort, the team examined the effects of gender and race on the development of dementia after TBI (Aim 1). The final analytic cohort included 999,642 Veterans, 9.6% (n=96,178) with TBI, after excluding 24,959 Veterans with incident dementia during the two-year baseline period (defined as 2 years before the TBI diagnosis date or random selection date, respectively). Results show that males and females have fairly similar risks of dementia after TBI (males HR=2.60, 95%CI: 2.54-2.66; females HR=2.36, 95%CI: 2.08-2.69). Upon examining race/ethnicity, we found that Hispanic veterans had the lowest

risk of developing dementia after TBI (HR=1.74, 95%CI: 1.51-2.01), while White veterans had the highest risk (HR=2.71, 95%CI: 2.64-2.77). These results suggest that among older Veterans, TBI slightly differentially increases risk for dementia based on race. Further research is needed to understand mechanisms for this discrepancy. We wrote the results into a manuscript, which has been submitted for publication and is currently under review.

In the first year we also got started working on the PAR portion of the project (Aim 5). We completed an updated literature search, working with the UCSF library to pull the appropriate papers. Search terms include: “brain injuries traumatic” or “brain injuries” or “head injuries” or “head injury” or “brain injury” or “head trauma” or “brain trauma” or “brain damage” and “dementia” or “cognitive dysfunction” or “Alzheimer’s disease” or “AD” or “Alzheimer’s” or “cognitive decline” or “neurocognitive impairment”. We finished the literature search and have started working on the new meta-analysis. We developed inclusion/exclusion criteria and are in the process of screening the 800 studies found in the initial pull.

For the Twin Registry, we’ve compiled approximately 20 years of longitudinal data collection for analyses for this project. Ensuring consistency across the multiple variables and time points has been labor intensive and time consuming. We have cleaned and finalized data containing information on demographics, cognitive screening scores traumatic brain injuries, and diagnoses of dementia for over 15,000 twins. We have started descriptive analyses on variables of interest as specified in the project aims and have addressed the first part of Specific Aim 3 of the project. Our statistical programming for the analyses has been coded and reviewed by the senior statistician. To date, we have estimated the risk of dementia, Alzheimer’s disease, and other types of dementia due to TBI.

All team members have participated in weekly individual core meetings, monthly project-specific team meetings to review analyses and monitor progress, and we’ve started interdisciplinary quarterly team meetings.

- **What opportunities for training and professional development has the project provided?**
  - Nothing to report
- **How were the results disseminated to communities of interest?**
  - For this project we have selected national/international meetings to disseminate our work through poster and oral presentations in which a broad range of multidisciplinary researchers and clinicians invested in reducing the effects of traumatic brain injury on cognitive aging and improving Veteran’s health would be present. We have also submitted our completed manuscript to a journal that also targets multidisciplinary researchers and clinicians who are invested in improving Veteran’s health.
- **What do you plan to do during the next reporting period to accomplish the goals?**
  - In the second year of the grant Dr. Yaffe and Dr. Plassman will continue to work together and meet or exceed the goals for this project. We will continue to work on the analyses using the Twin Registry to address Aims 3 and 4 of the grant. To address Aim 3, we will also obtain the information necessary to create the neighborhood socio-economic status index score. We plan to write up the Aim 3 results as an abstract for the 2020 AAIC. Additionally, we will work to compile the medical and psychiatric conditions in the archived data to address Aim 4. Using the VA TBI Cohort, we will begin planning analyses to address Aim 2, finding novel ways to utilize the medical and psychiatric data in our large veteran dataset. For the Aim 5 meta-analysis, we will select which studies meet inclusion and exclusion criteria, enter the study data, then import the data into data management software for analysis. Once the analyses have been completed, we will draft up the manuscript.

- **IMPACT:**
    - **What was the impact on the development of the principal discipline(s) of the project?**
        - Nothing to report
    - **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
- **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**
        - Compiling decades of data is intense and takes time. While it has taken us some time to set up the dataset, we do not anticipate any further delays at this point and expect to meet our deliverables on time.
    - **Changes that had a significant impact on expenditures**
        - Due to delays from first level UCSF/DUKE IRB, VA ACOS/R&D, and second level HRPO approval, we were delayed in initiating spending. Per our institutional rules, we are required to have approvals in place before we can begin to spend. The project and spending are now on track and we plan to complete the project as originally designed.
    - **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**
        - N/A
- **PRODUCTS:**
    - **Publications, conference papers, and presentations**
        - **Journal publications.**

          Kornblith, E., Peltz, C., Xia, F., Plassman, B., Novakovic-Apopain, T., Yaffe, K. Sex, Race, and Risk of Dementia after Traumatic Brain Injury among Older Veterans. Under review.
        - **Books or other non-periodical, one-time publications.**

          Nothing to report

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

  Kornblith, E., Peltz, C., Xia, F., Novakovic-Apopain, T., Yaffe, K. Sex, Race, and Risk of Dementia after Traumatic Brain Injury among Older Veterans. Poster presented at UCSF Health Disparities Symposium, October 2019, San Francisco, CA.

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

  Nothing to report

- **Technologies or techniques**
  Nothing to report

- **Inventions, patent applications, and/or licenses**
  Nothing to report

- **Other Products**

  - Duke compiled approximately 20 years of longitudinal data collection for analyses for this project. The researchers have cleaned and finalized data containing information on demographics, cognitive screening scores traumatic brain injuries, and diagnoses of dementia for over 15,000 twins. UCSF utilized a database containing demographic, psychiatric, medical information, etc., for nearly 2 million veterans who received healthcare in the VA from 2005-2015. The project researchers have used this database for analyses, selected subsamples, and created variables as appropriate for each project.

- **PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**

- **What individuals have worked on the project?**

Name:	Kristine Yaffe
Project Role:	Principal Investigator
Researcher Identifier (e.g. ORCID ID):	KYAFFE
Nearest person month worked:	1
Contribution to Project:	Dr. Yaffe, in coordination with Dr. Plassman, provides scientific leadership and input on the analyses and interpretation of results
Funding Support:	n/a

Name:	Carrie Peltz
Project Role:	Project Coordinator
Researcher Identifier (e.g. ORCID ID):	n/a
Nearest person month worked:	1
Contribution to Project:	Dr. Peltz coordinates the project and assists with data analysis and publication
Funding Support:	n/a

○

Name:	Erica Kornblith
Project Role:	Postdoctoral Researcher
Researcher Identifier (e.g. ORCID ID):	n/a
Nearest person month worked:	6
Contribution to Project:	Dr. Kornblith provides expertise in traumatic brain injury, leads projects, and publishes manuscripts
Funding Support:	n/a

Name:	Gary Tarasovsky
Project Role:	Programmer
Researcher Identifier (e.g. ORCID ID):	n/a
Nearest person month worked:	2
Contribution to Project:	Mr. Tarasovsky works on dataset creation and management
Funding Support:	n/a

Name:	Brenda L. Plassman
Project Role:	Co-Principal Investigator
Researcher Identifier (e.g. ORCID ID):	000-0003-2867-7198
Nearest person month worked:	2
Contribution to Project:	Dr. Plassman, in coordination with Dr. Yaffe, provides scientific leadership and input on the analyses and interpretation of results
Funding Support:	n/a

Name:	Marianne Chanti-Ketterl
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	000-002-0438-676X
Nearest person month worked:	6
Contribution to Project:	Dr. Chanti-Ketterl performs statistical analyses for the project
Funding Support:	n/a

Name:	Heather McDonald
Project Role:	Data Manager
Researcher Identifier (e.g. ORCID ID):	n/a
Nearest person month worked:	1
Contribution to Project:	Ms. McDonald is involved in the creation and documentation of datasets
Funding Support:	n/a

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**
- **Dr. Yaffe**: Summary: Dr. Yaffe had two grants end and two grants begin in the past year.

  Title: Change in Sleep & Cognition in Older Women
  (Yaffe: Multiple-PI)
  Time Commitment: 0.12 calendar months
  Supporting Agency: NIA
  Performance Period: 10/12 – 03/19 NCE
  Level of Funding: $2,068,666

  Title: Alzheimer's Disease Research Centers: Data and Statistical Core
  (Yaffe: PI of Data and Statistical Core C)
  Time Commitment: 1% (0.12 calendar months
  Supporting Agency: NIA
  Performance Period: 04/14 – 03/19 NCE
  Level of Funding: $528,482 TDC (core)

  Title: Hillblom Network for the Prevention of Age-Associated Cognitive Decline
  (Yaffe: Co-Investigator)
  Time Commitment: 1% (0.12 calendar months)
  Supporting Agency: Larry L. Hillblom Foundation
  Performance Period: 01/19 – 12/22
  Level of Funding: $810,000 TDC

  Title: New Approaches to Dementia Heterogeneity (Alzheimer's Disease Research Centers)
  (Yaffe: REC Lead, Co-Investigator on Core C)
  Time Commitment: 0.36 calendar months Core C, 0.36 calendar months, REC
  Supporting Agency: NIH/NIA
  Performance Period: 04/01/19 – 03/31/24
  Level of Funding: $2,055,368 Yr01 DC

- **Dr. Plassman**: Summary: Dr. Plassman had three grants end and two grants begin in the past year.

  Title: Innovating Tablet-Based Cognitive Assessment for CNS Disorders of Aging
  Time commitments: 0.60 calendar months
  Supporting agency: NeuroCog Trials/NIH
  Performance period: 5/15/16-10/31/18
  Level of funding: $65,047

  Title: Neuropsychology Lead Charter AD Prevention Studies
  Time commitments: 2.48 calendar months
  Supporting agency: Takeda Pharmaceuticals North America
  Performance period: 12/15/11-3/31/19
  Level of funding: $228,245

Title: Genes, Environments, Interactions, and Cognitive Decline in the HRS
Time commitments: 0.64 calendar
Supporting agency: Wake Forest University Health Sciences
Performance period: 7/15/16-10/31/18
Level of funding: $351,072

Title: Pesticides, Olfaction, and Prodromal Neurodegeneration among US Farmers
Time commitments: 2.26 calendar months
Supporting agency: Michigan State University/NIH
Performance period: 2/1/19-1/31/24
Level of funding: $400,743

Title: Improving Oral Health of Individuals with Mild Dementia
Time commitments: 3.6 calendar months
Supporting agency: NIH/New York University
Performance period: 9/21/18-8/31/23
Level of funding: $154,975

- **What other organizations were involved as partners?**
  - Nothing to report

- **SPECIAL REPORTING REQUIREMENTS**
  - Not Applicable

- **APPENDICES:** Nothing to report