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TITLE: Understanding the Connection Between Traumatic Brain Injury and Alzheimer's Disease: A Population-Based Medical Record Review Analysis

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CONTRACTING ORGANIZATION: Mayo Clinic
                               Rochester, MN 55905

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4. TITLE AND SUBTITLE

Understanding the Connection Between Traumatic Brain Injury and Alzheimer's Disease: A Population-Based Medical Record Review Analysis

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5b. GRANT NUMBER
W81XWH-15-1-0573

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

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

Mayo Clinic
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Rochester, MN 55905

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
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13. SUPPLEMENTARY NOTES

14. ABSTRACT

Purpose: The most accurate and reliable study design to determine whether the occurrence of TBI increases risk for the development of Alzheimer's disease and related disorders (ADRD) is to identify incident TBI events by medical record review within a defined population and classify each by injury severity, identify matched referents within that same population, and follow both cohorts over time to observe incidence rates of ADRD. **Scope:** Compared to other study designs, our approach significantly reduces the methodological problems of referral and recall bias, and selective survival, which have limited the scientific community's ability to determine whether TBI is indeed associated with an increased risk of ADRD. There are no published reports of a population-based analysis matching TBI cases, identified by medical record review and classified by injury severity into 3 strata, to population-based referents with non-head trauma. This is particularly important as non-head trauma may also increase the risk of ADRD. **Major Findings:** 6,939 individuals with 9,665 code dates for index injuries that occurred at or after the age of 40 years have been identified within the study period. 5,430 records of individuals (78% of total) that include 7,565 code dates have been reviewed, yielding 1,142 confirmed cases (yield rate of 21%).

15. SUBJECT TERMS
Population; epidemiology; dementia; neurocognitive disorders; brain injuries; Parkinsonian disorders

16. SECURITY CLASSIFICATION OF: U			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON USAMRMC
a. REPORT U	b. ABSTRACT U	c. THIS PAGE U	UU	11	19b. TELEPHONE NUMBER *(include area code)*

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1. **INTRODUCTION:**

    Subject: Epidemiological studies linking traumatic brain injury (TBI) and Alzheimer's disease and related disorders (ADRD: including Parkinson's disease, Lewy Body dementia, Frontotemporal dementia, and amyotrophic lateral sclerosis) have yielded conflicting results. These discrepant findings reflect methodological variation in defining TBI, classifying injury severity, and studying clinical cohorts not representative of the broader population. The epidemiology of TBI in military and civilian populations is dominated by the least severe injuries, exposing the greatest number of individuals to potential risk for developing ADRD, yet most previous analysis studying the connection between TBI and ADRD do not include this category of injury severity. **Purpose:** The most accurate and reliable study design to determine whether the occurrence of TBI increases risk for the development of ADRD is to identify incident TBI events by medical record review within a defined population and classify each by injury severity, identify matched referents within that same population, and follow both cohorts over time to observe incidence rates of ADRD. **Scope:** Mayo Clinic has been at the forefront of population-based epidemiological research related to both TBI and ADRD, and has a unique capability to study their association. Compared to other study designs, our approach significantly reduces the methodological problems of referral and recall bias, and selective survival, which have limited the scientific community's ability to determine whether TBI – including number and severity – is indeed associated with an increased risk of ADRD. To our knowledge, there are no published reports of a population-based analysis matching TBI cases, identified by medical record review and classified by injury severity into 3 strata (definite or 'moderate-severe'; probable or 'mild'; possible or 'concussive'), to population-based referents with non-head trauma. This is particularly important as non-head trauma may also increase the risk of ADRD.

2. **KEYWORDS:** Population; epidemiology; dementia; neurocognitive disorders; brain injuries; Parkinsonian disorders

3. **ACCOMPLISHMENTS**:

    Major Goals

    a. Mayo Clinic/Olmsted Medical Center IRB Approval
    b. HRPO approval
    c. Identify all potential individuals with TBI. Target completion 1-6 months

d. Confirm and classify TBI events. Target completion 3-24 months

e. Match individuals with a confirmed TBI to age- and sex-matched individuals from the population without a TBI. Target completion 6-24-months

f. Determine presence of ADRD based on medical record review and assess relationship between TBI and ADRD. Target completion 24-36 months

g. Data sharing via FITBIR. Target completion 12-36 months:

What was accomplished under these goals?

a. Mayo Clinic/Olmsted Medical Center IRB Approval
   1) major activities: achieved <u>25-Aug-2015/16-Nov-2015</u>

b. HRPO approval
   1) major activities: achieved <u>03-Dec-2015; HRPO continuing review submitted 22-Sep-2016</u>

c. Identify all potential individuals with TBI. Target completion 1-6 months
   1) major activities: computer-based screening of Rochester Epidemiology Project data sets for potential cases.
   2) specific objectives: Construct a list of potential individuals consisting of all Olmsted County residents with any diagnosis suggestive of head injury or TBI from 1/1/1985 through 12/31/2012
   3) significant results: <u>6,939 individuals with 9,665 code dates for index injuries that occurred at or after the age of 40 years have been identified within the study period.</u>

d. Confirm and classify TBI events. Target completion 3-24 months
   1) major activities: All available clinical data is reviewed either in the paper or Electronic Medical Record including, but not limited to, general history notes, ED notes, hospital records, radiological imaging findings, surgical records, and autopsy reports.
   2) specific objectives: Confirm incident TBI events
   3) significant results: <u>5,430 records of individuals (78% of total) that include 7,565 code dates have been reviewed, yielding 1,142 confirmed cases (yield rate of 21%).</u>

e. Match individuals with a confirmed TBI to age- and sex-matched individuals from the population without a TBI. Target completion 6-24-months: Nothing to Report

f. Determine presence of ADRD based on medical record review and assess relationship between TBI and ADRD. Target completion 24-36 months: Nothing to Report

g. Data sharing via FITBIR. Target completion 12-36 months:

   1) major activities:

   2) specific objectives: Enter the Mayo TBI Classification System into the FITBIR data dictionary as unique data elements; A de-identified data set of the subjects used in this research will be sent to the FITBIR Informatics System when the data is made ready for analysis and this analysis is complete. FITBIR variables will include: The Abbreviated Injury Scale (AIS) as it relates to assigning non-head trauma severity to TBI cases and their controls; Age; Birth Country name; Death cause; Education type and year count; Ethnicity USA category; Gender type; Imaging study and date; Injury cause; Injury date and time; Injury ICD e-codes; Loss of consciousness (LOC) duration; LOC indicators; post-traumatic amnesia (PTA) duration range; Race category; Seizure indicators; TBI mechanism type; and Vital status.

   3) significant results: All key personnel are registered with FITBIR and have current passwords; Our data screens submitted to FITBIR 7-Mar-2016; Data Access Agreement is in place and Data Submission Request to establish the Mayo Classification System for TBI Severity as a FITBIR data element was submitted 16-Mar-2016; FITBIR updates include the GUID Expiration Date has changed to 15-Mar-2017; The Data Repository Expiration Date has changed to 15-Mar-2017; The Query Expiration Date has changed to 15-Mar-2017; The Data Dictionary Expiration Date has changed to 15-Mar-2017; 600 pseudo-GUIDs have been assigned to cases and will be uploaded to FITBIR when administratively cleared.

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

Nothing to Report

How were the results disseminated to communities of interest?

<u>Nothing to Report</u>

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

a. Confirm incident TBI events; trained nurse abstractors will conduct this review, under direction of Dr. Brown and Dr. Mielke. All available clinical data will be reviewed either in the paper or Electronic Medical Record including, but not limited to, general history notes, ED notes, hospital records, radiological imaging findings, surgical records, and autopsy reports.

b. Classify each TBI event by cause, injury severity, and determine the number of TBI events per individual.

c. Cause and mechanism of injury will be classified according to methods developed by the National Center for Injury Prevention and Control, Division of Injury Disability, Outcomes, and Programs.

d. The number of TBI events and their severity will be identified in the medical record for each individual during the period before and after the index injury.

e. Match individuals with a confirmed TBI to age- and sex-matched individuals from the population without a TBI.

f. For TBI events that were associated with other non-head injuries, each of the accompanying non-head injuries will be assigned an empiric measure of severity, to which the Trauma Mortality Prediction Model will be applied to assign an overall measure of non-head injury severity to each individual.

g. For all individuals, determine the whether they have a diagnosis of any ADRD after the index date and up to December 31, 2014, and type of ADRD.

h. Enter the Mayo TBI Classification System into the FITBIR data dictionary as unique data elements per protocol and with FITBIR consultation.

i. A de-identified data set of the subjects used in this research will be sent to the FITBIR Informatics System when the data is made ready for analysis and this analysis is complete. FITBIR variables will include: The Abbreviated Injury Scale (AIS) as it relates to assigning non-head trauma severity to TBI cases and their controls; Age; Birth Country name; Death cause; Education type and year count;

Ethnicity USA category; Gender type; Imaging study and date; Injury cause; Injury date and time; Injury ICD e-codes; Loss of consciousness (LOC) duration; LOC indicators; post-traumatic amnesia (PTA) duration range; Race category; Seizure indicators; TBI mechanism type; and Vital status.

4. **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

5. **CHANGES/PROBLEMS:**

Nothing to Report

6. **PRODUCTS:**

Nothing to Report

7. **PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**
What individuals have worked on the project?

Name:	*Allen Brown, MD*
Project Role:	*Principal Investigator*

Researcher Identifier (e.g. ORCID ID):	*0000-0001-7228-3351*
Nearest person month worked:	*0.5*
Contribution to Project:	*Dr. Brown is responsible for all administrative aspects of the grant and research activity, including IRB approval, working with Dr. Mielke to oversee the epidemiological design of the study and the data abstractors. Dr. Brown provides clinical direction about case definition, injury classification, and assigning severity level for non-head trauma of cases and controls.*
Name:	*Michelle Mielke, PhD*
Project Role:	*Co-investigator*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*0.5*
Contribution to Project:	*Dr. Mielke oversees the epidemiological design of the study and the data abstractors.*
Name:	*Jane Emerson*
Project Role:	*Nurse Abstractor*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*9*
Contribution to Project:	*Medical record abstraction.*
Name:	*Dawn Pereda*
Project Role:	*Nurse Abstractor*
Researcher Identifier (e.g.	

ORCID ID):	
Nearest person month worked:	*9*
Contribution to Project:	*Medical record abstraction.*
Name:	*Jeanine Ransom*
Project Role:	*Data Analyst*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*7*
Contribution to Project:	*Identification of potential cases, data cleaning and review, identifying control subjects, identifying overlap between TBI cases and controls, and their development of Alzheimer's disease and related disorders.*

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**

Quad Chart

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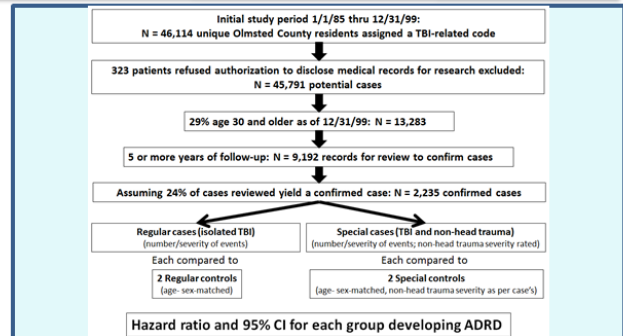**PI:** Allen Brown   **Org:** Mayo Clinic and Foundation, Rochester   **Award Amount:** $794,377

Study/Product Aim(s)
- Identify an incident cohort of individuals who experience TBI in the population of Olmsted County, MN); classify each TBI event by cause, injury severity, and determine the number of TBI events per individual
- Match each case with a matched population-based referent confirmed to not have a TBI and account for non-head trauma
- Determine the relationship between TBI, including number and severity, and risk of Alzheimer's Disease and related disorders (ADRD)
- Data sharing via FITBIR

Approach
All Aims will utilize Mayo Clinic's Rochester Epidemiology Project (REP) medical records linkage system for this population-based medical record review study. The existing REP TBI cohort of individuals aged 30 years and older who met record-review TBI criteria between 1985 and 2000 and age- and sex-matched individuals without a TBI during this timeframe will be expanded. We will determine diagnoses of ADRD among the expanded cohort and will also determine whether TBI increases the risk of ADRD within the population.

Initial study period 1/1/85 thru 12/31/99:
N = 46,114 unique Olmsted County residents assigned a TBI-related code

323 patients refused authorization to disclose medical records for research excluded:
N = 45,791 potential cases

29% age 30 and older as of 12/31/99: N = 13,283

5 or more years of follow-up: N = 9,192 records for review to confirm cases

Assuming 24% of cases reviewed yield a confirmed case: N = 2,235 confirmed cases

Regular cases (isolated TBI) (number/severity of events) — Each compared to — 2 Regular controls (age- sex-matched)

Special cases (TBI and non-head trauma) (number/severity of events; non-head trauma severity rated) — Each compared to — 2 Special controls (age- sex-matched, non-head trauma severity as per case's)

Hazard ratio and 95% CI for each group developing ADRD

Accomplishments: Population-based TBI cohort has been identified; record review/case confirmation occurring at greater than the anticipated rate (n=1,142); a study has been created in the FITBIR repository; pseudo GUID creation = 600.

Timeline and Cost

Activities	CY	15-16	16-17	17-18	
Identify cohort, classify events					
Match cases with referents					
Determine relationship re: ADRD					
Data sharing with FITBIR					
Estimated Budget ($794,377)		$356,535	$356,535	$81,307	

Updated: 14Oct2016

Goals/Milestones
CY15-16 Goals – IRB approval, identify cohort, classify events
- ☑ Mayo Clinic IRB approval 09-Sep-2015; Olmsted Medical Center IRB approval 29-Sep-2015; HRPO approval 03-Dec-2015
- ☑ FITBIR repository study exists, pseudo-GUIDs are being created
- ☑ Case confirmation, injury classification proceeds at high rate (n=1142 vs 674 last quarter).

CY16-17 Goals – Match cases with referents
- ☐ age- and sex-matching cases with controls
- ☐ matching special cases with controls adjusted for non-head trauma

CY17-18 Goals – Determine relationship re: ADRD
- ☐ Determine overlap: TBI/ADRD

Comments/Challenges/Issues/Concerns
- There has been no change in the timeline.

Budget Expenditure to Date
Projected Expenditure: $359,673
Actual Expenditure: $308,673

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9. **APPENDICES:**

Nothing to Report