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PRINCIPAL INVESTIGATOR: Allen W. Brown, MD

CONTRACTING ORGANIZATION: Mayo Clinic
Rochester, MN 55905

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Allen W. Brown

E-Mail: brown.allen@mayo.edu

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Mayo Clinic
200 First Street SW
Rochester, MN 55905

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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:** 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, 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:** TBI is associated with increased risk for ADRD in an injury severity-dependent manner, particularly in men; an age effect for ADRD was observed only for Definite TBI in those <70 years at the time of TBI; no associations were found between any TBI severity and either Alzheimer's disease, vascular dementia or Parkinson's disease; considering non-brain trauma consistently increased the association between TBI and developing neurodegenerative disease.

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

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1. **INTRODUCTION:**

Subject: Epidemiological studies linking traumatic brain injury (TBI) and Alzheimer's disease and related dementias (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. Maintain Mayo Clinic/Olmsted Medical Center IRB approval
b. Maintain HRPO approval
c. Identify all potential individuals with TBI in the target cohort.

d. Confirm TBI cases by manual record review and classify injury severity.
e. Matched all cases by age and sex to two (2) referents from the population without a TBI.
f. Match all TBI cases with non-head trauma by age and sex to two (2) referents from the population with traumatic injuries of the same severity of their cases, but without TBI.
g. Determine the proportion of ADRD in cases and referent cohorts and make the following comparisons: 1) A group containing all TBI cases (including those with TBI only – called 'regular' cases – and those with TBI and non-head trauma – called 'special' cases) with two (2) age and sex matched referents (all 'regular' referents; 2) A group of 'regular' TBI cases matched with two (2) 'regular' referents and 'special' cases matched with two (2) 'special' referents.
h. Share data with FITBIR

What was accomplished under these goals?

a. Mayo Clinic/Olmsted Medical Center IRB Approval
    1) major activities: achieved, expiration 20-Jul-2020 (Mayo)/16-Nov-2020 (OMC)
b. HRPO approval
    1) major activities: achieved expires 03-Dec-2015; HRPO continuing review last approved 11-Dec-2019
c. Identify all potential individuals with TBI: COMPLETE
    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: 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.
d. Confirm and classify TBI events. COMPLETE

1) Major activities: All available clinical data was 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: 5,430 records of individuals (78% of total) that include 7,565 code dates have been reviewed, yielding **1,430** confirmed cases (yield rate of 26%).
4) Injury severity: 7% definite (consistent with moderate-severe); 32% probable (consistent with mild); 61% possible (consistent with concussive).
5) Cases and their matched referents are summarized in the tables below.

TBI cases n = 1430

	Regular	Special	Total
Possible	794	76	870 (61%)
Probable	365	90	455 (32)
Definite	82	23	105 (7)
Total	1241	189	1430

Referents n = 2860

	Regular	Special	Total
Possible	1588	152	1740
Probable	730	180	910
Definite	164	46	210
Total	2482	378	2860

e. Determine the proportion of ADRD in cases and referent cohorts and make the following comparisons: 1) A group containing all TBI cases (including those with TBI only – called 'regular' cases – and those with TBI and non-head trauma – called 'special' cases) with two (2) age and sex matched referents (all 'regular' referents; 2) A group of 'regular' TBI cases matched with two (2) 'regular' referents and 'special' cases matched with two (2) 'special' referents.
    1) Major activities and significant results: the tables below describe these comparisons.

TBI cases and their regular matched referents

	Case (n=1430)	Regular Referent (n=2860)	Total (n=4290)	P value
Sex				1.0000
F (%)	812 (56.8)	1624 (56.8)	2436 (56.8)	
M	618 (43.2)	1236 (43.2)	1854 (43.2)	
Age at event				0.9189
n	1430	2860	4290	
Mean (SD)	57.0 (13.5)	57.0 (13.5)	57.0 (13.5)	
Median	54.0	54.0	54.0	
Q1, Q3	46.0, 66.0	46.0, 66.0	46.0, 66.0	
Any diagnosis				0.0006
No (%)	1133 (79.2)	2388 (83.5)	3521 (82.1)	
Yes	297 (20.8)	472 (16.5)	769 (17.9)	
Age at diagnosis				0.0383
n	297	472	769	
Mean (SD)	82.3 (9.3)	83.6 (9.3)	83.1 (9.3)	
Median	84.0	85.0	84.0	
Q1, Q3	77.0, 89.0	79.0, 90.0	78.0, 89.0	
Range	(50.0-102.0)	(44.0-105.0)	(44.0-105.0)	
Years event to diagnosis				0.5024
n	297	472	769	
Mean (SD)	13.7 (8.1)	13.2 (7.5)	13.4 (7.7)	
Median	13.1	12.1	12.4	
Q1, Q3	6.8, 20.4	7.1, 18.8	6.9, 19.4	
Range	(1.2-33.4)	(0.3-32.1)	(0.3-33.4)	
Diagnosis				0.0788
AIDS dementia (%)	0 (0.0)	1 (0.0)	1 (0.0)	
ALS	2 (0.1)	3 (0.1)	5 (0.1)	
Alcohol dementia	8 (0.6)	4 (0.1)	12 (0.3)	
Alzheimer's disease	145 (10.1)	279 (9.8)	424 (9.9)	
CBD	2 (0.1)	1 (0.0)	3 (0.1)	
DLB	18 (1.3)	15 (0.5)	33 (0.8)	
DLB & AD	0 (0.0)	2 (0.1)	2 (0.0)	
DLB and vascular	0 (0.0)	1 (0.0)	1 (0.0)	
Dementia NOS	12 (0.8)	21 (0.7)	33 (0.8)	
Dementia due to MS	0 (0.0)	2 (0.1)	2 (0.0)	
Dementia due to TBI	2 (0.1)	3 (0.1)*	5 (0.1)	
FTD	1 (0.1)	0 (0.0)	1 (0.0)	
MSA	0 (0.0)	1 (0.0)	1 (0.0)	
Mixed dementia	37 (2.6)	64 (2.2)	101 (2.4)	
NPH and Alzheimer’s	1 (0.1)	0 (0.0)	1 (0.0)	
None	1133 (79.2)	2348 (82.1)	3481 (81.1)	
PD	20 (1.4)	32 (1.1)	52 (1.2)	
PD, Alzheimer's	0 (0.0)	1 (0.0)	1 (0.0)	
PDD	1 (0.1)	5 (0.2)	6 (0.1)	
PPA	2 (0.1)	0 (0.0)	2 (0.0)	
PSP	2 (0.1)	2 (0.1)	4 (0.1)	
Vascular dementia	44 (3.1)	75 (2.6)	119 (2.8)	
Diagnostic categories				

TBI cases and their regular matched referents

	Case (n=1430)	Regular Referent (n=2860)	Total (n=4290)	P value
Alzheimer's				0.1405
No (%)	1247 (87.2)	2538 (88.7)	3785 (88.2)	
Yes	183 (12.8)	322 (11.3)	505 (11.8)	
Lewy body				0.0406
No	1411 (98.7)	2840 (99.3)	4251 (99.1)	
Yes	19 (1.3)	20 (0.7)	39 (0.9)	
Parkinson's				0.3700
No	1410 (98.6)	2829 (98.9)	4239 (98.8)	
Yes	20 (1.4)	31 (1.1)	51 (1.2)	
Vascular				0.0697
No	1349 (94.3)	2734 (95.6)	4083 (95.2)	
Yes	81 (5.7)	126 (4.4)	207 (4.8)	

* Three of the referents developed a TBI with subsequent dementia and were censored at that time.

ALS – amyotrophic lateral sclerosis; CBD – corticobasel degeneration; DLB – Lewy Body dementia; AD – Alzheimer's disease; NPS n- not otherwise specified; MS – multiple sclerosis; TBI – traumatic brain injury; FTD – frontotemporal dementia; MSA – multi-system atrophy; NPH – normal pressure hydrocephalus; PD – Parkinson's disease; PDD – Parkinson's disease dementia; PPA – progressive primary aphasia; PSP – progressive supranuclear palsy

Diagnoses included in categories
Alzheimer's: Alzheimer's disease, DLB and AD; Mixed dementia; NPH and Alzheimer's; PD and Alzheimer's
Lewy body: DLB; DLB and AD; DLB and vascular; PDD
Parkinson's: PD; PD and AD
Vascular: DLB and vascular; Mixed dementia; vascular dementia

TBI cases and their matched regular and special referents

	Cases (regular n=1241 special n=189) Total n=1430	Referents (regular n=2482 special n=378) Total n=2860	Total (n=4290)	P value
Sex				1.0000
F (%)	812 (56.8)	1624 (56.8)	2436 (56.8)	
M	618 (43.2)	1236 (43.2)	1854 (43.2)	
Age at event				0.8888
n	1430	2860	4290	
Mean (SD)	57.0 (13.5)	56.9 (13.5)	56.9 (13.5)	
Median	54.0	54.0	54.0	
Q1, Q3	46.0, 66.0	45.0, 66.0	46.0, 66.0	
Range	(39.0-97.0)	(36.0-97.0)	(36.0-97.0)	
Any diagnosis				0.0005
No (%)	1133 (79.2)	2390 (83.6)	3523 (82.1)	

TBI cases and their matched regular and special referents

	Cases (regular n=1241 special n=189) Total n=1430	Referents (regular n=2482 special n=378) Total n=2860	Total (n=4290)	P value
Yes	297 (20.8)	470 (16.4)	767 (17.9)	
Age at diagnosis				0.0792
n	297	470	767	
Mean (SD)	82.3 (9.3)	83.3 (9.7)	82.9 (9.6)	
Median	84.0	85.0	84.0	
Q1, Q3	77.0, 89.0	78.0, 90.0	78.0, 89.0	
Range	(50.0-102.0)	(44.0-105.0)	(44.0-105.0)	
Years event to diagnosis				0.7372
n	297	470	767	
Mean (SD)	13.7 (8.1)	13.4 (7.6)	13.5 (7.8)	
Median	13.1	12.2	12.5	
Q1, Q3	6.8, 20.4	7.2, 19.5	7.0, 19.7	
Range	(1.2-33.4)	(0.2-32.1)	(0.2-33.4)	
Diagnosis				0.0028
AIDS dementia (%)	0 (0.0)	1 (0.0)	1 (0.0)	
ALS	2 (0.1)	3 (0.1)	5 (0.1)	
Alcohol dementia	8 (0.6)	3 (0.1)	11 (0.3)	
Alzheimer's disease	145 (10.1)	251 (8.8)	396 (9.2)	
CBD	2 (0.1)	1 (0.0)	3 (0.1)	
DLB	18 (1.3)	13 (0.5)	31 (0.7)	
DLB & AD	0 (0.0)	3 (0.1)	3 (0.1)	
Dementia - NOS	0 (0.0)	5 (0.2)	5 (0.1)	
Dementia NOS	12 (0.8)	19 (0.7)	31 (0.7)	
Dementia due to MS	0 (0.0)	2 (0.1)	2 (0.0)	
Dementia due to TBI	2 (0.1)	1 (0.0)*	3 (0.1)	
FTD	1 (0.1)	0 (0.0)	1 (0.0)	
MSA	0 (0.0)	1 (0.0)	1 (0.0)	
Mixed dementia	37 (2.6)	60 (2.1)	97 (2.3)	
NPH and Alzheimer’s	1 (0.1)	0 (0.0)	1 (0.0)	
None	1133 (79.2)	2390 (83.6)	3523 (82.1)	
PD	20 (1.4)	28 (1.0)	48 (1.1)	
PD, Alzheimer's	0 (0.0)	1 (0.0)	1 (0.0)	
PDD	1 (0.1)	5 (0.2)	6 (0.1)	
PPA	2 (0.1)	0 (0.0)	2 (0.0)	
PSP	2 (0.1)	2 (0.1)	4 (0.1)	
Vascular dementia	44 (3.1)	71 (2.5)	115 (2.7)	
Diagnostic categories				
Alzheimer’s				0.0856
No (%)	1247 (87.2)	2545 (89.0)	3792 (88.4)	
Yes	183 (12.8)	315 (11.0)	498 (11.6)	
Lewy body				0.0562
No	1411 (98.7)	2839 (99.3)	4250 (99.1)	
Yes	19 (1.3)	21 (0.7)	40 (0.9)	
Parkinson’s				0.2638
No	1410 (98.6)	2831 (99.0)	4241 (98.9)	
Yes	20 (1.4)	29 (1.0)	49 (1.1)	

TBI cases and their matched regular and special referents

	Cases (regular n=1241 special n=189) Total n=1430	Referents (regular n=2482 special n=378) Total n=2860	Total (n=4290)	P value
Vascular				0.1226
No	1349 (94.3)	2729 (95.4)	4078 (95.1)	
Yes	81 (5.7)	131 (4.6)	212 (4.9)	

*One of the referents developed a TBI with subsequent dementia and was censored at that time.

ALS – amyotrophic lateral sclerosis; CBD – corticobasel degeneration; DLB – Lewy Body dementia; AD – Alzheimer's disease; NPS n- not otherwise specified; MS – multiple sclerosis; TBI – traumatic brain injury; FTD – frontotemporal dementia; MSA – multi-system atrophy; NPH – normal pressure hydrocephalus; PD – Parkinson's disease; PDD – Parkinson's disease dementia; PPA – progressive primary aphasia; PSP – progressive supranuclear palsy

Diagnoses included in categories
Alzheimer's: Alzheimer's disease, DLB and AD; Mixed dementia; NPH and Alzheimer's; PD and Alzheimer's
Lewy body: DLB; DLB and AD; DLB and vascular; PDD
Parkinson's: PD; PD and AD
Vascular: DLB and vascular; Mixed dementia; vascular dementia

f. Below are tables summarizing comparisons between the sample of all cases (1241 regular and 189 special) and their matched referents (2482 regular and 378 special).

Risk of developing any neurodegenerative diagnosis, by injury severity and by diagnostic category: 1430 total cases (1241 regular, 189 special); 2860 matched referents (2482 regular, 378 special)

	Hazard Ratio	95% CI	P value
Any neurodegenerative diagnosis			
All cases	1.37	1.15-1.64	<0.001
Definite (n=105)	1.50	0.84-2.67	0.173
Probable (n=455)	1.45	1.07-1.96	0.018
Possible (n=870)	1.31	1.04-1.66	0.025
Diagnostic category			
Alzheimer's disease (n=498)	1.18	0.94-1.48	0.149
Definite (n=39)	1.30	0.60-2.80	0.505
Probable (n=162)	1.20	0.80-1.79	0.371
Possible (n=297)	1.16	0.86-1.55	0.335
Vascular dementia (n=212)	1.35	0.98-1.85	0.066
Definite (n=25)	1.00	0.41-2.44	1.000
Probable (n=66)	1.46	0.85-2.53	0.172
Possible (n=121)	1.37	0.89-2.12	0.152
Parkinson's disease (n=49)	1.26	0.68-2.32	0.456
Lewy body and Parkinson's dementia (n=40)	1.62	0.81-3.24	0.171

Risk of developing any neurodegenerative diagnosis by sex and injury severity: 1430 total cases; 2860 matched regular and special referents.

	Hazard Ratio	95% CI	P value
Male (n=1854)	1.70	1.28-2.28	<0.001
Definite (n=66 cases)	2.71	1.21-6.06	0.015
Probable (n=250)	1.79	1.17-2.74	0.008
Possible (n=302)	1.39	0.88-2.18	0.157
Female (n=2436)	1.20	0.96-1.51	0.110
Definite (n=39 cases)	0.74	0.30-1.82	0.507
Probable (n=205)	1.16	0.74-1.80	0.518
Possible (n=568)	1.28	0.97-1.69	0.077

Risk of developing any neurodegenerative diagnosis by age <70 or >/= 70 and by injury severity: 1430 total cases (1135 < 70, 295 >/= 70); 2860 matched regular and special referents (2270 < 70, 590 >/= 70).

Any neurodegenerative diagnosis	Hazard Ratio	95% CI	P value
Age <70 (n=3405 cases and referents)	1.24	0.97-1.58	0.092
Definite (n=70 cases)	2.65	1.00-7.00	0.049
Probable (n=359)	1.32	0.88-1.97	0.184
Possible (n=706)	1.08	0.78-1.51	0.629
Age >/=70 (n=885 cases and referents)	1.54	1.19-1.98	0.001
Definite (n=35 cases)	1.07	0.51-2.25	0.849
Probable (n=96)	1.64	1.03-2.61	0.037
Possible (n=164)	1.60	1.14-2.24	0.006

g. The following tables shows how considering non-head trauma in cases and their referents affects risk for developing a neurodegenerative condition after TBI.

Comparing referent groups: all cases matched with their regular referents against regular cases matched with their regular referents and special cases matched with their with special referents

	Cases (regular n=1241 special n=189) n=1430	Referents All regular n=2860	Referents (regular n=2482 special n=378) n=2860	P value all regular referents	P value regular and special
Any diagnosis				0.0788	0.0028
Diagnostic category					
Alzheimer's				0.1405	0.0856
No (%)	1247 (87.2)	2538 (88.7)	2545 (89.0)		
Yes	183 (12.8)	322 (11.3)	315 (11.0)		
Vascular				0.0697	0.1226
No	1349 (94.3)	2734 (95.6)	2729 (95.4)		
Yes	81 (5.7)	126 (4.4)	131 (4.6)		
Parkinson's				0.3700	0.2638
No	1410 (98.6)	2829 (98.9)	2831 (99.0)		
Yes	20 (1.4)	31 (1.1)	29 (1.0)		
Lewy body				0.0406	0.0562
No	1411 (98.7)	2840 (99.3)	2839 (99.3)		
Yes	19 (1.3)	20 (0.7)	21 (0.7)		

Comparing referent groups: all cases matched with their regular referents against regular cases matched with their regular referents and special cases matched with their special referents

	HR Regular	HR Special	95% CI Regular	95% CI Special	P value Regular	P value Special
Any neurodegenerative diagnosis						
All cases	1.30	1.37	1.09-1.55	1.15-1.64	0.003	<0.001
Definite (n=105)	1.50	1.50	0.84-2.67	0.84-2.67	0.173	0.173
Probable (n=455)	1.31	1.45	0.97-1.78	1.07-1.96	0.079	0.018
Possible (n=870)	1.27	1.31	1.00-1.6	1.04-1.66	0.046	0.025
Diagnostic category						
Alzheimer's disease (n=498)	1.10	1.18	0.88-1.38	0.94-1.48	0.409	0.149
Vascular dementia (n=212)	1.30	1.35	0.94-1.78	0.98-1.85	0.110	0.066
Parkinson's disease (n=49)	1.24	1.26	0.69-2.25	0.68-2.32	0.471	0.456
Lewy body/Parkinson's (n=40)	1.66	1.62	0.83-3.31	0.81-3.24	0.152	0.171

Diagnoses included in categories
Alzheimer's: Alzheimer's disease, DLB and AD; Mixed dementia; NPH and Alzheimer's; PD and Alzheimer's
Lewy body: DLB; DLB and AD; DLB and vascular; PDD
Parkinson's: PD; PD and AD
Vascular: DLB and vascular; Mixed dementia; vascular dementia

h. Result summary and conclusions

1) Considering all types of neurodegenerative diseases, TBI is associated with increased risk and there appears to be a dose-response relationship such that the risk is highest for Definite (consistent with moderate-severe) cases, followed by Probable (consistent with mild) and then Possible (consistent with concussive).
2) This association is strongly in men, particularly for Definite and Probable TBI cases, but not Possible.
3) There is an effect of age of TBI. Risk of neurodegenerative diseases after a Definite TBI was only observed in those <70 years at the time of TBI. This suggests that in younger individuals (<70), only a Definite TBI is associated with increased risk. In contrast, for those aged 70 and older at the time of the TBI, those with Probable and Possible TBI were at greater risk. There is likely a survival bias in the older cohort that is contributing to the lack of association between a Definite TBI and a neurodegenerative disease.
4) Examining categories of neurodegenerative disease, there were no associations between any TBI severity and either Alzheimer's disease, vascular dementia or Parkinson's disease. Any TBI was associated with an increased risk of Lewy body and Parkinson's disease, but these results were not significant. These findings are consistent with a previous report using two

autopsy cohorts (Crane PK, JAMA Neurology 2016; 73(9):1062-1069), that a history of TBI was not associated with amyloid plaques or neurofibrillary tangles, but was associated with Lewy bodies. Our cohort had only 40 cases of Lewy Body or Parkinson's disease dementia, making the analysis underpowered to observe an association and likely explains why it did not reach significance.

5) Considering non-brain trauma in TBI cases and their matched referents consistently strengthened the association between TBI and developing neurodegenerative disease.

i. An Extension Without Funds (EWOF) was requested to extend this award for 12 months to complete the work within the scope of our original Statement of Work (SOW) as stated in the grant application.

1) The EWOF was approved 15-Sep-2018 thru 04-Mar-2020
2) No additional funds were requested.
3) This extension was needed because: 1) a greater number of cases of traumatic brain injury (TBI) than anticipated have had to be confirmed by manual abstraction of the paper record (rather than the Electronic Health Record); 2) a greater number of population-based referents (matched to these cases) than anticipated have had to be confirmed by manual abstraction of the paper record; 3) There have been unanticipated technical delays in calculating the severity index of non-head trauma for 'special' cases (TBI cases with head and non-head trauma) and matching them to their 'special' referents.
4) The work needed to complete the SOW during this extension was funded by institutional Division supplemental and base-budget resources which are intended for this purpose.
5) The process of determining the proportion of the cases and referents which developed ADRD diagnoses is complete.

j. Data sharing via FITBIR. COMPLETE. FITBIR continues work on establishing the Mayo Classification System for Traumatic Brain Injury Severity as a FITBIR common data element.

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

Mayo Clinic Brain Rehabilitation Medicine fellows and Physical Medicine and Rehabilitation residents have been exposed to this analysis and this research process.

How were the results disseminated to communities of interest?

A manuscript reporting the results of this analysis is in preparation and will be submitted to a high-impact medical journal. These results will also be disseminated at regional, national, and international meetings in the fields of neuroepidemiology and brain rehabilitation research.

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

This is the final report.

4. **IMPACT:**

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

This analysis will have high impact on and uniquely contribute to the fields of neuroepidemiology, neurology, and brain rehabilitation research because for the first time, this analysis used unique methodology to identify and confirm TBI cases in a defined population by medical record review, stratified these cases by injury severity, and compared the risk for developing neurodegenerative conditions to matched population-based referents that were controlled for non-brain trauma. New knowledge that will impact these research fields includes:

- an injury severity-dependent increase in risk of developing neurodegenerative disease overall after TBI that is strongest for men;
- no increase in risk associated with TBI for the development of the most common categories of neurodegenerative disease was found;
- Considering non-brain trauma in TBI cases and their referents consistently increased risk for developing a neurodegenerative condition.

What was the impact on other disciplines?

It is expected that this new knowledge will influence other investigators by focusing their efforts on using population-based samples, confirming them by medical record review, and comparing outcomes of interest to population-based referents. This will improve accuracy and consistency, allowing for more meaningful comparisons between different communities and countries.

What was the impact on technology transfer?

Nothing to Report

What was the impact on society beyond science and technology?

The primary finding that TBI is unassociated with increased risk for developing the most common types of neurodegenerative disease (e.g., Alzheimer's and Parkinson's) will be of great importance to individuals who experience a TBI and develop heightened health concerns about this risk. These findings will also be important for individuals who are reluctant to regularly participate in non-professional recreational activities which might be associated with an increased risk for TBI, avoiding these activities with known health benefits due to previous reports of an increased risk for developing these conditions.

5. **CHANGES/PROBLEMS:**

An extension without funds was approved 27-Nov-2018. This was needed because: 1) a greater number of cases of traumatic brain injury (TBI) than anticipated have had to be confirmed by manual abstraction of the paper record (rather than the Electronic Health Record); 2) a greater number of population-based referents (matched to these cases) than anticipated have had to be confirmed by manual abstraction of the paper record; 3) There have been unanticipated technical delays in calculating the severity index of non-head trauma for 'special' cases (TBI cases with head and non-head trauma) and matching them to their 'special' referents.

6. **PRODUCTS:**

A manuscript reporting these findings is in the final stages of preparation for submission to a high-impact medical journal.

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 referents.*
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:	*Jay Mandrekar, PhD*
Project Role:	*Biostatistician*

Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*0.2*
Contribution to Project:	*Statistical design, data analysis, manuscript preparation*
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	*7*

month worked:	
Contribution to Project:	*Identification of potential cases, data cleaning and review, identifying referent subjects, identifying overlap between TBI cases and referents, and their development of Alzheimer's disease and related dementias.*

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

Understanding the Connection Between Traumatic Brain Injury and Alzheimer's Disease: A Population-Based Medical Record Review Analysis
AZ140069
W81XWH-15-1-0573

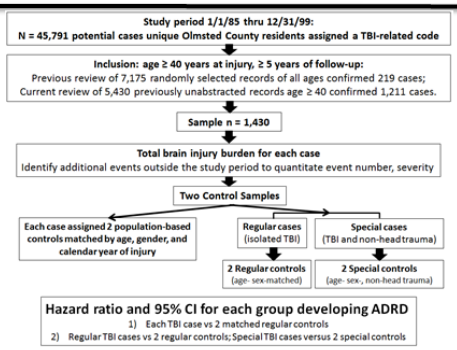
PI: Allen Brown **Org:** Mayo Clinic and Foundation, Rochester **Award Amount:** $794,377

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 dementias (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 40 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.



Accomplishments: 1) Final cases = **1,430**; 2) Identification of 2 matched 'regular' controls is complete; 3) 'Special' cases = 189 (13%); 4) Identification of 2 matched 'special' controls is complete; 5) determining hazard ratio 95% CI of TBI/ADRD among groups in final stages

Timeline and Cost

Activities CY	15-16	16-17	17-18	18-19
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: 30Mar2020

Goals/Milestones

CY15-16 Goals – IRB approval, identify cohort, classify events
☑ Continuing review approval: Mayo Clinic IRB 20-Jul-2020; Olmsted Medical Center IRB 16-Nov-2020; HRPO confirmed 11-Dec-2019
☑ 1,430 cases have been submitted to FITBIR
☑ Incident TBI during study period (≥40 years, ≥ 5 years f/u: n = **1,430**)

CY16-17 Goals – Match cases with referents
☑ quantitate number/severity TBI events per case outside study period
☑ age- and sex-matching cases to controls: regular controls
☑ matched special cases with controls adjusted for non-head trauma

CY17-18-19 Goals – Determine relationship re: ADRD
☑ Determine overlap: TBI/ADRD – complete per final report

Comments/Challenges/Issues/Concerns

- EWOF approved 15-Sep-2018 to 04-Mar-2020

Budget Expenditure to Date

Projected Expenditure: $794,377
Actual Expenditure: $794,377

9. APPENDICES:

Nothing to Report