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Education

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Grant and Contract Support

Active Grants

3/1/17-present	Role: Graduate Research Assistant, 20% Title: "Demonstrating the value of board certification in sleep medicine: Trends in diagnosis and impact on quality of care and economic

outcomes among Medicare beneficiaries, 2006-2013"
American Sleep Medicine Foundation (PI Wickwire)
Annual Direct Costs: $125,000

9/1/17-present Role: Pre-doctoral Fellow, 80%
Title: "Research Training in the Epidemiology of Aging"
National Institutes of Health, National Institute on Aging
Grant Number: 5T32AG000262-20
Annual Direct Costs: $328,894

Peer-reviewed Publications

1. Riedel DJ, Stafford KA, **Vadlamani A**, Redfield RR. Virologic and Immunologic Outcomes in HIV-Infected Patients with Cancer. AIDS Res Hum Retroviruses, 2016; [Epub ahead of print].

2. Albrecht JS, Wickwire EM, **Vadlamani A**, Scharf SM, Tom SE. Trends in Insomnia Diagnosis and Treatment among Medicare Beneficiaries, 2006-2013. Am J Geriatr Psychiatry. 2019 Mar;27(3):301-309

3. Wickwire EM, Tom SE, Scharf SM, **Vadlamani A**, Bulatao IG, Albrecht JS. Untreated insomnia increases all-cause health care utilization and costs among Medicare beneficiaries. Sleep. 2019 Apr 1;42(4).

4. Glass NE, **Vadlamani A**, Hwang F, Sifri ZC, Kunac A, Bonne S, Pentakota SR, Yonclas P, Mosenthal AC, Livingston DH, Albrecht JS. Bleeding and Thromboembolism After Traumatic Brain Injury in the Elderly: A Real Conundrum. J Surg Res. 2019 Mar; 235: 615-620.

5. **Vadlamani A**, Perry JA, McCunn M, Stein DM, Albrecht JS. Racial Differences in Discharge Location Following Traumatic Brain Injury among Older Adults. Arch Phys Med Rehab. 2019 Sep;100(9):1622-1628

6. Wickwire EM, **Vadlamani A**, Tom SE, Johnson AM, Scharf SM, Albrecht JS. Economic Aspects of Insomnia Medication Treatment Among Medicare Beneficiaries. Sleep. 2019. In press.

7. Wickwire EM, Tom SE, **Vadlamani A**, Diaz-Abad M, Cooper LM, Johnson AM, Scharf SM, Albrecht JS. Older adult US Medicare beneficiaries with untreated obstructive sleep apnea are heavier users of health care than matched control patients. J Clin Sleep Med. 2020 Jan 15; 16(1):81-89.

8. Wickwire EM, Albrecht JS, Dorsch JJ, Parthasarathy S, Collen J, Capaldi VF 2nd, Johnson A, **Vadlamani A**, Scharf SM. Practice patterns of board-certified sleep medicine providers: A national analysis among older adult Medicare beneficiaries. J Clin Sleep Med. 2020. In Press.

9. **Vadlamani A**, Albrecht JS. Severity of Traumatic Brain Injury in Older Adults and Risk of Ischemic Stroke and Depression. J Head Trauma Rehabil. 2020. In Press.

Abstracts

1. Glass NE, **Vadlamani A**, Hwang F, Sifri ZC, Kunac A, Bonne S, Pentakota SR, Yonclas P, Mosenthal AC, Livingston DH, Albrecht J. Bleeding and Thromboembolism After TBI in the Elderly: a Real Conundrum. 31st EAST Annual Scientific Assembly, Lake Buena Vista, FL, January 9-13, 2018. (podium presentation)

2. Albrecht JS, Tom SE, **Vadlamani A**, Scharf SM, Wickwire, EM.Trends in Insomnia Diagnosis Among Medicare Beneficiaries, 2006-2013. 32nd Annual Meeting of the Associated Professional Sleep Societies, LLC. Baltimore, Maryland, June 3-5, 2018.

3. Tom SE, Albrecht JS, **Vadlamani A**, Scharf SM, Wickwire, EM. Trends in Insomnia Prescription Medication Use Among Medicare Beneficiaries, 2006-2013. 32nd Annual Meeting of the Associated Professional Sleep Societies, LLC. Baltimore, Maryland, June 3-5, 2018.

4. **Vadlamani A**, Albrecht JS. Traumatic Brain Injury Severity is Associated with Increased Risk of Stroke in Older Adults. In: Proceedings from the Gerontological Society of America's 70th Annual Scientific Meeting; November 14-18, 2018; Boston, MA

5. **Vadlamani A**, Albrecht JS. Sensitivity of Self-Reported Comorbidities Compared to Medicare Claims in Older Adults with Traumatic Brain Injury. In: Proceedings from the Gerontological Society of America's 70th Annual Scientific Meeting; November 13-17, 2019; Austin, TX

Abstract

Title of Dissertation: **Neurological and Psychological Sequelae and Healthcare Utilization Patterns of Older US Adults with Repetitive Traumatic Brain Injury**

Aparna Vadlamani Chauhan, Doctor of Philosophy, 2020

Dissertation Directed By: Jennifer S. Albrecht, PhD
Associate Professor
Department of Epidemiology and Public Health

Background: Traumatic brain injury (TBI) is a leading cause of injury-related death and disability among older adults. Older adults experience adverse health outcomes and increased healthcare utilization following TBI. Additionally, they are at risk of repetitive TBI, which may compound health problems and increase resource utilization further. However, little is known about repetitive TBI among older adults.

Objective: To identify incidence, predictors, and outcomes of repetitive TBI. Specifically, I investigated the association between repetitive TBI and depression, ischemic stroke, Alzheimer's disease and related dementias (ADRD), and insomnia. In addition, I assessed healthcare utilization following repetitive TBI in inpatient, outpatient, and emergency department settings.

Methods: I conducted a retrospective cohort study of a 5% sample of US Medicare beneficiaries ≥65 years of age. I estimated incidence of and identified risk factors for repetitive TBI using a log-binomial model. Repetitive TBI was identified as another diagnostic code for TBI occurring >90 days after the index TBI. Associations between repetitive TBI and selected outcomes were assessed using a discrete time model with a

complementary log-log link. Negative binomial models were used to assess healthcare utilization associated with repetitive TBI.

Results: Among 38,064 beneficiaries in the sample, annual incidence of repetitive TBI was 3%. Age, epilepsy, Parkinson's disease, ADRD, depression, and atrial fibrillation were associated with increased risk of repetitive TBI. Incidence of depression and ADRD was elevated following single TBI, and was even more elevated following repetitive TBI. Healthcare utilization was significantly higher in those with repetitive TBI, beyond single TBI, across all points of service.

Conclusions: In this sample of older adult Medicare beneficiaries, I found 3% annual incidence of repetitive TBI and identified factors associated with repetitive TBI. Additionally, I found that repetitive TBI was associated with increased risk of depression and ADRD and increased healthcare utilization that was even greater than the risk observed with single TBI. Targeting interventions to reduce the occurrence of repetitive TBI in older adults could reduce risk of these adverse health outcomes and inform healthcare utilization.

Neurological and Psychological Sequelae and Healthcare Utilization Patterns of Older US Adults with Repetitive Traumatic Brain Injury

by
Aparna Vadlamani Chauhan

Dissertation submitted to the faculty of the Graduate School of the
University of Maryland, Baltimore in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
2020

I dedicate this dissertation to my family for their love, patience, and encouragement during my tenure in this program. The completion of this research would not have been possible without their continual efforts and support, now and always.

Vadlamani Kumar
Nagabala Vadlamani
Amar Chauhan
Adhya Chauhan

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LIST OF ABBREVIATIONS

TBI	Traumatic Brain Injury
ED	Emergency Department
ADRD	Alzheimer's Disease and Related Dementias
OR	Odds ratio
RtR	Rate Ratio
HR	Hazard Ratio
CMS	Centers for Medicare and Medicaid Services
CCW	Chronic Conditions Warehouse
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
RR	Relative Risk

I. INTRODUCTION AND SPECIFIC AIMS

Traumatic brain injury (TBI) is one of the leading causes of injury-related disability among adults ≥65 years. In the United States, >65,000 older adults experienced TBI-related disability in 2003.[1] TBI-related hospitalizations among older adults increased from 90,492 in 1997 to 123,510 in 2013 and TBI-related emergency department (ED) visits increased from 222,280 to 485,734 during the same time period.[2] Falls are the primary cause of TBI among older adults and because they are at higher risk of repetitive falls due to gait issues, balance issues, and frailty, older adults are at increased risk of repetitive head injury.[2,3] There is currently limited information on the epidemiology and outcomes following repetitive TBI among older adults.[2,4,5]

Older adults are at increased risk of neurological and psychological disorders following TBI, however few studies have examined outcomes following repetitive TBI in this population.[6,7] One study by Gardner et al. found no significant difference in risk of Alzheimer's disease between adults ≥55 years of age with a single vs repetitive TBI.[7] A study by Nordstrom et al. provides some evidence of increased risk of dementia with increasing number of mild TBIs in adults ≥50.[8] Other studies have reported increased risk of depression, anxiety, and ischemic stroke following a single TBI in older adults, however, repetitive TBI was not assessed.[9,10] Evidence in younger populations suggests that outcomes such as depression, sleep disturbances, and cognitive deficits increase in severity with each subsequent TBI.[11-13] Given their increased risk of repetitive TBI, it is important to improve understanding of risk factors and sequelae of repetitive TBI among older adults.

Increased risk of neurological and psychological sequelae following repetitive TBI may also lead to increased healthcare utilization. A study by Thompson et al. was conducted to assess healthcare utilization following a single TBI among older adults and found higher healthcare utilization among those aged 75-84 compared to those less than 75 years of age but did not make comparisons with a non-TBI group.[14] Furthermore, that study did not look at repetitive TBI, excluded those with mild injury, and was conducted in a relatively small sample.[14] Identifying trends in healthcare utilization among older adults who sustain repetitive TBI can inform allocation of resources to prevention and treatment.

A. Specific Aims

The objectives of the proposed work are to use Medicare administrative claims data to 1) Identify factors associated with repetitive TBI in older adults; 2) Analyze the association between repetitive TBI and risk of depression, sleep disturbances, ischemic stroke, and Alzheimer's disease and related dementias (ADRD); and 3) Assess healthcare utilization associated with repetitive TBI. As part of my dissertation, I propose to achieve these objectives via the following aims:

Aim 1: Characterize older adult Medicare beneficiaries who have sustained single and repetitive head injury and compare baseline characteristics between these two groups, as well as calculate incidence of repetitive TBI.

Hypothesis: Individuals who have sustained repetitive TBI are likely to have more comorbid conditions compared to individuals who sustained a single TBI at baseline (index TBI).

Aim 1.1: Identify predictors of repetitive injury among these individuals.

Aim 2: Estimate the incidence of depression, insomnia, ischemic stroke, and dementia among beneficiaries who sustained repetitive TBIs and compare to those who have sustained a single TBI and pre TBI, over up to 7 years of follow-up.

Hypothesis: The incidence of depression, insomnia, ischemic stroke, and dementia will be higher among those who sustained repetitive TBIs compared to those who sustained a single TBI and pre TBI.

Aim 3: Assess healthcare utilization, outside of care for TBI, among those who sustained repetitive TBIs and compare to those who have sustained a single TBI and pre TBI, , over up to 7 years of follow-up.

Hypothesis: Healthcare utilization, defined as monthly counts of visits in inpatient, outpatient, and emergency department visits, will be higher among those who sustained repetitive TBIs compared to those who have sustained a single TBI and pre TBI.

II. BACKGROUND AND SIGNIFICANCE

Traumatic brain injury (TBI) is one of the leading causes of injury related disability and death in the United States with 2.8 million people sustaining a TBI annually and 282,000 resulting in hospitalization.[2] The highest rates of TBI related-hospitalization and death are among adults greater than 75 years and falls are the primary cause of TBI in this demographic.[15] Rates of TBI among older adults are rising, with emergency department visits for mild TBI increasing more than 60% from 2002-2009.[16,17] Older adults are at higher risk of repetitive falls and thus repetitive head injury, however, there is little information on short and long-term outcomes, specifically depression, ischemic stroke, and Alzheimer's disease and related dementias, following repetitive TBI in this population.[4,5] Furthermore, known predictors of single and recurrent TBI, including alcohol consumption, dementia, epilepsy, and prior TBI have been identified in mixed age populations but no study has specifically examined risk factors for repetitive TBI among older adults.[4,18-22]

There is evidence suggesting that the aging brain has increased susceptibility to negative outcomes such as microglial activation that mediates lasting effects of TBI and neuronal loss that results in slower cognitive recovery.[23,24] Age-related cognitive decline can be exacerbated by TBI, resulting in damage to neuronal networks and diffuse axonal injury, which in turn results in declines in behavioral and cognitive functioning.[25]

A single TBI can interrupt biological processes resulting in worse health outcomes.[5] TBI can disrupt normal cerebrovascular circulation, potentially producing ischemia that precipitates other adverse biological events.[26] For example, ischemia results in inflammation, subsequently leading to microglial activation which ultimately causes a

cascade of events resulting in brain cell damage.[27] Presence of Alzheimer's disease is mainly characterized by deposition of beta-amyloid plaques and hyperphosphorylated tau proteins which occur following axonal damage post-TBI.[28] Evidence from animal studies points to cumulative effects of recurrent TBI. Mice and rat models have suggested that mild head injuries result in axonal damage, microglial activation, memory impairment and deficits in spatial learning and that these effects are exacerbated with each repeat injury.[23,29,30] It is unclear whether adverse effects on these processes in the brain are compounded by each subsequent TBI event in humans. Experimental studies of focal and diffuse injuries have been conducted only in animals and although these studies do suggest long-term effects due to repetitive injury, the mechanisms and effects of injury may not translate to humans due to differences in brain structure among different species.[31]

Most human studies on repetitive TBI have focused on adverse outcomes of multiple concussions in athletes or military service members and reported that risk of depression, cognitive dysfunction, and memory impairment increases with each subsequent concussion.[11,13,18,32,33] However, these populations comprised younger, healthier individuals whose outcomes may not generalize to older adults. Few studies have examined outcomes associated with repetitive TBI among older adults, yet there is evidence of chronic sequelae of single TBI in older populations.[8,34] Such sequelae include Alzheimer's disease and related dementia, chronic depression, and increased mortality.[14] Studies have shown that older adults with TBI often have worse functional outcomes and cognitive recovery compared younger populations who sustain a single TBI.[7,15,35] Pre-

existing comorbid conditions in older adults are risk factors for TBI but it's unclear whether the same risk factors are associated with multiple TBI.[36]

Healthcare utilization following TBI has been assessed in younger adult populations who have experienced single and repetitive TBI, with increased utilization after a subsequent injury.[37] These studies report increased utilization post-TBI, however, the disease profiles of younger individuals differ from older adults who have a higher burden of comorbid conditions and may have higher healthcare utilization to begin with. Thompson et al. assessed healthcare utilization following single TBI in adults ≥65 years of age and reported that those aged 75-84 had higher healthcare utilization, measured by number of rehospitalizations, physician visits, receipt of paid homecare services, and family care, compared to those less than 75 years of age.[14] However, given that the oldest of the older adults are likely to have greater utilization given increasing age associated comorbidities, this study failed to capture the impact of TBI in this age group as well as those 65-74. That study also did not assess repetitive TBI and only looked at older adults with moderate to severe injury. Healthcare utilization varies by severity of the index TBI as well as with development of new comorbidities in studies of adults of mixed ages.[38] Thus far, studies have not looked at healthcare utilization among older adults with repetitive head injury. A better understanding of healthcare utilization among older adults following repetitive TBI could inform programs to promote favorable health outcomes, possibly through immediate receipt of cognitive and physical rehabilitation and programs preventing subsequent falls.

A. Neuropathology of TBI

Clinical evidence suggests that TBI can have long lasting adverse effects due to biological mechanisms such as white matter degradation, persistent inflammation, protein mis-folding, neuronal loss, diffuse axonal damage, and focal cortical contusion.[5,39] Focal contusions lead to neuronal destruction as a result of hemorrhagic lesions in gray matter. Diffuse axonal injuries result in downstream differentiation of once intact nerve fibers and recovery is based on injury severity when this occurs.[39] Glutamate and γ-aminobutyric acid (GABA) homeostasis, both responsible for normal neurological functioning, can result in reduced neuroplasticity when alterations occur as a result of TBI.[40] A study by List et al. reported that young to middle-aged subjects with higher number of mild TBIs showed lower cortical thickness on an MRI compared controls without a history of mild TBI.[41] This structural deterioration could result in neuropsychological declines leading to early dementia.[41] Mielke et al. found that patients with mild cognitive impairment following head trauma showed greater amyloid deposition which is often associated with Alzheimer's disease, compared to those who were cognitively normal, but head injury was based on self-report and caution should be taken in interpreting their results.[42] It is known that adverse biological effects following a single TBI event can occur, however, it is unclear whether adverse effects on these biological processes are compounded by each subsequent TBI event in humans.

B. Risk factors for recurrent TBI

Several factors are associated with increased risk for recurrent TBI and will be discussed in this section and the subsequent section on risk factor for falls. Most TBIs and subsequent TBIs are due to falls in older adults, thus, risk factors for falls will be

discussed consequently, followed by sequelae of single and multiple TBI, respectively. Factors associated with single and recurrent TBI include falls, alcohol consumption, dementia, epilepsy.[4,18-21] Cognitive impairment is a risk factor for fall-related injuries, as is a diagnosis of dementia.[43] Wilson et al. reported that patients with epilepsy or seizure disorder were more likely to sustain a repetitive injury compared to those without.[20] Another study, conducted in patients in the South Carolina Traumatic Brain Injury Follow-up Registry, reported that those with a severe index TBI event were more likely to experience more subsequent TBIs compared to those with a mild/moderate index TBI, however, these results were not statistically significant.[44] A study by Winqvist et al. reported that a first injury due to alcohol or urban birth place were risk factors associated with recurrent TBI.[21] Vaaramo et al. also reported that an alcohol related index trauma was associated with increased risk for subsequent TBI.[19] A history of single TBI with loss of consciousness has also been associated with increased risk for a subsequent re-injury.[45] These studies did have several limitations which included use of administrative data, not systematically collecting information on alcohol use or gait instability, not having refined categories of injury severity, collection of self-reported data, and other limitations that would result in residual confounding between these risk factors and their association with TBI. Additionally, there are factors that might apply to older adults but not younger adults, such as medical comorbidities and medication use.[46,47]

C. Studies on risk factors for falls

Falls are the leading cause of TBI in older adults, resulting in 141,998 emergency department visits and 81,500 hospitalizations in the US due to fall-related TBI.[34] Fall-

related TBI rates are especially high for those over 75.[48] A population based study by Fu et al. reported that among older adults, those with advanced age >85 had nearly 4-fold increased risk of falling compared to those 65-75.[49] Additionally, that study also reported increased risk of falls among older adults with five or more comorbidities.[49] Another study by Hwang et al. looked at risk factors for TBI during falls.[50] That study reported that those who took antiarrhythmic medication, were negotiating stairs, or getting in and out of bed were more likely to sustain moderate/severe TBI than those who fell while walking.[50]

D. Sequelae of single TBI

The majority of studies have examined sequelae of a single TBI event. This review will first discuss sequelae of single TBI and subsequently present sequelae of multiple TBI. Major sequelae of TBI include sleep disturbances, depression, chronic traumatic encephalopathy (CTE), cognitive deficits, psychiatric illness, and other neurodegenerative diseases.[51] Lesser known sequelae of TBI include neuroendocrine dysregulation, metabolic dysregulation, and bladder and bowel incontinence.[51] These sequelae can have lasting effects on recovery and overall quality of life. Although there are many sequelae of single TBI, for the purposes of this dissertation, the following sections will address studies specifically related to the outcomes of interest; depression, insomnia, ischemic stroke, and dementia.

i. TBI and Depression

Depression is common following TBI and is associated with slower cognitive recovery, poorer social functioning, and reduced quality of life.[52] A case-control study by

Jorge et al. found increased prevalence of depression post-TBI compared to controls without TBI in a mixed-age group of 91 patients.[53] A recent study by McGuire et al. stratified the association between TBI and depression by history of fall among older adults who received home care between 2003 and 2013.[54] They found increased incidence of depression post-TBI among those with (OR 1.24, 95% CI 1.03-1.48) and without (OR 1.10, 95% CI 093-1.31) a history of falls, respectively, compared to this without TBI.[54] In this study, TBI was identified through the administration of the Resident Assessment Instrument-Home Care (RAI-CH) which lacks the sensitivity to capture TBI in the same manner as diagnostic codes. A study by Albrecht et al. using Medicare administrative claims among older adults hospitalized with TBI reported evidence that risk of depression increases following TBI in older adults.[9] That study reported an annualized incidence rate of depression of 123.9 per 1,000 beneficiaries (95% CI 121.6-126.2) following TBI compared to 62.8 per 1,000 beneficiaries (95% CI 61.6-64.1) pre-TBI.[9]

ii. TBI and Insomnia

Although there are many adverse effects of TBI, sleep disturbances are some of the most common sequelae following TBI.[55] Sleep disturbances range from insomnia, fragmented sleep, night terrors, etc. and lack of adequate sleep can impede recovery and further exacerbate cognitive decline.[55,56] Insomnia is the most prevalent sleep disorder following TBI and can result in reduced quality of life if it persists, which it most often does after TBI.[56-58] One study of sleep disturbances in older adults reported increased risk of newly reported insomnia for those with TBI compared to those without TBI (RtR 1.17; 95% CI 1.09-1.26).[59] Although sleep disturbances in general have been noted as a

consequence of TBI, the association between repetitive TBI and insomnia has not been specifically studied in older adults.

iii. TBI and Ischemic Stroke

Risk of ischemic stroke is elevated following a single TBI event and can lead to increased disability and poorer cognitive recovery. A study by Burke et al. conducted among mixed-age patients in California with an emergency department visit or hospitalization for TBI reported increased risk of stroke following TBI (HR 1.31, 95% CI 1.25-1.36).[60] Another study conducted among adult beneficiaries in Taiwan also found increased risk of ischemic stroke following mild TBI (HR 1.46, 95% CI 1.33-1.62) compared to those without TBI, however, this study was restricted only to those with mild TBI.[61] One study conducted specifically among older adult Medicare beneficiaries reported an increased rate of ischemic stroke post-TBI compared to pre-TBI rates (RR 1.3, 95% CI 1.2-1.4).[62]

iv. TBI and Dementia

A population based cohort study in Denmark reported increased risk of all-cause dementia among those with a history of TBI compared to those without a history of TBI (HR 1.24, 95% CI 1.21-1.27), with the risk of dementia being highest in the first six months post TBI (HR 4.06, 95% CI 3.79-4.34).[63] This study was conducted in a mixed age population and looked at history of TBI, therefore, these results may not reflect the association between TBI sustained as an older adult and subsequent risk of dementia. Gardner et al. reported increased risk of dementia post-TBI compared to non-TBI trauma in adults ≥55 years of age in a California administrative database of inpatient and emergency department encounters (HR 1.46, 95% CI 1.41-1.52).[7] This study also showed

significantly higher healthcare utilization, based on total inpatient or ED visits, for those with TBI compared to those with non-TBI trauma.[7] Another study conducted among adult beneficiaries in Taiwan also found increased risk of dementia following mild TBI (HR 3.26, 95% CI 2.69-3.94) compared to those in the general population, however, this study was restricted only to those with mild TBI.[64] A subgroup analysis among those ≥65 reported increased risk of dementia following mild TBI (HR 3.27, 95% CI 2.67-4.00).[64] Caution should be exercised when interpreting these results given that the relationships between dementia and TBI could be bidirectional and dementia is often underdiagnosed in early stages and may have existed prior to TBI.

E. Studies of Repetitive TBI in Animals

Many animal studies have examined the effects of repetitive mild TBI and evidence from these studies suggest there are cumulative effects of recurrent TBI. Mice and rat models have suggested that mild head injuries result in axonal damage and microglial activation and that these effects are exacerbated with each repeat injury.[23] An animal study performed in rats reported that neurocognitive and neurobehavioral impairment was more severe in the group that sustained multiple mild TBIs compared to the group that sustained a single TBI event, potentially due to the effects of increased inflammation in the brain.[29] A mouse model study found that mice with repetitive mild TBI exhibited a reduction in global cerebral blood flow and that memory impairment persisted at least six months post-injury.[65] Another animal model study suggested long-term deficits in motor functioning following repetitive brain injury.[66] A study by Petraglia et al. reported that mice with multiple TBI events demonstrated deficits in

memory and spatial learning that were more persistent than in mice with a single TBI event, and that the mice with repetitive TBI were more likely to engage in risk taking behaviors.[30] A study in neonatal pigs, demonstrated worsening executive functioning and memory with each head injury impact experienced by the piglets, suggesting that the decline in these outcome measures is compounded due to increasing white matter axonal injury.[67] Although these studies support the hypothesis that recurrent TBI results in cumulative effects, results may not translate to humans due to differences in brain structure.[31]

F. Studies of Repetitive TBI in athletes

Many studies on repetitive TBI have focused on adverse outcomes of multiple concussions in athletes or military service members and reported that outcomes such as depression, reduced cognitive functioning, memory impairment, etc. are compounded with each subsequent concussion.[11,13,18,32] A study by Guskiewicz et al. reported that lifetime prevalence of depression increases with increasing number of concussions among retired football players.[13] A study by Kerr et al. reported similar results in former collegiate athletes.[68] A study conducted by Chen and colleagues observed increased risk of amyotrophic lateral sclerosis (ALS) among New England soccer players who sustained more than one head injury.[69] Multiple TBI has also been shown to lead to motor function deficits, slower recovery from subsequent TBI, and other neurocognitive deficits among athletes.[70,71] De Beaumont et al. noted that athletes with a history of concussions 30 years prior experienced deficits in neuropsychological measures and memory function compared to former athletes without a history of concussions.[12] Another study in

Division I college football and hockey players noted that repetitive head injury results in poor performance on measures of learning such as verbal tests, reaction times, and trails.[40] Mez et al. reported that among deceased football players who donated their brains for research, neuropathological evidence of chronic traumatic encephalopathy (CTE) was present also with reported behavioral symptoms, cognitive symptoms, and signs of dementia.[72] The frequency of behavioral and cognitive symptoms were similar among those with mild and severe CTE, however, frequency of signs of dementia was higher in those with severe CTE. Although studies in athletes suggest cumulative effects multiple TBIs on neurocognitive functioning, depression, and learning, these younger, healthier populations may have different experiences compared to older adults.

G. Studies of Repetitive TBI in military personnel

Several studies of multiple TBI have been conducted in military personnel. A study by Bryan reported that repetitive TBI among male military service members on deployment resulted in increased sleep disturbances.[11] Another study by Bryan et al. demonstrated increased risk of depression and PTSD symptoms and suicidal ideation with increasing number of TBIs.[73] Miller et al. conducted a study among soldiers at Fort Bragg to assess the association between self-reported mild TBI and post-concussive symptoms based on the Post MTBI Symptom Checklist.[74] They compared soldiers with no TBI, one TBI, and more than one TBI and reported that soldiers with more than one TBI reported more post-concussive symptoms compared to those who experienced a single TBI.[74] A study conducted among members of the Florida National Guard reported cumulative TBI effects of major depression, generalized anxiety, PTSD, and post-

concussion symptoms compared to a single TBI event.[75] This study, however, had several limitations including self-report of physical injuries and information collected using novel questions that were not validated. Another study conducted among Gulf War veterans had similar results, finding that more health symptoms such as cardiac, dermatological, gastrointestinal, genitourinary, musculoskeletal, and neurological symptoms were reported with increasing number of mild TBIs, but extended their event numbers to one, two, or three or more.[76] One study specifically conducted in United States Marines reported greater emotional distress with multiple concussions, independent of deployment history, combat exposure, and symptoms of post-traumatic stress disorder and depressive symptoms.[77] Military service members, if on deployment, are more likely to have blast-related TBI, so these findings might not translate to older adults given that the primary mechanism of injury in that population is falls.

H. Studies of Repetitive TBI in general populations

Few studies of recurrent TBI and functional decline or neurocognitive outcomes have been conducted in the general population. One study assessed this relationship using a large population-based approach in New Zealand, and reported that individuals with multiple TBI experienced more severe post-concussion symptoms at one year compared to controls who experienced a single TBI.[78] These findings corroborate the aforementioned studies conducted in military and athlete populations, however, this study did not specifically assess predictors and functional outcomes of recurrent TBI in older adults.[11,13] Gardner et al. reported increased risk of dementia in older adults (N=10,961) who experience multiple TBI vs single TBI.[7] A study by Nordstrom et al. reported

increased risk of young onset dementia with at least two occurrences of mild TBI among a cohort of Swedish men, however, they found that this association was attenuated after multivariate adjustment.[8] Although animal models and some human studies conducted in younger populations have suggested that the effects of recurrent TBI may be cumulative, current studies of repetitive TBI in older adults have reported mixed results.

Sequelae of single TBI demonstrates increased risk of adverse outcomes in older adults. Repetitive TBI has shown increased risk of adverse outcomes such as sleep disturbances, depression, and dementia in younger athlete and military populations. It is important to elucidate these associations since these associations have not been studied in older adults who are more susceptible to these adverse effects and for whom trajectories of recovery would be different from their young adult counterparts.

I. Medications associated with increased risk of falls and polypharmacy studies

As previously mentioned, falls are the leading cause of traumatic brain injury in older adults.[14] Medications have been known to play a role in increased risk of falls and potentially TBI due to side effects such as dizziness, arrhythmias, and reduced levels of consciousness.[79] Several classes of medications are known to be risk factors for falls in older adults including antihypertensive agents, diuretics, beta blockers, sedatives and hypnotics, neuroleptics and antipsychotics, antidepressants, benzodiazepines, narcotics, and nonsteroidal anti-inflammatory drugs.[80,81] A study by Tom et al. conducted among Medicare beneficiaries 65 and older reported a nearly two-fold increased risk of TBI following use of a nonbenzodiazepine sedating hypnotic prior to the occurrence of TBI.[82] A study of risk factors for TBI during falls in adults aged 60+ reported a 3-fold increased

risk of moderate/severe TBI in those who took two or more medications associated with increased risk of falls within four hours of the fall.[50] A study by Tinetti et al. reported a 2-fold increased risk of serious fall injury for both those taking a moderate and high-intensity antihypertensive agent compared to nonusers.[83] However, these results were not statistically significant due to small sample size and limited information on duration of antihypertensive treatments. A study of English adults ≥60 years assessed the association between polypharmacy, all drugs (syrups, pills, puffs, and ointments) prescribed by a doctor or nurse, and falls and found a 21% increased rate of falls among those with polypharmacy compared to those without polypharmacy.[84] This study incorporated any medication use including medications associated with increased risk of falls, however, did not delineate the rate of falls due to these medications specifically. Medication will not be assessed in this thesis, however, it is important to acknowledge the role they play in increased fall risk and subsequent TBI.

J. Healthcare utilization studies

Direct costs, which can be indicative of utilization, for fatal and non-fatal falls among older US adults were $616.5 million for fatal and $30.3 billion for non-fatal injuries in 2012 with costs increasing to $637.5 million and $31.3 billion in 2015, respectively.[85] However, this study did not breakdown costs by injury type. Few studies have examined healthcare utilization as a result of TBI in older adults. One study by Thompson et al. assessed TBI-related healthcare utilization in adults aged 55-84.[14] This study used the National Study on the Costs and Outcomes of Trauma (NSCOT) dataset, which included data from 69 hospitals in the US.[14] Unadjusted total mean 1-year cost of

care post-TBI was $77,872 in persons 55-64 years of age, $76,903 in persons aged 65-74, and $72,733 in persons aged 75-84. In adjusted models, re-hospitalization costs were significantly higher among the oldest category of age compared to the other categories of age and was a driver of increased costs among this age group.[14] A more recent study by Albrecht et al. assessed costs of TBI treatment stratified by sex among hospitalized older adults.[86] That study reported mean unadjusted hospital costs of $36,075 (standard deviation [SD], $63,073), with hospitalization charges lower for women than for men.[86]

Other studies have assessed utilization directly. One study reported 4.2 as the mean number of services used following TBI, however, this study was conducted in a relatively small (N=119) mixed age sample.[87] One thing to note in many studies of TBI-related HCU, it is difficult to capture the burden of TBI on HCU given that many of these studies do not have appropriate comparison groups to gauge the impact of TBI on utilization. Thus, this thesis will attempt to assess the impact of repetitive TBI on healthcare utilization compared to single TBI and a pre-TBI period.

K. Significance

Studies in animals and younger populations have shown cumulative adverse effects of multiple TBI, however, these effects have not been studied in older adults who are more likely to experience falls resulting in TBI and in whom the aging brain is more susceptible to negative outcomes. This study will identify characteristics that will help identify populations at increased risk of repetitive TBI and its sequelae.

Evidence suggests increased risk of insomnia, depression, ischemic stroke, and ADRD following a single TBI in older adults, but it is unknown how subsequent TBI

affects these outcomes. This study will produce results on risk of insomnia, depression, ischemic stroke, and ADRD associated with recurrent TBI in older adults. This information can help guide treatment of older adults with TBI in order to maximize recovery and minimize risk of studied sequelae.

The proposed dissertation will also identify healthcare utilization patterns associated with recurrent TBI in older adults, providing a quantitative picture of the financial burden of sustaining such an injury. This information can help guide policy on rehabilitation following TBI and allocation of resources.

L. Innovation

This study is novel in that it will be the first study to assess predictors of recurrent TBI in older adults. It will provide information on a problem of public health importance in an understudied population. Furthermore, it is the first study to examine the risk of depression, ischemic stroke, insomnia, and Alzheimer's disease and related dementias associated with repetitive TBI among older adults. These outcomes are often associated with single head injury and the aging process and it is important to understand and minimize the occurrence of further disability due to these outcomes as a result of a subsequent injury, by aiming to minimize risk of the subsequent injury in the first place.

The study design is unique in that everyone has TBI. This design will reduce residual confounding by characteristics that would otherwise differ between those with and without TBI. Evidence suggests that the effects of TBI are worse in the aging brain, resulting in poor health outcomes which in turn can also result in increased healthcare utilization and costs for a single TBI. Thus, we will examine utilization and costs

following subsequent head injury in older adults to assess whether utilization is higher among those with a second injury compared to those with a single injury.

III. METHODS

A. Study Design

I conducted a retrospective cohort study to achieve my research objective.

B. Data Source and Participants

The data for this study come from a 5% random sample of Medicare beneficiaries obtained from the Center for Medicare & Medicaid Services (CMS) Chronic Conditions Warehouse (CCW).[88] The dataset covered the period from January, 2007-September, 2015, prior to the change from the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes to the tenth revision (ICD-10-CM) codes, and only included individuals aged 65 or older. The CCW contains Medicare files for fee-for-service institutional and non-institutional claims, enrollment data, and eligibility information. Additionally, it also contains files for part D prescription drug event data which includes plan, pharmacy, and prescriber characteristics, as well as formulary data and costs. The CCW chronic condition variables include date of first diagnosis and annual flags and are identified using an algorithm that looks for Medicare Severity Diagnosis Related Groups (MS-DRG) or procedure codes for 27 common chronic conditions: acquired hypothyroidism, acute myocardial infarction, Alzheimer's disease, Alzheimer's disease and related dementias (ADRD), anemia, asthma, atrial fibrillation, benign prostatic hyperplasia, colorectal cancer, endometrial cancer, breast cancer, lung cancer, prostate cancer, cataract, chronic kidney disease, chronic obstructive pulmonary disease, depression, diabetes, glaucoma, heart failure, hip/pelvic fracture,

hyperlipidemia, hypertension, ischemic heart disease, osteoporosis, rheumatoid arthritis/osteoarthritis, and stroke/transient ischemic attack.

C. Coverage Criteria

All aims: Continuous coverage refers to having Medicare Parts, A, B, and D coverage for each month of the study period, with no Part C (Medicare Advantage) coverage. Requiring continuous coverage ensures that all claims are captured, and no exposure or outcome events are missed. Participants were required to have 18 months of continuous coverage prior to the index diagnosis for TBI. This permitted an initial 6 month baseline period in which to collect information on comorbid conditions prior to the start of follow-up, which was 12 months prior to the index TBI for aims 1 and 3. For aim 2, this permitted an initial 9 month baseline period in which to collect information on comorbidities prior to start of follow-up, which is 9 months prior to the index TBI here. We also required a minimum of 12 months of continuous coverage post-TBI to allow enough time for the occurrence of a second TBI and outcome evaluation. Claims are not consistently available for beneficiaries with Medicare Part C, thus beneficiaries with this coverage were excluded. For aim 2.2, we incorporated an external non-TBI cohort with random index dates created based on the same inclusion criteria, including continuous coverage, used for the TBI cohort.

D. Independent Variable

i. Definition of TBI

Diagnosis of TBI is defined by the International Classification of Disease, 9th Revision, Clinical Modification [ICD-9-CM] codes 800.xx, 801.xx, 803.xx, 804.xx,

850.xx-854.1x, 950.1-950.3, and 959.0. We created a flag for concussions in further analyses using ICD-9-CM code 850.xx. These codes are the Centers for Disease Control and Prevention (CDC) surveillance codes often used in epidemiologic studies of TBI.[89,90]

ii. TBI Cohort Criteria

a. Aim 1: All beneficiaries were required to have 18 months of coverage prior to their initial TBI. The single TBI group was defined as those with one TBI diagnosis with no subsequent TBI in the time following the initial TBI. The repetitive TBI group was defined as those with one additional TBI occurring during the 36-months following the initial TBI. Repetitive TBI was defined as at least two TBIs for all aims. A minimum of 3 months was required between the first and second TBI to reduce the possibility that the second encounter is a follow-up to the first. Studies often consider a 14-day window after an initial TBI as part of that initial TBI encounter, and consider a TBI outside of that window to be another TBI event.[78] Therefore, our 3-month requirement between TBIs is conservative and provides an adequate window to distinguish two separate TBI events.

b. Aim 2: The TBI exposure was allowed to vary with time. Each study participant had at least 30 months of continuous Medicare coverage as defined previously. The 9 months prior to the initial TBI was considered unexposed (no TBI) time. Time after the initial TBI was attributed to single TBI, and time following an additional TBI was attributed to repetitive TBI.

c. Aim 3: The TBI exposure varied with time. Each study participant had at least 30 months of continuous Medicare coverage as defined previously. The 12 months prior to the initial TBI was considered unexposed time. Time after the initial TBI was

attributed to single TBI, and time following an additional TBI was attributed to repetitive TBI.

E. Dependent Variables Aim 2

1. Depression was defined as the first claim for any of the following diagnostic codes in any position on inpatient and outpatient claims in the study period (defined by ICD-9-CM codes 296.20, 296.21, 296.22, 296.23, 296.24, 296.25, 296.26, 296.30, 296.31, 296.32, 296.33, 296.34, 296.35,296.36, 296.51, 296.52, 296.53, 296.54, 296.55, 296.56, 296.60, 296.61, 296.62, 296.63, 296.64, 296.65, 296.66, 296.89, 298.0, 300.4, 309.1, or 311). These codes are based on validated case definitions for depression.[9,91]
2. Ischemic stroke was defined as the first claim for any of the following diagnostic codes in any position on inpatient claims in the study period (defined by ICD-9-CM codes 433.xx-435.xx, 437.0x, or 437.1x). We searched inpatient claims only for ischemic stroke given that it is a rare outcome that often results in hospitalization.
3. Insomnia was defined using a combination of ICD9 codes and prescription fills. Insomnia was defined as the first claim for the following diagnostic codes in any position on inpatient and outpatient claims in the study period (defined by ICD-9-CM codes 307.41, 307.42, 307.49, 327.00, 327.01, 327.09, 780.52, V69.4). Insomnia diagnosis was also characterized by prescription fills for FDA approved insomnia medications given that prescribers may not code for diagnosis directly but there is evidence of a fill. These medications are butabarbital, doxepin,

estazolam, eszopiclone, flurazepam, quazepam, ramelteon, secobarbital, temazepam, triazolam, zaleplon, and zolpidem.

4. Dementia was defined using a combination of ICD9 codes and prescription fills. Dementia diagnosis was defined as the first claim for the following diagnostic codes in any position on inpatient and outpatient claims in the study period: Alzheimer's disease (331.0), mild cognitive impairment (331.83), vascular dementia (290.4x), frontotemporal dementia (331.1x), dementia with Lewy bodies (331.82), and dementia not otherwise specified (290.0x-290.3x, 290.8x, 290.9x, 294.10, 294.11, 294.20, 294.21, and 797).[92] Numerous studies using administrative claims have used these codes for dementia and thus these codes are based on validated case definitions.[93-95] Those with Part D claims for at least one fill for AD medication will also be categorized as having dementia since a diagnosis for dementia may not be coded but medication for dementia has been prescribed. Those drugs include donepezil, rivastigmine, galantamine, and memantine.

For depression, ischemic stroke, and insomnia, I have also used CCW dates of first diagnoses to identify and exclude anyone with these conditions prior to the start of follow-up.

F. Dependent Variables Aim 3

Healthcare utilization was defined as monthly utilization across three types of claims: inpatient, outpatient, and emergency department. Healthcare utilization was operationalized as counts of events on a monthly level. Inpatient and outpatient claims

were identified in respective inpatient and outpatient yearly claim files. The inpatient claims file comprises fee-for-service claims submitted by inpatient hospital providers for reimbursement of facility costs.[96] The outpatient contains fee-for-service claims submitted by institutional outpatient providers such as hospital outpatient departments, rural health clinics, outpatient rehabilitation, etc.[97] It also includes outpatient facility charge amounts. ED visits can be found in both inpatient and outpatient claims. ED visits were identified in outpatient claims and inpatients revenue files through ED revenue codes (0450, 0451, 0452, 0456, 0459, 0981). These are billed provider-assigned codes for each cost center. Inpatient and outpatient ED claims were then combined for total ED utilization. Multiple claims on the same visit date were collapsed into a single encounter. The month of TBI and second TBI were excluded in an attempt to separate utilization outside of the acute TBI encounter.

G. Covariates

Based on my literature search, I have identified variables associated with TBI as well as each dependent variable: age, sex, race, original reason for entitlement code (OREC), type of TBI at diagnosis, and comorbid conditions. Type of TBI, concussion (ICD-9-CM code 850.xx), unspecified (ICD-9-CM code 959.01), and other TBI (ICD-9-CM codes 800.xx, 801.xx, 803.xx, 804.xx, 850.xx-854.1x, and 950.1-950.3),will be used as proxy measures to indicate severity of TBI since no direct measures of TBI severity are available in the data. Concussion and unspecified head injury are more likely suggestive of mild head injury.[98]

H. Analysis

i. Aim 1: The objective of this aim was to assess incidence of repetitive TBI and identify baseline characteristics of repetitive TBI. We identified those with single TBI and multiple TBI as two independent cohorts and compare group characteristics at baseline (first TBI). Variables associated with falls and TBI were identified based on the literature review and clinical input. Differences in the distributions of covariates between TBI cohorts were assessed using Chi-square tests for categorical variables. Differences in the distributions of covariates between TBI categories for continuous variables were assessed using Student's t test for normally distributed variables and the Wilcoxon rank sum test for non-normally distributed variables. Unadjusted incidence of repetitive TBI and 95% confidence intervals (CI) were calculated per 100 person-years at risk by dividing the number of repetitive TBI events by total person-time contributed. Person-time at risk was calculated by adding the number of months between first and second TBI or end of follow-up for those without a second TBI. All analyses were performed using SAS v9.4 (Cary, NC).

ii. Aim 1.1: We assessed predictors of the second TBI in the TBI cohort. To identify predictors of repetitive TBI, second TBI was modeled as a function of characteristics present at the time of index TBI using a log-binomial model. Log-binomial models produce an unbiased estimate of relative risk for a dichotomous outcome when using a log link.[99] *A priori* variables associated with TBI were considered for model building, specifically age, sex, race, depression, dementia, seizure disorders, atrial fibrillation, alcohol and substance abuse disorders, congestive heart failure, ischemic stroke, and TBI severity.[100,101] A single model was built to identify predictors of repetitive TBI by adding in covariates one at a time and assessing increases in -2 log-

likelihood as well as assessing the statistical significance of each covariate. Variables that were considered statistically significant at $p<0.001$, a p-value cutoff chosen due to large sample size, were retained in the model. We reported relative risk (RR) estimates and 95% confidence intervals (CI).

iii. Aim 2: The objective of this aim was to identify incidence of depression, ischemic stroke, insomnia, and ADRD following single and repetitive TBI. I will describe my analytic approach for aim 2 using depression as an example. Bivariate associations between the covariate and depression and between the covariate and TBI were assessed to determine which covariates would be included in the model as potential confounders. Anyone with a diagnosis of depression, based on the date of first diagnosis for depression, occurring prior to the start of the study period (9-month comorbidity capture period) was excluded from analysis. The first 9 months of follow-up occurs prior to the TBI and was designated as the 'pre TBI' exposure time. The discrete time unit for this analysis was month. Depression was coded on a monthly level and individuals were followed forward in time and were censored after the first diagnosis of depression or at the end of the study period, whichever came first. A person was considered unexposed until they experienced their first TBI. Moving forward in time, they then contributed follow-up time to the single TBI exposure group. If they experienced a subsequent TBI following the initial TBI, then that individual contributed follow-up time to the multiple TBI exposure group. This is how changes in exposure were captured. We used a discrete time model to model time to first diagnosis of depression as a function of time-varying TBI status (none, 1, or >1) using generalized estimating equations with a complimentary log-log link. This model is appropriate for analyzing these data since results based on a

complimentary log-log link are robust to the categorization of time units, months in this case. A discrete time model also allows covariates to vary as the exposure varies. We initially measured covariates at 9 months prior to the initial TBI and updated covariate status, specifically age, CCW comorbidities, and fall-related medications, when the exposure changed (e.g. from no-TBI to single TBI). The initial model assessed the unadjusted association between TBI status and depression. From the literature, I have identified variables associated with single TBI, such as advanced age and specific comorbid conditions.[36,48,50] These variables were included in the models along with additional variables associated with recurrent TBI identified in bivariate analysis, as well as variables that are associated with depression in the literature. Models were built by adding in one variable at a time and looking at changes in -2 log likelihood and p-values using an alpha cutoff of <0.001. Sex was assessed for potential effect modification by adding an interaction term for sex and time-varying TBI, as evidence suggests that sex modifies the effect of TBI on incidence of depression.[102] Hazard ratios and 95% confidence intervals were reported with significance set at $p<0.05$. Contrast results were also produced to test whether incidence of depression was higher for those with single TBI compared to those with repetitive TBI. Other outcomes were modelled using the same approach.

iv. Aim 2 Sensitivity Analysis: The objective of this sensitivity analysis was to determine whether the results from Aim 2 could be corroborated when using an external non-TBI cohort. I will again use depression as an example to describe sensitivity analyses. This analysis used the same TBI cohort but also includes an external no-TBI cohort. To obtain the sample of beneficiaries without TBI, I deleted those individuals in

the data with TBI and pulled 140,000 random beneficiaries. More beneficiaries were pulled with the understanding that some would drop out after applying coverage criteria and age restrictions. Individuals were followed forward in time and were censored after the first diagnosis of depression or at the end of the study period, whichever came first. Anyone with a diagnosis of depression, based on the date of first diagnosis for depression, in the first 18 months preceding date of index TBI or index date in the non-TBI cohort was excluded from analysis. Follow-up began at the date of first TBI, or index date in the external comparison group. The discrete time unit for this analysis was month. Moving forward in time, the external comparison cohort contributed person time to the 'no TBI group'. Those with TBI contributed person-time to the 'single TBI' group and if they experienced a subsequent TBI following the initial TBI, then that individual contributed follow-up time to the 'repetitive TBI' exposure group. We used a discrete time model to model time to first diagnosis of depression as a function of time-varying TBI status using the same approach outlined in aim 2 above. We initially measured covariates at the time of initial TBI and updated covariate status, specifically CCW comorbidities, when the exposure changed (e.g. from single-TBI to repetitive TBI). Bivariate associations between the covariate and depression and between the covariate and TBI were assessed to determine which covariates were included in the model as potential confounders. The initial model assessed the unadjusted association between TBI status and depression, accounting for competing risk of death. The censoring variable was coded on a monthly level and the individual was censored after the occurrence of depression, death, or the end of the study period, whichever came first.[103] Variables known to be associated with single TBI, such as advanced age and comorbid conditions

were considered for analysis, as well as variables associated with depression in the literature. These variables were included in the models along with additional variables associated with recurrent TBI identified in bivariate analysis. Models were built by adding in one variable at a time and looking at changes in -2 log likelihood and p-values using an alpha cutoff of <0.001. Hazard ratios and 95% confidence intervals were reported. Although I am using the same discrete time modeling approach outlined in Aim 1.1 and Aim 2, this model was run with a multinomial distribution and cumulative complimentary log-log link to accommodate the additional censoring for deaths. Other outcomes were modelled using the same approach.

v. Aim 3: The objective of this aim was to assess healthcare utilization across three points of service for those with single and repetitive TBI. Healthcare utilization was modeled on a monthly level using generalized estimating equations with a negative binomial model, allowing the exposure to change with time. This model was appropriate for this analysis since our primary outcome involves discrete monthly counts. Both Poisson and negative binomial models can model the rate of healthcare utilization but the decision of which model was used ultimately depended on the amount of overdispersion in the data. Overdispersion indicates that the observed variance is larger than anticipated, leading to erroneous conclusions. To determine whether overdispersion was present, the overdispersion parameter (alpha) was assessed in a negative binomial model. The negative binomial model was selected due to the presence of overdispersion. Additionally, the best fitting covariance structure was assessed using the QIC, selecting the model with the lowest QIC as the preferred optimal model. Exploratory analyses performed in Aim 1 informed decisions regarding covariates. Number of TBIs was

categorized as none, one TBI, or more than one TBI. Healthcare utilization was modeled for three claim types using counts of claims associated with inpatient, outpatient, and emergency department encounters. Unadjusted models were developed comparing HCU for those with single TBI or >1 TBI to those with no TBI. Models were then built and adjusted for relevant demographic and clinical covariates using the same approach outlined in aim 2 above.

IV. RESULTS

The following manuscripts present the findings of this dissertation in sequential order by aim. The Aim 1 manuscript reports findings on incidence and predictors of repetitive TBI among older adult Medicare beneficiaries who experience a single TBI. The manuscript for Aim 2 reports increased risk of ischemic stroke following single TBI but not repetitive TBI. The manuscript for Aim 3 reports increased healthcare utilization following single and repetitive TBI. Following the three manuscripts, additional results are reported for Aim 2 on incidence of depression, insomnia, and ADRD following single and repetitive TBI. Aim 2 also includes results on incidence of depression, ischemic stroke, insomnia, and ADRD among those with single and repetitive TBI compared to an external cohort with no TBI.

V. REPETITIVE TRAUMATIC BRAIN INJURY AMONG MEDICARE BENEFICIARIES[1]

Abstract

Objective: To determine the incidence of and assess risk factors for repetitive traumatic brain injury (TBI) among older adults in the United States.

Design: Retrospective cohort study.

Setting: Centers for Medicare and Medicaid Services Chronic Conditions Data Warehouse

Participants: Individuals aged ≥65 years and diagnosed with TBI between July 2008-September 2012 drawn from a 5% random sample of US Medicare beneficiaries.

Main Measures: We estimated incidence of and identified factors associated with repetitive TBI using a log-binomial model.

Results: A total of 38,064 Medicare beneficiaries experienced a TBI between 2008-2012. Of these, 4,562 (12%) beneficiaries sustained at least two TBIs. Incidence of repetitive TBI was 3.0 (95% CI 2.9-3.1) per 100 person-years. Epilepsy, Parkinson's disease, depression, Alzheimer's disease and related dementia (ADRD), atrial fibrillation, and age at first TBI were associated with increased risk of repetitive TBI. Epilepsy was the strongest predictor of repetitive TBI (relative risk (RR) 1.44, 95% confidence interval (CI) 1.25-1.56), followed by ADRD (RR 1.32, 95% CI 1.20-1.45), and depression (RR 1.30, 95% CI 1.21-1.38).

[1] Chauhan et al. In preparation for submission to the Journal of Head Trauma and Rehabilitation.

Conclusions: In this population of older adult Medicare beneficiaries diagnosed with TBI, incidence of repetitive TBI was 3%. Injury prevention initiatives could be targeted to identified groups at increased risk of repetitive head injury.

Key words: TBI; incidence; risk factors; older adults

Background

Traumatic brain injury (TBI) is one of the leading causes of injury-related death and disability among older adults. Furthermore, older adults have the highest incidence of TBI and rates are on the rise.[1,2] TBI is associated with a number of adverse sequelae and studies have shown that older adults with TBI often have poorer functional and cognitive recovery compared to younger adults with TBI.[3-8] Among older adults, falls are the primary cause of TBI.[1,9] Due to increased mobility limitations, underlying comorbidities, and prescription medication use, older adults are more likely to suffer repetitive falls and therefore are at risk of repetitive TBI.[10-12]

Most studies on repetitive TBI have focused on athletes and military personnel.[13,14] Identified risk factors include repetitive sports hits or explosive blasts, but these might not apply to older adults given differences in mechanism of injury as well as underlying comorbidity profiles. Although there is limited information on repetitive TBI among older adults, risk factors for single TBI in this population have been identified and may be predictive of a second TBI. These include risk factors for repetitive falls such as frailty and impaired gait and balance, cognitive impairment, depression, sleep disturbances, dementia, alcohol use, and use of medications associated with increased risk of falls.[1,3,15-19]

To date, there are no estimates for incidence of repetitive TBI among older adults. However, incidence for single TBI in 2013 was 1,410.8 per 100,000.[1] A single TBI in older adults often leads to deleterious health effects, which would likely be worsened by subsequent head injury, yet understanding of factors leading to repetitive TBI in older adults is lacking.[2] Given the public health importance of TBI and increased risk of repetitive falls in older adults, the objective of this study was to estimate the incidence of and identify factors associated with repetitive TBI in this population.

Methods

Study design and data source

We conducted a retrospective cohort study using a 5% random sample of US Medicare beneficiaries obtained from the Centers for Medicare and Medicaid Services (CMS) Chronic Conditions Data Warehouse (CCW) for years 2007-2015. Ninety-six percent of older adults are covered by Medicare.[20] The CCW includes files include beneficiary eligibility, enrollment, and use of medical services by beneficiaries (fee-for-service institutional and non-institutional claims) data. The CCW also contains information about beneficiary prescription medication usage, (Part D Prescription Drug Event data). Beneficiaries aged ≥65 years who experienced an initial TBI and maintained continuous Medicare Parts A, B, and D, and no Part C coverage for 18-months prior to first diagnosis of TBI and at least 12 months post-TBI were eligible for inclusion. Applying continuous coverage guarantees that all claims are captured, without missing exposure or outcome events.

Traumatic Brain Injury

TBI was defined using International Classification of Disease, 9th Revision, Clinical Modification [ICD-9-CM] codes. We grouped the ICD-9 TBI codes into three groups: (1) concussion (850.xx), (2) unspecified TBI (959.01), and (3) other TBI (800.xx-804.xx [fracture of the skull], 850.xx-854.1x [intracranial injury, excluding those with skull fracture], and 950.1-950.3[injury to the optic nerve and pathways]). ICD codes have been previously used in epidemiologic studies of TBI.[21,22] We searched both inpatient (which include emergency department visits) and outpatient claims from July 2008-September 2012 for the codes listed above, restricting our sample to those where the TBI was in the primary position on the claim, to best attempt to capture primary diagnosis. The index TBI was defined as the first ICD-9-CM diagnostic code found during the study period following an 18-month TBI-free period. For each beneficiary, the date of their index TBI was established at the start of their follow-up (baseline). The claims themselves do not provide data describing TBI severity, To estimate severity, we created categories (see above) of initial TBI based on the ICD-9-CM codes listed in claims, unspecified, concussion, and other. Concussion and unspecified head injury are more likely indicative of mild TBI.[23] Next, we searched for a second TBI occurring at least 90-days after the index TBI (the 90-day separation minimized the identification of follow-up visits in the 3-month period immediately following the index TBI as a new TBI). Beneficiaries with no additional TBI over a minimum of 12 months of follow-up post-index TBI were categorized as single TBI. Those with at least one additional TBI that met 90-day criteria over the follow-up period were classified as repetitive TBI.

Covariates

Risk factors, at the time of index TBI, associated with increased risk of falls or that are highly correlated with TBI were identified a priori and included age, sex, race, original reason for Medicare entitlement code, type of initial TBI (unspecified, other, and concussion), and comorbid conditions, such as depression, dementia, and alcohol dependence disorder. The original reason for Medicare entitlement code indicates whether a beneficiary was eligible for Medicare benefits based on age, disability, end stage renal disease (ESRD), or both disability and ESRD. Use of anticoagulant therapy, (Warfarin, Coumadin, rivaroxaban, dabigatran, apixaban, edoxaban, and enoxaparin) and antiplatelet therapy (clopidogrel, ticagrelor, prasugrel, dipyridamole, ticlopidine, and eptifibatide) use was also captured, given their wide use among older adults and the increased morbidity among users of these medications who experience TBI.[24] Prescription medication usage was obtained from the Part D event file. A subject with at least one prescription fill during the 18 months prior to the TBI and outpatient pharmacy was characterized as being a user of that medication. The CCW data include variables for 27 common chronic conditions and also include data for other disabling conditions, based on validated algorithms that search for specific diagnostic codes within the CMS administrative claims.[25] In addition to the CCW comorbid conditions, we created a flag for Parkinson's disease (ICD-9-CM code 332). Comorbid conditions were identified at the index TBI using the first dates of diagnosis for each condition available in the CCW. Burden of disease was measured using the Deyo clinical comorbidity index (CCI), which is an adaptation of the Charlson comorbidity index specifically modified for use with administrative claims data.[26,27] The comorbid conditions used in this index are weighted based on the contribution of the comorbid disease to mortality risk, and the CCI was

categorized as 0, 1, 2, or 3 or more, with higher values associated with increased mortality risk.

Statistical Analysis

Differences in the distribution of characteristics by TBI status (single vs repetitive) were assessed at the time of the index TBI using Chi-square tests for categorical variables and Student's t-test for continuous variables. Unadjusted incidence of repetitive TBI and 95% confidence intervals (CI) were calculated per 100 person-years at risk by dividing the number of repetitive TBI events by total person-time contributed. Person-time at risk was calculated by summing the number of months between first and second TBI or end of follow-up for those without a second TBI.

To identify predictors of repetitive TBI, we modeled the occurrence of second TBI as a function of characteristics present at the time of index TBI using a log-binomial model. This model was selected as it produces an unbiased estimate of relative risk for a dichotomous outcome when using a log link.[28] *A priori* variables associated with TBI were considered for model building; these included age, sex, race, depression, dementia, seizure disorders, atrial fibrillation, alcohol and substance abuse disorders, congestive heart failure, ischemic stroke, and TBI severity.[29,30] We built a single model to identify predictors of repetitive TBI by adding in covariates one at a time and assessing changes in -2 log-likelihood as well as assessing the statistical significance of each covariate. Given our large sample size, we kept those variables that were considered statistically significant at $p<0.001$. We report relative risk (RR) estimates and 95% CI. The data analysis for this paper was generated using SAS software version 9.4 (SAS Institute,

Cary NC). This study was approved by the Institutional Review Board of the University of Maryland, Baltimore.

Results

We identified 38,064 older adult Medicare beneficiaries with TBI who met inclusion criteria. Of these, 4,562 (12%) sustained at least two TBIs (Table 1). The mean age of the cohort was 80.7 years, and the cohort was predominantly female (72%) and white (90%). Most individuals had an unspecified head injury (63%), followed by other TBIs (23%) and concussions (14%). With the exception of asthma and substance dependence disorder, prevalence of comorbidities was significantly higher among those who sustained repetitive TBI compared to those with a single TBI. Those with repetitive TBI were also significantly more likely to have a higher burden of multimorbidity with 62% scoring a 3 or more on the Deyo CCI compared to those with single TBI (56%, $p<0.001$). Anticoagulant (17% vs 15% $p<0.001$) and antiplatelet (16% vs 14%, $p<0.001$) use was higher among those with a repetitive TBI compared to those with a single TBI.

Table 1. Characteristics of Medicare Beneficiaries ≥65 years diagnosed with a single or repetitive TBI July 2008-September 2012, at first TBI, N=38,064

	Total (N=38,064)	Single TBI (N=33,502)	>=2 TBI (N=4,562)	p-value[a]
Age (mean,SD)	80.7 (7.8)	80.6 (7.9)	81.9 (7.5)	<0.001
Sex (n,%)				0.31
Female	27,345 (71.8)	24,039 (71.8)	3,306 (72.5)	
Male	10,719 (28.2)	9,463 (28.2)	1,256 (27.5)	
Race (n,%)				0.001
White	34,198 (89.9)	30,054 (89.7)	4,144 (90.8)	
Black	2,101 (5.5)	1,902 (5.7)	199 (4.4)	
Other	1,765 (4.6)	1,546 (4.6)	219 (4.8)	
Type of TBI (n,%)				<0.001
Concussion	5,476 (14.4)	4,951 (15.8)	525 (11.5)	
Other	8,574 (22.5)	7,264 (21.7)	1,310 (28.7)	
Unspecified	24,014 (63.1)	21,287 (63.5)	2,727 (59.8)	
Anemia (n,%)	27,392 (72.0)	23,830 (71.1)	3,562 (78.1)	<0.001
Asthma (n,%)	6,311 (16.6)	5,568 (16.6)	743 (16.3)	<0.001

Atrial fibrillation (n,%)	9,807 (25.8)	8,429 (25.2)	1,378 (30.2)	<0.001
Congestive heart failure (n,%)	16,428 (43.2)	14,190 (42.4)	2,238 (49.1)	<0.001
Chronic kidney disease (n,%)	11,707 (30.8)	10,193 (30.4)	1,514 (33.2)	<0.001
COPD (n,%)	13,364 (35.1)	11,643 (34.8)	1,721 (37.7)	<0.001
Diabetes (n,%)	15,883 (41.7)	13,875 (41.4)	2,008 (44.0)	<0.001
Hip fracture (n,%)	3,552 (9.3)	3,024 (9.0)	528 (11.6)	<0.001
Hypertension (n,%)	34,649 (91.0)	30,404 (90.8)	4,245 (93.1)	<0.001
Hypothyroidism (n,%)	13,177 (34.6)	11,523 (34.4)	1,654 (36.3)	0.01
Osteoporosis (n,%)	13,930 (36.6)	12,064 (36.0)	1,866 (40.9)	<0.001
Rheumatoid arthritis (n,%)	27,736 (72.9)	24,219 (72.3)	3,517 (77.1)	<0.001
Alcohol dependence disorder (n,%)	745 (2.0)	633 (1.9)	112 (2.5)	0.01
Substance dependence disorder (n,%)	2,979 (7.8)	2,617 (7.8)	362 (7.9)	0.77
Parkinson's disease (n,%)	1,707 (4.5)	1,427 (4.3)	280 (6.1)	<0.001
Epilepsy (n,%)	1,947 (5.1)	1,616 (4.8)	331 (7.3)	<0.001
Depression (n,%)	8,687 (22.8)	7,380 (22.0)	1,307 (28.7)	<0.001
Ischemic stroke (n,%)	8,558 (22.5)	7,386 (22.1)	1,172 (25.7)	<0.001
Insomnia (n,%)	1,683 (4.4)	1,450 (4.3)	233 (5.1)	0.02
ADRD (n,%)	2,727 (7.2)	2,243 (6.7)	484 (10.6)	<0.001
DEYO CCI[b] (n,%)				<0.001
0	2,904 (7.6)	2,681 (8.0)	223 (4.9)	
1	6,787 (17.8)	6,095 (18.2)	692 (15.2)	
2	6,925 (18.2)	6,121 (18.3)	804 (17.6)	
3 or more	21,448 (56.4)	18,605 (55.5)	2,843 (62.3)	
Anticoagulants (n,%)	5,696 (15.0)	4,931 (14.7)	765 (16.8)	<0.001
Antiplatelets (n,%)	5,350 (14.0)	4,629 (13.8)	721 (15.8)	<0.001

[a]Chi-square p-value for categorical variables and student's t-test for continuous variables
[b]CCI=Charlson Comorbidity Index

The unadjusted incidence of repetitive TBI was 3.02 (95% CI 2.94-3.11) per 100 person-years (Table 2).

Table 2. Unadjusted incidence of second TBI per 100 person-years among Medicare Beneficiaries ≥65, where TBI was the primary diagnosis, July 2008-September 2012, at time of first TBI, N=38,064

Number of Second TBIs	Total Person-Years At Risk	Rate/100 Person-Years (95% Confidence Interval)
4,562	150,972	3.02 (2.94, 3.11)

Several conditions present at the time of the index TBI were significantly associated with increased risk of repetitive TBI in our log-binomial model. These included older age, epilepsy, Parkinson's disease, depression, Alzheimer's disease and related dementia (ADRD), and atrial fibrillation (Table 3). Epilepsy (RR 1.44, 95% CI 1.25-1.56) and ADRD (RR1.32, 95% CI 1.20-1.45) were strong predictors of repetitive TBI. These results are from a single model and these variables are independently predictive of repetitive TBI.

Table 3. Baseline Characteristics Associated with Repetitive TBI among Medicare Beneficiaries ≥65 years, N=38,064

	Relative Risk (95% Confidence Interval)	p-value
Age	1.02 (1.01, 1.02)	<0.001
Epilepsy	1.44 (1.25, 1.56)	<0.001
Parkinson's Disease	1.26 (1.13, 1.44)	<0.001
Depression	1.30 (1.21, 1.38)	<0.001
Alzheimer's and related dementias	1.32 (1.20, 1.45)	<0.001
Atrial fibrillation	1.19 (1.11, 1.26)	<0.001

Discussion

To the best of our knowledge, this is the first study to report the incidence and predictors of repetitive TBI among older adults. Older adults with TBI experienced a 3% higher risk of repetitive TBI. Age, epilepsy, Parkinson's disease, depression, Alzheimer's disease and related dementias, and atrial fibrillation present at the time of index TBI were associated with increased risk of a repetitive TBI. Most of these conditions are neurological or psychological in nature, whereas atrial fibrillation is a physiologic condition.

Incidence of repetitive TBI has not been reported in older adults, however, studies have reported increased incidence of single TBI in older as compared to younger adults,

and we would expect increased risk of repetitive TBI among this demographic due to their high risk of falls.[1,2] The incidence rate for combined TBI-related hospitalizations and ED visits among older adults in 2013 was 681.9 per 100,000.[1] Our incidence rate was nearly 4-fold higher than this, suggesting that risk of a second TBI among older adults who sustain TBI is significantly elevated.

Older adults who experience TBI are more likely to have pre-existing medical conditions compared to those without TBI.[12] In this study of older adults with TBI, those who ultimately sustained a second TBI had a higher burden of comorbidities compared to those with a single TBI. The presence of certain comorbidities at the time of single TBI have been shown to be predictive of repetitive TBI. In this population of older adult Medicare beneficiaries who experienced TBI, epilepsy, Parkinson's disease, depression, ADRD, and atrial fibrillation were predictive of a second TBI. Seizure disorders, primarily epilepsy, are likely to result in multiple falls which can subsequently result in repetitive TBI.[31,32] Our findings are consistent with findings of increased risk of repetitive TBI following epilepsy in mixed age populations and these results extend to older Medicare beneficiaries.[33,34] ADRD is also associated with increased risk of falls in older adults, but this is the first study to report an association with repetitive TBI in a large representative sample of older adults.[15,35] This finding is supported by a wealth of information demonstrating increased risk of falls among older adults with dementia, mainly due to cognitive and motor deficits, balance impairment, vision problems, use of psychotropic medications, and severity of disease.[31,35]

Many studies of depression and TBI often find that there is increased risk of depression following TBI.[17,36,37] Few studies have looked at increased risk of single or

repetitive TBI following a diagnosis of depression. Older adults with TBI are likely to have depression at baseline compared to those without TBI. Albrecht et al. report that the prevalence of depression at baseline in older adults with TBI is more than double those without TBI.[7] In another study, increased risk of incident TBI was reported among older adults with depression, supporting our findings on depression as a risk factor for TBI and consequently second TBI.[12] Studies that have assessed the association between depression and falls suggest that antidepressant medications or functional impairment secondary to the underlying depression may increase fall risk .[8,38]

Atrial fibrillation was the only non-neurological, non-psychiatric comorbidity associated with increased risk of repetitive TBI. Studies indicate increased risk of falls in older adults with atrial fibrillation.[30,39] Mechanistically, the irregular and rapid heartbeat characteristic of atrial fibrillation can impair cardiac output to the brain, leading to dizziness or syncope. Physiologic pathways between atrial fibrillation and falls make our association between atrial fibrillation and repetitive TBI plausible, given that atrial fibrillation is the most common cardiac arrhythmia in older adults.[40]

This study has several strengths. It is the first study to characterize older adults with repetitive TBI and that reports the incidence of repetitive TBI in this population. The CCW is the largest and most representative database of older adults in the United States, implying that the results of this study are likely generalizable to other older adults. The large sample size allows us to capture a relatively rare outcome such as repetitive TBI. Additionally, we used validated ICD-9-CM code for TBI.

This study is not without limitations. Firstly, administrative claims data does not contain measures of TBI severity. Our proxy measure of TBI severity based on type of

TBI has not been validated. Secondly, there is potential for misclassification of repetitive TBI if the visit was a follow-up from the initial TBI. We attempted to mitigate misclassification bias by allowing a minimum of 90 days between the first and second TBI. Unlike other studies, our incidence rate does not account for TBI-related deaths.

Among Medicare beneficiaries who sustained an index TBI from 2008-2012, we found an annual 3% incidence of repetitive TBI. Repetitive TBI can exacerbate existing health problems that result from the occurrence of single TBI. Older adults with conditions such as epilepsy, Parkinson's disease, dementia, depression, and atrial fibrillation may require further attention to mitigate the occurrence of a second TBI. Future studies should focus on strategies to reduce risk of future TBI in those who have already experienced a single TBI.

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VI. INCIDENCE OF ISCHEMIC STROKE AMONG OLDER ADULT MEDICARE BENEFICIARIES WITH REPETITIVE TRAUMATIC BRAIN INJURY[1]

Abstract

Objective: To assess the risk of ischemic stroke associated with repetitive traumatic brain injury (TBI) among older adults.

Design: Retrospective cohort study.

Setting: Centers for Medicare and Medicaid Services (CMS) Chronic Conditions Warehouse (CCW) administrative data.

Participants: 5% sample of Medicare beneficiaries diagnosed with TBI from January 2008 to September 2012

Main Measures: We assessed the association between single and repetitive TBI and ischemic stroke among older adults using a discrete time model. The 9-month period prior to the first TBI served as the reference period for this analysis. TBI was identified using ICD-9-CM codes. Second TBI was identified as another diagnostic code for TBI occurring >90 days after the index TBI.

Results: Of 6,693 Medicare beneficiaries diagnosed with TBI and without history of ischemic stroke, 1,027 experienced repetitive TBI and 3,953 experienced ischemic stroke. Adjusting for atrial fibrillation, there was increased risk of ischemic stroke following a single TBI (HR 1.08, 95% CI 1.01-1.07) but not repetitive TBI (HR 0.95, 95% CI 0.83-

[1] Chauhan et al. In preparation for submission to the Journal of Head Trauma and Rehabilitation.

1.09), compared to the pre-index TBI period. There was no significant difference between the effect of single and repetitive TBI on risk of stroke (p=0.04).

Conclusions: In this sample of older adult Medicare beneficiaries, risk of ischemic stroke was elevated following TBI but a second TBI did not further increase risk. Lack of an observed increased incidence of ischemic stroke following repetitive TBI warrants investigation into the mechanisms underlying this finding.

Key words: TBI; ischemic stroke; older adults

Background

Traumatic brain injury (TBI) is one of the leading causes of injury-related disability among older adults ≥65 years of age, often resulting in adverse neurological outcomes.[1,2] A higher risk of falls among older adults places them at increased risk of repetitive TBI, which may have a multiplicative effect on risk of TBI sequelae.[3,4] For example, although risk of ischemic stroke is elevated following TBI, the impact of repetitive TBI on risk of ischemic stroke, particularly among older adults, may result in far more deleterious consequences.[5-10] Mechanisms by which TBI affects ischemic stroke risk are unclear, yet evidence suggests that ischemia following TBI can be due to a disruption of the blood-brain barrier, cervical dissection, and changes in the coagulation cascade, among others.[5,10,11]

While no studies have assessed the association between repetitive TBI and risk of ischemic stroke, a dose response effect for TBI has been observed for other neurological disorders, like dementia. For example, one study conducted among adults ages 55 and older found a 2-fold increase in risk of dementia following more than one TBI compared to those with single TBI.[12] The mechanisms behind increased risk of dementia following

TBI (diffuse β-amyloid plaque accumulation, tau immunoreactive neurofibrillary tangles, and cerebral atrophy) and ischemic stroke post-TBI may be different; thus, it is unknown if risk of ischemic stroke following repetitive TBI will be dose-dependent.[13]

Ischemic stroke can result in disability and could impede recovery among older adults with TBI who already have poorer recovery compared to younger TBI patients.[12,14,15] In addition, older adults are at increased risk of ischemic stroke.[16] The objective of this study was to estimate the association between repetitive TBI and subsequent risk of ischemic stroke. We hypothesized that there would be an increased risk of ischemic stroke following repetitive TBI compared to those with single TBI and pre TBI.

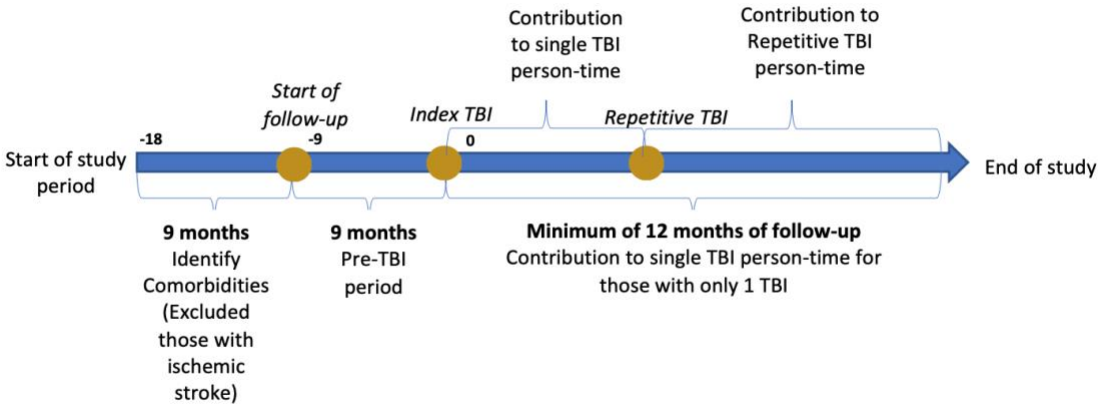
Methods

Study design

We conducted a retrospective study of Medicare beneficiaries diagnosed with TBI. To be eligible for our study, a beneficiary had to have at least one TBI, with 18 months of Medicare claims data before the index TBI, and during this time period the beneficiary could not have had a claim for TBI. Comorbidities present at the start of the 'pre-TBI' follow-up were assessed during the -18 to -10 month period before index TBI (Figure 1). Follow-up for the pre-TBI period started at 9-months pre-TBI and continued until the date of the index TBI (month 0). These 9 months directly preceding the index TBI were considered the pre-TBI reference period in subsequent analyses. Anyone with a diagnosis of ischemic stroke prior to this 9-month pre-TBI period was excluded from analysis. Additionally, each beneficiary had to have a minimum of 12 months of follow-up after the index TBI. Finally, we allowed beneficiaries to contribute person-time to

single TBI until they reached the end of follow-up or sustained another TBI, at which point they began contributing person-time to the repetitive TBI period.

Figure 1. Study Timeline



Data source

Our data comes from a 5% sample of Medicare beneficiaries obtained from the Centers for Medicare and Medicaid Services (CMS) Chronic Conditions Warehouse (CCW) administrative data for years 2007-2015. The CCW includes beneficiary enrollment information, claims for medical encounters, and data describing prescription medication usage, linked by a unique beneficiary identifier, masked to maintain anonymity, which allows for linkage of all CMS CCW data files. Beneficiaries in our sample were required to be ≥65 years at the index TBI with at least one TBI and continuous coverage of Medicare Parts A (hospital insurance) , B (medical insurance), and D (prescription drug coverage), but no C (Medicare Advantage Plan) during the study period. Claims are not consistently available for beneficiaries with Medicare Part C, thus beneficiaries with this coverage will be excluded. Follow-up continued for as long as continuous coverage of Medicare Parts, A, B, and D, no C was sustained until the end of the study period (September 2015).

Traumatic Brain Injury

We identified TBI by searching for International Classification of Disease, 9th Revision, Clinical Modification [ICD-9-CM] codes 800.xx, 801.xx, 803.xx, 804.xx, 850.xx-854.1x, 950.1-950.3, and 959.01 in the first position on both inpatient and outpatient files between July 2008 and September 2012 (to allow up to 36 months of follow-up post-TBI). Beneficiaries were required to have no TBI diagnoses in the 18-month period prior to first identified TBI, which was considered the index TBI. A second TBI was any TBI that occurred >90 days after the index TBI. The 90-day criterion was used to minimize misclassification bias in capturing diagnoses that were follow-up visits for the index TBI. We divided beneficiaries into two groups, a single TBI group comprised of beneficiaries with no additional TBI diagnoses in the time period post-index TBI. The second group, the repetitive TBI group was comprised of beneficiaries with at least one additional claim for TBI in the post-index TBI period.

Ischemic stroke

Ischemic stroke was identified by searching for the first claim for ICD-9-CM codes 433.xx-435.xx, 437.0x, or 437.1x. We searched inpatient claims only for ischemic stroke given that it is a rare outcome that often results in hospitalization and we wanted to avoid outpatient claims that may have been related to stroke history. Presence of ischemic stroke was coded on a monthly level. Additionally, we used the CCW dates of first diagnosis for stroke/ischemic events to eliminate those with a history of ischemic stroke prior to the start of follow-up.

Covariates

Covariates associated with increased risk of falls and single TBI were identified *a priori* and include demographic characteristics (age, sex, and race) and comorbid conditions.[4,17] The CCW data contain indicators and dates of first diagnosis for 27 common chronic conditions and 40 other chronic or potentially disabling conditions, updated periodically to reflect changes in beneficiary health status, to facilitate the identification of cohorts for research purposes.[17] From these conditions, we specifically considered for analysis diabetes, hypertension, depression, atrial fibrillation, alcohol use disorder, and epilepsy given that these are risk factors associated with ischemic stroke and TBI.[5,8] Additionally, we also recorded the presence of Parkinson's disease (ICD-9-CM code 332.0), as it is associated with increased risk of falls. Any comorbidities present at the start of the 9-month pre-TBI period were considered to be baseline comorbidities. Presence of new comorbidities were subsequently captured after the first TBI and then after the second TBI, where applicable. The Deyo clinical comorbidity index (CCI), an adaptation of the Charlson comorbidity index modified for use with administrative claims data, was used to measure burden of disease.[18,19] TBI severity is not readily available in administrative claims data, but we created a variable to capture type of TBI. Unspecified head injury (ICD-9-CM code 959.01) and concussion (ICD-9-CM code 850.xx) may be suggestive of milder injury whereas other TBI codes (800.xx-804.xx [fracture of the skull], 850.xx-854.1x [intracranial injury, excluding those with skull fracture], and 950.1-950.3[injury to the optic nerve and pathways]) may be more severe.[20]

Statistical Analysis

We used Chi-square tests for categorical variables and Student's t-test for continuous variables to assess baseline differences in the distribution of characteristics by

TBI status (single vs repetitive) at the time of the index TBI. Covariates significantly associated with TBI and known to be associated with ischemic stroke were considered as potential confounders.

We used a discrete-time model, in which the unit of analysis was month, to model the occurrence of ischemic stroke as a function of TBI status. This was accomplished using generalized estimating equations with a complimentary log-log link and binary distribution.[21] We updated TBI status at each event (pre-TBI, first TBI, and second TBI). This method reduces residual confounding because the cohort includes only those with TBI, whose characteristics may otherwise differ from those without TBI. Beneficiaries contributed follow-up time to the pre-TBI period until they experienced an ischemic stroke or the index TBI. Here, they were either censored at stroke occurrence or began contributing follow-up time to the single TBI group if no stroke occurred. Similarly, beneficiaries were censored if they experienced an ischemic stroke during the single TBI period. If no stroke occurred during this time, beneficiaries were either censored at end of study (no repetitive TBI) or went on to contribute follow-up time to the repetitive TBI group, subject to the same censoring endpoints during this period. We built our regression model by adding in covariates one at a time and assessing the statistical significance of each covariate. We retained any covariate significant at $p<0.001$ in our final models. We used a more stringent p-value cut-off of $p<0.001$ given our large sample size. We constructed contrast estimates to determine if effect estimates differed significantly between those with single and repetitive TBI.

We reported the hazard ratios (HR) and 95% confidence intervals (CI). The data analysis for this paper was performed using SAS 9.4, SAS Institute Inc., Cary, NC, USA.

This study was approved by the Institutional Review Board of the University of Maryland, Baltimore.

Results

We identified 6,693 beneficiaries diagnosed with TBI and meeting inclusion criteria. Of these, 1.027 (15%) experienced repetitive TBI. The mean age of our sample was 80.6 (standard deviation (SD)=7.6) and the sample was predominantly female (68%) and white (89%; Table 4). Those in the repetitive TBI group were slightly older age (mean=80.8, SD=7.5) than those with single TBI (mean=80.4, SD=7.7) (p<0.001). Prevalence of atrial fibrillation, congestive heart failure, diabetes, hypertension, epilepsy, Parkinson's disease, and depression were not significantly higher in the repetitive TBI group compared to the single TBI group. Those in the repetitive TBI group were not more likely to have a DEYO CCI score of 3 or more, which indicates greater disease burden.

Table 4. Characteristics of Medicare Beneficiaries ≥65 years, without prior history of ischemic stroke, diagnosed with a single or repetitive TBI July 2008-September 2012, at first TBI, N=6,693

	Total (N=6,693)	Single TBI (N=5,666)	>=2 TBI (N=1,027)	p-value[a]
Age (mean,SD)	80.6 (7.6)	80.6 (7.7)	80.8 (7.5)	<0.001
Sex (n,%)				0.76
Female	4,574 (68.3)	3,868 (68.3)	706 (68.7)	
Male	2,119 (31.7)	1,798 (31.7)	321 (31.3)	
Race (n,%)				0.57
White	5,931 (88.6)	5.014 (88.5)	917 (89.2)	
Black	407 (6.1)	352 (6.2)	55 (5.4)	
Other	355 (5.3)	300 (5.3)	55 (5.4)	
Type of TBI (n,%)				<0.001
Concussion	788 (11.8)	707 (12.5)	81 (7.9)	
Other	2,706 (40.4)	2,228 (39.3)	478 (46.5)	
Unspecified	3.199 (47.8)	2,731 (48.2)	468 (45.6)	
Alcohol dependence disorder (n,%)	157 (2.4)	124 (2.2)	33 (3.2)	0.05
Atrial fibrillation (n,%)	1,859 (27.8)	1,557 (27.5)	302 (29.4)	0.20

Congestive heart failure (n,%)	2,932 (43.8)	2,46 (43.4)	471 (45.9)	0.15
Depression (n,%)	1,485 (22.2)	1,223 (21.6)	262 (25.5)	0.005
Diabetes (n,%)	2,963 (44.3)	2,499 (44.1)	464 (45.2)	0.52
Epilepsy (n,%)	354 (5.3)	285 (5.0)	69 (6.7)	0.03
Hypertension (n,%)	6,228 (93.1)	5,281 (93.2)	947 (92.2)	0.25
Parkinson's disease (n,%)	293 (4.5)	239 (4.2)	54 (5.3)	0.13
DEYO CCI[b] (n,%)				0.32
0	456 (6.8)	384 (6.8)	72 (7.0)	
1	1,165 (17.4)	1,001 (17.7)	164 (16.0)	
2	1,222 (18.3)	1,046 (18.5)	176 (17.1)	
3 or more	3,850 (57.5)	3,235 (57.1)	615 (59.9)	

[a]Chi-square p-value for categorical variables and student's t-test for continuous variables
[b]CCI=Charlson Comorbidity Index

There were 3,953 ischemic stroke events during the study period (Table 5). Following adjustment for atrial fibrillation, risk of ischemic stroke was elevated after single TBI compared to the pre-TBI period (HR 1.08, 95% CI 1.01-1.07). A second TBI did not significantly increase risk of stroke compared to the pre-TBI period (HR 0.95, 95% CI 0.83-1.09). The risk of ischemic stroke was not significantly different for those with repetitive TBI compared to those with single TBI (p=0.04).

Table 5. Unadjusted and adjusted time-dependent hazard ratios (95% confidence intervals) between categories of TBI and risk of ischemic stroke among Medicare Beneficiaries ≥65 years with a primary diagnosis of single or repetitive TBI, July 2008-September 2012, n=6,693

	Number of Events	Person-years at risk	Unadjusted	Adjusted
Ischemic stroke				
Pre TBI	845	4,718	Reference	Reference
Single TBI	2,838	14,587	1.09 (1.01-1.18)	1.08 (1.01-1.07)[*]
Repetitive	270	1,548	0.98 (0.85-1.12)	0.95 (0.83-1.09)[*]

[*]Adjusted for atrial fibrillation

Discussion

In this sample of Medicare beneficiaries with TBI, we observed increased risk of ischemic stroke in those with single TBI compared to their pre-TBI period, but an additional TBI did not result in increased risk of stroke.

We observed a relative increase in risk of ischemic stroke following TBI that was lower than that reported in prior studies (i.e. 80% vs 8%).[5,9] One possible explanation may be that we required diagnosis of TBI to be in the first position of the claim (primary diagnosis), ensuring that TBI was the primary reason for seeking medical attention. Moreover, our sample was restricted to adults aged 65 and older who likely have comorbidities that may have contributed to the development of ischemic stroke over time. A prior study by Burke et al. did not restrict their sample to older adults, which could account for the difference in risk of ischemic stroke reported in our study.

Ischemic stroke is a process caused by atherosclerosis, resulting in cerebral thrombosis or cerebral embolism.[22] Our cohort had underlying comorbidities that may have contributed to atherosclerotic build up, a process that is unaffected by TBI. This may account for the observed lack of a dose response effect with repetitive TBI. One feature of TBI that is actually related to increased risk of ischemic stroke is the development of blunt cerebrovascular injury (BCVI). Ischemic stroke in this case is caused by a non-penetrating injury to the vertebral or carotid arteries as a result of trauma, however BCVI is considered rare and thus did not likely contribute to our findings.[23,24] There were also fewer ischemic stroke events which may be suggestive of a power issue. Moreover, the amount of time that elapses between the index TBI and the

repetitive TBI is roughly a year, which may not be enough time for health to decline rapidly to where the risk of ischemic stroke is any greater than it was after the first TBI.

This study has several strengths. This is the first study to investigate the risk of ischemic stroke associated with repetitive TBI. A large national database permitted capture of a rare exposure and outcome, TBI and ischemic stroke. Another strength of our study is that we compared those with single and repetitive TBI directly to their own pre-TBI period, which helped to minimize residual confounding.

Nonetheless, our study had limitations that are important to consider. First, although we required a minimum of 3 months between the first and second claim for TBI to ensure that these were two independent TBI events, there is potential for misclassifying someone with two claims as having repetitive TBI. Additionally, we did not have direct measures of TBI severity, which could be a risk factor for repetitive TBI and ischemic stroke. However, type of TBI was not statistically significant in our regression model.

Results from this study suggest that there may not be an increased risk of ischemic stroke for those who sustain repetitive TBI compared to their pre-TBI period, and that this risk is not elevated compared to the risk of ischemic stroke following single TBI. Future studies should consider additional measures of injury severity as well as mechanistic pathways of the association between TBI and ischemic stroke.

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VII. HEALTHCARE UTILIZATION ELEVATED AMONG OLDER ADULTS WITH REPETITIVE TRAUMATIC BRAIN INJURY COMPARED TO SINGLE TRAUMATIC BRAIN INJURY[1]

Abstract

Objective: Among older adults, to determine the impact of single and repetitive traumatic brain injury (TBI) on rates of healthcare utilization (HCU).

Design: Retrospective cohort study.

Setting: Centers for Medicare and Medicaid Services Chronic Conditions Data Warehouse.

Participants: US Medicare beneficiaries aged ≥65 years and diagnosed with TBI between July 2008-September 2012 identified from a 5% random sample of US Medicare beneficiaries.

Main Measures: HCU was operationalized as monthly counts of visits across three points of service: inpatient, outpatient, and emergency department. We used generalized estimating equations with a negative binomial model to estimate the association between single and repetitive TBI and HCU, compared to the pre-TBI (reference) period.

Results: Compared to the pre-TBI period, HCU was increased following the initial TBI across all point of service categories. HCU following repetitive TBI was significantly higher than that observed following single TBI across all point of service categories.

Conclusions: Among older adults with TBI, experiencing a subsequent TBI results in significantly increased HCU compared to the first TBI.

[1] Chauhan et al. In preparation for submission to the Journal of Head Trauma and Rehabilitation.

Key words: TBI; healthcare utilization; older adults

Background

Traumatic brain injury (TBI) is a common cause of injury-related disability among older adults.[1,2] TBI increases risk for sequelae such as stroke, depression, and insomnia that impede recovery and may increase interaction with the healthcare system.[3-6] In 2003, aggregate hospital charges for treatment of a principal diagnosis of TBI were upward of $2 billion among older US adults.[7] In fact, studies suggest that healthcare utilization (HCU) is elevated in the year following a TBI event in older adults, increasing the burden on the healthcare system beyond treatment of the original injury.[3,8] That burden is substantial.

Older adults are at risk of repetitive falls due to mobility limitations, multimorbidity, and polypharmacy and consequently are at increased risk of subsequent TBI.[9] Repetitive TBI may worsen the negative impact of a single TBI, particularly among older adults who have diminished physiologic and cognitive reserve.[10,11] For example, when compared to younger adults with single TBI, older adults with single TBI have slower cognitive and functional recovery and are more likely to require lengthier hospital stays, rehabilitative services, and home healthcare visits.[10] In fact, as many as 52% of older adults are discharged to inpatient rehabilitation following treatment for TBI.[12] Repetitive TBI could compound these disparities, resulting in more sequalae, longer recovery, and increased need for healthcare resources.

Despite their increased risk of TBI and higher baseline levels of HCU, no studies have assessed HCU following repetitive TBI among older adults. Such information could help inform resource allocation related to rehabilitation following TBI in older adults.

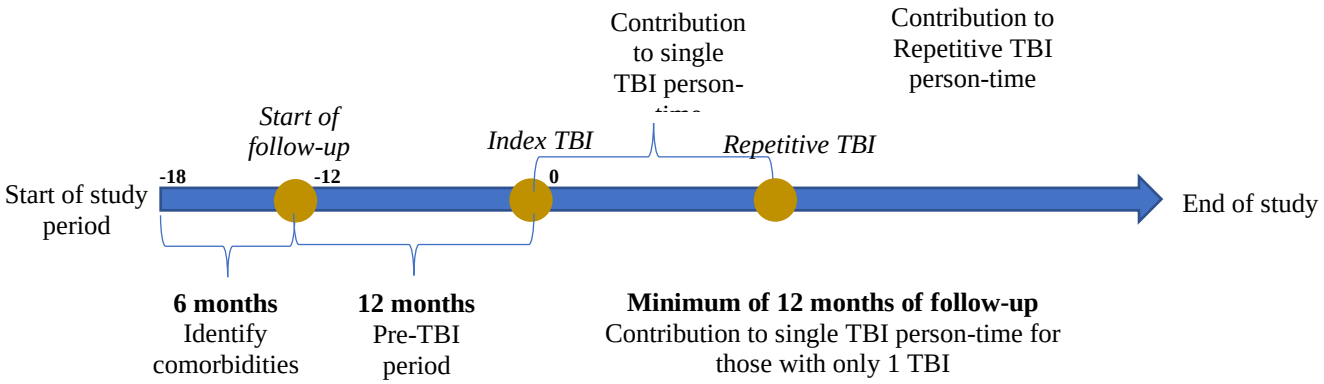
Thus, the objective of this study was to assess the impact of repetitive TBI on HCU among older adults, comparing with both single and repetitive TBI to the pre-TBI period. We hypothesized that HCU would be higher for those with repetitive TBI beyond that of single TBI.

Methods

Study design and data source

The data for this study were derived from a 5% random sample of US Medicare beneficiaries aged 65 and older acquired from the Centers for Medicare and Medicaid Services (CMS) Chronic Conditions Data Warehouse (CCW). The longitudinal data spanned years 2007-September 2015. The CCW includes fee-for-service institutional and non-institutional claims, enrollment data, and Part D Prescription Drug Event data. Continuous coverage of Medicare Parts A, B, and D, with no Part C coverage, for 18 months prior to the index TBI and at least 12 months of continuous coverage following the index TBI was required for inclusion in the study. Comorbidities present at the start of the 'pre-TBI' follow-up were assessed during 18- to 12- month period before TBI (Figure 1). Follow-up for the pre-TBI period started at 12-months pre- TBI and continued until the date of the TBI. The 18-month period prior to the index TBI included a six-month period in which baseline comorbidities were assessed with start of follow-up at 12 months before the index TBI. This 12-month period before TBI was considered the 'pre-TBI' period in our analyses.

Figure 1. Study Timeline



Traumatic brain injury

We searched both inpatient and outpatient claims for International Classification of Disease, 9th Revision, Clinical Modification [ICD-9-CM] codes for concussion (ICD-9-CM code 850.xx), unspecified TBI (ICD-9-CM code 959.01), and other TBI (ICD-9-CM codes 800.xx-804.xx [fracture of the skull], 850.xx-854.1x [intracranial injury, excluding those with skull fracture], and 950.1-950.3[injury to the optic nerve and pathways]). We restricted to beneficiaries with TBI in the first diagnostic position on inpatient or outpatient claims and captured index TBIs between July 2008 and September 2012. Beneficiaries with a claim for an index TBI with no subsequent TBI in the period >90 days following the index TBI were considered the single TBI group. Those beneficiaries with at least one additional claim for TBI >90 days after the index TBI were considered the repetitive TBI group. Measures of TBI severity are not readily available in claims, however, we used the categories of TBI based on diagnostic codes listed above related to the type of index TBI; unspecified, concussion, and other. Concussion and unspecified head injury are more likely to be milder head injury.[13]

Healthcare utilization

Healthcare utilization was assessed for three claim types: inpatient, outpatient, and emergency department. HCU was operationalized as monthly counts of unique visits. The inpatient claims file contains fee-for-service claims submitted by inpatient facilities for the reimbursement of facility costs.[14] The outpatient file includes facility charge amounts and fee-for-service claims submitted by institutional outpatient providers such as hospital outpatient departments, rural health clinics, outpatient rehabilitation, etc.[15] ED claims reflect visits to emergency departments for acute care needs. We identified ED visits in outpatient claims and inpatient revenue files via ED revenue codes (0450, 0451, 0452, 0456, 0459, 0981), which are provider-assigned codes for each cost center (in this case the emergency department) for which separate charges are billed. We then combined both inpatient and outpatient ED claims for total ED utilization. Multiple claims on the same visit date were counted as one encounter. Identified ED claims were removed from the inpatient and outpatient claims to avoid double counting. Skilled nursing facility and nursing home stays were not captured. We excluded the month of the index TBI and of the second TBI to tease apart utilization outside of the acute TBI encounter.

Covariates

We identified covariates *a priori* with known association with single TBI and with an increased risk of falls were considered for analysis. These included demographic characteristics and CCW comorbid chronic conditions. The CCW data includes the dates of first diagnosis as well as binary indicators for the presence of 27 common chronic conditions that are identified using a predefined validated algorithm.[16] Of the CCW chronic conditions, we considered atrial fibrillation, chronic kidney disease, rheumatoid

arthritis, alcohol dependence disorder, substance dependence disorder, epilepsy, depression, ischemic stroke, and Alzheimer's disease and related dementias (ADRD) for analysis. In addition to the CCW comorbidities, we created an indicator for Parkinson's disease (ICD-9-CM 332.0). Monthly covariate indicators were updated at baseline (12 months prior to the index TBI), index TBI, and second TBI, where applicable. We also accounted for months of follow-up time contributed to each TBI category (i.e. pre-TBI, single TBI, and repetitive TBI if applicable). Deyo clinical comorbidity index (CCI), an adaptation of the Charlson comorbidity index, weighted comorbidities based on the contribution of the comorbid disease to mortality risk.[17,18] CCI was categorized as 0, 1, 2, or 3 or more, with higher values associated with increased mortality risk.

Statistical Analysis

We assessed demographic and clinical characteristics at the time of index TBI and tested differences in distribution of these variables between those with single and repetitive TBI using Chi-square tests for categorical variables and Student's t-test for continuous variables. HCU was modeled at the monthly level using generalized estimating equations with a negative binomial model, allowing the exposure to change with time. TBI status was updated monthly with each person contributing person-time to their own pre-TBI period, single TBI period, and repetitive TBI period, if applicable. Separate models for inpatient, outpatient, and ED visits were used to assess the associations between single TBI and repetitive TBI with HCU, compared to the pre-TBI period. Models were adjusted for covariates based on statistical significance (at $p<0.001$) and QIC, with the lowest QIC indicating the most optimal model. Contrast estimates were used to determine if estimates significantly differed between those with single and

repetitive TBI. We reported rate ratios (RR) and 95% confidence intervals (CI). Since HCU could vary by severity of TBI, a sensitivity analysis stratified individuals by TBI type. Data analysis was carried out using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA). This study was approved by the Institutional Review Board of the University of Maryland, Baltimore.

Results

Among 38,064 beneficiaries who met inclusion criteria, 33,502 (88%) experienced single TBI and 4,562 (12%) experienced repetitive TBI. The sample was largely white (90%) and female (72%) with a mean age of 80.7 (standard deviation (SD)=7.8) (Table 6). Type of TBI was predominantly unspecified (63%), followed by other TBI (23%), and concussion (14%). At the time of the index TBI, prevalence of comorbidities was significantly higher among those with repetitive TBI compared to those with single TBI (Table 6). Large differences between those with repetitive TBI vs single TBI were observed for prevalence of atrial fibrillation (30% vs 25%, p<0.001), depression (29% vs 22%, p<0.001), and rheumatoid arthritis (77% vs 72%, p<0.001). Beneficiaries with repetitive TBI were more likely to have a DEYO CCI score of 3 or more compared to those with single TBI (62% vs 56%, p<0.001).

Table 6. Characteristics of Medicare Beneficiaries ≥65 years diagnosed with a single or repetitive TBI July 2008-September 2012, at first TBI, N=38,064

	Total (N=38,064)	Single TBI (N=33,502)	>=2 TBI (N=4,562)	p-value[a]
Age (mean,SD)	80.7 (7.8)	80.6 (7.9)	81.9 (7.5)	<0.001
Sex (n,%)				0.31
Female	27,345 (71.8)	24,039 (71.8)	3,306 (72.5)	
Male	10,719 (28.2)	9,463 (28.2)	1,256 (27.5)	
Race (n,%)				0.001
White	34,198 (89.9)	30,054 (89.7)	4,144 (90.8)	
Black	2,101 (5.5)	1,902 (5.7)	199 (4.4)	
Other	1,765 (4.6)	1,546 (4.6)	219 (4.8)	

Type of TBI (n,%)				<0.001
Concussion	5,476 (14.4)	4,951 (15.8)	525 (11.5)	
Other	8,574 (22.5)	7,264 (21.7)	1,310 (28.7)	
Unspecified	24,014 (63.1)	21,287 (63.5)	2,727 (59.8)	
Comorbidities (n,%)				
Alcohol dependence disorder	745 (2.0)	633 (1.9)	112 (2.5)	0.01
ADRD	2,727 (7.2)	2,243 (6.7)	484 (10.6)	<0.001
Atrial fibrillation	9,807 (25.8)	8,429 (25.2)	1,378 (30.2)	<0.001
Chronic kidney disease	11,707 (30.8)	10,193 (30.4)	1,514 (33.2)	<0.001
Depression	8,687 (22.8)	7,380 (22.0)	1,307 (28.7)	<0.001
Epilepsy	1,947 (5.1)	1,616 (4.8)	331 (7.3)	<0.001
Ischemic stroke	8,558 (22.5)	7,386 (22.1)	1,172 (25.7)	<0.001
Parkinson's disease	1,707 (4.5)	1,427 (4.3)	280 (6.1)	<0.001
Rheumatoid arthritis	27,736 (72.9)	24,219 (72.3)	3,517 (77.1)	<0.001
Substance dependence disorder	2,979 (7.8)	2,617 (7.8)	362 (7.9)	0.77
DEYO CCI[b] (n,%)				<0.001
0	2,904 (7.6)	2,681 (8.0)	223 (4.9)	
1	6,787 (17.8)	6,095 (18.2)	692 (15.2)	
2	6,925 (18.2)	6,121 (18.3)	804 (17.6)	
3 or more	21,448 (56.4)	18,605 (55.5)	2,843 (62.3)	

[a]Chi-square p-value for categorical variables and student's t-test for continuous variables
[b]CCI=Charlson Comorbidity Index

By design, all beneficiaries had 12 months of follow-up pre-TBI. Median follow-up after index TBI for individuals who experienced a single TBI was 40 (IQR 23-56) months and 33 (IQR 17-47) months for individuals with a repetitive TBI (Table 7). Mean monthly outpatient HCU increased from 0.96 (SD=2.93) encounters/month in the pre-TBI period to 1.26 (SD=7.82) encounters/month following single TBI, to 1.92 (SD=10.22) encounters/month following repetitive TBI. The same trend in increasing utilization was also observed for both outpatient and ED encounters.

Table 7. Median months of follow-up time and average monthly healthcare utilization by place of service among Medicare Beneficiaries ≥65 years with single or repetitive TBI, July 2008-September 2012

	Monthly Follow-up Time (Median, IQR)	Monthly Counts (Mean, SD)

Inpatient		
Pre TBI	12	0.13 (1.29)
Single TBI	40 (23-56)	0.30 (4.65)
Repetitive	33 (17-47)	0.53 (6.16)
Outpatient		
Pre TBI	12	0.96 (2.93)
Single TBI	40 (23-56)	1.26 (7.82)
Repetitive	33 (17-47)	1.92 (10.22)
Emergency Department		
Pre TBI	12	0.08 (0.80)
Single TBI	40 (23-56)	0.22 (3.80)
Repetitive	33 (17-47)	0.41 (5.12)

In unadjusted analyses, healthcare utilization was higher for those with single TBI and with repetitive TBI compared to the pre-TBI period for all points of service (Table 3). In adjusted models (see Table 8 for adjustment variables), inpatient HCU was higher for those with single (RR 1.32, 95% CI 1.25-1.39) and repetitive (RR 1.87, 95% CI 1.69-2.07) TBI compared to the pre-TBI period, respectively. Outpatient HCU, following adjustment, also was higher for those with single (RR 1.15, 95% CI 1.12-1.18) and repetitive (RR 1.50, 95% CI 1.41-1.60) TBI compared to the pre-TBI period, respectively. Emergency department HCU was higher for those with single (RR 1.41, 95% CI 1.34-1.48) and repetitive (RR 2.08, 95% CI 1.90-2.28) TBI correspondingly compared to the pre-TBI period in adjusted models.

Table 8. Unadjusted and adjusted rate ratios (95% confidence intervals) of healthcare utilization by place of service among Medicare Beneficiaries ≥65 years with single or repetitive TBI, July 2008-September 2012

	Unadjusted	Adjusted
Inpatient		
Pre TBI	Reference	Reference
Single TBI	2.22 (2.14-2.31)	1.32 (1.25-1.39)*
Repetitive	3.95 (3.67-4.24)	1.87 (1.69-2.07)*
Outpatient		
Pre TBI	Reference	Reference
Single TBI	1.31 (1.29-1.34)	1.15 (1.12-1.18)†
Repetitive	2.00 (1.91-2.10)	1.50 (1.41-1.60)†

Emergency Department		
Pre TBI	Reference	Reference
Single TBI	2.61 (2.51-2.71)	1.41 (1.34-1.48)[‡]
Repetitive	4.90 (4.57-5.26)	2.08 (1.90-2.28)[‡]

[*]Adjusted for sex, atrial fibrillation, epilepsy, Parkinson's disease, depression, ischemic stroke, substance dependence disorder, and count of follow-up months
[†]Adjusted for atrial fibrillation, epilepsy, Parkinson's disease, Alzheimer's disease and related dementias, depression, substance dependence disorder, and follow-up months
[‡]Adjusted for atrial fibrillation, epilepsy, Parkinson's disease, depression, ischemic stroke, substance dependence disorder, and follow-up months

Based on contrast estimates and across all points of service, HCU was higher for those with repetitive TBI beyond single TBI ($p<0.001$). In sensitivity analyses, we observed no significant differences in HCU by TBI type.

Discussion

In this population of older adult Medicare beneficiaries with TBI, the rate of HCU was higher within inpatient, outpatient, and emergency department settings in the post-TBI compared to the pre-TBI period. Point estimates were generally higher for inpatient HCU than outpatient HCU, implying that TBI has a significant impact on inpatient utilization. Among adults aged 65 years and older, post-index hospitalization care and rehospitalizations account for the bulk of HCU following TBI.[3] Experiencing a subsequent TBI resulted in a 30%-50% rate ratio increase in HCU compared to single TBI. Findings for those with single TBI are consistent with other studies and suggest that the effect of TBI on HCU is cumulative.[3,19-22] We anticipated the observed increase in HCU following a repetitive TBI in older adults given that the impact of subsequent head injury can increase risk of additional sequelae resulting in declines in neurological and psychological functioning. This may result in lengthier hospital stays, more appointments

for rehabilitative services, exacerbation of existing comorbidities, or development of new comorbidities, resulting in increased overall HCU.

No prior studies to our knowledge have examined HCU following repetitive TBI in any age group and most studies have focused on costs following a single TBI. In one such study, elevated healthcare costs were observed in the 6-months following single TBI compared to those without TBI in a mixed age population. However, TBI-related costs did not differ between groups 12 months to 6 years post-TBI.[20] Another mixed-age study conducted among Veterans reported increased utilization in the first year after a single mild TBI and decreasing costs in the second year.[23] Our study differed in that we examined individuals with all types of TBI, followed individuals with TBI for a much longer period of time (i.e., up to 7 years), and focused on older adults only. However, our results are consistent with the increased utilization seen in other studies immediately following a TBI event and expand them to a subsequent TBI.

There is evidence to suggest that prevalence of comorbidities is greater in those with single TBI compared to those without TBI, but these studies have not focused on repetitive TBI.[1,10] We observed that beneficiaries ≥65 years of age who ultimately experienced repetitive TBI were older, with an even greater burden of comorbidities compared to those with single TBI. Although these individuals may have had a higher baseline level of HCU as a result of their higher comorbidity burden, they contributed follow-up time to the single TBI group until they experienced a subsequent TBI. This would have biased results toward the null. Yet, we still observed significantly increased HCU following repetitive TBI, suggesting the effect was related to more than baseline comorbidity burden.

There are several strengths of this study. It was the first study, to our knowledge, to assess the association between repetitive TBI and HCU. Our study design helped to minimize residual confounding by permitting all beneficiaries to contribute person-time to each period of TBI exposure as well as provide their own pre-TBI reference period. Additionally, the use of administrative claims data for a longitudinal cohort permitted us to capture HCU up to 84 months post-TBI.

Still, our study has limitations that should be considered. First, while we have information on the setting of the HCU, we did not capture procedure codes and thus do not know what services were billed for. Secondly, we did not have an external non-TBI comparison group; thus, our findings are likely conservative estimates of utilization compared to the general older adult population. We did not capture nursing home and skilled nursing facility stays which could affect utilization. Lastly, we did not have measures of disability or frailty which can be potential drivers of HCU in older adults.

In conclusion, repetitive TBI significantly increased HCU over that of single TBI in older adults. Future research should focus on illuminating drivers of increased healthcare utilization for those who sustain repetitive TBI in order to determine more efficient resource allocation.

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VIII. ADDITIONAL RESULTS

Results of Analyses Using TBI Cohort Only

These results report the association between repetitive TBI and incidence of insomnia, depression, and ADRD in a cohort of Medicare beneficiaries with TBI. Exclusion of those not at risk of the outcome at the start of follow-up resulted in different cohorts for each analysis. For a complete description of baseline characteristics for each cohort, please refer to Appendix I Tables. Following adjustment for ischemic stroke, Alzheimer's disease and related dementias, and insomnia, incidence of depression was higher for those who experience single TBI (HR 1.28, 95% CI 1.17-1.40) as well as for those who experience a repetitive TBI (HR 1.53, 95% CI 1.33-1.75), compared to their pre-index TBI period. Assessing statistical significance at $p<0.05$, there was increased incidence of depression for those with repetitive TBI compared to those with single TBI ($p=0.003$). Risk of insomnia was not significantly higher for those who experienced a single TBI (HR 0.75, 95% CI 0.70-0.81) nor a second TBI (HR 0.71, 95% CI 0.62-0.81) compared to their pre-index TBI, after adjusting for age, rheumatoid arthritis, substance dependence disorder, and depression. Repetitive TBI was not associated with increased risk of insomnia beyond single TBI ($p=0.35$). There was increased risk of ADRD following adjustment for age, ischemic stroke, and insomnia during the single (HR 1.56, 95% CI 1.42-1.71) and repetitive (HR 1.75, 95% CI 1.54-1.99) TBI periods compared to the pre-index TBI period. Risk of ADRD was significantly higher for those with a repetitive TBI compared to those with a single TBI ($p=0.03$).

Table 9. Unadjusted and adjusted hazard ratios (95% confidence intervals) between categories of TBI and risk of depression, insomnia, and Alzheimer's disease and related dementias among Medicare Beneficiaries ≥65 years with a primary diagnosis of single or repetitive TBI, July 2008-September 2012

	Number of Events	Person-years at risk	Unadjusted	Adjusted
Depression (N=7,621)				
Pre TBI	593	5,511	Reference	Reference
Single TBI	2,660	19,060	1.31 (1.20-1.43)	1.28 (1.17-1.40)*
Repetitive	328	1,859	1.64 (1.43-1.87)	1.53 (1.33-1.75)*
Insomnia (N=35,330)				
Pre TBI	867	26,172	Reference	Reference
Single TBI	2,874	111,277	0.78 (0.73-0.85)	0.75 (0.70-0.81)‡
Repetitive	268	9,916	0.82 (0.71-0.94)	0.71 (0.62-0.81)‡
ADRD (N=10,952)				
Pre TBI	519	8,042	Reference	Reference
Single TBI	2,965	29,899	1.55 (1.41-1.70)	1.56 (1.42-1.71)§
Repetitive	409	3,641	1.74 (1.53-1.98)	1.75 (1.54-1.99)§

*Adjusted for ischemic stroke, Alzheimer's disease and related dementias, and insomnia
‡Adjusted for age, rheumatoid arthritis, substance dependence disorder, and depression
§Adjusted for age, ischemic stroke, and insomnia

Results of Analyses Using External Non-TBI Cohort

These results report the association between single and repetitive TBI and incidence of insomnia, depression, and ADRD compared to an external cohort of beneficiaries without TBI. Upon exclusion of beneficiaries with selected TBI ICD-9-CM codes, I selected a random sample of 140,000 beneficiaries without TBI. After applying continuous coverage criteria, we were left with 63,380 beneficiaries who formed the non-TBI cohort. Characteristics of the sample are presented in Table 10. This sample was predominantly female and white. The mean age for those without TBI was 76.7 (standard deviation (SD)=7.4)) and was less than that of those with single TBI (80.6 (SD=7.9)) and repetitive TBI (81.9 (SD=7.5)). Prevalence of all comorbidities, except substance dependence disorder, was significantly higher among those with repetitive TBI, followed by single TBI and no TBI, respectively.

Table 10. Characteristics of Medicare Beneficiaries ≥65 years diagnosed with a single or repetitive TBI July 2008-September 2012, at first TBI, N=101,744

	No TBI (N=63,680)	Single TBI (N=33,502)	>=2 TBI (N=4,562)	p-value[a]
Age (mean,SD)	76.7 (7.4)	80.6 (7.9)	81.9 (7.5)	
Sex (n,%)				<0.001
Female	39,208 (61.6)	24,039 (71.8)	3,306 (72.5)	
Male	24,472 (38.4)	9,463 (28.2)	1,256 (27.5)	
Race (n,%)				<0.001
White	56,080 (88.1)	30,054 (89.7)	4,144 (90.8)	
Black	4,596 (7.2)	1,902 (5.7)	199 (4.4)	
Other	3,004 (4.7)	1,546 (4.6)	219 (4.8)	
Type of TBI (n,%)				<0.001
Concussion	0 (0.0)	4,951 (14.8)	525 (11.5)	
Other	0 (0.0)	7,264 (21.7)	1,310 (28.7)	
Unspecified	0 (0.0)	21,287 (63.5)	2,727 (59.8)	
Atrial fibrillation (n,%)	9,567 (15.0)	8,429 (25.2)	1,378 (30.2)	<0.001
Congestive heart failure (n,%)	16,972 (26.7)	14,190 (42.4)	2,238 (49.1)	<0.001
Chronic kidney disease (n,%)	13,301 (20.9)	10,193 (30.4)	1,514 (33.2)	<0.001
COPD (n,%)	16,135 (25.3)	11,643 (34.8)	1,721 (37.7)	<0.001
Diabetes (n,%)	22,439 (35.2)	13,875 (41.4)	2,008 (44.0)	<0.001
Hypertension (n,%)	52,628 (82.6)	30,404 (90.8)	4,245 (93.1)	<0.001
Rheumatoid arthritis (n,%)	35,745 (56.1)	24,219 (72.3)	3,517 (77.1)	<0.001
Alcohol dependence disorder (n,%)	689 (1.1)	633 (1.9)	112 (2.5)	<0.001
Substance dependence disorder (n,%)	4,772 (7.5)	2,617 (7.8)	362 (7.9)	0.15
Parkinson's disease (n,%)	840 (1.3)	1,427 (4.3)	280 (6.1)	<0.001
Epilepsy (n,%)	1,235 (1.9)	1,616 (4.8)	331 (7.3)	<0.001
Depression (n,%)	6,700 (10.5)	7,380 (22.0)	1,307 (28.7)	<0.001
Ischemic stroke (n,%)	7,851 (12.3)	7,386 (22.1)	1,172 (25.7)	<0.001
Insomnia (n,%)	1,830 (2.9)	1,450 (4.3)	233 (5.1)	<0.001
ADRD (n,%)	1,260 (2.0)	2,243 (6.7)	484 (10.6)	<0.001

[a]Chi-square p-value for categorical variables and student's t-test for continuous variables

Following adjustment for sex, epilepsy, Parkinson's disease, chronic kidney disease, ischemic stroke, and insomnia, those with single TBI had nearly a 2-fold

increased incidence of depression (HR 1.89, 95% CI 1.85-1.94) compared to those without TBI. That incidence was 3-fold higher for those with repetitive TBI compared to those without TBI (HR 3.12, 95% CI 2.97-3.28). There was increased risk of ischemic stroke for those with single (HR 1.52, 95% CI 1.49-1.56) and repetitive (HR 2.44, 95% CI 2.32-2.56) TBI respectively compared to those with no TBI, following adjustment for age, sex, race, epilepsy, atrial fibrillation, alcohol dependence disorder, diabetes, and hypertension. Incidence of insomnia was higher for those with single TBI compared to those without TBI (HR1.45, 95% CI 1.41-1.48), after adjusting for age, sex, epilepsy, Parkinson's disease, ADRD, substance dependence disorder, alcohol dependence disorder, and rheumatoid arthritis. Adjusted incidence of insomnia was even higher for those with repetitive TBI compared to those with no TBI (HR 2.52, 95% CI 2.41-2.63). Similarly, following adjustment for age, sex, race, diabetes, ischemic stroke, depression, substance dependence disorder, and alcohol dependence disorder, incidence of ADRD was higher among those with single (HR 1.55, 95% CI 1.51-1.59) and repetitive (HR 2.65, 95% CI 2.53-2.77) TBI respectively compared to those with no TBI.

Table 11. Unadjusted and adjusted hazard ratios (95% confidence intervals) modeling the risk of outcomes as a function of TBI status among Medicare Beneficiaries ≥65 years without TBI or with either a primary diagnosis of single or repetitive TBI , July 2008-September 2012*

	Unadjusted	Adjusted
Depression (N=11,277)		
No TBI	Reference	Reference
Single TBI	2.16 (2.11-2.21)	1.89 (1.85-1.94)†
Repetitive	4.21 (4.02-4.42)	3.12 (2.97-3.28)†
Ischemic stroke (N=13,216)		
No TBI	Reference	Reference
Single TBI	1.98 (1.93-2.06)	1.52 (1.49-1.56)‡
Repetitive	3.54 (3.38-3.71)	2.44 (2.32-2.56)‡
Insomnia (N=3,661)		
No TBI	Reference	Reference
Single TBI	1.96 (1.91-2.01)	1.45 (1.41-1.48)§

Repetitive	3.96 (3.79-4.13)	2.52 (2.41-2.63)[§]
ADRD (N=5,561)		
No TBI	Reference	Reference
Single TBI	1.46 (1.42-1.51)	1.55 (1.51-1.59)[¶]
Repetitive	4.31 (4.12-4.51)	2.65 (2.53-2.77)[¶]

[*]Analysis accounts for competing risk of death

[†]Adjusted for sex, epilepsy, Parkinson's disease, chronic kidney disease, ischemic stroke, and insomnia

[‡]Adjusted for age, sex, race, epilepsy, atrial fibrillation, alcohol dependence disorder, diabetes, and hypertension

[§]Adjusted for age, sex, epilepsy, Parkinson's disease, ADRD, substance dependence disorder, alcohol dependence disorder, and rheumatoid arthritis

[¶]Adjusted for age, sex, race, diabetes, ischemic stroke, depression, substance dependence disorder, and alcohol dependence disorder

IX. DISCUSSION

Traumatic brain injury is a growing public health concern among older adults, but there is a paucity of information on the impact of repetitive TBI in this vulnerable population. This dissertation characterized older adults who experience a repetitive TBI, reporting that 12% of older adults who experience one TBI between 2008 and 2012 go on to sustain another. At the time of the initial TBI, these individuals have increased comorbidity compared to older adults who only sustain a single TBI. Additionally, I have found increased risk of depression and ADRD, but not ischemic stroke and insomnia, following repetitive TBI beyond that of single TBI.

Given the observation that repetitive TBI was associated with increased risk of depression and ADRD, it is not surprising that I also observed increased healthcare utilization following repetitive TBI beyond that of single TBI across inpatient, outpatient, and emergency department claims. Longer hospitalizations and greater use of rehabilitative services following single TBI already result in increased healthcare utilization and costs, further compounded by another TBI event. This dissertation, guided primarily by studies of single TBI in older adults or repetitive TBI in mixed age studies, has sought to highlight the importance of repetitive TBI in older adults. Repetitive TBI afflicts many older adults and can inform trajectories of health for susceptible individuals. What follows is a more detailed discussion of our findings from all the aims.

A. Incidence and Predictors of Repetitive TBI

I reported 3% annual incidence of repetitive TBI in this cohort of older adults with an initial TBI. This study has provided the first estimate of risk of repetitive TBI

among older adults with an initial TBI. Given that older adults are at increased risk of falls, we would anticipate that older adults are likely to experience repetitive TBI. Rates of combined TBI-related hospitalizations and ED visits were 681.9 per 100,000 in 2013 among those ≥65 years of age.[2] Compared to these rates, I observed a 4-fold higher incidence rate for repetitive TBI than a single TBI suggesting those who experience a TBI are at significantly increased risk of a subsequent head injury.[44] Older adults often have underlying age-associated comorbidities that predispose them to repetitive head injury compared to younger populations, also likely resulting in increased incidence of repetitive TBI.[3]

Compared to those who never experience TBI, older adults who experience TBI are more likely to have pre-existing conditions.[104] In this dissertation, I observed that burden of comorbidities was even higher among older adults with repetitive TBI compared to those with single TBI. Epilepsy, Parkinson's disease, depression, ADRD, and atrial fibrillation, comorbidities known to be associated with single TBI, were also associated with increased risk of a second TBI.

Seizure disorders such as epilepsy predispose individuals to multiple falls which in turn can result in repetitive TBI.[20,105] Studies of increased risk of repetitive TBI in mixed age populations support our findings. For example, a study by Saunders et al. reported that epilepsy was associated with 2.3 times the risk of repetitive TBI compared to those without epilepsy.[105] My study extends these results to older adults.

There is ample literature to support the association between ADRD and increased risk of falls in older adults, however, no studies to date have assessed the association between ADRD and repetitive TBI in a large representative sample of older adults.[7,43,104]

Most studies of dementia and TBI focus on dementia as a consequence of TBI and do not directly assess dementia preceding TBI.[7,106] However, studies have reported increased risk of falls among those with dementia, with falls being the primary mechanism of TBI in older adults.[34,104] Increased risk of falls among older adults with dementia are primarily due to balance impairment, vision problems, motor and neurocognitive deficits, memory impairment, use of psychotropic medications, and disease progression.[104,107]

Most prior studies have focused on depression following TBI.[9,52-54] However, one study reported more than double the prevalence of baseline depression in older adults with TBI compared to those without TBI.[59] Another study discovered that higher baseline depression scores were associated with incident TBI, lending support to our findings on depression as a risk factor for TBI and consequently second TBI.[36] Side effects of anti-depressant medications may increase fall risk which, in turn, can lead to multiple TBIs.[81,108]

Atrial fibrillation is the most common cardiac arrythmia in older adults and was the only non-neurological/non-psychiatric comorbidity associated with increased risk of repetitive TBI.[109] Studies have documented increased risk of falls among older adults with atrial fibrillation.[101,109-111] Atrial fibrillation can cause dizziness or syncope as a result of the irregular heartbeat that limits cardiac output to the brain. A study by Arita et al. suggests that the presence of atrial fibrillation can also be indicative of poorer health and functional impairment that leads to increased risk of falls.[112]

B. Outcomes of Repetitive TBI

TBI in older adults results in numerous sequelae which often have devastating consequences. Some of the identified predictors of repetitive TBI can also be

consequences of TBI, suggesting a bidirectional relationship. This dissertation focused on ischemic stroke, insomnia, depression, and Alzheimer's disease and related dementias following repetitive TBI.

Ischemic stroke

Ischemic stroke risk increases with age with three quarters of strokes occurring in older adults.[113] We observed a 9% increase in the risk of ischemic stroke following single TBI compared to a pre-TBI period among older adult beneficiaries. Our results show a lower risk of stroke following TBI than prior studies that reported a 30% increased risk of ischemic stroke following single TBI.[60,62] However, the design differences in these prior studies may have affected their estimates. For example, the study by Burke et al. was conducted in adults 18 and older, and also compared the risk of ischemic stroke following TBI to a non-TBI trauma cohort.[60] A study conducted among older adults, assessing incidence of ischemic stroke following TBI compared to a pre-TBI period, did not exclude ischemic stroke events in the pre-TBI period.[62] That study may have captured follow-up visits for an ischemic stroke that actually occurred pre-TBI which could have biased the results. This could explain why the 30% increased risk of ischemic stroke after TBI is higher than the risk observed in our study. The methods employed in our study may actually provide more reliable estimates of ischemic stroke risk following single TBI in older adults given that we excluded those with ischemic stroke before our 9-month pre-TBI period, and could control for confounders specific to those with TBI.

We did not observe increased risk of ischemic stroke following repetitive TBI beyond that of single TBI. Ischemic stroke is a result of atherosclerosis, a complex disease process that develops over time.[114] Typically, ischemic stroke is a result of

atherosclerosis, a product of physical inactivity, smoking, fatty diet, etc.[115] Blunt cerebrovascular injury (BCVI), caused by TBI, is associated with ischemic stroke, but BCVI is considered extremely rare and is more often associated with injuries resulting from motor vehicle collisions.[116,117] This study adds to the literature on ischemic stroke following repetitive TBI, however, further study into the underlying mechanisms of this risk is warranted.

Insomnia

Insomnia is the most prevalent sleep disturbance following TBI. It can result in poor psychological and cognitive recovery, hindering a return to normal functioning.[118] Decreased risk of insomnia was observed after single TBI, inconsistent with findings in other studies conducted in populations of all ages.[11,58,59] Additionally, we did not find significantly increased risk of insomnia after repetitive TBI compared to single TBI. Prior studies that reported increased risk of insomnia after multiple TBIs were conducted in military personnel who primarily experienced blast injuries.[11,119] However, overall health profiles of younger able-bodied military members differ from older adults. There is evidence to suggest that external stressors play a role in increased risk for sleep problems. A study by Hu et al. observed higher severity of sleep disturbances in middle-aged patients compared to older patients, positing that older patients experienced fewer daily stressors which could account for the lack of an elevated risk of insomnia following repetitive TBI more so than single TBI.[120] Additionally, we could not eliminate those with a history of insomnia prior to the years of data available and may not have accurately captured the use of FDA approved insomnia medications which could also account for the differences in these findings.

Depression

Depression is a well-established consequence of TBI, resulting in slower cognitive recovery.[121] We reported a nearly 30% increased risk of depression following single TBI compared to the pre-TBI period. Our results are consistent with findings from other studies.[4,9,121] Depression post-TBI may manifest as a result of physiological alterations in the brain, emotional stress (e.g. loss of functional ability), or underlying neuropsychological problems that may have existed prior to TBI but worsened after head injury.[52] There is also a potential for unmasking bias in which a patient who experiences TBI may receive more intensive medical care to identify health problems that may have preceded the TBI.

We observed an increased risk of depression after repetitive TBI beyond that of single TBI. No studies have assessed risk of depression after repetitive TBI in older adults. However, one study conducted in deployed military personnel reported increasing depressive symptoms with increasing number of TBIs.[73]

Alzheimer's disease and related dementias

There is a wealth of information to support the association between Alzheimer's disease and related dementias and TBI. Our findings of increased risk of dementia following single TBI compared to the pre-TBI period are consistent with the literature. One study conducted in those 55 and older reported a 46% increased risk of dementia among those with TBI compared to those with non-TBI trauma (NTT).[7] That same study then stratified patients by NTT vs single TBI vs >1 TBI and reported similar increased risk for single TBI vs NTT that was observed in their main analysis. However, that risk was double for those with >1 TBI compared to those with NTT, demonstrating increased

risk of dementia following repetitive TBI similar to our own study. Our incidence rates were higher but this is likely due to restricting our sample to those ≥65 and conducting our analyses solely in a cohort with TBI. There is evidence to suggest that structural deterioration due to repetitive TBI, precipitating in a cascade of events leading to neurodegeneration, is a biologically plausible mechanism for the development of dementia.[7,41]

C. Outcomes of Repetitive TBI with External Non-TBI Cohort

In sensitivity analyses, we conducted our outcomes analysis using an external non-TBI cohort as the reference group instead of the pre-TBI period. We found increased risk of all outcomes for those with single TBI compared to those with no TBI. Additionally, we found that risk of all four outcomes was elevated for those with repetitive TBI compared to single TBI. In our main analysis we did not observe elevated risk of ischemic stroke and insomnia for those with repetitive TBI compared to single TBI. The non-TBI cohort was younger than the TBI cohort with lower prevalence of comorbidities, unlike older adults with TBI who are likely to have other problems that predispose them to TBI.[36] Given the higher estimates, there is likely residual confounding that we could not account for, as there are certainly underlying factors that make those with TBI different from those without TBI. Our initial approach provides more valid estimates of these outcomes following repetitive TBI, however, the approach using an external non-TBI cohort is not without its merits. The results of this approach are easier to digest and demonstrate elevated risk of these outcomes following repetitive TBI compared to the general older adult population.

D. Healthcare Utilization Following Repetitive TBI

This is the first study to my knowledge to examine HCU following repetitive TBI in older adults. Many studies have addressed HCU following single TBI. Older adults who experience one TBI take longer to recover compared to younger adults, which entails lengthier hospital stays or increased use of rehabilitative services.[14] Our findings of increased HCU for those with single TBI compared to their pre-TBI period are consistent with prior studies.[14,87,122] None of these studies, however, have quantified HCU following a second TBI. We observed increased healthcare utilization following repetitive TBI compared to single TBI across three claim types, inpatient, outpatient, and emergency department. Beneficiaries with repetitive TBI were older and had a greater burden of comorbidities compared to those who sustain a single TBI. HCU is likely already elevated in these individuals at baseline given the burden of their existing comorbidities, however, these individuals previously contributed to the single TBI group until they experienced the second TBI. This would have potentially biased the results toward the null, however, HCU was significantly increased following repetitive TBI suggesting that the burden of comorbidities was not driving this effect. This suggests that the repetitive TBI may be more deleterious, particularly in the acute period following the TBI, and warranting increased utilization (e.g. longer hospital stays, increased management of existing or newly developed comorbidities, etc.) compared to a single TBI event.

E. Strengths

This study addressed several gaps in knowledge on repetitive TBI in older adults. Studies of repetitive TBI performed in younger populations have reported increases in neuropsychological deficits and other comorbidities but this work has not been done in older adults. This is the first study to assess healthcare utilization and outcomes of repetitive TBI in older adults using a large nationally representative sample of Medicare beneficiaries across multiple points of service. Large sample size permits assessment of a relatively rare exposure such as repetitive TBI. Using claims data on a monthly level allows incident diagnoses to be captured over up to 60 months of follow-up post index TBI. This is also the first study to characterize a geriatric population with repetitive TBI. Other strengths of this study include using well-validated ICD9 codes for TBI as well as depression, ADRD, ischemic stroke, and insomnia.[89,90] Additionally, definitions for both insomnia and dementia include prescription fills for related drugs, which helped to increase the sensitivity of the measure for these underdiagnosed conditions. This study was also conducted in a cohort of beneficiaries with TBI, reducing residual confounding that may otherwise occur due to differences in characteristics between those with and without TBI. Results from this study add a wealth of knowledge to the literature on repetitive TBI in older adults and will inform future studies and clinical management of geriatric TBI patients, by identifying which patients are at risk of repetitive TBI and identifying which outcomes to look out for following TBI.

F. Limitations

This study has several limitations. One limitation of this study is the potential misclassification of participants with repetitive TBI. If a second claim for TBI is a

follow-up related to the first TBI, we might classify it as another TBI. We expect any mis-classification to be non-differential and bias our results towards the null, specifically for aims 2 and 3. To address this limitation, we required a minimum of 3 months between the first and second TBI to best ensure that the two claims were identifying independent TBI events. Administrative claims data do not contain measures of TBI severity. To address this limitation, we used TBI type (concussion, non-specific head injury, and other TBI) as indicators of TBI severity, although this method has not been validated. Most older adults are insured through Medicare. However, since we did not have information from private insurance or Medicare Advantage plans, our results may not generalize to all adults aged 65 and older. Outcome measures may have been present before detection and diagnosis which could result in an overestimation of the risk of studied outcomes. We were unable to account for use of medications associated with increased risk of falls which may confound the observed associations.

G. Implications and Summary

Overall, the research conducted in this thesis sought to gain an understanding of risk factors and sequalae associated with repetitive TBI. TBI in older adults is a growing public health concern in an ever aging population. Given their increased risk of repetive falls, it is important to understand the impact of repetitive TBI on health outcomes among older adults. It is incumbent upon public health practitioners to promote measures resulting in favorable health outcomes for the geriatric TBI patients.

Fall prevention programs could be targeted to those at high risk of repetitive TBI based on characteristics identified in this study. Such programs have been evaluated and

have proven to be effective at preventing recurrent falls.[123,124] Cognitive rehabilitation has been shown to effectively increase cognitive functioning and future research could focus on the impact of cognitive rehabilitation on the outcomes studied in this dissertation .[125] Cognitive rehabilitation has been known to accelerate recovery and attention processing, resulting in increased functional recovery which could reduce the occurrence of another TBI and subsequent sequelae.[126]

This study also contributes to the understanding and quantification of where most resource utilization occurs following a second injury compared to a single injury. This research has provided evidence of increased risk of several sequelae following repetitive TBI which could affect utilization and costs for hospital systems, insurance payers, and patients.[127] This work can help inform and direct care management and resource utilization for older adults who sustain numerous TBIs.

Future directions should focus on research addressing TBI severity, inclusion of frailty measures, and long-term impact of sustaining a second head injury compared to a single injury among this vulnerable demographic. There is also an opportunity to investigate clinical trajectories pre and post repetitive TBI via a longitudinal study design. This type of research could further illuminate the role aging plays in repetitive head injuries and recovery, as well as identify those at increased risk of repetitive head trauma to employ preventive measures.

X. APPENDIX I. TABLES

Table 12. Characteristics of Medicare Beneficiaries ≥65 years, without prior history of depression, diagnosed with a single or repetitive TBI July 2008-September 2012, at first TBI, N=7,621

	Total (N=7,621)	Single TBI (N=6,491)	>=2 TBI (N=1,130)	p-value[a]
Age (mean,SD)	80.9 (7.8)	80.7 (7.8)	82.1 (7.4)	<0.001
Sex (n,%)				0.32
Female	5,230 (68.6)	4,469 (68.9)	761 (67.3)	
Male	2,391 (31.4)	2,022 (31.1)	369 (32.7)	
Race (n,%)				0.03
White	6,911 (90.7)	5,871 (90.5)	1,040 (92.0)	
Black	384 (5.0)	345 (5.3)	39 (3.5)	
Other	326 (4.3)	275 (4.2)	51 (4.5)	
Type of TBI (n,%)				<0.001
Concussion	1,057 (13.9)	912 (14.0)	145 (12.8)	
Other	2,014 (26.3)	1,621 (25.0)	393 (34.8)	
Unspecified	4,550 (59.7)	3,958 (61.0)	592 (52.4)	
Depression (n,%)	945 (12.4)	814 (12.5)	131 (12.0)	0.37
Alcohol dependence disorder (n,%)	147 (1.9)	125 (1.9)	22 (2.0)	0.96
Chronic kidney disease (n,%)	2,364 (31.0)	2,015 (31.0)	349 (30.9)	0.92
Epilepsy (n,%)	371 (4.9)	296 (4.6)	75 (6.6)	0.003
Insomnia (n,%)	260 (3.4)	220 (3.4)	40 (3.5)	0.80
Ischemic stroke (n,%)	1,778 (23.3)	1,479 (22.8)	299 (26.5)	0.007
Parkinson's disease (n,%)	332 (4.4)	270 (4.2)	62 (5.5)	0.04
Substance dependence disorder (n,%)	551 (7.2)	482 (7.4)	69 (6.1)	0.11
DEYO CCI (n,%)				0.20
0	522 (6.8)	458 (7.1)	64 (5.7)	
1	1,449 (19.0)	1,247 (19.2)	202 (17.9)	
2	1,414 (18.6)	1,199 (18.5)	215 (19.0)	
3 or more	4,236 (55.6)	3,587 (55.2)	649 (57.4)	

[a]Chi-square p-value for categorical variables and student's t-test for continuous variables

*Adjusted for sex, race, epilepsy, Parkinson's disease, chronic kidney disease, ischemic stroke, and insomnia

Table 13. Characteristics of Medicare Beneficiaries ≥65 years, without prior history of insomnia, diagnosed with a single or repetitive TBI July 2008-September 2012, at first TBI, N=35,330

	Total (N=35,330)	Single TBI (N=31,128)	>=2 TBI (N=4,202)	p-value[a]
Age (mean,SD)	80.8 (7.8)	80.6 (7.9)	82.0 (7.5)	<0.001
Sex (n,%)				0.20
Female	25,168 (71.2)	22,139 (71.1)	3,029 (72.1)	
Male	10,162 (28.8)	8,9892 (28.9)	1,173 (27.9)	
Race (n,%)				<0.001
White	31,733 (89.8)	27,907 (89.6)	3,826 (91.0)	
Black	1,979 (5.6)	1,796 (5.8)	183 (4.4)	
Other	1,618 (4.6)	1,425 (4.6)	193 (4.6)	
Type of TBI (n,%)				<0.001
Concussion	5,058 (14.3)	4,585 (14.7)	473 (11.3)	
Other	8,019 (22.7)	6,796 (21.8)	1,223 (29.1)	
Unspecified	22,253 (63.0)	19,747 (63.5)	2,506 (59.6)	
Alcohol dependence disorder (n,%)	674 (1.9)	575 (1.9)	99 (2.4)	0.02
Alzheimer's disease and related dementias (n,%)	5,240 (14.8)	4,408 (14.2)	832 (19.8)	<0.001
Chronic kidney disease (n,%)	10,722 (30.4)	9,344 (30.0)	1,378 (32.8)	<0.001
Congestive heart failure (n,%)	15,040 (42.6)	13,014 (41.8)	2,026 (48.2)	<0.001
Depression (n,%)	7,506 (21.3)	6,375 (20.5)	1,131 (26.9)	<0.001
Epilepsy (n,%)	1,765 (5.0)	1,462 (4.7)	303 (7.2)	<0.001
Ischemic stroke (n,%)	7,804 (22.1)	6,742 (21.7)	1,062 (25.3)	<0.001
Parkinson's disease (n,%)	1,549 (4.4)	1,296 (4.2)	253 (6.0)	<0.001
Rheumatoid arthritis (n,%)	25,431 (72.0)	22,220 (71.4)	3,211 (76.4)	<0.001
Substance dependence disorder (n,%)	2,606 (7.4)	2,298 (7.4)	308 (7.3)	0.90
DEYO CCI (n,%)				<0.001
0	2,656 (7.5)	2,453 (7.8)	203 (4.8)	
1	6,080 (17.2)	5,473 (17.6)	607 (14.5)	
2	6,439 (18.2)	5,714 (18.4)	725 (17.2)	
3 or more	20,155 (57.1)	17,488 (56.2)	2,667 (63.5)	

[a]Chi-square p-value for categorical variables and student's t-test for continuous variables

Table 14. Characteristics of Medicare Beneficiaries ≥65 years, without prior history of Alzheimer's disease and related dementias, diagnosed with a single or repetitive TBI July 2008-September 2012, at first TBI, N=10,952

	Total (N=10,952)	Single TBI (N=9,164)	>=2 TBI (N=1,788)	p-value[a]
Age (mean,SD)	82.2 (7.4)	82.2 (7.5)	81.9 (7.3)	<0.001
Sex (n,%)				0.94
Female	7,836 (71.6)	6,558 (71.6)	1,278 (71.5)	
Male	3,116 (28.5)	2,606 (28.4)	510 (28.5)	
Race (n,%)				0.002
White	9,938 (90.7)	8,291 (90.5)	1,647 (92.1)	
Black	550 (5.0)	490 (5.3)	60 (3.4)	
Other	464 (4.3)	383 (4.2)	81 (4.5)	
Type of TBI (n,%)				<0.001
Concussion	1,520 (13.9)	1,315 (14.3)	205 (11.5)	
Other	2,850 (26.0)	2,269 (24.8)	581 (32.5)	
Unspecified	6,582 (60.1)	5,580 (60.9)	1,002 (56.0)	
Congestive heart failure (n,%)	5,094 (46.5)	4,206 (45.9)	888 (49.7)	0.004
Diabetes (n,%)	4,723 (43.1)	3,936 (43.0)	787 (44.0)	0.41
Hypertension	10,163 (92.8)	8,494 (92.7)	1,669 (93.3)	0.33
Ischemic stroke (n,%)	2,676 (24.4)	2,202 (24.0)	474 (26.5)	0.03
DEYO CCI (n,%)				0.05
0	603 (5.5)	507 (5.5)	96 (5.4)	
1	1,787 (16.3)	1,533 (16.7)	254 (14.2)	
2	2,014 (18.4)	1,684 (18.4)	330(18.4)	
3 or more	6,548 (59.8)	5,440 (59.4)	1,108 (62.0)	

[a]Chi-square p-value for categorical variables and student's t-test for continuous variables

XI. APPENDIX II. HEALTHCARE UTILIZATION TABLES BY TYPE OF TBI

Table 15. Unadjusted and adjusted rate ratios (95% confidence intervals) of healthcare utilization by place of service among Medicare Beneficiaries ≥65 years with single or repetitive TBI, Concussions, July 2008-September 2012

	Unadjusted	Adjusted
Inpatient		
Pre TBI	Reference	Reference
Single TBI	2.50 (2.27-2.75)	1.32 (1.25-1.39)*
Repetitive	5.05 (4.09-6.24)	1.87 (1.69-2.07)*
Outpatient		
Pre TBI	Reference	Reference
Single TBI	1.35 (1.29-1.42)	1.15 (1.12-1.18)†
Repetitive	2.15 (1.88-2.45)	1.50 (1.41-1.60)†
Emergency Department		
Pre TBI	Reference	Reference
Single TBI	2.61 (2.51-2.71)	1.41 (1.34-1.48)‡
Repetitive	4.90 (4.57-5.26)	2.08 (1.90-2.28)‡

*Adjusted for sex, atrial fibrillation, epilepsy, Parkinson's disease, depression, ischemic stroke, substance dependence disorder, and count of follow-up months

†Adjusted for atrial fibrillation, epilepsy, Parkinson's disease, Alzheimer's disease and related dementias, depression, substance dependence disorder, and follow-up months

‡Adjusted for atrial fibrillation, epilepsy, Parkinson's disease, depression, ischemic stroke, substance dependence disorder, and follow-up months

Table 16. Unadjusted and adjusted rate ratios (95% confidence intervals) of healthcare utilization by place of service among Medicare Beneficiaries ≥65 years with single or repetitive TBI, Other TBI, July 2008-September 2012

	Unadjusted	Adjusted
Inpatient		
Pre TBI	Reference	Reference
Single TBI	2.41 (2.22-2.61)	1.32 (1.25-1.39)*
Repetitive	5.05 (4.09-6.24)	1.87 (1.69-2.07)*
Outpatient		
Pre TBI	Reference	Reference
Single TBI	1.31 (1.29-1.34)	1.15 (1.12-1.18)†
Repetitive	2.00 (1.91-2.10)	1.50 (1.41-1.60)†
Emergency Department		
Pre TBI	Reference	Reference
Single TBI	2.61 (2.51-2.71)	1.41 (1.34-1.48)‡
Repetitive	4.90 (4.57-5.26)	2.08 (1.90-2.28)‡

*Adjusted for sex, atrial fibrillation, epilepsy, Parkinson's disease, depression, ischemic stroke, substance dependence disorder, and count of follow-up months

†Adjusted for atrial fibrillation, epilepsy, Parkinson's disease, Alzheimer's disease and related dementias, depression, substance dependence disorder, and follow-up months

‡Adjusted for atrial fibrillation, epilepsy, Parkinson's disease, depression, ischemic stroke, substance dependence disorder, and follow-up months

Table 17. Unadjusted and adjusted rate ratios (95% confidence intervals) of healthcare utilization by place of service among Medicare Beneficiaries ≥65 years with single or repetitive TBI, Unspecified TBI, July 2008-September 2012

	Unadjusted	Adjusted
Inpatient		
Pre TBI	Reference	Reference
Single TBI	2.11 (2.01-2.22)	1.32 (1.25-1.39)*
Repetitive	3.76 (3.42-4.13)	1.87 (1.69-2.07)*
Outpatient		
Pre TBI	Reference	Reference
Single TBI	1.31 (1.29-1.34)	1.15 (1.12-1.18)†
Repetitive	2.00 (1.91-2.10)	1.50 (1.41-1.60)†
Emergency Department		
Pre TBI	Reference	Reference
Single TBI	2.11 (2.01-2.22)	1.41 (1.34-1.48)‡
Repetitive	4.90 (4.57-5.26)	2.08 (1.90-2.28)‡

*Adjusted for sex, atrial fibrillation, epilepsy, Parkinson's disease, depression, ischemic stroke, substance dependence disorder, and count of follow-up months

†Adjusted for atrial fibrillation, epilepsy, Parkinson's disease, Alzheimer's disease and related dementias, depression, substance dependence disorder, and follow-up months

‡Adjusted for atrial fibrillation, epilepsy, Parkinson's disease, depression, ischemic stroke, substance dependence disorder, and follow-up months

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