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Sleep Disturbances among Older Adults Following Traumatic Brain Injury

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Abstract

Sleep disturbances are common sequelae of traumatic brain injury (TBI) that are associated with poorer recovery. This is important among older adults who fare worse following TBI relative to younger adults and have higher prevalence of sleep disorders. The objective of this study was to assess the risk of newly diagnosed sleep disorders following TBI among adults ≥ 65 years. Using a large commercial insurance database, we identified older adults diagnosed with TBI 2008–2014 (n=78,044) and non-TBI controls (n=76,107). First dates of diagnosis of four sleep disorders (hypersomnia, insomnia, obstructive sleep apnea, and restless legs syndrome) and a composite of any sleep disorder were identified. To compare groups, we used a difference-in-differences (DID) approach, accounting for pre-index differences between cohorts and the time trends in sleep diagnoses. Individuals with TBI were more likely to have any newly diagnosed sleep disorder before (14.1% vs. 9.4%, $p<0.001$) and after (22.7% vs. 14.1%, $p<0.001$) the index date. In fully adjusted DID models, TBI was associated with increased risk of insomnia (rate ratio (RR) 1.17; 95% confidence interval (CI) 1.08, 1.26) and any sleep disorder (RR 1.13; 95% CI 1.08, 1.19). Following TBI among older adults, screening and education on sleep disorders should be considered.

Introduction

Traumatic brain injury (TBI) is a major public health concern, particularly among older adults. Each year in the United States, TBI results in over 600,000 emergency department visits and hospitalizations among adults aged 65 and older. (Taylor, Bell, Breiding, & Xu, 2017) Hospitalization rates for TBI among older adults are more than double those observed in other age groups and are increasing. (Taylor et al., 2017) Further, older adults have poorer short and long-term outcomes following TBI, including longer length of hospital stay, increased functional limitations and disability, and higher mortality. (Mosenthal et al., 2002;

Mosenthal et al., 2004; Selassie et al., 2008; Susman et al., 2002; Thompson, McCormick, & Kagan, 2006; Utomo, Gabbe, Simpson, & Cameron, 2009)

Sleep disturbances are common sequelae of TBI. For example, compared to non-injured controls, individuals with TBI demonstrate poorer sleep efficiency, shorter sleep duration, longer sleep onset, and more wake after sleep time.(Grima, Ponsford, Rajaratnam, Mansfield, & Pase, 2016; Mollayeva et al., 2017; Wickwire et al., 2018a; Wickwire et al., 2016) Further, many clinical sleep disorders are common following TBI, with prevalence rates among TBI patients nearly double those among non-TBI controls.(Mathias & Alvaro, 2012; Wickwire et al., 2018a; Wickwire et al., 2016) Insomnia, defined as difficulty initiating or maintaining sleep with an associated daytime consequence, is the most common sleep disorder following TBI (range 30%–60%).(Orff, Ayalon, & Drummond, 2009; Ouellet, Beaulieu-Bonneau, & Morin, 2015; Wickwire et al., 2018a; Wickwire et al., 2016) High prevalences of hypersomnia (range 10%–30%) and sleep-related breathing disorders such as obstructive sleep apnea (OSA) (range 10%–30%) following TBI have also been reported. (Mathias & Alvaro, 2012; Ouellet et al., 2015; Wickwire et al., 2018a; Wickwire et al., 2016)

Whereas healthy sleep is associated with positive brain function including synaptic growth, neural plasticity, and glymphatic clearance of neurotoxins, poor sleep is associated with cognitive dysfunction, functional impairment, and mood disturbances.(Cirelli, 2012; Orff et al., 2009; Rao et al., 2008; Van Dongen, Maislin, Mullington, & Dinges, 2003; Wickwire et al., 2018a) Thus, sleep disturbances and clinical sleep disorders can impede recovery from TBI both directly (i.e., by inhibiting neural recovery) as well as indirectly (i.e., increasing risk for cognitive, functional, and mood disturbances).(Wickwire et al., 2016) Furthermore, poor sleep among older adults is a risk factor for falls, increasing risk of repetitive injury. (Stone et al., 2008)

Importantly, sleep disturbances are not only well-known sequelae of TBI, but they are also risk factors for TBI among older adults. This bidirectional association makes it difficult to elucidate causal relationships between pre-morbid sleep disturbances, TBI, and subsequent sleep disturbances.(Mathias & Alvaro, 2012; Orff et al., 2009; Ouellet et al., 2015; Stone et al., 2008; Wickwire et al., 2016) In order to advance understanding and identify optimal prevention and treatment strategies, studies employing large sample sizes and appropriate non-TBI control groups are required. Thus, the objective of the present study was to leverage a large national cohort of older adults with and without TBI to assess the risk of sleep disorders following TBI using a difference-in-differences (DID) methodological approach. This sophisticated analytic framework enables researchers to disentangle causal effects of TBI from the effects of pre-existing sleep disorders and baseline clinical characteristics on subsequent sleep disturbances post-TBI. We hypothesized that relative to controls, older adults with TBI would demonstrate increased risk of sleep disorders.

Methods

Study Design and Data source

We conducted a retrospective cohort study using data from the OptumLabs® Data Warehouse (OLDW), which includes medical and pharmacy claims, laboratory results, and enrollment records for commercial and Medicare Advantage (MA) enrollees. The database contains longitudinal health information on enrollees and patients, representing a diverse mixture of ages, ethnicities and geographical regions across the United States.(OptumLabs, 2019) Enrollees have comprehensive, full insurance coverage for physician, hospital, and prescription drug services. In the OLDW, anyone 18 years is assigned an age of 89 years to maintain compliance with the Health Insurance Portability and Accountability Act of 1996. This study involved analysis of pre-existing, de-identified data and was determined exempt from Institutional Review Board approval by the University of Maryland, Baltimore.

Participants

Data for this study were derived from a larger dataset comprising participants aged 18 years who were diagnosed with TBI between January 1, 2008 and June 30, 2014 and continuously enrolled in medical and pharmacy benefits for a minimum of 12 months before TBI and 24 months after TBI (i.e. 36 months total). TBI was defined using 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 that are recommended for TBI surveillance by the Centers for Disease Control and Prevention and have been shown to have good sensitivity and specificity to detect TBI.(Carroll, Cochran, Guse, & Wang, 2012; CDC, 2007; Marr A, 2004; Thurman DJ, 1995) We searched inpatient and outpatient claims for the presence of TBI defined as any of the ICD-9-CM codes in any position on the claim. A non-TBI control cohort was created by randomly selecting individuals without a TBI diagnosis who met continuous enrollment criteria. These individuals were frequency matched 1:2 on index date with the TBI cohort. In this study, the term 'index date' will refer to the date of TBI in the TBI cohort and the matched index date in the non-TBI cohort.

For this study, we restricted the original dataset to individuals aged 65 and older. Because age was not a matching factor, the ratio of TBI cases to non-TBI controls is not 1:2 in this study.

Outcomes

Sleep disturbances were identified based on prior work from our group as well as expert opinion and were defined using ICD-9-CM codes.(Albrecht, Wickwire, Vadlamani, Scharf, & Tom, 2019; Ford et al., 2014) Operational definitions of sleep disorders are presented in Table 1. In preliminary analyses we identified the most common sleep disturbances and focused subsequent analyses on insomnia, obstructive sleep apnea (OSA), restless legs syndrome (RLS), and hypersomnia. Because sleep disorders are highly comorbid, participants could be diagnosed with more than one type of sleep disorder during the study period. All sleep disturbances were also grouped to form a composite category of any sleep

disorder. To facilitate person-time calculations, we identified the date of first sleep disorder diagnosis occurring within the study period.

Person-Time Calculation

To maintain consistency in person-time, we censored follow-up at 12 months post-index for this study. We calculated person-time pre-index by subtracting the index date from the start of follow-up (i.e. 12 months earlier). Individuals diagnosed with a sleep disorder during the pre-index period contributed person-time only until the diagnosis and were censored thereafter. Excluding individuals diagnosed with a sleep disorder pre-index, we calculated person-time post-index by subtracting the end of follow-up from the index date (i.e. 12 months earlier). Individuals diagnosed with a sleep disorder during the post-index period contributed person-time only until the diagnosis and were censored thereafter. These calculations were performed for each sleep disorder as well as for the composite variable reflecting any sleep disorder. Contributed person-time was used as an off-set in our Poisson DID regression models.

Covariates

Age, sex, race, education, census region, and type of insurance were obtained from the OLDW files. Comorbid illnesses were identified based on the presence of ICD-9-CM codes on any inpatient or outpatient claim. Any comorbidity identified during the twelve months prior to the index date was considered present at baseline.

Statistical Analysis

We compared the distribution of all variables between the TBI and non-TBI cohorts using Chi-square goodness of fit and Student's t-tests. Our prior work suggests significant differences in baseline characteristics between individuals who experience TBI and controls. (Albrecht, Barbour, Abariga, Rao, & Perfetto, 2019) These differences could contribute to residual confounding of the effect of TBI on risk of sleep disturbances. Thus, to minimize potential residual confounding, we used a DID estimation approach for regression modelling. DID uses a quasi-experimental design to estimate causal effects by comparing changes in a treated group (i.e., the TBI cohort) to changes in a control group (i.e., non-TBI cohort) over time.(Lechner, 2010)

We used generalized estimating equations with a Poisson distribution and log link with an offset for the log of contributed person-time, accounting for repeated measures on some individuals (i.e. pre- and post-index date if uncensored). The DID estimator was created using an interaction term between the cohort (TBI) and time (post-index date).(Lechner, 2010) Rate ratios (RtR) and 95% confidence intervals (CI) are reported. Because we had only a single diagnosis date for each sleep disorder and censored individuals after they received a diagnosis (in each separate analysis), all analyses are based on newly diagnosed and not recurrent sleep disorders.

Results

We identified 78,044 individuals aged 65 and older meeting inclusion criteria and diagnosed with TBI during the study period. The non-TBI cohort comprised 76,107 individuals. Average age was 76.6 (standard deviation [sd] 6.1) years in the TBI cohort and 73.4 (sd 5.8) years in the non-TBI cohort ($p<0.001$; Table 1). Individuals with TBI were more likely to be women (64.9% vs. 55.8%, $p<0.001$) and had higher prevalence of all measured comorbid conditions ($p<0.001$ for all). Please see Table 2 for complete comorbidity information. Both cohorts were primarily insured through Medicare Advantage (80.5% and 77.3% for the TBI and non-TBI cohorts, respectively, $p<0.001$).

The TBI cohort demonstrated higher prevalence of any diagnosed sleep disturbances both pre-index (14.1% vs. 9.4% pre-index ($p<0.001$) and post-index (27.9% vs 18.0%, $p<0.001$; Table 1). During the 12-months pre-index, insomnia and OSA were the two most commonly diagnosed sleep disturbances. Higher prevalences of both were observed in the TBI cohort: 6.3% vs. 3.8%, $p<0.001$ for insomnia and 6.4% vs. 4.8%, $p<0.001$ for OSA. During the 12 months post-index, insomnia (12.0% vs. 6.6%, $p<0.001$) and OSA (9.4% vs. 6.7%, $p<0.001$) were also the most commonly diagnosed sleep disturbances, with higher prevalences observed in the TBI cohort.

In order to evaluate differences between participants with and without TBI, we employed a DID approach. The DID estimator is equal to the change in the TBI cohort over time (i.e. from the pre- to the post-index period) compared to the change in the non-TBI cohort over the same period. Thus, it is interpreted as the change in risk of new sleep diagnoses caused by TBI. Prior to adjustment and accounting for differences between cohorts and the time trend, TBI increased risk of new insomnia diagnoses (RtR 1.09; 95% CI 1.02, 1.17) and new diagnoses of the composite any sleep disturbance (RtR 1.10; 95% CI 1.05, 1.16)(Table 2). Following adjustment and accounting for differences between cohorts and the time trend, (see Appendix for adjustment variables) increased risk of newly diagnosed insomnia (RtR 1.17; 95% CI 1.09, 1.26) and any newly diagnosed sleep disturbance (RtR 1.13; 95% CI 1.08, 1.19) remained significant. No other significant associations were observed.

Discussion

In the present analysis of a large national sample of older adults primarily insured through Medicare Advantage, newly diagnosed sleep disorders were common both before and after TBI. Relative to non-TBI controls, individuals who subsequently experienced TBI were more likely to be newly diagnosed with insomnia and OSA during the pre-index period. This is perhaps not surprising, as insomnia and OSA are the two most common sleep disorders and are highly comorbid among older adults.(Wickwire & Collop, 2010) These conditions are associated with a broad range of adverse health and economic consequences in addition to conferring risk for TBI.(Wickwire & Collop, 2010; Wickwire et al., 2018b) At the same time, we observed that development of new sleep disturbances was heightened following TBI. Relative to controls and after controlling for pre-index differences as well as multiple covariates, TBI was associated with increased risk of insomnia as well as any sleep disturbance during the 24-month follow-up period. Given the elevated prevalence of

insomnia among older adults(Albrecht, Wickwire, et al., 2019), these results suggest particular importance of insomnia-related sleep disturbances following TBI in this population. Indeed, as the most common sleep disorder among older adults and the most common sleep disorder following TBI, present results suggest that insomnia is an important, modifiable treatment target to enhance outcomes post-TBI among older adults.(Mathias & Alvaro, 2012; Wickwire et al., 2018a; Wickwire et al., 2016)

Higher prevalence of sleep disorders among individuals who eventually develop TBI is consistent with previous findings among Medicare fee-for-service beneficiaries. For example, our prior work has documented higher prevalences of neuropsychiatric disorders among individuals who subsequently experience a TBI.(Albrecht et al., 2015; Albrecht, Peters, Smith, & Rao, 2017) In this context, present results are perhaps not surprising given that sleep disorders are often comorbid with neuropsychiatric disorders such as depression, anxiety, and chronic pain. The influence of pre-TBI sleep disorders on risk of TBI and development of related sequelae among older adults should be explored in future research. Nonetheless, these novel data highlight the burden of sleep disorders post-TBI among older adults, expanding an important body of sleep-TBI research to the vulnerable older adult population.(Wickwire et al., 2018a; Wickwire et al., 2016) In addition, the comorbidity of sleep and neuropsychiatric disorders supports our use of the DID model to help disentangle the baseline propensity to have a higher sleep and neuropsychiatric burden following TBI.

At the same time, although our hypothesis that insomnia would increase following TBI was supported, we did not observe an increase in the risk of OSA, RLS, or hypersomnia. These disorders represent distinct pathologies, with both shared and divergent mechanistic underpinnings that may be impacted differently by TBI. It is also possible that the impact of TBI on sleep changes with age, which would help explain why present results differ from previous meta-analytic findings.(Mathias & Alvaro, 2012) As noted below, the sensitivity and specificity of our operational definitions of sleep disorders are unknown, and it is possible that our administrative approach lacked sensitivity to detect between-groups differences. Finally, given the significant differences in prevalence of pre-existing sleep disturbances between individuals with TBI and non-TBI controls, increased risk of OSA and hypersomnia following TBI reported in prior studies may have been due to confounding. (Mathias & Alvaro, 2012; Ouellet et al., 2015; Wickwire et al., 2018a; Wickwire et al., 2016)

Our results have clinical implications. Insomnia is the most common sleep disorder following TBI and associated with worsened outcomes.(Mathias & Alvaro, 2012; Mollaveya et al., 2017; Orff et al., 2009; Ouellet et al., 2015; Wickwire et al., 2018a; Wickwire et al., 2016) For these reasons and the availability of safe, effective treatments, sleep has been identified as a modifiable treatment target to enhance recovery from TBI.(Wickwire et al., 2018a; Wickwire et al., 2016) In this vein, it is important to understand that sleep complaints increase with age and are common among the elderly.(Ancoli-Israel, 2009) Present results thus highlight not only that insomnia and OSA are risk factors for TBI in the geriatric population but also that TBI causes insomnia, which is a known risk factor for adverse medical, psychiatric, and economic outcomes among older adults.(Cirelli, 2012; Orff et al.,

2009; Rao et al., 2008; Van Dongen et al., 2003; Wickwire et al., 2018a; Wickwire et al., 2019)

In terms of post-TBI insomnia, it is important to consider opportunities for treatment research. In other disease states, treatment of insomnia has been shown to improve health-related outcomes as well as quality of life.(Wickwire et al., 2018a; Wickwire et al., 2016) Although the FDA has approved multiple medications for treatment of insomnia, these medications are generally ill-advised among older adults due to unfavorable risk-benefit ratios.(Neubauer, Pandi-Perumal, Spence, Buttoo, & Monti, 2018; Panel, 2015) Indeed, data from our group and others demonstrates increased risk for falls, associated with the most common insomnia medications.(Tom, Wickwire, Park, & Albrecht, 2016) Furthermore, there has been limited evaluation of sleep medications among individuals with TBI, and a dearth of evidence is available to evaluate these medications among older adults with TBI. (Flanagan, Greenwald, & Wieber, 2007) As a result, non-pharmacological treatments such as cognitive-behavioral therapy for insomnia (CBTI), considered first-line treatments among older adults, should be evaluated for efficacy among older adults with TBI.(Buysse et al., 2011; Sivertsen et al., 2006). Similarly, newer insomnia medications (i.e., orexin receptor antagonists) warrant study, as they might present more favorable risk/benefit profiles among TBI patients.

To our knowledge, this is the first study to examine the risk for common sleep disorders among a cohort of older adults with TBI. Strengths of this study include a large national sample, three years of follow-up data, and use of the DID estimation method to reduce residual confounding. Nonetheless, this study has limitations that should be considered. Our dataset contained only the first diagnosis of each sleep disorder; thus, we could not confirm the duration, persistence, or remission of sleep complaints. Second, although our operational definition of sleep disorders relied on physician-assigned diagnoses, we were unable to confirm accuracy of these diagnoses or provide other clinical information of interest, such as objective or subjective measures of sleep, or severity of symptoms. Third, the study population comprises individuals insured primarily through Medicare Advantage, who are older with a higher burden of comorbidities compared to traditional fee-for-service Medicare.(Byhoff, Harris, & Ayanian, 2016) Thus, results may not generalize to all older adults.

In conclusion, in this large nationally representative cohort study of older adults, TBI increased risk of insomnia. Following TBI among older adults, screening and education on sleep disorders should be considered.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Conflicts of Interest and Source of Funding:

Dr. Albrecht was supported by AHRQ grant 1K01HS024560. Dr. Albrecht and Dr. Wickwire's institution has received research funding from the AASM Foundation, the Department of Defense, Merck, and ResMed. Dr. Wickwire has served as a scientific consultant for DayZz, Eisai, Merck, and Purdue, and is an equity shareholder in WellTap.

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Table 1.

Operational Definitions of Sleep Disorders

Disorder	Clinical Description	International Classification of Disease, Version 9 Codes
Hypersomnia	Pathological sleepiness and inability to stay awake that interferes with normal waking activities.	307.43, 307.44, 327.10, 327.11, 327.12, 327.13, 327.14, 327.15, 780.53, 780.54
Insomnia	Difficulty initiating or maintaining sleep, including early morning awakening, with associated daytime impairment.	307.41, 307.42, 307.49, 327.00, 327.01, 327.09, 780.51, 780.52, V69.4
Obstructive sleep apnea	A sleep-related breathing disorder involving repetitive collapse of the upper airway during sleep, causing oxyhemoglobin desaturation, cortical arousal, and increased sympathetic activity.	327.23, 327.24, 327.25, 780.57
Restless legs syndrome	Discomfort and irresistible urge to move the legs, particularly as bedtime approaches and/or when lying in bed.	333.94

Table 2.

Characteristics of Individuals Aged 65 and Older with a Diagnosis of Traumatic Brain Injury (TBI) Identified from OptumLabs Data Warehouse and Controls in 2008 to 2014, n=154,151

	TBI, n=78,044	No TBI, n=76,107	p-value
Age, mean(SD)	76.6 (6.1)	73.4 (5.8)	<0.001
Age categories, n(%)			<0.001
65–74	29,494 (37.8)	46,168 (60.7)	
75–84	43,041 (55.2)	27,458 (36.1)	
85+	5,509 (7.1)	2,481 (3.3)	
Sex, n(%)			<0.001
Male	27,422 (35.1)	33,634 (44.2)	
Female	50,622 (64.9)	42,473 (55.8)	
Race, n(%)			<0.001
White	60,307 (77.3)	57,958 (76.2)	
Black	8,332 (10.7)	8,364 (11.0)	
Hispanic	4,199 (5.4)	4,207 (5.5)	
Other	5,206 (6.7)	5,578 (7.3)	
Medicare, n(%)	62,818 (80.5)	58,826 (77.3)	<0.001
Comorbidities, n(%)			
ADRD ¹	10,111 (13.0)	2,473 (3.3)	<0.001
Anemia	8,471 (10.9)	4,456 (5.9)	<0.001
Anxiety	9,636 (12.4)	4,819 (6.3)	<0.001
Arthritis	29,265 (37.5)	19,387 (25.5)	<0.001
Atrial Fibrillation	12,621 (16.2)	5,625 (7.4)	<0.001
Chronic kidney disease	13,839 (17.7)	8,191 (10.8)	<0.001
COPD ²	14,018 (18.0)	9,017 (11.9)	<0.001
Depression	14,698 (18.8)	5,797 (7.6)	<0.001
Diabetes	24,635 (31.2)	19,201 (25.2)	<0.001
Heart Failure	10,762 (13.8)	4,566 (6.0)	<0.001
Hyperlipidemia	50,598 (64.8)	46,848 (61.6)	<0.001
Hypertension	59,643 (76.4)	49,905 (65.6)	<0.001
Ischemic Heart Disease	22,432 (28.7)	14,182 (18.6)	<0.001
Ischemic stroke	12,599 (16.1)	6,067 (8.0)	<0.001
Sleep diagnoses 12-Months pre-index, n(%)			
Any sleep disorder	10,975 (14.1)	7,153 (9.4)	<0.001
Hypersomnia	1,301 (1.7)	784 (1.0)	<0.001
Insomnia	4,943 (6.3)	2,900 (3.8)	<0.001
Obstructive sleep apnea	4,968 (6.4)	3,632 (4.8)	<0.001
Restless leg syndrome	1,307 (1.7)	631 (0.8)	<0.001
Sleep diagnoses 12-Months post-index, n(%)			
Any sleep disorder	17,695 (22.7)	10,745 (14.1)	<0.001
Hypersomnia	2,118 (2.7)	1,291 (1.7)	<0.001

	TBI, n=78,044	No TBI, n=76,107	p-value
Insomnia	9,349 (12.0)	5,017 (6.6)	<0.001
Obstructive sleep apnea	7,302 (9.4)	5,074 (6.7)	<0.001
Restless leg syndrome	2,291 (2.9)	1,048 (1.4)	<0.001

¹ Alzheimer's disease and related dementias;

² Chronic obstructive pulmonary disease

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Table 3.

Rate Ratios (95% Confidence Intervals) of the Association between Traumatic Brain Injury (TBI) and Newly Diagnosed Sleep Disorders over the 12 Months Pre- and Post-Index, n=154,151

	Hypersomnia	Insomnia	Restless Leg Syndrome	Obstructive Sleep Apnea	Any Sleep Disorder
<i>Unadjusted</i>					
TBI cohort vs. non-TBI cohort	1.62 (1.49, 1.78)	1.69 (1.61, 1.77)	2.03 (1.85, 2.23)	1.35 (1.29, 1.41)	1.55 (1.50, 1.59)
Non-TBI cohort post-index vs. pre-index	0.62 (0.56, 0.70)	0.76 (0.72, 0.81)	0.68 (0.60, 0.77)	0.40 (0.37, 0.42)	0.54 (0.52, 0.56)
TBI cohort post-index vs. Non-TBI cohort pre-index (DID) ¹	0.94 (0.82, 1.09)	1.09 (1.02, 1.17)	0.89 (0.76, 1.04)	1.02 (0.94, 1.11)	1.10 (1.05, 1.16)
<i>Adjusted²</i>					
TBI cohort vs. non-TBI cohort	1.27 (1.16, 1.39)	1.13 (1.07, 1.18)	1.37 (1.24, 1.51)	1.06 (1.01, 1.11)	1.30 (1.26, 1.34)
Non-TBI cohort post-index vs. pre-index	0.66 (0.59, 0.74)	0.93 (0.88, 0.99)	0.70 (0.62, 0.79)	0.56 (0.52, 0.59)	0.56 (0.54, 0.58)
TBI cohort post-index vs. Non-TBI cohort pre-index (DID)	0.96 (0.83, 1.11)	1.17 (1.08, 1.26)	0.93 (0.79, 1.08)	1.01 (0.93, 1.10)	1.13 (1.08, 1.19)

¹ Difference-in-difference estimator;

² adjustment variables for each model are listed in the Appendix