

# **HHS Public Access**

Author manuscript *J Head Trauma Rehabil*. Author manuscript; available in PMC 2023 January 01.

#### Published in final edited form as:

J Head Trauma Rehabil. 2022; 37(3): E186–E195. doi:10.1097/HTR.0000000000000703.

## Pre-Injury Health Status of Adults with Traumatic Brain Injury: A Preliminary Matched Case-Control Study

## Ashlyn M. Bulas,

Department of Rehabilitation & Human Performance, Icahn School of Medicine at Mount Sinai, New York, NY

## Lihua Li,

Department of Population Health Science and Policy, Icahn School of Medicine at Mount Sinai, New York, NY

## Raj G. Kumar,

Department of Rehabilitation & Human Performance, Icahn School of Medicine at Mount Sinai, New York, NY

## Madhu Mazumdar,

Department of Population Health Science and Policy, Icahn School of Medicine at Mount Sinai, New York, NY

## Andrea L. Rosso,

Department of Epidemiology, University of Pittsburgh Graduate School of Public Health, Pittsburgh, PA

## Ada O. Youk,

Department of Biostatistics, Department of Epidemiology, University of Pittsburgh Graduate School of Public Health, Pittsburgh, PA

## Kristen Dams-O'Connor

Department of Rehabilitation Medicine, Department of Neurology, Icahn School of Medicine at Mount Sinai, New York, NY

## Abstract

**OBJECTIVE:** To discern whether there is evidence that individuals who sustained a traumatic brain injury (TBI) had greater odds of pre-existing health conditions and/or poorer health behaviors compared to matched controls without TBI.

**SETTING:** Brain Injury Inpatient Rehabilitation Unit at Mount Sinai Hospital. Midlife in the United States (MIDUS) control data were collected via random-digit-dialing phone survey.

**PARTICIPANTS:** TBI cases were enrolled into the TBI Health Study and met at least one of four injury severity criteria: abnormal computed tomography scan, Glasgow Coma Scale score between

ashlyn.bulas@mountsinai.org .

Conflicts of Interests:

None. We acknowledge that no party involved in this manuscript and its results has or will benefit from associated organizations. We additionally certify all financial disclosures were mentioned on title page of manuscript.

3–12, loss of consciousness >30 minutes, or post-TBI amnesia longer than 24 hours. n=62 TBI cases and n=171 matched MIDUS controls were included in analyses; controls were excluded if they reported having a history of head injury.

DESIGN: Matched Case-Control Study.

**MAIN MEASURES:** Self-reported measures of depression symptoms, chronic pain, health status, alcohol use, smoking status, abuse of controlled substances, physical activity, physical health composite score, and behavioral health composite score.

**RESULTS:** Pre-index injury depression was nearly 4 times higher in TBI cases compared to matched controls (OR=3.98 [95% CI=1.71–9.27, p-value=0.001]). We found no significant differences in the odds of self-reporting 3 or more medical health conditions in year prior to index injury (OR=1.52 [95% CI=0.82–2.81, p-value=0.183]) or reporting more risky health behaviors (OR= 1.48 [95% CI=0.75–2.91, p-value=0.254]) in individuals with TBI compared to controls.

**CONCLUSION:** These preliminary findings suggest that odds of depression in the year prior to index injury far exceed those reported in matched controls. Further study in larger samples is required to better understand the relative odds of prior health problems in those who sustain a TBI, with a goal of elucidating the implications of pre-injury health on post-TBI disease burden.

#### Keywords

Brain Injuries; Traumatic; Adult; Neuropsychology; Rehabilitation; TBI; Pre-Injury; Data Analysis

#### Introduction

Traumatic brain injury (TBI) is a major public health concern with an estimated 5.3 million Americans living with TBI-related disabilities. TBI stems from a plethora of causes with varying levels of severity; most common causes include falling, being struck by an object, sports and military-related injuries.<sup>1</sup> Knowledge of TBI risk factors remains limited, and heterogeneity exists among adults who sustain a TBI concerning clinical representation and post-TBI disease progression.<sup>2,3</sup>

TBI can result in neurologic and physical impairments, which can be long-standing and drastically limit activities of daily living.<sup>3,4</sup> Over time, cognitive impairments can manifest in behavioral and mood changes, and even long-term neurodegenerative diseases like Alzheimer's and Parkinson's Disease.<sup>5,6</sup> Besides debilitating cognitive impairments, severe TBI cases can result in long-term physical disabilities including, but are not limited to post-traumatic stress disorder (PTSD), substance abuse, depression, hypertension, visual problems, and general decline in physical motility.<sup>7</sup> The prevalence of prolonged cognitive and multi-system physical health problems post-TBI has contributed to a shift in the field's conceptualization of TBI from an injury event to a disease process. Leaders in the field have begun to think about TBI as an evolving condition that may be disease causative and/or disease accelerative.<sup>8</sup> Much of the research supporting the conceptualization of TBI as a chronic disease comes from cohort studies without comparison groups, and the presence of pre-injury health problems is seldom considered. As such, it remains unknown whether or

to what extent the elevated rates of cognitive and physical health problems described in TBI survivors may be reflective of pre-existing disease processes.<sup>3,7</sup>

Determining whether individuals who sustain a TBI have poorer health pre-injury relative to their uninjured counterparts is foundational to quantifying whether and how TBI may exacerbate pre-existing health problems, or initiate new ones. Certain prior health conditions may predispose an individual to be at a greater risk for a TBI. For example, poor physical health and clinical frailty may lead to falls and have been associated with increased risk for TBI.<sup>9,10</sup> In addition, certain behavioral risk factors like illicit drug use and excessive alcohol consumption are associated with higher rates of accidents and falls, which may increase the likelihood of sustaining a TBI.<sup>11,12</sup> The ability to identify modifiable pre-injury risk factors for sustaining a TBI could drastically reduce the substantial societal and public health burden attributed to TBIs. Furthermore, the same pre-injury conditions that increase TBI risk may interact with injury-related pathology to influence post-TBI course by accelerating cognitive and physical decline.

In this preliminary study, we attempt to better understand whether individuals sustaining a TBI have certain health risk factors in the year prior to index injury that may increase their odds for sustaining a TBI. This understanding will help inform upon whether post-TBI health and disease progression is related to a pre-existing disease process, or if TBI initiates a cascade of events leading to poor long-term health consequences. We conducted a demographically-matched historical case-control study (1:3 matching ratio) using existing data from a national health survey and harmonized exposure question data with our TBI cohort to test the hypothesis that adults who sustain a TBI have poorer health status and riskier health behaviors in the year *prior to* injury compared to their uninjured counterparts.

## Methods

#### Samples

**Individuals with TBI**—We recruited 87 individuals with TBI via the TBI Health Study conducted at the brain injury inpatient rehabilitation unit at Mount Sinai Hospital from 2012 to 2017. To be eligible for the TBI Health Study, individuals with TBI must meet one of four criteria: an abnormal computed tomography (CT) scan consistent with TBI pathology, post-resuscitation Glasgow Coma Scale (GCS) score between 3–12, loss of consciousness (LOC) >30 minutes, or post-TBI amnesia (PTA) longer than 24 hours.<sup>13</sup> Inclusion criteria are intended to create a study sample of individuals who sustained a complicated mild, moderate, or severe TBI; mild TBI cases did not meet study inclusion criteria.

All participants who enrolled into the TBI Health Study were above the age of 40 at the time of injury and consented to study participation. We collected data via in-person and phone interviews with the individual who sustained the TBI. In cases where the patient with TBI was unable to complete a subset of questions, we collected information from a close family member familiar with the patient's medical history. In the TBI sample only, we assessed TBI exposure, mechanisms and severity via the Brain Injury Screening Questionnaire (BISQ). The BISQ is a 20-item questionnaire that uses contextual and etiological cues to facilitate recall of injuries to the head, presence and duration of a loss of consciousness and mental

status (feelings of being "dazed and confused").<sup>14</sup> Due to missing data for key exposure information, the sample was reduced to 64 individuals with TBI prior to applying the matching protocol. A majority of individuals with TBI showed an abnormal computed tomography (CT) scan positive for TBI pathology (87.1%). Four cases had normal CT scans but scored between a 3–12 on the Glasgow Coma Scale indicating a moderate to severe TBI.<sup>15</sup> 48.8% were classified as complicated mild TBI cases by having abnormal CT scan with TBI pathology but only mild/no concussive symptoms and no post-traumatic amnesia.<sup>16</sup>

**Non-TBI Controls**—We extracted non-TBI controls from the Midlife in the United States (MIDUS) II and MIDUS Refresher cohorts, which are longitudinal, random-digit-dialing follow-up studies of the original MIDUS study of cognitive aging in mid-life. The initial MIDUS cohort included non-institutionalized, English-speaking adults aged 24–74 years residing in the contiguous United States (n=7,108), and data were from 1995–1996.<sup>17</sup> The MIDUS II study was initiated in 2004 to reassess baseline questionnaires and conduct cognitive assessments on the original cohort, now aged 35 to 86 years (n=4,963).<sup>18</sup> The MIDUS Refresher study recruited new participants (n=3,577) from 2011–2014, with an emphasis of younger and more racially diverse sample, who completed similar assessments and questionnaires to MIDUS II. The average response rate (adjusted for individuals who died) was 86%, thus compiling a comprehensive and representative cohort of adults throughout the United States. Metropolitan populations were oversampled to increase racial, ethnic, and geographic representativeness.<sup>18</sup>

For this study, we identified matched non-TBI controls from both MIDUS II and MIDUS Refresher cohorts. If the MIDUS participant reported 'Yes' to having a 'history of serious head injury', they were excluded as controls (n=306). Each TBI case was matched with up to three control participants based on the following demographic variables: age (caliper width  $\pm/-5$  years), sex, education, employment, and race.<sup>19</sup>

#### Past Year/Pre-Injury Health Measures

During data collection, we utilized questions from the MIDUS questionnaire about participant health status and lifestyle in the year prior, as well as at the time of admission. The statement "...*prior to injury*" was added by Mount Sinai researchers to the Health Questionnaires for the TBI Health Study to assess health prior to the index TBI.<sup>13</sup> Because both the TBI Health Study and the MIDUS studies used identical structured interview questions, we harmonized all item-level exposure data to allow direct comparisons between TBI population and controls by ensuring all demographic and past year health measures coding aligned. Figure 1 illustrates study timeline and exposure/outcome assessment schedule for both cases and controls.

**Physical Health Composite Score**—In both the TBI Health Study and MIDUS Study, participants endorsed either: 1=yes or 0=no for "being treated for any of the following [30 conditions] in the year prior [to injury]." We generated a single-item, physical health composite score by summing individual health condition responses.<sup>17,18,20</sup> Physical health

composite score was assessed as a dichotomous variables, endorsing '3 or more' medical health conditions or 'less than 3' conditions.<sup>21</sup>

**Behavioral Health Risk Factors**—We queried four behavioral health risk factors in the prior year, each coded as binary variables (Yes/No): alcohol use, cigarette smoking, physical inactivity, and substance use, defining each by an affirmative response to the following items. We defined the *'Alcohol Use'* as "having alcohol related problems during the past 12 months."<sup>22</sup> The *'Smoking Status'* variable was defined by "smoking cigarettes regularly during the past 12 months." We defined the *'Substance Use'* as "any use of drugs or medications without a doctor's prescriptions, in larger amounts than prescribed, or for a longer period during the past 12 months." Examples of substances in the MIDUS questionnaire included: sleeping pills, amphetamines, marijuana, hallucinogens, and heroin. <sup>17,18</sup> Consistent with prior work, a 'Physically Active' individual was defined as "engaging in vigorous and/or moderate physical activity several times a week at a paid job, while performing chores in and around home, and/or during leisure or free time."<sup>23,24</sup> The 'Physical Inactivity' variable was reverse scored such that 0=indicated *no* physical *inactivity* and 1=indicated physical *inactivity*.

We created a behavioral risk factor composite score consisting of all four of these health behaviors: 'Alcohol Use', 'Smoking Status', 'Substance Use' and 'Physical Inactivity.' The composite score ranged from 0–4: 0, indicating no risky health behaviors and 4, indicating endorsement of all 4 risky health behaviors.<sup>24</sup> The behavioral health composite score was assessed as a dichotomous variable: endorsing at least one of the risky health behaviors above, or endorsing none. The utilization of the behavioral health composite score avoided multiple analyses and splitting p-values among risky health behaviors.

Additional Past 12 Months Health Measures—We assessed 'Self-Reported Physical Health' in the year prior to injury on a 5-point Likert Scale ranging from poor to excellent. Responses were assessed on an ordinal level then re-categorized as a binary variable, 'excellent/very good/good' and 'fair/poor.' Additionally, we queried 'Self-Reported Chronic Pain' during the past 12 months as a binary (Yes/No) exposure defined as 'pain that persisted beyond the time of normal healing and has lasted anywhere from a few months to many years.' Lastly, to further assess whether depression alone was a risk factor for TBI, we assessed 'Self-Reported Depressive Symptoms' as 'during the past 12 months, was there ever a time when you felt sad, blue, or depressive Symptoms' if they responded 'Yes' or 'I did not feel depressed because I was on anti-depressant medication' for the above question.

#### Study Variables

Sociodemographic covariates included age, sex, race (Caucasian, African-American, other), employment (employed/working for pay or unemployed), and education (less than high school, high school, some college, and college degree). While not included as covariates for matching, Spanish ethnicity, marital status, TBI severity frequencies were assessed within study population. Primary predictor variables were all self-reported and included: health

status, chronic pain, depressive symptoms, excessive alcohol use, smoking status, substance abuse, physical inactivity, physical health composite score, and behavioral health composite score.

#### **Statistical Analyses**

The specific method of matching used between TBI cases and controls was a 'greedy matching,' or nearest neighbor matching without replacement. The greedy matching algorithm found the closest control for each TBI case, which produced a matched sample with balanced distribution of the demographic covariates across the two groups.<sup>19</sup> We performed descriptive analyses on all demographic and outcome variables to assess variable distribution and to describe both cases and controls. To assess the balance of variables after matching, standardized differences were reported, and the variables with differences >10% were considered for further adjustment in the model. <sup>25,26</sup>

We performed conditional logistic regression analyses for primary and secondary exposures and reported odds ratio (OR) with 95% confidence intervals (CI). We compared the frequencies of prior year exposure to behavioral and physical health risk factors in cases (i.e., those with TBI) and controls to determine the relationship between these exposures and TBI case status.<sup>27</sup> ORs were estimated to assess the odds of prior year physical health and behavioral exposure in TBI cases compared to matched controls.<sup>28</sup> Models were conditional on the matched strata. We conducted subgroup analyses by age and sex to examine if the association differed among pre-specified subgroups. Subgroup analyses by age were stratified as >=65 years and <65 years at the time of interview.<sup>4</sup> We considered a *p-value*<0.05 to be statistically significant for both physical and behavioral health risk factor domains.<sup>29</sup>

All statistical analyses were performed using SAS enterprise guide SAS Enterprise Guide (version 7.1, SAS Institute Inc, Cary, NC) and SAS 9.4.

## Results

We matched 62 patients with TBI to 1–3 controls, (96.9% matching rate). The final cohort included 62 individuals with TBI and 171 matched MIDUS controls (See Figure 2).

Table 1 presents the overall demographic characteristics of the TBI cases and non-TBI controls after matching. The standardized difference in age was greater than 10% (0.18 for mean and 0.16 for median). The standardized differences post-matching for sex, race, employment, and education were all less than 10%.<sup>26</sup>

Table 1 shows the proportions and balance of the self-reported past-year health and behavioral outcomes in the TBI and non-TBI samples after matching. A majority of cases (80.7%) and controls (84.1%) reported their previous years' health status as good-excellent. A smaller proportion of those with TBI reported chronic pain in the year prior (17.7%) compared to those without a TBI (33.3%). A higher proportion of individuals with TBI reported depressive symptoms in the year prior compared to the controls (27.4% versus

9.9%). There were higher proportions of individuals reporting excessive alcohol use, current smoking status, and substance abuse in the TBI sample, as seen in Table 1.

To illustrate results of the primary analyses, Table 2 shows the results of the conditional logistic regression while accounting for matched pairs. We found the odds of having prior-year depressive symptoms was roughly four times higher in TBI cases compared to matched controls (OR=4.16 [95% CI=1.79–9.67, p=0.001]). The odds of having the remaining health and behavioral health risk factors in the past year did not significantly differ between TBI cases and controls, though it should be noted that several odds ratios (e.g., past year alcohol use, smoking, and abuse of illegal substances) suggested greater odds in the TBI group.

The results of sub-group analyses for each analytic outcome, stratified by sex and age (>=65 years or <65 years), are reported in Table 3. The odds of having prior year, preindex injury depressive symptoms was significantly higher in male TBI cases versus male controls (OR=7.31 [95% CI=2.39-22.30, p-value=<0.001]) but not in females (OR=1.62 [95% CI=0.42–6.27, p=0.459]). Remaining differences in pre-injury health status by sex did not reach statistical significance, but nonetheless warrant mention in this preliminary study. When stratified by age, the odds of having prior year, pre-index injury exposure of depressive symptoms was 7.32 times higher in TBI cases >=65 years compared to controls >=65 years (OR=7.32 [95% CI=2.02-26.52, p-value=0.003]), but the odds were not significantly different in those below the age of 65 (OR=2.38 [95% CI=0.74-7.72, p-value=0.148]). The odds of reporting prior year excessive alcohol use was 6.58 times higher in TBI cases >= 65 years compared to individuals >=65 without TBI (OR=6.58 [95% CI=1.17-37.1, p-value=0.033] vs OR=0.82 [95% CI=0.17-3.97, p-value=0.808] in the younger subgroup). Finally, the odds of smoking regularly in the year prior to injury was 4.29 higher in TBI cases >=65 years old compared to controls >=65 years old (OR=4.29) [95% CI=1.03–17.98, p-value=0.0462]). No remaining subgroup analyses of the behavioral health risk factors yielded significant differences between TBI cases and controls.

## Discussion

The current preliminary study complements the accumulating evidence of elevated post-TBI disease burden by investigating whether and what types of health conditions were already higher before the injury among those who sustain a TBI, relative to their uninjured counterparts. Our largely null findings suggest that, with the notable exception of past-year depression, adults who sustain a TBI do not differ markedly in past year health compared to individuals who do not sustain a TBI. When considered in context of existing literature reporting high post-TBI disease burden, the current findings may suggest that many post-TBI health conditions do not simply reflect premorbid differences.

However, the current findings should be considered in context of the study's small sample. While our preliminary study contributes important information to the conceptualization of post-TBI disease burden, we acknowledge that the limitation of small TBI case sample size leads to a higher likelihood of Type 2 error and lack of power to detect the significance of effect size estimates. There is some indication that odds of prior year alcohol use, smoking, and abuse of illicit substances were also greater in the TBI sample, particularly those over

age 65; in a larger sample these differences may have reached statistical significance. Odds of self-reported poor health status and odds of reporting more than 3 health conditions are somewhat higher in cases, particularly those under age 65. Of potential interest is the trend toward lower odds of self-reported chronic pain in the TBI group, which is surprising given that chronic pain is one of the most commonly reported problems among TBI survivors and prevalence in some subgroups of TBI survivors is nearly double that of their uninjured peers.<sup>30</sup> In any case, the current results and their implications should be interpreted as preliminary. One of our greatest study strengths was the utilization of a well-established TBI case definition based on inpatient rehabilitation severity criterion and the use of incident TBI diagnoses to accurately classify cases and injury timeline.<sup>13</sup> Nonetheless, this strict study inclusion criterion limited our pool of eligible TBI cases since mild TBI cases do not usually receive inpatient rehabilitation services, and thus would not be considered for the TBI Health Study.

Concerning our preliminary results, when matched on age, sex, race, education, and employment, the odds of having depressive symptoms in the year prior to injury for cases with TBI was roughly four times higher compared to non-TBI controls. Previous literature has shown that individuals who sustained a TBI have higher rates of depressive symptoms compared to the general population.<sup>5</sup> Approximately half of all people with TBI report depressive symptoms one-year post-TBI, which are often attributed to both the neurophysiological changes within the brain and the emotional response to TBI-related disability.<sup>2,31,32</sup> Current findings suggest that a pre-injury history of depressive symptoms may contribute to high rates of depression in this group. Odds of pre-injury depressive symptoms were particularly high among males and those over age 65, consistent with prior research identifying depression as a significant risk factor for late-life TBL<sup>10</sup> The current findings may also help identify individuals with increased odds of sustaining a TBI; namely, those with depressive symptoms and/or undergoing treatment for depression (particularly among males and adults over age 65), and older adults who engage in excessive alcohol use or cigarette smoking. Previous work has shown that older adults with depression have higher incident and overall frailty as measured by a short performance physical battery.<sup>10,31</sup> The higher rates of frailty in older individuals with depression can lead to an increased risk for injurious falls that could potentially result in a TBI. Current findings of elevated odds of past-year alcohol use among those with TBI age 65 coincide with previous literature showing that excessive alcohol use is associated with higher rates of injurious falls that may result in more injuries to the head.<sup>12</sup>

There are some additional limitations to this study beyond sample size and low power which warrant consideration. The TBI Health Study was limited to those who received acute inpatient rehabilitative care for TBI so findings may not generalize to those who do not seek or require extensive medical treatment. Further, methods for selection into the MIDUS study differed from that of our study; in particular MIDUS recruitment was not related to an index event. TBI case selection depended on an index TBI event and in-patient care, thus leading to an increased likelihood of capturing prior-year exposures in cases relative to controls. Additionally, while MIDUS participants who reported a 'history of serious head injury' were excluded from the study, we cannot guarantee that all MIDUS controls included in the analyses never experienced a TBI. This non-differential misclassification makes the

direction of bias towards the null. The retrospective study design of both our TBI Health Study and MIDUS Study are subject to recall bias in the reporting of prior year health conditions, and post-TBI cognitive impairment may result in under-reporting of pre-injury health conditions and behaviors and thereby contribute to the null findings between TBI cases and controls.<sup>33</sup> For TBI cases, approximately 35.5% of case responses were provided by a proxy informant, and 9.7% used a combination of proxy and self-reporting methods; proxy report may differ in accuracy from self-report.<sup>34</sup> Finally, because we only matched TBI cases to controls based on age, sex, race, employment, and education, there may be unmeasured confounding from covariates on which groups were not matched.

There are several important strengths to the design of this study. By using the same questionnaires in the TBI Health Study as those utilized in the MIDUS Health Questionnaires (adding only the "prior to injury" clause), we were able to readily harmonize data from TBI cases and controls for direct comparison. And as mentioned above, our definition of TBI was based on inpatient rehabilitation and their validated TBI severity indices, thus ensuring accurate TBI case classification. Likewise, the use of random population controls instead of hospital or deceased individuals reduced the amount of Berkson's selection bias, or bias from hospital-based control sampling.<sup>35</sup> Demographically-matched TBI cases and controls ensured the two groups were similar, allowing for a more robust estimate of association of prior year health conditions and sustaining a TBI.

The current findings should be investigated for replicability in a larger study. It is possible that some of the null findings may become significant with a larger sample, which would lend support to the idea that at least some post-TBI behavioral problems are reflective of pre-injury health status. In particular, the odds of having certain behavioral health conditions, particularly substance use, are higher in the year prior to injury among those with TBI compared to uninjured counterparts but did not reach the threshold for statistical significance in the present study. High rates of substance use prior to TBI have in fact been well documented in the literature.<sup>30,36</sup> Additionally, future research in larger samples might consider matching on additional factors such as ethnicity and marital status, and also be better suited to investigate the individual components of the health summary and composite scores used herein, which may provide more insight on specific health conditions and their relationship to sustaining a TBI. Certain behavioral health conditions like physical inactivity were dichotomized to fit the logistic regression model, but assessing these risk factors on multiple levels may yield more granular estimates.

In summary, we found higher odds of pre-injury depressive symptoms among individuals who sustain a TBI compared to matched, non-TBI controls. Older individuals and males who sustain a TBI have particularly elevated odds of prior year depressive symptoms. Previous literature documenting elevated disease burden among individuals with TBI has suggested that TBI is disease causative and/or disease accelerative, but it is important to consider whether these observed differences may simply reflect a continuation of elevated pre-injury health conditions.<sup>37</sup> Although individuals with TBI in the current study were not significantly more likely to report medical health problems in the past year relative to controls, observed trends of greater behavioral health problems among those with TBI warrant further study in larger samples with more detailed characterization of other

potentially relevant behavioral risk factors like sleeping habits, diet, sexual health, and health management practices. The current findings may help inform secondary and primary TBI prevention methods to reduce the enormous individual and population-level economic and public health burden of TBI.

## Acknowledgements:

Disclosures:

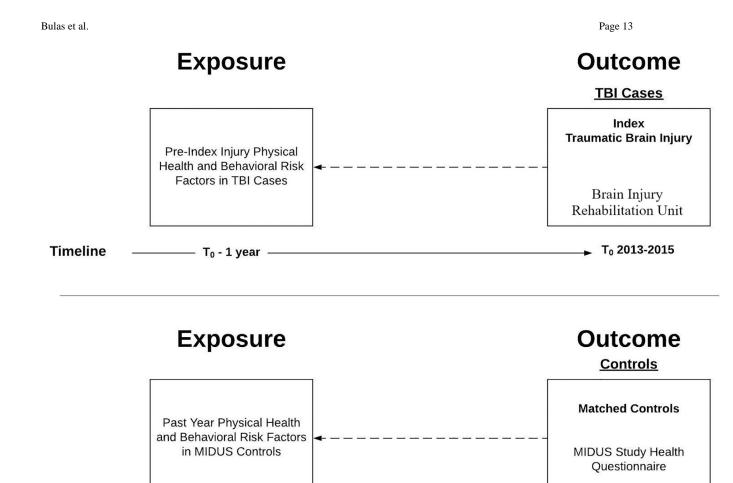
Contents of this manuscript were developed under a grant from Center for Disease Control and Prevention (CDC) to Dr. Kristen Dams-O'Connor at the Icahn School of Medicine (Award Number: 5 U49 CE002092-05). Matters within this manuscript do not necessarily represent CDC policy, nor should one assume endorsement by the Federal Government.

## References

- Faul MXL, Wald MW, Coronado VG. Traumatic brain injury in the united states: Emergency department visits, hospitalizations, and deaths 2002 – 2006. In: Centers for Disease Control and Prevention NCfIPaC, ed2010.
- Marquez de la Plata CD, Hart T, Hammond FM, et al. Impact of age on long-term recovery from traumatic brain injury. Archives of physical medicine and rehabilitation. 2008;89(5):896–903. [PubMed: 18452739]
- Breed S, Sacks A, Ashman TA, Gordon WA, Dahlman K, Spielman L. Cognitive functioning among individuals with traumatic brain injury, Alzheimer's disease, and no cognitive impairments. The Journal of head trauma rehabilitation. 2008;23(3):149–157. [PubMed: 18520427]
- 4. Breed ST, Flanagan SR, Watson KR. The relationship between age and the self-report of health symptoms in persons with traumatic brain injury. Archives of physical medicine and rehabilitation. 2004;85(4 Suppl 2):S61–67. [PubMed: 15083423]
- 5. Rehabilitation of persons with traumatic brain injury. NIH consensus statement. 1998;16(1):1-41.
- 6. Health IoMCoGWA. Psychiatric outcomes. In: Health GWa, ed2009:256.
- Saatman KE, Duhaime AC, Bullock R, Maas AI, Valadka A, Manley GT. Classification of traumatic brain injury for targeted therapies. Journal of neurotrauma. 2008;25(7):719–738. [PubMed: 18627252]
- Wilson L, Stewart W, Dams-O'Connor K, et al. The chronic and evolving neurological consequences of traumatic brain injury. The Lancet Neurology. 2017;16(10):813–825. [PubMed: 28920887]
- Park E, Bell JD, Baker AJ. Traumatic brain injury: can the consequences be stopped? CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 2008;178(9):1163–1170.
- Dams-O'Connor K, Gibbons LE, Landau A, Larson EB, Crane PK. Health Problems Precede Traumatic Brain Injury in Older Adults. Journal of the American Geriatrics Society. 2016;64(4):844–848. [PubMed: 26925541]
- Ek S, Rizzuto D, Fratiglioni L, et al. Risk Factors for Injurious Falls in Older Adults: The Role of Sex and Length of Follow-Up. Journal of the American Geriatrics Society. 2019;67(2):246–253. [PubMed: 30496601]
- Chen CM, Yoon YH. Usual Alcohol Consumption and Risks for Nonfatal Fall Injuries in the United States: Results From the 2004–2013 National Health Interview Survey. Substance use & misuse. 2017;52(9):1120–1132. [PubMed: 28524713]
- Dams-O'Connor K R2: TBI and Health in Older Adults: An Exploratory Study. In: Center for Disease Control and Prevention; 2012–2017.
- Dams-O'Connor K, Cantor JB, Brown M, Dijkers MP, Spielman LA, Gordon WA. Screening for traumatic brain injury: findings and public health implications. The Journal of head trauma rehabilitation. 2014;29(6):479–489. [PubMed: 25370440]

- Jain STG, Iverson LM. Glasgow Coma Scale. 2019; https://www.ncbi.nlm.nih.gov/books/ NBK513298/.
- 16. Lingsma HF, Yue JK, Maas AI, Steyerberg EW, Manley GT. Outcome prediction after mild and complicated mild traumatic brain injury: external validation of existing models and identification of new predictors using the TRACK-TBI pilot study. Journal of neurotrauma. 2015;32(2):83–94. [PubMed: 25025611]
- 17. Ryff C, Almeida DM, Ayanian J, et al. Midlife in the United States (MIDUS 2), 2004–2006. In: Inter-university Consortium for Political and Social Research [distributor]; 2017.
- Ryff C, Almeida D, Ayanian J, et al. Midlife in the United States (MIDUS Refresher), 2011–2014. In: Inter-university Consortium for Political and Social Research [distributor]; 2017.
- Austin PC. A comparison of 12 algorithms for matching on the propensity score. Statistics in medicine. 2014;33(6):1057–1069. [PubMed: 24123228]
- Marmot M, Ryff CD, Bumpass LL, Shipley M, Marks NF. Social inequalities in health: next questions and converging evidence. Social science & medicine (1982). 1997;44(6):901–910. [PubMed: 9080570]
- 21. Piazza JR, Charles ST, Almeida DM. Living With Chronic Health Conditions: Age Differences in Affective Well-Being. The Journals of Gerontology: Series B. 2007;62(6):P313–P321.
- Grzywacz JG, Marks NF. Family solidarity and health behaviors: Evidence from the National Survey of Midlife Development in the United States. Journal of Family Issues. 1999;20(2):243– 268.
- Fine LJ, Philogene GS, Gramling R, Coups EJ, Sinha S. Prevalence of multiple chronic disease risk factors. 2001 National Health Interview Survey. American journal of preventive medicine. 2004;27(2 Suppl):18–24. [PubMed: 15275670]
- 24. Linardakis M, Papadaki A, Smpokos E, Micheli K, Vozikaki M, Philalithis A. Association of Behavioral Risk Factors for Chronic Diseases With Physical and Mental Health in European Adults Aged 50 Years or Older, 2004–2005. Preventing chronic disease. 2015;12:E149. [PubMed: 26378895]
- Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Statistics in medicine. 2009;28(25):3083– 3107. [PubMed: 19757444]
- 26. Austin PC. Using the Standardized Difference to Compare the Prevalence of a Binary Variable Between Two Groups in Observational Research. Communications in Statistics - Simulation and Computation. 2009;38(6):1228–1234.
- Kuo CL, Duan Y, Grady J. Unconditional or Conditional Logistic Regression Model for Age-Matched Case-Control Data? Frontiers in public health. 2018;6:57. [PubMed: 29552553]
- 28. Pearce N Analysis of matched case-control studies. BMJ (Clinical research ed). 2016;352:i969.
- 29. Benjamini Y, Hochberg Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. Journal of the Royal Statistical Society Series B (Methodological). 1995;57(1):289–300.
- Adams RS, Corrigan JD, Dams-O'Connor K. Opioid Use among Individuals with Traumatic Brain Injury: A Perfect Storm? J Neurotrauma. 2020 Jan 1;37(1):211–216. doi: 10.1089/neu.2019.6451. Epub 2019 Aug 16. PMID: 31333067; PMCID: PMC7364315. [PubMed: 31333067]
- Soysal P, Veronese N, Thompson T, et al. Relationship between depression and frailty in older adults: A systematic review and meta-analysis. Ageing research reviews. 2017;36:78–87. [PubMed: 28366616]
- Albrecht JS, Barbour L, Abariga SA, Rao V, Perfetto EM. Risk of Depression after Traumatic Brain Injury in a Large National Sample. Journal of neurotrauma. 2019;36(2):300–307. [PubMed: 29808770]
- 33. Silverberg ND, Iverson GL, Brubacher JR, Holland E, Hoshino LC, Aquino A, Lange RT. The Nature and Clinical Significance of Preinjury Recall Bias Following Mild Traumatic Brain Injury. J Head Trauma Rehabil. 2016 Nov/Dec; 31(6):388–396. doi: 10.1097/HTR.000000000000198. PMID: 26580693. [PubMed: 26580693]

- Cusick CP, Gerhart KA, Mellick DC. Participant-proxy reliability in traumatic brain injury outcome research. J Head Trauma Rehabil. 2000 Feb;15(1):739–49. doi: 10.1097/00001199-200002000-00012. PMID: 10745189. [PubMed: 10745189]
- 35. Feinstein AR, Walter SD, Horwitz RI. An analysis of Berkson's bias in case-control studies. Journal of chronic diseases. 1986;39(7):495–504. [PubMed: 3722313]
- Corrigan JD, Bogner J, Holloman C. Lifetime history of traumatic brain injury among persons with substance use disorders. Brain Inj. 2012;26(2):139–50. doi: 10.3109/02699052.2011.648705. PMID: 22360520. [PubMed: 22360520]
- Masel BE, DeWitt DS. Traumatic brain injury: a disease process, not an event. J Neurotrauma. 2010 Aug;27(8):1529–40. doi: 10.1089/neu.2010.1358. PMID: 20504161. [PubMed: 20504161]



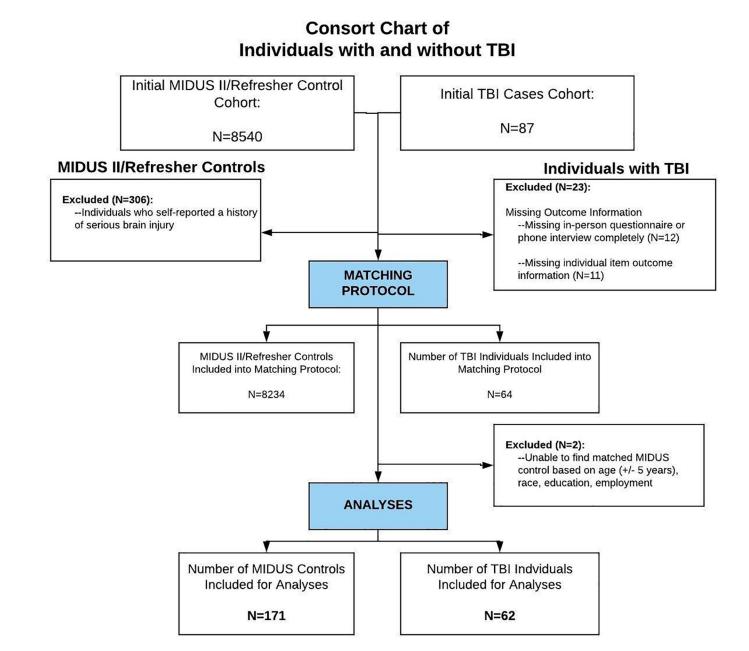
#### Timeline

#### Figure 1.

— T<sub>0</sub> - 1 year —

Study timeline of risk factor and outcome assessment of individuals with traumatic brain injury compared to matched controls in year prior to index date.

► T<sub>0</sub> 1994-2014



#### Figure 2.

Consort chart of individuals with and without traumatic brain injuries used for matching protocol and final analyses. For analyses, n=62 cases and n=171 controls were retained.

#### Table 1:

Demographic Characteristics and Self-Report Exposures of Matched Individuals with and without Traumatic Brain Injury at Baseline (n=233).

Participants Demographic Characteristics and Self- Reported Exposures	Total n=233	TBI n=62	No TBI n=171	Standardized Differences (Absolute Value)
Age <sup>*</sup>				
Mean ± SD	65.62±12.17	66.53±12.81	65.30±11.95	0.18 **
Median (IQR)	68 (58–75)	69 (59–75)	68 (58–74)	0.16**
Sex *				
Male	160 (68.7%)	42 (67.7%)	118 (69.0%)	0.03
Female	73 (31.3%)	20 (32.3%)	53 (31.0%)	0.03
Race <sup>*</sup>				
Caucasian	177 (76.0%)	47 (75.8%)	130 (76.0%)	0.01
African-American	23 (9.9%)	6 (9.7%)	17 (9.9%)	0.01
Other	33 (14.2%)	9 (14.5%)	24 (14.0%)	0.01
Employment *				
Employed	120 (51.5%)	30 (48.4%)	90 (52.6%)	0.08
Unemployed	113 (48.5%)	32 (51.6%)	81 (47.4%)	0.08
Education *				
<high school<="" td=""><td>23 (9.9%)</td><td>6 (9.7%)</td><td>17 (9.9%)</td><td>0.01</td></high>	23 (9.9%)	6 (9.7%)	17 (9.9%)	0.01
High School	35 (15.0%)	9 (14.5%)	26 (15.2%)	0.02
Some College	26 (11.2%)	7 (11.3%)	19 (11.1%)	0.01
College Degree	149 (63.9%)	40 (64.5%)	109 (63.7%)	0.02
Marital Status				
Married	148 (63.5%)	36 (58.1%)	112 (65.5%)	0.15
Separated	5 (2.1%)	2 (3.2%)	3 (1.8%)	0.09
Divorced	22 (9.4%)	2 (3.2%)	20 (11.7%)	0.33
Widowed	31 (13.3%)	9 (21.0%)	22 (12.9%)	0.05
Never Married	26 (11.2%)	13 (21.0%)	13 (7.6%)	0.39
Missing	1 (0.4%)	2 (3.2%)	1 (0.6%)	0.11
Spanish Ethnicity				
Yes	19 (8.2%)	10 (16.1%)	9 (5.3%)	0.36
No	212 (91.0%)	50 (80.6%)	162 (94.7%)	0.44
Missing	2 (0.9%)	2 (3.2%)	0 (0.00%)	0.26
TBI Severity				
Mild/Complicated Mild		30 (48.4%)		
Moderate/Severe		32 (51.6%)		
$LOC^{+} = <30$ minutes		10 (16.1%)		
$LOC^{+}>30$ minutes		15 (24.2%)		
$PTA^{++} >= 24$ hours		22 (35.5%)		

Participants Demographic Characteristics and Self- Reported Exposures	Total n=233	TBI n=62	No TBI n=171	Standardized Differences (Absolute Value)
Health Status				
Fair/Poor	38 (16.3%)	11 (17.7%)	27 (15.7%)	0.11
Excellent/Very Good	194 (83.3%)	50 (80.7%)	144 (84.1%)	0.28
Missing	1 (0.4%)	1 (1.6%)	0 (0.00%)	0.18
Chronic Pain				
Yes	68 (29.2%)	11 (17.7%)	57 (33.3%)	0.36
No	164 (70.4%)	50 (80.6%)	114 (66.7%)	0.32
Missing	1 (0.4%)	1 (1.6%)	0 (0.00%)	0.18
Depressive Symptoms				
Yes	34 (14.6%)	17 (27.4%)	17 (9.9%)	0.46
No	198 (85.0%)	44 (71.0%)	154 (90.1%)	0.50
Missing	1 (0.4%)	1 (1.6%)	0 (0.00%)	0.18
Physical Health Composite				
<3 Conditions	129 (55.4%)	29 (46.7%)	100 (58.5%)	0.24
>=3 Conditions	104 (44.6%)	42 (53.3%)	71 (41.5%)	0.24
Behavioral Health Composite				
0	85 (36.5%)	19 (30.6%)	66 (38.6%)	0.17
>=1	148 (63.5%)	43 (69.4%)	105 (61.4%)	0.01
Excessive Alcohol Use				
Yes	17 (7.3%)	7 (11.3%)	10 (5.9%)	0.19
No	216 (92.7%)	55 (88.7%)	161 (94.2%)	0.20
Currently Smoking				
Yes	19 (8.2%)	7 (11.3%)	12 (7.0%)	0.15
No	214 (91.8%)	55 (88.7%)	159 (93.0%)	0.15
Substance Abuse				
Yes	24 (10.3%)	9 (14.5%)	15 (8.8%)	0.21
No	209 (89.7%)	53 (85.5%)	156 (91.2%)	0.18
Physical Inactivity				
Yes	123 (52.8%)	33 (53.3%)	90 (52.6%)	0.01
No	110 (47.2%)	29 (46.8%)	81 (47.4%)	0.01

+=Loss of Consciousness

++ =Post-Traumatic Amnesia

\* Demographic Variables Used in Nearest Neighbor Matching Protocol

\*\* Standardized Differences >10%, adjusted for residual confounding in final models<sup>2</sup>

Author Manuscript

#### Table 2.

Odds Ratios of Past Year Exposures in Individuals with Traumatic Brain Injury and Non-TBI Controls

Participant Prior Year Self-Reported Exposures <sup>+</sup>	Matched Sets, OR (n=62) (95% CI)	p-value
Self-reported Depression	4.16 (1.79–9.67)	0.001 **
Self-reported Chronic Pain	0.56 (0.27–1.14)	0.11
Self-reported Poor Health Status	1.36 (0.57–3.24)	0.49
Physical Health Composite Score >= 3 Conditions	1.61 (0.86–3.01)	0.14
Behavioral Health Composite Score >0 Risk Factors	1.52 (0.77–3.00)	0.23
Excessive Alcohol Use	2.05 (0.74–5.71)	0.17
Currently Smoking	1.93 (0.67–5.55)	0.22
Reported Abuse of Illegal/Controlled Substance	2.22 (0.88-5.59)	0.09
Self-reported Physical Inactivity	0.95 (0.49–1.73)	0.81

\*\* significant with p-value<0.05

<sup>+</sup>All exposures represent separate analyses

#### Table 3.

Odds Ratios of Past Year Exposures in Individuals with Traumatic Brain Injury and Controls Stratified by Age (>=65 years vs. <65 years) and Sex

Participant Prior Year Exposures By Age and Sex	Matched Sets, OR (n=62) (95% CI)	p-value	
Self-reported Depressive Symptoms			
>=65 years old	7.32 (2.02–26.5)	0.002 **	
<65 years old	2.38 (0.74–7.72)	0.15	
Male	7.31 (2.39–22.3)	0.0005**	
Female	1.62 (0.42-6.27)	0.49	
Self-reported Chronic Pain			
>=65 years old	0.49 (0.20–1.22)	0.12	
<65 years old	0.77 (0.24–2.45)	0.65	
Male	0.63 (0.20-2.03)	0.44	
Female	0.52 (0.21–1.30)	0.16	
Self-reported Poor Health Status			
>=65 years old	1.28 (0.44–3.74)	0.65	
<65 years old	1.97 (0.41–9.45)	0.40	
Male	0.61 (0.07–5.72)	0.67	
Female	1.57 (0.61–4.02)	0.35	
Physical Health Composite Score >= 3 Conditions			
>=65 years old	1.30 (0.60–2.85)	0.51	
<65 years old	2.23 (0.79-6.30)	0.13	
Male	1.44 (0.43–4.85)	0.56	
Female	1.96 (0.88–4.35)	0.09	
Behavioral Health Composite Score >0 Risk Factors			
>=65 years old	1.49 (0.61–3.63)	0.38	
<65 years old	1.55 (0.54–4.45)	0.42	
Male	0.74 (0.22–2.48)	0.62	
Female	2.07 (0.88-4.87)	0.10	
Excessive Alcohol Use			
>=65 years old	6.58 (1.17-37.1)	0.03 **	
<65 years old	0.82 (0.17-3.97)	0.81	
Male	7.94 (0.77-81.8)	0.08	
Female	1.34 (0.39–4.60)	0.64	
Currently Smoking			
>=65 years old	4.29 (1.03–18.0)	0.05 **	
<65 years old	0.44 (0.05–3.88)	0.46	
Male	0.68 (0.10-4.51)	0.69	
Female	3.39 (0.92–12.5)	0.07	
Reported Abuse of Illegal/			
Controlled Substance			

Participant Prior Year Exposures By Age and Sex	Matched Sets, OR (n=62) (95% CI)	p-value
>=65 years old	3.62 (0.94–14.0)	0.06
<65 years old	1.64 (0.44–6.12)	0.46
Male	4.55 (0.67–31.1)	0.12
Female	1.71 (0.58–5.04)	0.33
Self-reported Physical Inactivity		
>=65 years old	0.96 (0.43-2.19)	0.93
<65 years old	0.90 (0.34–2.39)	0.83
Male	0.42 (0.12–1.36)	0.15
Female	1.28 (0.59–2.77)	0.54

\*\* significant with p-value<0.05

<sup>+</sup>All exposures represent unique analyses