TRAUMATIC BRAIN INJURY SURVEILLANCE AND RESEARCH WITH ELECTRONIC HEALTH RECORDS: BUILDING NEW CAPACITIES

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DEDICATION

To Ashley, Jim, Rhonda, and Diane. This dissertation is dedicated to you as a small token of my immense gratitude for your unwavering support and encouragement. Your love and sacrifice have been the driving force behind my academic journey, and I could not have come this far without your guidance and inspiration. I am forever grateful for the opportunities you have given me. Thank you for always believing in me and for being my rock throughout this journey.

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Introduction

Between 3.2 and 5.3 million U.S. civilians live with traumatic brain injury (TBI)-related disabilities. Although the post-acute phase of TBI has been recognized as both a discrete disease process and risk factor for chronic conditions, TBI is not recognized as a chronic disease. TBI epidemiology draws upon untimely, incomplete, cross-sectional, administrative datasets. The adoption of electronic health records (EHR) may supplement traditional datasets for public health surveillance and research.

Methods

Indiana constructed a state-wide clinical TBI registry from longitudinal (2004-2018) EHRs. This dissertation includes three distinct studies to enhance, evaluate, and apply the registry: 1) development and evaluation of a natural language processing algorithm for identification of TBI severity within free-text notes; 2) evaluation and comparison of the performance of the ICD-9-CM and ICD-10-CM surveillance definitions; and 3) estimating the effect of mild TBI (mTBI) on the risk of post-acute chronic conditions compared to individuals without mTBI.

Results

Automated extraction of Glasgow Coma Scale from clinical notes was feasible and demonstrated balanced recall and precision (F-scores) for classification of mild (99.8%), moderate (100%), and severe (99.9%) TBI. We observed poor sensitivity for ICD-10-CM TBI surveillance compared to ICD-9-CM (0.212 and 0.601, respectively), resulting in potentially 5-fold underreporting. ICD-10-CM was not statistically equivalent to ICD-9-CM for sensitivity ($d\tilde{d}$=0.389, 95% CI [0.388,0.405]) or positive predictive value ($d\tilde{d}$=-0.353, 95% CI [-0.362,-0.344]). Compared to a matched cohort, individuals with mTBI were more likely to be diagnosed with mental health, substance use, neurological, cardiovascular, and endocrine conditions.

Conclusion

ICD-9-CM and ICD-10-CM surveillance definitions were not equivalent, and the transition resulted in a underreporting incidence for mTBI. This has direct implications on existing and future TBI registries and the Report to Congress on Traumatic Brain Injury in the United States. The supplementation of state-based trauma registries with structured and unstructured EHR data is effective for studying TBI outcomes. Our findings support the classification of TBI as a chronic disease by funding bodies, which may improve public funding to replace legacy systems to improve standardization, timeliness, and completeness of the epidemiology and post-acute outcomes of TBI.

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LIST OF ABBREVIATIONS

AIS	Abbreviated Injury Scale
ADL	Activities of Daily Living
ADHD	Attention Deficit Hyperactivity Disorder
CDC	Centers for Disease Control and Prevention
CMS	Centers for Medicare and Medicaid Services
CCW	Chronic Conditions Data Warehouse
CT	Computed Tomography
CI	Confidence Interval
DMI	Data Modernization Initiative
EHR	Electronic Health Records
ED	Emergency Department
GCS	Glasgow Coma Scale
HR	Hazard Ratio
IHIE	Indiana Health Information Exchange
INPC	Indiana Network for Patient Care
ICD-9-CM	International Classification of Disease, Ninth Revision, Clinical Modification
ICD-10-CM	International Classification of Disease, Tenth Revision, Clinical Modification
IHD	Ischemic Heart Disease
LR-	Likelihood Ratio Negative
LR+	Likelihood Ratio Positive

LOC	Loss of consciousness
MRI	Magnetic Resonance Imaging
mTBI	Mild Traumatic Brain Injury
MI	Myocardial Infarction
NCSS	National Concussion Surveillance System
NLP	Natural Language Processing
NPV	Negative Predictive Value
PPV	Positive Predictive Value
PTA	Post traumatic amnesia
PTSD	Post-Traumatic Stress Disorder
TIA	Transient Ischemic Attack
TBI	Traumatic Brain Injury
TOST	Two One-Sided Test
WHO	World Health Organization

CHAPTER 1

INTRODUCTION

1.1 Chronic Disease

During the 20th century, the United States and other industrial nations underwent an epidemiologic transition in which the predominant causes of morbidity and mortality shifted from infectious, parasitic, and nutritional deficiencies to noninfectious chronic diseases.[1] The Centers for Disease Control and Prevention (CDC) defines chronic diseases as those lasting one year or more and require ongoing medical attention, limits activities of daily living, or both.[2]

Chronic diseases dominate contemporary health problems around the world and are the leading cause of death, disability, and health care costs in the United States. In 2020, despite the global emergence of a novel, highly infectious, and deadly respiratory coronavirus, seven of the top ten leading causes of death in the United States were chronic in nature, a proportion that has remained a constant for the past several decades.[1,3] A nationally representative study of over 4.5 million individuals spanning three decades demonstrated older adults with chronic diseases had greater incidence and earlier onset of disability across all Activities of Daily Living (ADL).[4] Over half of the United States lives with one or more chronic disease (51.8%), which accounts for an estimated 90% of the $3.8 trillion in annual health care expenditures.[5-7] Table 1.1 details the prevalence of several major chronic conditions as self-reported in the 2019 National Health Interview Survey.

Table 1.1. Self-Reported Chronic Disease Prevalence in the United States, Results from the 2019 National Health Interview Survey.

Chronic Disease	**Prevalence (%)**
Hypertension	48.10%
Arthritis	20.90%
Anxiety	11.70%
Hyperlipidemia	11.50%
Diabetes	11.30%
Cancer	9.60%
Asthma	8.40%
Chronic obstructive pulmonary disease	5.00%
Depression	4.70%
Coronary Heart Disease	4.60%
Stroke	3.10%
Kidney Disease	2.40%

The high prevalence and cost of chronic disease has been met with national surveys for surveillance and sizable annual funding allocations for research into treatments and prevention of diseases as well as their risk factors.[8,9] For example, in the year 2021, the National Institutes of Health reported a combined $14.7 billion in research funding for cardiovascular disease, cancer, stroke, and Alzheimer's disease and related dementias.[10]

1.2 Traumatic Brain Injury

A Traumatic Brain Injury (TBI) "is a sudden injury that causes damage to the brain", disrupting the normal function.[11,12] A disruption in brain function is defined as one or more of the following: any duration of loss of or decreased consciousness; loss of memory before or after the injury; neurological deficits, including muscle weakness, loss of balance and coordination, vision disruption, loss of senses, or changes to speech and language; and altered mental status at the time of injury, such as confusion, disorientation, or difficulty concentrating.[13] The mechanism of TBI is most commonly closed head trauma from impact by a blunt object or force and sudden acceleration and deceleration of the head.[14] Often, rotational acceleration will result in focal and diffuse injuries to the brain while blunt impacts are more commonly localized.[15] The leading causes of closed head TBI are falls, struck by or against an object, motor vehicles traffic incidents, and assault.[16] The distribution of causes varies by age; for example, falls occur more frequently among young children and the elderly and athletic injuries among adolescents and teenagers.[17]

The severity of TBI is classified as mild, moderate, or severe by clinical evaluation of neurological signs and symptoms as well as neuroimaging using computed tomography (CT) and magnetic resonance imaging (MRI). Largely due to heterogeneous clinical presentation and a lack of molecular diagnosis, the classification of TBI severity remains a challenge within the neuroscience community. TBI is typically classified based upon the physical mechanism of injury, location of the lesion, and the clinical severity.[18] While the mechanism of injury and location of lesion within the brain can be determined through context and CT imaging, severity is often derived from signs and symptoms.

Combined with post-traumatic amnesia and alteration of consciousness, the Glasgow Coma Scale (GCS) is the most employed scoring system for determining TBI consciousness and severity. Because GCS can be misclassified as a result of external factors (e.g., medical sedation and drug or alcohol intoxication), it is often used in conjunction with the Abbreviated Injury Scale (AIS), which incorporates anatomic descriptors of the injury as well as acute sequelae.[19-21] Table 1.2 depicts the criteria used to classify TBI severity.[19] More recently, the ALERT-TBI clinical trial demonstrated high positive and negative predictive value (97.5% and 99.6%, respectively) for intracranial lesions through the detection of the biomarkers ubiquitin C-terminal hydrolase-L1 (UCH-L1) and glial fibrillary acidic protein (GFAP), representing a potential breakthrough in TBI clinical decision making.[22]

Table 1.2. Criteria for Classification of Traumatic Brain Injury Severity.

Criteria	**Mild**	**Moderate**	**Severe**
Abbreviated injury scale	1-2	3	4-6
Loss of consciousness	0-30 minutes	>30 min and <24 hours	>24 hours
Glasgow Coma Scale	13-15	9-12	3-8
Post-traumatic amnesia	< 1 hour	1-24 hours	>1 day

1.3 Traumatic Brain Injury as a Chronic Disease

Although professional and scholarly awareness of the public health significance of possible long-term effects of TBI has increased over the past two decades, public health surveillance of TBI remains primarily centered around the acute event. This is in part due to the natural history of TBI. TBI has undergone a recent epidemiologic transition; it was not until the end of the 20th century that survival from moderate-to-severe TBI became a common outcome.[23] The nature of the underlying mechanism of injury (i.e., traumatic incident) often results in emergency treatment and management of polytrauma, such as lacerations and bone fractures. Extreme injuries notwithstanding, the structural components of the integumentary and musculoskeletal systems are amenable to treatment without long-term sequalae, and as such would not meet any definition of a chronic disease. However, the brain does not possess a similar ability of returning to a pre-injury state; a bone and the brain do not have synonymous pathophysiology or regulatory control. Several reviews have summarized long-term changes in pathology, imaging, functioning, emotional regulation, and cognition following brain injury.[24-28] This suggests that TBI may be viewed through two distinct lenses – the acute period with injuries present from the underlying mechanism of injury and the post-acute period that, in some cases, marks the beginning of a chronic disease process.

Because duration is long, chronic diseases are often referred to as diseases of prevalence. Disease prevalence in a population is most simply expressed in direct relation to the incidence and duration of disease, accounting for losses due to mortality. There are an estimated 2.5 million annual acute TBI events each year in the United States, of which 2% of individuals do not survive acute complications.[29] Considering the high incidence, foundationally, for TBI to be considered a chronic disease there must necessarily exist demonstrable long-term morbidity among survivors of TBI. In fact, an estimated 3.2 to 5.3 million U.S. civilians (1.1%-1.7% of the population) live with TBI-related disabilities.[30,31] Approximately 10% of the 2.5 million annual TBI events will result in lasting post-injury symptoms and 43% of the 250,000 hospitalized patients with TBI will develop post-injury disability.[32,33] Disability from TBI limits activities of daily living, social integration, and vocational ability, costing $63.9 billion annually due to lost productivity.[31,34,35] The health care needs of TBI patients extend far beyond the care provided at the time of injury. Evidence suggests that TBI outcomes may demonstrate improvement followed by deterioration years after injury and many individuals living in the post-acute TBI phase experience underdiagnosed and poorly managed outcomes.[36-40]

1.3 Public Health Surveillance of Traumatic Brain Injury

Recognition of post-acute TBI has developed slowly over the past two decades, fueled initially by many small, single center studies, and more recently by larger multi-center and administrative datasets. Key to accelerating understanding of post-acute TBI outcomes is building population-based surveillance systems capable of integrating with clinical, community, and social services data. However, implementation of such systems is challenging due to complex interactions between legislation, public funding, technology, workforce, and data governance.

In 1996, Congress passed the TBI Act of 1996 (P.L. 104-166), which defined TBI, authorized federal government research, and demonstration grant funding for public programming to improve access to services. An amendment to this bill in 2000 (P.L. 104-166) reauthorized research, programming, and public reporting aligned with Healthy People 2020 as well as added a CDC provision to expand state surveillance of TBI incidence and prevalence in institutional settings through the creation of registries.

In practice, state statutes defining the operation and funding of TBI registries are varied, resulting in a lack of standards for the methods and scope of reporting, variety and velocity of data exchange, and service delivery intervention. The lack of standards further prevents the use of state TBI registry data for a national surveillance program. State registries often operate on unfunded – or underfunded – mandates, on legacy systems with unsustainable operating models, are deficient in quality control, and possess insufficient resources for key activities, including analysis and reporting, establishing data sharing partnerships, and record linkage for service coordination.[41] Likewise, data limitations result in challenges for population-based research aimed to understand post-acute TBI outcomes and evaluate models of care. Recognizing the limitations of existing registries, the Common Data Elements (CDE) project was launched to define data standards for clinical research.[42] The CDE model has been implemented in large-scale studies but is not integrated into routine state or federal surveillance.[43,44]

1.4 Strengthening Surveillance of Traumatic Brain Injury

Recognizing the pervasive existence of data siloes and legacy systems throughout the public health enterprise, the Centers for Disease Control invested more than four billion dollars in the Data Modernization Initiative (DMI) between 2022 and 2026. The DMI implementation plan cites five key priorities and several objectives that, together, could address many of the underlying issues limiting TBI surveillance and research. These include the following: building scalable, integrated, and analytics-enabled infrastructure and systems; use of standards for interoperable systems, record linkage, and advanced analytics; training a modern, IT, cybersecurity, and data science workforce; improving strategic relationships between partners within the public health enterprise; and establishing data governance, exchange, and culture that enables modernization and adoption.[45]

The replacement of legacy systems, use of data standards, and deployment of record linkage will improve the ability to integrate disparate and cross-sector TBI data, including clinical data from electronic health records (EHR). In 2016, the Indiana Department of Health and Regenstrief Institute collaborated to develop a state-wide clinical TBI registry to study long-term outcomes and health service utilization.[46] Integration between the Indiana trauma registry and Indiana clinical TBI registry may provide several benefits to the understanding of the epidemiology and post-acute outcomes of TBI, including more complete and timely capture and reporting of TBI events, detection, control, and prevention of complications and comorbidities, comparative effectiveness for treatment modalities, and study of the effectiveness and efficacy of services oriented at community reintegration.[47,48]

1.5 Research Aims

This dissertation integrated data from Indiana trauma center EHRs, the Indiana trauma registry, and the Indiana TBI registry using methodology from the fields of health informatics and epidemiology. First, we developed and evaluated a method for extracting TBI severity from clinical documentation, filling a critical gap in the use of secondary clinical data for epidemiological studies by enabling positive identification of individuals with TBI and quantifying the severity of their injury. Second, we examined the performance of the standard code set used for identification of TBI in administrative and clinical data in public health surveillance as well as the report to congress on TBI in the United States. Finally, we reported incidence and risk of post-acute outcomes among individuals with mild TBI in support of formal recognition of TBI as a chronic disease process.

This dissertation reports on three original studies with the following research aims:

1) To develop and evaluate a natural language processing algorithm for identification of clinical markers of TBI severity within free-text notes;

2) To evaluate and compare the performance of the Center for Disease Control and Prevention ICD-9-CM and ICD-10-CM surveillance codes for the identification and reporting of TBI; and

3) To construct cohorts to estimate the effect of mild TBI on the risk of post-acute chronic conditions compared to individuals without a documented history of TBI.

CHAPTER 2

AUTOMATED EXTRACTION OF GLASGOW COMA SCALE FROM FREE-TEXT CLINICAL NOTES

2.1 Introduction

Population-based studies for Traumatic Brain Injury (TBI) often rely on national administrative databases such as the National Discharge Survey, the National Ambulatory Medical Care Survey, and the National Vital Statistics System.[49-51] These large databases allow for deep descriptive analyses of TBI, estimating morbidity and mortality by person, place, and time characteristics at the national- and state-level. One such example, is the Center for Disease Control and Prevention's Report to Congress on Traumatic Brain Injury Epidemiology and Rehabilitation.[17] However, the cross-sectional nature of these data limits the ability to observe post-acute TBI care patterns, long-term outcomes, and generation of real-world evidence for treatment and rehabilitation. The CDC has called for increased use of health information technology, such as Electronic Health Records (EHRs), to improve follow-up and evaluate rehabilitation for TBI patients.[17]

Accelerated by the Centers for Medicare and Medicaid Services meaningful use and promoting interoperability incentives, adoption of EHRs among non-federal acute care hospitals increased from 28% in 2011 to 96% in 2017.[52] EHRs contain longitudinal, patient-centric records with rich documentation for a patient's medical history, diagnoses, procedures, medications, treatment plans, test results, and radiology images. EHRs allow clinicians to view a longitudinal record of patients' history of contact with the health care system and facilitate in-depth documentation of care episodes. However, given the heterogeneity of clinical encounters, systems are not capable of capturing all parameters as structured data fields, resulting in up to 80% of patient data stored as unstructured free text, inaccessible to traditional statistical methods.[53]

A powerful, and increasingly common, technique for examining unstructured free text is natural language processing (NLP).[54] NLP for information extraction creates structured fields through rapid and automated identification of linguistic patterns in massive amounts of text.[55] Methodologies capable of incorporating unstructured EHR data demonstrate superior recall and precision over those dependent on structured fields only.[56] Secondary usage of EHR data for epidemiological research often extends beyond the available structured clinical data elements, resulting in a need for exploration of unstructured data, such as clinical notes. NLP has been used to support several clinical and epidemiological studies ranging from coronary artery disease risk factor identification, case identification and outcomes prediction, discovery of adverse drug events, identifying opioid abuse, and breast cancer recurrence.[57-61]

The Glasgow Coma Scale (GCS) is the most commonly employed scoring system for determining TBI consciousness and severity, yet is not commonly stored as structured data within a patient's EHR.[21,62] The lack of robust structured data limits the usefulness of EHR data for observational and quasi-experimental studies. Often the researcher must choose between a complete case analysis, perform manual chart review, or draw upon a surrogate severity measure such as the International Classification of Diseases Programs for Injury Categorization (ICDPIC) generated Abbreviated Injury Scale.[63] Manual review of clinical notes and complete case analysis generally present a small sample size problem, particularly for the study of rare outcomes, and may introduce selection bias if records are not selected at random. While imputed measures such as ICDPIC allow complete case analysis for all TBI cases with an ICD code, performance depends on presence of specific ICD codes (e.g., ICD9CM 5th digit) and does not allow for differentiation between mild, moderate, and severe TBI. Furthermore, ICD codes for TBI are frequently coded as head injury, unspecified, limiting validity of severity imputation.[64]

If GCS documentation is occurring in unstructured free text, the application of NLP for automated extraction of GCS in large administrative and clinical databases may offer the benefits of chart review without the costly and time-consuming investment. The primary aim of this work was to develop an NLP approach to extract GCS accurately and rapidly from clinical notes and classify TBI severity for a large cohort. The secondary aim was to assess feasibility for extraction of other TBI-related parameters, including loss of consciousness (LOC), intubation, sedation, post-traumatic amnesia (PTA), and abbreviated injury scale (AIS).

2.2 Materials and Methods

2.2.1 Study Population and Clinical Notes

All study data was obtained from longitudinal EHR records contained within the Indiana Network for Patient Care (INPC). The INPC is the nation's largest interorganizational clinical data repository, containing more than 10 billion clinical data elements from 38 health systems, including 117 participating hospitals and affiliated ambulatory care practices across the state of Indiana.[65] The INPC receives data from a wide variety of EHR vendors in both structured (e.g., diagnoses codes, vitals, laboratory results) and unstructured (e.g., free text notes) format.

Study participants were included if they had presumptive TBI clinical encounter at an Indiana trauma-verified emergency department between 2004 and 2018. Presumptive TBI was defined as a primary ICD-9-CM or ICD-10-CM diagnosis code consistent with the Center for Disease Control and Prevention TBI surveillance definition for the mandated report to congress, which are detailed in Appendix B.[17] At the time of the study, Indiana had 20 trauma-verified centers, including four level I, six level II, and ten level III centers. Fifteen (75%) of these centers participate in the INPC, including all four trauma I centers. Clinical notes were included if any of the following words were present in the note name – note, summary, visit, form, consultation, battery, discharge, admission, ambulance, or consult. In total, 29 different note types were included.

2.2.2 NLP Approach

The method to extract severity measures from free text clinical notes was developed using the Regenstrief Institute's NLP tool, nDepth. nDepth is an Apache Unstructured Information Management Applications-based NLP system that uses open-source applications for NLP processing released under the Apache license 2.0 (apache.org). Using nDepth, we developed a classification engine following the commonly applied approach of developing NLP-based systems: iteration informed by experimentation, logic, term discovery, and domain expertise.[66] At each iteration, the candidate classification engine was tested using a training corpus by manually reviewing for errors, omissions, and discrepancies. The final classification engine was applied to a hold-out test corpus to evaluate performance against manual review according to recall, precision, accuracy, and F-score.

2.2.3 Training

The classification engine training approach is outlined in Figure 2.1. We began by extracting clinical notes among patients with positive evidence of the target condition from structured data (i.e., ICD-9-CM or ICD-10-CM TBI diagnosis). We used a Boolean-structured query using the terms "GCS" or "Glasgow Coma Scale" to create the training corpus, from which all notes were fully available for review by developers. The preliminary classification engine identified each GCS term and extracted a quantitative result for 3,145 patients and 3,542 notes. From this, a random sample of 1,836 patients and 2,368 notes was generated for further development of the classification engine (training corpus).

Additional terms were added by mining common phrases among observations and supplemented with fuzzy parameters and a lexical variants generator. The ConText algorithm was applied to understand if mentions of concepts were negated or historical.[67] Notes were iteratively reviewed for accuracy of concept identification, quantitative value extraction, and context interpretation. Errors and inconsistencies were noted and used to inform the next iteration of development. For example, the classification engine was altered to extract ranges of GCS (e.g., 3-9) and notes containing character representations of GCS (e.g., fifteen). The iterative process described continued for three rounds until no additional information was gained. The terms used in the final classification engine are listed in Table 2.1. The JSON used to develop the classifications may be found in Appendix A.

Table 2.1. Search Terms for Identification of Traumatic Brain Injury Severity Classification

Concept	Terms
Glasgow Coma Scale	glasgow coma score glasgow coma scale score glasgow coma scale gcs
Intubation of airway	intubation intubate intubated intubating
Chemical sedation	sedation sedate sedated sedating
Loss of consciousness	loss of consciousness
Post traumatic amnesia	post traumatic amnesia
Abbreviated injury scale	abbreviated injury scale abbreviated injury score

2.2.4 Testing

The final classification engine was productionized to extract severity measures on the notes of all patients with presumptive TBI. A random sample of patients, not involved in training, were selected as the testing corpus. For each record, the full text recognized by the state machine was extracted from clinical notes and manually reviewed. The number of patients manually reviewed was determined by a sample size calculation for an interrater reliability of 0.7 and 10% margin of error, resulting in 961 patient reviews with 161 overlapping patients between reviewers. We considered manual review the gold standard, and thus all measures of performance are calculated using the reviewer extraction as the source of truth. In the case of GCS, reviewers indicated if a GCS value was present and, when relevant, recorded the value. Intubation and sedation were reviewed for applicability to the patient. Loss of consciousness, post traumatic amnesia, and abbreviated injury score were evaluated only by the presence of the concept (yes or no). Both reviewers were blinded to the classification engine results. The reviewer procedure is detailed in Appendix A.1.

To estimate the false negative rate of the classification engine, we further reviewed 825 clinical notes which were negative for all measures in this study. Notes were randomly selected and loaded into the nDepth graphical user interface where reviewers completed an eight-question validation survey.

2.2.5 Statistical Analysis

Reviewer and classification engine GCS results were mapped to the standard severity categories: mild, 13-15; moderate, 9-12; and severe, 3-8. When a GCS range was reported in the note, both reviewers and the classification engine extracted the low and high values separately. When applicable, final TBI severity classification was calculated using the midpoint of the reported range. Any extracted GCS result less than 3 or greater than 15 was flagged for human review. Algorithm results were compared to reviewers using a confusion matrix at both the note- and patient-level (Table 2.2). At the patient-level, the lowest reported GCS determined TBI severity. All discordant results were investigated to determine the source of disagreement.

The performance of the classification engine was evaluated with recall, precision, accuracy, and F-scores, calculated for each level of severity. For brevity, we have detailed the calculations for mild TBI in equations 2.1-2.4.

Table 2.2. Confusion Matrix for Traumatic Brain Injury Glasgow Coma Scale Severity Comparing the Classification Engine to Manual Review

		Manual Review Result		
		Mild	Moderate	Severe
Classification Engine Result	Mild	TP_{mild}	$E_{mod\text{-}mild}$	$E_{sev\text{-}mild}$
	Moderate	$E_{mild\text{-}mod}$	TP_{mod}	$E_{sev\text{-}mod}$
	Severe	$E_{mild\text{-}sev}$	$E_{mod\text{-}sev}$	TP_{sev}

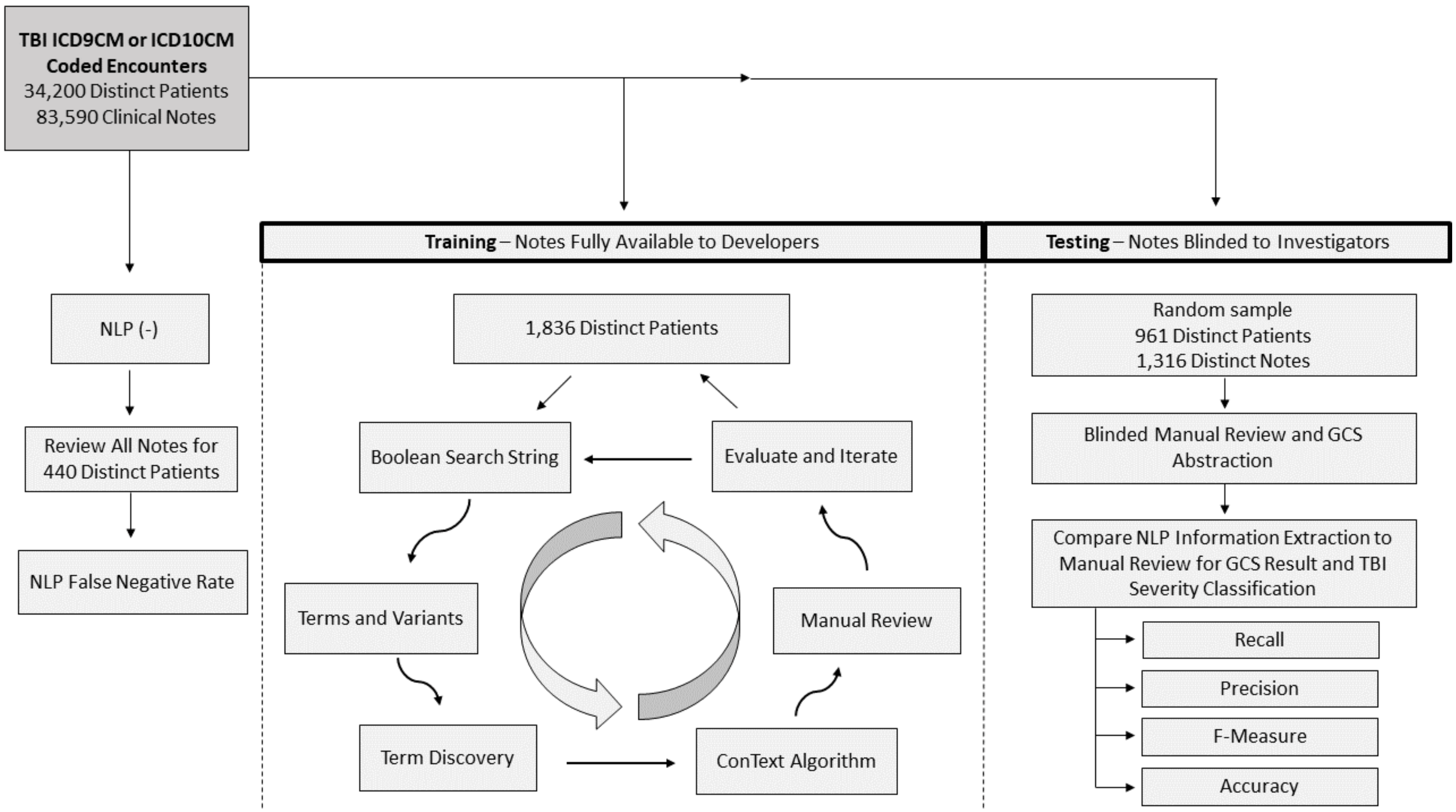
$$(2.1)\ \ Recall = \frac{TP_{mild}}{TP_{mild} + (E_{mild\text{-}mod} + E_{mild\text{-}sev})}$$

$$(2.2)\ \ Precision = \frac{TP_{mild}}{TP_{mild} + (E_{mod\text{-}mild} + E_{sev\text{-}mild})}$$

$$(2.3)\ Accuracy = \frac{TP_{mild} + (TP_{mod} + E_{sev\text{-}mod} + E_{mod\text{-}sev} + TP_{sev})}{N}$$

$$(2.4)\ F - measure = 2 * \frac{precision * recall}{precision + recall}$$

Figure 2.1. Training, Testing, and Evaluating a Classification Engine for Glasgow Coma Scale in Clinical Notes.



2.3 Results

The sampling frame included 34,200 distinct presumptive TBI patients with 83,950 clinical notes between 2004 and 2019. The clinical notes of all presumptive TBI patients were parsed through the classification engine. In total, GCS was extracted for 4,883 distinct patients (14.3%), of which 4,749 (97.3%) were identified in the Indiana Traumatic Brain Injury Registry and had diagnosis code and demographic information available. The majority of GCS values were extracted from emergency department MD progress notes (72.7%), followed by emergency department discharge notes (9.8%), emergency department notes (8.7%), and consultation notes (1.8%). The remaining 26 note types included made up 8.4% of the GCS values but each individually represented less than 1% of total GCS values extracted.

The percent agreement for the 248 notes assessed by both reviewers was 99.6% and the kappa statistic for interrater reliability was 98.6%. Reviewers disagreed on only one GCS value, which was adjudicated by a third reviewer (TDM). In total, according to the classification engine, the testing corpus included 919 (95.6%) mild TBIs, 7 (0.7%) moderate TBIs, and 35 (3.6%) severe TBIs.

2.3.1 Performance of GCS Information Extraction

Figure 2.2 depicts the confusion matrices for GCS values mapped to TBI severity (mild, moderate, and severe) according to the reviewers and classification engine at the note- and patient-level. Agreement was observed between the classification engine and reviewers among 99.5% of clinical notes and 99.7% of patients. All discordance between reviewers and the classification engine occurred among GCS values classified as mild. A third reviewer (TDM) reviewed all note-level (n=6) and patient-level (n=3) discordance.

In each case of patient-level disagreement, reviewers recorded text pertaining to a GCS component score (e.g., V6, E3) rather than the summary score, or total, GCS value. On the other hand, the classification engine correctly disregarded GCS component scores and reported the full GCS summary scores.

At the note-level, a total of 14 records were excluded from the analysis due to results outside the valid GCS range (i.e., 3 to 15). No GCS summary was documented in the text for 11 clinical notes. In each case, reviewers incorrectly recorded a GCS component score as a GCS summary score and the classification engine correctly identified that no GCS summary score was provided in the note, resulting in a missing value for GCS. For the remaining three notes, the classification engine recorded a ZIP Code as the GCS summary score and reviewers correctly recorded a missing value for GCS.

Although it was determined manual reviewers miscategorized several records, all analyses of evaluating the classification engine performance were performed using manual review as the source of truth. Accordingly, Table 2.3 details the performance of the classification engine at each level of TBI severity. The overall performance of the classification engine was nearly perfect (F-scores 99.8% or higher) for mild, moderate, and severe TBI at the patient-level. For mild and moderate TBI, information retrieval and classification demonstrated balance between recall and precision (99.7% to 100%). While the precision of identifying severe TBI was 100%, the slightly lower recall (92.1%) demonstrated the possibility of false negatives. However, the three patients identified as false negative severe TBI were later deemed reviewer error.

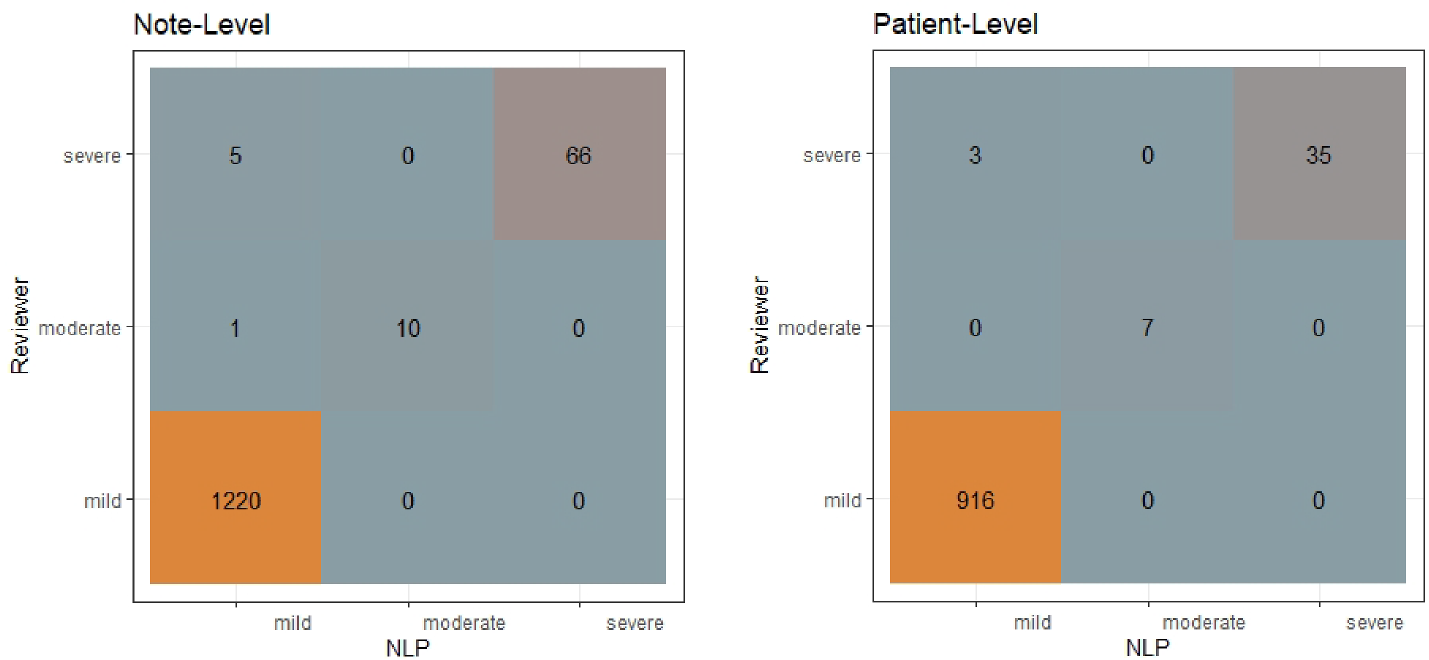
Table 2.3. Performance of Glasgow Coma Scale Information Extraction from a Testing Corpus of 961 Patients.

	Note-Level Analysis			**Patient-Level Analysis**		
TBI severity	*Mild*	*Moderate*	*Severe*	*Mild*	*Moderate*	*Severe*
Recall (%)	100	90.9	93	100	100	92.1
Precision (%)	99.5	100	100	99.7	100	100
Accuracy (%)	99.5	99.9	99.6	99.7	100	99.7
F-score (%)	99.8	95.2	96.4	99.8	100	99.9

2.3.2 False Negative GCS Extraction

The testing corpus evaluated the classification engine's ability to extract the correct GCS value from clinical notes but did not assess the rate at which GCS values were detected. To estimate the false negative rate, we reviewed a total of 825 notes among 440 distinct individuals with presumed TBI for which the classification engine did not detect any measures in this study. Among these, 5 (0.61%) contained GCS component scores without a summary score or explicit mention of "GCS" or synonyms. For example, one clinician documented the following - "Eyes: 4/4; Verbal: 5/5; Motor: 6/6".

Figure 2.2. Confusion Matrices for GCS-Based TBI Severity, Note-Level and Patient-Level Classification Engine Versus Manual Review of Patient Notes.



2.4.3 Additional Traumatic Brain Injury Indicators and Measures

As a secondary objective, PTA, AIS, LOC, sedation, and intubation did not undergo the full training and testing process. Rather, we searched for simple terms (see Table 2.1) to identify if the concepts were documented in the clinical notes of patients with presumed TBI. The classification engine failed to detect included terms for PTA or AIS. As depicted in Table 2.4, manual review of a sample of negative notes (n=825), revealed 13 notes (1.6%) with documented PTA and 10.5% with LOC.

Table 2.4. Frequency of Mentions for TBI-Related Parameters in Clinical Notes

Measure	Present in Notes n (%) Full population = 83,950*	False negative n (%) Negative Sample = 825
Post-traumatic amnesia	0 (0)	13 (1.6)
Abbreviated Injury Score	0 (0)	0 (0)
Loss of consciousness	377 (0.5)	87 (10.5)
Sedation	38 (0.1)	1 (0.1)
Intubation	32 (<0.1)	3 (0.4)

* Full sample includes all available notes of patients with ICD-9-CM or ICD-10-CM codes for traumatic brain injury

2.3.5 Diagnoses Codes by TBI Severity

Examining the first and highest priority TBI ICD-9-CM and ICD-10-CM diagnoses codes revealed most cases are coded as unspecified head injury (Table 2.5). For all levels of TBI severity, the most common ICD-9-CM diagnoses code was 959.01 (n=1,277) and the most common ICD-10-CM diagnoses code was S09.90XA (n=2,050).

Table 2.5. First and Highest Priority ICD-9-CM and ICD-10-CM Traumatic Brain Injury Diagnoses Codes Among Cases with Documented Glasgow Coma Scale.

ICD-9-CM	Description	Total n (%[a])	Mild n (%[b])	Moderate n (%[b])	Severe n (%[b])
959.01	Head injury, unspecified	1357 (71.5)	1277 (94.1)	18 (1.3)	62 (4.6)
850.9	Concussion, unspecified	157 (8.3)	153 (97.5)	1 (0.6)	3 (1.9)
850.5	Concussion with loss of consciousness of unspecified duration	124 (6.5)	117 (94.4)	3 (2.4)	4 (3.2)
850.11	Concussion with loss of consciousness of 30 minutes or less	51 (2.7)	48 (94.1)	1 (2.0)	2 (3.9)
801.01	Closed fracture of base of skull without mention of intra cranial injury, with no loss of consciousness	24 (1.3)	24 (100.0)	0 (0.0)	0 (0.0)
ICD-10-CM	Description	Total n (%[a])	Mild n (%[b])	Moderate n (%[b])	Severe n (%[b])
S09.90XA	Unspecified injury of head, initial encounter	2083 (73.0)	2050 (98.4)	11 (0.5)	22 (1.1)
S06.0X0A	Concussion without loss of consciousness, initial encounter	371 (13.0)	367 (99.0)	1 (0.2)	3 (0.8)
S06.0X9A	Concussion with loss of consciousness of unspecified duration, initial encounter	165 (5.8)	162 (98.2)	2 (1.2)	1 (0.6)
S06.0X1A	Concussion with loss of consciousness of 30 minutes or less, initial encounter	34 (1.2)	34 (100.0)	0 (0.0)	0 (0.0)
S06.5X0A	Traumatic subdural hemorrhage without loss of consciousness, initial encounter	32 (1.2)	25 (78.1)	1 (3.1)	6 (18.8)

[a] percent of all ICD-9-CM or ICD-10-CM coded cases (column percent)
[b] percent of cases with a specific diagnoses code (row percent)

2.3.6 Demographic Composition of Confirmed TBI Population

The classification engine was applied to the Indiana TBI registry to identify a subgroup with confirmed TBI and documented GCS. Table 2.6 depicts the age, sex, race, and rurality by TBI severity. Most commonly, TBI patients with documented GCS were aged 15-24 (21.3%) years, though severe TBI was more common among older patients (χ^2 p = 0.0005). Cases were more likely to be male as severity increased (χ^2 p = 0.0004), representing 52.2% and 66.9% of mild and severe cases, respectively. Race and ethnicity were missing for 21.4% of observations, limiting interpretation of the distribution. Although the majority of TBI cases live in an urban area, the proportion which are rurally located increased with increasing TBI severity.

2.4 Discussion

Automated extraction of GCS from clinical notes was equivalent to performing manual chart review and can be deployed to improve data quality for TBI research using large clinical databases. Using only four synonyms, we developed a classification engine to extract GCS from EHR clinical notes with 99.8% to 100% accuracy. To date, no prior research has developed or evaluated NLP for GCS extraction. Longitudinal clinical databases contain pre- and post-morbid medical and personal data, and with TBI severity indicators, may be used to improve population surveillance, identify novel post-acute disease associations, define and evaluate care patterns, and generate real-world evidence for treatment and rehabilitation.

Table 2.6. Demographic Characteristics of Traumatic Brain Injury Patients with Documented Glasgow Coma Scale in the Indiana Traumatic Brain Injury Registry, 2004-2019.

Demographic	**Total**	**Mild**	**Moderate**	**Severe**
Age				
0-4	525 (11.1)	511 (11.3)	8 (16.7)	6 (3.4)
5-14	636 (13.4)	622 (13.7)	3 (6.2)	11 (6.3)
15-24	1013 (21.3)	964 (21.3)	9 (18.8)	40 (22.9)
25-44	966 (20.3)	904 (20.0)	13 (27.1)	49 (28.0)
45-64	759 (16.0)	712 (15.7)	8 (16.7)	39 (22.3)
65+	850 (17.9)	813 (18.0)	7 (14.6)	30 (17.1)
Sex				
Female	2239 (47.1)	2162 (47.8)	19 (39.6)	58 (33.1)
Male	2510 (52.9)	2364 (52.2)	29 (60.4)	117 (66.9)
Race/Ethnicity				
Asian	10 (0.2)	8 (0.2)	0 (0.0)	2 (1.1)
Black/AA	519 (10.9)	484 (10.7)	11 (22.9)	24 (13.7)
Other	175 (3.7)	172 (3.8)	1 (2.1)	2 (1.1)
Unknown	1017 (21.4)	970 (21.4)	11 (22.9)	36 (20.6)
White	2991 (63.0)	2858 (63.1)	25 (52.1)	108 (61.7)
Hispanic	37 (0.8)	34 (0.8)	0 (0.0)	3 (1.7)
Rurality				
Rural	515 (11.9)	474 (11.5)	8 (18.2)	33 (22.3)
Urban	3802 (88.1)	3651 (88.5)	36 (81.8)	115 (77.7)

While the absence of structured GCS data may be overcome with automated extraction, the maximum potential of clinical databases will continue to be stunted by the absence of GCS and other severity measures in unstructured clinical notes. In our sample of presumptive TBI patients, only 14.3% had a GCS value documented. Our findings are lower than previously reported in an Olmsted County, MN cohort (26%), likely due to our inclusion of multiple health systems with heterogeneous EHR platforms and data sharing practices.[62] While GCS is the most widely used severity indicator, other factors that alter consciousness such as chemical sedation, intubation, and intoxication should be considered.[18] We observed the included terms for sedation and intubation among only

0.1% of presumptive TBI patients, though our lack of pre-hospital data and paramedic procedures may explain the absence of this contextual documentation.[68] Because of the potential misclassification of TBI severity when relying solely on GCS, it is recommended to include additional criteria such as imaging, LOC, PTA, and AIS.[18] We found documentation to be largely absent for PTA, LOC, and AIS among presumptive TBI patients. However, for the purposes of retrospective research, it is possible to extract LOC from the ICD-9-CM or ICD-10-CM diagnoses codes.

Specific ICD-9-CM and ICD-10-CM TBI diagnoses codes indicate LOC for the patient's event. For example, The ICD-10-CM S06.0X1A is coded for "concussion with loss of consciousness of 30 minutes of less, initial encounter". However, these modifiers are not useful for TBI severity classification when less specific codes are used, such as ICD-10-CM S09.90XA for "unspecified injury of head, initial encounter". Among our sample with successful GCS extraction, 86.3% and 78.8% of ICD-9-CM and ICD-10-CM TBI codes, respectively, were coded as unspecified, limiting usefulness of combining GCS with ICD codes to improve severity classification. Similar results (75.9%) were reported by Brazarian and colleagues at a large academic emergency department.[64]

Although no GCS value was available for most patients in the Indiana TBI registry, the demographic characteristics of the GCS subgroup closely resembled national TBI estimates. Overall, the GCS subgroup was 52% male, matching national estimates (52%) from 2013.[69] Similarly, the age distribution reported in Table 2.6 matched 2013 national estimates within 1%, with the exception of ages 15-24 years which was 3% higher in the GCS subgroup.[69]

The internal and external validity of this study should be interpreted considering several limitations. The clinical notes included in training and testing represent multiple health systems participating in the INPC and include several EHR platforms with varied data sharing practices. While we excluded health systems that do not share clinical notes with the INPC, some notes are locked in .pdf format and not machine readable. Although interrater reliability was strong, both reviewers recorded incorrect GCS values on several occasions, leading to a shift in TBI severity for those individuals. Similarly, a small number of results required manual review due to extraction of a ZIP Code. However, a simple validation rule to extract values within the reportable GCS range (i.e., 3-15) may prevent such errors in future iterations. Caution should be taken in interpreting documentation practices for other TBI-related parameters as these did not undergo full NLP development. These data represent only patients with presumptive TBI from emergency departments with a trauma facility designation and, as a result, our methodology may not generalize to non-trauma facilities with fewer TBI patients and differing documentation practices. Finally, a lack of pre-hospital notes and a low occurrence of GCS documentation in emergency department notes resulted in only a subgroup of patients available for future research.

In the absence of improved documentation, future work should focus on integration of disparate data sources and more complex information extraction and classification for TBI severity. For example, Malec and colleagues developed the Mayo Classification System, which leverages all available evidence to define TBI severity, including death, neuroimaging, GCS, PTA, LOC, and post-concussive symptoms. Although we did not extract post-concussive symptoms, we found PTA, LOC, and AIS were rarely documented among presumptive TBI patients. Completeness of severity measures and mechanism of injury can be further augmented through patient-level integration with other data sources such as state trauma registries. With only a small proportion of clinicians documenting GCS, more sophisticated machine learning techniques could be developed to train classification engines based on additional notes and clinical context, such as the review of systems.

2.5 Conclusion

GCS is readily extracted from free text clinical notes. Due to the unique structure of GCS documentation, automated NLP extracted values were equivalent to manually extracted values. However, low rates of documentation for GCS results in classification of TBI severity for only a subgroup of patients. This study is the first to automate extraction of GCS from unstructured EHR data and can improve the use of clinical databases for secondary analyses. As interoperability between health IT systems progresses, additional work is needed to improve capture and extraction of key contextual factors, such as sedation and intubation, and additional measures of TBI severity, such as LOC, PTA, and AIS.

CHAPTER 3

EVALUATION OF TRANSITIONAL ICD-9-CM and ICD-10-CM SURVEILLANCE DEFINITIONS FOR TRAUMATIC BRAIN INJURY

3.1 Introduction

Traditional public health surveillance systems are fueled by single sources of data (e.g., case reports, siloed information systems) and are rarely integrated, often leading to incompleteness and blind spots. Like other diseases of public health significance, surveillance and epidemiologic investigation of traumatic brain injury (TBI) relies primarily upon International Classification of Disease, Clinical Modification (ICD-CM) diagnostic codes for case identification.[32,70-72] Since passage of the Traumatic Brain Injury Act of 1996, the Centers for Disease Control and Prevention (CDC) has enabled surveillance of TBI from emergency department and hospital visits based on a set of ICD-9-CM codes.[31,73] In 2015, the Department of Health and Human Services mandated the transition from ICD-9-CM to ICD-10-CM, resulting in new definitions of TBI for public health surveillance.[74] The revised definitions from CDC, National Center for Health Statistics, and National Center for Injury Prevention and Control utilize the General Equivalence Maps between ICD-9-CM and ICD-10-CM.[75] In general, ICD-10-CM has greatly expanded the number of available codes to provide more specific injury diagnosis data, leading to an opportunity to better align surveillance definitions with clinical diagnoses for TBI. Although, there are 50% less ICD-10-CM TBI surveillance codes than ICD-9-CM in the surveillance definition, largely due to how loss of consciousness is documented, and the working group excluded non-“S” or -“T” ICD-10-

CM codes (e.g., R40.24x Glasgow Coma Scale, total scale) in order to maintain consistency with ICD-9-CM.

Previous studies demonstrate variability in ICD-9-CM performance for TBI surveillance, and many patients with mild TBI may not be captured by ICD-9-CM alone, suggesting a need for improving definitions, use of appropriate codes in the clinical setting, and integration of data sources for surveillance. Brazarian and colleagues prospectively assessed medical records from emergency department visits for the presence of mild TBI compared to the assigned ICD-9-CM codes and observed poor sensitivity (45.9%) and positive predictive value (23.7%) and high specificity (97.8%).[64] Although, sensitivity has been shown to improve when limited to surveillance of severe TBI (89%), as reported by Carroll et al. in a retrospective review of medical records and computed tomography of the head. Carroll and colleagues further demonstrated variable performance across ICD-9-CM surveillance code groups, with sensitivity ranging from 28% to 89% and specificity ranging from 58% to 96%.[76] Shore and colleagues compared the Maryland Hospital Discharge dataset to the Maryland Trauma Registry and found discharge data better captured anatomic injuries, poorly captured symptoms, and significantly underreported all levels of TBI severity (61% and 95%, respectively).[72]

Less is known about the performance of ICD-10-CM for TBI surveillance. Two studies have assessed positive predictive value among emergency department visits and inpatient hospitalizations, demonstrating moderate to high diagnostic value (0.74 to 0.97) for specific surveillance codes.[77,78] These validation studies are informative for the purpose of constructing research cohorts but did not assess the capability of ICD-10-CM to detect TBI for public health surveillance. To date, no study has evaluated the sensitivity and specificity of the ICD-10-CM TBI surveillance definition. Further, no comparison of the two standards has been performed to aid interpretation of TBI morbidity and mortality following the coding transition.

To understand the impact of the transition to ICD-10-CM for TBI surveillance and provide context for the appropriateness of temporal trending and cohort formation across ICD-9-CM and ICD-10-CM implementations, we performed a retrospective cohort study among 15 trauma centers in the State of Indiana, integrating data from clinical notes, imaging notes, and the Indiana Trauma Registry. For both ICD-9-CM and ICD-10-CM, we report the surveillance-based TBI encounter rates, gold standard estimated incidence, performance of surveillance definitions, and tests for equivalence across the coding transition.

3.2 Materials and Methods

3.2.1 Study Population

With groundwork laid in the 1990s, the Indiana Health Information Exchange (IHIE) is the oldest and most comprehensive HIE in the U.S., connecting more than 100 hospitals, 14,000 practices, and nearly 40,000 providers.[79] The platform that enables IHIE, the Indiana Network for Patient Care (INPC), is the nation's largest clinical data repository, with more than 10 billion clinical data elements. The INPC is a statewide clinical data repository that aggregates patient health information from disparate clinical information systems using a patient matching registry, creating a shared longitudinal record of care for each patient. For the current study, emergency department (ED) visits from 15 of 21 verified Indiana trauma centers were included in the sampling frame, representing 4 (100%), 2 (33%), and 9 (81%) of trauma I, II, and III centers, respectively.

3.2.2 Study Design and Sampling

The primary use of administrative billing codes (i.e., ICD-CM) are clinical documentation and filling claims for reimbursement of services rendered. Public health entities may subsequently acquire these data through a variety of mechanisms, including admission and discharge data sets, claims databases, and health information exchanges. To study the performance of administrative billing codes for TBI as a secondary source of surveillance data for both ICD-9-CM and ICD-10-CM, two separate population-based cohorts were formed from the trauma center sampling frames.

Figure 3.1 depicts the sampling and classification procedure. The sampling frames included all ED visits from 2012 to 2014 for the ICD-9-CM implementation (568,304 unique visits) and all ED visits from 2016 to 2018 for the ICD-10-CM implementation (762,286 unique visits). The year 2015 was excluded as it was the transitional year from ICD-9-CM to ICD-10-CM. For each implementation, a simple random sample of 15,000 visits without replacement was obtained using the R package dplyr. To estimate performance measures that most accurately reflect public health surveillance in practice, we did not stratify by trauma facility level or facility census during sampling.

3.2.3 Classification

The diagnostic codes for all visits were categorized as surveillance definition positive TBI or surveillance definition negative TBI according to the Center for Disease Control's ICD-9-CM and ICD-10-CM definitions of TBI for public health surveillance (Appendix B)[75] . Although the CDC excluded "unspecified injury of head (S09.90) from the proposed ICD-10-CM surveillance definition, it is included in the current study to remain comparable to ICD-9-CM surveillance. We previously observed 73% of head injury visits contain S09.90 as a primary diagnosis (Chapter 2, Table 2.5), and exclusion is likely to result in inflation of false negatives. Because a high proportion of patients with a TBI may not be assigned ICD-CM codes, the gold standard for TBI was determined using an ensemble approach (Figure 3.1). First, visits were analyzed using a Natural Language Processing (NLP) classification engine designed to automatically extract Glasgow Coma Scale (GCS) values from free-text notes. If a GCS value was present, the encounter was considered gold standard positive for TBI. The performance of the classification engine for identification of TBI in free-text notes previously demonstrated F-measures of 99.8% or higher for all TBI severity classifications (Chapter 2, Table 2.3). A key finding of the evaluation was the relative absence of unambiguously documented GCS composite or summary scores among patients with ICD-9-CM or ICD-10-CM TBI diagnoses codes (14.3%). Thus, if used in isolation, the gold standard would result in a high false negative rate. To supplement the classification engine, all visits were shared with the Indiana Department of Health Division of Injury Prevention where they were matched to records in the Indiana Trauma Registry using both deterministic and probabilistic methods. If the individual and encounter date matched a documented TBI in the registry, the encounter was categorized as gold standard positive, and GCS values were returned. Visits negative for NLP extracted GCS, absent from the Indiana Trauma Registry, and surveillance definition negative (no TBI ICD code) were considered concordant and classified as true negatives. Visits negative for GCS, absent from the Indiana Trauma Registry, and surveillance definition positive (i.e., TBI ICD code present) were manually reviewed to protect against false negative gold standard classification.

For each surveillance definition positive, gold standard negative visit all available ED notes, hospital notes, and radiological imaging findings within 48 hours of the encounter date were manually reviewed by two reviewers. A TBI event was defined using the Mayo TBI Severity Classification System developed by Malec and colleagues.[62] Briefly, this system classifies individuals as symptomatic (possible) TBI, mild (probable) TBI, and moderate-severe TBI based the occurrence of signs and symptoms, which are outlined in Table 3.1. Visit notes were loaded in the Regenstrief Institute nDepth application and a reviewer survey capturing the Mayo Classification System data was completed for each note (Appendix C). *A priori* sample size determination to observe a minimum inter-rater reliability kappa of 0.7 with a margin of error equal to 10% specified both reviewers would review all notes for 123 and 107 individuals for ICD-9-CM and ICD-10-CM, respectively. Note-level survey results were subsequently coalesced at the individual level to determine the presence of TBI. If any of the Mayo TBI Severity Classification criteria were met, the encounter was considered gold standard positive.

3.2.4 Statistical Analysis

Annual incidence of TBI was calculated as the number of unique individuals with gold standard positive TBI divided by the number of unique individuals in the sample during the year. We further stratified incidence by TBI severity (possible, mild, moderate to severe).

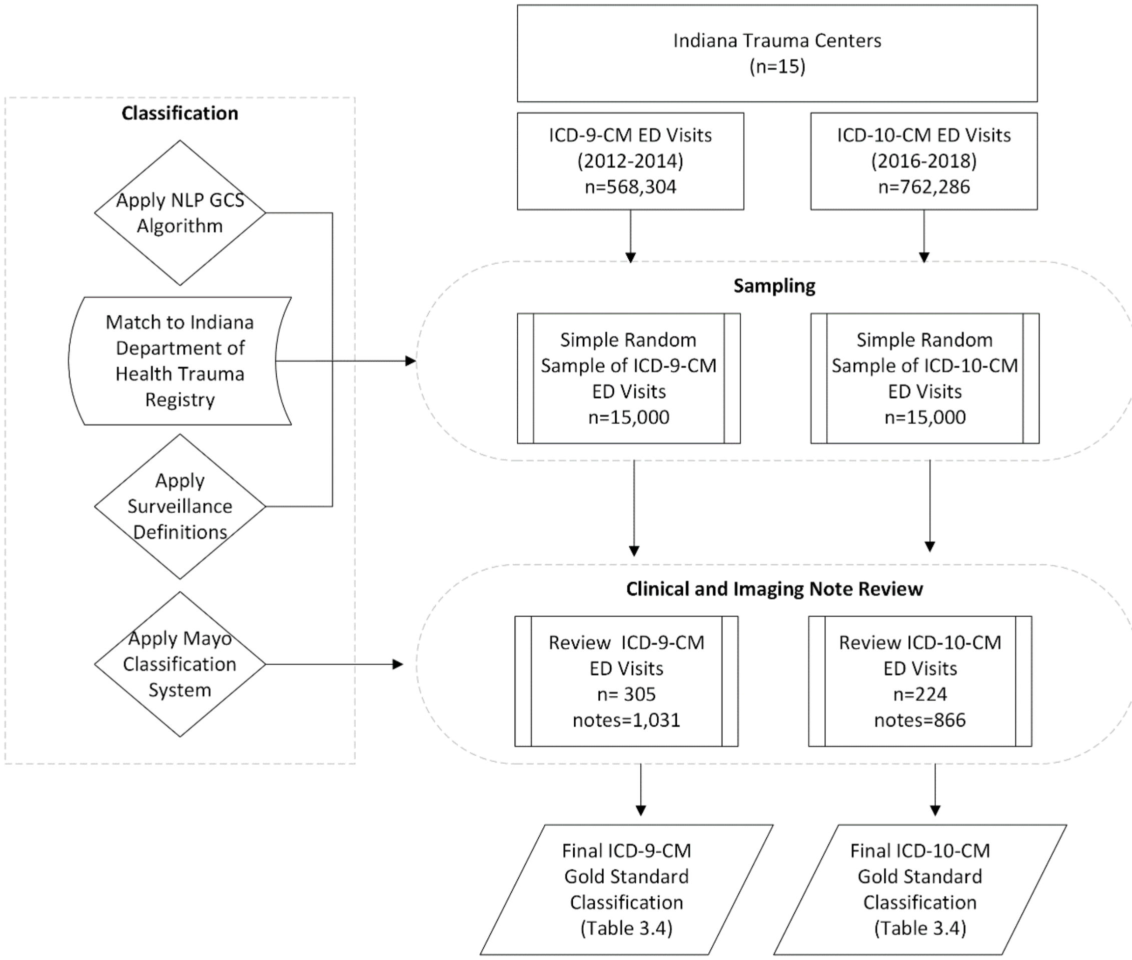
The gold standard classification of TBI was compared to the public health surveillance definitions for ICD-9-CM and ICD-10-CM diagnostic codes using sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, negative likelihood ratio, accuracy, and error rate (Table 3.2 and Formulas 3.1 to 3.8).

Table 3.1. Mayo Traumatic Brain Injury (TBI) Severity Classification System to Detect TBI and Classify Severity.

Moderate-Severe TBI	
Measure	*Definition*
Mortality	Death due to TBI
Loss of consciousness	30 minutes or more
Post-traumatic anterograde amnesia	24 hours or more
Glasgow coma scale	Less than 13 (unless invalidated by intoxication, sedation, or systemic shock)
Imaging	One of more of the following: • Intracerebral hematoma • Subdural hematoma • Epidural hematoma • Cerebral contusion • Hemorrhagic contusion • Penetrating TBI (dura penetrated) • Subarachnoid hemorrhage • Brain Stem Injury
If none of the above then (Probable) Mild TBI if	
Loss of consciousness	Momentarily to less than 30 minutes
Post-traumatic anterograde amnesia	Momentarily to less than 24 hours
Imaging	Depressed, basilar or linear skull fracture (dura intact)
If none of the above then (Possible) Symptomatic TBI if	
Symptoms	Blurred vision Confusion (mental state changes) Dazed Dizziness Focal Neurologic Symptoms Headache Nausea

Adapted from Malec et al. [64]

Figure 3.1. Traumatic Brain Injury Gold Standard Ascertainment.



Confidence intervals for estimates of incidence, sensitivity, specificity, predictive values, accuracy, and error rate were calculated using the Wilsons Score method, which is a modification of the simple asymptotic method that demonstrated computational simplicity and good, symmetric probability coverage for two-sided confidence intervals (Formula 3.9).[80,81] Likelihood Ratio Positive (LR+) and Likelihood Ratio Negative (LR–) were obtained using the asymptotic approach described by Zhou (Formulas 3.10 and 3.11).[82]

Table 3.2. Organization of Binary Surveillance Definition and Gold Standard Data for Calculation of Performance Measures.

		Gold Standard		
		NLP GCS + Trauma Registry + Mayo +	NLP GCS - Trauma Reg – Mayo -	
ICD Result	Positive	s_1	r_1	m_1
	Negative	s_0	r_0	m_0
		n_1	n_0	N

$$\text{(3.1) Sensitivity} = \widehat{Se} = \frac{s_1}{n_1}$$

$$\text{(3.2) Specificity} = \widehat{Sp} = \frac{r_0}{n_0}$$

$$\text{(3.3) Positive Predictive Value} = \widehat{PPV} = \frac{s_1}{m_1}$$

$$\text{(3.4) Negative Predictive Value} = \widehat{NPV} = \frac{r_0}{m_0}$$

$$\text{(3.5) Likelihood Ratio Positive} = \widehat{LR}+ = \frac{\widehat{Se}}{1-\widehat{Sp}}$$

$$\text{(3.6) Likelihood Ratio Negative} = \widehat{LR}- = \frac{1-\widehat{Se}}{\widehat{Sp}}$$

$$\text{(3.7) Accuracy} = \hat{A} = \frac{s_1 + r_0}{N}$$

$$\text{(3.8) Error rate} = \widehat{Err} = 1 - \hat{A}$$

$$\text{(3.9) Wilson's Score Method } 100(1-\alpha)\%\ CI = \frac{2np + z^2_{1-\alpha/2} \pm z_{1-\alpha/2}\sqrt{\left(z^2_{1-\alpha/2} + 4npq\right)}}{2(n + z^2_{1-\alpha/2})}$$

$$\text{(3.10) Likelihood Ratio Positive } 100(1-\alpha)\%\ CI = \frac{\widehat{Se}}{1-\widehat{Sp}}\, exp^{\pm z_{1-\alpha/2}\sqrt{\frac{1-\widehat{Se}}{s_1} + \frac{\widehat{Sp}}{r_1}}}$$

$$\text{(3.11) Likelihood Ratio Negative } 100(1-\alpha)\%\ CI = \frac{1-\widehat{Se}}{\widehat{Sp}}\, exp^{\pm z_{1-\alpha/2}\sqrt{\frac{\widehat{Se}}{s_0} + \frac{1-\widehat{Sp}}{r_0}}}$$

The performance of ICD-9-CM and ICD-10-CM for identification of TBI was compared between surveillance definitions using equivalence tests for each study measure. For a full review of equivalence testing in diagnostic tests, refer to Obuchowski, 1997.[83] Traditional hypothesis tests assess a difference between groups, often with the objective of demonstrating superiority of one group. Such tests set the null hypothesis difference as zero (Formula 3.12) and the alternative hypothesis difference as non-zero (Formula 3.13), wherein a Type I error results in concluding the groups differ when they are equivalent and a Type II error results in concluding the groups are equivalent when they differ. Difference hypothesis tests are typically more conservative in controlling Type I error (i.e., $\alpha = 0.05$) than Type II error (i.e., $\beta = 0.2$), resulting in a probability of Type II error that exceeds $p > 0.05$. Thus, a conclusion of equivalence for a non-significant difference test results in error greater than 5% of the time. Equivalency inference would only be appropriate if Type II error were also fixed to $\beta = 0.05$.

$$(3.12)\ H_0: (\theta_1 - \theta_2) = 0$$

$$(3.13)\ H_A: (\theta_1 - \theta_2) \neq 0$$

Equivalence hypothesis tests take the opposite approach and assess for equivalence between two groups, with the objective of demonstrating groups are neither inferior nor superior. Accordingly, the interpretation of Type I and II error are reversed from the traditional difference approach, wherein a Type I error results in concluding two groups are equivalent when they differ and a Type II error results in concluding two groups differ when they are equivalent. To test for equivalence, hypotheses are set to test both superiority and noninferiority (Formulas 3.14 and 3.15), and a conservative approach to controlling Type I error ($\alpha = 0.05$) now controls probability of a false conclusion of equivalence at less than or equal to 5%.

$$(3.14)\ H_0: (p_1 - p_2) < \Delta_L \text{ or } H_0: (p_1 - p_2) > \Delta_U$$

$$(3.15)\ H_A: (p_1 - p_2) > \Delta_L \text{ and } H_A: (p_1 - p_2) < \Delta_U$$

Any difference between p_1 and p_2 which is contained within the interval (Δ_L, Δ_U) is considered equivalent. Consequently, this interval must represent no practical change in the ability to detect TBI through public health surveillance. Current estimates of the sensitivity of ICD-9-CM codes for TBI identification vary between 28% and 61%, and 58% and 98% for specificity, and no studies to-date have addressed overall ICD-10-CM performance.[64,72,76] Considering the variability across studies, we considered ICD-9-CM and ICD-10-CM performance equivalent if the difference between measures fell within the interval (-10%, 10%). We performed two one-sided tests (TOST) from both sides of the difference interval using the methods described by Schuirmann (1987) and constructed (1 - 2α)% confidence intervals confidence to test for equivalence of performance measures between ICD-9-CM and ICD-10-CM (Formula 3.16).[84] The (1-2α)% method using a 90% confidence interval is equivalent to performing two one-sided tests with a $\alpha = 0.05$ level of significance.[85]

$$(3.16)\ \text{TOST}\ (1 - 2\alpha)\% = \hat{d} \pm z_{1-2\alpha}\sqrt{\frac{\widehat{p_1}(1-\widehat{p_1})}{n_1} + \frac{\widehat{p_2}(1-\widehat{p_2})}{n_2}}$$

3.3 Results

3.3.1 Sample Demographics

The demographics of individuals sampled are presented in Table 3.3. During both periods, TBI was more common among White, Non-Hispanic, Females. Compared to those in the sample with no evidence of TBI, Black or African American and Hispanic individuals represented a higher-than-expected percentage of mild TBI events. The median age for TBI was less than 34 years for all severity levels apart from moderate-severe during the ICD-10-CM period (48 years). However, the age ranges were observed to be highly dispersed, with interquartile ranges from 10 year to 36 years.

3.3.2 Gold Standard Traumatic Brain Injury Classification

Sampling frames and samples exhibited similar TBI surveillance definition event rates for ED visits during both ICD-9-CM (2.3% and 2.1%) and ICD-10-CM (2.0% and 2.0%) periods. In total, 1,897 notes from 529 visits were reviewed, most commonly Head CT without contrast (20%), Emergency Department MD progress notes (15%), ED Discharge Notes (10%), Visit Data (7.8%), and Spine Cervical CT without contrast (7%). The Mayo TBI Severity Classification was applied by both reviewers for 229 visits, resulting in an ordinal inter-rater reliability of 0.846. All notes from visits with discordant results (n=30) were reviewed by both reviewers a second time and agreed upon. The most common reason for lack of agreement between reviewers was a difference in abstracted signs or symptoms (77%) and documentation of loss of consciousness (20%).

Figures 3.2 and 3.3 depict the workflow for construction of the gold standard TBI, and Table 3.4 details the classification of gold standard with and without application of the Mayo Classification System. Of the 568,304 visits between 2012 and 2014, we randomly sampled 15,000 representing 14,336 individuals. Of the 319 ICD-9-CM TBI positive visits, 14 were classified as gold standard positive by trauma registry records or NLP GCS extraction. The remaining 305 ICD-9-CM TBI positive ED visits underwent manual review of 1,031 notes and were classified according to the Mayo TBI Severity

Classification System. The Mayo system resulted in a gold standard TBI classification for an additional 90 visits.

Of the 762,286 visits between 2016 and 2018, we randomly sampled 15,000 representing 14,446 individuals. Gold standard classification by trauma registry verification or NLP GCS extraction was more common among ICD-10-CM, classifying 75 of 299 ICD-10-CM TBI positive ED visits. The remaining 224 ED visits without a gold standard signal were reviewed (866 notes) for classification by the Mayo TBI Severity Classification System. After review and assignment, an additional 128 ED visits were classified as gold standard TBI positive.

Table 3.3. Demographic Distribution by Traumatic Brain Injury Severity for 14,336 Individuals During the ICD-9-CM Period (2012-2014) and 14,446 Individuals During the ICD-10-CM Period (2016-2018).

	ICD-9-CM				**ICD-10-CM**			
	No TBI	*Possible*	*Mild*	*Mod-Severe*	*No TBI*	*Possible*	*Mild*	*Mod-Severe*
Race								
Asian / PI	13 (0.1%)	0 (0%)	0 (0%)	0 (0%)	16 (0.1%)	0 (0%)	5 (0.6%)	0 (0%)
AI/AN	41 (0.3%)	0 (0%)	0 (0%)	0 (0%)	150 (1.1%)	0 (0%)	0 (0%)	1 (5.3%)
Black / AA	3042 (21.4%)	9 (15.8%)	28 (29.8%)	2 (25%)	2994 (22.6%)	20 (22%)	256 (30.4%)	3 (15.8%)
White	10401 (73.2%)	47 (82.5%)	63 (67%)	6 (75%)	9720 (73.3%)	65 (71.4%)	562 (66.7%)	15 (78.9%)
Multiracial	41 (0.3%)	0 (0%)	0 (0%)	0 (0%)	41 (0.3%)	0 (0%)	0 (0%)	0 (0%)
Unknown/Other	665 (4.7%)	1 (1.8%)	3 (3.2%)	0 (0%)	342 (2.6%)	6 (6.6%)	20 (2.4%)	0 (0%)
Ethnicity								
Hispanic	532 (3.7%)	2 (3.5%)	5 (5.3%)	0 (0%)	864 (6.5%)	6 (6.6%)	59 (7%)	0 (0%)
Not Hispanic	7799 (54.9%)	30 (52.6%)	63 (67%)	5 (62.5%)	10952 (82.6%)	73 (80.2%)	741 (87.9%)	18 (94.7%)
Unknown/Other	5872 (41.3%)	25 (43.9%)	26 (27.7%)	3 (37.5%)	1447 (10.9%)	12 (13.2%)	43 (5.1%)	1 (5.3%)
Gender								
Female	7823 (55.1%)	36 (63.2%)	48 (51.1%)	5 (62.5%)	7358 (55.5%)	45 (49.5%)	455 (54%)	6 (31.6%)
Male	6306 (44.4%)	20 (35.1%)	46 (48.9%)	3 (37.5%)	5904 (44.5%)	46 (50.5%)	388 (46%)	13 (68.4%)
Unknown	74 (0.5%)	1 (1.8%)	0 (0%)	0 (0%)	1 (0%)	0 (0%)	0 (0%)	0 (0%)
Age (years)								
Median (IQR)	31 (32)	27 (34)	29.5 (26.5)	20.5 (10)	31 (33)	27 (30.5)	33 (36)	48 (22.5)

Abbreviations: PI = Pacific Islander, AI = American Indian, AN = Alaskan Native, AA = African American, IQR = Interquartile Range

Figure 3.2. Construction of Gold Standard TBI Classification for Evaluation of the ICD-9-CM TBI Surveillance Definition.

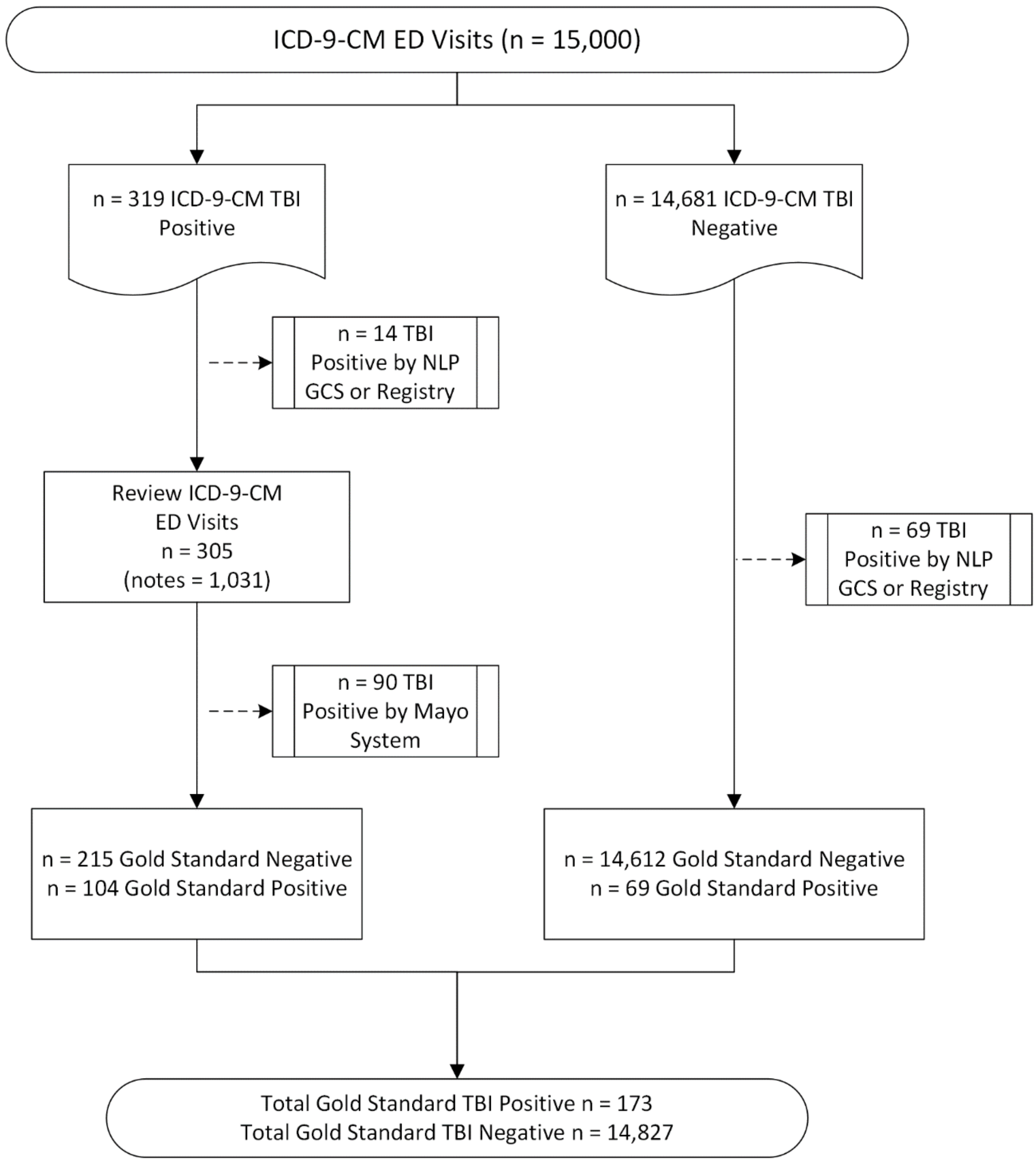


Figure 3.3. Construction of Gold Standard TBI Classification for Evaluation of the ICD-9-CM TBI Surveillance Definition.

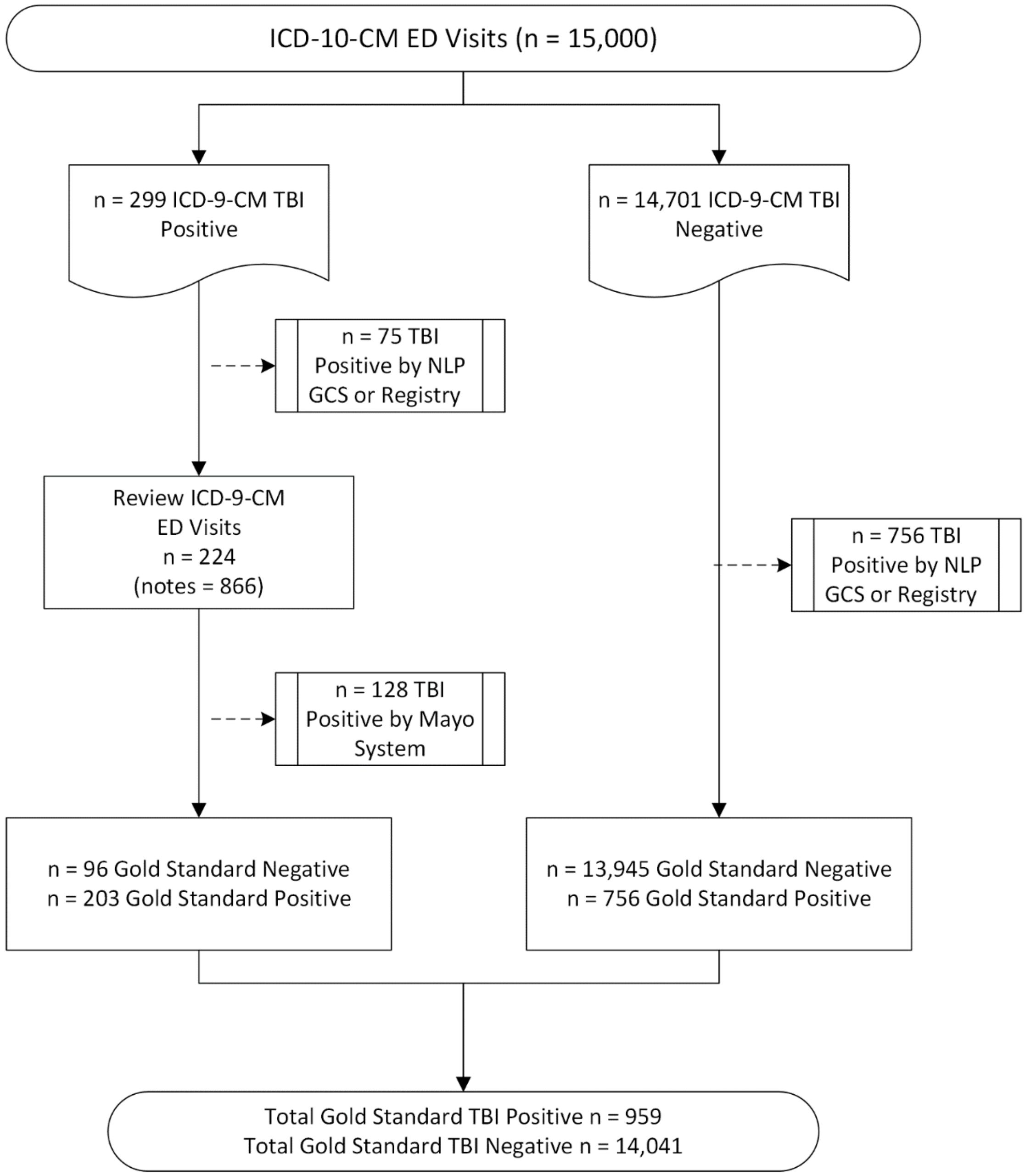


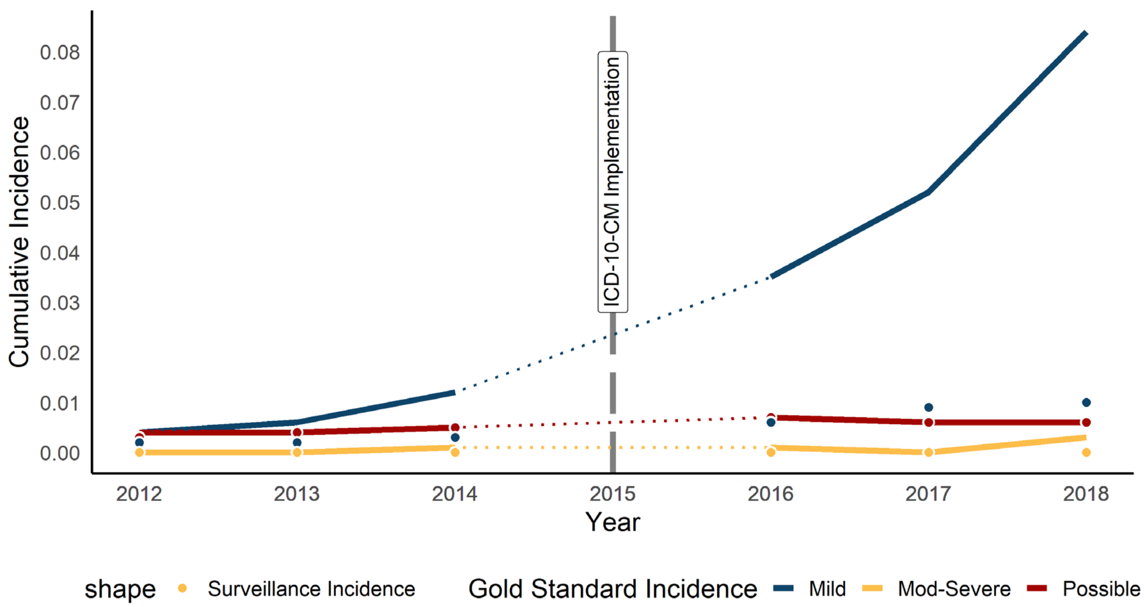
Table 3.4. Gold Standard Classification of Traumatic Brain Injury With and Without Application of the Mayo Traumatic Brain Injury Classification System.

	Without Mayo Classification		**Including Mayo Classification**	
	NLP (+) or TM (+)	*NLP (-) and TM (-)*	*Positive*	*Negative*
ICD-9-CM				
Positive	14	305	104	215
Negative	69	14612	69	14612
ICD-10-CM				
Positive	75	224	203	96
Negative	756	13945	756	13945

3.3.3 Traumatic Brain Injury Incidence

Overall, the cumulative incidence of TBI increased between surveillance definitions periods from 1.1% (95% CI 0.0% - 6.9%) during 2012-2014 to 6.7% (95% CI 0.0% - 15.7%) during 2016-2018. As depicted in Figure 3.4, possible and moderate-severe TBI incidence remained stable across the periods. Mild TBI increased gradually during 2012-2014 followed by sharp increases in 2016, 2017, and 2018. Figure 3.4 also depicts the cumulative incidence proportion of gold standard positive TBI detected by ICD-9-CM and ICD-10-CM surveillance definitions. The surveillance definition incidence of moderate-severe and possible TBI was similar to gold standard incidence during both periods. On the other hand, surveillance definition incidence underreported underlying mild TBI incidence, most notably during the ICD-10-CM 2016-2018 period.

Figure 3.4. Annual Incidence of Traumatic Brain Injury as Detected by Gold Standard Measurement and ICD-9-CM or ICD-10-CM Surveillance Definitions (2012-2014 and 2016-2018).



3.3.3 Performance of ICD-9-CM and ICD-10-CM for TBI Surveillance

The surveillance performance of each surveillance definition was quantified separately and subsequently compared for statistical equivalence (Table 3.5). Each surveillance definition performed well when classifying visits in which no TBI event occurred, as demonstrated by high specificity (0.985-0.993) and negative predictive value (0.949-0.995). Specificity and negative predictive value remained statistically equivalent across the transition of surveillance definitions. Likewise, accuracy remained high (0.943-0.981) and error rate low (0.019-0.057) across surveillance definitions, resulting in statistically equivalent performance.

Performance measures that failed to demonstrate equivalence between surveillance definitions included sensitivity, positive predictive value, likelihood ratio positive, and likelihood ratio negative. ICD-9-CM exhibited superior sensitivity (0.601) over ICD-10-CM (0.212) but inferior positive predictive value (0.326 and 0.679, respectively). While both surveillance definitions exhibited diagnostic value (i.e., LR ≠ 1), we observed a greater probability of gold standard TBI for the ICD-9-CM TBI surveillance definition than ICD-10-CM. Similarly, the absence of an ICD-9-CM surveillance code resulted in a relative greater probability of not having a TBI.

Table 3.5. Performance of ICD-9-CM and ICD-10-CM Traumatic Brain Injury Surveillance Definitions and Two One-Sided Tests for Equivalence Across Definitions.

	ICD-9-CM		**ICD-10-CM**		**Difference**	
Measure	$\hat{p}$	*95% CI*	$\hat{p}$	*95% CI*	$\hat{d}$	*95% CI*
Sensitivity	0.601	(0.524,0.674)	0.212	(0.187,0.239)	0.389	(0.388,0.405)
Specificity	0.985	(0.983,0.987)	0.993	(0.992,0.994)	-0.008*	(-0.01,-0.006)
PPV	0.326	(0.275,0.381)	0.679	(0.622,0.731)	-0.353	(-0.362,-0.344)
NPV	0.995	(0.994,0.996)	0.949	(0.945,0.952)	0.047*	(0.044,0.05)
LR+	41.457	(34.634,49.625)	30.960	(24.506,39.115)	10.497	(10.495,10.499)
LR-	0.405	(0.337,0.486)	0.794	(0.768,0.82)	-0.389	(-0.39,-0.388)
Accuracy	0.981	(0.979,0.983)	0.943	(0.939,0.947)	0.0379*	(0.034,0.042)
Error rate	0.019	(0.017,0.021)	0.057	(0.053,0.061)	-0.0379*	(-0.042,-0.034)

Abbreviations: $\hat{p}$ = point estimate; $\hat{d}$= difference estimate; PPV = positive predictive value; NPV = negative predictive value; LR+ = Likelihood Ratio Positive; LR- = Likelihood Ratio Negative
*Two One-Sided Test (TOST) significantly equivalent to zero.

3.4 Discussion

The current study found both surveillance definitions failed to detect a significant proportion of TBI events when compared to clinical and imaging notes and trauma registry records. Moreover, the sensitivity of ICD-9-CM and ICD-10-CM surveillance definitions were not statistically equivalent (0.601 and 0.212, respectively). The observed sensitivity of ICD-9-CM for all TBI severity levels is consistent with previous evaluations of discharge data (61%).[72] The current study is the first to report the sensitivity of ICD-10-CM surveillance definitions.

ICD-9-CM and ICD-10-CM codes are commonly used in public health surveillance definitions to describe the epidemiology of TBI as well as perform population-based research using electronic health record and administrative data. To perform surveillance and understand the significance of TBI to the public's health, sensitive case definitions at a population-level are paramount. Poor sensitivity can result in inadequate funding for health systems, research institutions, and local, state, and federal governments develop evidence-based interventions and programs. The validity of health service utilization and comparative effectiveness research is dependent upon the positive predictive value of case definitions. Poor positive predictive value results in systematic error due to misclassification of participants, possibly resulting in limited understanding of short- and long-term sequelae as well as ineffective evaluation of therapies.

Following the implementation of the ICD-10-CM surveillance definition, the percentage of total ED visits with a TBI diagnosis remained stable (range 2.0% to 2.3%), which is consistent with national estimates (2.2%).[69] While this stability may suggest comparable surveillance definitions, we also found annual increases in the gold standard incidence of mild TBI among Indiana trauma center emergency departments (n=15) between 2012 and 2018. Overall, based on clinically documented GCS, trauma registry records, or Mayo TBI Severity Classification, the incidence of TBI increased from 1.1% during the ICD-9-CM study period (2012-2014) to 6.7% during the ICD-10-CM study period (2016-2018). The immediate and consistent upward trend in TBI visits following

ICD-10-CM implementation was also observed among hospitalizations across 12 states, as reported by Sebastiao et al.[86] On the contrary, between 2012 and 2017, stable encounter rates were observed at Colorado emergency departments during the transition from ICD-9-CM to ICD-10-CM when including "unspecified injury of head" (S09.90), similar to the current study.[87] However, neither study estimated underlying incidence through medical chart and imaging review (i.e., gold standard incidence) and thus are more reflective of how surveillance definitions were utilized by health professionals during the transition than trends in underlying TBI incidence.

Similar to sensitivity, the estimated positive predictive values for ICD-9-CM and ICD-10-CM were not statistically equivalent between the periods. While sensitivity measures the probability of detection by a surveillance definition, positive predictive value measures the probability of a true TBI case. The probability of an ICD-10-CM TBI coded encounter representing a true TBI was greater (0.679) than observed in the ICD-9-CM surveillance definition (0.326), which is directionally consistent with previous work. Brazarian and colleagues reported positive predictive value of ICD-9-CM compared to medical record review ranged from 0.237 to 0.38 among patients with mild TBI and specific code groups (e.g., concussion, skull fracture, intracranial injury).[64] Gabella et al. reviewed emergency department encounter medical records compared to intracranial injury ICD-10-CM codes and found positive predictive value to vary from 0.82 to 0.92 across four sites in four states.[78] The lower ICD-10-CM positive predictive observed in the current study may be attributed to the inclusion of less specific codes (i.e., unspecified injury of head).

The study results should be interpreted in the context of several limitations. Most notably, we performed manual review for only a small percentage of emergency department encounter clinical and imaging notes. This is particularly relevant for surveillance definition-negative and gold standard-negative pairs, which represent most unreviewed records. However, due to the high specificity of surveillance definitions for TBI in both previous work and the current study, combined with supplementation of NLP GCS extraction and verification in the Indiana Trauma Registry, we estimate the impact on misclassification to be negligible. Further, because the specificity measures between surveillance definitions were equivalent, any misclassification would be non-differential. To improve the validity of our gold standard classification, all encounter notes for positive surveillance definitions and negative NLP GCS extraction and Indiana Trauma Registry were manually reviewed and classified according to the Mayo TBI Classification System. While the Mayo system is highly sensitive (89%) and specific (98%) for TBI classification, in some cases, our review was limited by data sharing practices from participating trauma centers.[62]

Despite limiting included trauma centers to facilities sharing clinical data with IHIE during both periods, we observed a temporal increase in the volume and variety of data. Expanded access to encounter and imaging notes in the ICD-10-CM period increases the probability of NLP GCS extraction and sufficient documentation for application of the Mayo TBI Classification System compared to the ICD-9-CM period, potentially leading to a differential ability to classify gold standard positive TBI visits. We mitigated the impact of this limitation by not restricting our review to specific note types and reviewing all available clinical documentation. Finally, using the CDC's clinical definition, Koval and colleagues reported that only 45.9% of emergency department patients screening positive for mild TBI had a documented TBI evaluation.[88] Thus, we must recognize that an absence of documented signs and symptoms of TBI may not reflect the true clinical diagnosis.

3.5 Conclusion

Results of this population-based, retrospective cohort study of ED visits across 15 Indiana trauma centers suggest TBI surveillance using either ICD-9-CM or ICD-10-CM alone may be insufficient for detection of TBI. Our findings indicate that ICD-9-CM and ICD-10-CM surveillance definitions are not equivalent for the purposes of public health surveillance and the current surveillance definition for ICD-10-CM may be starkly underestimating true mild TBI incidence. Research cohorts spanning the coding transition should be avoided or carefully constructed using specific, validated code sets in favor of the standard surveillance definitions. This work has implications on existing and future TBI registries and the epidemiological profile outlined in the Report to Congress on Traumatic Brain Injury in the United States.[17] Given the lack of comparability between ICD-9-CM and ICD-10-CM, future work should focus on integration of disparate surveillance systems and piloting the use of additional ICD-10-CM codes to improve detection of TBI and better reflect the clinical diagnoses of TBI.

CHAPTER 4

MULTISYSTEM POST-ACUTE OUTCOMES OF MILD TRAUMATIC BRAIN INJURY: A POPULATION-BASED COHORT STUDY

4.1 Introduction

The public health significance of chronic diseases is unequivocally recognized by professional institutions and scholars. Yet, there is a degree of opacity in the definition of what makes a disease chronic. The World Health Organization (WHO) defines chronic diseases as not being passed from person to person, of long duration and slow progression, and including four main types – cardiovascular, cancers, chronic respiratory diseases, and diabetes.[89] The Centers for Disease Control and Prevention (CDC) states chronic diseases last one year or more and require ongoing medical attention, limits activities of daily living, or both.[2] Historically, the CDC defines and reports chronic diseases as heart disease, cancer, lung disease, stroke, Alzheimer's disease, diabetes, and kidney disease, while recently including epilepsy and dental cavities. The Centers for Medicare and Medicaid Services (CMS) includes an expanded list of 21 chronic conditions that, in addition to the CDC major diseases, includes chronic infectious agents with well-characterized natural history (e.g., HIV/AIDS, Hepatitis B and C), substance abuse, mental health, and developmental disorders.[90] Although dozens of chronic disease definitions exist in scientific literature, as reviewed by Goodman and colleagues, common threads include non-self-limiting disease, an association with persistent and recurrent health problems, and duration measured in months and years, rather than days and weeks.[91]

The CDC recognizes moderate to severe traumatic brain injury (TBI) as “a lifelong condition” that “can lead to a lifetime of physical, cognitive, emotional, and behavioral changes”.[92] Yet, to date, TBI has not been recognized as a chronic disease by the CDC, CMS, or WHO. The classification of TBI solely as an acute event was widely first challenged by Masel and DeWitt in a 2010 review, where they assert the importance of separating the acute event resulting in a TBI from the pathological sequence that may follow.[47] Over the past two decades evidence and support for Masel and DeWitt’s theory has grown in the clinical and neuroscience communities, particularly in reference to moderate and severe TBI.[38,48] The CDC has made a call to researchers to continue studying TBI as a chronic health condition by understanding the role of pre-existing and co-occurring conditions, risk factors for sequalae, primary intervention strategies, and treatments.[92] The degree to which researchers can study risk of pathology after TBI and develop evidence-based care for individuals with post-acute TBI depends on the availability of longitudinal and integrated data sources. Unfortunately, as described in Chapter 1.4, cross-sectional administrative datasets are currently the primary sources of information for studying TBI epidemiology.

In 2016, the Indiana Department of Health and Regenstrief Institute collaborated to develop a state-wide clinical TBI registry to study long-term outcomes and health service utilization.[46] At the time of the current study, the state-wide registry included all demographic, encounter, medication, and clinical information for individuals with a head injury ICD-9-CM or ICD-10-CM diagnosis code between 2004 and 2018. The registry has supported several initiatives, including quantifying the risk of acute ischemic stroke, development of a GCS classification engine (Chapter 2), and evaluating public health surveillance definitions (Chapter 3).[93] To quantify the incidence of multisystem chronic conditions following a mild TBI (mTBI) event, we constructed several large cohorts using the Indiana TBI registry. This chapter reports the observed incidence of chronic conditions among those with a history of mTBI and compares risk to an exact-matched population without a TBI.

4.2 Materials and Methods

4.2.1 Data Source

The Indiana Health Information Exchange (IHIE) is the oldest and most comprehensive HIE in the U.S., connecting more than 100 hospitals, 14,000 practices, and nearly 40,000 providers[79]. The platform that enables IHIE, the Indiana Network for Patient Care (INPC), is the nation's largest clinical data repository, with more than 10 billion clinical data elements. The INPC is a statewide clinical data repository that aggregates patient health information from disparate clinical information systems using a patient matching registry, creating a shared longitudinal record of care for each patient.

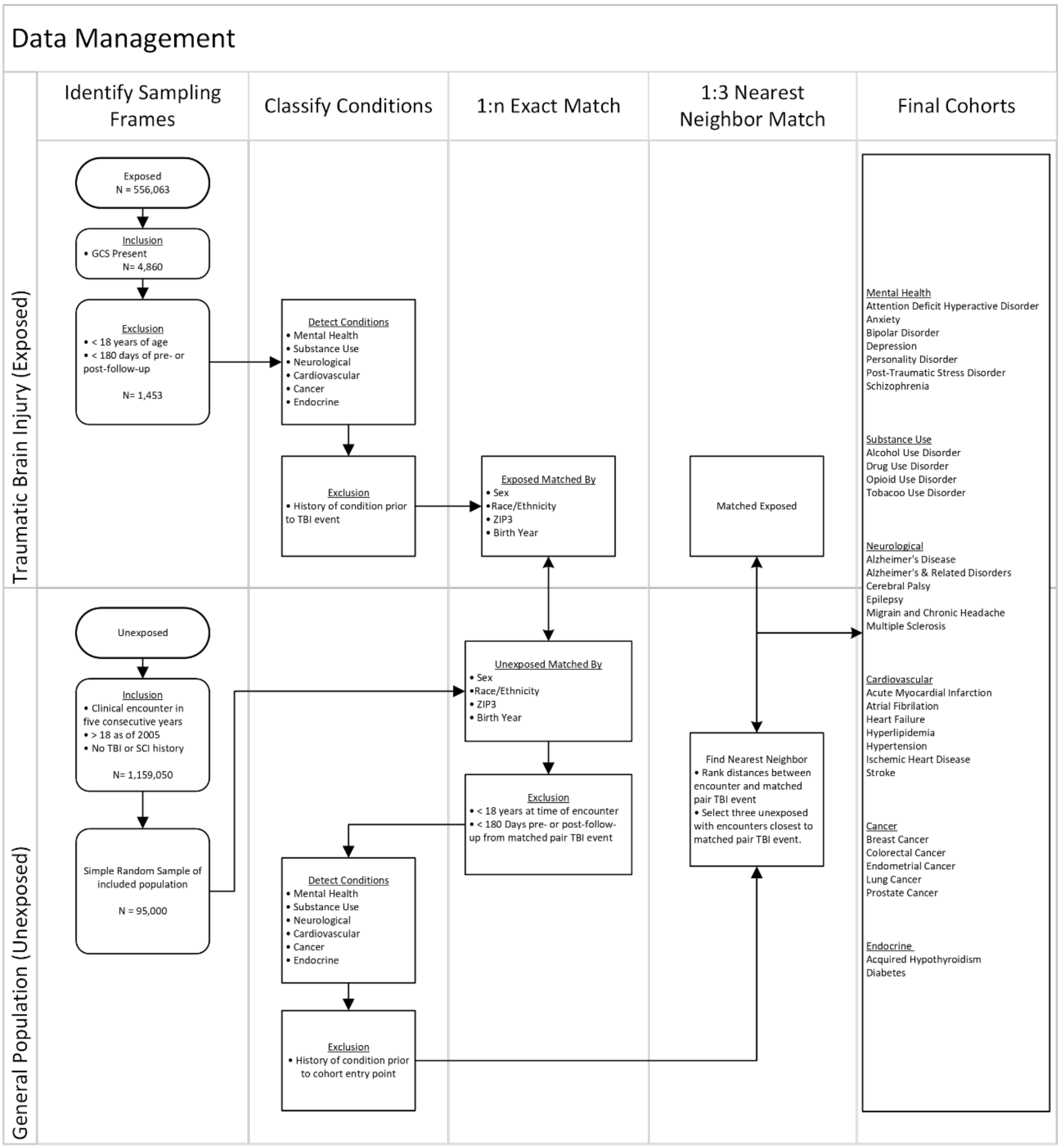
The Indiana TBI registry was constructed by identifying individuals in the INPC with ICD-9-CM or ICD-10-CM TBI diagnosis codes (Appendix B). Included individuals had their first TBI event or the "index" event between 2004 and 2018. For each included individual, encounter-level health record data was extracted, including demographics (e.g., age, sex, race, rurality), encounter information (e.g., visit type, location, diagnosis, length of stay), prescriptions (e.g., dispensed medications, dose, strength), and clinical data elements (e.g., screening and diagnostic tests and results, procedures, vitals).

4.2.2 Study Design and Population

A series of open population cohorts were formed from clinical data contained within the INPC, which included individuals aged 18 years and older between 2004 and 2018. The exposed populations were defined as individuals with a history of mTBI and recorded in the Indiana TBI registry. The unexposed population was drawn from a simple random sample of individuals with clinical data in the INPC and no history of TBI. A summary of the data management procedures described below is depicted in Figure 4.1.

At the time of the study, the Indiana TBI registry included 556,063 unique individuals with ICD-9-CM or ICD-10-CM TBI codes between 2004 and 2018. However, as detailed in Chapter 3, the positive predictive value for administrative codes was poor and varied across ICD-9-CM and ICD-10-CM implementations (0.326 and 0.679, respectively). To prevent exposure misclassification, the mTBI exposed subgroup was limited to individuals with a documented Glasgow Coma Scale (GCS). GCS was extracted from free-text clinical notes using a Natural Language Processing classification engine, which was described and evaluated in Chapter 2. In the event GCS was documented multiple times for a given individual, the lowest recorded score was used to classify their TBI severity. In total, 4,860 individuals had a documented GCS. Any individual who was less than 18 years of age at the time of their TBI event was excluded. Individuals with documented moderate (GCS 9-12) or severe (GCS 3-8) TBI were excluded. To allow time for observing pre-existing conditions and post-acute conditions, individuals with less than 180 days of follow-up before or after their mTBI event were excluded. Following the application of the exclusion criteria, 1,453 individuals with mTBI remained.

Figure 4.1. Data management procedures for construction of chronic condition cohorts and matching individuals with a history of mTBI to unexposed individuals from the general population.



To be included in the unexposed sampling frame, an individual must have non-claims-based clinical encounter data linked to diagnosis codes during at least five years of the study period (2004-2018), been 18 years of age as of January 1st, 2005, absent documented history of ICD-9-CM or ICD-10-CM TBI codes, and not be present in the Indiana TBI or Spinal Cord Injury registries. In total, 1,159,050 individuals met the inclusion criteria, from which a simple random sample of 95,000 was drawn. Among those selected into the unexposed sample, all clinical encounters occurring before 18 years of age were excluded.

4.2.3 Outcome Condition Classification

Condition definitions were derived from algorithms developed by the Chronic Conditions Data Warehouse (CCW) for identification of cohorts with chronic, mental health, and substance abuse conditions.[94] The CCW develops condition algorithms to support states and researchers in meaningful use of Centers for Medicare and Medicaid claims data. We examined six categories of conditions concerning mental health, substance use, cancer, neurological, cardiovascular, and endocrine conditions. We considered an individual positive for a condition if one or more encounters included a valid ICD-9-CM or ICD-10-CM diagnosis code. Valid diagnoses for each condition and algorithm references are available from the CCW.[94] Although several condition definitions include ICD-9-CM, ICD-10-CM, MS DRG, and HCPCS procedure codes, the current study relies solely upon diagnosis codes for condition identification.

4.2.4 Matching

Prior to matching, the CCW condition algorithms were applied to all diagnosis codes for each encounter to create a condition-specific indicator among the exposed and unexposed samples. Those with mTBI who experienced the condition of interest prior to their index date were excluded from the condition-specific cohort at baseline. The data management and two-stage matching procedure were replicated identically for each condition of interest by developing custom R functions. First, individuals with mTBI were exact matched to the unexposed general population by demographics and residential geography, generating a subgroup of candidate matches with identical observed covariate distributions. Second, within each subgroup, a 1:3 ratio of mTBI to unexposed were matched using a modified nearest neighbor approach to establish the unexposed cohort entry point and align exclusion criteria, calendar time, and follow-up time.

For each condition cohort, individuals with mTBI were exact matched, without replacement to all available unexposed individuals by year of birth, sex, race or ethnicity, and three-digit ZIP Code. For the purposes of matching, sex was categorized as binary – male or female. Due to the method of data capture in the INPC, it was not possible to separate race from ethnicity, resulting in the following categories: Asian; Black or African American; Hispanic; White; unknown; and other, which included American Indian and Alaska Native, Native Hawaiian and other Pacific Islander, Multiracial, and records with a coded "other" value. All exact matches were generated using the R library MatchIt.[95,96] The matching procedure creates a subclass identifier for each unique covariate combination, which is applied to all individuals with the same covariate combination.

Within each subclass, there may exist several individuals with mTBI and hundreds of unexposed individuals. To identify optimal matches within a subclass, each exposed individual with mTBI was compared to all possible unexposed candidate matches. For each mTBI – unexposed candidate match, the maximum observed follow-up time was determined. Unexposed individuals without at least 180 days of follow-up after the date of the matched mTBI event (index date) were excluded. Encounters within 180 days of the exposed index date were further considered as potential optimal matches.

Within each subclass, optimal matches were formed using a modified nearest neighbor approach. First, for each unexposed individual, we kept only the encounter closest to the matched mTBI candidate/s index date/s. Next, within a subclass and candidate match, the distance between each unexposed encounter and mTBI index date was ranked. The rank, which minimized the distance between encounter and mTBI index, was selected, limiting each unexposed to a single candidate mTBI match. In the event of ties, preference was given to the mTBI match with the fewest unexposed candidates available. With the unexposed cohort entry point defined, any history of conditions before or at baseline resulted in exclusion from the cohort. For each individual with mTBI, the three nearest remaining unexposed neighbors were selected to form the final cohorts.

Annual health insurance status was defined as the most coded, highest priority insurance status for each year of the study. Regardless of frequency, individuals were considered dually eligible if Medicaid and Medicare payers were indicated within the same year. Follow-up time was calculated as the time between entry into the cohort and death, lost to follow-up, or diagnosis for the condition of interest.

4.2.5 Statistical Analysis

The distribution of matching variables by exposure status was examined for all condition cohorts. Balance was verified using Pearson Chi-Square tests or Fishers Exact Tests for nominal variables and Student's t-tests for discrete and interval variables (Appendix D). Follow-up time by condition and exposure status was described in days by Kaplan-Meier quantiles from which we report medians and interquartile ranges.

Onset of conditions was quantified through cumulative incidence percentage and incidence density per person days of follow-up. Cumulative incidence measures do not account for censoring or competing events and were calculated as the sum of individuals with the condition divided by the number of condition-free individuals entering the cohort. On the other hand, incidence density accounts for unbalanced follow-up and common competing events by quantifying incidence as the number of individuals with the condition divided by the sum of observed follow-up time, with censoring for death or unexplained lost to follow-up.

Kaplan Meier curves were constructed for each condition of interest for visual inspection of survival probabilities and censoring patterns by exposure group. Serial follow-up time was plotted in days until one of three events occurred – the condition of interest, lost to follow-up, or death. When a condition of interest occurred, the group survival probability decreased. Lost to follow-up or death were considered censoring events and did not impact the group survival probability, only the number at risk for subsequent time periods. Curves were stratified by the exposure group for ease of comparison of survival functions between mTBI and unexposed and for visual inspection of proportional hazards.

Separate Cox proportional hazards models were fit for each condition of interest. The condition was classified as binary and independent variables included the exposure group, time-varying annual insurance status, and time invariant matching variables. Although all matching variables within the matched subpopulations were balanced at baseline, we included additional adjustment for two reasons. First, in the absence of censoring, ratios across strata of matching variables remain equal and omission of matching variables in analyses produce unbiased point estimates.[97] However, we observed significant censoring within each condition cohort, resulting in potential loss of covariate balance over time. Second, at the inclusion of additional confounders (i.e., insurance status), new paths of association are opened, and the matching variables and exposure status may no longer be independent within the matched subpopulation.[98]

Because Hazard Ratios (HR) are non-collapsible, our approach prevented determination of the marginal HR as well as causal interpretations from the matched models. As a result, all Cox model HR are conditional and represent associations observed within the matched subpopulation, without causal inference to the target population. It is common practice for authors to report the coefficients or HR for confounding variables alongside the exposure of interest. However, sampling, study design, and measured confounders typically focus only on adjustment for factors known to be associated with the exposure and outcome. Thus, even in the case where the relationship between the exposure of interest and outcome is unconfounded, the relationship between a given confounding variable and condition is likely confounded. This phenomenon, known as Table 2 fallacy, results in inappropriate interpretation of multiple regression findings.[99] To prevent Table 2 fallacy, we omitted all HR between confounding variables and conditions. Thus, the reported HR from Cox proportional hazards models represent the conditional HR between mTBI and conditions of interest.

For each model, the proportional hazards assumption was assessed visually by plotting a weighted least-squares line fitted to the residual plot, and through hypothesis testing using the Schoenfeld residuals test. When violated, the Cox proportional hazards model was refit taking a time stratified approach, and conditional HR were reported separately for intervals of follow-up.

Traditional absolute measures of public health significance, including attributable risk and population attributable risk, require estimation of causal parameters, which were unavailable under the current study design. To assess which chronic conditions may be of greatest public health significance to individuals with mTBI, a pseudo measure of importance relative to the subpopulation and conditions studied was constructed. In this context, relative importance represents a linear combination of the chronic condition incidence rate in the mTBI population and the conditional HR from the Cox proportional hazards model. While it is not appropriate to generalize this measure to the target population, it facilitated comparison of chronic conditions to one another within the matched subpopulation. For example, a relatively rare condition (low incidence rate) and small effect size (e.g., HR close to 1.0) demonstrates little public health significance within the subpopulation, whereas a common condition with a large effect size represents a greater relative importance. To improve interpretation, this measure was rescaled from one to one hundred, wherein values of one and one hundred represent the lowest and highest relative importance, respectively.

4.3 Results

At baseline, the matching procedure produced unequivocally balanced cohorts at a ratio of one mTBI to three unexposed individuals (see Appendix D). In general, due to the exclusion of condition positive individuals at baseline, cohort sample sizes were indirectly related to condition prevalence; more prevalent conditions resulted in smaller sized cohorts. Cohorts ranged between 52% and 60% female, 88% and 90% White race, with a mean age of 54 years to 58 years. We observed a lower mean age among the hyperlipidemia and hypertension cohorts (47 years and 49 years, respectively), due to exclusion of prevalence conditions at baseline. Although included three-digit ZIP Codes varied by cohort, on average each cohort included individuals from 11 distinct regions in Indiana.

4.3.1 Mental Health Conditions

Conditions included in the analysis of mental health included attention deficit hyperactivity disorder (ADHD), anxiety, bipolar disorder, depression, personality disorder, post-traumatic stress disorder (PTSD), and schizophrenia. Table 4.1 details cohort sample sizes, median and interquartile ranges for follow-up, cumulative incidence, and incidence rates. Final cohort sample sizes ranged from 2,444 to 3,760. The median number of follow-up days ranged between 887 and 1,035 days and was similar between mTBI and unexposed individuals within each cohort.

Incidence rates were markedly higher among those with mTBI for all mental health conditions. Most notably, incidence was 7.5- to 8-fold greater among mTBI for anxiety, bipolar disorder, and depression. Figure 4.2 depicts the Kaplan Meier curves for each cohort, wherein survival is equivalent to absence of disease, failure is an incident event, and vertical lines represent censoring due to lost to follow-up or death. Consistent with incidence estimates, we observed strong separation between mTBI and unexposed survival probabilities for anxiety and depression beginning in the acute period and persisting throughout the study period into the post-acute period. While the incidence of other mental health conditions was relatively lower among both groups, we did observe separation between mTBI and unexposed. Although no hazards crossover was observed, depression exhibited a significant deviation from proportionality due to changing hazards over time (p = 0.008).

Table 4.1. Cohort sizes, follow-up, and incidence of mental health conditions for individuals exposed to mTBI and a matched unexposed population.

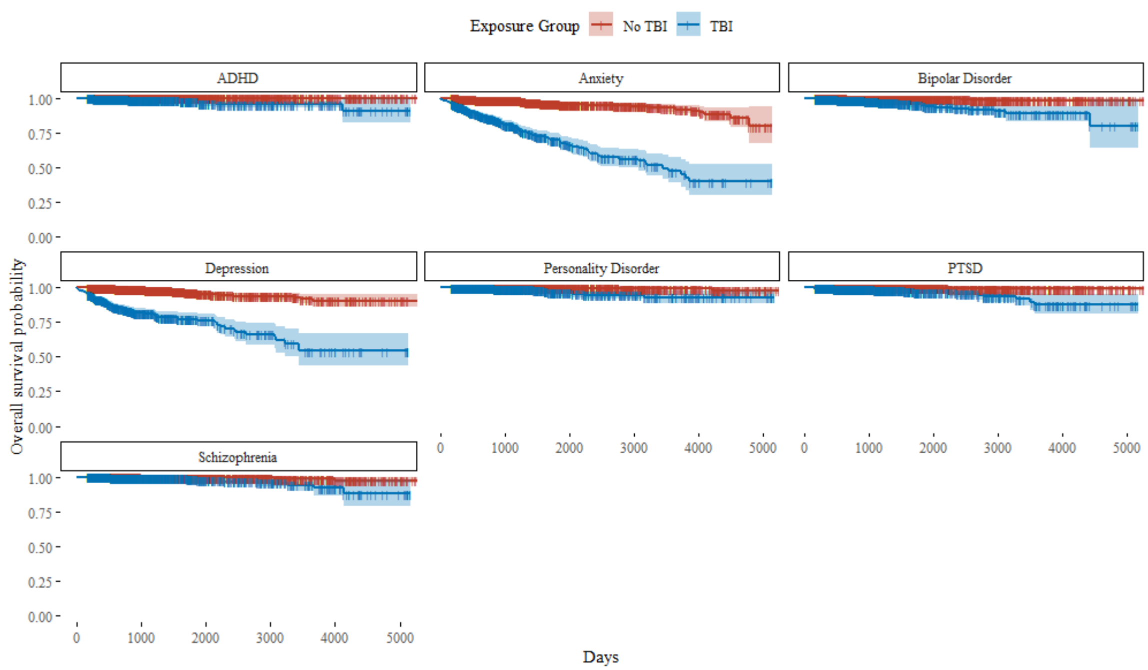
	Matched Sample size		**Follow Up (Days)**		**Cumulative Incidence (%)**		**Incidence Rate (1,000 pdy[1])**	
Condition	*Unxp*	*Exp*	*Unxp M (IQR)[1]*	*Exp M (IQR)[1]*	*Unxp*	*Exp*	*Unxp*	*Exp*
ADHD[1]	2,775	925	942 (1,136)	887 (1,147)	0.22	1.41	0.63	4.26
Anxiety	2,304	768	964 (1,150)	1,035 (1,451)	3.3	22.4	9.6	78.0
Bipolar Disorder	2,703	901	943 (1,129)	890 (1,144)	0.41	3.11	1.18	9.5
Depression	1,833	611	937 (1,107)	979 (1,251)	2.89	18.33	8.76	65.65
Personality Disorder	2,745	915	937 (1,131)	887 (1,112)	0.36	1.64	1.05	5.01
PTSD[1]	2,760	920	941 (1,141)	895 (1,158)	0.40	2.28	1.15	6.90
Schizophrenia	2,820	940	948 (1,157)	892 (1,150)	0.60	1.49	1.72	4.43

[1]ADHD = Attention Deficit Hyperactive Disorder; PTSD = Post-Traumatic Stress Disorder; pdy = person-days; M = Median; IQR = Interquartile Range

Exposure to mTBI significantly increased the observed hazard of each mental health condition under study, with the exception of schizophrenia (Table 4.2). After adjustment for annual health insurance status and demographic matching variables, anxiety was 7 times as likely among mTBI (aHR = 7.60 95% CI 5.77, 10.0). The mTBI group also demonstrated 6-fold the hazard of the unexposed for ADHD (aHR = 6.65 95% CI 2.09-21.1) and bipolar disorder (aHR = 6.55 95% CI 3.13-13.7), and approximately 5-

fold for PTSD (aHR = 5.09 95% CI 2.39, 10.8). The smallest hazard magnitude related to a history of mTBI was observed for personality disorders and schizophrenia (aHR = 3.12 95% CI 1.33, 7.76 and aHR = 1.85 95% CI 0.89, 3.82, respectively). The hazard of depression was greatest in the first year (aHR=17.5 95% CI 8.58-35.8) and decreased over time, remaining significant in the second year (aHR = 6.94 95% CI 3.67-13.1), as well as after two or more years of follow-up (aHR=3.18 95% CI 1.91-5.30).

Figure 4.2. Kaplan Meier curves for mental health conditions stratified by exposure group.



Note: ADHD = Attention Deficit Hyperactive Disorder; PTSD = Post-Traumatic Stress Disorder

Table 4.2. Unadjusted and adjusted Cox proportional hazard ratios for mental health conditions among individuals exposed to mTBI compared to an unexposed matched population.

		ADHD[1,2]			**Anxiety[2]**			**Depression[3]**			**PTSD[1,2]**		
Model	*Exposure*	*HR[1]*	*95% CI[1]*	*p-value*	*HR[1]*	*95% CI[1]*	*p-value*	*HR[1]*	*95% CI[1]*	*p-value*	*HR[1]*	*95% CI[1]*	*p-value*
Unadjusted	Unexposed	1.0	-	<0.001	1.0	1.0	<0.001	1.0	-		1.0	-	<0.001
	Exposed	6.89	2.61, 18.2		8.18	6.24, 10.7					6.03	2.91, 12.5	
	<= 1 Year	-	-		-	-		18.5	9.11, 37.5		-	-	
	1-2 Years	-	-		-	-		7.57	4.02, 14.3	<0.0001	-	-	
	> 2 Years	-	-		-	-		3.70	2.23, 6.14		-	-	
Adjusted	Unexposed	1.0	-	0.001	1.0	-	<0.001	1.0	-		1.0	-	0.001
	Exposed	6.65	2.09, 21.1		7.60	5.77, 10.0					5.09	2.39, 10.8	
	<= 1 Year	-	-		-	-		17.5	8.58, 35.8		-	-	
	1-2 Years	-	-		-	-		6.94	3.67, 13.1	<0.001	-	-	
	> 2 Years	-	-		-	-		3.18	1.91, 5.30		-	-	

		Personality Disorders[2]			**Bipolar Disorder[2]**			**Schizophrenia[2]**		
Model	*Exposure*	*HR[1]*	*95% CI[1]*	*p-value*	*HR[1]*	*95% CI[1]*	*p-value*	*HR[1]*	*95% CI[1]*	*p-value*
Unadjusted	Unexposed	1.0	-	<0.001	1.0	-	<0.001	1.0	-	0.008
	Exposed	4.87	2.19, 10.8		8.20	4.07, 16.5		2.61	1.29, 5.27	
Adjusted	Unexposed	1.0	-	0.010	1.0	-	<0.001	1.0	-	0.100
	Exposed	3.21	1.33, 7.76		6.55	3.13, 13.7		1.85	0.89, 3.82	

[1]HR = Hazard Ratio; CI = Confidence Interval; PTSD = Post Traumatic Stress Disorder; ADHD = Attention Deficit Hyperactive Disorder
[2]Conditional Cox Proportional Hazards model adjusted for matching variables sex, race or ethnicity, age, and time varying health insurance status.
[3]Time stratified conditional Cox Proportional Hazards model adjusted for matching variables sex, race or ethnicity, age, and annual health insurance status.

4.3.2 Substance Use Conditions

Conditions included in the analysis of substance use included alcohol, drug, opioid, and tobacco use disorders. Table 4.3 details cohort sample sizes, median and interquartile ranges for follow-up, cumulative incidence, and incidence rates. Final cohort sample sizes ranged from 2,588 to 3,696. The median number of follow-up days ranged between 900 and 969 days and was similar between the exposed and unexposed within each cohort.

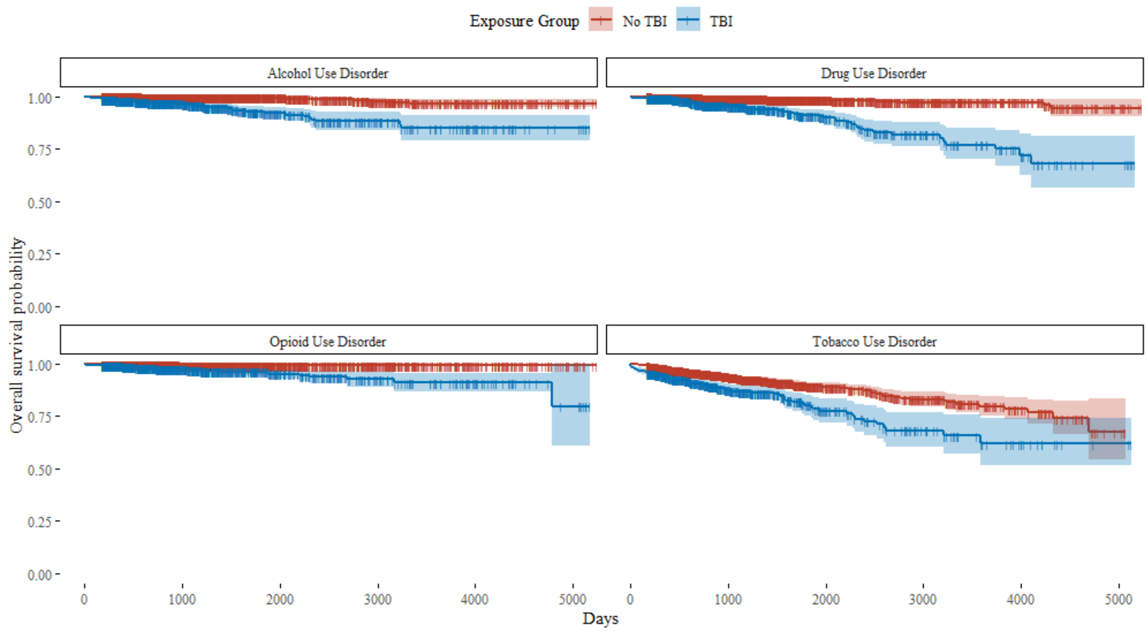
Table 4.3. Cohort sizes, follow-up, and incidence of substance use conditions for individuals exposed to mTBI and a matched unexposed population.

	Matched Sample size		**Follow Up (Days)**		**Cumulative Incidence (Percent)**		**Incidence Rate (1,000 pdy[1])**	
Condition	*Unxp*	*Exp*	*Unxp M (IQR)[1]*	*Exp M (IQR)[1]*	*Unxp*	*Exp*	*Unxp*	*Exp*
Alcohol	2670	890	955 (1183)	900 (1227)	0.60	5.06	1.69	15.49
Drug	2667	889	969 (1163)	934 (1228)	1.12	6.75	3.16	20.74
Opioid	2772	924	962 (1173)	912 (1202)	0.54	3.25	1.53	9.73
Tobacco	1941	647	945 (1188)	934 (1221)	7.37	13.76	22.50	47.90

[1]pdy = person-days; M = Median; IQR = Interquartile Range

Across all conditions studied, the incidence of substance use was elevated among those with mTBI. The most common condition in both mTBI and unexposed individuals was tobacco use, followed by drug use. Relative to the unexposed, those with a history of mTBI were 9-fold as likely to experience an alcohol use condition and were 6-fold as likely to experience a drug or opioid use condition during follow-up. Kaplan Meier curves demonstrated separation between the exposure groups without crossover and no evidence of proportional hazards violation. We observed immediate tobacco use events among both the mTBI and unexposed groups, suggesting imperfect exclusion of prevalent use at baseline (Figure 4.3).

Figure 4.3. Kaplan Meier curves for substance use conditions stratified by exposure group.



Consistent with crude incident rates, history of mTBI significantly increased the hazards of substance use conditions among the cohorts studied (Table 4.4). After adjustment for annual health insurance and demographic matching variables, documented alcohol use disorder was 9 times as likely among those exposed to mTBI (aHR = 8.98 95% CI 4.93, 16.4). The mTBI group also demonstrated 5-fold the hazard of the unexposed for opioid use disorder (aHR = 5.48 95% CI 2.91, 10.3) and substance use disorder (aHR = 5.12 95% CI 3.19, 8.21). Tobacco use disorder exhibited the weakest association of the substance use conditions yet was twice as likely among those with mTBI (aHR 1.99 95% CI 1.50, 2.64).

Table 4.4. Unadjusted and adjusted Cox proportional hazard ratios for substance use conditions among individuals exposed to mTBI compared to an unexposed matched population.

		Tobacco Use Disorder[2]			**Alcohol Use Disorder**[2]			**Substance Use Disorder**[2]			**Opioid Use Disorder**[2]		
Model	*Exposure*	*HR*[1]	*95% CI*[1]	*p-value*	*HR*[1]	*95% CI*[1]	*p-value*	*HR*[1]	*95% CI*[1]	*p-value*	*HR*[1]	*95% CI*[1]	*p-value*
Unadjusted	Unexposed	1.0	-	<0.001	1.0	-	<0.001	1.0	-	<0.001	1.0	-	<0.001
	Exposed	2.13	1.63, 2.77		9.18	5.22, 16.1		6.72	4.34, 10.4		6.29	3.38, 11.7	
Adjusted	Unexposed	1.0	-	<0.001	1.0	-	<0.001	1.0	-	<0.001	1.0	-	<0.001
	Exposed	1.99	1.50, 2.64		8.98	4.93, 16.4		5.12	3.19, 8.21		5.48	2.91, 10.3	

[1]HR = Hazard Ratio; CI = Confidence Interval;
[2]Conditional Cox Proportional Hazards model adjusted for matching variables sex, race or ethnicity, age, and time varying health insurance status.

4.3.3 Neurological Conditions

Conditions included in the analysis of neurological outcomes included Alzheimer's Disease alone, Alzheimer's Disease and related disorders, cerebral palsy, epilepsy, migraine and chronic headache, and multiple sclerosis. Final cohort sample sizes ranged from 3,644 to 3,812 (Table 4.5). The median number of follow-up days ranged between 895 and 969 days. The unexposed had minimally longer median follow-up times and the exposed moderately wider interquartile ranges.

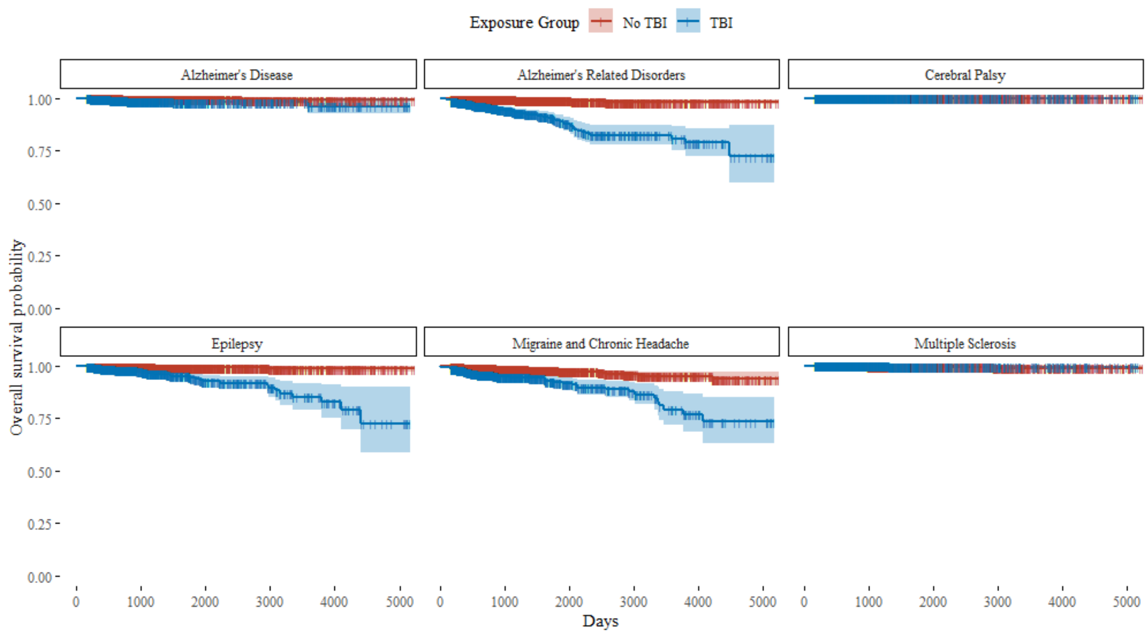
Table 4.5. Cohort sizes, follow-up, and incidence of neurological conditions for individuals exposed to mTBI and a matched unexposed population.

	Matched Sample size		**Follow Up (Days)**		**Cumulative Incidence (Percent)**		**Incidence Rate (1,000 pdy[1])**	
Condition	*Unxp*	*Exp*	*Unxp M (IQR)[1]*	*Exp M (IQR)[1]*	*Unxp*	*Exp*	*Unxp*	*Exp*
Alzheimer's	2850	940	953 (1164)	906 (1652)	0.21	1.26	0.60	3.68
Alzheimer's & related	2775	925	964 (1175)	969 (1240)	0.65	7.57	1.82	22.5
Cerebral Palsy	2859	953	951 (1172)	897 (1163)	0.035	0.0	0.099	0.0
Epilepsy	2784	928	960 (1163)	906 (1202)	0.50	4.20	1.43	12.6
Migraine & Chronic Headache	2733	911	962 (1171)	934 (1249)	1.68	6.26	4.79	19.01
Multiple Sclerosis	2835	945	949 (1156)	895 (1164)	0.14	0.11	0.40	0.31

[1]pdy = person-days; M = Median; IQR = Interquartile Range

With the exception of cerebral palsy and multiple sclerosis, the incidence of neurological conditions was elevated among those with mTBI. The most common neurological condition in those with mTBI was Alzheimer's Disease and related disorders, followed by migraine and chronic headache. Relative to the unexposed, those with mTBI were 12-fold as likely to be diagnosed with Alzheimer's Disease or related disorders and were 8-fold as likely to have an epilepsy diagnosis during follow-up. During follow-up, we did not observe any cerebral palsy diagnoses among those with mTBI. Kaplan Meier curves demonstrate separation between the exposure groups consistent with differences in observed incidence without crossover or evidence of proportional hazards violation (Figure 4.4).

Figure 4.4. Kaplan Meier curves for neurological conditions stratified by exposure group.



After adjustment for annual health insurance and demographic matching variables, Alzheimer's Disease and related disorders were nearly 13 times as likely among those exposed to mTBI (aHR = 12.8 95% CI 7.61, 21.5; Table 4.6). mTBI also demonstrated 7-fold the hazard of the unexposed for an epilepsy diagnosis (aHR = 7.07 95% CI 3.70, 13.5) and three times the hazard of a migraine and chronic headache diagnosis (aHR = 3.72 95% CI 2.47, 5.62).

Table 4.6. Unadjusted and adjusted Cox proportional hazard ratios for neurological conditions among individuals exposed to mTBI compared to an unexposed matched population.

		Alzheimer's Disease[2]			Alzheimer's and Related Disorders[2]			Epilepsy[2]			
Model	*Exposure*	*HR[1]*	*95% CI[1]*	*p-value*	*HR[1]*	*95% CI[1]*	*p-value*	*HR[1]*	*95% CI[1]*	*p-value*	*HR[1]*
Unadjusted	Unexposed	1.0	-	<0.001	1.0	-	<0.001	1.0	-	<0.001	1.0
	Exposed	6.21	2.34, 16.5		12.3	7.35, 20.7		8.88	4.81, 16.4		3.99
Adjusted	Unexposed	1.0	-	<0.001	1.0	-	<0.001	1.0	-	<0.001	1.0
	Exposed	5.74	2.22, 14.8		12.8	7.61, 21.5		7.07	3.70, 13.5		3.72
		Multiple Sclerosis[2]			**Cerebral Palsy[3]**			**Migraine and Chronic Headache[2]**			
Model	*Exposure*	*HR[1]*	*95% CI[1]*	*p-value*	*HR[1]*	*95% CI[1]*	*p-value*	*HR[1]*	*95% CI[1]*	*p-value*	
Unadjusted	Unexposed	1.0	-	0.80		NA		1.0	-	<0.001	
	Exposed	0.78	0.09, 6.99					3.99	2.71, 5.88		
Adjusted	Unexposed	1.0	-	>0.90		NA		1.0	-	<0.001	
	Exposed	1.01	0.09, 11.9					3.72	2.47, 5.62		

[1]HR = Hazard Ratio; CI = Confidence Interval;
[2]Conditional Cox Proportional Hazards model adjusted for matching variables sex, race or ethnicity, age, and time varying health insurance status.
[3]Cerebral palsy was not modeled due to an absence of observed incident events

4.3.4 Cardiovascular Conditions

Conditions included in the analysis of cardiovascular outcomes included acute myocardial infarction, atrial fibrillation, heart failure, hypertension, hyperlipidemia, stroke and transient ischemic attack, and ischemic heart disease. Final cohort sample sizes ranged from 1,724 to 3,736 (Table 4.7). Median follow-up ranged between 912 and 1,154 days and was similar between mTBI and the unexposed.

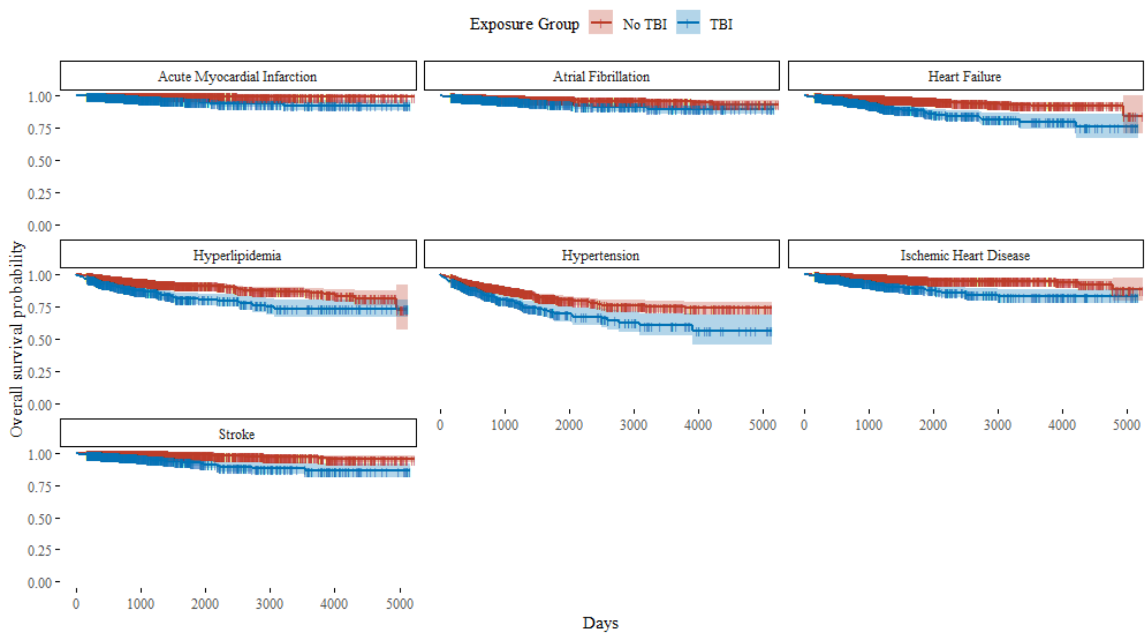
Table 4.7. Cohort sizes, follow-up, and incidence of cardiovascular conditions for individuals exposed to mTBI and a matched unexposed population.

	Matched Sample size		**Follow Up (Days)**		**Cumulative Incidence (Percent)**		**Incidence Rate (Per 1,000 pdy[1])**	
Condition	*Unxp*	*Exp*	*Unxp M (IQR)[1]*	*Exp M (IQR)[1]*	*Unxp*	*Exp*	*Unxp*	*Exp*
Acute MI[1]	2802	934	951 (1170)	912 (1207)	0.32	2.68	0.91	7.90
Atrial Fibrillation	2601	867	971 (1216)	934 (1259)	2.23	4.27	0.62	1.25
Heart Failure	2584	814	982 (1212)	954 (1244)	2.67	8.02	7.5	24.1
Hyperlipidemia	1719	573	1104 (1273)	1112 (1640)	6.98	14.14	18.9	41.9
Hypertension	1293	431	1152 (1273)	1154 (1643)	13.5	21.8	39.7	71.5
IHD[1]	2355	785	968 (1202)	947 (1261)	2.72	7.64	7.69	23.29
Stroke	2496	832	964 (1176)	913 (1230)	1.24	5.17	3.49	15.54

[1] MI = myocardial infarction; IHD = ischemic heart disease; pdy = person-days; M = Median; IQR = Interquartile Range

The observed incidence of cardiovascular conditions was greater among those with mTBI across all cohorts. The most common conditions were hypertension, hyperlipidemia, heart failure, and ischemic heart disease. The greatest ratio of incidence in mTBI to the unexposed was acute myocardial infarction (8-fold), stroke and transient ischemic attack (4-fold), and heart failure (3-fold). Kaplan Meier curves demonstrated minimal-to-moderate separation between the exposure groups without visual or statistical evidence of crossover (Figure 4.5). Events were observed within the first 180 days of follow-up for hypertension and hyperlipidemia, which may suggest imperfect exclusion of conditions at baseline among both the exposed and unexposed.

Figure 4.5. Kaplan Meier curves for cardiovascular conditions stratified by exposure group.



Exposure to mTBI significantly increased the hazard of all cardiovascular condition diagnoses among the cohorts studied (Table 4.8). After adjustment for annual health insurance and demographic matching variables, Acute Myocardial Infarction was 9 times as likely among those exposed to mTBI (aHR = 8.98 95% CI 4.21, 19.1). mTBI also demonstrated 3.8-fold the hazard of the unexposed for stroke and transient ischemic attack (aHR = 3.77 95% CI 2.28, 6.25) and two times the hazard of heart failure (aHR = 2.92 95% CI 2.07, 4.13), ischemic heart disease (aHR = 2.70 95% CI 1.87, 3.91), hyperlipemia (aHR = 2.44 95% CI 1.83, 3.24), and hypertension (aHR = 1.95 95% CI 1.52, 2.51).

Table 4.8. Unadjusted and adjusted Cox proportional hazard ratios for cardiovascular conditions among individuals exposed to mTBI compared to an unexposed matched population.

		Acute Myocardial Infarction[2]			Atrial Fibrillation[2]			Heart Failure[2]			Hypertension[2]		
Model	*Exposure*	*HR[1]*	*95% CI[1]*	*p-value*	*HR[1]*	*95% CI[1]*	*p-value*	*HR[1]*	*95% CI[1]*	*p-value*	*HR[1]*	*95% CI[1]*	*p-value*
Unadjusted	Unexposed	1.0	-	<0.001	1.0	-	0.001	1.0	-	<0.001	1.0	-	<0.001
	Exposed	8.71	4.06, 18.7		1.99	1.32, 3.01		3.21	2.31, 4.46		1.77	1.38, 2.28	
Adjusted	Unexposed	1.0	-	<0.001	1.0	-	0.006	1.0	-	<0.001	1.0	-	<0.001
	Exposed	8.98	4.21, 19.1		1.84	1.19, 2.85		2.92	2.07, 4.13		1.95	1.52, 2.51	

		Hyperlipidemia[2]			Stroke and TIA[1,2]			Ischemic Heart Disease[2]		
Model	*Exposure*	*HR[1]*	*95% CI[1]*	*p-value*	*HR[1]*	*95% CI[1]*	*p-value*	*HR[1]*	*95% CI[1]*	*p-value*
Unadjusted	Unexposed	1.0	-	<0.001	1.0	-	<0.001	1.0	-	<0.001
	Exposed	2.18	1.64, 2.90		4.40	2.77, 6.99		2.99	2.10, 4.26	
Adjusted	Unexposed	1.0	-	<0.001	1.0	-	<0.001	1.0	1.87, 3.91	<0.001
	Exposed	2.44	1.83, 3.24		3.77	2.28, 6.25		2.70		

[1]HR = Hazard Ratio; CI = Confidence Interval; TIA = transient ischemic attack
[2]Conditional Cox Proportional Hazards model adjusted for matching variables sex, race or ethnicity, age, and time varying health insurance status.

4.3.5 Cancer

Cancer cohorts were formed around the most common cancers observed in the general population, including breast, colorectal, endometrial, lung, and prostate cancer. Table 4.9 details cohort sample sizes, median and interquartile ranges for follow-up, cumulative incidence, and incidence rates. Final cohort sample sizes ranged from 1,512 (sex-specific reproductive cancers) to 3,803. Median follow-up ranged between 897 and 1,212 days and was similar between the exposed and unexposed.

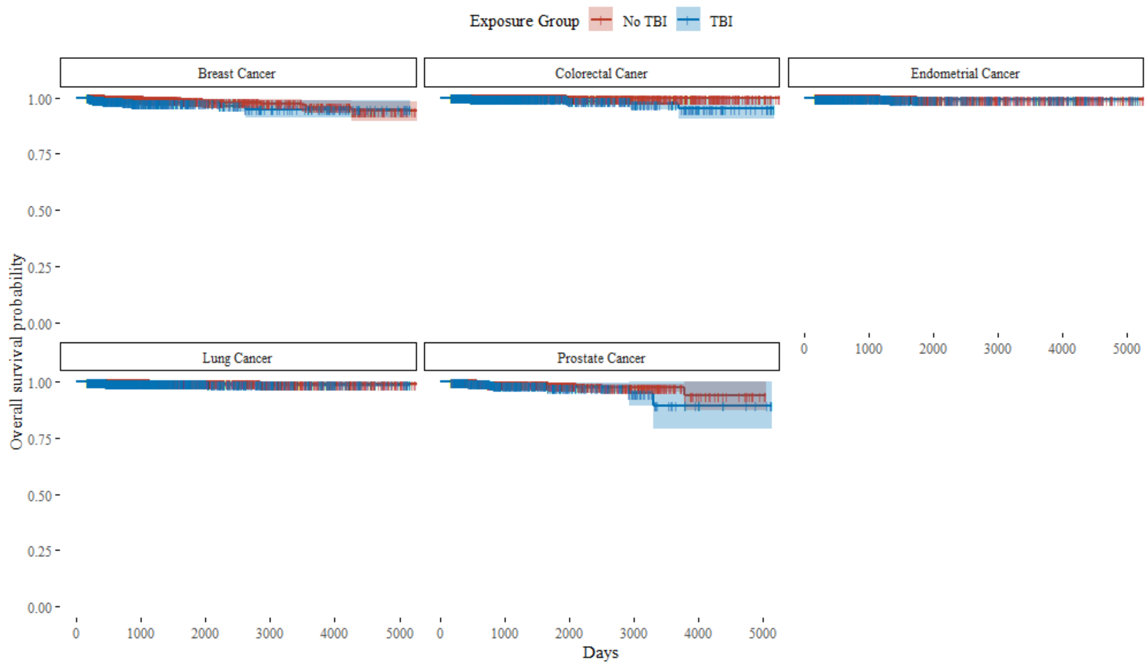
Table 4.9. Cohort sizes, follow-up, and incidence of cancer for individuals exposed to mTBI and a matched unexposed population.

	Matched Sample size		**Follow Up (Days)**		**Cumulative Incidence (Percent)**		**Incidence Rate (Per 1,000 pdy[1])**	
Condition	*Unxp*	*Exp*	*Unxp M (IQR)[1]*	*Exp M (IQR)[1]*	*Unxp*	*Exp*	*Unxp*	*Exp*
Breast[2]	1569	523	943 (1144)	897 (1157)	2.10	2.10	6.05	6.25
Colorectal	2829	943	960 (1158)	900 (1167)	0.25	0.85	0.70	2.5
Endometrial[2]	1677	559	910 (1159)	888 (1131)	0.30	0.54	0.86	1.59
Lung	2856	947	953 (1182)	899 (1165)	0.67	0.53	1.89	1.54
Prostate[3]	1134	378	1073 (1212)	952 (1199)	1.76	2.12	0.48	0.60

[1]pdy = person-days; M = Median; IQR = Interquartile Range
[2]Cohort restricted to females
[3]Cohort restricted to males

Generally, the observed incidence of cancer was similar among those with and without mTBI. Breast cancer was the most common condition observed among both groups. The greatest ratio of incidence among mTBI to unexposed was observed for colorectal cancer (3.5-fold). Kaplan Meier curves depicted no discernable separation between the exposure groups (Figure 4.6).

Figure 4.6. Kaplan Meier curves for cancer stratified by exposure group.



Exposure to TBI significantly increased the hazards of a subsequent colorectal cancer diagnoses (Table 4.10). After adjustment for annual health insurance and demographic matching variables, colorectal cancer was 3 times as likely among those exposed to TBI (HR = 3. 13 95% CI 1.20, 8.19).

Table 4.10. Unadjusted and adjusted Cox proportional hazard ratios for cancer among individuals exposed to mTBI compared to an unexposed matched population.

		Lung Cancer[2]			**Colorectal Cancer[2]**			**Breast Cancer[2,3]**		
Model	*Exposure*	*HR[1]*	*95% CI[1]*	*p-value*	*HR[1]*	*95% CI[1]*	*p-value*	*HR[1]*	*95% CI[1]*	*p-value*
Unadjusted	Unexposed	1.0	-	0.70	1.0	-	0.015	1.0	-	>0.90
	Exposed	0.81	0.30, 2.17		3.51	1.28, 9.67		1.03	0.52, 2.04	
Adjusted	Unexposed	1.0	-	0.40	1.0	-	0.020	1.0	-	>0.90
	Exposed	0.63	0.23, 1.73		3.13	1.20, 8.19		1.02	0.49, 2.13	
		Prostate Cancer[2,4]			**Endometrial Cancer[2,3]**					
Model	*Exposure*	*HR[1]*	*HR[1]*	*HR[1]*	*HR[1]*	*95% CI[1]*	*p-value*			
Unadjusted	Unexposed	1.0	1.0	1.0	1.0	-	0.60			
	Exposed	1.25	1.86	1.86	1.86	0.45, 7.71				
Adjusted	Unexposed	1.0	1.0	1.0	1.0	-	0.30			
	Exposed	1.51	2.01	2.01	2.01	0.45, 9.03				

[1]HR = Hazard Ratio; CI = Confidence Interval;
[2]Conditional Cox Proportional Hazards model adjusted for matching variables sex, race or ethnicity, age, and time varying health insurance status.
[3]Cohort restricted to females
[4]Cohort restricted to males

4.3.6 Endocrine Conditions

Two endocrine condition cohorts studied, including acquired hypothyroidism and diabetes. Table 4.11 details cohort sample sizes, median and interquartile ranges for follow-up, cumulative incidence, and incidence rates. Incidence was elevated among those with mTBI for acquired hypothyroidism (2.7-fold) and diabetes (1.7-fold), with clear separation observable on Kaplan Meier curves and no evidence of proportional hazards violation (Figure 4.7). After adjusting for demographic matching variables and annual health insurance, hazards associated with mTBI were statistically significant and similar in magnitude to the crude incidence ratios (Table 4.12).

Table 4.11. Cohort sizes, follow-up, and incidence of endocrine conditions for individuals exposed to mTBI and a matched unexposed population.

	Matched Sample size		**Follow Up (Days)**		**Cumulative Incidence (Percent)**		**Incidence Rate Per 1,000 pdy[1])**	
Condition	*Unxp*	*Exp*	*Unxp M (IQR)*	*Exp M (IQR)*	*Unxp*	*Exp*	*Unxp*	*Exp*
Acquired Hypothyroidism	2301	767	984 (1,205)	931 (1,235)	2.04	5.08	5.73	15.22
Diabetes	2437	813	1,044 (1,262)	1,017 (1,309)	5.7	9.35	15.9	27.7

[1]pdy = person-days; M = Median; IQR = Interquartile Range

Figure 4.7. Kaplan Meier curves for endocrine conditions stratified by exposure group.

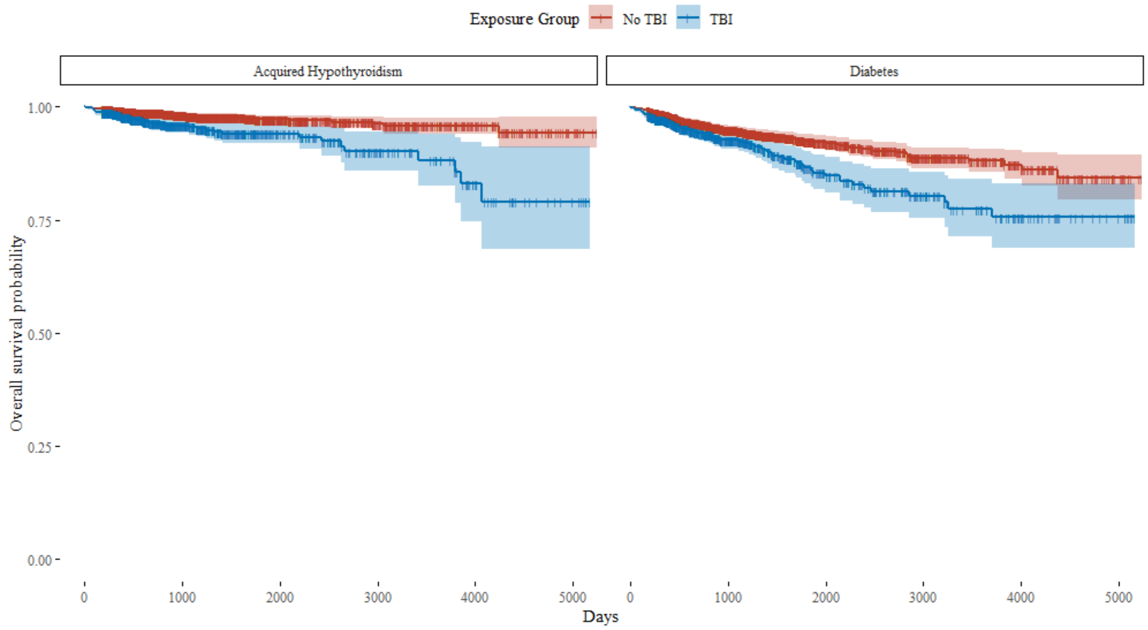


Table 4.12. Unadjusted and adjusted Cox proportional hazard ratios for endocrine conditions among individuals exposed to mTBI compared to an unexposed matched population.

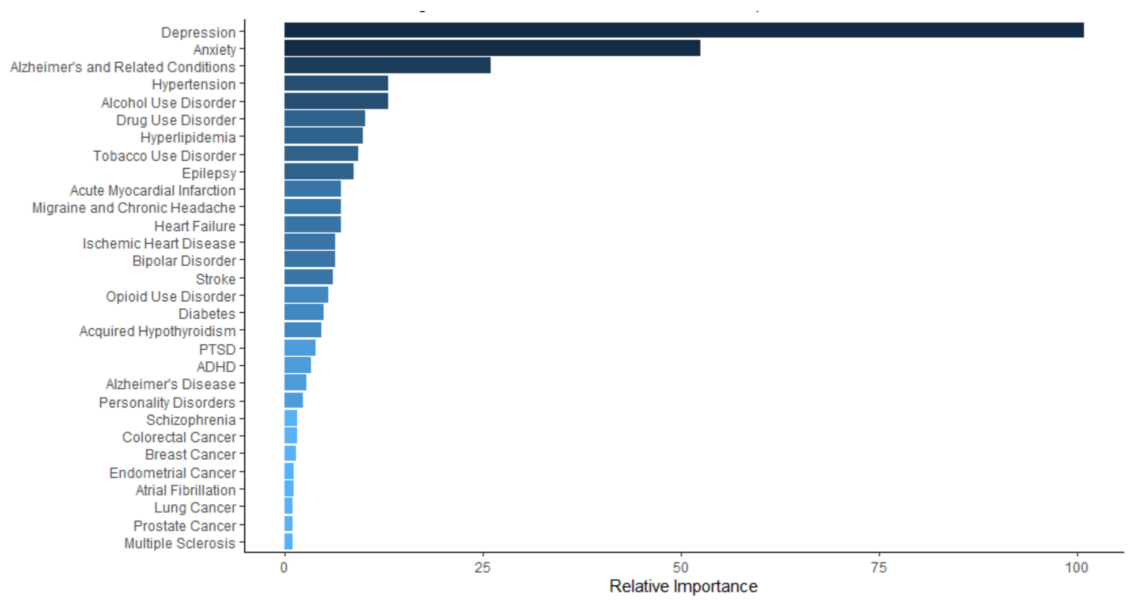
		Diabetes[2]			**Acquired Hypothyroidism**[2]		
Model	*Exposure*	*HR*[1]	*95% CI*[1]	*p-value*	*HR*[1]	*95% CI*[1]	*p-value*
Unadjusted	Unexposed	1.0	-	<0.001	1.0	-	<0.001
	Exposed	1.73	1.31, 2.29		2.64	1.73, 4.03	
Adjusted	Unexposed	1.0	-	<0.001	1.0	-	<0.001
	Exposed	1.68	1.24, 2.27		2.83	1.85, 4.35	

[1]HR = Hazard Ratio; CI = Confidence Interval
[2]Conditional Cox Proportional Hazards model adjusted for matching variables sex, race or ethnicity, age, and time varying health insurance status.

4.3.7 Public Health Significance in the Matched Subpopulation

Among all conditions, depression and anxiety stood out as the most significant. Although we observed similar incidence between depression and anxiety among those with a history of mTBI, the relative importance of depression was demonstrably greater due to a larger magnitude of the association. After depression and anxiety, Alzheimer's Disease and related conditions demonstrated high importance in the subpopulation relative to other conditions studied. The remaining conditions in the top ten of relative importance consisted of a mix of substance use conditions (alcohol, drugs, and tobacco), cardiovascular conditions (hypertension and acute myocardial infarction), and epilepsy, a neurological condition (Figure 4.8).

Figure 4.8. Estimated, relative importance of each condition to individuals with traumatic brain injury.



4.4 Discussion

We hypothesized that a history of mTBI would be associated with greater incidence of chronic conditions. Our study observed individuals with mTBI experienced greater incidence of mental health, substance use, neurological, cardiovascular, and endocrine conditions than a group of age, sex, race, and residential ZIP code exact-matched individuals with no history of TBI. Among these, due to the relative strength of the associations and high incidence rates, several conditions may have a relatively greater public health significance, including depression, anxiety, Alzheimer's and related disorders, hypertension, alcohol use disorder, drug use disorder, hyperlipidemia, tobacco use disorder, and epilepsy. While no causative conclusions should be drawn from the current study, the results are consistent with literature indicating TBI as accelerative for other chronic conditions. These results add to the literature in support of recognition and development of a post-acute chronic disease definition for individuals with TBI at the federal level as well as the development of a chronic care model for individuals with TBI.

In 2013, Malec and colleagues (2013) recommended implementation of the Chronic Care Model (CCM) for individuals with brain injury while also highlighting the need for enhanced surveillance technologies, such as clinical registries capable of measuring outcomes across the care continuum.[48] While state-wide clinical registries, such as the Indiana TBI registry, and multicenter registries, such as TRACK-TBI and TBI Model Systems National Dataset have been developed, expansion and modernization of public health surveillance systems for TBI remains under-developed.[43,46,100]

Currently, TBI epidemiology is sourced from the CDC's TBI Report to Congress, last published in 2015.[29] In this report, TBI incidence and mortality is described using administrative datasets for emergency department and hospital discharges and vital statistics. These data present several limitations, including poor sensitivity and underreporting, an inability to capture and characterize TBI incidence by personal and demographic characteristics, poor timeliness, no state or small area estimates for health care and public health program planning, and an inability to quantify post-acute health service utilization, vocational stability, or health outcomes. Supported by a thorough review of literature and subject matter expertise, the report to congress convincingly asserts the public health importance of post-acute TBI.[17] Yet, to date, public health surveillance systems fail to capture the incidence, prevalence, management, and outcomes of TBI-related disability and outcomes and TBI is not recognized by the CDC as a chronic disease.

Considering solely disability, post-acute TBI meets the broadly specified definition of a chronic disease, including limiting ADLs, non-self-limiting, an association with persistent and recurrent health problems, and a duration measured in months and years (Chapter 1.3). While this definition highlights TBI as a distinct pathological process, it fails to recognize TBI as an accelerator of other chronic conditions. Masel and DeWitt's 2010 review demonstrated an increased risk of mortality (all cause and specific cause), neurological, neuroendocrine, sleep, neurodegenerative, mental health, substance use, metabolic, and musculoskeletal disorders, primarily among individuals with moderate-to-severe TBI.[47] Evidence of post-acute outcomes among those with moderate-to-severe TBI has continued to grow, including increased risk of cognitive impairment and Alzheimer's disease neuroendocrine impairment, neurological conditions, mental health conditions, and cardiovascular disease.[93,101-113] While less studied, mTBI has demonstrated increased risk of dementia, mild cognitive impairment, Parkinson's disease, new onset depression and anxiety, and chronic sleep disturbances.[114-119] Consistent with the methodological approach and findings of the current study, Izzy and colleagues (2022) recently reported individuals with mTBI had increased incidence of cardiovascular (stroke or TIA, hypertension, hyperlipidemia), endocrine (diabetes, hypothyroidism), neurologic (dementia, posttraumatic seizures), and psychiatric disorders (anxiety, bipolar, depression, alcoholism, drug abuse, opioid abuse, sleep disorders, and suicidal ideation) compared to unexposed individuals.[120]

Although an exhaustive review of the biological pathways is not in the scope of the current paper, we add an environmental scan for conditions that may be accelerated by TBI for future study, particularly among a cohort of individuals with mTBI. The underlying mechanism of the observed associations is likely multifactorial in nature, related to social, behavioral, health service utilization, and biological factors. For example, the observed relationship between ischemic stroke and brain dysfunction from mTBI may have biochemical (e.g., oxidative stress), mechanical (e.g., disruption or occlusion of cerebrovascular circulation), hemostatic (e.g., abnormal platelet aggregation), behavioral (e.g., increased sedentary lifestyle following mTBI), or changes in health care utilization and health maintenance patterns (e.g., emphasis on tertiary care and not primary prevention). [101,121]

The results of this work are subject to several design and analysis limitations. Most notably, several conditions studied are likely subject to reverse causality. For example, individuals with Alzheimer's and related conditions are often at increased fall risk. Further, onset of these conditions often precedes diagnosis by months to years. As a result, a fall leading to a mTBI may be followed by a condition diagnosis unrelated to the TBI. Although delayed diagnosis is common among many of the conditions studied, the effect may be considered non-differential unless a precipitating event (e.g., alcohol use disorder and motor vehicle accident) increases the likelihood of diagnosis (i.e., detection bias). Some of the observed associations may be, at least in part, attributable to misdiagnosis. For example, neurocognitive disorder due to mTBI may be misdiagnosed as ADHD due to similarity in presenting signs and symptoms. Despite the potential for systematic error due to missing condition data and misclassification of outcomes, we observed greater magnitudes of association among conditions with plausible etiologic pathways and little to no association among conditions with implausible biological pathways (e.g., cancers) and strong genetic links (e.g., cerebral palsy and schizophrenia). While the matching procedure accounted for total follow-up time, we did not quantify the number of clinical encounters by exposure group, thus it remains plausible that individuals exposed to a mTBI had more contact with healthcare providers during follow-up. Although all individuals required a minimum of six months of observation prior to entry into the cohort, the rapid onset of several conditions suggested imperfect exclusion of prevalent cases at baseline, resulting in inflated incidence measures.

4.5 Conclusion

This cohort study found that individuals with mTBI were at increased risk of several post-acute mental health, substance use, neurological, cardiovascular, and endocrine conditions. This work, along existing evidence of post-acute disability and outcomes among those with moderate-to-severe TBI, supports recognition of TBI as a chronic disease by federal funding and reporting agencies, such as the CDC and CMS.

Defining TBI as a chronic disease may improve public funding to replace legacy surveillance systems to improve standardization, timeliness, and completeness of the epidemiology and post-acute outcomes of TBI. Improved data quality and availability coupled with funding could ignite research for comparative effectiveness studies and development of models of care in support of a person-centered chronic care that includes targeted health service utilization and secondary prevention of sequalae among the millions of individuals living with chronic TBI.

CHAPTER 5

CONCLUSIONS

Taken together, this dissertation highlights the value of integrating methods from health informatics and epidemiology to leverage electronic health records (EHRs) in TBI surveillance and outcomes measurement. First, we developed novel and effective application of advanced analytics for quantitative Glasgow Coma Scale extraction. Currently, TBI-related epidemiologic and health service research using EHRs is severely limited by the lack of data on the most central clinical TBI parameter for examining long-term sequalae and health service utilization – the severity of the injury. This dissertation applied tools from health informatics to unlock TBI severity data from free-text clinical notes and incorporate these data into structured data fields, creating a variable that can be explored as a factor of interest or, when included as a confounding variable, improve the validity of research examining other risk factors and patient trajectories in the post-acute phase of TBI. This study is the first to automate extraction of GCS from unstructured EHR data and can improve the use of clinical databases for secondary analyses. However, the relative absence of GCS documentation in clinical notes limits the potential of clinical databases for epidemiological research.

Second, this dissertation informed annual surveillance conducted by state health agencies, the CDC, and National Center for Health Statistics by evaluating the performance of surveillance definitions and how the update to ICD-10-CM will impact TBI incidence and temporal trends. Accurate and comprehensive identification of TBI is critical to ensure adequate allocation of funding and health care resources at federal, state, and local levels. Our findings indicated that ICD-9-CM and ICD-10-CM surveillance definitions were not equivalent for the purposes of public health surveillance and the current surveillance definition for ICD-10-CM may be starkly underestimating true mild TBI incidence. To date, this is the first study to evaluate the performance of ICD-10-CM for TBI surveillance and the first to evaluate surveillance definitions at a range of trauma facilities. Research cohorts spanning the coding transition should be avoided or carefully constructed using specific, validated code sets in favor of the standard surveillance definitions. This work has implications on existing and future TBI registries and the epidemiological profile outlined in the Report to Congress on Traumatic Brain Injury in the United States.[17]

Finally, this dissertation quantified incidence and relative hazard for chronic conditions affecting multiple organ systems among cohorts of individuals with mild TBI. We found that individuals with mTBI were at increased risk of several post-acute mental health, substance use, neurological, cardiovascular, and endocrine conditions. These findings support defining TBI as a chronic disease. Future research of the post-acute TBI phase, including comparative effectiveness for rehabilitation, will depend on the availability of longitudinal and integrated data. Data integration must be accompanied by public sector data modernization and funding. Recognition of TBI as a chronic disease may improve public funding to replace legacy surveillance systems to improve standardization, timeliness, and completeness of the epidemiology and post-acute outcomes of TBI.

5.1 Key Learnings of Electronic Health Records for Epidemiology

EHRs represent one potential pathway to improving data velocity, variety, and volume for large-scale, population-based epidemiology studies. However, the standardization, expansion, and integration of disparate data for TBI registries will continue to be limited until prioritized by federal funding agencies. Further, construction and use of EHR-augmented surveillance systems must take into consideration several notable limitations.

EHRs primarily serve a clinical and administrative purpose. Compared to traditional epidemiology studies collecting primary data, EHR-based studies represent a convenient source of secondary data. The benefits of EHRs include lower cost, high velocity data, ease of access, large sample sizes, ability to observe rare outcomes, availability of certain biomarkers, and a shorten timeframe for study completion (for retrospective studies).[122]

Although often more convenient than primary data collection, EHR-based epidemiology studies are highly susceptible to systematic design errors. Perhaps most notably, EHRs only represent individuals seeking health care in a particular catchment area (i.e., selection bias). This selection bias may be attenuated when multiple EHRs are pooled and data are available for an entire defined geographic region, such as the case in HIEs and the current dissertation. A second source of selection bias in EHRs is the ubiquitous finding of missing data. Traditional analysis to identify missing data mechanisms (i.e., missing completely at random, missing at random, or not missing at random) may be too simple to account for the complex interaction between payers, health systems, clinicians, patients, and social determinants of health. Haneuse and Daniels (2016) proposed a framework for addressing the complexity of missing data in EHRs by shifting the analytical mindset from “what data are missing and why” to “what data are present and why”.[123] In this approach, relationships are broken down into a series of manageable components by testing relationships between covariables and modeling the process giving rise to EHR data.[123] Selection bias may then be controlled through the application of advanced statistical methods such as inverse probability weighting (IPW) to remove the association between mechanisms of data existence and entry into the study. Using a similar approach, McFarlane (2019) demonstrated selection bias associated with acute versus wellness encounters could be attenuated for measurement of childhood obesity prevalence.[124] The result of selection bias is a lack of representativeness. A simple test of representativeness can be conducted through comparison of sample demographics and characteristics to that of the target population. For example, in a random sample of trauma center encounters, we observed the demographic distribution of individuals in the Indiana TBI Registry were similar to national reports (Chapter 2). On the other hand, in Chapter 3, the study cohort overrepresented females with TBI, possibly indicating selection bias due to likelihood of seeking health care.

Like selection bias, EHR-based epidemiology studies must pay careful attention to the definitions of exposures, outcomes, and confounding factors. The implication of imperfect measurement and classification are inaccurate incidence or prevalence estimation and biased effect measures. The direction and magnitude of bias is dependent upon the variable type (exposure, outcome, confounder) and whether misclassification is differential across groups of interest. Traditional epidemiology studies have the benefit of deliberate inclusion, construction, and collection of variables using a standard method across participants. On the other hand, secondary use of EHR data requires strong assumptions about the semantic equivalence of EHR inputs, application of diagnostic codes, and homogenous clinical decision-making. Semantic interoperability between

EHRs has encountered many barriers, such as a reliance on propriety terminologies in favor of native harmonization between standard terminologies and ontologies.[125] As a result, integration of EHRs requires a complex normalization process.[126] ICD codes are subject to error at any point in the patient trajectory, and are often influenced by the quality of intake information, communication, and clinical expertise and decision-making.[127] In cases of secondary analysis, the context of an ICD code is lost. Further, the absence of an ICD code can be mistakenly interpreted as an absence of the variable of interest. Evaluation of ICD code sets (Chapter 3) or construction of disease "phenotypes" that combine ICD codes with additional parameters may improve classification accuracy and predictive value for EHR-based surveillance and epidemiology studies.[128] Finally, EHRs often lack the structured data necessary to control for key confounding factors, severely limiting etiologic and comparative effectiveness studies. This dissertation solved the "locked data problem" by extracting information from free-text notes (Chapter 2). Application of this methodology enabled a gold standard TBI classification to which ICD codes could be compared (Chapter 3) and accurate exposure classification for individuals with mild TBI (Chapter 4). Chapter 2 employed an iterative feature engineering approach not suitable for all types of information extraction, but recent trends in Deep Neural Networks show promise for wide application of natural language processing for clinical information extraction.[129]

5.2 Call to Action

At any level of severity, for some, TBI represents a distinct pathological process as well as a risk factor for subsequent chronic conditions. Consistent with recent findings, this dissertation reported mild TBI increased the risk of multisystem chronic conditions

(Chapter 4).[120] The risk of physical disability and chronic conditions in moderate and severe TBI has been consistently reported over the past two decades (Chapter 4.4). This dissertation further demonstrated that current surveillance capacities possess severe limitations to understanding the epidemiology of TBI and associated post-acute outcomes. Recognition of TBI as a chronic disease by federal health and human services agencies would unlock critical funding for state health department trauma divisions to collect, manage, analyze, report, and exchange data. Population health interventions and chronic disease management relies upon the ability to identify individuals at risk, have the right data at the right time, and the infrastructure and skills to produce statistical and visual analytics to guide interventions and health promotion.[130]

As previously discussed (Chapter 1), the Data Modernization Initiative (DMI) has allocated more than four billion dollars to modernize public health infrastructure, systems, workforce, governance, and data exchange.[45] The DMI is heavily focused on the need to improve surveillance systems related to communicable, notifiable diseases and mortality. These systems include the National Notifiable Disease Surveillance System, National Syndromic Surveillance Program, National Electronic Surveillance Base System, and National Vital Statistics System.[131] Similarly, DMI emphasis for public health data interoperability with healthcare is placed on electronic case reporting, electronic laboratory reporting, and syndromic surveillance.[131] Indeed these key surveillance systems are overdue for modernization, and the public health activities they support require rich, accurate, complete, and timely data to support investigations and disease control but they are also among the most well-funded systems each year.[132]

In contrast, the majority of TBI registries operate unfunded and with no standardization of data collection, elements, management, use, and reporting. In 2018, The Traumatic Brain Injury Program Reauthorization Act directed the CDC to implement a survey-based National Concussion Surveillance System (NCSS).[133] Although five million dollars was authorized, as of the most recent House Appropriations Committee of the 117th Congress, the NCSS remains unfunded.[134] Table 5.1 depicts responses to a survey of 29 states conducted for the Administration for Community Living in 2021.[41] The survey results highlight several critical issues consistent with DMI priorities and objectives. Only 79% of states report having an established process for collecting TBI data. The most common data source reported was a "combination of data sources" (38%), followed by state trauma registry (33%), and discharge or hospital association data (19%). Statewide data collection occurred in only 72% of states. Most registries were established before the year 2000 (37%) or between 2000 and 2009 (31%), yet 58% operate without funding and only 29% receiving funding from the CDC. The use of registries also varied, with only 48% using TBI data to connect people to services and 65% creating a TBI report.

Table 5.1. Selected Questions from a Survey of 29 States for the Administration for Community Living.[41]

Question and Responses	**Percentage**
Does your state have an established process for TBI data collection (e.g., TBI registry, trauma registry, hospital association data)?	
Yes	79%
No	21%
What is the source for your state TBI data?	
State Trauma Registry	33%
Discharge/Hospital Association	19%
Independent Registry	5%
Combination	38%

Question and Responses	Percentage
Other Source	5%
Does your state TBI registry use data to link people to services?	
Yes	48%
No	52%
Is TBI registry data analyzed and aggregated into a report by the lead agency?	
Yes	65%
No	35%
Does your state use ICD-10 codes for inclusion criteria to collect TBI or trauma registry data?	
Yes: CDC-Recommended	77%
Yes: Other Recommended	9%
No	9%
Unknown	5%
What year was your TBI registry established?	
Before 2000	37%
2000-2009	31%
2009-2019	16%
In Development	16%
Is your registry funded?	
Yes	42%
No	58%
Does your state receive funding from the Centers for Disease Control to systematically collect data on TBI incidence?	
Yes	29%
No	71%
Is the registry statewide, or only a portion of the hospitals across the state?	
Statewide	72%
Portion of the State	28%

The COVID-19 pandemic revealed critical vulnerabilities in public health infrastructure, systems, data, and capabilities, resulting in unprecedented investment in modernization. Although the spotlight was shining on infectious disease, the public health enterprise is fraught with legacy systems and data siloes. Currently, the minimal investment in TBI data does not match the substantial public health impact of acute and chronic TBI. Federal and state health officials are urged to incorporate trauma or TBI registries into their DMI plans. Investment in state TBI data capabilities will allow enhancement in surveillance data capture to create more complete, timely, and accurate epidemiological TBI reports.

5.3 Future Research

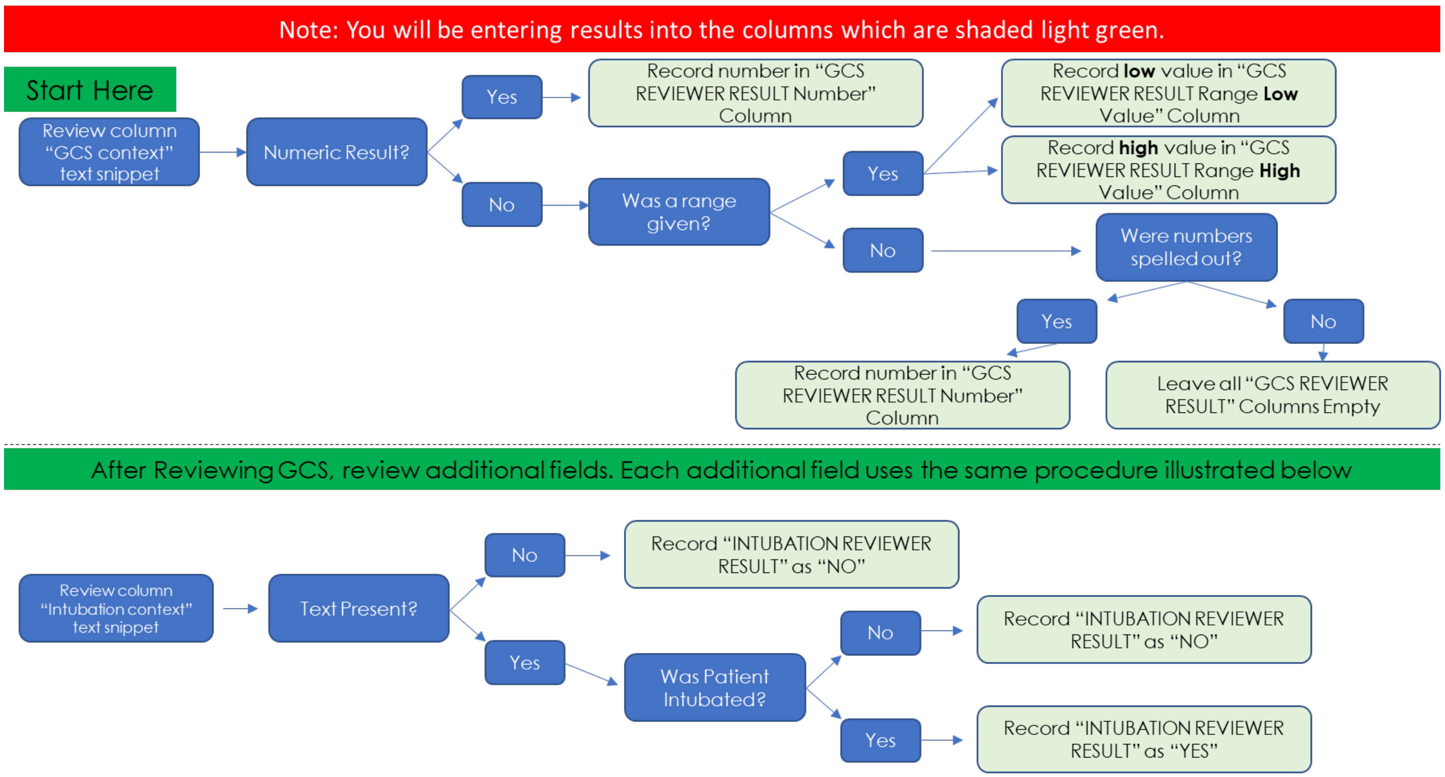
Future work should focus on building robust technical architecture (e.g., standards implementation, API calls, scalable and burstable analytics, data virtualization), data governance, and workforce skills required to integrate and analyze disparate TBI-related data sources across the public health enterprise. Integration of key data sources, such as emergency medical services systems, the Indiana Trauma Registry, and EHRs, will improve data capture for public health surveillance, epidemiology studies, and health service research. Investment in TBI data capabilities will allow enhancement in surveillance data capture to create more complete, timely, and accurate epidemiological TBI reports. Interoperable systems and effective data governance and exchange will further facilitate the creation of long-term cohorts to evaluate the impact of ongoing treatments; detect, control, and prevent complications and comorbidities; improve psychosocial and vocational outcomes; and study the effectiveness and efficacy of services oriented at community reintegration.[47,48]

Each research aim should be expanded to improve methodology and application to practice. NLP demonstrated efficacious information extraction for GCS and can be improved by further training the model to input clinical context and the review of systems. Integration of pre-hospital, hospital, trauma registry data is necessary to improve the quantity and quality of information available in free-text notes. Additional data will improve sensitivity and allow more sophisticated algorithms to be developed, which we observed is key for information extraction of other commonly used measures for TBI severity, including LOC, PTA, and AIS (Chapter 2). Detection of TBI using ICD-10-CM codes demonstrated poor sensitivity and was inequivalent to previous ICD-9-CM definitions (Chapter 3). Future work should pilot the use of additional ICD-10-CM codes and severity measures to create phenotypes that better reflect the clinical diagnoses of TBI, such as the Mayo TBI Classification System.[62] Finally, the finding that mild TBI may present as an independent risk factor for several chronic conditions requires additional studies more suited for causal inference including formation of prospective, longitudinal cohorts that incorporate comprehensive baseline assessments, imaging, and biomarkers.

APPENDICES

Appendix A: Developing and Evaluating an NLP Algorithm for TBI Severity Indicators

Figure A.1. TBI severity note reviewer workflow



A.2 JSON Script for TBI Severity Information Extraction

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"states": [{

"name": "START",

"type": "DICTIONARY",

"dictionaryName": "ANDREA_GCS_AIS",

"acceptStateName": "AFTER_PHRASE_CONTEXT",

"rejectStateName": "END",

"comments": "Looks for a gcs phrase somewhere in the text. Here as a basic check to see whether the input has anything interesting at all."

}, {

"name": "AFTER_PHRASE_CONTEXT",

"regex": "^([^\\n\\.\\,]+|$)",

"acceptStateName": "CONTEXT_WITH_NUMBER",

"rejectStateName": "END",

"checkWindowStateName": "START",

"checkWindowType": "AFTER_START",

"comments": "Gets the after context for the gcs term. The after context goes from the start of the term to the first character that we consider to end the context. It uses AFTER_START so that it will include the term so that we can intersect the term with its context later."

}, {

"name": "CONTEXT_WITH_NUMBER",

"regex": "(?i)((?i)([^\\d]|^)([3-9]|[1][0-5])(?=[^\\d]|(\\-|\\,|\\s|\\.|$)))|(three|four|five|six|seven|eight|nine|ten|eleven|twelve|thirteen|fourteen|fifteen)",

"checkWindowType": "INSIDE",

"checkWindowStateName": "AFTER_PHRASE_CONTEXT",

"expandMatchType": "CHECK_WINDOW",

"acceptStateName": "PHRASE_CONTEXT",

"rejectStateName": "END",

"comments": "Checks for a number (regular or alpha numeric) in the context of the gcs phrase. Keeps the whole context (the check window) if we have one. Sometimes there will be a term without a score and we don't care about those."

}, {

"name": "PHRASE_CONTEXT",

"type": "JOIN",

"joinType": "INTERSECT",

"joinStateNames": ["START", "CONTEXT_WITH_NUMBER"],

"joinIntersectType": "ALL",

"acceptStateName": "GCS_BRANCH",

"rejectStateName": "END",

"comments": "Combines the phrase and the phrase context with a number into one match so we get the phrase and the after words in one. Since the after context includes the phrase, it should overlap with each phrase itself."

}, {

"name": "GCS_BRANCH",

"type": "DICTIONARY",

"dictionaryName": "ANDREA_GCS_AIS",

"dictionaryTerms": ["type:gcs"],

"matchFilterType": "KEEP_MATCHES",

"matchFilterStateName": "PHRASE_CONTEXT",

"acceptStateName": "GCS_FILTER_CONTEXT",

"rejectStateName": "END",

"comments": "The start of the gcs branch of the machine. Looks specifically for a gcs term in the contexts. If it doesn't find a gcs word, it quits because if there's no gcs word, we don't care about the text."

}, {

"name": "GCS_FILTER_CONTEXT",

"regex": "(?i)(\\b(motor|eye|eyes|verbal)\\b)",

"matchFilterType": "KEEP_NON_MATCHES",

"matchFilterStateName": "GCS_BRANCH",

"acceptStateName": "GCS_PHRASE",

"rejectStateName": "GCS_TOTAL_SCORE_CHECK",

"comments": "Filters out gcs phrases that have the word motor, eye, eyes, or verbal in them so we dont consider them to be phrases we care about."

}, {

"name": "GCS_TOTAL_SCORE_CHECK",

"regex":

"(?i)(glasgow[\\s\\r\\n]*coma[\\s\\r\\n]*scale:)[\\s\\r\\n]*(eye[\\s\\r\\n]*response:[\\s\\r\\n]
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\\s\\r\\n]*/[\\s\\r\\n]*\\d)[\\s\\r\\n]*,[\\s\\r\\n]*(motor[\\s\\r\\n]*response:[\\s\\r\\n]*\\d[\\s\\r\
\n]*/[\\s\\r\\n]*\\d)[\\s\\r\\n]*,[\\s\\r\\n]*total[\\s\\r\\n]*score:[\\s\\r\\n]*total[\\s\\r\\n]*score
:[\\s\\r\\n]*\\d+\\.",

"acceptStateName": "GCS_TOTAL_SCORE_PHRASE",

"rejectStateName": "END",

"comments": "Looks for a specific gcs phrase that has eye, verbal, motor, and a total score in it. The reports often have linebreaks in random places, so the \\s and \\n subsitute for spaces. We usually expect the total score to be by the gcs phrase, but in this situation, its far away, so we have to handle it in a special case. If it doesnt find this phrase, then there is no gcs anything, so we should just quit."

}, {

"name": "GCS_TOTAL_SCORE_PHRASE",

"regex": "(?i)glasgow[\\s\\r\\n]*coma[\\s\\r\\n]*scale",

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"acceptStateName": "GCS_TOTAL_SCORE",

"rejectStateName": "END",

"comments": "If we found what we were looking for, the phrase should be glasgow coma scale (with a case insensitive match)."

}, {

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"checkWindowType": "INSIDE",
"acceptStateName": "GCS_ALL_PHRASES",
"rejectStateName": "END",
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    "analyzerType": "METADATA",
    "action": "PUT",
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        "isGCSScoreAlphabetic": "No"
    },
    "nextAnalyzerName": "END"
}],
"comments": "The total score we want is at the end right after the words total score.  Using the capturing group so we can skip the spaces in front of the number."
}, {
    "name": "GCS_PHRASE",
    "type": "DICTIONARY",
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"dictionaryTerms": ["type:gcs"],
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"rejectStateName": "END",
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"checkWindowType": "INSIDE",
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"matchLimit": "1",
"comments": "Gets the first gcs phrase in the contexts that weren't filtered out in the previous state. These are the official gcs terms we're interested in."
}, {
"name": "GCS_PHRASE_CONTEXT",
"type": "DICTIONARY",
"dictionaryName": "ANDREA_GCS_AIS",
"dictionaryTerms": ["type:gcs"],
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"rejectStateName": "END",
"checkWindowStateName": "GCS_FILTER_CONTEXT",
"checkWindowType": "INSIDE",
"matchType": "LIMIT",
"matchLimit": "1",
"expandMatchType": "CHECK_WINDOW",

"comments": "Gets the context for the real phrases that we're interested in. Looks for the gcs term in the filtered context and expands to include the whole context if it finds one. This is here so we have the gcs term and context for contexts that weren't filtered out."
}, {
"name": "GCS_SCORE_RANGE_CHECK",
"regex": "(?<![A-Z\\-\\d\\/])([3-9]|[1][0-5])(?!\\d)\\s*-\\s*([3-9]|[1][0-5])(?![\\d\\/]|\\-\\d)",
"acceptStateName": "GCS_SCORE_RANGE_LOW",
"rejectStateName": "GCS_SCORE_CHECK",
"checkWindowStateName": "GCS_PHRASE_CONTEXT",
"checkWindowType": "INSIDE",
"matchType": "LIMIT",
"matchLimit": "1",
"analyzers": [{
"analyzerName": "START",
"analyzerType": "METADATA",
"action": "PUT",
"metadata": {
"isGCSScoreRange": "Yes",
"isGCSScoreAlphabetic": "No"
},
"nextAnalyzerName": "END"

```
}],
"comments": "Looks for the first number (between 3 and 15) range after the gcs phrase, thats not preceded by a capital letter, dash, or slash (part of a date). If it doesnt find it, it will look for a single number."
}, {
"name": "GCS_SCORE_RANGE_LOW",
"regex": "(?<![A-Z\\-])([3-9]|[1][0-5])(?=\\s*-)(?!\\d)",
"acceptStateName": "GCS_SCORE_RANGE_HIGH",
"rejectStateName": "GCS_SCORE_CHECK",
"checkWindowStateName": "GCS_SCORE_RANGE_CHECK",
"checkWindowType": "INSIDE",
"matchType": "LIMIT",
"matchLimit": "1",
"comments": "Looks for the low part of the range (between 3 and 15 and not preceded by a capital letter or dash)."
}, {
"name": "GCS_SCORE_RANGE_HIGH",
"regex": "(?<=-)\\s*([3-9]|[1][0-5])(?!\\d)",
"acceptStateName": "GCS_SCORE_CHECK",
"rejectStateName": "GCS_SCORE_CHECK",
"checkWindowStateName": "GCS_SCORE_RANGE_CHECK",
"checkWindowType": "INSIDE",
"matchType": "LIMIT",
```

```
"matchLimit": "1",
"comments": "Looks for the high part of the range (between 3 and
15)."
}, {
"name": "GCS_SCORE_CHECK",
"regex": "(([^A-Z\\d\\-\\/]|[^\\d]\\-)(?<singledigit>[3-9])(?!\\-
\\d|[\\d\\/]))|(([^A-Z\\d\\-\\/]|[^\\d]\\-)(?<doubledigit>[1][0-5])(?![\\d\\/]|\\-\\d))",
"capturingGroupNames": ["singledigit", "doubledigit"],
"acceptStateName":
"GCS_SCORE_OUT_OF_TOTAL_CHECK",
"rejectStateName": "GCS_SCORE_OUT_OF_TOTAL_CHECK",
"checkWindowStateName": "GCS_PHRASE_CONTEXT",
"checkWindowType": "INSIDE",
"matchType": "LIMIT",
"matchLimit": "1",
"analyzers": [{
"analyzerName": "START",
"analyzerType": "METADATA",
"action": "PUT",
"metadata": {
"isGCSScoreRange": "No",
"isGCSScoreAlphabetic": "No"
},
```

"nextAnalyzerName": "END"

}],

"comments": "Looks for a single gcs score number (between 3 and 15). Doesnt match if the number is: preceded by a capital letter, dash, or slash (for a date); preceded by a number and a dash; part of a 3 or more digit number; or followed by a dash and a number."

}, {

"name": "GCS_SCORE_OUT_OF_TOTAL_CHECK",

"regex": "([3-9]|[1][0-5])(?=/15)",

"acceptStateName": "GCS_PHRASE_CONTEXT_WITHOUT_NUMERIC_SCORE",

"rejectStateName": "GCS_PHRASE_CONTEXT_WITHOUT_NUMERIC_SCORE",

"checkWindowStateName": "GCS_PHRASE_CONTEXT",

"checkWindowType": "INSIDE",

"matchType": "LIMIT",

"matchLimit": "1",

"analyzers": [{

"analyzerName": "START",

"analyzerType": "METADATA",

"action": "PUT",

"metadata": {

"isGCSScoreRange": "No",

"isGCSScoreAlphabetic": "No"

},

"nextAnalyzerName": "END"

}],

"comments": "Looks for a specific pattern where the score is like 12/15. We exclude slashes when looking for scores so we don't get tripped up by dates. But, some scores show up as like: out of 15, and we want to keep those scores. That's what this state will look for."

}, {

"name": "GCS_PHRASE_CONTEXT_WITHOUT_NUMERIC_SCORE",

"regex": "(?i)((?i)([^\\/|\\d]|^)([3-9]|[1][0-5])(?=[^\\/|\\d]|(\\-|\\,|\\s|\\.|$)))",

"matchFilterType": "KEEP_NON_MATCHES",

"matchFilterStateName": "GCS_PHRASE_CONTEXT",

"acceptStateName": "GCS_ALPHABETIC_SCORE_CHECK",

"rejectStateName": "GCS_ALL_PHRASES",

"comments": "This state will get the gcs phrase contexts that don't have a numeric score in them (matchFilterType = KEEP_NON_MATCHES). These will be the phrase contexts that have an alphabetic score in them. It goes through each phrase context match and keeps the ones that have a match that doesn't match the numeric regex. These are the contexts without numeric values."

}, {

"name": "GCS_ALPHABETIC_SCORE_CHECK",
"regex":
"(?i)\\b(three|four|five|six|seven|eight|nine|ten|eleven|twelve|thirteen|fourteen|fifteen)\\b",
"checkWindowStateName":
"GCS_PHRASE_CONTEXT_WITHOUT_NUMERIC_SCORE",
"checkWindowType": "INSIDE",
"matchType": "LIMIT",
"matchLimit": "1",
"acceptStateName": "GCS_ALL_PHRASES",
"rejectStateName": "GCS_ALL_PHRASES",
"analyzers": [{
"analyzerName": "START",
"analyzerType": "METADATA",
"action": "PUT",
"metadata": {
"isGCSScoreRange": "No",
"isGCSScoreAlphabetic": "Yes"
},
"nextAnalyzerName": "END"
}],
"comments": "Goes through and finds the alphabetic scores, marking them as alphabetic in their metadata. Doesn't use a dictionary because of a bug that's fixed on the new server but not on the original one."

}, {

"name": "GCS_ALL_PHRASES",

"type": "JOIN",

"joinType": "UNION",

"joinStateNames": ["GCS_PHRASE",
"GCS_TOTAL_SCORE_PHRASE"],

"acceptStateName": "GCS_ALL_CONTEXTS",

"rejectStateName": "END",

"comments": "Gets all the phrase matches together in one state so we can extract them from one state."

}, {

"name": "GCS_ALL_CONTEXTS",

"type": "JOIN",

"joinStateNames": ["GCS_PHRASE_CONTEXT",
"GCS_TOTAL_SCORE_CHECK"],

"joinType": "UNION",

"acceptStateName": "GCS_SCORE",

"rejectStateName": "END",

"comments": "Gets all the phrase contexts together in one state so we can extract them from one state."

}, {

"name": "GCS_SCORE",

"type": "JOIN",

"joinType": "UNION",

"joinStateNames": ["GCS_SCORE_RANGE_CHECK", "GCS_SCORE_CHECK", "GCS_ALPHABETIC_SCORE_CHECK", "GCS_TOTAL_SCORE", "GCS_SCORE_OUT_OF_TOTAL_CHECK"],

"acceptStateName": "GCS_ALPHBETIC_SCORE_EXTRACT",

"rejectStateName": "END",

"comments": "Combines all the different kinds of scores into one state so we can extract them all as one column. If there is no score, it will reject the input."

}, {

"name": "GCS_ALPHBETIC_SCORE_EXTRACT",

"type": "DICTIONARY",

"dictionaryName": "ALPHABETIC_NUMBERS",

"checkWindowStateName": "GCS_SCORE",

"checkWindowType": "INSIDE",

"matchType": "LIMIT",

"matchLimit": "1",

"swapMatchType": "EMPTY_MATCH_WHEN_NO_MATCH",

"acceptStateName": "DESCRIPTORS_CHECK",

"rejectStateName": "DESCRIPTORS_CHECK",

"comments": "UNDOCUMENTED FEATURE - Should be removed! - Goes through and either gets the alphabetic numbers for each score or an

empty string so that the alphabetic score column has the same number of entries as the score column (so they line up)."
}, {
"name": "DESCRIPTORS_CHECK",
"regex":
"(?i)\\b(intubation|intubate|intubated|intubating|sedation|sedate|sedated|sedating|loss of consciousness|post traumatic amnesia|post-traumatic amnesia|abbreviated injury score|abbreviated injury scale)\\b",
"acceptStateName": "CHUNK_FOR_DESCRIPTORS",
"rejectStateName": "ANYTHING_FOUND_CHECK",
"comments": "Looks for a descriptor word. Not using a dictionary because of a bug in with dictionaries and analyzers. If it doesn't find anything, it will go check to see if it should accept the report or not."
}, {
"name": "CHUNK_FOR_DESCRIPTORS",
"type": "STATE_MACHINE",
"stateMachines": [{
"stateMachineName": "STANDARD_CHUNKER",
"resultStateNames": ["SENTENCE"]
}
],
"regexMatchType": "SPLIT",
"acceptStateName": "INTUBATION_CHECK",

"rejectStateName": "DUMMY_ACCEPT",

"comments": "Chunks up the input into sentences so that we can check the negation and context status of each descriptor with an analyzer. If there is a problem chunking, it will accept the input since, at this point, we know there is a gcs score. If there werent a score, we wouldnt be here."

}, {

"name": "INTUBATION_CHECK",

"regex": "(?i)\\b(intubation|intubate|intubated|intubating)\\b",

"acceptStateName": "SEDATION_CHECK",

"rejectStateName": "SEDATION_CHECK",

"checkWindowType": "INSIDE",

"checkWindowStateName": "CHUNK_FOR_DESCRIPTORS",

"analyzers": [{

"analyzerName": "START",

"analyzerType": "NEGATION",

"negationDictionaryName": "STANDARD_NEGATION",

"nextAnalyzerName": "CONTEXT_ANALYZER"

}, {

"analyzerName": "CONTEXT_ANALYZER",

"analyzerType": "CONTEXT",

"experiencer": ["Patient"],

"nextAnalyzerName": "END"

```
                }
            ],
            "comments": "Looks for an intubation word and runs each one
through the analyzer using the sentence as the context.  It will filter out matches that dont
have the patient as the experiencer.  It wont filter out based on negation status, but will do
the negation so we can show the status."
        }, {
            "name": "SEDATION_CHECK",
            "regex": "(?i)\\b(sedation|sedate|sedated|sedating)\\b",
            "acceptStateName": "LOSS_OF_CONSCIOUSNESS_CHECK",
            "rejectStateName": "LOSS_OF_CONSCIOUSNESS_CHECK",
            "checkWindowType": "INSIDE",
            "checkWindowStateName": "CHUNK_FOR_DESCRIPTORS",
            "analyzers": [{
                    "analyzerName": "START",
                    "analyzerType": "NEGATION",
                    "negationDictionaryName":
"STANDARD_NEGATION",
                    "nextAnalyzerName": "CONTEXT_ANALYZER"
                }, {
                    "analyzerName": "CONTEXT_ANALYZER",
                    "analyzerType": "CONTEXT",
                    "experiencer": ["Patient"],
```

"nextAnalyzerName": "END"
}
],
"comments": "Looks for a sedation word and runs each one through the analyzer using the sentence as the context. It will filter out matches that dont have the patient as the experiencer. It wont filter out based on negation status, but will do the negation so we can show the status."
}, {
"name": "LOSS_OF_CONSCIOUSNESS_CHECK",
"regex": "(?i)\\b(loss of consciousness)\\b",
"acceptStateName": "AMNESIA_CHECK",
"rejectStateName": "AMNESIA_CHECK",
"checkWindowType": "INSIDE",
"checkWindowStateName": "CHUNK_FOR_DESCRIPTORS",
"analyzers": [{
"analyzerName": "START",
"analyzerType": "NEGATION",
"negationDictionaryName":
"STANDARD_NEGATION",
"nextAnalyzerName": "CONTEXT_ANALYZER"
}, {
"analyzerName": "CONTEXT_ANALYZER",
"analyzerType": "CONTEXT",

"experiencer": ["Patient"],

"nextAnalyzerName": "END"

}

],

"comments": "Looks for a loss of consciousness word and runs each one through the analyzer using the sentence as the context. It will filter out matches that dont have the patient as the experiencer. It wont filter out based on negation status, but will do the negation so we can show the status."

}, {

"name": "AMNESIA_CHECK",

"regex": "(?i)\\b(post traumatic amnesia|post-traumatic amnesia)\\b",

"acceptStateName": "ABBREVIATED_INJURY_SCORE_CHECK",

"rejectStateName": "ABBREVIATED_INJURY_SCORE_CHECK",

"checkWindowType": "INSIDE",

"checkWindowStateName": "CHUNK_FOR_DESCRIPTORS",

"analyzers": [{

"analyzerName": "START",

"analyzerType": "NEGATION",

"negationDictionaryName": "STANDARD_NEGATION",

"nextAnalyzerName": "CONTEXT_ANALYZER"
}, {
"analyzerName": "CONTEXT_ANALYZER",
"analyzerType": "CONTEXT",
"experiencer": ["Patient"],
"nextAnalyzerName": "END"
}
],
"comments": "Looks for an amnesia word and runs each one through the analyzer using the sentence as the context. It will filter out matches that dont have the patient as the experiencer. It wont filter out based on negation status, but will do the negation so we can show the status."
}, {
"name": "ABBREVIATED_INJURY_SCORE_CHECK",
"regex": "(?i)\\b(abbreviated injury score|abbreviated injury scale)\\b",
"acceptStateName": "END",
"rejectStateName": "DUMMY_ACCEPT",
"checkWindowType": "INSIDE",
"checkWindowStateName": "CHUNK_FOR_DESCRIPTORS",
"analyzers": [{
"analyzerName": "START",
"analyzerType": "NEGATION",

"negationDictionaryName":
"STANDARD_NEGATION",
"nextAnalyzerName": "CONTEXT_ANALYZER"
}, {
"analyzerName": "CONTEXT_ANALYZER",
"analyzerType": "CONTEXT",
"experiencer": ["Patient"],
"nextAnalyzerName": "END"
}
],
"comments": "Looks for an abbreviated injury score word and runs each one through the analyzer using the sentence as the context. It will filter out matches that dont have the patient as the experiencer. It wont filter out based on negation status, but will do the negation so we can show the status."
}, {
"name": "ANYTHING_FOUND_CHECK",
"type": "JOIN",
"joinType": "UNION",
"joinStateNames": ["GCS_ALL_PHRASES", "GCS_SCORE",
"DESCRIPTORS_CHECK"],
"acceptStateName": "END",
"rejectStateName": "END",

```
                    "comments": "Checks to see if either a gcs score or descriptor was
found.  Unions all the states that should have results together and accepts if there is at
least one result.  Rejects if there isnt.  Here for when we dont find a descriptor.  In that
situation, we should only accept if we found a gcs score too."
            }, {
                    "name": "DUMMY_ACCEPT",
                    "regex": "^",
                    "acceptStateName": "END",
                    "rejectStateName": "END",
                    "comments": "Here for when we know we want to accept the input,
but we maybe didnt find what we were looking for in a state."
            }
    ],
    "extractors": [{
                    "name": "GCS_INFO",
                    "type": "COLUMNS",
                    "columns": [{
                            "columnLabel": "GCS phrase",
                            "columnStateName": "GCS_ALL_PHRASES"
                    }, {
                            "columnLabel": "GCS Score",
                            "columnStateName": "GCS_SCORE"
                    }, {
```

"columnLabel": "GCS range?",

"columnStateName": "GCS_SCORE",

"columnTarget": "METADATA",

"columnMetadataKey": "isGCSScoreRange"

}, {

"columnLabel": "GCS Range",

"columnStateName":

"GCS_SCORE_RANGE_CHECK"

},{

"columnLabel": "GCS Range low",

"columnStateName":

"GCS_SCORE_RANGE_LOW"

}, {

"columnLabel": "GCS Range high",

"columnStateName":

"GCS_SCORE_RANGE_HIGH"

}, {

"columnLabel": "GCS alphabetic score?",

"columnStateName": "GCS_SCORE",

"columnTarget": "METADATA",

"columnMetadataKey": "isGCSScoreAlphabetic"

}, {

"columnLabel": "GCS alphabetic number value",

"columnStateName":
"GCS_ALPHBETIC_SCORE_EXTRACT",
"columnTarget": "METADATA",
"columnMetadataKey": "numeric_value"
}, {
"columnLabel": "GCS Context",
"columnStateName": "GCS_ALL_CONTEXTS"
}, {
"columnLabel": "Intubation found?",
"columnStateName": "INTUBATION_CHECK",
"columnTarget": "LITERAL_VALUE_CHOICE",
"acceptLiteralValue": "Yes",
"rejectLiteralValue": "No"
}, {
"columnLabel": "Inutbation phrase",
"columnStateName": "INTUBATION_CHECK"
}, {
"columnLabel": "Intubation negation status",
"columnStateName": "INTUBATION_CHECK",
"columnTarget": "METADATA",
"columnMetadataKey": "negationStatus"
}, {
"columnLabel": "Intubation context",

"columnStateName": "INTUBATION_CHECK",
"columnTarget": "CHECK_WINDOW"
}, {
"columnLabel": "Sedation found?",
"columnStateName": "SEDATION_CHECK",
"columnTarget": "LITERAL_VALUE_CHOICE",
"acceptLiteralValue": "Yes",
"rejectLiteralValue": "No"
}, {
"columnLabel": "Sedation phrase",
"columnStateName": "SEDATION_CHECK"
}, {
"columnLabel": "Sedation negation status",
"columnStateName": "SEDATION_CHECK",
"columnTarget": "METADATA",
"columnMetadataKey": "negationStatus"
}, {
"columnLabel": "Sedation context",
"columnStateName": "SEDATION_CHECK",
"columnTarget": "CHECK_WINDOW"
}, {
"columnLabel": "Loss of consciousness found?",

"columnStateName":
"LOSS_OF_CONSCIOUSNESS_CHECK",
"columnTarget": "LITERAL_VALUE_CHOICE",
"acceptLiteralValue": "Yes",
"rejectLiteralValue": "No"
}, {
"columnLabel": "Loss of consciousness phrase",
"columnStateName":
"LOSS_OF_CONSCIOUSNESS_CHECK"
}, {
"columnLabel": "Loss of consciousness negation
status",
"columnStateName":
"LOSS_OF_CONSCIOUSNESS_CHECK",
"columnTarget": "METADATA",
"columnMetadataKey": "negationStatus"
}, {
"columnLabel": "Loss of consciousness context",
"columnStateName":
"LOSS_OF_CONSCIOUSNESS_CHECK",
"columnTarget": "CHECK_WINDOW"
}, {
"columnLabel": "Post traumatic amnesia found?",

"columnStateName": "AMNESIA_CHECK",
"columnTarget": "LITERAL_VALUE_CHOICE",
"acceptLiteralValue": "Yes",
"rejectLiteralValue": "No"
}, {
"columnLabel": "Post traumatic amnesia phrase",
"columnStateName": "AMNESIA_CHECK"
}, {
"columnLabel": "Post traumatic amnesia negation status",
"columnStateName": "AMNESIA_CHECK",
"columnTarget": "METADATA",
"columnMetadataKey": "negationStatus"
}, {
"columnLabel": "Post traumatic amnesia context",
"columnStateName": "AMNESIA_CHECK",
"columnTarget": "CHECK_WINDOW"
}, {
"columnLabel": "Abbreviated injury score found?",
"columnStateName": "ABBREVIATED_INJURY_SCORE_CHECK",
"columnTarget": "LITERAL_VALUE_CHOICE",
"acceptLiteralValue": "Yes",

"rejectLiteralValue": "No"

}, {

"columnLabel": "Abbreviated injury score",

"columnStateName":

"ABBREVIATED_INJURY_SCORE_CHECK"

}, {

"columnLabel": "Abbreviated injury score negation

status",

"columnStateName":

"ABBREVIATED_INJURY_SCORE_CHECK",

"columnTarget": "METADATA",

"columnMetadataKey": "negationStatus"

}, {

"columnLabel": "Abbreviated injury score context",

"columnStateName":

"ABBREVIATED_INJURY_SCORE_CHECK",

"columnTarget": "CHECK_WINDOW"

}

]

}

]

}

Appendix B: ICD-9-CM and ICD-10-CM TBI Surveillance Definitions

Table B.1. ICD-9-CM surveillance definition

800: fracture of vault of skull;
801: fracture of the base of skull;
803: other and unqualified skull fractures;
804: multiple fractures involving skull or face with other bones;
850: concussion;
851: cerebral laceration and contusion;
852: subarachnoid, subdural, and extradural hemorrhage, following injury;
853: other and unspecified intracranial hemorrhage following injury;
854.0, 854.1: intracranial injury of other and unspecified nature;
950.1–950.3: injury to the optic nerve and pathways;
959.01: head injury, unspecified; and
995.55: shaken infant syndrome.

Table B.2. ICD-10-CM surveillance definition

S02.0, S02.1-: fracture of skull;
S02.8: fracture of other specified skull and facial bones;
S02.91: unspecified fracture of skull;
S04.02: injury of optic chiasm;
S04.03-:injury of optic tract and pathways;
S04.04-: injury of visual cortex;
S06-: intracranial injury;
S07.1: crushing injury of skull; and
T74.4: shaken infant syndrome.

Appendix C: Mayo Traumatic Brain Injury Classification System reviewer survey

Table C.1. TBI severity note reviewer survey

Question	nDepth Field
Does the note state the patient died as a result of a TBI?	Y/N;
Does the note indicate the patient experienced any loss of consciousness?	Y/N;
IF Yes	
If so, how long was did the patient experience loss of consciousness?	numeric field (time) and text field (unit) Mentions of LOC without timeframe recorded as Y; NULL
Does the note indicate the patient experienced post traumatic amnesia?	Y/N;
IF Yes	
If so, how long was did the patient experience loss of consciousness?	numeric field (time) and text field (unit) Mentions of PTA without timeframe recorded as Y; NULL
Does the note include a Glasgow Coma Scale (GCS) Result?	Y/N;
IF Yes	
If so, what is the numeric GCS value recorded [3-15]?	numeric field (full GCS, limits 3-15) Mentions of GCS without quantitative value recorded as Y; NULL
Does the note indicate the patient was intoxicated, sedated, intubated, or in systemic shock?	Y/N;
IF Yes	
Record keyword from note	text field

Question	nDepth Field
Does the note indicate the patient experienced any of the following signs:	
· Intracerebral haematoma	Y/N;
· Subdural haematoma	Y/N;
· Epidural haematoma	Y/N;
· Cerebral contusion	Y/N;
· Haemorrhagic contusion	Y/N;
· Penetrating TBI (dura penetrated)	Y/N;
· Subarachnoid haemorrhage	Y/N;
· Brainstem injury	Y/N;
· Depressed, basilar or linear skull fracture	Y/N;
Does the note indicate one or more of the following symptoms are present:	
· Blurred vision	Y/N;
· Confusion (mental state changes)	Y/N;
· Daze	Y/N;
· Dizziness	Y/N;
· Focal neurological symptoms	Y/N;
· Headache	Y/N;
· Nausea	Y/N;

Appendix D: Matched cohort characteristics for mental health, substance use, neurological, cardiovascular, cancer, and endocrine conditions.

Table D.1. Attention Deficit Hyperactivity Disorder cohort characteristics

ADHD. Matched Cohort Characteristics

Variable	**N**	**No TBI**, N = 2,775	**TBI**, N = 925	**p-value**[1]
Sex, n (%)	3,700			>0.999
F		1,623 (58%)	541 (58%)	
M		1,152 (42%)	384 (42%)	
Race/Ethnicity, n (%)	3,700			>0.999
Black/AA		234 (8.4%)	78 (8.4%)	
Other		39 (1.4%)	13 (1.4%)	
White		2,502 (90%)	834 (90%)	
Age, Mean (SD)	3,700	57 (18)	57 (18)	0.989
ZIP3, n (%)	3,700			>0.999
460		117 (4.2%)	39 (4.2%)	
461		135 (4.9%)	45 (4.9%)	
462		672 (24%)	224 (24%)	
463		9 (0.3%)	3 (0.3%)	
469		84 (3.0%)	28 (3.0%)	
472		12 (0.4%)	4 (0.4%)	
473		450 (16%)	150 (16%)	
474		396 (14%)	132 (14%)	
475		90 (3.2%)	30 (3.2%)	
478		39 (1.4%)	13 (1.4%)	
479		771 (28%)	257 (28%)	

[1] Pearson's Chi-squared test; Welch Two Sample t-test; Fisher's exact test

Table D.2. Anxiety cohort characteristics

Anxiety. Matched Cohort Characteristics

Variable	**N**	**No TBI**, N = 2,304	**TBI**, N = 768	**p-value**[1]
Sex, n (%)	3,072			>0.999
F		1,293 (56%)	431 (56%)	
M		1,011 (44%)	337 (44%)	
Race/Ethnicity, n (%)	3,072			>0.999
Black/AA		222 (9.6%)	74 (9.6%)	
Other		33 (1.4%)	11 (1.4%)	
White		2,049 (89%)	683 (89%)	
Age, Mean (SD)	3,072	58 (18)	58 (19)	0.992
ZIP3, n (%)	3,072			>0.999
460		96 (4.2%)	32 (4.2%)	
461		117 (5.1%)	39 (5.1%)	
462		588 (26%)	196 (26%)	
463		9 (0.4%)	3 (0.4%)	
469		75 (3.3%)	25 (3.3%)	
472		9 (0.4%)	3 (0.4%)	
473		333 (14%)	111 (14%)	
474		303 (13%)	101 (13%)	
475		78 (3.4%)	26 (3.4%)	
478		36 (1.6%)	12 (1.6%)	
479		660 (29%)	220 (29%)	

[1] Pearson's Chi-squared test; Welch Two Sample t-test; Fisher's exact test

Table D.3. Bipolar Disorder cohort characteristics

Bipolar. Matched Cohort Characteristics

Variable	**N**	**No TBI**, N = 2,703	**TBI**, N = 901	**p-value**[1]
Sex, n (%)	3,604			>0.999
F		1,575 (58%)	525 (58%)	
M		1,128 (42%)	376 (42%)	
Race/Ethnicity, n (%)	3,604			>0.999
Black/AA		240 (8.9%)	80 (8.9%)	
Other		39 (1.4%)	13 (1.4%)	
White		2,424 (90%)	808 (90%)	
Age, Mean (SD)	3,604	57 (18)	57 (18)	0.992
ZIP3, n (%)	3,604			>0.999
460		111 (4.1%)	37 (4.1%)	
461		132 (4.9%)	44 (4.9%)	
462		669 (25%)	223 (25%)	
463		9 (0.3%)	3 (0.3%)	
469		81 (3.0%)	27 (3.0%)	
472		9 (0.3%)	3 (0.3%)	
473		426 (16%)	142 (16%)	
474		384 (14%)	128 (14%)	
475		84 (3.1%)	28 (3.1%)	
478		36 (1.3%)	12 (1.3%)	
479		762 (28%)	254 (28%)	

[1] Pearson's Chi-squared test; Welch Two Sample t-test; Fisher's exact test

Table D.4. Depression cohort characteristics

Depression. Matched Cohort Characteristics				
Variable	**N**	**No TBI**, N = 1,833	**TBI**, N = 611	**p-value**[1]
Sex, n (%)	2,444			>0.999
F		948 (52%)	316 (52%)	
M		885 (48%)	295 (48%)	
Race/Ethnicity, n (%)	2,444			>0.999
Black/AA		189 (10%)	63 (10%)	
Other		30 (1.6%)	10 (1.6%)	
White		1,614 (88%)	538 (88%)	
Age, Mean (SD)	2,444	57 (19)	57 (19)	0.990
ZIP3, n (%)	2,444			>0.999
460		69 (3.8%)	23 (3.8%)	
461		90 (4.9%)	30 (4.9%)	
462		483 (26%)	161 (26%)	
463		9 (0.5%)	3 (0.5%)	
469		57 (3.1%)	19 (3.1%)	
472		9 (0.5%)	3 (0.5%)	
473		270 (15%)	90 (15%)	
474		261 (14%)	87 (14%)	
475		63 (3.4%)	21 (3.4%)	
478		33 (1.8%)	11 (1.8%)	
479		489 (27%)	163 (27%)	

[1] Pearson's Chi-squared test; Welch Two Sample t-test; Fisher's exact test

Table D.5. Post-Traumatic Stress Disorder cohort characteristics

PTSD. Matched Cohort Characteristics

Variable	**N**	**No TBI**, N = 2,760	**TBI**, N = 920	**p-value**[1]
Sex, n (%)	3,680			>0.999
F		1,590 (58%)	530 (58%)	
M		1,170 (42%)	390 (42%)	
Race/Ethnicity, n (%)	3,680			>0.999
Black/AA		243 (8.8%)	81 (8.8%)	
Other		36 (1.3%)	12 (1.3%)	
White		2,481 (90%)	827 (90%)	
Age, Mean (SD)	3,680	57 (18)	57 (18)	0.990
ZIP3, n (%)	3,680			>0.999
460		120 (4.3%)	40 (4.3%)	
461		132 (4.8%)	44 (4.8%)	
462		681 (25%)	227 (25%)	
463		9 (0.3%)	3 (0.3%)	
469		84 (3.0%)	28 (3.0%)	
472		12 (0.4%)	4 (0.4%)	
473		444 (16%)	148 (16%)	
474		393 (14%)	131 (14%)	
475		87 (3.2%)	29 (3.2%)	
478		39 (1.4%)	13 (1.4%)	
479		759 (28%)	253 (28%)	

[1] Pearson's Chi-squared test; Welch Two Sample t-test; Fisher's exact test

Table D.6. Personality Disorder cohort characteristics

Personality Disorder. Matched Cohort Characteristics

Variable	**N**	**No TBI**, N = 2,745	**TBI**, N = 915	**p-value**[1]
Sex, n (%)	3,660			>0.999
F		1,605 (58%)	535 (58%)	
M		1,140 (42%)	380 (42%)	
Race/Ethnicity, n (%)	3,660			>0.999
Black/AA		234 (8.5%)	78 (8.5%)	
Other		39 (1.4%)	13 (1.4%)	
White		2,472 (90%)	824 (90%)	
Age, Mean (SD)	3,660	57 (18)	57 (18)	0.988
ZIP3, n (%)	3,660			>0.999
460		123 (4.5%)	41 (4.5%)	
461		132 (4.8%)	44 (4.8%)	
462		672 (24%)	224 (24%)	
463		6 (0.2%)	2 (0.2%)	
469		81 (3.0%)	27 (3.0%)	
472		12 (0.4%)	4 (0.4%)	
473		426 (16%)	142 (16%)	
474		399 (15%)	133 (15%)	
475		84 (3.1%)	28 (3.1%)	
478		39 (1.4%)	13 (1.4%)	
479		771 (28%)	257 (28%)	

[1] Pearson's Chi-squared test; Welch Two Sample t-test; Fisher's exact test

Table D.7. Schizophrenia cohort characteristics

Schizophrenia. Matched Cohort Characteristics

Variable	**N**	**No TBI**, N = 2,820	**TBI**, N = 940	**p-value**[1]
Sex, n (%)	3,760			>0.999
F		1,671 (59%)	557 (59%)	
M		1,149 (41%)	383 (41%)	
Race/Ethnicity, n (%)	3,760			>0.999
Black/AA		240 (8.5%)	80 (8.5%)	
Other		42 (1.5%)	14 (1.5%)	
White		2,538 (90%)	846 (90%)	
Age, Mean (SD)	3,760	56 (18)	56 (18)	0.992
ZIP3, n (%)	3,760			>0.999
460		123 (4.4%)	41 (4.4%)	
461		135 (4.8%)	45 (4.8%)	
462		693 (25%)	231 (25%)	
463		9 (0.3%)	3 (0.3%)	
469		81 (2.9%)	27 (2.9%)	
472		12 (0.4%)	4 (0.4%)	
473		444 (16%)	148 (16%)	
474		408 (14%)	136 (14%)	
475		87 (3.1%)	29 (3.1%)	
478		39 (1.4%)	13 (1.4%)	
479		789 (28%)	263 (28%)	

[1] Pearson's Chi-squared test; Welch Two Sample t-test; Fisher's exact test

Table D.8. Alcohol Use Disorder cohort characteristics

Alcohol Use Disorder. Matched Cohort Characteristics				
Variable	**N**	**No TBI**, N = 2,670	**TBI**, N = 890	**p-value**[1]
Sex, n (%)	3,560			>0.999
F		1,614 (60%)	538 (60%)	
M		1,056 (40%)	352 (40%)	
Race/Ethnicity, n (%)	3,560			>0.999
Black/AA		222 (8.3%)	74 (8.3%)	
Other		33 (1.2%)	11 (1.2%)	
White		2,415 (90%)	805 (90%)	
Age, Mean (SD)	3,560	57 (19)	57 (19)	0.998
ZIP3, n (%)	3,560			>0.999
460		114 (4.3%)	38 (4.3%)	
461		126 (4.7%)	42 (4.7%)	
462		648 (24%)	216 (24%)	
463		9 (0.3%)	3 (0.3%)	
469		84 (3.1%)	28 (3.1%)	
472		12 (0.4%)	4 (0.4%)	
473		426 (16%)	142 (16%)	
474		372 (14%)	124 (14%)	
475		87 (3.3%)	29 (3.3%)	
478		39 (1.5%)	13 (1.5%)	
479		753 (28%)	251 (28%)	

[1] Pearson's Chi-squared test; Welch Two Sample t-test; Fisher's exact test

Table D.9. Drug Use Disorder cohort characteristics

Drug Use Disorder. Matched Cohort Characteristics				
Variable	**N**	**No TBI**, N = 2,667	**TBI**, N = 889	**p-value**[1]
Sex, n (%)	3,556			>0.999
F		1,560 (58%)	520 (58%)	
M		1,107 (42%)	369 (42%)	
Race/Ethnicity, n (%)	3,556			>0.999
Black/AA		243 (9.1%)	81 (9.1%)	
Other		39 (1.5%)	13 (1.5%)	
White		2,385 (89%)	795 (89%)	
Age, Mean (SD)	3,556	57 (18)	57 (18)	0.993
ZIP3, n (%)	3,556			>0.999
460		114 (4.3%)	38 (4.3%)	
461		132 (4.9%)	44 (4.9%)	
462		660 (25%)	220 (25%)	
463		9 (0.3%)	3 (0.3%)	
469		84 (3.1%)	28 (3.1%)	
472		12 (0.4%)	4 (0.4%)	
473		423 (16%)	141 (16%)	
474		369 (14%)	123 (14%)	
475		84 (3.1%)	28 (3.1%)	
478		39 (1.5%)	13 (1.5%)	
479		741 (28%)	247 (28%)	

[1] Pearson's Chi-squared test; Welch Two Sample t-test; Fisher's exact test

Table D.10. Opioid Use Disorder cohort characteristics

Opioid Use Disorder. Matched Cohort Characteristics

Variable	**N**	**No TBI**, N = 2,772	**TBI**, N = 924	**p-value**[1]
Sex, n (%)	3,696			>0.999
F		1,623 (59%)	541 (59%)	
M		1,149 (41%)	383 (41%)	
Race/Ethnicity, n (%)	3,696			>0.999
Black/AA		249 (9.0%)	83 (9.0%)	
Other		39 (1.4%)	13 (1.4%)	
White		2,484 (90%)	828 (90%)	
Age, Mean (SD)	3,696	57 (18)	57 (18)	0.992
ZIP3, n (%)	3,696			>0.999
460		120 (4.3%)	40 (4.3%)	
461		132 (4.8%)	44 (4.8%)	
462		693 (25%)	231 (25%)	
463		9 (0.3%)	3 (0.3%)	
469		84 (3.0%)	28 (3.0%)	
472		12 (0.4%)	4 (0.4%)	
473		432 (16%)	144 (16%)	
474		405 (15%)	135 (15%)	
475		84 (3.0%)	28 (3.0%)	
478		39 (1.4%)	13 (1.4%)	
479		762 (27%)	254 (27%)	

[1] Pearson's Chi-squared test; Welch Two Sample t-test; Fisher's exact test

Table D.11. Tobacco Use Disorder cohort characteristics

Tobacco Use. Matched Cohort Characteristics				
Variable	**N**	**No TBI**, N = 1,941	**TBI**, N = 647	**p-value**[1]
Sex, n (%)	2,588			>0.999
F		1,137 (59%)	379 (59%)	
M		804 (41%)	268 (41%)	
Race/Ethnicity, n (%)	2,588			>0.999
Black/AA		183 (9.4%)	61 (9.4%)	
Other		27 (1.4%)	9 (1.4%)	
White		1,731 (89%)	577 (89%)	
Age, Mean (SD)	2,588	60 (18)	60 (18)	0.998
ZIP3, n (%)	2,588			>0.999
460		75 (3.9%)	25 (3.9%)	
461		105 (5.4%)	35 (5.4%)	
462		441 (23%)	147 (23%)	
463		9 (0.5%)	3 (0.5%)	
469		69 (3.6%)	23 (3.6%)	
472		6 (0.3%)	2 (0.3%)	
473		294 (15%)	98 (15%)	
474		291 (15%)	97 (15%)	
475		63 (3.2%)	21 (3.2%)	
478		33 (1.7%)	11 (1.7%)	
479		555 (29%)	185 (29%)	

[1] Pearson's Chi-squared test; Welch Two Sample t-test; Fisher's exact test

Table D.12. Alzheimer's Disease cohort characteristics

Alzheimer's Disease. Matched Cohort Characteristics

Variable	**N**	**No TBI**, N = 2,856	**TBI**, N = 952	**p-value**[1]
Sex, n (%)	3,808			>0.999
F		1,674 (59%)	558 (59%)	
M		1,182 (41%)	394 (41%)	
Race/Ethnicity, n (%)	3,808			>0.999
Black/AA		249 (8.7%)	83 (8.7%)	
Other		39 (1.4%)	13 (1.4%)	
White		2,568 (90%)	856 (90%)	
Age, Mean (SD)	3,808	56 (18)	56 (18)	0.990
ZIP3, n (%)	3,808			>0.999
460		123 (4.3%)	41 (4.3%)	
461		135 (4.7%)	45 (4.7%)	
462		711 (25%)	237 (25%)	
463		9 (0.3%)	3 (0.3%)	
469		84 (2.9%)	28 (2.9%)	
472		12 (0.4%)	4 (0.4%)	
473		450 (16%)	150 (16%)	
474		414 (14%)	138 (14%)	
475		90 (3.2%)	30 (3.2%)	
478		39 (1.4%)	13 (1.4%)	
479		789 (28%)	263 (28%)	

[1] Pearson's Chi-squared test; Welch Two Sample t-test; Fisher's exact test

Table D.13. Alzheimer’s Disease and related disorders cohort characteristics

Alzheimer's Disease and Related Disorders. Matched Cohort Characteristics

Variable	**N**	**No TBI**, N = 2,775	**TBI**, N = 925	**p-value**[1]
Sex, n (%)	3,700			>0.999
F		1,635 (59%)	545 (59%)	
M		1,140 (41%)	380 (41%)	
Race/Ethnicity, n (%)	3,700			>0.999
Black/AA		243 (8.8%)	81 (8.8%)	
Other		36 (1.3%)	12 (1.3%)	
White		2,496 (90%)	832 (90%)	
Age, Mean (SD)	3,700	56 (18)	56 (18)	0.992
ZIP3, n (%)	3,700			>0.999
460		117 (4.2%)	39 (4.2%)	
461		132 (4.8%)	44 (4.8%)	
462		702 (25%)	234 (25%)	
463		9 (0.3%)	3 (0.3%)	
469		84 (3.0%)	28 (3.0%)	
472		12 (0.4%)	4 (0.4%)	
473		435 (16%)	145 (16%)	
474		393 (14%)	131 (14%)	
475		87 (3.1%)	29 (3.1%)	
478		39 (1.4%)	13 (1.4%)	
479		765 (28%)	255 (28%)	

[1] Pearson's Chi-squared test; Welch Two Sample t-test; Fisher's exact test

Table D.14. Cerebral Palsy cohort characteristics

Cerebral Palsy. Matched Cohort Characteristics

Variable	**N**	**No TBI**, N = 2,859	**TBI**, N = 953	**p-value**[1]
Sex, n (%)	3,812			>0.999
F		1,683 (59%)	561 (59%)	
M		1,176 (41%)	392 (41%)	
Race/Ethnicity, n (%)	3,812			>0.999
Black/AA		249 (8.7%)	83 (8.7%)	
Other		42 (1.5%)	14 (1.5%)	
White		2,568 (90%)	856 (90%)	
Age, Mean (SD)	3,812	56 (18)	56 (18)	0.991
ZIP3, n (%)	3,812			>0.999
460		123 (4.3%)	41 (4.3%)	
461		135 (4.7%)	45 (4.7%)	
462		711 (25%)	237 (25%)	
463		9 (0.3%)	3 (0.3%)	
469		84 (2.9%)	28 (2.9%)	
472		12 (0.4%)	4 (0.4%)	
473		456 (16%)	152 (16%)	
474		414 (14%)	138 (14%)	
475		90 (3.1%)	30 (3.1%)	
478		39 (1.4%)	13 (1.4%)	
479		786 (27%)	262 (27%)	

[1] Pearson's Chi-squared test; Welch Two Sample t-test; Fisher's exact test

Table D.15. Epilepsy cohort characteristics

Epilepsy. Matched Cohort Characteristics

Variable	**N**	**No TBI**, N = 2,784	**TBI**, N = 928	**p-value**[1]
Sex, n (%)	3,712			>0.999
F		1,644 (59%)	548 (59%)	
M		1,140 (41%)	380 (41%)	
Race/Ethnicity, n (%)	3,712			>0.999
Black/AA		243 (8.7%)	81 (8.7%)	
Other		42 (1.5%)	14 (1.5%)	
White		2,499 (90%)	833 (90%)	
Age, Mean (SD)	3,712	56 (18)	56 (18)	0.989
ZIP3, n (%)	3,712			>0.999
460		117 (4.2%)	39 (4.2%)	
461		135 (4.8%)	45 (4.8%)	
462		702 (25%)	234 (25%)	
463		9 (0.3%)	3 (0.3%)	
469		81 (2.9%)	27 (2.9%)	
472		9 (0.3%)	3 (0.3%)	
473		438 (16%)	146 (16%)	
474		384 (14%)	128 (14%)	
475		90 (3.2%)	30 (3.2%)	
478		39 (1.4%)	13 (1.4%)	
479		780 (28%)	260 (28%)	

[1] Pearson's Chi-squared test; Welch Two Sample t-test; Fisher's exact test

Table D.16. Migraine and Chronic Headache cohort characteristics

Migraine and Chronic Headache. Matched Cohort Characteristics

Variable	**N**	**No TBI**, N = 2,733	**TBI**, N = 911	**p-value**[1]
Sex, n (%)	3,644			>0.999
F		1,569 (57%)	523 (57%)	
M		1,164 (43%)	388 (43%)	
Race/Ethnicity, n (%)	3,644			>0.999
Black/AA		234 (8.6%)	78 (8.6%)	
Other		30 (1.1%)	10 (1.1%)	
White		2,469 (90%)	823 (90%)	
Age, Mean (SD)	3,644	57 (18)	57 (18)	0.993
ZIP3, n (%)	3,644			>0.999
460		117 (4.3%)	39 (4.3%)	
461		132 (4.8%)	44 (4.8%)	
462		675 (25%)	225 (25%)	
463		9 (0.3%)	3 (0.3%)	
469		81 (3.0%)	27 (3.0%)	
472		6 (0.2%)	2 (0.2%)	
473		441 (16%)	147 (16%)	
474		384 (14%)	128 (14%)	
475		90 (3.3%)	30 (3.3%)	
478		33 (1.2%)	11 (1.2%)	
479		765 (28%)	255 (28%)	

[1] Pearson's Chi-squared test; Welch Two Sample t-test; Fisher's exact test

Table D.17. Multiple Sclerosis cohort characteristics

Multiple Sclerosis. Matched Cohort Characteristics				
Variable	**N**	**No TBI**, N = 2,835	**TBI**, N = 945	**p-value**[1]
Sex, n (%)	3,780			>0.999
F		1,662 (59%)	554 (59%)	
M		1,173 (41%)	391 (41%)	
Race/Ethnicity, n (%)	3,780			>0.999
Black/AA		249 (8.8%)	83 (8.8%)	
Other		42 (1.5%)	14 (1.5%)	
White		2,544 (90%)	848 (90%)	
Age, Mean (SD)	3,780	56 (18)	56 (18)	0.994
ZIP3, n (%)	3,780			>0.999
460		123 (4.3%)	41 (4.3%)	
461		132 (4.7%)	44 (4.7%)	
462		705 (25%)	235 (25%)	
463		9 (0.3%)	3 (0.3%)	
469		81 (2.9%)	27 (2.9%)	
472		9 (0.3%)	3 (0.3%)	
473		450 (16%)	150 (16%)	
474		411 (14%)	137 (14%)	
475		90 (3.2%)	30 (3.2%)	
478		39 (1.4%)	13 (1.4%)	
479		786 (28%)	262 (28%)	

[1] Pearson's Chi-squared test; Welch Two Sample t-test; Fisher's exact test

Table D.18. Acute Myocardial Infarction cohort characteristics

Acute Myocardial Infarction. Matched Cohort Characteristics				
Variable	**N**	**No TBI**, N = 2,802	**TBI**, N = 934	**p-value**[1]
Sex, n (%)	3,736			>0.999
F		1,659 (59%)	553 (59%)	
M		1,143 (41%)	381 (41%)	
Race/Ethnicity, n (%)	3,736			>0.999
Black/AA		240 (8.6%)	80 (8.6%)	
Other		39 (1.4%)	13 (1.4%)	
White		2,523 (90%)	841 (90%)	
Age, Mean (SD)	3,736	56 (18)	56 (18)	0.991
ZIP3, n (%)	3,736			>0.999
460		120 (4.3%)	40 (4.3%)	
461		129 (4.6%)	43 (4.6%)	
462		690 (25%)	230 (25%)	
463		9 (0.3%)	3 (0.3%)	
469		78 (2.8%)	26 (2.8%)	
472		12 (0.4%)	4 (0.4%)	
473		450 (16%)	150 (16%)	
474		411 (15%)	137 (15%)	
475		90 (3.2%)	30 (3.2%)	
478		39 (1.4%)	13 (1.4%)	
479		774 (28%)	258 (28%)	

[1] Pearson's Chi-squared test; Welch Two Sample t-test; Fisher's exact test

Table D.19. Atrial Fibrillation cohort characteristics

Atrial Fibrillation. Matched Cohort Characteristics				
Variable	**N**	**No TBI**, N = 2,601	**TBI**, N = 867	**p-value**[1]
Sex, n (%)	3,468			>0.999
F		1,548 (60%)	516 (60%)	
M		1,053 (40%)	351 (40%)	
Race/Ethnicity, n (%)	3,468			>0.999
Black/AA		240 (9.2%)	80 (9.2%)	
Other		36 (1.4%)	12 (1.4%)	
White		2,325 (89%)	775 (89%)	
Age, Mean (SD)	3,468	55 (18)	55 (18)	0.988
ZIP3, n (%)	3,468			>0.999
460		114 (4.4%)	38 (4.4%)	
461		114 (4.4%)	38 (4.4%)	
462		681 (26%)	227 (26%)	
463		9 (0.3%)	3 (0.3%)	
469		81 (3.1%)	27 (3.1%)	
472		6 (0.2%)	2 (0.2%)	
473		414 (16%)	138 (16%)	
474		360 (14%)	120 (14%)	
475		81 (3.1%)	27 (3.1%)	
478		30 (1.2%)	10 (1.2%)	
479		711 (27%)	237 (27%)	

[1] Pearson's Chi-squared test; Welch Two Sample t-test; Fisher's exact test

Table D.20. Heart Failure cohort characteristics

Heart Failure. Matched Cohort Characteristics				
Variable	**N**	**No TBI**, N = 2,655	**TBI**, N = 885	**p-value**[1]
Sex, n (%)	3,540			>0.999
F		1,557 (59%)	519 (59%)	
M		1,098 (41%)	366 (41%)	
Race/Ethnicity, n (%)	3,540			>0.999
Black/AA		237 (8.9%)	79 (8.9%)	
Other		33 (1.2%)	11 (1.2%)	
White		2,385 (90%)	795 (90%)	
Age, Mean (SD)	3,540	55 (18)	55 (18)	0.987
ZIP3, n (%)	3,540			>0.999
460		111 (4.2%)	37 (4.2%)	
461		129 (4.9%)	43 (4.9%)	
462		678 (26%)	226 (26%)	
463		9 (0.3%)	3 (0.3%)	
469		84 (3.2%)	28 (3.2%)	
472		12 (0.5%)	4 (0.5%)	
473		411 (15%)	137 (15%)	
474		375 (14%)	125 (14%)	
475		87 (3.3%)	29 (3.3%)	
478		39 (1.5%)	13 (1.5%)	
479		720 (27%)	240 (27%)	

[1] Pearson's Chi-squared test; Welch Two Sample t-test; Fisher's exact test

Table D.21. Hyperlipidemia cohort characteristics

Hyperlipidemia. Matched Cohort Characteristics

Variable	**N**	**No TBI**, N = 1,719	**TBI**, N = 573	**p-value**[1]
Sex, n (%)	2,292			>0.999
F		996 (58%)	332 (58%)	
M		723 (42%)	241 (42%)	
Race/Ethnicity, n (%)	2,292			>0.999
Black/AA		183 (11%)	61 (11%)	
Other		18 (1.0%)	6 (1.0%)	
White		1,518 (88%)	506 (88%)	
Age, Mean (SD)	2,292	49 (17)	49 (17)	0.988
ZIP3, n (%)	2,292			>0.999
460		78 (4.5%)	26 (4.5%)	
461		87 (5.1%)	29 (5.1%)	
462		522 (30%)	174 (30%)	
463		6 (0.3%)	2 (0.3%)	
469		51 (3.0%)	17 (3.0%)	
472		6 (0.3%)	2 (0.3%)	
473		285 (17%)	95 (17%)	
474		258 (15%)	86 (15%)	
475		51 (3.0%)	17 (3.0%)	
478		18 (1.0%)	6 (1.0%)	
479		357 (21%)	119 (21%)	

[1] Pearson's Chi-squared test; Welch Two Sample t-test; Fisher's exact test

Table D.22. Hypertension cohort characteristics

Hypertension. Matched Cohort Characteristics				
Variable	**N**	**No TBI**, N = 1,293	**TBI**, N = 431	**p-value**[1]
Sex, n (%)	1,724			>0.999
F		744 (58%)	248 (58%)	
M		549 (42%)	183 (42%)	
Race/Ethnicity, n (%)	1,724			>0.999
Black/AA		123 (9.5%)	41 (9.5%)	
Other		15 (1.2%)	5 (1.2%)	
White		1,155 (89%)	385 (89%)	
Age, Mean (SD)	1,724	47 (16)	47 (16)	0.987
ZIP3, n (%)	1,724			>0.999
460		57 (4.4%)	19 (4.4%)	
461		60 (4.6%)	20 (4.6%)	
462		405 (31%)	135 (31%)	
463		3 (0.2%)	1 (0.2%)	
469		36 (2.8%)	12 (2.8%)	
472		3 (0.2%)	1 (0.2%)	
473		198 (15%)	66 (15%)	
474		180 (14%)	60 (14%)	
475		42 (3.2%)	14 (3.2%)	
478		12 (0.9%)	4 (0.9%)	
479		297 (23%)	99 (23%)	

[1] Pearson's Chi-squared test; Welch Two Sample t-test; Fisher's exact test

Table D.23. Ischemic Heart Disease cohort characteristics

Variable	N	**No TBI**, N = 2,355	**TBI**, N = 785	p-value[1]
Ischemic Heart Disease. Matched Cohort Characteristics				
Sex, n (%)	3,140			>0.999
F		1,416 (60%)	472 (60%)	
M		939 (40%)	313 (40%)	
Race/Ethnicity, n (%)	3,140			>0.999
Black/AA		222 (9.4%)	74 (9.4%)	
Other		30 (1.3%)	10 (1.3%)	
White		2,103 (89%)	701 (89%)	
Age, Mean (SD)	3,140	54 (18)	54 (18)	0.981
ZIP3, n (%)	3,140			>0.999
460		102 (4.3%)	34 (4.3%)	
461		111 (4.7%)	37 (4.7%)	
462		603 (26%)	201 (26%)	
463		9 (0.4%)	3 (0.4%)	
469		63 (2.7%)	21 (2.7%)	
472		9 (0.4%)	3 (0.4%)	
473		375 (16%)	125 (16%)	
474		336 (14%)	112 (14%)	
475		78 (3.3%)	26 (3.3%)	
478		27 (1.1%)	9 (1.1%)	
479		642 (27%)	214 (27%)	

[1] Pearson's Chi-squared test; Welch Two Sample t-test; Fisher's exact test

Table D.24. Stroke cohort characteristics

Stroke. Matched Cohort Characteristics

Variable	**N**	**No TBI**, N = 2,496	**TBI**, N = 832	**p-value**[1]
Sex, n (%)	3,328			>0.999
F		1,482 (59%)	494 (59%)	
M		1,014 (41%)	338 (41%)	
Race/Ethnicity, n (%)	3,328			>0.999
Black/AA		216 (8.7%)	72 (8.7%)	
Other		39 (1.6%)	13 (1.6%)	
White		2,241 (90%)	747 (90%)	
Age, Mean (SD)	3,328	55 (18)	55 (18)	0.984
ZIP3, n (%)	3,328			>0.999
460		99 (4.0%)	33 (4.0%)	
461		111 (4.4%)	37 (4.4%)	
462		630 (25%)	210 (25%)	
463		9 (0.4%)	3 (0.4%)	
469		72 (2.9%)	24 (2.9%)	
472		12 (0.5%)	4 (0.5%)	
473		405 (16%)	135 (16%)	
474		354 (14%)	118 (14%)	
475		81 (3.2%)	27 (3.2%)	
478		33 (1.3%)	11 (1.3%)	
479		690 (28%)	230 (28%)	

[1] Pearson's Chi-squared test; Welch Two Sample t-test; Fisher's exact test

Table D.25. Breast Cancer cohort characteristics

Breast Cancer. Matched Cohort Characteristics

Variable	N	No TBI, N = 1,569	TBI, N = 523	p-value[1]
Sex, n (%)	2,092			
F		1,569 (100%)	523 (100%)	
Race/Ethnicity, n (%)	2,092			>0.999
Black/AA		138 (8.8%)	46 (8.8%)	
Other		21 (1.3%)	7 (1.3%)	
White		1,410 (90%)	470 (90%)	
Age, Mean (SD)	2,092	55 (19)	55 (19)	0.998
ZIP3, n (%)	2,092			>0.999
460		57 (3.6%)	19 (3.6%)	
461		66 (4.2%)	22 (4.2%)	
462		387 (25%)	129 (25%)	
463		3 (0.2%)	1 (0.2%)	
469		48 (3.1%)	16 (3.1%)	
472		6 (0.4%)	2 (0.4%)	
473		258 (16%)	86 (16%)	
474		216 (14%)	72 (14%)	
475		39 (2.5%)	13 (2.5%)	
478		21 (1.3%)	7 (1.3%)	
479		468 (30%)	156 (30%)	

[1] Pearson's Chi-squared test; Welch Two Sample t-test; Fisher's exact test

Table D.26. Colorectal Cancer cohort characteristics

Colorectal Cancer. Matched Cohort Characteristics

Variable	**N**	**No TBI**, N = 2,829	**TBI**, N = 943	**p-value**[1]
Sex, n (%)	3,772			>0.999
F		1,659 (59%)	553 (59%)	
M		1,170 (41%)	390 (41%)	
Race/Ethnicity, n (%)	3,772			>0.999
Black/AA		246 (8.7%)	82 (8.7%)	
Other		42 (1.5%)	14 (1.5%)	
White		2,541 (90%)	847 (90%)	
Age, Mean (SD)	3,772	56 (18)	56 (18)	0.990
ZIP3, n (%)	3,772			>0.999
460		123 (4.3%)	41 (4.3%)	
461		135 (4.8%)	45 (4.8%)	
462		705 (25%)	235 (25%)	
463		9 (0.3%)	3 (0.3%)	
469		84 (3.0%)	28 (3.0%)	
472		12 (0.4%)	4 (0.4%)	
473		450 (16%)	150 (16%)	
474		411 (15%)	137 (15%)	
475		84 (3.0%)	28 (3.0%)	
478		39 (1.4%)	13 (1.4%)	
479		777 (27%)	259 (27%)	

[1] Pearson's Chi-squared test; Welch Two Sample t-test; Fisher's exact test

Table D.27. Endometrial Cancer cohort characteristics

Endometrial Cancer. Matched Cohort Characteristics				
Variable	**N**	**No TBI**, N = 1,677	**TBI**, N = 559	**p-value**[1]
Sex, n (%)	2,236			
F		1,677 (100%)	559 (100%)	
Race/Ethnicity, n (%)	2,236			>0.999
Black/AA		141 (8.4%)	47 (8.4%)	
Other		27 (1.6%)	9 (1.6%)	
White		1,509 (90%)	503 (90%)	
Age, Mean (SD)	2,236	56 (19)	56 (19)	0.994
ZIP3, n (%)	2,236			>0.999
460		60 (3.6%)	20 (3.6%)	
461		66 (3.9%)	22 (3.9%)	
462		393 (23%)	131 (23%)	
463		3 (0.2%)	1 (0.2%)	
469		51 (3.0%)	17 (3.0%)	
472		6 (0.4%)	2 (0.4%)	
473		276 (16%)	92 (16%)	
474		243 (14%)	81 (14%)	
475		42 (2.5%)	14 (2.5%)	
478		24 (1.4%)	8 (1.4%)	
479		513 (31%)	171 (31%)	

[1] Pearson's Chi-squared test; Welch Two Sample t-test; Fisher's exact test

Table D.28. Lung Cancer cohort characteristics

Lung Cancer. Matched Cohort Characteristics				
Variable	**N**	**No TBI**, N = 2,856	**TBI**, N = 952	**p-value**[1]
Sex, n (%)	3,808			>0.999
F		1,677 (59%)	559 (59%)	
M		1,179 (41%)	393 (41%)	
Race/Ethnicity, n (%)	3,808			>0.999
Black/AA		249 (8.7%)	83 (8.7%)	
Other		42 (1.5%)	14 (1.5%)	
White		2,565 (90%)	855 (90%)	
Age, Mean (SD)	3,808	56 (18)	56 (18)	0.989
ZIP3, n (%)	3,808			>0.999
460		123 (4.3%)	41 (4.3%)	
461		135 (4.7%)	45 (4.7%)	
462		711 (25%)	237 (25%)	
463		9 (0.3%)	3 (0.3%)	
469		84 (2.9%)	28 (2.9%)	
472		12 (0.4%)	4 (0.4%)	
473		456 (16%)	152 (16%)	
474		405 (14%)	135 (14%)	
475		90 (3.2%)	30 (3.2%)	
478		39 (1.4%)	13 (1.4%)	
479		792 (28%)	264 (28%)	

[1] Pearson's Chi-squared test; Welch Two Sample t-test; Fisher's exact test

Table D.29. Prostate Cancer cohort characteristics

Prostate Cancer. Matched Cohort Characteristics				
Variable	**N**	**No TBI**, N = 1,134	**TBI**, N = 378	**p-value**[1]
Sex, n (%)	1,512			
M		1,134 (100%)	378 (100%)	
Race/Ethnicity, n (%)	1,512			>0.999
Black/AA		108 (9.5%)	36 (9.5%)	
Other		15 (1.3%)	5 (1.3%)	
White		1,011 (89%)	337 (89%)	
Age, Mean (SD)	1,512	55 (17)	55 (17)	0.983
ZIP3, n (%)	1,512			>0.999
460		54 (4.8%)	18 (4.8%)	
461		63 (5.6%)	21 (5.6%)	
462		312 (28%)	104 (28%)	
463		6 (0.5%)	2 (0.5%)	
469		33 (2.9%)	11 (2.9%)	
472		6 (0.5%)	2 (0.5%)	
473		174 (15%)	58 (15%)	
474		153 (13%)	51 (13%)	
475		48 (4.2%)	16 (4.2%)	
478		15 (1.3%)	5 (1.3%)	
479		270 (24%)	90 (24%)	

[1] Pearson's Chi-squared test; Welch Two Sample t-test; Fisher's exact test

Table D.30. Acquired Hypothyroidism cohort characteristics

Acquired Hypothyroidism. Matched Cohort Characteristics

Variable	**N**	**No TBI**, N = 2,301	**TBI**, N = 767	**p-value**[1]
Sex, n (%)	3,068			>0.999
F		1,248 (54%)	416 (54%)	
M		1,053 (46%)	351 (46%)	
Race/Ethnicity, n (%)	3,068			>0.999
Black/AA		228 (9.9%)	76 (9.9%)	
Other		24 (1.0%)	8 (1.0%)	
White		2,049 (89%)	683 (89%)	
Age, Mean (SD)	3,068	54 (18)	54 (18)	0.989
ZIP3, n (%)	3,068			>0.999
460		108 (4.7%)	36 (4.7%)	
461		120 (5.2%)	40 (5.2%)	
462		630 (27%)	210 (27%)	
463		9 (0.4%)	3 (0.4%)	
469		66 (2.9%)	22 (2.9%)	
472		9 (0.4%)	3 (0.4%)	
473		372 (16%)	124 (16%)	
474		330 (14%)	110 (14%)	
475		69 (3.0%)	23 (3.0%)	
478		36 (1.6%)	12 (1.6%)	
479		552 (24%)	184 (24%)	

[1] Pearson's Chi-squared test; Welch Two Sample t-test; Fisher's exact test

Table D.31. Diabetes cohort characteristics

Diabetes. Matched Cohort Characteristics

Variable	N	No TBI, N = 2,439	TBI, N = 813	p-value[1]
Sex, n (%)	3,252			>0.999
F		1,410 (58%)	470 (58%)	
M		1,029 (42%)	343 (42%)	
Race/Ethnicity, n (%)	3,252			>0.999
Black/AA		234 (9.6%)	78 (9.6%)	
Other		36 (1.5%)	12 (1.5%)	
White		2,169 (89%)	723 (89%)	
Age, Mean (SD)	3,252	54 (18)	54 (18)	0.988
ZIP3, n (%)	3,252			>0.999
460		111 (4.6%)	37 (4.6%)	
461		126 (5.2%)	42 (5.2%)	
462		648 (27%)	216 (27%)	
463		9 (0.4%)	3 (0.4%)	
469		75 (3.1%)	25 (3.1%)	
472		12 (0.5%)	4 (0.5%)	
473		384 (16%)	128 (16%)	
474		327 (13%)	109 (13%)	
475		87 (3.6%)	29 (3.6%)	
478		33 (1.4%)	11 (1.4%)	
479		627 (26%)	209 (26%)	

[1] Pearson's Chi-squared test; Welch Two Sample t-test; Fisher's exact test

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CURRICULUM VITAE

Timothy D. McFarlane

Education

Indiana University	Richard M. Fairbanks School of Public Health, Department of Epidemiology Dates attended: September 2013 – March 2023 Degree: Doctor of Philosophy; Epidemiology (major), Health Informatics (minor) GPA: 3.99
Indiana University	Richard M. Fairbanks School of Public Health, Department of Epidemiology Degree: Master of Public Health; Epidemiology Dates attended: January 2012 – December 2013 GPA: 4.0
Ball State University	Dates attended: September 2006 – May 2010 Degree: Bachelor of Science; Medical Technology (major), Chemistry (minor) Summa cum laude graduation honors

Teaching Experience

Indiana University	Adjunct Faculty, O'Neil Executive Education, 2022-Present Adjunct Faculty, 2019-Present Lecturer and Undergraduate Program Director, 2016-2019 Associate Instructor, 2015-2016 Teaching Assistant, 2013
Ball State University	Supplemental Instructor, 2009 Teaching Assistant, 2008 University Tutor, 2008-2009

Professional Experience

Indiana Family and Social Services Administration	Chief Data Officer, 2022-Present Deputy Chief Data Officer, 2021-2022 Deputy Director, Data Science, 2019-2021
Eli Lilly & Company	Epidemiologist, 2015-2017
Indiana Department of Health	Survey Coordinator, 2014

Alverno Clinical Laboratories	Medical Laboratory Scientist II, 2009-2014

Publications

- Balio CP, Norwood C, **McFarlane TD**, Rusyniak D, Blackburn J (2022). Health Care and Behavioral Service Use by Medicaid-Enrolled Adults After Release From Incarceration. Psychiatr Serv. PMID: 35855622
- Balio C, Norwood C, **McFarlane TD,** Blackburn J. Healthcare Utilization Among Justice-Involved Individuals Enrolled in Medicaid: Lessons from a Midwestern State. Health Services Research. 56(52).
- **McFarlane TD**, Love J, Hanley S, Dixon BE, Hammond F (2019). Increased risk of stroke among young adults with serious traumatic brain injury. Journal of Head Trauma Rehabilitation. 35(3): E310-E319.
- **McFarlane TD**, Dixon BE, Grannis SJ, & Gibson PJ (2019). Public health informatics in local and state health agencies: an update from the public health workforce interests and needs survey. Journal of Public Health Management and Practice 25, S67-S77. PMID: 30720619
- Rahurkar S, **McFarlane TD**, Wang J, Hoover S, Hammond F, Kean J, Dixon BE. (2018). Leveraging Health Information Exchange to Construct a Registry for Traumatic Brain Injury, Spinal Cord Injury and Stroke in Indiana. American Medical Informatics Association Annual Symposium Proceedings: 16;1440-1449. PMID: 29854213
- Dixon BE, **McFarlane TD**, Dearth S, Grannis SJ, & Gibson PJ (2015). Characterizing informatics roles and needs of public health workers: results from

the Public Health Workforce Interests and Needs Survey. Journal of Public Health Management and Practice, 21, S130-S140. PMID: 26422483.

Textbook Chapters

- Magnuson, J.A., **McFarlane, T.D**., Hopkins, R. (2020) Informatics in Disease Prevention and Epidemiology. In JA Magnuson and B Dixon (Eds), Public Health Informatics and Information Systems (2ND). Springer.
- **McFarlane, T.D.,** Dixon, B.E., Grannis, S. (2016). Client registries: Identifying and linking patients. In B. Dixon (Ed.), Health Information Exchange: Navigating and Managing a Network of Health Information Systems (1st ed., Vol. 1). Elsevier.
- **McFarlane, T.D.,** Teesdale, S., Dixon, B.E. (2016). Facility registries: Metadata for where care is delivered. In B. Dixon (Ed.), Health Information Exchange: Navigating and Managing a Network of Health Information Systems (1st ed., Vol. 1). Elsevier.

Conference Proceedings

- **McFarlane TD**. Reducing Inequities thru Technology. American Public Human Services Association, IT Management Solutions, 2021 [oral]
- **McFarlane TD**, Shao Y. Towards a holistic picture of health: Integration of social determinants and Medicaid claims. Academy Health, 2021 [poster]
- **McFarlane TD**. Data Governance: The key to unlocking the power of state health data. Academy Health Data Palooza and National Health Policy Conference, 2020 [poster]

- **McFarlane TD**, Sloan S. A Pandemic to enable telehealth: States to ensure its future in vulnerable populations. Academy Health Data Palooza and National Health Policy Conference, 2020 [poster]
- Dixon BD, **McFarlane TD**, Grannis SJ, Gibson PJ. Local and State Public Health Informatics Workforce Skills and Needs: A Descriptive Analysis using the PH WINS. American Medical Informatics Association, 2019 [oral]
- **McFarlane TD**. Towards Obesity Surveillance Using Electronic Health Records. International Society for Disease Surveillance, 2019 [oral].
- **McFarlane TD**. The Hidden Cost of the Opioid Epidemic: Spatial and Temporal Trends of Opioid-Related Premature Death. American Public Health Association, 2018 [poster].
- **McFarlane TD**, Dixon BE, Gibson PJ. Using Electronic Health Records for Public Health Hypertension Surveillance. International Society for Disease Surveillance, 2018 [oral].
- Cocke A, Raftery AK, **McFarlane TD**. Impact of Area-Poverty Rate on Late-Stage Colorectal Cancer Incidence in Indiana, 2010-2014. North American Association of Central Cancer Registries Annual Meeting, 2017 [oral].
- **McFarlane TD**, Kirbiyik U, Henderson M, Dixon BE. What's age got to do with it? Fatal accidents among the elderly in the coming decade. American Public Health Association, October 2016 [poster]
- **McFarlane TD**, Aalsma, M. Adverse childhood experiences as an effect modifier for the association between traumatic brain injury and disruptive behavior

disorders: Results from the 2011 National Survey of Children's Health. American Public Health Association, October 2016. [poster]

- **McFarlane TD**, Henderson M, Kirbiyik U, Dixon B. Public health engagement with a statewide health information exchange: A case study. Public Health Infromatics. Atlanta, GA, August 2016 [oral]
- Henderson M, **McFarlane TD**, Massie A, Segev D, Dixon B. Gender differences in longitudinal eGFR of living kidney donors in a health information exchange. American Transplant Congress, June 2016. [poster]

Courses Instructed

- Introduction to Public Health (PBHL-P109)
- Zombie Apocalypse and Doomsday Infections (PBHL-E210)
- Principles of Epidemiology (PBHL-E322)
- The Lurking Pandemic: Chronic Disease Epidemiology (PBHL-E335)
- Study Abroad: London (PBHL-P450)
- Advanced Epidemiology (PBHL-E601)
- Applied Epidemiology Methods I (PBHL-E711)
- Applied Epidemiology Methods II (PBHL-E712)

Awards

- Indy's Best and Brightest Finalist in Government, 2021
- Indiana Family and Social Services Administration Secretary's Health Impact Award, 2020, 2021
- State Health Commissioner Award for Excellence in Public Health, 2020
- Sherry Queener Graduate Student Excellence Award, 2019

- Indiana University Purdue University Indianapolis Elite 50 and Premier 10, 2019
- Best Student Abstract ISDS Annual Conference, 2018
- Richard M. Fairbanks School of Public Health CORPS Student of the Year, 2013
- Susan Rogers Outstanding Medical Technology Student Award, 2010