# Impact of Social Deprivation Index on Severe Traumatic Brain Injury Outcomes

by

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University of Pittsburgh, 2022

## Abstract

Severe Traumatic Brain Injury (TBI) is a considerable public health concern worldwide, as it is one of the leading causes of death and disability among young people. Even with extensive research on the subject, there are many unknowns regarding risk factors for recovery from severe TBI, and much of the outcome variability is unaccounted for. Neurobehavioral recovery is particularly difficult to predict using current models. After examining the literature to find established and potential risk factors for TBI outcomes, the aim was to see if there is any association between social determinants of health and global, functional, or neurobehavioral outcomes from 3 months to 2 years post-hospitalization in a sample of 287 participants. Post-injury outcomes were measured and recorded by a clinical technician at 3, 6, 12, and 24 months using three scales: the Glasgow Outcome Score (GOS), the Disability Rating Score (DRS), and the Neurobehavioral Rating Score (NRS). These three measures as well as reported death (yes/no) at timepoints 3, 6, 12, and 24 months were included in this analysis. Social Deprivation Index (SDI) was used as a way to quantify unmeasured social determinants of health based on patients' 5-digit zip codes. A series of regressions were performed, which included age, sex, Glasgow Coma Score (GCS), and SDI as predictors, to determine any association between these variables and the outcome measures. Based on this analysis, there was no evidence that SDI is associated with TBI recovery, though the association between SDI and NRS at 6-months did approach statistical significance. Age and GCS were both significantly associated with recovery, with higher age and

lower GCS correlating to worse recovery. Missing data was a concern in this sample, and there was evidence of an association between higher SDI and more missing data, which may have impacted the results for the group with high SDI. Further research could use a larger, more diverse sample and additional ways to identify and quantify social determinants of health to try and parse out the differential recovery patterns that are seen in TBI patients.

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## 1.0 Introduction

Traumatic brain injury (TBI) is the primary cause of death and disability among the younger population in the United States and is a significant public health concern worldwide, yet there are still many unknowns concerning the recovery timeline and outcomes (Ghajar, 2000). If more was known about contributing factors in the recovery process, it may inform the treatment protocol for patients at-risk for poor outcomes. Social determinants of health including education level, socioeconomic status, racism, and environment are known to impact numerous health outcomes. Social stressors have even been found to cause epigenetic changes that can impact health in the long run, such as differing DNA methylation trajectories and accelerated telomere shortening (Notterman & Mitchell, 2015). Knowing the implications that social deprivation can have on health, it is possible that these factors contribute to the outcome variability seen in traumatic brain injury patients.

The topic of this research is to examine Social Deprivation Index based on 5-digit zip code data and its relationship to short and long-term patient outcomes after a severe TBI. Social Deprivation Index is a composite measure of seven different social determinants of health based on the area in which someone lives. This research is important because it could help identify risk factors in treating TBI patients and provide some insight into why there is such variability in outcomes even between seemingly similar injuries. Subsequent analysis could delve deeper into the differences in methylation patterns between patients and whether social deprivation contributes to these epigenetic differences.

The hypothesis is that, on average, patients who live in areas with higher social deprivation indices have worse short-term and long-term outcomes than those who live in areas with a lower

deprivation score. Outcomes were recorded at 3, 6, 12, and 24 months after injury and include neurobehavioral changes, degree of disability, and mortality. The goal is to shed some light on whether or not social determinants can help us understand the variability in outcomes among patients with similar injuries who are being treated in the same way. Ideally, TBI treatment and therapy could be individualized to consider each patient's specific combination of risk factors. Before this precision approach is possible, risk factors for poor outcomes and approaches to best address them need to be determined.

## 1.1 Background

### 1.1.1 Traumatic Brain Injury

According to the CDC, a traumatic brain injury is defined as an injury that affects brain function. This can be caused by a bump, blow, jolt, or penetrating injury to the head and can be characterized as either mild, moderate, or severe (CDC, 2017). A TBI is considered mild if changes to brain function last no longer than a minute or two. Moderate TBI is when individuals experience changes in brain function for longer than a couple of minutes and have slightly worse symptoms or symptoms that last longer. These symptoms include headache, confusion, drowsiness, and nausea. It can be difficult to distinguish between mild versus moderate TBI. A person is generally characterized as having severe traumatic brain injury if the injury causes an extended period of unconsciousness or amnesia. These injuries tend to cause longer-term changes in the brain's motor and/or sensory function (University of Alabama at Birmingham, 2022). The majority of severe traumatic brain injuries can be attributed to falls, motor vehicle accidents, assault, or intentional

self-harm (Taylor et. al, 2017). This project focuses on severe traumatic brain injury, specifically in patients who spent time in the Intensive Care Unit and who did not have a skull fracture, or penetrating head injury.

Severe traumatic brain injury is a major contributor to death and disability worldwide, and the majority of these deaths are in low and middle-income countries (Iaccarino et. al, 2018). In the United States alone, about 1.6 million people sustain a TBI annually. In 2018, there were about 223,000 TBI-related hospitalizations and 60,611 deaths in the United States (CDC, 2021). Individuals aged 75 plus and children zero to four years of age account for a disproportionate amount of TBI hospitalizations (Capizzi et. al, 2020). Among TBI survivors, thousands will experience long-term disability as a result of their injuries.

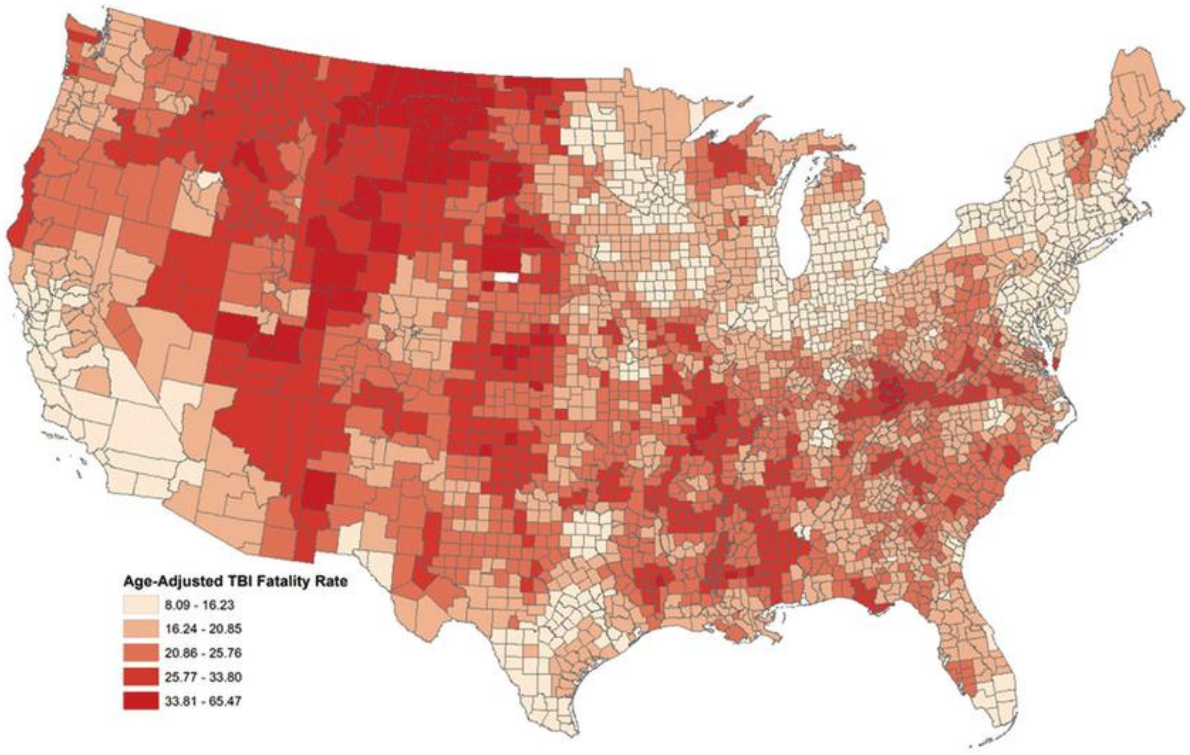



**Figure 1. Traumatic brain injury fatality rate per 100,000 in the United States by county (Brown et. al., 2019)**

Certain groups of people are at higher risk of sustaining a TBI and/or having worse outcomes. These groups include racial and ethnic minorities, members of the military and veterans, incarcerated individuals, homeless people, and domestic abuse survivors. People without health insurance and people living in rural areas are more likely to die from TBI due to a lack of access to care (Figure 1) (CDC, 2021). Zip code data can be used to examine medical resources or lack thereof, such as rehabilitation centers, as well as employment and average economic wellbeing of the area, which can shed light on personal and family resources.

### 1.1.2 Costs of Traumatic Brain Injury

Costs associated with traumatic brain injury in the United States are high. In 2000, over $206 billion was spent on TBI, $54 billion of which was associated with nonfatal injuries that required hospitalization, such as in the population we are studying (Miller et. al, 2009). These figures consider quality of life costs and work-loss costs in addition to actual medical costs. Costs due to loss in quality of life were the largest, and quality-of life lost added up to the equivalent of 20,000 lifetimes (Miller et. al, 2009). Many severe TBI patients never fully recover their independence and often require continued assistance years after their injury (Humphreys et. al, 2013). This puts a financial and emotional burden on families and caregivers. Longstanding changes in patients' behavior, cognitive function, and mood are not uncommon, which can exacerbate this burden (Tate, 1987).

### 1.1.3 Traumatic Brain Injury Outcome Measures

Several standard measures are used to quantify the severity and different outcomes of TBI. This study uses the Glasgow Outcome Scale (GOS), Neurobehavioral Rating Scale (NRS), Disability Rating Scale (DRS), and death to examine recovery.

The GOS was first published in 1975 and has been a common outcome measure for severe traumatic brain injuries ever since. It is a complement to the Glasgow Coma Scale, which measures severity of the injury early-on, rather than a long-term outcome. The GOS is multidimensional, meaning that it considers social, emotional, cognitive, and physical aspects of recovery (McMillan et. al, 2016). There are five outcomes: 'Death' (1), 'Persistent Vegetative State' with no awareness (2), 'Severe Disability' requiring fulltime care (3), 'Moderate Disability' that may impact ability to work (4), and 'Good Recovery' which is not necessarily complete recovery (5) (Lindsay et. al, 2010).

The NRS considers four factors to rate the neurobehavioral recovery of patients who have withstood closed head traumatic injuries, meaning there is no skull fracture. These factors include cognition/energy, metacognition, somatic/anxiety, and language (Levin et. al, 1987). To determine the NRS score, patients are given a structured interview and asked to complete certain cognitive tasks. The goal is to obtain information about memory and orientation, recall, common knowledge, attention capabilities, and information processing capacities at a given timepoint after injury (Conley et. al, 2014). To administer the tool, there are 27 sub-tests, which are each scored from 0 (no impairment) to 7 (extreme impairment). The sum of these sub-scores provides a total score, with higher numbers representing greater impairment (Sandberg, 2018). Though it has some limitations, such as bedridden patients being unable to complete all of the tasks, the NRS was

found to be a reliable and valid measure of neurobehavioral recovery and progress after survival of a closed head injury (Levin et. al, 1987).

The DRS is a measure to quantify the level of disability of severe TBI patients. It ranges from 0 to 29 and includes categories examining patient arousal and awareness, self-care abilities, degree of physical dependence on caretakers, and psychosocial ability to work or attend school (Rappaport et. al, 1982). A score of zero corresponds to no disability, and higher scores indicate greater degrees of disability. The DRS has good reliability and predictive validity, at least in the inpatient rehabilitation setting. It was also found to be reasonably accurate at predicting unfavorable outcomes up to 6-months after discharge (Deepika, et. al).

Hospital length of stay (LOS), which is not examined in this study but may be worth exploring in future research, is a measure that can be informative of injury severity and short-term recovery. According to the 2016 National Health Statistics Report, the average length of stay for TBI patients who required treatment in the ICU was 7.3 days. During this time, many patients undergo CT scans, MRIs, diagnostic radiology, and physical, occupational, and speech therapies (Levant, Chari, & DeFrances, 2016). Though LOS can be a useful measure, there is some evidence that social factors, notably insurance status, can influence hospital LOS in ways unrelated to injury severity alone (Brasel et. al, 2007). This is an important consideration when if using this measure to assess patient outcomes.

### 1.1.4 Outcome Variability in TBI Patients

Despite the prevalence and associated costs of brain injury, there is still a significant gap in knowledge regarding differential outcomes in patients with seemingly similar injuries. Current predictors, including age, injury type, injury severity, second insults, and imaging abnormalities,

only explain about a third of outcome variance (Maas et. al, 2015). Based on current knowledge, the three most important predictors of outcome are age, Glasgow Coma Score (injury severity), and absence of pupil reactivity (Reynolds, 2011). Glasgow Coma Score is given on a scale of 3-15 and is the initial measure of injury severity, with 3 being the worst. It was developed in Glasgow over forty years ago, and is still commonly used to classify head injury severity by assessing a patient's consciousness level. The Glasgow Coma Score is determined using three criteria: eye opening ability, verbal response, and motor response. A total score of three means that a patient had no response in any of the categories (Mehta & Chinthapalli, 2019).

Results from CT scan imaging can also be important in predicting certain outcomes, including mortality (Reynolds, 2011).

### 1.1.5 Established and Potential Risk Factors for Poor Outcomes

Experts in the field agree that an association exists between increasing age and worse outcomes, but there is some debate as to whether the association is continuous across all ages or whether the difference in risk occurs around 30-40 years of age and increases thereafter (Maas et. al, 2015). More recently, the continuous association seems to be accepted.

Several studies have indicated that race/ethnicity disparities in TBI recovery do exist. Shafi et. al (2007) found that minority patients with comparable injury severity were more likely than white patients to have moderate or severe disability at follow-up. Once controlling for insurance status, the difference was negligible. Therefore, socioeconomic status, rather than other confounders associated with race, may be responsible for the racial disparity found in TBI recovery. However, a study conducted by Arango-Lasprilla et. al (2009) found that African American patients reported significantly lower Satisfaction with Life scores at 1-year post injury

compared to their white counterparts. This difference existed after controlling for many important factors including cause of injury, marital status, employment status, injury severity and functional status.

As previously stated, insurance status looks to be a determinant for TBI outcome. Another determinant shown to be weakly associated with outcome is education level. In an analysis by Mushkudiani et. al (2007), higher levels of education were related to slightly better outcomes in TBI patients. Research is lacking in regard to socioeconomic status and other social determinants of health as they relate to TBI outcome trends, but education level and insurance status are both aspects of socioeconomic risk factors with some evidence of association.

As research on the topic has progressed, studies have turned to epigenetics in an attempt to answer some of the questions regarding the extent of TBI outcome variability. Using DNA methylation data from severe TBI patients, Treble-Barna et. al (2021) examined associations between Brain-derived Neurotrophic Factor (*BDNF*) DNA methylation and patient outcomes. The DNA methylation was from serial cerebrospinal fluid samples taken from patients in the ICU during the first five days after brain injury, and the researchers measured global outcome using GOS, neurobehavioral outcome using NRS, and functional outcome using DRS. High methylation of *BDNF* was associated with better outcomes, and this effect increased with increasing patient age. High methylation generally leads to lower expression of a protein, so it is hypothesized that high BDNF protein level may curb recovery in severe TBI patients (Treble-Barna, 2021).

### 1.1.6 Prognostic Value of Main Outcome Predictors

Prediction research for severe TBI patients is ongoing, and some factors have more predictive value than others. Attempting to relate a single predictor to prognosis is problematic

due to confounding factors that may play a role in recovery. Logistic regression can be used to adjust for confounding factors, and odds ratios and explained variation are a common way to relate the prognostic value of different factors (Lingsma et. al, 2010).

In the International Mission for Prognosis and Clinical Trial design in TBI (IMPACT) study, researchers were able to quantify some well-known risk factors by degree of prognostic value for moderate and severe TBI. They found that severity of the injury had the highest value in predicting outcome with an $R^2$ value of about 0.23. Information obtained from CT scans had the second-highest $R^2$ value of about 0.15 (Lingsma, 2010). That being said, cumulatively, the model only explained 35 percent of the variation seen between patients. In a five-year study with the aim to develop a prognostic tool, Walker et. al (2018) found post-traumatic amnesia to be the most valuable predictor for long-term outcomes. They also found that initial GCS score was not significantly associated with outcome, which conflicts with some other studies.

There is a correlation between older age and poorer outcomes, which is the most notable demographic predictor and the leading secondary predictor in the study conducted by Walker et. al (2018). The effects of other demographic predictors including sex, race, and education level are difficult to assess because of potentially confounding social determinants, and there is little consensus as to whether or not these factors have significant predictive power. Instead of attempting to look at each of these factors on their own, it may be beneficial to group social determinants together and examine recovery in patients with higher versus lower social deprivation. The approach of quantifying social determinants of health using social deprivation indices is discussed below.

Though research is ongoing, studies have yet to fully explain the differences in recovery among individuals with very clinically similar injuries, which may include contributions of

genetic, epigenetic, or social factors. Neuropsychological recovery can be the most difficult to predict long-term, and recovery does not seem to be consistent among individuals with similar injuries (Millis et. al, 2001). For example, Millis et. al (2001) examined neuropsychological recovery over five years in patients who had received inpatient rehabilitation and found that about 22 percent improved, 15 percent declined, and 63 percent had no change in neuropsychological function. These changes were measured based on the Reliable Change Index, which uses 15 different cognitive tests. The tests examine memory, attention, cognitive speed, visual construction skills, and language. The group who declined in progress did have the highest age, but age alone did not explain the difference in cognitive function between the groups (Millis, et. al). In a similar study, Rabinowitz et. al (2018) found an association between educational attainment and neuropsychological recovery, higher education level being associated with more favorable outcomes. This research could be extended by looking at the potential association of additional social determinants with recovery.

Stunted cognitive and neurobehavioral recovery can have serious mental health implications when patients are unable to resume day-to-day responsibilities well after their physical injuries have healed. Therefore, it is important to examine the various factors that may contribute to these differential healing patterns. Long-term cognitive improvement after severe TBI is possible, and if we know more about the risk factors for poor outcomes we can better personalize therapy to promote improvement.

### 1.1.7 Social Determinants of Health

Social determinants of health are factors that influence health and health outcomes beyond medical care itself. Increasingly, research has shown that factors including housing, education,

employment, income, racism, air and water quality, food desert status, and other day-to-day elements of life have a definite impact on individuals' health. Social determinants have been found to affect life expectancy, infant mortality, heart disease, diabetes, cancer and cancer mortality, and many other indicators of health (Braveman & Gottlieb, 2014). These determinants also tend to perpetuate the health disparities that already exist. Not only do people of lower socioeconomic status tend to have more health issues, they are also less likely to be able to afford the medical care and/or medication that they need to mitigate these issues.

Common examples that demonstrate the intersection between social factors and health include lead exposure in children who live in run-down homes, a lack of affordable healthy food options in certain neighborhoods leading to increased obesity and other health problems, and chronic stress caused by economic hardship and overworking. Chronic stress has recently received more scrutiny because it is either directly or indirectly linked to most of our biological pathways, including developmental, immune, vascular, and neuroendocrine (Notterman & Mitchell, 2015). Abundant and perpetual release of stress hormones has been linked to earlier onset of chronic illnesses as well as accelerated cellular aging, which is an epigenetic change (Notterman & Mitchell, 2015; Braveman & Gottlieb, 2014).

Epigenetic changes are structural alterations to DNA or histones that lead to different expression patterns of genes (Notterman & Mitchell, 2015). The underlying DNA remains the same, but epigenetic effects can cause functional changes in proteins and cells due to altered expression. It is not fully understood what types of environmental factors affect the epigenome, but there is evidence that social and life experience can alter DNA methylation patterns and lead to differing gene expression (Notterman & Mitchell, 2015).

Social determinants of health have also been shown to affect telomere length and cell aging.

Telomeres are repeated nucleotide sequences on the end of chromosomes that protect them from damage (Giurgescu et. al, 2021). Examining telomere length is a way to determine cell "age" and health. Accelerated cell aging and telomere shortening is correlated with certain social factors, including residence in more deprived areas and having high levels of stress, often due to racial discrimination (Giurgescu et. al, 2022). This accelerated aging makes individuals more prone to chronic illnesses, and may also impact their recovery capability after severe injury, though there are many unknowns regarding the mechanism and full impact of the process (Notterman & Mitchell, 2015).

In addition to telomere shortening, there is evidence that social determinants can have a direct influence on epigenetic patterns of specific loci. Notably, a study in mice found that stress, isolation, and nutritional deprivation led to decreased methylation of central nervous system gene promoters, and that higher levels of methylation of BDNF were associated with a greater ability to handle stressful situations (Notterman & Mitchell, 2015). In humans, adverse events in childhood have been shown to cause differential epigenetic patterns with mental health implications later in life (Galea, Uddin, & Koenen, 2011).

Though not fully understood, epigenetic changes due to social and environmental stressors could contribute to differential health outcomes. If there is a correlation between social determinants of health and TBI outcomes, it is possible that changes to the epigenome are involved. First, it is important to see whether this correlation does exist between social stressors and TBI outcomes. This can be accomplished using Social Deprivation Index from the Robert Graham Center to quantify social determinants of health.

### 1.1.8 Social Deprivation Index

The Social Deprivation Index (SDI) was originally developed in 2012 as a way to quantify social determinants of health and deprivation by geographic location. Using 2005-2009 Census Data, Butler et. al established criteria to rank census tracts by level of deprivation, and found these measures to be correlated with health outcomes and healthcare access (Butler et. al, 2013). Since then, SDI measures have been updated based on 2011-2015 census data, specifically the American Community Survey (Robert Graham Center, 2018).

SDI is a composite measure that uses several characteristics when assigning scores. These measures include: percent of the population living below the federal poverty line, percent of the adult population without a high school degree, the unemployment rate, percent renting as opposed to owning a home, percent living in an overcrowded housing unit, percent of single parents whose children still live at home, and percent of the population without a car (Robert Graham Center, 2018). Social Deprivation Indices are expressed as a value from zero to one hundred, with higher numbers representing greater deprivation. These indices will allow us to assign a degree of deprivation to each patient and relate this to the four different outcome measures mentioned above. Socioeconomic information is often excluded from medical records, but this information is crucial when examining health disparities. To work around this issue, zip code data is a potential proxy for socioeconomic status since address information is typically accessible. Several studies have looked at whether zip code-based indicators are actually correlated with health outcomes. Notably, Berkowitz et. al. (2015) compared geography-based SES indicators with self-reported educational attainment, a key social determinant, to see whether something like educational attainment can be accurately estimated based on zip code or census block. They also looked at specific SES indicators

including median household income, educational attainment, and percent unemployed to see how accurately they reflected health disparities.

Berkowitz et. al. (2015) found that area-based indicators were associated with health outcomes in a similar way to self-reported data in every outcome that they looked at besides diabetes prevalence. For all other clinical outcomes, there was no statistical difference between disparities detected by the area-based indicators versus those from self-reported SES information. Additionally, the researchers compared block group, census tract, and zip code data, and found that missing data was a more significant problem for the block group and census tract data than for the zip code data. They also found that zip code data was not significantly worse at detecting health care disparities than either of the other two measures, making it the most favorable indicator overall. Median household income, educational attainment, and percent unemployed were found to be appropriate indicators of socioeconomic status. All of those measures and more are included in the Social Deprivation Index determination, so it does seem like an adequate way to quantify social determinants for the scope of this project.

## 1.2 Public Health Significance

This project has the potential to highlight how inequities and social determinants impact quality of life from a clinical point of view and to help understand why there is so much variability among TBI patient recovery. Traumatic Brain Injury is a significant public health issue considering the prevalence and costs associated with these injuries. There is a lack of consensus concerning risk factors for short and long-term recovery from severe TBI, which many be genetic, environmental, or likely a combination of the two. There is considerable opportunity for future

research once it is determined whether or not an association exists between social deprivation and TBI outcomes.

## 1.3 Specific Aims

Aim 1. Determine the association between social deprivation index and short and long-term patient outcomes in severely injured TBI patients. Outcomes are quantified using the Glasgow Outcome Scale, Neurobehavioral Rating Scale, and Disability Rating Scale.

Aim 2. Examine trends in missing outcome data to see whether the trends are indicative of potential bias in the study.

# 2.0 Methods

## 2.1 Study Sample

The study sample consisted of 287 patients admitted to the University of Pittsburgh Medical Center-Presbyterian Hospital Neuroscience Intensive Care Unit for severe traumatic brain injury. Patients were excluded if they were brain-dead, had a penetrating head injury, or were outside the age range of 16 to 80 years. To be classified as a "severe" TBI, the patient had to be assigned a Glasgow Coma Score of less than or equal to eight prior to or upon hospital admission (Conley et. al, 2014).

At the outset, there were data for 287 TBI patients, but not all subjects were used in each analysis due to death at any timepoint or missing information either about outcome or social deprivation index. Individuals who died at any timepoint were not included in the GOS, NRS, or DRS outcome analyses since recovery was not an option for these patients, but they were used in a separate analysis to examine whether death is associated with SDI. After removing these individuals, 191 remained. Of these 191, in general, missing data was more prevalent for the outcomes at the later timepoints.

## 2.2 Data Collection

The data set for the analysis consisted of two main components: outcome measures and deprivation indices. The four outcome measures used for this analysis were the Glasgow Outcome

Score (GOS), Disability Rating Score (DRS), Neurobehavioral Rating Score (NRS), and death. Values were taken at timepoints 3, 6, 12, and 24 months after injury. As mentioned above, GOS is a global outcome measure that tracks recovery of a patient and ranges from 1 (death) to 5 (good recovery). The DRS quantifies the level of disability and takes several factors into account, including degree of dependence on caregivers, self-care abilities, arousal and awareness, and ability to attend work or school. The DRS is determined on a scale from 0 (no disability) to 30 (death). The NRS uses cognition/energy, metacognition, somatic/anxiety, and language to assess patients' neurobehavioral recovery. To assign a total NRS score, 27 sub-tests are administered, each scored from 0 (no impairment) to 7 (extreme impairment).

The clinical outcomes used in this analysis were determined by a clinical technician and directed by a Brain Trauma Research Center neuropsychologist. The GOS scores were determined either from medical records or based on observation ($n_{3\ months}$= 176; $n_{6\ months}$= 169; $n_{12\ months}$= 160; $n_{24\ months}$= 124). The DRS were determined by observation either by the patient's primary caregiver or by the patient themselves at each time point ($n_{3\ months}$= 167; $n_{6\ months}$= 168; $n_{12\ months}$ 154; $n_{24\ months}$= 111). The NRS were determined through interview, cognitive tasks, and observation of the patients (Conley et. al, 2014). Due to the comprehensive nature of the NRS as an outcome measure and the requirement for the patient to be present and physically able to complete the tasks, the sample sizes for this measure were the smallest ($n_{3\ months}$= 102; $n_{6\ months}$= 121; $n_{12\ months}$ 121; $n_{24\ months}$= 70).

Social Deprivation Indices were the second component of the data set. These were assigned using data from the Robert Graham Center based on patient's 5-digit zip-codes from de-identified medical records. Using SDI to quantify social determinants of health is based on seven demographic qualities that are primarily related to housing and socioeconomic characteristics

within a census block. The scores range from 0 to 100, with higher numbers representing a greater degree of deprivation (Robert Graham Center, 2018). To assign an SDI score to each patient, their zip-code was located in the Robert Graham Center database, which uses 2015 census data, and the corresponding SDI score was recorded for analysis.

### 2.3 Statistical Analysis

All statistical analyses were performed using R 4.1.1 or Stata/SE 16.1. To analyze death as an outcome, I first wanted to compare the Social Deprivation Indices for patients whose death was reported at any point during the study versus patients whose death was not reported by two years. Participants were characterized as "reported dead" if their GOS was equal to one and/or their DRS was equal to 30 at the timepoint in question. In this analysis, the proportion of deaths may be underestimated due to a lack of reporting for participants lost to follow up. A two-sample t-test was conducted to determine if the mean SDI of the group who were reported as dead (n = 93) was significantly different than that of group who was not (n = 191). To further assess the potential relationship, logistic regressions were used to see whether an association exists between Social Deprivation Index and death at each timepoint. The outcome was death reported, yes or no, and age, sex, GCS, and SDI were included as potential predictors. Age, sex, and GCS were included in the regression to account for any predictive value that they may have based on prior studies.

A series of linear regressions were run to assess any association between SDI and the outcomes GOS, NRS, and DRS at timepoints 3, 6, 12, and 24 months. If a patient was missing data for any timepoint, they were excluded from that or those specific linear regressions, but were included in any regression for which data was available. For example, a patient may be missing a

value for DRS at 12 months but have a value at 24 months. In this case, they were included in the 24-month DRS regression but not the 12-month DRS regression. Twelve linear regressions were performed in this fashion, with predictors including age, sex, GCS, and SDI for the outcome of interest GOS, NRS, or DRS at a given timepoint.

Missing outcome values were prevalent enough in this data set that an analysis examining potential association between SDI and missing GOS, NRS, and DRS values seemed warranted. The total number of data points that an individual was missing for any outcome at any timepoint was regressed on SDI to assess the relationship. A multitude of factors could be responsible for missing data values, but the reasoning behind each missing point is not given. Therefore, we are unsure if the patient died and their death went unreported, or if they were lost to follow-up for other reasons. Data missingness is important to consider because it does have the potential to alter the results. If data missingness is correlated with SDI, the implications are worth looking into.

This project, examining risk factors for outcomes in Traumatic Brain Injured adults, has been approved by the IRB (see Appendix B).

# 3.0 Results

## 3.1 Patient Demographics

The sex distribution of the sample was 80 percent male and 20 percent female, which is not reflective of the general population, though males do experience TBI at a higher rate than females. The sample was 91 percent white, 8 percent African American, and 2 percent Asian, with only two Asian patients in the sample and 23 African American patients. The age distribution of the sample was heavily skewed toward younger ages, with 62 percent under the age of 42. The greatest number of participants fell between the ages of 16 and 25, with 80 participants.

**Table 1. Population Demographics**

| Variable | Count (%) |
|---|---|
| Sex | |
| Male | 231 (80.5) |
| Female | 56 (19.5) |
| Ethnicity | |
| White | 262 (91.3) |
| African American | 23 (8.0) |
| Asian | 2 (0.7) |
| Age | |

| | |
|---|---|
| 16 – 25 | 80 (27.9) |
| 25 – 33 | 51 (17.8) |
| 33 – 42 | 47 (16.4) |
| 42 – 51 | 41 (14.3) |
| 51 – 60 | 30 (10.5) |
| 60 – 68 | 22 (7.7) |
| 68 – 77 | 16 (5.6) |

### 3.2 Data Set Distributions

The average SDI score among the patients in the sample was 41, with a median of 40, a maximum of 100, and a minimum of 1. The standard deviation was 21.1. The histogram shows a slightly right-skewed distribution.

In addition to SDI, predictors including age, sex, and GCS are included in the multiple regression models used for this analysis. The relationship between each of these variables to SDI is shown in Appendix A, and no notable correlation existed between SDI and the other potential predictors.

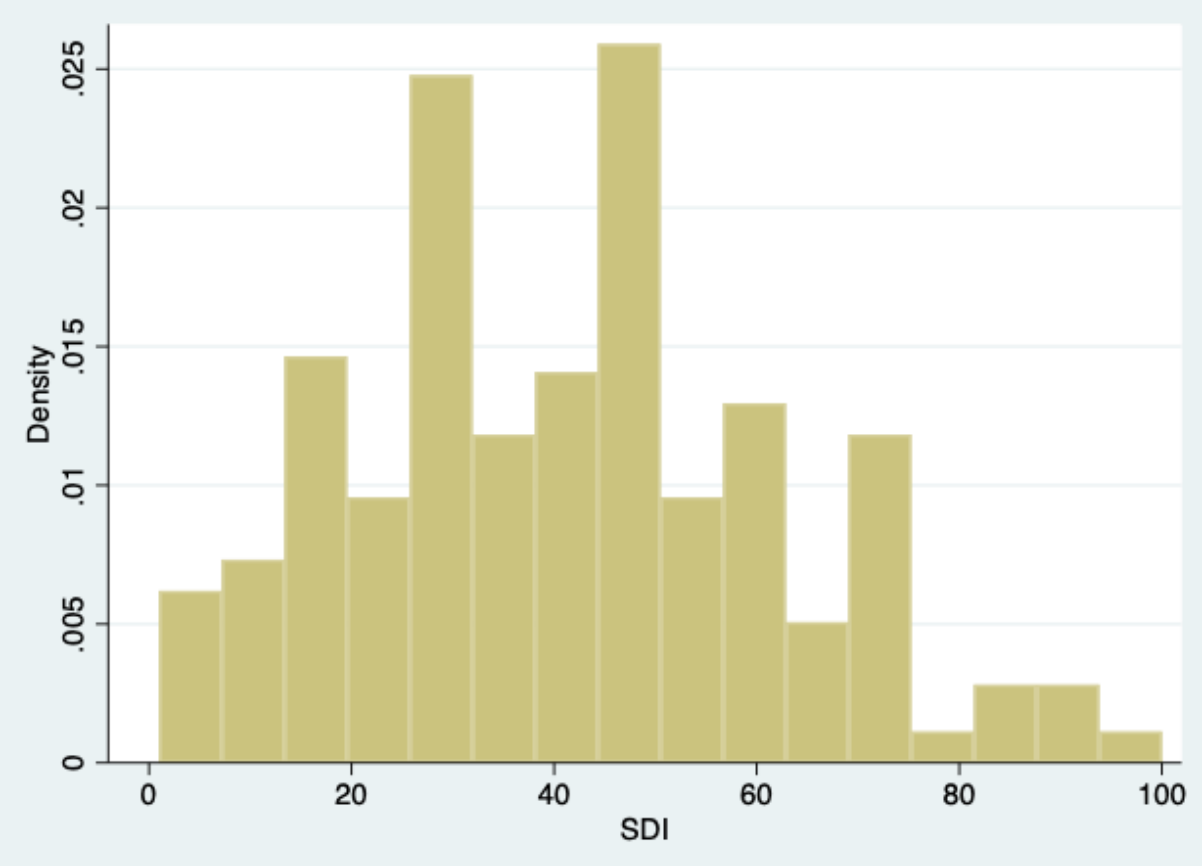



**Figure 2. Distribution of Social Deprivation Indices**

The overall distributions of each outcome measure over time for all patients can also be found in Appendix A. The average GOS and DRS scores improved over time, but the average NRS score did not improve. The average GOS at 3 months was 3.37 and by 24 months it had increased to 3.99. The average DRS at 3 months was 7.98, and decreased to 4.26 by 24 months. The average NRS at 3 months was 41.63 and had increased to 43.24 at 24 months. Higher scores for NRS and DRS indicate worse recovery, while higher GOS indicates better recovery.

### 3.3 SDI as a predictor for death and other outcomes

In a preliminary analysis, the patient population were grouped into two categories: death reported at any timepoint in the study (yes) and death not reported at any timepoint (no). The SDI characteristics of each group were compared to determine whether a significant difference existed between the two groups and in what direction. The average SDI for the death (yes) group was 42.3, and the average SDI for the death (no) group was 40.5 (Figure 3). A two-sample t-test concluded that there was not a significant difference in mean between the two groups, so there is no evidence that those who died had a higher level of deprivation, on average, than those who survived.

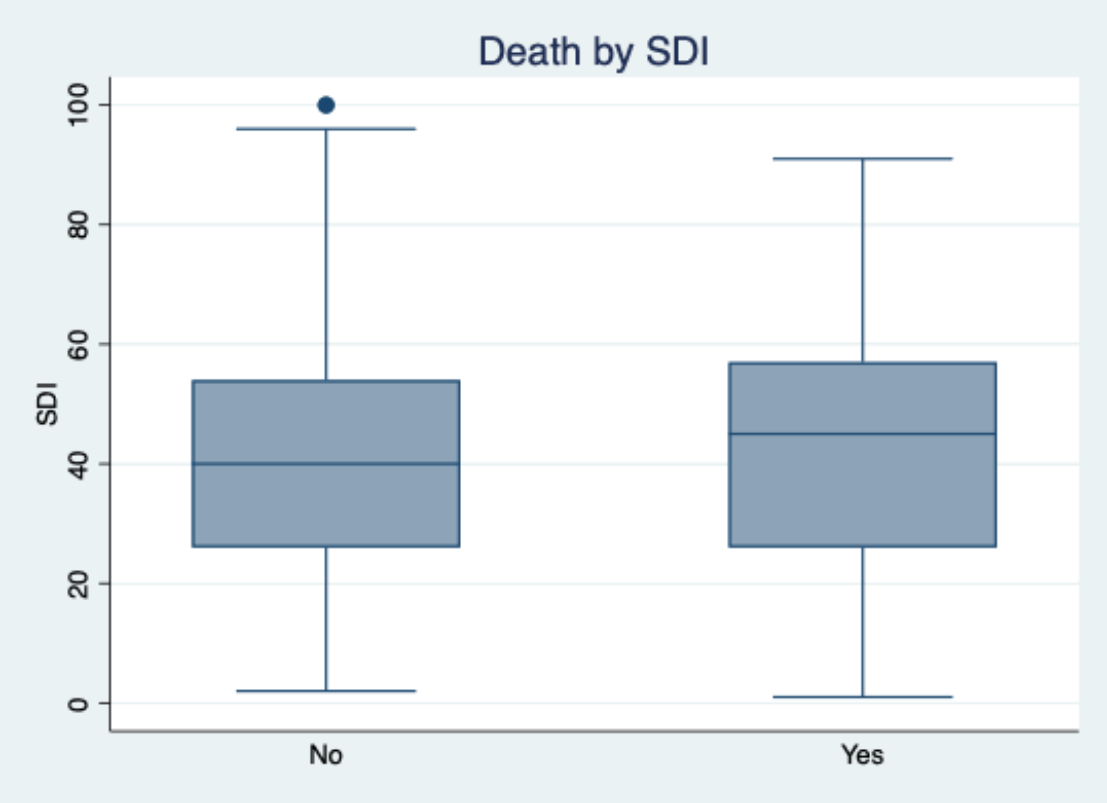



**Figure 3. Comparison of SDI for the group that survived versus the group that died at any timepoint. Average SDI for the group who were reported as dead was 42.3, and average SDI for group who was not reported as dead was 40.5. Two-sample t-test comparison of means: Pr ( |T| > |t| ) = 0.491; Pr ( T < t ) = 0.256**

Analyzing death further, the results of logistic regressions that account for any potential effects of age, sex, and GCS are presented in Table 2. SDI was not significantly associated with death at any of the timepoints, with the smallest p-value of 0.126 at 6 months. The odds ratios for each timepoint were slightly greater than one, meaning that the trend was suggestive of a positive relationship between SDI and odds of death, though no conclusions can be drawn without a significant association between the two factors.

**Table 2. Significance of age, sex, GCS, and SDI as predictors for death reported by each time period**

| | ***Age*** | | ***Sex*** | | ***GCS*** | | ***SDI*** | |
|---|---|---|---|---|---|---|---|---|
| **Death** | **p-value** | **Odds ratio** | **p-value** | **Odds ratio** | **p-value** | **Odds ratio** | **p-value** | **Odds ratio** |
| **3 mo.** | $6.92 \times 10^{-12}$* | 1.010 | 0.634 | 1.029 | $1.73 \times 10^{-7}$* | 0.918 | 0.364 | 1.001 |
| **6 mo.** | $1.11 \times 10^{-12}$* | 1.011 | 0.949 | 1.004 | $3.12 \times 10^{-8}$* | 0.912 | 0.126 | 1.002 |
| **12 mo.** | $7.66 \times 10^{-13}$* | 1.011 | 0.824 | 1.014 | $2.61 \times 10^{-8}$* | 0.911 | 0.156 | 1.002 |
| **24 mo.** | $6.8 \times 10^{-15}$* | 1.012 | 0.620 | 1.031 | $6.1 \times 10^{-9}$* | 0.907 | 0.230 | 1.001 |

*statistically significant with p-value < 0.05

Table 3 displays results from twelve regressions examining the association between potential predictor variables, age, sex, GCS, and SDI, and the outcome measures at each timepoint. These adjusted models were used in order to account for any effects of potentially important covariates while simultaneously examining the relationship between SDI and each outcome measure. Looking at SDI specifically, there is not sufficient evidence to suggest that deprivation level is associated with GOS, DRS, or NRS at any timepoint. The smallest p-value resulted from the association between SDI and NRS at 6 months, at 0.078, which is not statistically significant at the traditional p-value threshold of 0.05, although may be suggestive of a trend. Then, six months later at 12 months, the p-value is 0.748, also not statistically significant. The fluctuation in p-values

for the NRS analyses could be partially due to the amount of missing data for that outcome measure.

Though there is no significant association between SDI and the outcome measures, the trends of the outcomes in relation to SDI are notable. The beta coefficients are positive for all of the NRS timepoints, and GOS at 3 months. The beta coefficients are negative for the remaining GOS timepoints and all of the DRS timepoints. If higher deprivation were correlated with impeded recovery, we would expect there to be a positive association between SDI and death, SDI and NRS, and SDI and DRS. We would expect a negative association between SDI and GOS.

**Table 3. Significance of age, sex, GCS, and SDI as predictors for TBI outcomes**

| | | ***Age*** | | ***Sex*** | | ***GCS*** | | ***SDI*** | |
|---|---|---|---|---|---|---|---|---|---|
| **Outcome** | **n** | **p-value** | **Beta** | **p-value** | **Beta** | **p-value** | **Beta** | **p-value** | **Beta** |
| **GOS** | | | | | | | | | |
| **3 mo.** | 176 | 0.562 | -0.002 | 0.648 | 0.092 | 0.002* | 0.115 | 0.539 | 0.002 |
| **6 mo.** | 169 | 0.011* | -0.011 | 0.304 | 0.154 | 0.002* | 0.139 | 0.438 | -0.002 |
| **12 mo.** | 160 | 0.008* | -0.012 | 0.165 | 0.212 | $7.9x10^{-5}$* | 0.184 | 0.596 | -0.002 |
| **24 mo.** | 124 | 0.058 | -0.010 | 0.055 | 0.359 | 0.003* | 0.163 | 0.754 | -0.001 |
| **DRS** | | | | | | | | | |
| **3 mo.** | 167 | 0.602 | 0.018 | 0.072 | -2.200 | $2.5x10^{-5}$* | -1.578 | 0.263 | -0.027 |
| **6 mo.** | 168 | 0.169 | 0.047 | 0.341 | -1.120 | 0.0001* | -1.380 | 0.675 | -0.010 |
| **12 mo.** | 154 | 0.156 | 0.043 | 0.279 | -1.088 | $1.1x10^{-6}$* | -1.517 | 0.461 | -0.016 |
| **24 mo.** | 111 | 0.393 | 0.032 | 0.285 | -1.399 | 0.0049* | -1.104 | 0.968 | -0.001 |
| **NRS** | | | | | | | | | |
| **3 mo.** | 102 | 0.168 | 0.113 | 0.343 | -3.134 | 0.591 | -0.491 | 0.124 | 0.090 |
| **6 mo.** | 121 | 0.003* | 0.158 | 0.715 | 0.661 | 0.655 | -0.246 | 0.078 | 0.065 |
| **12 mo.** | 121 | 0.002* | 0.215 | 0.796 | -0.589 | 0.480 | -0.510 | 0.748 | 0.016 |
| **24 mo.** | 70 | 0.012* | 0.311 | 0.707 | -1.525 | 0.443 | 0.864 | 0.671 | 0.036 |

*statistically significant with p-value < 0.05

### 3.4 Additional Potential Predictors (Age, Sex, GCS)

Tables 2 and 3 display the overall results of the fifteen regressions performed. Statistically significant values (p-value < 0.05) are indicated with a star. Increased age was strongly associated with death at 3, 6, 12, and 24 months, with extremely small p-values at each timepoint. The odds ratios were about 1.01 for each timepoint, meaning that the odds of death increased by about 1 percent per year of age. Age was also significantly associated with GOS at timepoints 6 and 12 months, and with NRS at 6, 12, and 24 months. For both measures, there was an association between increased age and poorer outcomes. Age was not significantly associated with DRS at any timepoint.

There were no statistically significant associations between sex and any outcome at any timepoint.

GCS, the measure of initial injury severity, was strongly associated with death, GOS and DRS at all timepoints. There was a negative association between GCS and reported death, and the odds ratios show that with each unit increase in injury severity, the odds of death were reduced by almost 10 percent. This effect increased with increasing time from injury. GCS was positively associated with GOS and negatively associated with DRS. In other words, patients with worse injuries at the outset had poorer GOS and DRS scores in the months that followed. The most significant were GOS at 12 months (p-value = $7.9 \times 10^{-5}$), DRS at 3 months (p-value = $2.5 \times 10^{-5}$), and DRS at 12 months (p-value = $1.1 \times 10^{-6}$). Interestingly, GCS did not seem to be associated with NRS at any timepoint. In fact, the only factor significantly associated with NRS was age.

### 3.5 Missing Data and SDI

**Table 4. Data Missingness and SDI**

| | **Beta coefficient** | **Standard error** | **t-value** | **p-value** |
|---|---|---|---|---|
| **(Intercept)** | 2.281 | 0.456 | 4.998 | $1.32x10^{-6}$ |
| **SDI** | 0.028 | 0.010 | 2.761 | 0.0063* |

The distribution of the number of missing outcome values for each patient can be found in Appendix A. The maximum was 11 and the minimum was 0 missing values out of 12. The mean was 3.4, the median was 3, and the mode was 0. Missing values in this data set could potentially be due to death that was not accounted for or loss to follow-up for various reasons. The results of the regression examining the relationship between the amount of missing data and SDI are shown in Table 4. There was a significant positive association between patient SDI and missing data, with a p-value of 0.0063. Thus, there is evidence that level of deprivation is related to whether or not patients participated in follow-up measurements of recovery, with higher levels of deprivation associated with greater data missingness. A series of box plots showing the relationship between missing data and SDI can be found in Appendix A.

# 4.0 Discussion

A multitude of studies concerning severe TBI patients have found various factors to be associated with good or bad recovery. Notably, age and initial injury severity score (GCS) are, for the most part, agreed upon factors that have legitimate prognostic value. Therefore, we expected to see a correlation between age and recovery as well as GCS and recovery. Additional research examined the predictive power of social factors for TBI recovery, but it has been difficult to quantify these factors and to account for confounding variables. Education and insurance status are two factors shown to be weakly associated with recovery patterns, as well as urban versus rural status (Mushkudiani et. al., 2007 & Brown et. al., 2019).

In this study, self-reported demographic factors such as education level, income, and number of dependents were not available, so zip code information by way of SDI was used as proxy for these social determinants. Based on past research linking social determinants of health to various other health outcomes and the TBI research showing a loose correlation between some of these factors and recovery, it was expected that people living in areas with higher deprivation would have impaired recovery compared to those living in areas with low deprivation.

## 4.1 Predictors for Survival

From this sample, 93 patients were reported as deceased before the end of the study, leaving 191 presumed living at 24 months. With a p-value of 0.2, there was not a significant association between death and SDI. The mean SDI for the death(yes) group was slightly higher than the mean

SDI for the death(no) group, which follows the trend that was expected, but the difference is not great enough to draw any conclusions (Figure 3). In the logistic regressions, where factors including age, sex, and GCS were included to account for their potential predictive value, the overall conclusion was the same: there was not sufficient evidence to infer a relationship between SDI and death, though the trends suggested a slight increase in odds of death for individuals from more deprived areas.

There was, however, a significant association between death and both age and GCS. Higher age and lower GCS were strongly correlated with death reported by 24 months, with p-values of $6.8x10^{-15}$ and $6.1x10^{-9}$, respectively. Appendix Figures 7 and 8 show visuals of these trends. The mean age for the death(yes) group was 47.5 years and the mean age for the death(no) group was 33.5 years. These findings are consistent with the literature and highlight that age is a key predictor for survival. The mean initial injury severity score, or GCS, for the death(yes) group was 5.2, and the mean for the death(no) group was 6.1. There has been some debate in the literature about the prognostic value of GCS, but in this sample, it was found to be strongly correlated with survival up to two years.

### 4.2 SDI Relationship with GOS, DRS, and NRS

SDI was not significantly ($p<0.05$) associated with any of the outcome measures between three months and two years (Tables 2 ad 3). Therefore, we did not find evidence that SDI has a predictive value for GOS, NRS, or DRS scores. The most suggestive association was between SDI and NRS at 6 months, but with p-value of 0.078 it was not significant and no real conclusions could be drawn. With that in mind, the trends of each relationship were still of note.

Higher SDI values correspond to greater degrees of deprivation, so if deprivation status did relate to recovery measures we would expect higher SDI to do so in a negative way. As mentioned previously, a higher GOS score indicates better recovery, while high NRS and DRS scores indicate worse recovery. Therefore, the relationship between SDI and GOS was expected to be negative and the relationship between SDI and both DRS and NRS was expected to be positive. As shown in Table 3, the trends fit this expectation for NRS at all timepoints and for GOS at timepoints 6, 12, and 24 months. DRS, however, had a negative association with SDI for all timepoints, which is the opposite of what was expected.

Based on the p-values and beta coefficients, future SDI research could examine NRS specifically, and from a larger and more diverse sample. NRS is the outcome measure that is the most difficult to predict with current models, so there is reason for continued examination of that factor (Millis et. al., 2001).

### 4.3 Covariates associated with GOS, DRS, and NRS

GCS had the strongest and most consistent association with GOS. This association existed at all timepoints, with the smallest p-value ($7.9x10^{-5}$) at 12 months. Age had a statistically significant correlation to GOS at 6 months and 12 months, with higher age corresponding to lower GOS scores, or worse recovery. These results are consistent with the Maas et. al. (2015) paper, which found age and GCS to be two of the most important predictors of overall outcome, though age was only statistically significant at two timepoints in our examination (Table 3). Since the GOS outcome measure is the longer-term complement to the original GCS measure, it makes sense

that the two would follow a similar pattern and that the GCS would make a good predictor for GOS.

The only factor associated with DRS was GCS, the initial injury severity. There was a strong negative association between GCS and DRS at each timepoint, with the most significant at 3 months (p-value = $2.5x10^{-5}$) and 12 months (p-value = $1.1x10^{-6}$). Age was not associated with DRS at any timepoint, nor was SDI or sex. The DRS is scored based on the ability to perform basic functions including eye opening, responding to stimuli, communicating, feeding, etcetera. Therefore, it is unsurprising that severity of the injury would have the largest impact on DRS score. Appendix Figure 2 shows the distribution of DRS scores in the patient sample over time and highlights that most patients did have good recovery by 24 months, the vast majority having a DRS score of either 0 or 1. Based on this data, one can conclude that if a patient does survive their injury, their level of basic human function will likely improve over time regardless of age, sex, or social deprivation status.

Age was the only factor found to be significantly associated with NRS, and the positive association existed at timepoints 6 (p-value = 0.003), 12 (p-value = 0.002), and 24 months (p-value = 0.012). In other words, higher age was associated with greater neurobehavioral impairment, especially at the intermediate timepoints of 6 and 12 months. Neither GCS nor sex were even suggestively associated with the outcome at any timepoint. This is consistent with the study by Millis et. al. in 2001, who found neuropsychological recovery to be the most difficult to predict using standard measures. They did find age to be associated with declining neurobehavioral recovery, though age alone did not explain the long-term recovery patterns that they saw.

Out of the outcome measures examined, missing data was the largest problem with NRS. At 24 months, we only had NRS data for 70 patients compared to 124 with GOS data and 111 with

DRS data. The neurobehavioral rating scale is the most comprehensive of the three discussed in this paper, and patients are more involved in the sub-tests required to report an accurate score. Therefore, it is somewhat unsurprising that this outcome measure has a higher missing response rate than the others, but it may have impacted the results.

### 4.4 Missing Data and SDI

There was a positive association between the amount of missing data values for participants and their SDI. This means that, in this study, deprivation did seem to have a significant effect on the amount of missing data, with a correlation between higher SDI (greater deprivation) and more missing outcome values. Missing data can tell an important story because it signifies an inability or disinterest in continuing the study for one reason or another.

Common reasons for discontinuing a study include scheduling conflicts, personal or family reasons, anxiety, and lack of understanding (Harper & Neuer, 2009). If continuing a study is inconvenient for a patient for any reason, a patient may choose to discontinue. Examples of these inconveniences include living far away from the hospital or clinic, not having reliable transportation or phone/internet service, the inability to take time off work or relinquish caretaking duties of dependents, and more. Often, these concerns are more prevalent for those with lower socioeconomic status, which is why it is important to examine the trends in data missingness and assess whether these trends have the potential to impact the overall results. The association in this study between higher deprivation and more loss to follow-up is consistent with the trend that inability to continue a study has ties to socioeconomic status, which could be indicative of a potential bias.

### 4.5 Limitations

A primary limitation in this analysis was the lack of diversity in the sample, specifically race and sex. Racism and sexism are important social determinants of health, especially when considering allostatic load and stress response. White, male individuals are less likely to experience the everyday stressors of racism and/or sexism, which does not make them the best sample for looking at the impacts of social determinants of health. The inconsistency of the sample size is also a limitation, given that we do not have outcome values for every participant at each time point.

Another limitation is the use of 5-digit zip-codes rather than 9-digit zip-codes. Five-digit zip codes generally comprise a large area consisting of people with many different education levels, housing situations, and socioeconomic statuses. SDI considers the average in the area for each category, so if there are small areas with both extremes of deprivation (high and low) located within the same zip-code, then the concern is that they will neutralize each other. There is a database that provides an Area Deprivation Index given 9-digit zip-codes, which is much more telling because comprises a smaller area. For this study, due to de-identification reasons, 9-digit zip-codes were not accessible.

One key element that is not included in the SDI measurements but may have proved important in this study is rurality, specifically distance to a hospital or healthcare facility. In a 2019 study, Brown et. al. found that rurality impacted traumatic brain injury death. It is possible that it has predictive capabilities for other recovery measures as well, especially where access to rehabilitation services is concerned. Future research could include distance from a healthcare facility as a social determinant of health to investigate any potential relationship to short and long-term disability and neurobehavioral outcomes.

## 5.0 Conclusions

Based on this sample of severe TBI patients, there is no conclusive evidence that TBI recovery is influenced by social deprivation status. That being said, the association between SDI and NRS at 6-months did approach statistical significance and may warrant further research, especially because there is evidence of an association between higher SDI and more missing data points for outcome measures.

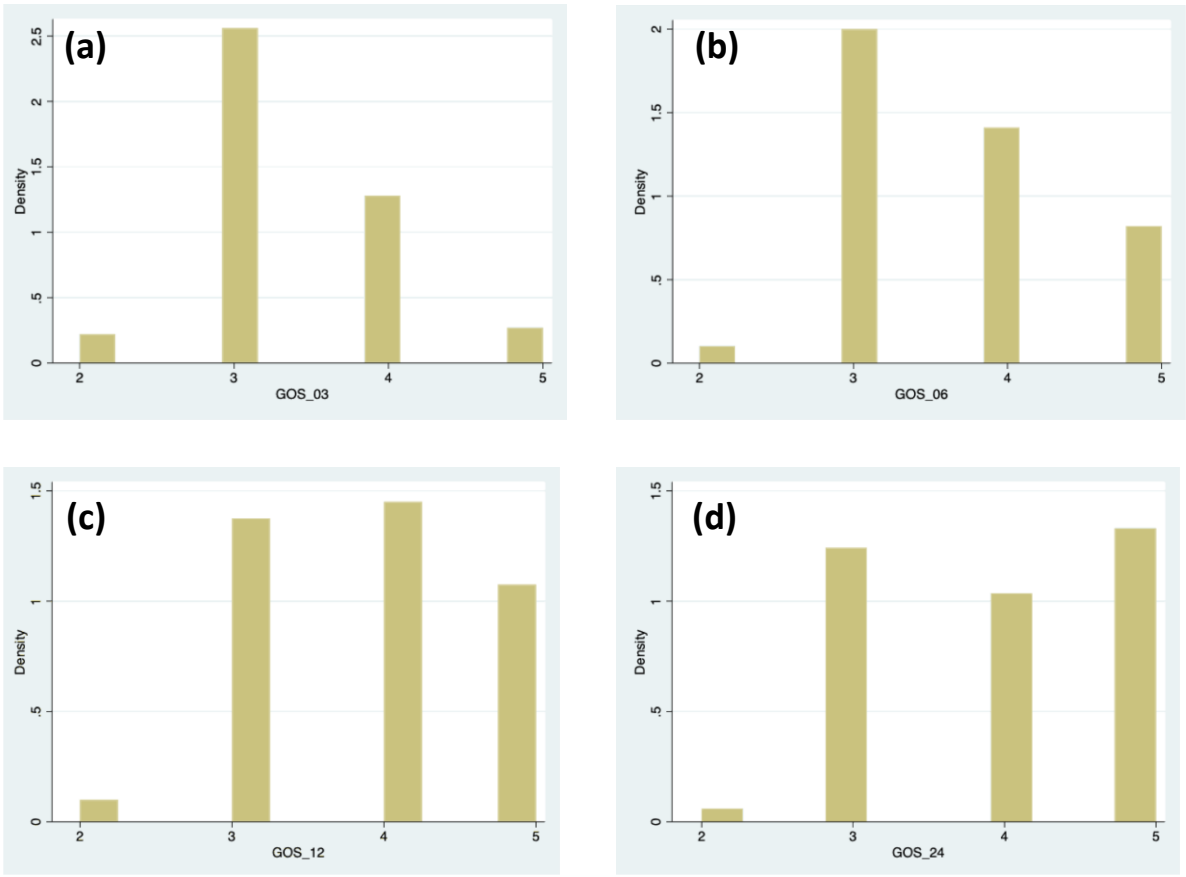
Consistent with the literature, age and GCS both seem to have important predictive value for survival and for recovery patterns over time. Higher age was strongly associated with death, worse global recovery, and impeded neurobehavioral recovery. A lower GCS was strongly associated with death, as well as with poorer global and functional outcomes.

Further research examining the neurobehavioral recovery of severe TBI patients is necessary in order to parse out the predictive value of potential risk factors other than age. When looking at social determinants of health, a more diverse, larger sample size with a continuous distribution of deprivation indices may provide increasingly telling results. Additionally, classifying deprivation status using smaller geographical areas may provide more accurate estimates of the patients' living conditions, and thus allow researchers to more easily identify key risk factors for poor recovery. Also, further research could treat rurality, or distance to the nearest healthcare facility, as a key covariate.

In addition to continued examination of long-term neurobehavioral recovery, further research could look at the potential impact that SDI has on short-term measures of recovery such as hospital length of stay. The more we know about risk factors for different elements of TBI

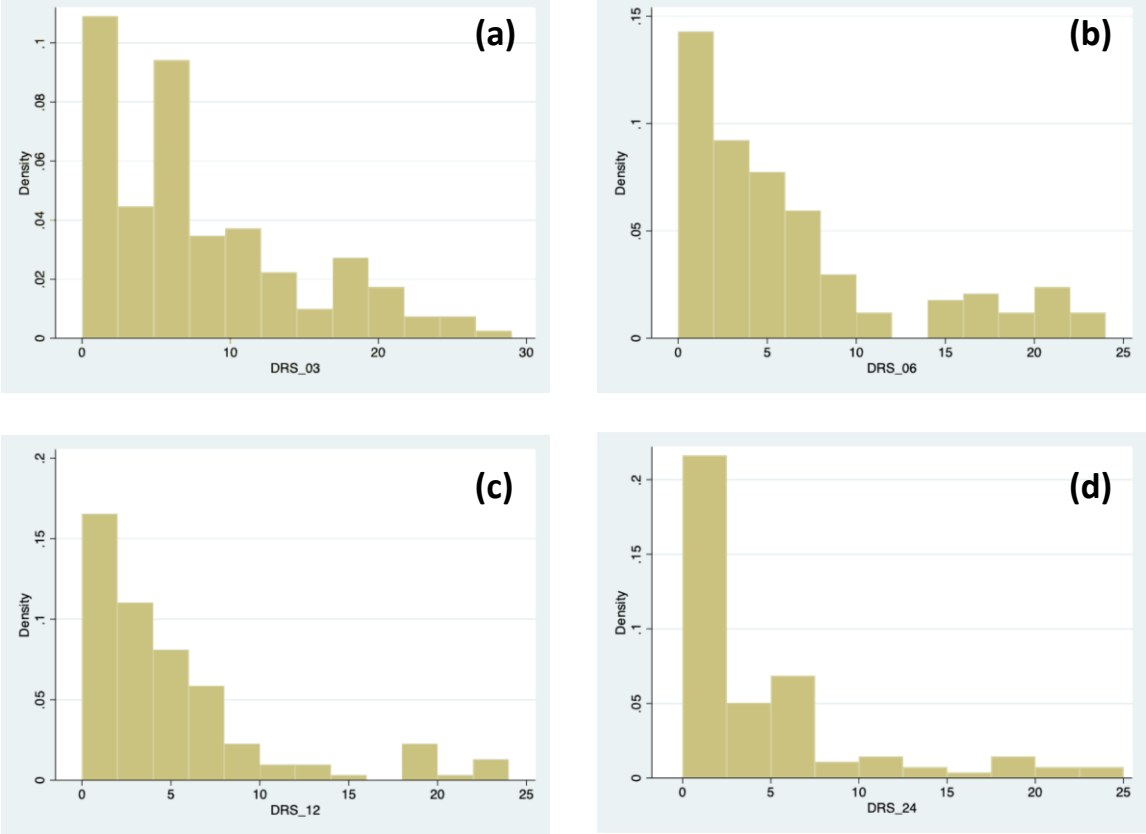
recovery, the better we can personalize both the initial treatment process and long-term therapy options for these patients.

# Appendix A



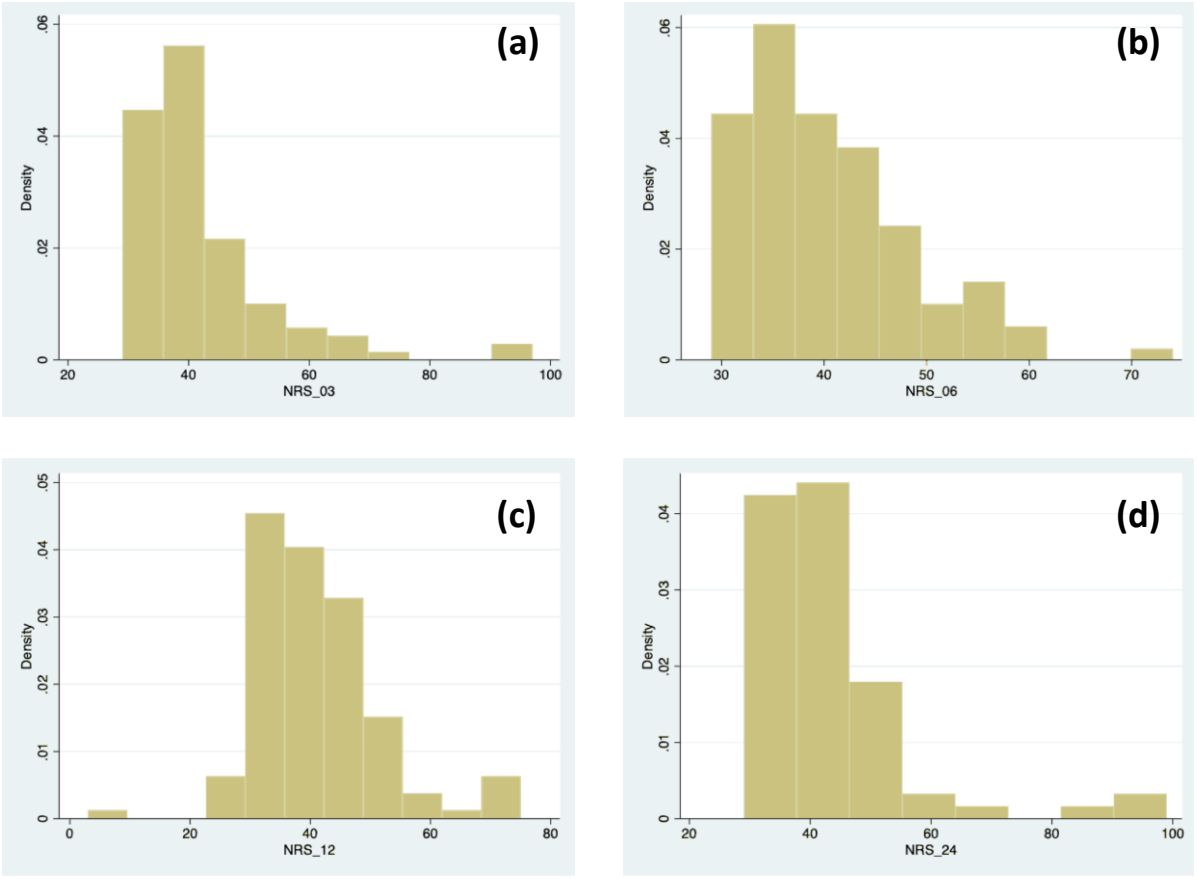

**Appendix Figure 1. Distribution of GOS over time**

**Histogram of GOS at three months (a): n = 176, mean = 3.37, standard deviation = 0.68; histogram of GOS at six months (b): n = 169, mean = 3.68, standard deviation = 0.81; histogram of GOS at twelve months (c): n = 160, mean = 3.88, standard deviation = 0.84; histogram of GOS at twenty-four months (d): n = 124, mean = 3.99, standard deviation = 0.88**



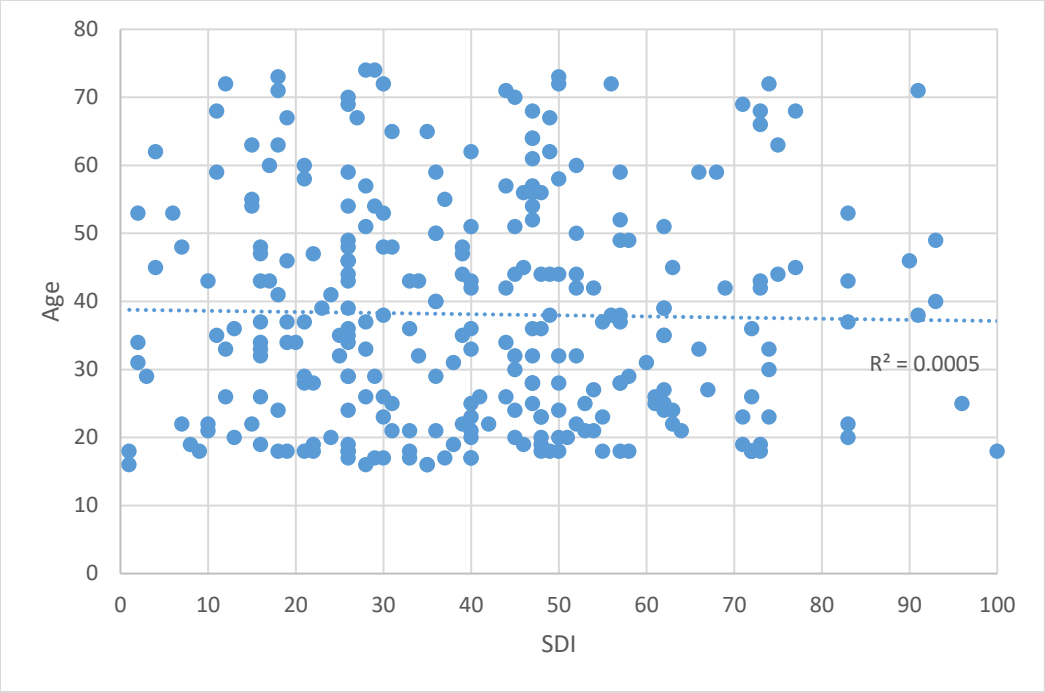

**Appendix Figure 2. Distribution of DRS over time**

**Histogram of DRS at three months (a): n = 167, mean = 7.98, standard deviation = 6.63; histogram of DRS at six months (b): n = 168, mean = 6.01, standard deviation = 6.35; histogram of DRS at twelve months (c): n = 154, mean = 4.62, standard deviation = 5.54; histogram of DRS at twenty-four months (d): n = 111, mean = 4.26, standard deviation = 5.72**

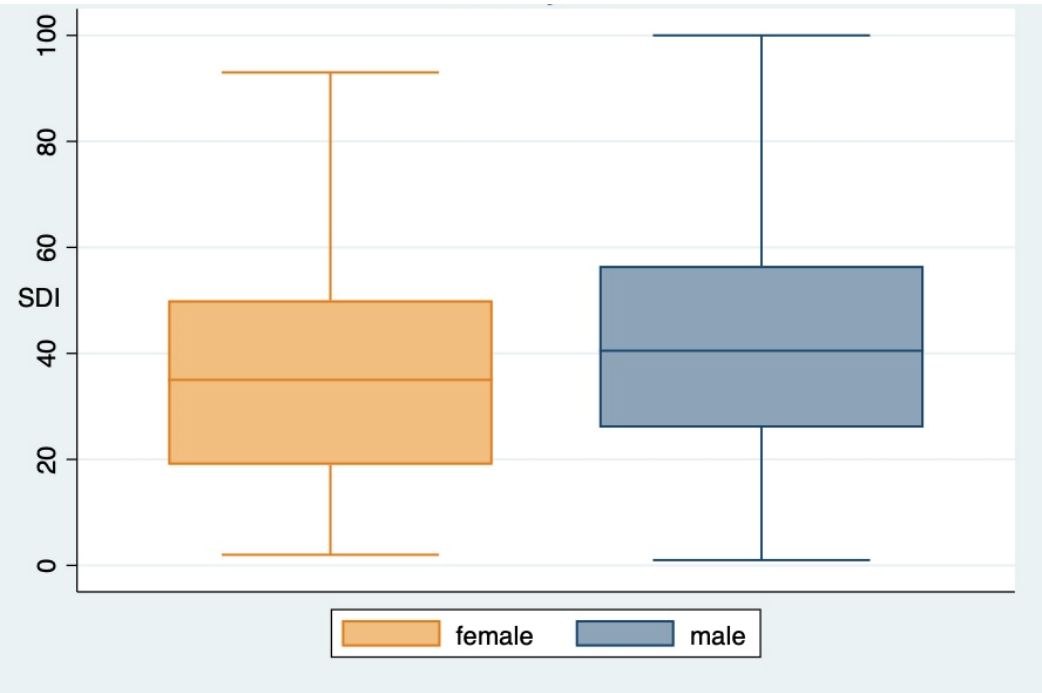



**Appendix Figure 3. Distribution of NRS over time**

**Histogram of NRS at three months (a): n = 102, mean = 41.63, standard deviation = 11.81; histogram of NRS at six months (b): n = 121, mean = 40.50, standard deviation = 8.04; histogram of NRS at twelve months (c): n = 121, mean = 40.83, standard deviation = 10.56; histogram of NRS at twenty-four months (d): n = 70, mean = 43.24, standard deviation = 13.67**

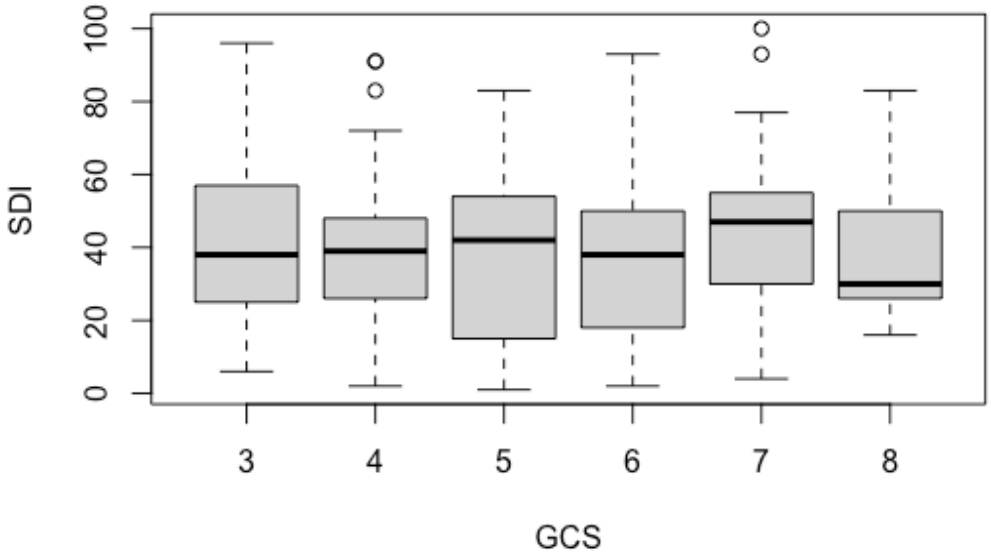



**Appendix Figure 4: Relationship between age and SDI**

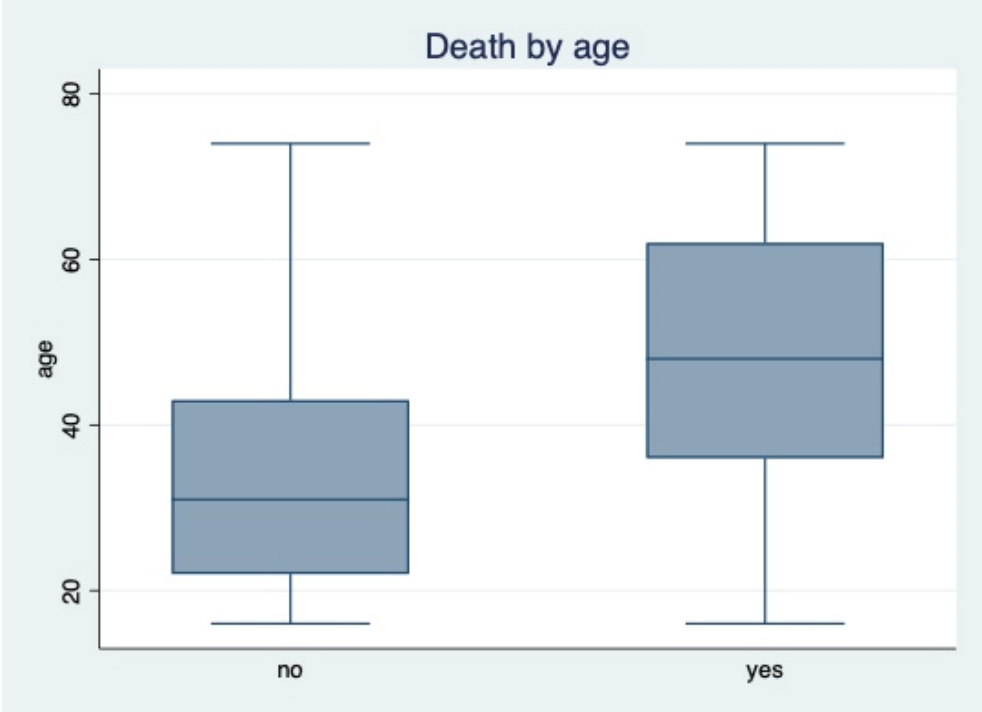



**Appendix Figure 5: Sex by SDI**

**The average SDI for the female group was 37.4, while the average SDI for the male group was 41.9.**

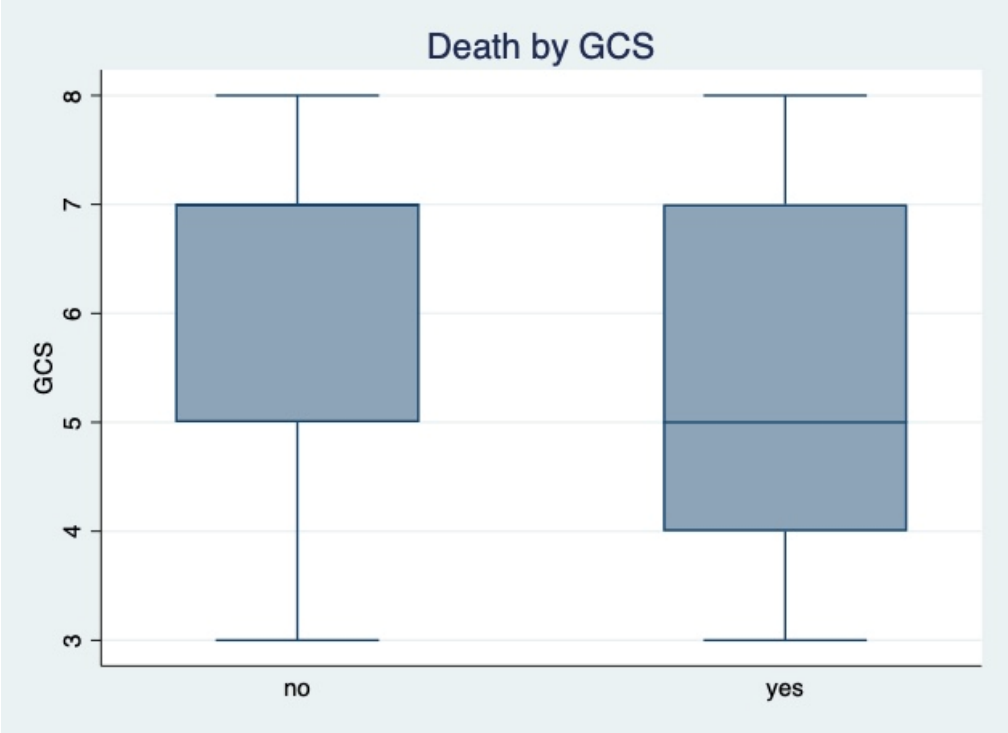



**Appendix Figure 6: GCS by SDI**



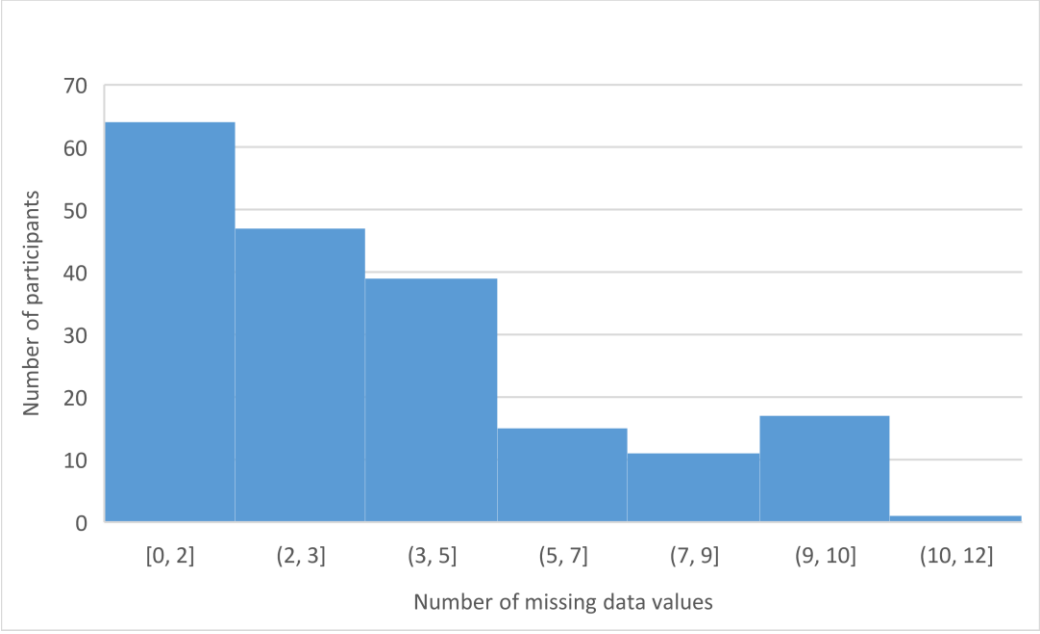

**Appendix Figure 7. Death by Age**

**The average age for the death (no) group was 33.5 years, while the average age for the death (yes) group was 47.5 years.**



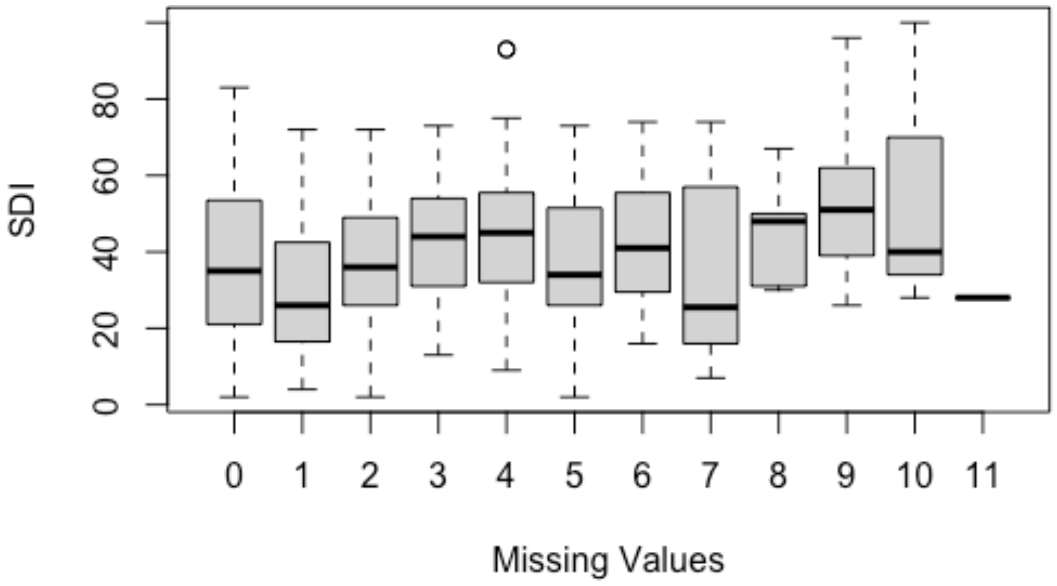

**Appendix Figure 8. Death by GCS**

**The average GCS for the death (no) group was 6.1, while the average GCS for the death (yes) group was 5.2**




**Appendix Figure 9. Distribution of the number of missing data values for surviving participants**

**Mean = 3.4; median = 3; mode = 0**




**Appendix Figure 10. Missing Values by SDI**

# Appendix B

University of Pittsburgh | Institutional Review Board
Office of Research Protections

## APPROVAL OF SUBMISSION (Expedited)

| | |
|---|---|
| Date: | July 31, 2020 |
| IRB: | STUDY20070163 |
| PI: | Yvette Conley |
| Title: | The Effect of Genetics on Outcome in Traumatic Brain Injured Adults |
| Funding: | Name: National Institutes of Health , Funding Source ID: R21NR015142; Name: National Institutes of Health , Funding Source ID: R01NR013342 |

The Institutional Review Board reviewed and approved the above referenced study. The study may begin as outlined in the University of Pittsburgh approved application and documents.

**Approval Documentation**

| | |
|---|---|
| Review type: | Initial Study |
| Approval Date: | 7/31/2020 |
| Expiration Date: | N/A Continuing Review is not required |
| Expedited Category | (9) Convened IRB determined minimal risk |
| Approved Documents: | • IRB971212 - The Effect of Genetics on Outcome in Traumatic Brain Injured Adults.pdf, Category: IRB Protocol; |

**Appendix Figure 11: IRB approval letter**

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