Analysis of Brain Diagnoses and the Incidence of Chronic Traumatic Encephalopathy (CTE)

Arjun Lakhanpal

Dr. Michelle Connolly, Faculty Advisor

Dr. Jason Luck, Faculty Advisor

Duke University

Durham, North Carolina

April 9, 2021

Abstract

Chronic traumatic encephalopathy (CTE) has become a significant area of scientific inquiry in relation to various sports with contact exposure, specifically boxing and professional football, resulting from many individuals who participated in these sports being diagnosed with CTE neuropathology after death. This paper contributes to the CTE literature by analyzing the various predictors of the progression of neurodegenerative disorders, including CTE, that are associated with a history of head impact exposure. In addition, it analyzes how manner of death shifts depending on an individual's clinical brain diagnosis, which is a decision based upon the clinical record and case review of a patient.

Through data from the NIH NeuroBioBank, the VA-BU-CLF Brain Bank, and data self-collected from living individuals with symptoms associated with CTE, this paper explores an analysis of various brain diagnoses through a large control population and small subset of athletes and veterans. Logistic regression models are established to analyze explanatory variables of clinical brain diagnosis, manner of death, and CTE presence and severity.

These logistic regression models confirm previous research surrounding the potential racial influence present in Black populations with schizophrenia related diagnoses and illustrate the degree to which neurodegenerative disorders, specifically Parkinson's Disease, are influenced by increased age. Specific to CTE, the analysis conducted through the sample population illustrates the influence of an extra year of football played at the professional level, while counteracting existing literature regarding the association between position and CTE.

1. Introduction

Repeated incidence of mild traumatic brain injury (mTBI), defined by repetitive concussive events or subconcussive head impact exposure is associated with the development of the degenerative brain disease chronic traumatic encephalopathy (CTE) (McKee et al., 2009). This concept of CTE was first introduced by Martland (1928) as the *punch-drunk syndrome.* Martland characterized this syndrome as the process of neurological deterioration that occurred in boxers after repetitive brain trauma. As more research was conducted on traumatic brain injury (TBI) and concussions in the general population (Langlois et al., 2006), the neuropathology of CTE began to be analyzed in deceased athletes from other collision sports, specifically football. A case study of a former 50-year-old professional football player diagnosed with CTE postmortem indicated the need for further cognitive and autopsy-based research on former National Football League (NFL) athletes (Omalu et al., 2005). Furthermore, in a sample of 266 former American football players from the Veteran Affairs-Boston University-Concussion Legacy Foundation (VA-BU-CLF) and Framingham Heart Study Brain Bank, Mez et al. (2019) conclude that 223 athletes met the neuropathological criteria for CTE. Military veterans also represent another group with relevant risk of head impact exposure as their neuropathology resembles that observed in American football players and boxers with concussive injuries (Goldstein et al., 2012).

The neuropathology of CTE is often characterized on a scale from 0-4, with zero representing the absence of the disease and four characterizing the most advanced form of the disease (McKee et al., 2014). McKee and colleagues' system has been used to illustrate significant associations of CTE with the level of American football play and cumulative exposure to repetitive head impacts (Alosco et al., 2018; McKee et al., 2013; Mez at al., 2020). From

these same studies, variables such as racial identity, years of education, and position played are determined to have no association with CTE stage, despite being a secondary element of the analysis.

Furthermore, when determining an individual's documented CTE level, there are a variety of socioeconomic, biomechanical, and health-related factors to consider (Asken et al., 2016). Specifically, the influence of socioeconomic factors in an individual's development and the eventual expression of neuropsychiatric problems has been discovered (Dodge and Pettit., 2003). However, the association between socioeconomic status (SES) and an individual's neurobehavioral functioning is complicated. Asken at al. (2016) recommend the inclusion of variables such as parental education and income when analyzing clinical outcomes in professional athletes due to their relevance to childhood and developmental influences.

Currently, postmortem neuropathological evaluation exists as the only way to confirm the presence of CTE in individuals (Omalu et al., 2018). Current research is focused on examining an individual's symptomatology while living to detect recurring trends that may be informative in improving our understanding of the progression of the disease. Corroborating former research done with the boxer population (Corsellis et al., 1973), Stern et al. (2013) find two distinct clinical presentations of CTE. While the first involves behavioral or mood changes that arise with younger group subjects, the second group, composed of older individuals, develop problems of cognitive impairment.

Beyond symptomatology, the clinical presentation of CTE shares many features of other neurodegenerative disorders, such as Alzheimer's Disease (AD) and Amyotrophic Lateral Sclerosis/Parkinson-Dementia Complex of Guam (ALS/PDC) (McKee at al., 2009). Although

McKee et al. (2009) conclude that CTE is neuropathologically distinct from these other disorders, an analysis of these clinical brain diagnoses in relation to CTE is important to consider due to the potential influence of head impact exposure on their development. While researchers have investigated the association between the neuropathology of CTE and clinical symptoms, more work must be done in determining whether a causal relationship exists.

Thus, through the National Institute of Health (NIH) NeuroBioBank and additional samples of athletes and veterans diagnosed with CTE, this paper examines various diagnoses classes and a more thorough analysis of the potentially statistically significant association between explanatory variables and the presence of CTE. The goal of this analysis is to ask: Do certain neurodegenerative diseases occur more frequently when examining patterns of environmental or genetic influences, such as demographic variables of age, race, and sex? How does the presence of CTE related symptoms associate with an eventual diagnosis of CTE postmortem? Given the emphasis on the demographic variables listed above and the exploration of the relationship of CTE level with clinical symptoms this paper introduces novelty into CTE research through use of the NIH NeuroBioBank as a control population and an increased sample size compared to existing literature.

2. Background

2.a. Literature Review

Increased attention to CTE in recent years has created more dialogue around various neurodegenerative diseases and their relationship with head impact exposure. Numerous diseases have an association with head impact exposure, such as Bipolar Disorder, Parkinson's Disease, and Schizophrenia (Morensen and Mors., 2003; Lee et al., 2012; Orlovska and Pedersen., 2014). This paper will also focus on the relationship of head injury to Alzheimer's

Disease (AD) and more broadly Dementia, Amyotrophic Lateral Sclerosis (ALS), and Major Depressive Disorder.

Epidemiologic evidence has suggested that head trauma is a risk factor for Alzheimer's Disease and dementia generally (Heyman et al., 1984; Mayeux et al., 1993; Plassman et al., 2000). Plassman et al. (2000) utilize a unique approach in using a prospective historical cohort design through military medical records and an assessment protocol to detect AD and other dementias. This approach differs from other studies that adopt a retrospective recall of head injury, which naturally creates errors and bias as individuals are asked to remember incidents from the past. Focusing more broadly on dementia, Kornblith et al. (2020) provide a comprehensive look into the differential risk for dementia diagnosis by race and sex following incidents of traumatic brain injury. Similar to Plassman et al. (2000), the researchers use medical record data in exploring that the risk of dementia diagnosis is doubled for all veterans after incidence of TBI, but white veterans show an increased risk above this average. This finding differs from previous research which finds that Black and Hispanic individuals have worse functional outcomes the year following a diagnosis of moderate to severe TBI (Lasprilla-Arango et al., 2007). However, other studies were unable to confirm head injury as a risk factor for AD or dementia (Fratiglioni 1993; Mehta et al., 1999). Given this inconsistency in the literature, an analysis of the various clinical diagnoses listed above will provide an added assessment of the relationship and strength between incidents of head impact exposure and the development of AD and dementia. Thus, by using the NIH NeuroBioBank, this paper will add to the existing studies that explore race differences within dementia and other diseases.

A similar dialogue regarding the relationship with head trauma has developed with Amyotrophic Lateral Sclerosis (ALS), a progressive disorder that involves degeneration of the motors system at all levels (Mitchell et al., 2007). As patients with ALS report the incidence of previous trauma in their lives, researchers hypothesize that mechanical trauma has an influence on the incidence of ALS (Kondo 1987; Kurtzke 1991). Through a case-control study and meta-analysis of the reported literature concerning ALS and head trauma, Chen et al. (2007) corroborate the hypothesis that head injury increases ALS risk as they find the odds ratio for ALS is 11 times higher among persons who have multiple head injuries. However, the mechanistic understanding of how head injury remain might result in these outcomes largely remains unknown despite biological explanations being introduced for disorders such as Alzheimer's Disease and Parkinson's Disease which share epidemiologic and pathological characteristics with ALS (Szczygielski et al., 2005; Goldman et al., 2006).

With this focus on head impact exposure and the associated clinical diagnoses, it is essential to consider the development of CTE and the main predictors of this neurodegenerative disorder. It has been found that age of first exposure (AFE) to football is associated with the development of various symptoms associated with CTE, such as executive dysfunction, behavioral dysregulation, and depression (Alosco et al., 2017). Similarly, the relationship between years played and CTE stage has been established, as the odds of the presence of CTE double for every 2.6 years of football played (Mez et al., 2019). A background knowledge of these common predictors of CTE will be beneficial when exploring other variables such as racial identity and income measures through this paper.

2.b. Theoretical/Empirical Framework

Given the literature involving head impact exposure mentions numerous cognitive deficits associated with CTE, various regression models are presented within this study to determine an association between these variables. These models better inform the decision of what model to use in this paper and provide numerous explanatory variables to consider.

Instrumental variable regression, with log concussions as the instrument for exposure history, is used when evaluating head impact exposure through the inclusion of concussion history (Montenigro et al., 2017). To quantify repetitive head impacts from exposure to football, the researchers create a measure of "Cumulative Head Impact Index" (CHII) which is determined through self-report measures of athletic exposure and objective measures based upon position played. The instrumental variable regression occurs in two stages with the first stage assessing the effect of the log number of concussions on the CHII metric. The second regression stage uses the predicted values from the first stage to measure the effect of CHII on the probabilities of impairment for the athletes. Montenigro et al. (2017) reason that a linear regression would not be feasible due to the problem of endogeneity that arises as concussion is directly caused by head impacts. Although not directly applicable to this paper's empirical specification, this research emphasizes the importance of including age and education as covariates in the regression, specifically given their potential influence on impairment outcomes such as depression and executive dysfunction.

Instrumental variable regression is also utilized when analyzing the effects of age of first exposure (AFE) to football on CTE presence (Alosco et al., 2018). The instrument within this regression is the decade during which the athlete was 12 years old. This consistency is

maintained to avoid violating the assumption that AFE affects the instrumental variable. Within this two-stage regression, the first stage estimates the effect of decade at age 12 on AFE; the second stage utilizes this result to predict the CTE pathology stage and age at which behavioral and cognitive symptoms arise. The instrumental variable regression is interesting to consider when evaluating potential regression analyses and this paper's exploration of various predictors of CTE pathology will leverage the work of Alosco and colleagues. In addition, Alosco et al. (2018) include age at death as a covariate when examining CTE pathology due to its association with pathological severity (McKee et al., 2013); thus, age at death will be an important independent variable when analyzing the dependent variable of CTE.

Another analysis of AFE uses a multivariate linear mixed-effect model to evaluate the relationship between AFE to football and various clinical measures which serve as continuous outcome variables (Alosco et al., 2017). Mixed-effects models are useful in that they reduce Type I error by accounting for correlations between groups and outcomes from tests that may be similar among participants. This model is relevant to this research as Alosco et al. (2017) quantified clinical measures such as self-reported measures of executive function, behavioral regulation, depression, and apathy that often had similar measurements for individuals within the sample population. With the presence of various clinical diagnoses in the NIH study, some of which have similar outcomes in regard to symptoms, this mixed-effects methodology could be a method to ensure that correlations among diagnoses do not bias results.

With studies that use brain bank data, previous research has illustrated the importance of accounting for the selection bias that may arrive from collecting postmortem data from individuals (Mez et al., 2019; Alosco et al., 2018). Mez et al. (2019) utilize inverse probability

weighting (IPW) based upon predictors of selection into a brain bank, such as age, race, and dementia status, that have been previously identified (Haneuse et al., 2009). A simplified explanation of IPW is that the process creates unbiased estimates of causal effects through the creation of a pseudosample in which the exposure effect is the same as it would have been in the original sample (Hernan et al., 2004). Given my research focuses on the NIH NeuroBioBank and Boston University (BU) associated brain banks, this selection bias is addressed through a large control population within the NIH NeuroBioBank given the limited number of individuals with a diagnosis of CTE.

Ultimately, this paper uses logistic regressions as the statistical framework through the development of four separate regression models to investigate relationships between explanatory variables and CTE stage, manner of death, and clinical diagnoses. This statistical model is a classification technique used to predict the probabilities of binary outcomes of a categorically distributed dependent variable given independent variables that can be categorical or continuous. The dependent variables of clinical brain diagnosis, manner of death, and levels of CTE span various categories, illustrating the first principle of logistic regression.

Within the first binary logistic regression below, clinical brain diagnosis, categorized into various disease classes affected by head trauma, is the dependent variable. Meanwhile, independent variables such as age, race, sex, athletic participation, football participation, and veteran status are included to determine how these variables are associated with an individual's diagnosis. Through this regression, the hypothesis is that the brain diagnoses, which have been most directly connected to head trauma within the literature, will have a higher

probability of occurrence with the presence of football and veteran status (and thus more exposure) in the regression.

Regression 1: Determining the Predictors of Various Clinical Brain Diagnosis

$$
\begin{aligned}
P(\text{Alzheimer's Disease}_i = 1) = \ & \beta_0 + \beta_1(I\{Age_i = 0-9\}) + \beta_2(I\{Age_i = 10-19\}) \\
& + \beta_3(I\{Age_i = 20-29\}) + \beta_4(I\{Age_i = 30-39\}) \\
& + \beta_5(I\{Age_i = 40-49\}) + \beta_6(I\{Age_i = 50-59\}) \\
& + \beta_7(I\{Age_i = 60-69\}) + \beta_8(I\{Age_i = 70-79\}) \\
& + \beta_9(I\{Age_i = 80-88\}) + \beta_{10}(I\{Age_i = 89+\}) \\
& + \beta_{11}(I\{Race_i = AmericanIndian\}) + \beta_{12}(I\{Race_i = Asian\}) \\
& + \beta_{13}(I\{Race_i = Black\}) + \beta_{14}(I\{Race_i = Hispanic\}) \\
& + \beta_{15}(I\{Race_i = NativeHawaiian\}) + \beta_{16}(I\{Race_i = White\}) \\
& + \beta_{17}I\{Sex_i = Female\}) + \beta_{18}(I\{Veteran_i = Yes\}) \\
& + \beta_{19}(I\{Athletics_i = Yes\}) + \beta_{20}(I\{Football_i = Yes\})
\end{aligned}
$$

$$
\begin{aligned}
P(\text{ALS Disease}_i = 1) = \ & \beta_0 + \beta_1(I\{Age_i = 0-9\}) + \beta_2(I\{Age_i = 10-19\}) \\
& + \beta_3(I\{Age_i = 20-29\}) + \beta_4(I\{Age_i = 30-39\}) \\
& + \beta_5(I\{Age_i = 40-49\}) + \beta_6(I\{Age_i = 50-59\}) \\
& + \beta_7(I\{Age_i = 60-69\}) + \beta_8(I\{Age_i = 70-79\}) \\
& + \beta_9(I\{Age_i = 80-88\}) + \beta_{10}(I\{Age_i = 89+\}) \\
& + \beta_{11}(I\{Race_i = AmericanIndian\}) + \beta_{12}(I\{Race_i = Asian\}) \\
& + \beta_{13}(I\{Race_i = Black\}) + \beta_{14}(I\{Race_i = Hispanic\}) \\
& + \beta_{15}(I\{Race_i = NativeHawaiian\}) + \beta_{16}(I\{Race_i = White\}) \\
& + \beta_{17}I\{Sex_i = Female\}) + \beta_{18}(I\{Veteran_i = Yes\}) \\
& + \beta_{19}(I\{Athletics_i = Yes\}) + \beta_{20}(I\{Football_i = Yes\})
\end{aligned}
$$

$$
\begin{aligned}
P(\text{Bipolar Disorder}_i = 1) = \ & \beta_0 + \beta_1(I\{Age_i = 0-9\}) + \beta_2(I\{Age_i = 10-19\}) \\
& + \beta_3(I\{Age_i = 20-29\}) + \beta_4(I\{Age_i = 30-39\}) \\
& + \beta_5(I\{Age_i = 40-49\}) + \beta_6(I\{Age_i = 50-59\}) \\
& + \beta_7(I\{Age_i = 60-69\}) + \beta_8(I\{Age_i = 70-79\}) \\
& + \beta_9(I\{Age_i = 80-88\}) + \beta_{10}(I\{Age_i = 89+\}) \\
& + \beta_{11}(I\{Race_i = AmericanIndian\}) + \beta_{12}(I\{Race_i = Asian\}) \\
& + \beta_{13}(I\{Race_i = Black\}) + \beta_{14}(I\{Race_i = Hispanic\}) \\
& + \beta_{15}(I\{Race_i = NativeHawaiian\}) + \beta_{16}(I\{Race_i = White\}) \\
& + \beta_{17}I\{Sex_i = Female\}) + \beta_{18}(I\{Veteran_i = Yes\}) \\
& + \beta_{19}(I\{Athletics_i = Yes\}) + \beta_{20}(I\{Football_i = Yes\})
\end{aligned}
$$

$$
\begin{aligned}
P(\text{CTE}_i = 1) = \ & \beta_0 + \beta_1(I\{Age_i = 0-9\}) + \beta_2(I\{Age_i = 10-19\}) \\
& + \beta_3(I\{Age_i = 20-29\}) + \beta_4(I\{Age_i = 30-39\}) \\
& + \beta_5(I\{Age_i = 40-49\}) + \beta_6(I\{Age_i = 50-59\}) \\
& + \beta_7(I\{Age_i = 60-69\}) + \beta_8(I\{Age_i = 70-79\}) \\
& + \beta_9(I\{Age_i = 80-88\}) + \beta_{10}(I\{Age_i = 89+\}) \\
& + \beta_{11}(I\{Race_i = AmericanIndian\}) + \beta_{12}(I\{Race_i = Asian\}) \\
& + \beta_{13}(I\{Race_i = Black\}) + \beta_{14}(I\{Race_i = Hispanic\}) \\
& + \beta_{15}(I\{Race_i = NativeHawaiian\}) + \beta_{16}(I\{Race_i = White\}) \\
& + \beta_{17}I\{Sex_i = Female\}) + \beta_{18}(I\{Veteran_i = Yes\}) \\
& + \beta_{19}(I\{Athletics_i = Yes\}) + \beta_{20}(I\{Football_i = Yes\})
\end{aligned}
$$

$$
\begin{aligned}
P(\text{Dementia}_i = 1) = \ & \beta_0 + \beta_1(I\{Age_i = 0-9\}) + \beta_2(I\{Age_i = 10-19\}) \\
& + \beta_3(I\{Age_i = 20-29\}) + \beta_4(I\{Age_i = 30-39\}) \\
& + \beta_5(I\{Age_i = 40-49\}) + \beta_6(I\{Age_i = 50-59\}) \\
& + \beta_7(I\{Age_i = 60-69\}) + \beta_8(I\{Age_i = 70-79\}) \\
& + \beta_9(I\{Age_i = 80-88\}) + \beta_{10}(I\{Age_i = 89+\}) \\
& + \beta_{11}(I\{Race_i = AmericanIndian\}) + \beta_{12}(I\{Race_i = Asian\}) \\
& + \beta_{13}(I\{Race_i = Black\}) + \beta_{14}(I\{Race_i = Hispanic\}) \\
& + \beta_{15}(I\{Race_i = NativeHawaiian\}) + \beta_{16}(I\{Race_i = White\}) \\
& + \beta_{17}I\{Sex_i = Female\}) + \beta_{18}(I\{Veteran_i = Yes\}) \\
& + \beta_{19}(I\{Athletics_i = Yes\}) + \beta_{20}(I\{Football_i = Yes\})
\end{aligned}
$$

$$
\begin{aligned}
P(\text{Major Depressive Disorder}_i = 1) = \ & \beta_0 + \beta_1(I\{Age_i = 0-9\}) + \beta_2(I\{Age_i = 10-19\}) \\
& + \beta_3(I\{Age_i = 20-29\}) + \beta_4(I\{Age_i = 30-39\}) \\
& + \beta_5(I\{Age_i = 40-49\}) + \beta_6(I\{Age_i = 50-59\}) \\
& + \beta_7(I\{Age_i = 60-69\}) + \beta_8(I\{Age_i = 70-79\}) \\
& + \beta_9(I\{Age_i = 80-88\}) + \beta_{10}(I\{Age_i = 89+\}) \\
& + \beta_{11}(I\{Race_i = AmericanIndian\}) + \beta_{12}(I\{Race_i = Asian\}) \\
& + \beta_{13}(I\{Race_i = Black\}) + \beta_{14}(I\{Race_i = Hispanic\}) \\
& + \beta_{15}(I\{Race_i = NativeHawaiian\}) + \beta_{16}(I\{Race_i = White\}) \\
& + \beta_{17}I\{Sex_i = Female\}) + \beta_{18}(I\{Veteran_i = Yes\}) \\
& + \beta_{19}(I\{Athletics_i = Yes\}) + \beta_{20}(I\{Football_i = Yes\})
\end{aligned}
$$

$$
\begin{aligned}
P(\text{Parkinson's Disease}_i = 1) = \ & \beta_0 + \beta_1(I\{Age_i = 0-9\}) + \beta_2(I\{Age_i = 10-19\}) \\
& + \beta_3(I\{Age_i = 20-29\}) + \beta_4(I\{Age_i = 30-39\}) \\
& + \beta_5(I\{Age_i = 40-49\}) + \beta_6(I\{Age_i = 50-59\}) \\
& + \beta_7(I\{Age_i = 60-69\}) + \beta_8(I\{Age_i = 70-79\}) \\
& + \beta_9(I\{Age_i = 80-88\}) + \beta_{10}(I\{Age_i = 89+\}) \\
& + \beta_{11}(I\{Race_i = AmericanIndian\}) + \beta_{12}(I\{Race_i = Asian\}) \\
& + \beta_{13}(I\{Race_i = Black\}) + \beta_{14}(I\{Race_i = Hispanic\}) \\
& + \beta_{15}(I\{Race_i = NativeHawaiian\}) + \beta_{16}(I\{Race_i = White\}) \\
& + \beta_{17}I\{Sex_i = Female\}) + \beta_{18}(I\{Veteran_i = Yes\}) \\
& + \beta_{19}(I\{Athletics_i = Yes\}) + \beta_{20}(I\{Football_i = Yes\})
\end{aligned}
$$

$$
\begin{aligned}
P(\text{Schizophrenia}_i = 1) = \ & \beta_0 + \beta_1(I\{Age_i = 0-9\}) + \beta_2(I\{Age_i = 10-19\}) \\
& + \beta_3(I\{Age_i = 20-29\}) + \beta_4(I\{Age_i = 30-39\}) \\
& + \beta_5(I\{Age_i = 40-49\}) + \beta_6(I\{Age_i = 50-59\}) \\
& + \beta_7(I\{Age_i = 60-69\}) + \beta_8(I\{Age_i = 70-79\}) \\
& + \beta_9(I\{Age_i = 80-88\}) + \beta_{10}(I\{Age_i = 89+\}) \\
& + \beta_{11}(I\{Race_i = AmericanIndian\}) + \beta_{12}(I\{Race_i = Asian\}) \\
& + \beta_{13}(I\{Race_i = Black\}) + \beta_{14}(I\{Race_i = Hispanic\}) \\
& + \beta_{15}(I\{Race_i = NativeHawaiian\}) + \beta_{16}(I\{Race_i = White\}) \\
& + \beta_{17}I\{Sex_i = Female\}) + \beta_{18}(I\{Veteran_i = Yes\}) \\
& + \beta_{19}(I\{Athletics_i = Yes\}) + \beta_{20}(I\{Football_i = Yes\})
\end{aligned}
$$

$$
\begin{aligned}
P(\text{Schizoaffective Disorder}_i = 1) = \ & \beta_0 + \beta_1(I\{Age_i = 0-9\}) + \beta_2(I\{Age_i = 10-19\}) \\
& + \beta_3(I\{Age_i = 20-29\}) + \beta_4(I\{Age_i = 30-39\}) \\
& + \beta_5(I\{Age_i = 40-49\}) + \beta_6(I\{Age_i = 50-59\}) \\
& + \beta_7(I\{Age_i = 60-69\}) + \beta_8(I\{Age_i = 70-79\}) \\
& + \beta_9(I\{Age_i = 80-88\}) + \beta_{10}(I\{Age_i = 89+\}) \\
& + \beta_{11}(I\{Race_i = AmericanIndian\}) + \beta_{12}(I\{Race_i = Asian\}) \\
& + \beta_{13}(I\{Race_i = Black\}) + \beta_{14}(I\{Race_i = Hispanic\}) \\
& + \beta_{15}(I\{Race_i = NativeHawaiian\}) + \beta_{16}(I\{Race_i = White\}) \\
& + \beta_{17}I\{Sex_i = Female\}) + \beta_{18}(I\{Veteran_i = Yes\}) \\
& + \beta_{19}(I\{Athletics_i = Yes\}) + \beta_{20}(I\{Football_i = Yes\})
\end{aligned}
$$

In the second binary logistic regression, manner of death is the dependent variable and is divided into four categories which establish the general cause of death: accidental, homicide,

natural, or suicide. Meanwhile, independent variables such as age, race, sex, athletic participation, football participation, veteran status, and clinical brain diagnoses are accounted for to determine how they contribute to the probability of an individual experiencing a certain type of death. These clinical brain diagnoses, which were the dependent variables within the first regression, are the only new independent variables added to this regression. Through this analysis, it is expected that the probability of suicide will be highest when CTE is the brain diagnosis; however, this result is difficult to state with certainty given the relationship that many disorders such as Alzheimer's Disease have with suicide risk (Erafini et al., (2016).

Regression 2: Determining the Predictors of Manner of Death

$$
\begin{aligned}
P(\text{Natural}_i = 1) = \ & \beta_0 + \beta_1(I\{Age_i = 0-9\}) + \beta_2(I\{Age_i = 10-19\}) \\
& + \beta_3(I\{Age_i = 20-29\}) + \beta_4(I\{Age_i = 30-39\}) \\
& + \beta_5(I\{Age_i = 40-49\}) + \beta_6(I\{Age_i = 50-59\}) \\
& + \beta_7(I\{Age_i = 60-69\}) + \beta_8(I\{Age_i = 70-79\}) \\
& + \beta_9(I\{Age_i = 80-88\}) + \beta_{10}(I\{Age_i = 89+\}) \\
& + \beta_{11}(I\{Race_i = AmericanIndian\}) + \beta_{12}(I\{Race_i = Asian\}) \\
& + \beta_{13}(I\{Race_i = Black\}) + \beta_{14}(I\{Race_i = Hispanic\}) \\
& + \beta_{15}(I\{Race_i = NativeHawaiian\}) + \beta_{16}(I\{Race_i = White\}) \\
& + \beta_{17}I\{Sex_i = Female\}) + \beta_{18}(I\{Veteran_i = Yes\}) \\
& + \beta_{19}(I\{Athletics_i = Yes\}) + \beta_{20}(I\{Football_i = Yes\}) \\
& + \beta_{21}(I\{\text{Alzheimer's Disease}_i = Yes\}) + \beta_{22}(I\{\text{ALS Disease}_i = Yes\}) \\
& + \beta_{23}(I\{\text{Bipolar Disorder}_i = Yes\}) + \beta_{24}(I\{\text{CTE}_i = Yes\}) \\
& + \beta_{25}(I\{Dementia_i = Yes\}) + \beta_{26}(I\{\text{Major Depressive Disorder}_i = Yes\}) \\
& + \beta_{27}(I\{\text{Parkinson's Disease}_i = Yes\}) + \beta_{28}(I\{\text{Schizophrenia}_i = Yes\}) \\
& + \beta_{29}(I\{\text{Schizoaffective Disorder}_i = Yes\})
\end{aligned}
$$

$$
\begin{aligned}
P(\text{Accidental}_i = 1) = \ & \beta_0 + \beta_1(I\{Age_i = 0-9\}) + \beta_2(I\{Age_i = 10-19\}) \\
& + \beta_3(I\{Age_i = 20-29\}) + \beta_4(I\{Age_i = 30-39\}) \\
& + \beta_5(I\{Age_i = 40-49\}) + \beta_6(I\{Age_i = 50-59\}) \\
& + \beta_7(I\{Age_i = 60-69\}) + \beta_8(I\{Age_i = 70-79\}) \\
& + \beta_9(I\{Age_i = 80-88\}) + \beta_{10}(I\{Age_i = 89+\}) \\
& + \beta_{11}(I\{Race_i = AmericanIndian\}) + \beta_{12}(I\{Race_i = Asian\}) \\
& + \beta_{13}(I\{Race_i = Black\}) + \beta_{14}(I\{Race_i = Hispanic\}) \\
& + \beta_{15}(I\{Race_i = NativeHawaiian\}) + \beta_{16}(I\{Race_i = White\}) \\
& + \beta_{17}I\{Sex_i = Female\}) + \beta_{18}(I\{Veteran_i = Yes\}) \\
& + \beta_{19}(I\{Athletics_i = Yes\}) + \beta_{20}(I\{Football_i = Yes\}) \\
& + \beta_{21}(I\{\text{Alzheimer's Disease}_i = Yes\}) + \beta_{22}(I\{\text{ALS Disease}_i = Yes\}) \\
& + \beta_{23}(I\{\text{Bipolar Disorder}_i = Yes\}) + \beta_{24}(I\{\text{CTE}_i = Yes\}) \\
& + \beta_{25}(I\{Dementia_i = Yes\}) + \beta_{26}(I\{\text{Major Depressive Disorder}_i = Yes\}) \\
& + \beta_{27}(I\{\text{Parkinson's Disease}_i = Yes\}) + \beta_{28}(I\{\text{Schizophrenia}_i = Yes\}) \\
& + \beta_{29}(I\{\text{Schizoaffective Disorder}_i = Yes\})
\end{aligned}
$$

$$
\begin{aligned}
P(\text{Homicide}_i = 1) = \ & \beta_0 + \beta_1(I\{Age_i = 0-9\}) + \beta_2(I\{Age_i = 10-19\}) \\
& + \beta_3(I\{Age_i = 20-29\}) + \beta_4(I\{Age_i = 30-39\}) \\
& + \beta_5(I\{Age_i = 40-49\}) + \beta_6(I\{Age_i = 50-59\}) \\
& + \beta_7(I\{Age_i = 60-69\}) + \beta_8(I\{Age_i = 70-79\}) \\
& + \beta_9(I\{Age_i = 80-88\}) + \beta_{10}(I\{Age_i = 89+\}) \\
& + \beta_{11}(I\{Race_i = AmericanIndian\}) + \beta_{12}(I\{Race_i = Asian\}) \\
& + \beta_{13}(I\{Race_i = Black\}) + \beta_{14}(I\{Race_i = Hispanic\}) \\
& + \beta_{15}(I\{Race_i = NativeHawaiian\}) + \beta_{16}(I\{Race_i = White\}) \\
& + \beta_{17}I\{Sex_i = Female\}) + \beta_{18}(I\{Veteran_i = Yes\}) \\
& + \beta_{19}(I\{Athletics_i = Yes\}) + \beta_{20}(I\{Football_i = Yes\}) \\
& + \beta_{21}(I\{\text{Alzheimer's Disease}_i = Yes\}) + \beta_{22}(I\{\text{ALS Disease}_i = Yes\}) \\
& + \beta_{23}(I\{\text{Bipolar Disorder}_i = Yes\}) + \beta_{24}(I\{\text{CTE}_i = Yes\}) \\
& + \beta_{25}(I\{Dementia_i = Yes\}) + \beta_{26}(I\{\text{Major Depressive Disorder}_i = Yes\}) \\
& + \beta_{27}(I\{\text{Parkinson's Disease}_i = Yes\}) + \beta_{28}(I\{\text{Schizophrenia}_i = Yes\}) \\
& + \beta_{29}(I\{\text{Schizoaffective Disorder}_i = Yes\})
\end{aligned}
$$

$$
\begin{aligned}
P(\text{Suicide}_i = 1) = \ & \beta_0 + \beta_1(I\{Age_i = 0-9\}) + \beta_2(I\{Age_i = 10-19\}) \\
& + \beta_3(I\{Age_i = 20-29\}) + \beta_4(I\{Age_i = 30-39\}) \\
& + \beta_5(I\{Age_i = 40-49\}) + \beta_6(I\{Age_i = 50-59\}) \\
& + \beta_7(I\{Age_i = 60-69\}) + \beta_8(I\{Age_i = 70-79\}) \\
& + \beta_9(I\{Age_i = 80-88\}) + \beta_{10}(I\{Age_i = 89+\}) \\
& + \beta_{11}(I\{Race_i = AmericanIndian\}) + \beta_{12}(I\{Race_i = Asian\}) \\
& + \beta_{13}(I\{Race_i = Black\}) + \beta_{14}(I\{Race_i = Hispanic\}) \\
& + \beta_{15}(I\{Race_i = NativeHawaiian\}) + \beta_{16}(I\{Race_i = White\}) \\
& + \beta_{17}I\{Sex_i = Female\}) + \beta_{18}(I\{Veteran_i = Yes\}) \\
& + \beta_{19}(I\{Athletics_i = Yes\}) + \beta_{20}(I\{Football_i = Yes\}) \\
& + \beta_{21}(I\{\text{Alzheimer's Disease}_i = Yes\}) + \beta_{22}(I\{\text{ALS Disease}_i = Yes\}) \\
& + \beta_{23}(I\{\text{Bipolar Disorder}_i = Yes\}) + \beta_{24}(I\{\text{CTE}_i = Yes\}) \\
& + \beta_{25}(I\{Dementia_i = Yes\}) + \beta_{26}(I\{\text{Major Depressive Disorder}_i = Yes\}) \\
& + \beta_{27}(I\{\text{Parkinson's Disease}_i = Yes\}) + \beta_{28}(I\{\text{Schizophrenia}_i = Yes\}) \\
& + \beta_{29}(I\{\text{Schizoaffective Disorder}_i = Yes\})
\end{aligned}
$$

In the third regression below, CTE stage is the dependent variable, and it ranges from stage 0-4 with 0 indicating the absence of CTE and 4 representing the most severe diagnosis of CTE. Numerous independent variables such as age, race, and position are included in the analysis. To

better comprehend other factors that contribute to the development of CTE stage, head impact exposure, which is represented by years played at the highest level, and median household income, are represented as independent variables. Median household income is calculated from the county in which the individual grew up and attended high school. Given there does not exist information regarding how many years an individual played the contact sport at the youth or high school level, this income variable defines an individual's entry into the sport and potential motivation to continue playing regardless of the risks posed by CTE. In addition, the income variable serves as a surrogate for healthcare access in an individual's hometown, with the assumption that lower income areas may not have the same level of education and resources dedicated to informing individuals of CTE and its associated risks. While exposure is a variable often included in CTE analysis in previous research (Stamm et al., 2015; Mez et al., 2019), median household income hasn't been the focus of many other studies within the field. Although not specifically focused on CTE, research has been conducted to investigate the influence of socioeconomic status with concussion management through widely adopted tests for concussions, such as vestibular and visual assessments (Wallace et al., 2020). Wallace and fellow researchers used the concept of free-reduced lunch (FRL) as a measure of school socioeconomic status with the hypothesis that individuals within a lower socioeconomic status group may be limited in seeking specialized care for concussion management. Overall, Wallace et al., (2020) find a higher likelihood of saccadic eye tracking deficits and uncorrected vestibular dysfunction, tests used to detect potential concussions, which are more prominent due to poverty or other health inequities. Through this analysis, the current hypothesis is that a more comprehensive understanding of the etiology of CTE is possible by investigating not only head

impact exposure but other socioeconomic factors that may be relevant to the presence of CTE. Given that athletes in the study span various age ranges and football levels, the history of exposure will not be accurately measured by just evaluating the number of years played. Rather, it may be useful to explore the games per season the player participated in, to the extent that information is available.

Regression 3: Evaluating Median Household Income as a Predictor of CTE Stage

$$
\begin{aligned}
P(\text{CTE Stage}_i = k) = \ & \beta_0 + \beta_1(I\{\text{Median Household Income}_i = 20-30\}) \\
& + \beta_2(I\{\text{Median Household Income}_i = 30-40\}) \\
& + \beta_3(I\{\text{Median Household Income}_i = 40-50\}) \\
& + \beta_4(I\{\text{Median Household Income}_i = 50-60\}) \\
& + \beta_5(I\{\text{Median Household Income}_i = 60-70\}) \\
& + \beta_6(I\{\text{Median Household Income}_i = 70-80\}) \\
& + \beta_7(I\{\text{Median Household Income}_i = 80-90\}) \\
& + \beta_8(I\{\text{Median Household Income}_i = 90-100\}) \\
& + \beta_9(I\{\text{Median Household Income}_i = 110+\})
\end{aligned}
$$

Regression 4: Measuring CTE Stage through independent variables of age, position, race, and football related variables at the college and professional levels

$$
\begin{aligned}
P(\text{CTE Stage}_i = k) = \ & \beta_0 + \beta_1(I\{Position_i = QB\}) + \beta_2(I\{Position_i = RB\}) \\
& + \beta_3(I\{Position_i = FB\}) + \beta_4(I\{Position_i = WR\}) \\
& + \beta_5(I\{Position_i = WR\}) + \beta_6(I\{Position_i = TE\}) \\
& + \beta_7(I\{Position_i = OL\}) + \beta_8(I\{Position_i = DL\}) \\
& + \beta_9(I\{Position_i = LB\}) + \beta_{10}(I\{Position_i = DB\}) \\
& + \beta_{11}(I\{Position_i = ST\}) + \beta_{12}(I\{Age_i = 0 - 9\}) \\
& + \beta_{13}(I\{Age_i = 10 - 19\}) + \beta_{14}(I\{Age_i = 20 - 29\}) \\
& + \beta_{15}(I\{Age_i = 30 - 39\}) + \beta_{16}(I\{Age_i = 40 - 49\}) \\
& + \beta_{17}(I\{Age_i = 50 - 59\}) + \beta_{18}(I\{Age_i = 60 - 69\}) \\
& + \beta_{19}(I\{Age_i = 70 - 79\}) + \beta_{20}(I\{Age_i = 80 - 88\}) \\
& + \beta_{21}(I\{Age_i = 89+\}) + \beta_{22}(I\{Race_i = AmericanIndian\}) \\
& + \beta_{23}(I\{Race_i = Asian\}) + \beta_{24}(I\{Race_i = Black\}) \\
& + \beta_{25}(I\{Race_i = Hispanic\}) + \beta_{26}(I\{Race_i = NativeHawaiian\}) \\
& + \beta_{27}(I\{Race_i = White\}) + \beta_{28}(I\{\text{College Football}_i = Yes\}) \\
& \beta_{29}(I\{\text{NFL Football}_i = Yes\}) + \beta_{30}\text{College Years}_i + \beta_{31}\text{NFL Years}_i
\end{aligned}
$$

where

- i is observation i,
- $z = 0...5$ where the baseline $(z = 0)$ indicates observation i is White, $(z = 1)$ is Black, $(z = 2)$ is Hispanic, $(i = 3)$ is Asian, $(z = 4)$ is Samoan, and $(z = 5)$ is Native Hawaiian/Pacific Islander,
- k is the diagnosis where $(k = 0)$ is Alzheimer's, $(k = 1)$ is amyotrophic lateral sclerosis (ALS), $(k = 2)$ is major depressive disorder, $(k = 3)$ is Parkinson's Disease, $(k = 4)$ is schizophrenia, $(k = 5)$ is dementia, $(k = 6)$ is bipolar disorder, $(k = 7)$ is schizoaffective disorder, and $(k = 8)$ is chronic traumatic encephalopathy.

3. Data

3.a. Methodology/Data Collection

In conducting this research, information is extracted from various brain repositories and a sample population that was created to account for individuals who are alive but have

reported symptoms associated with CTE. These four sources created the combined sample population of 14,122 individuals present within this study. An overview of the brain banks and information related to data sampling respective to each brain bank is presented below.

Table 1: Overview of Data Sources

Data Sources	*Number of Individuals*	*Population Type*	*Number of Individuals Diagnosed with CTE*	*Number of Football Players within Sample*	*Individuals with Recorded CTE Levels*
NIH NeuroBioBank	13,729	General population	2	Not Specified	Not Specified
Concussion Legacy Foundation (CLF)	149	Football players	149	144	Stage 1: 14 Stage 2: 22 Stage 3: 22 Stage 4: 27
Boston University (BU) Alzheimer Center	79	General population, athletes of various sports	44	34	Stage 0 (Control): 35 Stage 1: 3 Stage 2: 12 Stage 3: 13 Stage 4: 16
Other	12	Football players	12	12	Stage 1: 1 Stage 2: 1 Stage 4: 1
Living Individuals with Symptoms of CTE: Self-Collected	153	Football players	Unknown	149	Stage 1: 117 Stage 2: 10 Stage 3: 9 Stage 4: 14

**Within the Concussion Legacy Foundation (CLF), there are 85 individuals with a provided CTE Stage, while the other individuals within the repository have been diagnosed with CTE, but the exact severity of CTE is unavailable.

**The Other category represents a variety of brain banks that only have a few individuals in the sample with the exact number given in parentheses: Brain Injury Research Institute (BIRI) (5), Mayo Clinic (1), NIH (1), Touro College of Osteopathic Medicine (1), and Unknown Brain Bank (4).

**Only 3 individuals within the Other category have a CTE Stage specified online or in the literature, while the other 9 have a confirmed diagnosis of CTE.

**The number of individuals diagnosed with CTE is unknown for the self-collected population since these individuals are alive and CTE is only definitively diagnosed post-mortem. Recorded CTE levels were assigned based upon a CTE Staging Scheme proposed by Ann McKee, researcher from Boston University, in Table 2.

**4 CTE Stages within the Self-Reported population are unable to be collected due to lack of information available online

The NIH NeuroBioBank serves as a database for analysis of human brain tissue and related biospecimens when investigating neurological, developmental, and psychiatric disorders. As seen above, the NIH database constitutes the majority of the observations within this study and the individuals who participated in the brain donation process were among the general population. Therefore, there is no direct focus on CTE within the brain bank, but rather an overview of various diseases and disorders through their collaboration with six other biorepositories in the United States.

Next, the collaboration between the BU School of Medicine and the Concussion Legacy Foundation (CLF) has led to the creation of a brain bank focused on understanding repetitive head impact exposure through collision sport participation and military related exposure. As seen in Table 1, there are 149 individuals included in this study from the CLF database, and all but 5 individuals played football. Although there are many more individuals within the CLF database, it is necessary to know the specific stage of CTE experienced by individuals and this information is only publicly available for some individuals.

Furthermore, 79 individuals, including former athletes, military veterans, and civilians with a history of traumatic brain injury and control participants, from the Boston University (BU) Alzheimer Center are among the sample population. 44 individuals from the study have a CTE diagnosis, while the remaining 35 individuals are introduced as the control population absent of any presence of traumatic brain injury (McKee et al., 2013). As listed in Table 1, this study only includes 34 football players, which introduces the presence of other sports and highlights the wide-ranging impact of CTE in athletic populations. The original study proposed by McKee et al. (2013) included 103 individuals, but some of these individuals were also

represented through the Concussion Legacy Foundation (CLF), given the connection of the CLF with the BU CTE Center; thus, this subset of 24 individuals was excluded from this research study.

The last data source within in the table are former football players aggregated together who are currently living and presenting symptoms related to CTE. Since CTE can only be confirmed post-mortem, there is no definitive way to conclude whether these provided symptoms of CTE will be associated with an eventual diagnosis post-mortem. Thus, to include these individuals in the study sample, my research uses the CTE staging scheme from McKee et al. (2014) to designate a CTE level for the 153 individuals who have reported symptoms resembling known CTE pathology. The specific symptomology relating to this staging mechanism is listed below in Table 2.

Table 2: McKee's CTE Staging Scheme

CTE Stage	Symptomatology
1	• Preclinical: reports of vague and non-specific symptoms such as headache, loss of attention and concentration, short-term memory difficulties, and depression
2	• Variable symptoms: prominent behavioral and personality changes, paranoia, irritability, depression, headaches, and short-term memory loss
3	• Memory loss, executive dysfunction, explosivity, difficulty with attention and concentration, and aggression
4	• Severe executive dysfunction, memory loss with dementia, profound loss of attention and concentration, language difficulties, explosivity, aggressive tendencies, paranoia, depression, and gait/visuospatial difficulties

**Various assumptions were made when assigning these individuals a CTE Stage:
-Stage of 1 provided for individuals with ALS Disease if no additional symptoms are provided
-Any indication of aggression accompanied by memory loss in the symptomology is evidence of Stage 3
-If there only exists symptoms related to memory loss, a diagnosis of Stage 1 is given
-Dementia accompanied with memory loss as a symptom is evidence of Stage 4
-The appearance of mood swings, without aggressive tendencies listed, is associated with Stage 2

As more players have spoken publicly about symptoms associated with CTE and sued the NFL through the NFL Concussion Injuries Litigation, higher priority has been placed on research to determine factors that contribute to increased levels of head impact exposure and potential implications to downstream CTE neuropathology. These designated CTE levels above were determined through the information above presented by McKee, along with personal statements and litigation documents elaborating on the symptoms experienced by these living football players. While 32 individuals were found through online searches of living individuals with CTE related symptoms, the other 121 individuals are included within litigation documents against the NFL.

Other researchers have adopted a case series approach when identifying cases of CTE. This work is conducted through an analysis of a small subset of individuals with the goal being to explain an individual's background and the details of their autopsy report. Omalu et al., (2005, 2010) illustrate this approach through analyses of two retired professional football players and contact sport athletes who committed parasuicides and suicides (Omalu et al., 2008). These analyses, along with the information provided by the CLF and Framingham Heart Study Brain Banks, better informed the process of collecting the sample population of individuals with CTE diagnoses for this study.

3.b. Overview of the Dataset

In exploring the topic of brain diagnoses, the NeuroBioBank provides a sample's clinical brain diagnosis and neuropathology diagnosis. Clinical brain diagnoses are determined through an evaluation of a patient's clinical records and case review. Meanwhile, neuropathology diagnoses are concluded from neuropathological exams which are conducted postmortem.

Since clinical brain diagnoses are more frequently reported in sample analysis, this study places more emphasis on the diagnosis provided through the clinical evaluation. Furthermore, manner of death is a primary variable within the NIH dataset and the researchers divide this measure into various categories: accidental, homicide, natural, suicide, and none reported. Thus, when introducing the sample population of individuals with CTE into this study, it is important to ensure that information introduced with these individuals matches with how brain diagnoses and manner of death are organized within the NIH research.

Similarly, demographic variables such as age, race, and sex are provided from the NIH population and similarly included with the CTE samples in the study. Specific to football players with CTE, a measure of socioeconomic status based on median household income at the age of 14 is included for those individuals whose identities are known. This income metric serves as another predictor to the probability of an individual developing CTE.

Upon analyzing the final dataset, one weakness is that some observations are incomplete in the NIH database, with some samples missing data on race and manner of death. Moreover, the NIH database uses a broad categorization of manner of death which creates some ambiguity concerning what constitutes a “natural” vs “accidental” death. Despite these two deficiencies, the final dataset provides a unique outlook into CTE diagnosis and brain diagnoses through a large control population and CTE sample that includes premortem and postmortem individuals.

The Summary statistics for CTE Severity, Clinical Brain Diagnoses, and Manner of Death are presented in Tables 3-6 to further illustrate the distribution of the dependent variables within the study. The CTE statistics below are calculated from a range of 0-4, but do not include the

sample of self-reported individuals that will be matched through McKee's CTE staging scheme. Last, Manner of Death illustrates the prevalence of natural deaths within the dataset, but this likely results from the broad categorization of the term compared to the others causes of death.

Table 3- Analysis of CTE Severity in Sample Population

CTE Stage	Frequency	Percentage
0	35	22.1
1	18	11.4
2	32	20.2
3	29	18.4
4	44	27.9

**This table illustrates the 158 individuals within the study who are diagnosed with Chronic Traumatic Encephalopathy (CTE) post-mortem and have a publicly available CTE diagnosis on a scale of 0-4.

Table 4- Distribution of Clinical Brain Diagnoses

Disease Class	General Population	Athlete (Excluding Football)	Football	Veteran Status	Total	Percentage of Observations
ALS	271	0	12	0	283	2.0%
Alzheimer's Disease	1,927	1	15	5	1,948	13.8%
CTE	2	22	336	33	359	2.5%
Dementia	913	1	31	3	948	6.7%
Major Depressive Disorder	719	0	1	0	720	5.1%
Parkinson's Disease	680	0	3	0	683	4.8%
Schizophrenia	871	0	0	0	871	6.2%
Schizoaffective Disorder	107	0	0	0	107	0.8%

**Within CTE, there are numerous individuals who played football but were also veterans, which causes the distribution of numbers to be larger than the given total of 359 diagnoses.

Table 5- Analysis of Manner of Death in CTE Diagnosed Population

Manner of Death	*Frequency*	*Percent*
Natural	132	69.55
Suicide	39	17.73
Accidental	23	11.82
Homicide	0	0

Table 6- Breakdown of the Manner of Death Categories

Manner of Death	Frequency	Percent
Natural	7,848	56.2
Accidental	1,046	7.5
Suicide	771	5.6
Homicide	129	0.9
Undetermined	4,165	29.8

**Manner of Death only includes 13,961 observations due to the 149 living individuals that are introduced into the sample for having symptoms related to CTE onset.

4. Results

This section elaborates upon the logistic regression techniques provided when predicting the probability of developing a certain clinical brain diagnoses or having a certain manner of death. The first regression explores this probability of the development of clinical brain diagnosis through nine diagnoses: ALS Disease, Alzheimer's Disease, Bipolar Disorder, CTE, Dementia, Major Depressive Disorder, Parkinson's Disease, Schizophrenia, and Schizoaffective Disorder. The regression results are listed below for each of these nine diagnoses classes.

Table 7- Analysis of Brain Diagnoses

	Alzheimer's	ALSDisease	BipolarDisorder	CTE
main				
10-19			1.802**	0.206**
			(0.045)	(0.033)
20-29	0.00868***		4.418***	1.319
	(0.000)		(0.000)	(0.313)
30-39	0.00720***	0.383**	3.202***	0.487*
	(0.000)	(0.039)	(0.000)	(0.059)
40-49	0.0330***	1.405	2.771***	0.692
	(0.000)	(0.129)	(0.000)	(0.189)
50-59	0.239***	2.404***	2.580***	0.275***
	(0.000)	(0.000)	(0.000)	(0.001)
60-69	0.886	3.650***	1.773***	0.619*
	(0.171)	(0.000)	(0.002)	(0.082)
80-88	4.503***	0.726	0.856	0.571*
	(0.000)	(0.207)	(0.485)	(0.053)
89+	5.328***		0.432**	0.206***
	(0.000)		(0.020)	(0.008)
Asian	0.382**	2.821**	1.015	
	(0.031)	(0.016)	(0.977)	
Black	0.294***	0.219***	0.366***	1.250
	(0.000)	(0.000)	(0.000)	(0.298)
Hisp	0.744*	0.404*	0.585	0.416
	(0.055)	(0.074)	(0.117)	(0.220)
AmInd	1.659	4.034**		
	(0.325)	(0.025)		
NativeHaw				42.69***
				(0.000)
Female	1.298***	1.433***	1.508***	
	(0.000)	(0.004)	(0.000)	
Veteran	1.045			
	(0.953)			
Football	0.554	4.477***		
	(0.154)	(0.000)		
Athletics	0.266			
	(0.255)			
N	13908	13908	13908	13908
Brain Bank	BU-Alz,CLF,NIH	BIRI,NIH	NIH	All Banks

Exponentiated coefficients; p-values in parentheses
* p<0.1, ** p<0.05, *** p<0.01

-Age at death is represented through dummy variables above; thus, 10-19 consists of individuals who died between that age range
-"Hisp" represents individuals who identify as Hispanic or Latino
-"AmInd" represents individuals who identify as American Indian
-"Athletics" represents individuals who played Athletics (excluding football)

As listed above, the independent variables included are dummy variables for age, athletics, gender, football participation, race, and veteran status. In the analysis, the age range of 70-79 and the race variable white are excluded to prevent multicollinearity. These two variables are chosen since they have the largest observations within the age and race categories respectively; thus the values of the age variables are analyzed in relation to the age range of 70-79 and the race variables are analyzed in relation to White individuals. While Alzheimer's Disease illustrates increasing odds of diagnosis as one becomes older, ALS Disease peaks between the age range of 60-69 and Bipolar Disorder has the largest odds of potential diagnosis between the range of 20-29. This finding for Bipolar Disorder is interesting given many of the other diagnoses within the study are associated with a larger odds ratio as one becomes older, but the odds of developing Bipolar Disorder are lowest in the age range of 80-89, when evaluated against the benchmark of 70-79.

For the dependent variable of Alzheimer's Disease, the coefficients for the American Indian and Hispanic race variables are large in magnitude but not statistically significant. Thus, the null hypothesis cannot be rejected and these two race categories are indistinguishable from the effects of developing Alzheimer's Disease as a white individual.

Other conclusions derived from the race variables include the prevalence of ALS Disease in Asian and American Indian populations, as compared to White individuals. This result likely originates from the limited observations of Asian individuals (100) and American Indian individuals (30) within the sample population. However, the result is interesting as it contrasts with past research on the racial differences of ALS, which found that White individuals had the highest incidence rate of ALS compared with other races, followed by Black and Asian

individuals (Rechtman et al., 2015). This lower incidence in Black populations is confirmed through an odds ratio of 0.219, and thus the null hypothesis that the odds of being diagnosed with ALS are the same for Black and White populations is rejected.

The influence of football participation and gender is also a factor in the analysis as all the coefficients for the variable Female2 are statistically significant. Overall, women in this dataset have a higher probability of being diagnosed with Alzheimer's Disease, ALS, Bipolar Disorder, along with Major Depressive Disorder and Schizoaffective Disorder represented in Table 8. Particularly, the coefficient is strongest for the ALS disease class, which is interesting given the disease found to be more prevalent in men than women (McCombe et Henderson., 2010). In addition, the odds of being diagnosed with ALS are highest for individuals who played football and thus associated with CTE given 4-6% of patients with CTE also develop ALS, which is a rate higher than the incidence of ALS (2-3 per 100,000 individuals) within the general population (McKee et al., 2010).

Specific to the diagnosis of CTE, the race variables, besides Native Hawaiian individuals, are not significant which implies that the null hypothesis of them having the same effect as White individuals on the likelihood of developing CTE cannot be rejected. However, the odds ratio for the Native Hawaiian population is large, due to the limited sample size of 9 individuals, 3 of which played football and were diagnosed with CTE. The coefficients for the football and veteran status variables are excluded from the CTE regression due to nearly all individuals who participated in these two activities having a diagnosis of CTE within the study, creating extreme coefficients. Numerous odds ratios for the age range variables are significant but less than 1,

which indicates that individuals at those designated ages have lower odds of developing CTE compared to the benchmark of individuals between 70 and 79.

Table 8- Analysis of Brain Diagnoses (Continued)

	Dementia	MajorDepres.	Parkinson's	Schizophrenia	Schizoaff
main					
0-9		0.0308***			
		(0.001)			
10-19		5.433***		0.143***	0.445
		(0.000)		(0.001)	(0.433)
20-29	0.0128***	5.671***		0.787	1.041
	(0.000)	(0.000)		(0.267)	(0.943)
30-39	0.0116***	3.892***	0.0137***	2.040***	3.885***
	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)
40-49	0.0455***	3.391***	0.0176***	2.467***	1.497
	(0.000)	(0.000)	(0.000)	(0.000)	(0.319)
50-59	0.190***	2.625***	0.111***	2.613***	2.943***
	(0.000)	(0.000)	(0.000)	(0.000)	(0.001)
60-69	0.909	1.585***	0.583***	2.724***	2.884***
	(0.379)	(0.008)	(0.000)	(0.000)	(0.002)
80-88	2.299***	0.629**	1.832***	2.478***	1.370
	(0.000)	(0.034)	(0.000)	(0.000)	(0.429)
89+	2.679***	0.565**	1.090	2.720***	0.661
	(0.000)	(0.045)	(0.557)	(0.000)	(0.514)
Asian	1.626	1.823*	0.850	2.933***	1.408
	(0.185)	(0.082)	(0.729)	(0.000)	(0.736)
Black	0.936	0.784**	0.0808***	2.968***	1.772**
	(0.557)	(0.045)	(0.000)	(0.000)	(0.019)
Hisp	1.765***	1.166	0.407***	1.439*	0.673
	(0.000)	(0.466)	(0.002)	(0.058)	(0.582)
AmInd			1.282		
			(0.738)		
Female	0.701***	1.282***	0.571***	0.846**	1.617**
	(0.000)	(0.002)	(0.000)	(0.025)	(0.015)
Veteran	0.610				
	(0.480)				
Football	2.641***		0.108**		
	(0.000)		(0.027)		
Athlet	0.649				
	(0.689)				
N	13908	13908	13908	13908	13908
Brain Bank	BU-ALZ,CLF,NIH	CLF,NIH	CLF,NIH	NIH	NIH

Exponentiated coefficients; p-values in parentheses
* p<0.1, ** p<0.05, *** p<0.01
-"Schizoaff" represents the diagnosis of Schizoaffective Disorder
-"Hisp" represents individuals who identify as Hispanic or Latino
-"AmInd" represents individuals who identify as American Indian
-"Athlet" represents individuals who played Athletics (excluding football)
-Age range of 70-79 and White individuals are benchmarks

Among the five diagnoses analyzed above, the odds ratios for the dummy age variables increase as the age-range becomes higher, but the ratios peak at lower ages for Major

Depressive Disorder, resembling the result found with Bipolar Disorder as they are both mental health conditions. Particularly, the odds ratios for the age variables gradually increase for Parkinson's Disease, which introduces the question of whether the onset of Parkinson's Disease is strictly tied to a certain age group. This question has been explored and Hindle (2010) concluded that aging is the most significant factor that influences the course and progression of Parkinson's Disease.

In addition, the odds ratio for Black individuals within the Schizophrenia analysis is large in magnitude and significant, which corroborates evidence that African Americans are 2.4 times more likely to be diagnosed with a schizophrenia-spectrum diagnosis compared to White individuals (Schwartz et al., 2019). The odds ratio for Football participation within the dementia analysis is also large in magnitude and significant due to the connection between the onset of dementia and repetitive head impacts. More specifically, Guskiewicz et al. (2007) report that the onset of symptoms involving dementia and clinical depression can be started by repetitive cerebral concussions in professional football players. Given the majority of football players within the study have CTE and dementia is within McKee's symptomology criteria at the 4th stage, this higher odds ratio relative to other binary variables is expected.

Table 9- Analysis of Manner of Death Variables

	Natural	Accidental	Suicide	Homicide
main				
0-9	0.188***	6.845***	0.132**	0.868
	(0.000)	(0.000)	(0.047)	(0.888)
10-19	0.297***	19.46***	20.62***	64.53***
	(0.000)	(0.000)	(0.000)	(0.000)
20-29	0.256***	16.34***	9.842***	90.33***
	(0.000)	(0.000)	(0.000)	(0.000)
30-39	0.298***	11.18***	7.628***	28.28***
	(0.000)	(0.000)	(0.000)	(0.000)
40-49	0.516***	5.968***	4.839***	8.064***
	(0.000)	(0.000)	(0.000)	(0.008)
50-59	0.638***	3.273***	3.466***	8.260***
	(0.000)	(0.000)	(0.000)	(0.007)
60-69	0.945	1.473	2.196***	
	(0.421)	(0.120)	(0.001)	
80-88	1.116	0.529*	0.646	1.608
	(0.130)	(0.088)	(0.262)	(0.699)
89+	1.665***	0.331*		
	(0.000)	(0.071)		
Asian	1.562*	0.899	1.575	14.94***
	(0.051)	(0.779)	(0.251)	(0.000)
Black	1.945***	0.829**	0.613***	18.97***
	(0.000)	(0.041)	(0.000)	(0.000)
Hisp	4.548***	0.721	0.853	1.494
	(0.000)	(0.114)	(0.537)	(0.589)
NativeHaw	1.795	1.627	0.822	
	(0.425)	(0.569)	(0.867)	
AmInd	1.438	0.590	2.341	
	(0.374)	(0.613)	(0.419)	
Female	1.193***	0.824***	0.683***	0.211***
	(0.000)	(0.008)	(0.000)	(0.000)
Veteran	3.238**	1.249	0.245	
	(0.043)	(0.791)	(0.198)	
Football	0.411	1.009	8.431***	1.823
	(0.203)	(0.989)	(0.001)	(0.439)
Athletics	1.125	1.455	4.772**	
	(0.845)	(0.588)	(0.022)	
Alzheimer's	1.316***	0.259***	0.0588***	
	(0.000)	(0.001)	(0.005)	
ALSDisease	7.579***	0.0893**	0.173*	
	(0.000)	(0.016)	(0.083)	
BipolarDis	0.418***	1.861***	14.59***	
	(0.000)	(0.000)	(0.000)	
CTE	3.278*	1.304	1.325	
	(0.088)	(0.714)	(0.670)	
Dementia	2.064***	0.405**	0.221**	
	(0.000)	(0.034)	(0.012)	
MajorDep	0.509***	2.370***	20.92***	0.166**
	(0.000)	(0.000)	(0.000)	(0.014)
Parkinson's	1.038	0.589	0.495	
	(0.676)	(0.218)	(0.238)	
Schizophr	1.972***	0.983	4.328***	
	(0.000)	(0.919)	(0.000)	
SchizoAff	1.982***	1.030	2.850***	
	(0.002)	(0.937)	(0.001)	

N	13876	13876	13876	13876
Brain Bank	All Brain Banks	All Brain Banks	All Brain Banks	BU-Alz, NIH

Exponentiated coefficients; p-values in parentheses
* p<0.1, ** p<0.05, *** p<0.01
-"Hisp" represents individuals who identify as Hispanic or Latino
-"NativeHaw" represents individuals who identify as Native Hawaiian or Pacific Islander
-"AmInd" represents individuals who identify as American Indian
-"Athletics" represents individuals who played Athletics (excluding football)
-"MajorDep" refers to individuals who are diagnosed with Major Depressive Disorder
-"SchizoAff" refers to individuals who are diagnosed with Schizoaffective Disorder

One trend immediately observed is the large magnitude in the coefficients of the disease classes for the natural manner of death variable. This is understandable given the prevalence of natural deaths within the study, as 56.2% of individuals in the study passed away naturally. The odds ratio for CTE diagnosis is significant and supports the notion that an individual is 3.3 times more likely to die naturally. These large odds may originate from the cognitive impairment associated with CTE, which results in an individual facing difficulty failing to thrive. Another explanation for these large coefficients is the lack of specificity provided by the NIH NeuroBioBank regarding what exactly classifies a natural death. For example, ALS, which has an average life expectancy of between two and five years, is primarily constituted with a natural cause of death, as 91.2% of individuals with ALS die naturally. Within the definition schema produced by the NIH, this diagnosis falls under the natural death category, but this broad definition in nature may exacerbate the findings listed above.

The age range variables within the Accidental manner of death illustrate the danger of being young, as the age range from 10 to 19 years old has the highest odds ratio at 19.46. In addition, the odds ratios for Bipolar Disorder and Major Depressive Disorder are statistically significant and large in magnitude when predicting the likelihood of an individual committing suicide given those diagnoses. This supports the literature on suicide risk which cites mood

disorders, particularly major depressive disorder, as highly associative with suicide (Angst et Stassen., 1999). The odds ratio for Football Players is also large within Suicide, which indicates that the neuropathology of CTE may be associated with suicide, which current research recognizes is a question that needs additional research (Iverson et al., 2014). Another observation occurs within the analysis of the dependent variable of homicide, with an odds ratio of 14.94 for Asian individuals and 18.97 for Black individuals. The age ranges are also large and significant, with the odds ratio largest between the age of 20 to 29. This illustrates the risk of homicide and violence at a young age, and this quickly reduces as the odds ratios decline when individuals approach their 50s. These results reveal an interesting analysis of racial elements when analyzing various manners of death, while also hypothesizing whether certain diagnoses may position an individual towards a certain type of death.

Table 10- Analysis of CTE Severity by Median Household Income

	(1)
	CTE_Stage
CTE_Stage	
$20,000-$30,000	1.714
	(0.751)
$40,000-$50,000	0.492
	(0.614)
$50,000-$60,000	4.633
	(0.240)
$80,000-$90,000	1.941
	(0.545)
$90,000-$100,000	1.661
	(0.563)
$100,000-$110,000	0.492
	(0.614)
$110,000+	33.91*
	(0.020)
cut1	0.588
	(0.308)
cut2	4.995**
	(0.008)
cut3	26.20***
	(0.000)
N	35
Brain Bank	CLF

Exponentiated coefficients; p-values in parentheses
* p<0.05, ** p<0.01, *** p<0.001

The ordered logistic regression above has a dependent variable of CTE Stage, ranging from a scale of 0 to 4 (most severe), and an independent variable of median household income organized by range in various binary variables. This income variable is calculated using county data from the 1970s onwards, with the year measured as an individual's entry into high school at the age of 14. Given data was only accessible through 1970 for county specific information on the *Integrated Public Use Microdata Series (IPUMS)*, there are only 35 individuals in the study with data on median household income, which is modified to today's dollars using a CPI

index. The regression lacks significant results, besides the income measure from $110,000 and higher illustrating a large likelihood of CTE severity. This is an unexpected result given this income measure serves as a surrogate for healthcare access in an individual's hometown, with the hypothesis that lower income communities may be incentivized to continue playing football for monetary gains and thus be exposed to further head impact exposure.

Table 11: Extensive Analysis of CTE Severity

	CTE Stage	All CTE Stage
main		
QB	0.117*	0.478
	(0.083)	(0.347)
RB	0.599	1.466
	(0.606)	(0.430)
FB	8.498	16.46***
	(0.130)	(0.008)
WR	4.14e-08	0.291
	(0.998)	(0.138)
OL	0.198*	0.896
	(0.064)	(0.821)
DL	2.715	2.698*
	(0.305)	(0.068)
DB	0.441	0.627
	(0.431)	(0.337)
TE	0.161	0.782
	(0.228)	(0.758)
ST	2.16e-09	0.00000133
	(0.995)	(0.986)
10-19	2.47e-10	0.000000126
	(0.997)	(0.989)
20-29	0.00429***	0.101***
	(0.000)	(0.000)
30-39	0.00224***	0.0362***
	(0.000)	(0.001)
40-49	0.0694***	0.157***
	(0.004)	(0.000)
50-59	0.0531*	0.254***
	(0.056)	(0.007)
60-69	0.401	0.426*
	(0.327)	(0.084)
80-88	0.308	2.418
	(0.256)	(0.263)
89+	3487789.3	22845104.6
	(0.992)	(0.993)
Black	0.155*	0.231***
	(0.053)	(0.000)
Hisp	123.1*	12.42**
	(0.054)	(0.046)
NativeHaw	0.128	2.940
	(0.233)	(0.386)
College	2.181	1.504
	(0.579)	(0.677)
Professional	1.206	0.282**
	(0.835)	(0.027)
colyrs	1.327	1.048
	(0.327)	(0.785)
profyrs	1.104	1.028
	(0.258)	(0.553)

/		
cut1	0.0113***	0.158**
	(0.001)	(0.042)
cut2	0.249	0.393
	(0.260)	(0.298)
cut3	1.974	1.128
	(0.565)	(0.893)
N	76	231

Exponentiated coefficients; p-values in parentheses
* p<0.1, ** p<0.05, *** p<0.01

Explanation of Variables

-Football positions for individuals within the sample are included as independent variables:
  -QB(Quarterback), RB(Running Back), FB(Fullback), WR(Wide Receiver), TE(Tight End) OL (Offensive Line)are positions on Offense
  -DL(Defensive Line), DB(Defensive Back), LB(Linebackers…serves as benchmark in the study) are positions on Defense
  -ST(Special Teams) includes Kickers and Punters within the sample
-"Hisp" represents individuals who identify as Hispanic or Latino
-"Native Haw" represents individuals who identify as Native Hawaiian or Pacific Islander
-"College" is a binary variable which measures whether an individual played college football
-"Professional" is a binary variable which measures whether an individual played professional football
-"colyrs" is an interaction term of "College" * amount of years individual played football in college
-"profyrs" is an interaction term of "Professional Football" * amount of years individual played football in any professional league

This ordered logistic regression once again measures the severity of CTE, but this dependent variable is now analyzed through independent variables of age, position, race, and college and NFL performance. Within this table, there are two regressions with the dependent variable of CTE Stage. While they both measure CTE severity from 0-4, the first variable *CTE Stage* only includes postmortem individuals, while the second dependent variable *All CTE Stage* represents postmortem individuals but also those individuals diagnosed through McKee's CTE staging scheme.

When analyzing the position-based variables, the position of Linebacker on Defense serves as the benchmark as this position had the most observations within the sample population. Thus, the results indicate that the positions of Quarterback, Fullback, and Defensive Line are statistically significant, with Quarterbacks having much lower odds of increased CTE severity compared to Linebackers, while Fullbacks and Defensive Linemen have higher odds of developing a more extreme case of CTE. These results are different from previous research which has indicated that no correlation exists between position played and CTE presence (Schwab, Wennberg, et al., 2021). However, one potential explanation for these differing results is the small sample size of 61 individuals within this regression. While further individuals and thus observations with a diagnosed CTE Stage post-mortem were not publicly available, additional research should be done to investigate the potential association between CTE Stage and position.

Regarding the age variables, the results confirm previous analysis from Table 7 which illustrate statistically significant results that have odds ratios less than 1 when using age from 70 to 79 as the benchmark. Interestingly, the two interaction terms *colyrs* and *nflyrs* within the study are both not significant which means that one cannot make the assumption that an added year of football at the college or professional level is associated with higher odds of developing CTE. This explanation is contrary to findings by Mez et al. (2020) who conclude that the odds of CTE double every 2.6 years of football played and those individuals with CTE were 10 times as likely to have played more than 14.5 years compared to players without the disease. Meanwhile, Schwab et al., (2021) find that there is no association between duration of

career and CTE presence; thus, this illustrates two conflicting opinions regarding how influential an extra year of football is on the development of CTE.

5. Conclusion

This data population encapsulates a broad analysis of neurodegenerative diseases through the NIH NeuroBioBank, with a specific focus on the presence and severity of CTE through living and dead populations. When analyzing the clinical brain diagnoses as dependent variables, there are a few major observations involving ALS, Parkinson's Disease, and Schizophrenia related diseases. When measuring ALS as the dependent variable, there was a lack of statistical differentiation with the various age dummy variables, which illustrates the broad age range during which one can develop ALS, typically from 40-70 years old. In addition, a result which differs from current research surrounding ALS provided a larger coefficient for the female dummy variable which is unique given research has emphasized the greater tendency for men to develop ALS. The analysis of Parkinson's Disease provided an interesting outlook into the influence of age on the progression of a disease, as the coefficients for the age dummies increased and remained statistically significant as the age increased. This is expected given neurodegenerative diseases typically arise in older populations. Meanwhile, the racial impacts on the neurodegenerative spectrum are addressed through Schizophrenia-related diseases as African Americans exhibited much higher coefficients for these diagnoses compared to others in the sample.

On the CTE spectrum, previous conclusions from the current literature are confirmed through determining the negligible effects of position on CTE severity, and the minimal influence of years played at the college and professional level. The introduction of a living

population who self-reported CTE symptoms constitutes an original aspect of this study, but future research with these living individuals may prove useful in further understanding the influence of CTE beyond symptomology in living individuals.

References

Alosco, M. L., Cherry, J. D., Huber, B. R., Tripodis, Y., Baucom, Z., Kowall, N. W., Saltiel, N., Goldstein, L. E., Katz, D. I., Dwyer, B., Daneshvar, D. H., Palmisano, J. N., Martin, B., Cantu, R. C., Stern, R. A., Alvarez, V. E., Mez, J., Stein, T. D., & McKee, A. C. (2020). Characterizing tau deposition in chronic traumatic encephalopathy (CTE): utility of the McKee CTE staging scheme. *Acta neuropathologica*, *140*(4), 495–512. https://doi.org/10.1007/s00401-020-02197-9

Alosco, M. L., Kasimis, A.B., Stamm, J. M., Chua, A. S., Baugh, C. M., Daneshvar, D. H., . . . Stern, R.A. (2017). Age of first exposure to American football and long-term neuropsychiatric and cognitive outcomes. *Translational Psychiatry, 7(9).* doi:10.1038/tp.2017.197

Alosco, M. L., Koerte, I. K., Tripodis, Y., Mariani, M., Chua, A. S., Jarnagin, J., Rahimpour, Y., Puzo, C., Healy, R. C., Martin, B., Chaisson, C. E., Cantu, R. C., Au, R., McClean, M., McKee, A. C., Lin, A. P., Shenton, M. E., Killiany, R. J., & Stern, R. A. (2017). White matter signal abnormalities in former National Football League players. *Alzheimer's & dementia (Amsterdam, Netherlands)*, *10*, 56–65. https://doi.org/10.1016/j.dadm.2017.10.003

Angst, J., Angst, F., & Stassen, H. H. (1999). Suicide risk in patients with major depressive disorder. *The Journal of clinical psychiatry*, *60 Suppl 2*, 57–116.

Arango-Lasprilla, J. C., Rosenthal, M., Deluca, J., Komaroff, E., Sherer, M., Cifu, D., & Hanks, R. (2007). Traumatic brain injury and functional outcomes: does minority status matter?. *Brain injury*, *21*(7), 701–708. https://doi.org/10.1080/02699050701481597

Asken, B. M., McCrea, M. A., Clugston, J. R., Snyder, A. R., Houck, Z. M., & Bauer, R. M. (2016). "Playing Through It": Delayed Reporting and Removal From Athletic Activity After Concussion Predicts Prolonged Recovery. *Journal of athletic training*, *51*(4), 329–335. https://doi.org/10.4085/1062-6050-51.5.02

B.L. Plassman, R.J. Havlik, D.C. Steffens, M.J. Helms, T.N. Newman, D. Drosdick, C. Phillips, B.A. Gau, K.A. Welsh–Bohmer, J.R. Burke, J.M. Guralnik, J.C. S. Breitner
Neurology Oct 2000, 55 (8) 1158-1166; DOI: 10.1212/WNL.55.8.1158

Chen, H., Richard, M., Sandler, D. P., Umbach, D. M., & Kamel, F. (2007). Head injury and amyotrophic lateral sclerosis. *American journal of epidemiology*, *166*(7), 810–816. https://doi.org/10.1093/aje/kwm153

Corsellis, J. A., Bruton, C. J., & Freeman-Browne, D. (1973). The aftermath of boxing. *Psychological medicine*, *3*(3), 270–303. https://doi.org/10.1017/s0033291700049588

David Pear et al., Plaintiffs v. National Football League- Filed United States District Court Central District of California (2011)

Dodge, K. A., & Pettit, G. S. (2003). A biopsychosocial model of the development of chronic conduct problems in adolescence. *Developmental psychology*, *39*(2), 349–371. https://doi.org/10.1037//0012-1649.39.2.349
Erica Kornblith, Carrie B. Peltz, Feng Xia, Brenda Plassman, Tatjana Novakovic-Apopain, Kristine Yaffe Neurology Sep 2020, 95 (13) e1768-e1775; DOI: 10.1212/WNL.0000000000010617

Fratiglioni, L., Ahlbom, A., Viitanen, M., & Winblad, B. (1993). Risk factors for late-onset Alzheimer's disease: a population-based, case-control study. *Annals of neurology*, *33*(3), 258–266. https://doi.org/10.1002/ana.410330306

Gavett, B. E., Stern, R. A., Cantu, R. C., Nowinski, C. J., & Mckee, A. C. (2010). Mild traumatic brain injury: A risk factor for neurodegeneration. *Alzheimer's Research & Therapy, 2*(3), 18. doi:10.1186/alzrt42

Haneuse, S., Schildcrout, J., Crane, P., Sonnen, J., Breitner, J., & Larson, E. (2009). Adjustment for selection bias in observational studies with application to the analysis of autopsy data. *Neuroepidemiology*, *32*(3), 229–239. https://doi.org/10.1159/000197389

Hernán, Miguel A.*; Hernández-Díaz, Sonia†; Robins, James M.* A Structural Approach to Selection Bias, Epidemiology: September 2004 - Volume 15 - Issue 5 - p 615-625 doi: 10.1097/01.ede.0000135174.63482.43

Heyman, A., Wilkinson, W. E., Stafford, J. A., Helms, M. J., Sigmon, A. H., & Weinberg, T. (1984). Alzheimer's disease: a study of epidemiological aspects. *Annals of neurology*, *15*(4), 335–341. https://doi.org/10.1002/ana.410150406

Hindle, J. V. (2010). Ageing, neurodegeneration and Parkinson's disease. *Age and Ageing*, *39*(2), 156–161. https://doi.org/10.1093/ageing/afp223

Iverson GL Chronic traumatic encephalopathy and risk of suicide in former athletes *British Journal of Sports Medicine* 2014;**48:**162-164.

Kurland, L. T., Radhakrishnan, K., Smith, G. E., Armon, C., & Nemetz, P. N. (1992). Mechanical trauma as a risk factor in classic amyotrophic lateral sclerosis: lack of epidemiologic evidence. *Journal of the neurological sciences*, *113*(2), 133–143. https://doi.org/10.1016/0022-510x(92)90241-c

Kurtzke J. F. (1991). Risk factors in amyotrophic lateral sclerosis. *Advances in neurology*, *56*, 245–270.

Langlois, J. A., Rutland-Brown, W., & Wald, M. M. (2006). The epidemiology and impact of traumatic brain injury: a brief overview. *The Journal of head trauma rehabilitation*, *21*(5), 375–378. https://doi.org/10.1097/00001199-200609000-00001

Lee, H. M., & Koh, S. B. (2015). Many Faces of Parkinson's Disease: Non-Motor Symptoms of Parkinson's Disease. *Journal of movement disorders*, *8*(2), 92–97. https://doi.org/10.14802/jmd.15003

MARTLAND HS. PUNCH DRUNK. *JAMA.* 1928;91(15):1103–1107. doi:10.1001/jama.1928.02700150029009

Maxwell v NFL- Filed Superior Court of California County of Los Angeles (2011)

Mayeux, R., & Stern, Y. (2012). Epidemiology of Alzheimer disease. *Cold Spring Harbor perspectives in medicine*, *2*(8), a006239. https://doi.org/10.1101/cshperspect.a006239

McCombe, P. A., & Henderson, R. D. (2010). Effects of gender in amyotrophic lateral sclerosis. *Gender medicine*, *7*(6), 557–570. https://doi.org/10.1016/j.genm.2010.11.010
McKee, A. C., Cantu, R. C., Nowinski, C. J., Hedley-Whyte, E. T., Gavett, B. E., Budson, A. E., . . . Stern, R. A. (2009). Chronic Traumatic Encephalopathy in Athletes: Progressive Tauopathy After Repetitive Head Injury. *Journal of Neuropathology & Experimental Neurology, 68*(7), 709-735. doi:10.1097/nen.0b013e3181a9d503

McKee, A. C., Gavett, B. E., Stern, R. A., Nowinski, C. J., Cantu, R. C., Kowall, N. W., … Budson, A. E. (2010). TDP-43 Proteinopathy and Motor Neuron Disease in Chronic Traumatic Encephalopathy. *Journal of Neuropathology & Experimental Neurology*, *69*(9), 918–929. https://doi.org/10.1097/nen.0b013e3181ee7d85

McKee, A. C., Stern, R. A., Nowinski, C. J., Stein, T. D., Alvarez, V. E., Daneshvar, D. H., Lee, H. S., Wojtowicz, S. M., Hall, G., Baugh, C. M., Riley, D. O., Kubilus, C. A., Cormier, K. A., Jacobs, M. A., Martin, B. R., Abraham, C. R., Ikezu, T., Reichard, R. R., Wolozin, B. L., Budson, A. E., … Cantu, R. C. (2013). The spectrum of disease in chronic traumatic encephalopathy. *Brain : a journal of neurology*, *136*(Pt 1), 43–64. https://doi.org/10.1093/brain/aws307

Mckee, A. C., Daneshvar, D. H., Alvarez, V. E., & Stein, T. D. (2013). The neuropathology of sport. *Acta Neuropathologica, 127*(1), 29-51. doi:10.1007/s00401-013-1230-6

Mehta, M. A., Owen, A. M., Sahakian, B. J., Mavaddat, N., Pickard, J. D., & Robbins, T. W. (2000). Methylphenidate enhances working memory by modulating discrete frontal and parietal lobe regions in the human brain. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, *20*(6), RC65. https://doi.org/10.1523/JNEUROSCI.20-06-j0004.2000

Mez, J., Daneshvar, D. H., Kiernan, P. T., Abdolmohammadi, B., Alvarez, V. E., Huber, B. R., Alosco, M. L., Solomon, T. M., Nowinski, C. J., McHale, L., Cormier, K. A., Kubilus, C. A., Martin, B. M., Murphy, L., Baugh, C. M., Montenigro, P. H., Chaisson, C. E., Tripodis, Y., Kowall, N. W., Weuve, J., … McKee, A. C. (2017). Clinicopathological Evaluation of Chronic Traumatic Encephalopathy in Players of American Football. *JAMA*, *318*(4), 360–370. https://doi.org/10.1001/jama.2017.8334

Mez, J., Daneshvar, D. H., Abdolmohammadi, B., Chua, A. S., Alosco, M. L., Kiernan, P. T., Evers, L., Marshall, L., Martin, B. M., Palmisano, J. N., Nowinski, C. J., Mahar, I., Cherry, J. D., Alvarez, V. E., Dwyer, B., Huber, B. R., Stein, T. D., Goldstein, L. E., Katz, D. I., Cantu, R. C., … McKee, A. C. (2020). Duration of American Football Play and Chronic Traumatic Encephalopathy. *Annals of neurology*, *87*(1), 116–131. https://doi.org/10.1002/ana.25611

Mitchell, J. D., & Borasio, G. D. (2007). Amyotrophic lateral sclerosis. *Lancet (London, England)*, *369*(9578), 2031–2041. https://doi.org/10.1016/S0140-6736(07)60944-1

Montenigro, P. H., Alosco, M. L., Martin, B. M., Daneshvar, D. H., Mez, J., Chaisson, C. E., Nowinski, C. J., Au, R., McKee, A. C., Cantu, R. C., McClean, M. D., Stern, R. A., & Tripodis, Y. (2017). Cumulative Head Impact Exposure Predicts Later-Life Depression, Apathy, Executive Dysfunction, and Cognitive Impairment in Former High School and College Football Players. *Journal of neurotrauma*, *34*(2), 328–340. https://doi.org/10.1089/neu.2016.4413

Mori, H., Kondo, J., & Ihara, Y. (1987). Ubiquitin is a component of paired helical filaments in Alzheimer's disease. *Science*, *235*, 1641+.

Mortensen, P. B., Pedersen, C. B., Melbye, M., Mors, O., & Ewald, H. (2003). Individual and familial risk factors for bipolar affective disorders in Denmark. *Archives of general psychiatry*, *60*(12), 1209–1215. https://doi.org/10.1001/archpsyc.60.12.1209

Omalu, B. I., Dekosky, S. T., Minster, R. L., Kamboh, M. I., Hamilton, R. L., & Wecht, C. H. (2006). Chronic Traumatic Encephalopathy in a National Football League Player. *Neurosurgery*. doi:10.1097/00006123-200605000-00036

Omalu, B., Small, G. W., Bailes, J., Ercoli, L. M., Merrill, D. A., Wong, K. P., Huang, S. C., Satyamurthy, N., Hammers, J. L., Lee, J., Fitzsimmons, R. P., & Barrio, J. R. (2018). Postmortem Autopsy-Confirmation of Antemortem [F-18]FDDNP-PET Scans in a Football Player With Chronic Traumatic Encephalopathy. *Neurosurgery*, *82*(2), 237–246. https://doi.org/10.1093/neuros/nyx536

Orlovska, S., Pedersen, M. S., Benros, M. E., Mortensen, P. B., Agerbo, E., & Nordentoft, M. (2014). Head injury as risk factor for psychiatric disorders: a nationwide register-based follow-

up study of 113,906 persons with head injury. *The American journal of psychiatry*, *171*(4), 463–469. https://doi.org/10.1176/appi.ajp.2013.13020190

Rechtman, L., Jordan, H., Wagner, L., Horton, D. K., & Kaye, W. (2015). Racial and ethnic differences among amyotrophic lateral sclerosis cases in the United States. *Amyotrophic lateral sclerosis & frontotemporal degeneration*, *16*(1-2), 65–71. https://doi.org/10.3109/21678421.2014.971813

Rhonda N. Goldman, Leslie S. Greenberg & Lynne Angus (2006) The effects of adding emotion-focused interventions to the client-centered relationship conditions in the treatment of depression, Psychotherapy Research, 16:5, 537-549, DOI: 10.1080/10503300600589456

Serafini, G., Calcagno, P., Lester, D., Girardi, P., Amore, M., & Pompili, M. (2016). Suicide Risk in Alzheimer's Disease: A Systematic Review. *Current Alzheimer Research*, *13*(10), 1083–1099. https://doi.org/10.2174/1567205013666160720112608

Schwab, Nicole & Wennberg, Richard & Grenier, Karl & Tartaglia, Maria & Tator, Charles & Hazrati, Lili-Naz. (2021). Association of Position Played and Career Duration and Chronic Traumatic Encephalopathy at Autopsy in Elite Football and Hockey Players. Neurology. 10.1212/WNL.0000000000011668.

Schwartz, E. K., Docherty, N. M., Najolia, G. M., & Cohen, A. S. (2019). Exploring the racial diagnostic bias of schizophrenia using behavioral and clinical-based measures. *Journal of Abnormal Psychology*, *128*(3), 263–271. https://doi.org/10.1037/abn0000409

Tsao, J. W. (2012). Comment on "Chronic Traumatic Encephalopathy in Blast-Exposed Military Veterans and a Blast Neurotrauma Mouse Model". *Science Translational Medicine, 4*(157). doi:10.1126/scitranslmed.3004595

Wallace, J., Worts, P., Moran, R., Mason, J., Weise, K. K., Swanson, M., & Murray, N. (2020). Socioeconomic status and race as social determinants of health to be considered in clinical use of pre-season vestibular and oculomotor tests for concussion. *Journal of clinical and translational research*, *6*(4), 168–178.