The Effect of Head Injury on Neurologic and Cognitive Health Throughout the Life Course

THE EFFECT OF HEAD INJURY ON NEUROLOGIC AND COGNITIVE HEALTH THROUGHOUT THE LIFE COURSE

KATHRYN MARIE TAYLOR

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Abstract

Recent studies touting the potential long term negative effects of traumatic brain injuries have pushed these injuries in the forefront of public health concern. There is particular concern of whether or not there is a time window where these injuries are more dangerous. Using robust methods, our research suggests that early life head injuries tend to have worse effects on a latent outcome like the development of Parkinson's disease, as well as on a relatively short term outcome like cognitive function. For both of these outcomes this dissertation evaluated how the timing of head injuries in conjunction with disease onset or cognitive measurement may impact results. But after considering these time effects, a younger age at first head injury was still associated with adverse neurological effects. It is hypothesized that a head injury during key developmental time periods may actually serve to disrupt developmental processes. This disruption in these processes can potentially have both long term and permanent negative effects on brain function.

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Dedicated to my Grandmothers,

Ines Taylor and Francis Zamora,

For always believing

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CHAPTER 1

1 Introduction:

1.1 Background and Significance

There has been increased media attention on the growing prevalence of traumatic brain injuries (TBIs). Combining the increased prevalence of head injuries with their potential for long-lasting neurological damage even with milder forms of head injuries, these injuries once thought innocuous are now being pushed to the forefront of public health concerns. A growing number of medical bodies have issued statements touting the potential repercussions of head injuries with the consensus that there is not enough research evaluating the long-term effects of head injury nor is there sufficient research focused particularly on head injuries in children and adolescents[1-3]. In May 2014, recognizing the growing concern about head injuries in the United States, the White House held a widely publicized summit on sports-related concussions. The impetus for the summit was a recognition of the lack of research on the subject, leading to an inability to make definitive policy decisions[4]. Given this void of information, there is a critical need for head injury related research.

1.1.1 Traumatic Brain Injuries

Traumatic brain injuries are defined as any blow, bump or collision with the head, neck or elsewhere on the body that has enough force to result in abnormal brain function. In the United States, the Center for Disease Control estimated that 2.5 million people visited the hospital for TBI-related effects. The trend over the past couple of years suggests that these numbers are increasing annually[5]. Head injury incidence by age is bimodal with head injuries primarily occurring between the ages of 0-14 and in those 65 or older[6]. Within those who present to a hospital with a TBI, the vast majority are designated as having a mild traumatic brain injury (mTBI), also commonly referred to as a concussion[7]. However, the accuracy of these numbers is disputed given that head injuries tend to be under-reported[8,9].

Many factors influence the risk of mTBIs. These include but are not limited to gender, socioeconomic status and participation in certain sports. There is a reported difference between the rate and severity of mTBIs between males and females. In the literature, women tend to have higher incidence of head injuries than men when they are compared using sports that both men and women play[10,11]. This may be due to differences in gender norms regarding likelihood of reporting injuries in general. However, there is also reason to believe that physiologic differences such as neck strength, differences in sex hormones, and metabolic differences may also be important contributors for the observed gender differences[12]. Socioeconomic status has an inverse relationship with the rate of injury[13]. There are many proposed mechanisms for this including higher exposure to violence, increased risk of motor vehicle accidents and favorable selection of injury prone sports[14,15]. In children and adolescents, sports—specifically contact sports such as football, hockey and soccer—have been a significant risk factor for mTBIs.

Sports related head injuries have been given a great deal of attention in the past several years. This is primarily attributable to notable former athletes who have allegedly been affected negatively by their past head injuries. There has been increased concern for head injuries in athletes especially following the discovery of chronic traumatic encephalopathy (CTE) in former football, baseball and hockey player's brains[16-18]. CTE development is associated with having a repeated injuries to the brain[19]. Athletes are an ideal population for studying the effects of head injuries because of the particularly high incidence of head injury throughout most athletes' athletic careers. However, given that head injuries are not exclusively an issue for professional athletes, head injury research should also expand to the general population.

1.1.2 The brain and head injuries

Brain development starts prenatally and continues into adulthood. Because of the brain's importance, there are many anatomical and physiologic mechanisms in place to help protect it. For example the brain is surrounded by an external hard skull and has a selectively permeable barrier known as the blood brain barrier that protects the brain from exogenous agents in the body[20,21]. However, even with these protective mechanisms, the brain has been shown to be susceptible to environmental exposures such as pesticides and particulate matter. These exposures have been shown to induce brain inflammation, atypical neurodegeneration through chronic microglial activation and targeted loss of the dopaminergic cells[22,23]. Many of these effects have been associated with a variety of neurologic dysfunction and diseases throughout the life course.

Evidence suggests that mechanical injury to the brain can cause neurologic microstructural and physiologic changes which are similar to effects seen with the environmental

exposures mentioned above. These effects can have persistent and sometimes permanent impacts[24,25]. Because of this, there is increased interest on how a brain injury might influence both neurodevelopment and neurodegeneration and what that means for neurologic disease pathology. A brain injury can be separated into two principal stages. The first stage is related to the primary effects of the initial insult which occurs at the moment of the impact. The second stage is related to secondary damages caused by physiologic processes initiated by the effects of the impact[26].

Until recently, conventional imaging tended to underestimate the extent of damage to the brain caused by traumatic brain injuries. This is particularly true with concussions where concussed brains often appeared to look very similar to healthy brains in basic MRIs and CT scans[27]. With the improvements in functional MRIs, it is now possible to see that following a head injury, there can be white matter damage to the brain which is a result of axonal and myelin loss[28]. During this initial phase of injury, there is increased cerebral edema due to impaired regulation of cerebral blood flow, an increase in the release of excitatory neurons and an increase in permeability of the blood brain barrier[26,29]. This effect is exacerbated by a decrease in metabolic processes in the brain which can impact energy dependent membrane cellular pumps[26]. These initial effects of a head injury are associated with acute symptoms such as loss of consciousness, amnesia, behavioral changes, cognitive impairment, disruption in sleep and headaches[18].

The physiologic impacts of initial injury create a cascade of events that can have long-term physiologic impacts. There is an influx of microglial cells in the brain which are brought in to clear cellular debris after a head injury. But if these cells respond abnormally, microglial cells can induce a self-perpetuating cycle of neuroinflammation. While the underlying mechanism for

this process is poorly understood, chronic brain inflammation has been linked to many neurologic diseases[30]. Another potential long term impact of head injuries is on brain plasticity itself. Brain plasticity is defined as the brain's ability to structurally and functionally adapt to changes in the brain, regardless of their cause. Following a head injury, the brain may attempt to remodel neuronal pathways that are broken down during the injury by using alternative routes of neuronal circuitry. But by taking advantage of these alternative circuits, the brain may not be able to adapt to subsequent changes in the brain related to further head injuries, strokes and other neurologic diseases[31,32].

1.2 Overview of Thesis

There is particular concern as to whether or not there are specific windows of susceptibility for which having a head injury is more dangerous. There is ongoing debate as to whether or not having a head injury in early life is a particularly important window. On one side of the debate, people have argued that children have greater brain plasticity and can recover quickly from a head injury[33]. On the other hand, the brain undergoes rapid anatomical and functional changes during childhood and a head injury during this time period may interrupt these processes[34]. Using cognitive function and Parkinson's disease as my outcomes, my dissertation attempts to evaluate how timing of head injuries may affect these outcomes.

1.2.1 Head injuries and cognitive function

Cognitive function in children and adolescents (ages 5-17) have been shown to be associated with measures of academic performance[35,36]. During high school, there is a wide range of ranking-based metrics including grades, SAT scores and Advanced Placement (AP)

tests. Performance within these metrics can have affect college attendance, college major and job placement. During adolescence, there is also an anatomical reorganization of the brain. An increase in myelinated axons or white matter leads to a loss of gray matter [37]. This increase in white matter is linked to an increase in both cognitive and executive functions[38]. Since traumatic brain injuries are known to break down white matter, it is important to assess how these injuries might impact brain development during this important time. We used tests of cognitive function as an objective marker of neurological dysfunction in order to measure the cognitive effects of head injury.

1.2.2 Head injuries and Parkinson's disease

Parkinson's disease is the second most prevalent neurologic disease[39], known for its slow and progressive onset. One characteristic of the disease is a loss in dopaminergic cells. By the time the first symptoms of the disease appear, up to 60% of dopaminergic cells can have already been lost[40]. Early symptoms of the disease such as instability, forgetfulness, or fatigue can be confused with effects of ageing; this confusion often delays diagnosis even further[41]. Parkinson's disease onset has also been linked to brain inflammation in early life caused by environmental exposures. Head injuries are a known cause of brain inflammation.

Evidence suggests that head injuries can result in long-term microglial activation[30,42]. Microglial cells can have both neurotoxic and neuroprotective effects in the different settings[43]. In cases of injury or infection, the microglial cells are activated, promoting the production of inflammatory cytokines and reactive oxygen species. This process can serve a positive role, removing damaged neurons and cellular debris. However, when these cells are over-activated or go unregulated, there can be low level chronic neurodegeneration which can in turn activate the

production of more glial cells[44]. It is this self-perpetuating cycle of inflammation and neurodegeneration, often initiated by head injuries that has been linked to PD[45].

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CHAPTER 2

Title: The temporal effects of concussions on pre-season neuropsychological tests in a cohort of adolescent athletes

Authors: Kathryn M. Taylor[1], Marianthi-Anna Kioumourtzoglou[1], Jim Clover[2], Brent A. Coull[1,3], Jack T. Dennerlein[1,4], David C. Bellinger[1,5,], Marc G. Weisskopf[1,7]

1) Department of Environmental Health, Harvard T.H. Chan School of Public Health, Boston , MA
2) The Sport Foundation, Riverside, CA
3) Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston , MA
4) Department of Physical Therapy, Movement, and Rehabilitation Sciences, Northeastern University, Boston, Massachusetts
5) Children's Hospital, Harvard Medical School, Boston, MA, USA
6) Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston , MA

2.1 Abstract

Objective: To evaluate the effect of concussion history on cognitive function in adolescents.

Methods: Over 5 years, 5487 high school and junior high student athletes completed baseline pre-season neuropsychological tests, which were used to create 5 composite test scores. We used questionnaire data to evaluate concussion history and other covariates. Within our models we evaluated the effect of ever having a concussion, the number of concussions, time since last concussion, and age at first head injury on cognitive function. We used linear models to estimate adjusted effects of the 5 composite scores and their corresponding 95% confidence interval (CI) for the cognitive scores. We used a mixed model with random effects for the 5 composite scores to estimate the adjusted effect of concussion and its corresponding 95% confidence interval on the global cognitive score.

Results: Ever having a concussion was associated with a significantly ($p< 0.05$) lower score for the global cognitive score, the verbal memory composite, the visual memory composite and the impulse control composite. We found significantly lower scores for the same tests for each additional concussion. In evaluating time since last concussion prior to the test, the effect was non-linear and there appeared to be acute effects that dissipated with increasing time since last concussion. Concussion in early childhood had a greater negative impact on the global cognition score and all composite scores.

Conclusion: While several temporal factors were associated with cognitive function, longer term cognitive domain specific effects of concussions may be dependent upon the stage of development at which the concussion occurred.

2.2 Introduction:

During the 2013-2014 school year, approximately 7.8 million high school students participated in school sponsored sports[1]. Evidence suggests that the rate of sports-related head injuries within this population has been increasing over the past 10 years, with mild traumatic brain injuries (mTBIs) or concussions in individuals between the ages of 5-18 years old accounting for an estimated 65% of all sports-related concussions[2,3]. Given the prevalence of mTBIs in this population, focus should be given to evaluating the neuropsychological consequences of these types of injuries on the developing brain. Tests of cognitive function can be used as objective markers of neurological dysfunction.

Adolescence, loosely defined as the time period between 10-18 years of age, is often thought of as a transitional time from childhood into adulthood[4]. However, during these ages the brain is still very much at a developmental or pediatric stage. During adolescence there is an anatomical reorganization of cortical circuits in the brain. There is also an increase of white matter volume related to increased myelination of axons[5]. These changes are reflected by rapid growth in both cognitive and executive functions[6]. Whether an mTBI during this developmental time is associated with lasting changes in brain plasticity or evolving cognitive functions remains controversial[7,8].

Most studies evaluating the impact of concussions on cognitive function have been conducted in collegiate and professional athletes with conflicting findings. While most studies find short-term adverse effects on cognition, there is disagreement about the cognitive domains affected[9-13]. There is also disagreement on how long these effects may last making it difficult to draw any specific conclusions in these populations. Furthermore, given the difference in

developmental brain stages between adults and adolescents it is not clear if these findings are generalizable to an adolescent population[14].

Studies that have evaluated cognitive function in high school aged athletes have also been largely inconclusive, with some studies seeing a decrease in cognitive function across different cognitive domains after a head injury[15-17] and others finding no difference in scores between the concussed and non-concussed[18]. The difference in findings may be due to small sample sizes, insufficient follow-up time following a concussion, not accounting for potential confounders and lack of consideration for the timing of the concussions. To adequately address the effect of concussions on cognitive function in adolescents, we evaluated this association in a large cohort of adolescent student athletes from Southern California.

2.3 Methods:

Study Population:

From 2009 to 2014, 5487 student athletes ages 12-19 were administered cognitive function tests. All athletes were from school districts in San Bernardino and Riverside counties in California. Under the California Interscholastic Federation bylaw 503[19], student athletes are required to have a sports physical examination less than one year prior to participation in any interscholastic sport. For many schools in San Bernardino and Riverside County, cognitive tests have been added to these pre-participation physicals as standard practice. For most athletes these physicals were first administered in their freshmen year and for others these physicals were first administered prior to initiating their participation in a sport at a later grade. While individuals could have taken the cognitive tests multiple times while an athlete, for this analysis we used the test scores from an individual's first visit.

Prior to analysis we removed individuals for whom concussion history was unknown (N=36) and individuals who took the test in any language other than English (N=20). After exclusions, 5431 athletes, 780 with a history of concussion and 4651 who had never had a concussion, were included in the final analysis.

Exposure and Covariate Assessment:

Self-reported concussion history was collected using a questionnaire prior to taking the cognitive test. All athletes were asked to report the number of concussions they had experienced prior to the cognitive test. If they reported ever having a concussion they were asked to provide the timing of these events. From these responses, we created a binary variable for ever having a concussion (yes/no) which we used in our analysis. We also evaluated the effect of the number of concussions prior to cognitive testing as a continuous variable. Initial analyses included all individuals who had a concussion, irrespective of timing. Among those who gave information on the dates of their concussions (N=576), we assessed the potential differences between acute and chronic effects of concussion on cognitive function. We did this by calculating the time since last concussion from the date of the test and used this as a continuous variable in our model, excluding those who had a concussion but had not indicated the date. We also evaluated the effect of age at first concussion as a continuous variable, using the same exclusionary criteria. We calculated age at first concussion using the difference between their birthdate and the dates of their self-reported head injuries.

Data on a large number of covariates used in our analysis were also obtained on the pre-test questionnaires. Covariates considered in this analysis included gender (male/female), race/ethnicity (White, Hispanic, Black, Asian, Hawaiian Pacific Islander and Native American), current school district (1-12, categorical), handedness (left/right/ambidextrous), age at date of

visit (continuous), grade (7^{th}-12^{th}, continuous), BMI (continuous), first language (English, non-English). We also created a categorical variable for sport type, which included four categories: football, other contact or collision sport, limited contact sport and non-contact sport. These categories were created using the classification of sports by the American Academy of Pediatrics[25]. While we collected data on ADD/ADHD and sleep prior to the test we excluded these variables from our analyses because both of these covariates could be potential mediators for the effect of concussions on cognitive function[20-22].

Cognitive Testing:

For cognitive assessment we used the computer-based Immediate Post-concussion Assessment and Cognitive Test (ImPACT) which has become the validated standard for measuring cognitive function in athletes across the United States[23]. We utilized data from five composite test scores which included: the verbal memory composite, the visual memory composite, the visual motor speed composite, the reaction time composite and the impulse control composite. These 5 scores provide a validated assessment of a wide range of cognitive domains and together they can be used to provide a comprehensive assessment of cognitive function[24]. The score ranges vary by composite test. To make them comparable, we first inverted the scores obtained for both the impulse control composite and the reaction time composite so that for all composite scores a higher score would indicate better performance. We then standardized each test to our non-concussed population by calculating the z-score using the mean and standard deviation for our non-concussed population for each composite score separately.

Statistical Analysis:

To test the association between ever having a concussion and global cognitive function, we used a mixed model treating each composite test score as a repeated measure of global cognitive health within subjects. To account for the fact that we used 5 different test scores where within test scores may be more correlated than across test scores, we included a random intercept for each test score in our model. Within our model, we also included a random intercept for each individual to account for correlated observations across the five tests. To evaluate potential heterogeneity of the effect of concussion across tests, we compared this model to a model without the random slope for each test using Akaike's Information Criterion (AIC). We found heterogeneity so we present results from individual linear models for each domain specific test score.

In order to differentiate between acute and chronic effects of concussions, we used time since last concussion from the date of the test as a continuous variable in our models. We included an indicator for ever having a concussion in the model, with all those without a concussion assigned a constant value for time, in order to keep all subjects in the analysis. To test the potential non-linearity of the effect of time since last concussion on the cognitive test scores we applied a natural spline using 3 degrees of freedom to the continuous variable. We used this same technique to evaluate the effect of age at first concussion on cognitive scores.

Models were adjusted for variables mentioned in the covariate section above. When we evaluated the effect of duration since last concussion and age at first concussion, we included both terms simultaneously in the model. Within this model, we also controlled for number of concussions. Most variables had less than 1% missing data, however the variable with the most missingness was race which had approximately 10% missing. When data were missing for

variables used in our models, we used a single round of imputation to estimate the missing values using height, weight, handedness, grade, school district, age at date of visit, gender, sport, race, BMI and first language as our predictors. Analyses were conducted using SAS software (version 9.3; SAS Institute, Inc. Cary, NC) and R statistical software (version 3.1.1; R Development Core Team; 2014) for models that utilized splines.

2.4 Results:

The characteristics of our study population are summarized in Table 2.1. The mean age±standard deviation (SD) of our study population at the cognitive testing was 15.6±1.2. Our study population was predominantly Hispanic, male and football was the most commonly played sport. Female athletes comprised approximately 25% of our population. Football players were more likely to have a history of concussion than those in other sports. Among those who had a concussion, the number of concussions prior to the test date ranged from 1-7 and the average (± SD) age at first concussion among those with a concussion was 13.8± 3.5.

While our adjusted mixed models showed that ever having a concussion was associated with a significant decrement of 0.116 SD (95% CI= -0.232, -0.0002) on the global cognitive test score, our analysis suggested heterogeneity across cognitive tests. When we evaluated each test separately, ever having a concussion significantly decreased the score of the verbal memory composite (standardized units=-0.107, 95% CI=-0.184, -0.029), the visual memory composite (standardized units =-0.130, 95% CI=-0.208, -0.052), and the impulse control composite (standardized units =-1.340, 95% CI=-1.843, -0.844) (Table 2.2). When we considered the number of head injuries prior to the test date as a continuous variable in our mixed model, we found that each additional concussion was associated with a significant -0.044 standardized unit

Table 2.1: Characteristics of study population by concussion status

Characteristics	**Total Population** (N=5431)	**No History of Concussion** (N=4651)	**History of Concussion** (N=780)
Range of Concussions	1-7	NA	1-7
Age (years) of first concussion (mean± SD)	14.0± 3.2	NA	14.0± 3.2
Age (years) at date of visit (mean± SD)	15.6±1.2	15.5±1.2	15.9±1.2
BMI at date of visit (mean± SD)	23.6±4.7	23.5±4.7	24.1±4.8
Gender, n (%)			
Female	1340 (24.7)	1210 (26.0)	130 (16.7)
Male	4091 (75.3)	3441 (74.0)	650 (83.3)
Race/ Ethinicity, n (%)			
Hispanic	2049 (37.7)	1862 (40.0)	187 (24.0)
White	1258 (23.2)	1042 (22.4)	216 (27.7)
Mixed	810 (14.9)	685 (14.7)	125 (16.0)
Black	593 (10.9)	502 (10.8)	91 (11.7)
Asian	81 (1.5)	78 (1.7)	3 (0.4)
Hawaiian Pacific Islander	66 (1.2)	58 (1.2)	8 (1.0)
Native	29 (0.5)	25 (0.5)	4 (0.5)
Missing	545 (10.0)	399 (8.6)	146 (18.7)
Sport Class, n (%)			
Football	2793 (51.4)	2277(49.0)	516 (66.2)
Other Contact or Collision Sport	1917 (35.3)	1712 (36.8)	205 (26.3)
Limited Contact Sport	530 (9.8)	488 (10.5)	42 (5.4)
Non-Contact Sport	175 (3.2)	160 (3.4)	15 (1.9)
Missing	16 (0.3)	14 (0.3)	2 (0.3)

NA, not applicable.

Table 2.2: Mean difference in cognitive test score (standardized units) between those with and without a concussion.

Test	Unadjusted (95% CI)	p-value	Adjusted* (95% CI)	p-value
Global Cognition	-0.088 (-0.203, 0.027)	0.101	-0.116 (-0.232, -0.0002)	0.049
Verbal Memory	-0.085 (-0.160, -0.010)	0.026	-0.107 (-0.184,-0.029)	0.007
Visual Memory	-0.133 (-0.210,-0.055)	0.008	-0.130 (-0.208, -0.052)	0.001
Visual Motor	-0.006 (-0.081, 0.069)	0.874	-0.067 (-0.141, 0.007)	0.078
Reaction Time	-0.033 (-0.108, 0.042)	0.384	-0.068 (-0.144, 0.009)	0.083
Impulse Control	-1.365 (-1.815, -0.088)	<0.0001	-1.34 (-1.843, -0.844)	<0.0001

* Adjusting for BMI, gender, race, age, age^2, school district, sport category, first language, grade, handedness

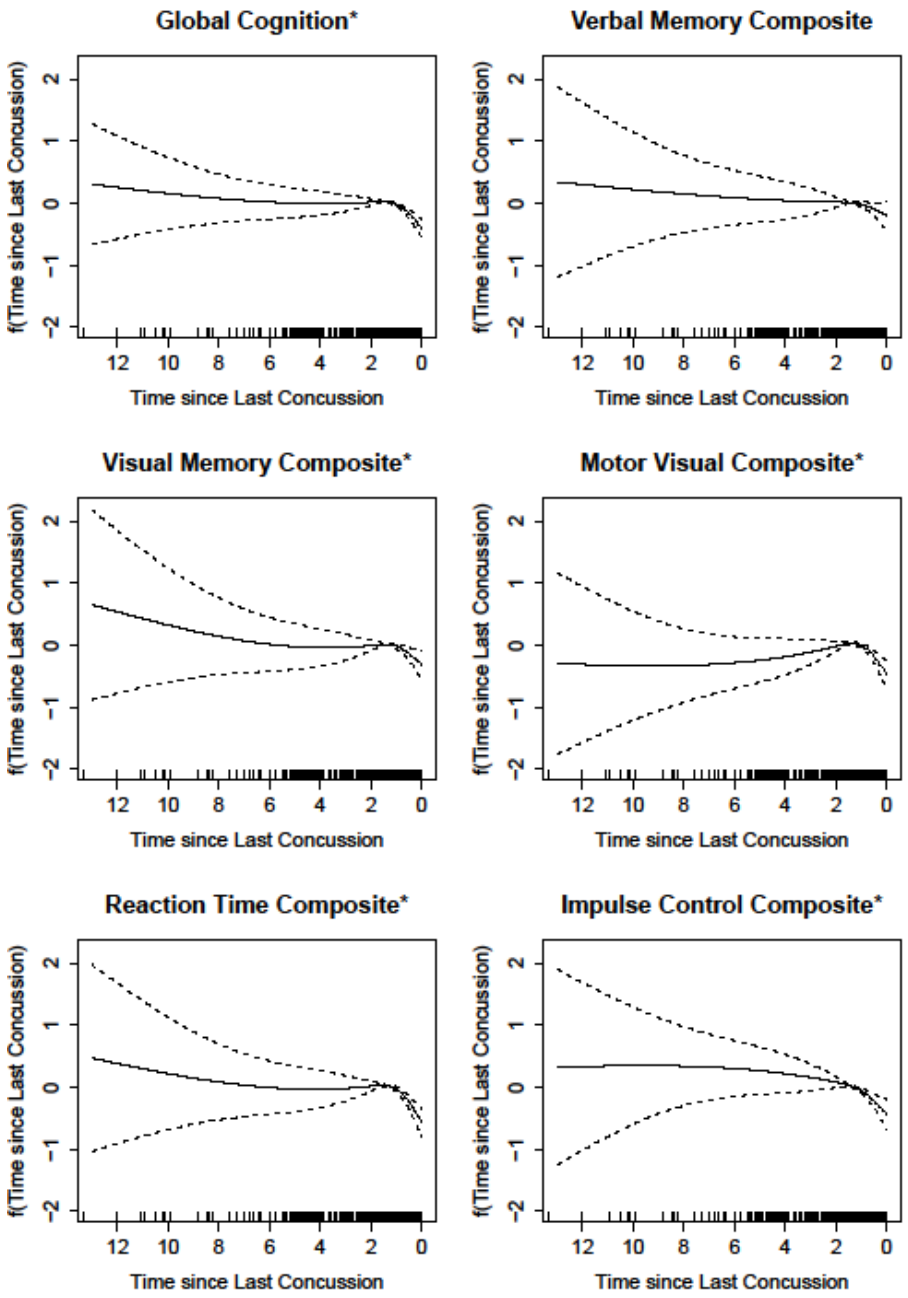
(95% CI= -0.088, -0.0007) decrease on the global cognitive test score. However, our analysis again suggested that there was heterogeneity across the tests. Evaluating each test separately, our individual linear models for each test indicated that for each additional concussion there was a significant reduction in the score for the verbal memory composite (standardized units =-0.087, 95% CI=-0.136, -0.038), the visual memory composite (standardized units =-0.087, 95% CI= -0.136, -0.038) and impulse control composite (standardized units =-0.636, 95% CI=-0.159, -0.059) (Table 2.3).

Table 2.3: Mean change in the cognitive test (standardized units) score per concussion

Test	Unadjusted (95% CI)	p-value	Adjusted* (95% CI)	p-value
Global Cognition	0.023 (-0.038, 0.090)	0.426	-0.044 (-0.088, -0.0007)	0.046
Verbal Memory	-0.071 (-0.119, -0.023)	0.004	-0.087 (-0.136, -0.038)	0.005
Visual Memory	-0.066 (-0.114, -0.018)	0.007	-0.085 (-0.134, -0.036)	0.007
Visual Motor	0.016 (-0.032, 0.064)	0.512	-0.026 (-0.073, 0.021)	0.284
Reaction Time	-0.006 (-0.054, 0.042)	0.780	-0.032 (-0.080, 0.017)	0.198
Impulse Control	-0.633 (-0.945, -0.322)	<0.0001	-0.636 (-0.953, -0.319)	<0.0001

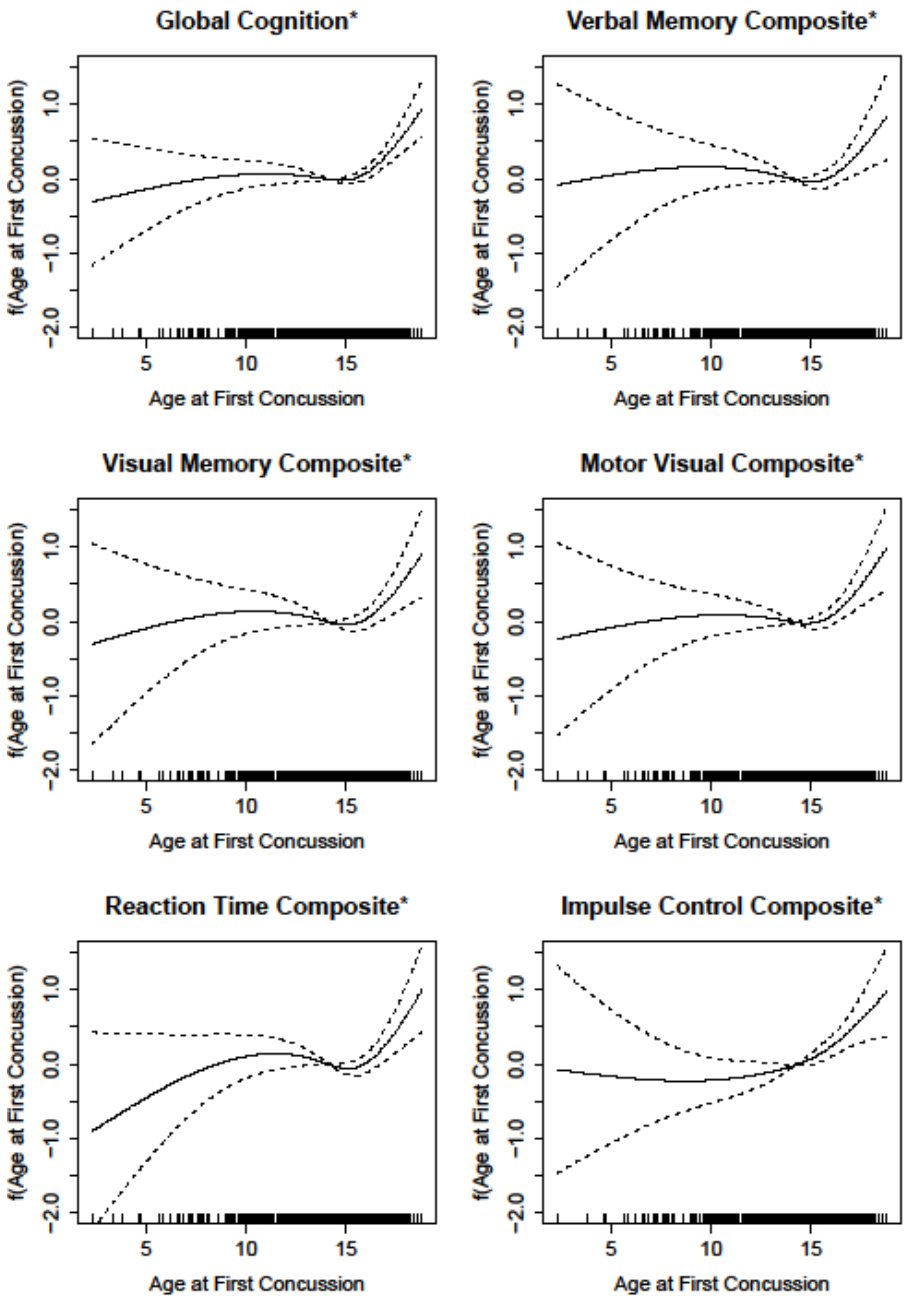
* Adjusting for BMI, gender, race, age, age^2, school district, sport category, first language, grade, handedness

When we considered the effect of time since last concussion, we found that the effect was not linear across all tests (<0.05) and there appeared to be an acute effect of concussions within about two years of cognitive testing with scores getting rapidly worse as the time between concussion and testing diminished (Figure 2.1). This transient effect appeared to be consistent across the five composite scores and global cognition. When we examined the effect of age at first concussion on the cognitive scores, we also found a significant non-linear effect across all tests (<0.05) and found that individuals who had a concussion earlier in life appeared to have lower scores than those who had a head injury later in adolescence (Figure 2.2). Individuals who had a head injury after age 15 seemed to fare better than individuals who had a head injury prior to age 15. This finding is consistent across for all composite scores, but the magnitude and shape of the effects differ slightly. This difference is especially apparent for the reaction time composite, where a concussion in early life had a particularly negative effect.



*p-value<0.05 for a non-linear effect

Figure 2.1: The impact of time (years) since last concussion from the test date on the z-score standardized baseline score for global cognitive function and each domain-specific test. The change in standardized units for each test score associated with each year of time since last concussion is indicated by the solid black line and 95% confidence intervals by the dotted lines.



*p-value<0.05 for a non-linear effect

Figure 2.2: The impact of age (year) at first injury on the z-score standardized baseline score for global cognitive function and each domain-specific test. The change in standardized units for

each test score associated with each year of age at first concussion is indicated by the solid black line and 95% confidence intervals by the dotted lines.

2.5 Discussion:

Our findings suggest that ever having a concussion is associated with a decrease in cognitive function across multiple domains. By taking into account the timing of the concussions using time since last concussion and age at first concussion, we found that while worse performance was associated with concussions closer in time to the cognitive testing, in our population, the reduced performance was also associated with concussions in earlier childhood. Most studies evaluating concussions on cognitive function have independently focused on recovery from short term effects[17,26,27] or on the duration of long term effects[28-33]. However, very few studies have attempted to consider both acute and chronic effects simultaneously and when they did, long term follow-up was limited[10,34]. Our study suggests that the acute effect of concussion on cognitive function, may have longer lasting effects than what prior studies have suggested. Previous studies that evaluated the duration of effects of concussion have focused on limited follow up periods, which might have resulted in their findings of shorter effect periods[35].

There has only been one study that has specifically focused on the association between age at which past concussions occurred and cognitive function in adolescents. That is study found no effect of age at first mTBI on cognitive function in a much smaller study population[36]. Our results suggest that cognitive domain specific effects depend on the stage of development at which the concussion occurred. In infancy and early childhood the brain is undergoing a rapid increase in gray matter which is associated with growth in basic cognitive functions including an increase in both attention and memory functioning [37]. As the brain continues to develop into puberty, maturation of the gray matter in the prefrontal cortex and increased volume of white

matter is associated with higher order cognitive and executive functioning[6,38]. These functions include the ability to assess risk and make goal oriented decisions. The findings from our models evaluating the effect of age at first concussion on the domain specific tests appear to demonstrate how concussions during specific developmental stages may have a greater impact on domain specific cognitive function.

In animal experiments, it was found that mTBIs in early life can inhibit brain plasticity. This was shown to reduce cognitive growth compared to uninjured rats[40]. Furthermore our findings are also supported by a recent study that found that early childhood exposure to concussions and sub-concussive impacts-- as measured by age at first exposure to playing football younger than 12 years-- are associated with long lasting effects on later-life cognition[41]. This may explain why there have been conflicting findings among studies evaluating chronic effects of concussion. When studies evaluate if ever having a concussion has an impact on cognitive function they are effectively averaging the effect across the distribution of age at first concussion and time since last concussion within their study population. The age at which the concussion occurs, however, is important and ignoring this could result in a masked true impact of concussions. Furthermore, conflicting findings in studies evaluating the impact of concussions on cognitive function in adolescents could also be driven by the fact that many studies presented unadjusted estimates of the effect for potential confounders of the relationship. Our study shows that the unadjusted effect estimates tended to underestimate the effect.

One limitation of our study is the use of self-reported concussions. We know that concussions tend to be underreported in athletic populations[42]. If such underreporting was similar regardless of cognitive function scores, then this should cause our results to be underestimated. To account for finding of worse cognition among those with a concussion, such underreporting

would have to be preferentially among those with better cognitive scores, which seems unlikely. Furthermore, since the effect of age at first concussion showed very consistent findings that seem to coincide with brain developmental stages, it is difficult to imagine a scenario where our study participants would recall earlier life exposures that ended up being associated with lower scores on some of the domain specific tests and with higher scores on other tests. A strength of our study is that we were able to evaluate the effect of concussion on cognitive function in a racially and ethnically diverse population, with both male and female athletes and across multiple sports which has been lacking in prior studies.

We conclude from our findings that concussions in early life and into adolescence can have an important impact on future cognitive development. Importantly, we find that more acute effects on cognitive function appear to last up to two years, rather than a shorter period of time as has generally been assumed. In addition, domain specific effects appear to depend on the stage of neuronal development an individual is in when their concussion occurs. While we cannot discount the numerous benefits of participating in sports during childhood and adolescence, these findings support a growing body of evidence suggesting that minimizing the exposure risk for concussions is important in youth sports.

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CHAPTER 3

Title: The impact of concussion history on cognitive change in an adolescent athlete population

Authors: Kathryn M. Taylor[1], Marianthi-Anna Kioumourtzoglou[1], Jim Clover[2], Brent A. Coull[1,3], Jack T. Dennerlein[1,4], David C. Bellinger[1,5,], Marc G. Weisskopf[1,6]

1) Department of Environmental Health, Harvard T.H. Chan School of Public Health, Boston , MA
2) The Sport Foundation, Riverside, CA
3) Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston , MA
4) Department of Physical Therapy, Movement, and Rehabilitation Sciences, Northeastern University, Boston, Massachusetts
5) Children's Hospital, Harvard Medical School, Boston, MA, USA
6) Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston , MA

3.1 Abstract:

Objective: To evaluate the effect of age at first concussion on the change in cognitive function over time.

Methods: Over 5 years, 796 student athletes evaluated in this analysis completed multiple neuropsychological tests from which 5 composite scores were created. Using questionnaires, we collected information on concussion history and other covariates. Mixed models were used to estimate the adjusted effects on the change in cognitive scores and their corresponding 95% confidence intervals (CI).

Results: We found that the change in cognitive score was higher for individuals who had concussions closer to their their first visit date. This appears to be capturing a phase of recovery following a concussion. But over time this increase in cognitive change appears to level out as time between the concussion and the test date increases. We also found that age at first concussion, does not appear to have an impact on cognitive change.

Conclusion: Change in cognitive function is affected by the timing of an individual's last concussion in conjunction with any subsequent test date.

3.2 Introduction:

Adolescence, frequently defined as the time period between 10 and 18 years of age, is characterized by rapid cognitive growth and an increase in cognitive flexibility. Evidence suggests that biomechanical injuries such as traumatic brain injuries (TBIs) during this developmental stage and during earlier life development can have an impact on future neurological development[1,2]. Disruptions caused by head injuries in these developmental trajectories can have potentially long lasting effects in social development, educational attainment and lifetime cognitive health[3-5]. Increased concern for the rise of traumatic brain injury incidence in childhood and adolescence has caused a growing awareness for the paucity of research being conducted on potential effects, with special interest focused on the adolescent population.

The majority of head injury related visits to the hospital are a result of mild traumatic brain injuries (mTBIs) or as they are commonly referred to, concussions[6]. Concussions can induce clinically heterogeneous outcomes, which includes both cognitive and behavioral specific impairments[7,8]. These effects can manifest as both acute and chronic effects making it difficult to evaluate the long term impact of head injuries on cognitive health especially in those who have had multiple concussions in their lifetime[9]. When evaluating cognitive function, concussions have been shown to have a negative impact on a range of domain-specific tests[10,11]. Nevertheless, a consensus on which domains are consistently affected and for how long has yet to be reached.

The growing awareness of the potential negative long term effects of mTBIs has led to an increase in research focused on these exposures. However, this research has primarily focused on adult populations, such as professional athletes or members of the military. While it was once though that children and adolescents were less impacted by long term neurological effects of

concussions, presumably because of increased brain plasticity, there is now a growing body of evidence that suggests the developing brain may be more sensitive than previously thought[2,12,13]. This is because concussions may have the potential to disrupt critical stages of neural development[14]. Furthermore, there is a lack of literature that assesses how cognitive growth might vary based on concussion history. We, thus, propose to evaluate the effect of past concussions on change in cognitive function over time in a large cohort of high school student athletes.

3.3 Methods:

Study Population

Between 2009 and 2014, 5487 high school student athletes from Riverside and San Bernardino county school districts were administered cognitive tests. The athlete's ages ranged from 12-19 years old. These tests were administered as part of standard practice for state required pre-season physicals. Of these athletes, 1065 individuals completed 2 or more tests with varying durations between each test. Individuals could have a repeated test score if they played multiple sports that required new cognitive scores prior to participation in each sport, they completed a two year follow-up test to define a new baseline for subsequent seasons, or they were injured in which case the test was used as an aid in diagnosis. In order to examine change over time, we only considered individuals with more than one visit for cognitive testing.

Individuals were excluded from analyses if they did not take the test in English (N=23), their concussion history was unknown (N=45), or the timing of their concussions was unknown (N=59). We also excluded individuals who had a concussion after their first test (N=187) so that we could evaluate change in cognition uninhibited by the effects of new concussions. The

remaining 796 athletes, 166 with a history of concussion and 630 without concussion were included in the analysis.

Exposure and Covariate Assessment

We collected each individual's concussion history using a questionnaire prior to their cognitive testing. We obtained information on the number of concussions prior to each test date. When a concussion was reported, the athlete was asked to provide the date for each past concussion. We used these responses to create a binary variable for ever having a concussion (yes/no), which was used in our analysis. We calculated the time between last concussion and their baseline test date and we used this variable as a continuous variable in our models. We also calculated the age at first concussion and used this as a continuous variable in our models.

Using the pre-test questionnaire, we obtained information on a wide range of potential covariates. For the analysis we considered the following covariates: gender (male/female), race/ethnicity (White, Hispanic, Black, and other), current school district (1-12, categorical), handedness (left/right), age at date of first visit (continuous), grade (7^{th}-12^{th}, continuous), BMI (continuous) and first language (English, non-English). We also created a categorical variable for sport type, which included four categories: football, other contact or collision sport, limited contact sport and non-contact sport. These categories were created using the classification of sports by the American Academy of Pediatrics[25].

Cognitive Testing

The cognitive tests were administered using a computer based test called the Immediate Post-concussion Assessment and Cognitive Test (ImPACT). This test is used as an assessment of cognitive function in athletes across the United States. It has been validated both within the test developing company and externally as a reliable and objective measure of cognitive function[15,16].

The assessment produces five composite scores including the verbal memory composite, the visual memory composite, the visual motor speed composite, the reaction time composite and the impulse control composite. We used these composite scores to provide a complete assessment of cognitive function.

The scores provided for the five composites were not all on the same scale, nor were they all in the same direction. To make the tests comparable, we inverted the test scores for the reaction time composite and the impulse control composite, so that for all tests a higher score indicated better performance. For each composite score, we then subtracted the score obtained at their baseline visit from each score produced at their subsequent visits to obtain the change in score from their first visit. Because we wanted to be able to compare change in test scores across all composite scores, we standardized all differences in score to our uninjured population, so that they would be on the same scale, by creating z-scores using the mean and the standard deviation of the change in scores in our uninjured population for each individual test. We used these standardized change scores as our continuous outcomes.

Statistical Analysis

We used mixed models to evaluate the effect of ever having a concussion. Our findings in Chapter 2 suggested that there was a recovery period for cognitive function following a concussion. In order to evaluate the long term effects of concussion on cognitive change, we need to account for this recovery period. We assessed the effect of ever having a concussion by creating four separate models using four different exposure groups: ever having a concussion within 6 months prior to the baseline visit, greater than 6 months prior to the baseline visit, within 18 months prior to the baseline visit and greater than 18 months prior to the baseline visit. To estimate a change in global cognition within the model we used each test's change in score as

a repeated measure of cognitive function. Because we used the results from 5 different scores to estimate the global cognitive score, we included a random intercept and slope for each test within the model. We did this because change scores for any given test would be more correlated then change scores across the different tests. We also included random intercepts in the model for each individual, to account for the within-person correlated observations across the five tests. To assess the potential heterogeneity of the effect of concussion across the five change scores, we compared our initial model to a model without a random slope for individual test using the Akaike's Information Criterion (AIC) to assess which model was a better fit.

We also used a similar model to evaluate the effect of time since last concussion from the baseline visit and age at first concussion. Both variable were treated as a continuous variable. We tested the potential non-linearity of these variable by applying a natural spline evaluating the effect using several degrees of freedom and selecting the best fitting model using the AIC. We ultimately settled on 3 degrees of freedom. We included an indicator variable for ever having a concussion and selected a constant value for time since last concussion for our non-concussed athletes, so that they remained in the analysis.

When we evaluated the effect of age at first concussion, we assessed the potential non-linearity of the effect by applying a spline to the term. After applying the spline to the term, we assessed the effect using 1 (ie linear association), 2 and 3 degrees of freedom, using the AIC to assess the fit. Ultimately a linear term for age at first head injury produced the best fit.

All models controlled for gender, race/ethnicity (white, hispanic/latino, black, and other), current school district (1-12), handedness (left, right), age at date of first visit, age at date of first visit squared, BMI at first visit (calculated using weight and height), first language (English, non-English), grade at first visit (6-12), visit number, time since first visit and number of

concussions. We also adjusted for sport category, including three categories: football, other contact or collision sport and limited and non-contact sports. These sports categories were produced using a combination of the categories created by the American Academy of Pediatrics[17]. Within our time since last head injury analysis, we also controlled for age at first concussion and number of concussions. We used a single round of imputation to estimate values for when there was missing values for variables in our models. We did this using height, weight, handedness, grade, district, age at date of visit, gender, sport, race, BMI and first language as our predictors. Analyses were conducted using SAS software (version 9.3; SAS Institute, Inc. Cary, NC) and R statistical software (version 3.1.1; R Development Core Team; 2014) for models that utilized splines.

3.4 Results

Our study population was predominantly Hispanic and male. Female athletes made up approximately a quarter of our athletes (23.1%). Most individuals played either football or another contact sport (77.5%). Football players had a higher number of concussions compared to other sports categories, making up the majority of concussed population (71.1%). Those who had a history of head injury on average were followed for fewer months (5.4±6.6 months) compared to those who did not have a history of concussion (14.9±6.5 months) (Table 1).

We detected no suggestion of heterogeneity in the effect estimates across tests. Therefore, the model evaluating the effect of time since last concussion suggested that the change in global score was sufficient to explain the effect of past concussions on cognitive change. This indicates that the effect of time since last concussion may be similar across tests. When we evaluated the effect for having a concussion within 6 months of the baseline test there was a statistically

significant higher change in the global score compared to the non-concussed (standardized units= 0.55 95% CI= 0.36, 0.76) which seems to demonstrate the acute cognitive recovery that is known to happen after a concussion. In individuals who had a concussion more than 6 months prior to the base line tests the effect estimate for score the change approaches zero (Table 3.2). When we

Table 1: Characteristics of study population by concussion status at baseline

Characteristics	**Total Population** (N=896)	**No History of Concussion** (N=630)	**History of Concussion** (N=166)
Age (years) of first concussion (mean± SD)	15.0±2.1	NA	15.0±2.1
Time (months) of followup (mean± SD)	12.1±7.0	15.0±6.5	5.3±6.8
Age (years) at first visit (mean± SD)	16.3±1.0	16.4±0.9	16.2±1.3
BMI at first visit (mean± SD)	24.3±4.8	24.2±4.6	25.0±5.3
Gender (%)			
Female	207 (23.1)	181 (28.7)	26 (15.7)
Male	589 (76.9)	449 (71.3)	140 (84.3)
Race/ Ethinicity (%)			
Hispanic	332 (37.1)	296 (47.0)	36 (21.7)
White	142 (15.8)	108 (17.1)	34 (20.5)
Mixed	140 (15.6)	124 (19.7)	16 (9.6)
Black	86 (9.6)	74 (11.7)	12 (7.2)
Other	25 (2.8)	22 (3.5)	3 (1.8)
Missing	71 (7.9)	6 (1.0)	65 (39.2)
Sport Class (%)			
Football	366 (40.8)	248 (39.4)	118 (71.1)
Contact or Collision Sport	329 (36.7)	291 (46.2)	38 (22.9)
Limited or Non-Contact Sport	99 (11.0)	89 (14.1)	10 (6.0)
Missing	2 (0.2)	1 (0.2)	1 (0.6)

NA, not applicable.

further stratified the population, evaluating the effect of ever having a concussion amongst those who had a concussion within 18 months of the test date, there still remains a statistically significant increase in cognitive change associated with every having a concussion in this time

window compared to never having a concussion (standardized units= 0.61 95% CI= 0.21, 0.89). In individuals who had a concussion more than 18 months prior to the baseline test, the effect estimates moved closer to zero and in some cases became negative (Table 3.3). Although none of the long term effects of concussion (concussions greater than 6 months and greater than 18 months prior to baseline) were significant. This is likely due to a large decrease in the number of concussed individuals used in the analysis. The plot for the effect estimate of time since last concussion on the change in global score suggests that the recovery period last as long as three years after a concussion (Figure 3.1). The change in score tends to decrease as the date at last concussion moves farther away from their visit date for every test.

Table 3.2: Mean change cognitive test standardized units comparing ever having a concussion to never having a concussion broken down by individuals who had head injuries within 6 months of their first test and individuals who had a concussion more than 6 months prior to their first test.

	Concussed ≤ 6 months of first test (95% CI)		Concussed > 6 months of first test (95% CI)	
	Exposed	**Unexposed**	**Exposed**	**Unexposed**
Test	N=101	N=630	N=61	N=630
Global Cognition	0.55 (0.36, 0.73)		0.097 (-0.05, 0.24)	
Verbal Memory	0.26 (0.02, 0.51)		0.004 (-0.28, 0.29)	
Visual Memory	0.56 (0.24, 0.88)		0.074 (-0.21, 0.36)	
Visual Motor	0.54 (0.21, 0.87)		0.014 (-0.26, 0.29)	
Reaction Time	0.64 (0.30, 0.99)		0.146 (-0.19, 0.45)	
Impulse Control	0.61 (0.27, 0.95)		0.070 (-0.21, 0.35)	

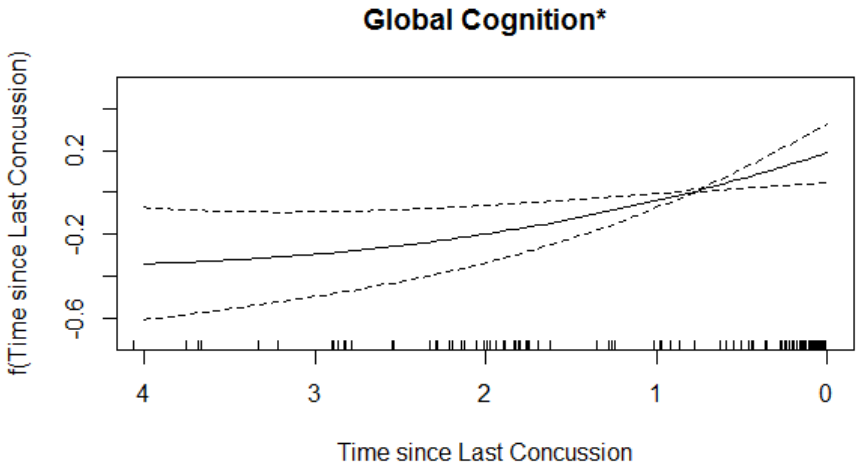
* Adjusting for BMI, gender, race, age at baseline, school district, sport category, first language, grade at baseline, handedness, time since first visit

Table 3.3: Mean change cognitive test standardized units comparing ever having a concussion to never having a concussion broken down by individuals who had head injuries within 18 months of their first test and individuals who had a concussion more than 18 months prior to their first test.

	Concussed ≤ 18 months of first test (95% CI)		Concussed > 18 months of first test (95% CI)	
	Exposed	**Unexposed**	**Exposed**	**Unexposed**
Test	N=113	N=630	N=49	N=630
Global Cognition	0.61 (0.21, 0.89)		-0.02 (-0.18, 0.14)	
Verbal Memory	0.25 (0.01, 0.50)		-0.08 (-0.40, 0.23)	
Visual Memory	0.58 (0.01, 0.50)		-0.08 (-0.39, 0.28)	
Visual Motor	0.58 (0.27, 0.88)		0.01 (-0.33, 0.31)	
Reaction Time	0.66 (0.33, 0.99)		0.001 (-0.33, 0.33)	
Impulse Control	0.57 (0.25, 0.88)		-0.004 (-0.31, 0.30)	

* Adjusting for BMI, gender, race, age at baseline, school district, sport category, first language, grade at baseline, handedness, time since first visit

Similar to our model using time since last concussion, the best fit model using age at first concussion as the exposure, indicated that there was not heterogeneity in effects across tests. Therefore the model evaluating the effect of age at first head injury on the change in global score was sufficient to explain the effect of concussion on cognitive change. Our models using age at first concussion among the entire population suggested that there was no significant effect of age at first head injury on the change in global score.



* p-value<0.05

Figure 3.1: The impact of time (years) since last concussion in years on the z-score standardized change in score for global cognitive function. The change in standardized units for each test score associated with each year of age at first concussion is indicated by the solid black line and 95% confidence intervals by the dotted lines.

3.5 Discussion

Our study demonstrates that the timing of concussions with respect to the test date is an important consideration for future research in this field. Including individuals with concussions very close to their visit, especially if there is a very short duration of time between follow-up visits, may inflate the change in cognitive function scores among the concussed. In fact, it could even make it appear as though concussions can have a positive effect on cognitive growth compared to those who have never have a concussion which is clearly demonstrated in tables 3.2 and 3.3. By excluding those individuals with concussions within 6 months and 18 months of the test date, we can see that this increase in cognitive change during the recovery period appears to diminish the farther back in time the concussion occurred.

We did not see an effect of age at first head injury on change in cognition. This in conjunction with our previous findings demonstrating that age at first head injury may have an impact on cognitive scores (Chapter 2), suggests that while cognitive change may be similar based on age at first head injury, individuals with concussion in early life may be operating at a deficit caused by their concussion, which does not completely recover. Even though there is a recovery phase, suggested in this paper, that recovery may not be sufficient to overcome the cognitive decline initially seen with concussed patients.

There are limited studies evaluating the effect of concussion on cognitive function that had access to repeat measures. Those who had multiple measures of cognitive function tended to use them to evaluate short term recovery from concussions. Their findings support our time from concussion to baseline analysis that showed a higher level of change in those who had concussion closest to the test date[18-20]. There are few studies that have evaluated how the age at first concussion may effect cognitive change. In one study, the effect of age at concussion in was evaluated in adults using one test score so they did not evaluate change in cognitive function[22]. Another study did evaluate the effect of age at concussion in children and adolescents, in a much smaller study population. They did not see a difference by age of mTBI on cognitive function, which supports our findings[21].

Concussions are associated with increased axonal injury, activation of microglial cells, both hypo- and hyper perfusion of blood to the brain and acute metabolic depression[7,23]. These effects have been shown to have an impact on both cognitive and executive functions, most notably in the acute effect phase of the concussion. It is still being explored how mechanical injury associated with neurologic interruption may have an impact on subsequent cognitive development. In animal models, early life brain injuries have been associated with negative

effects on experience dependent brain plasticity, which manifest as impaired neuropsychological outcomes in later life[1,24].

A weakness in our study is use of self-reported head injuries. Past studies have showed that there is underreporting of head injuries in athletic populations[25]. This would mean that there is the potential that some people who are in the non-concussed group may have had a prior concussion. This may cause our effect to be underestimated because our concussed and non-concussed groups would be more alike. It also could mean that it could mask an effect if one exists. A strength of our study is that we were able to use repeat visits to evaluate change in cognition over a prolonged period of time, which has not been done in past studies. Another strength of our study, we also were able to evaluate out association in a diverse population, with both genders across a wide range of sports with access to a wide range of potential confounders.

In this study we provide a detailed evaluation of the impact of time and age on cognitive change using a neuropsychological measurement. More studies are beginning to point to early childhood as a particularly vulnerable time period that is sensitive to the effects of head injuries. Our assessment shows that concussions in earlier life may have a negative effect on cognitive function that is present years later but they may not impact cognitive growth. While participation in sports in early childhood has its merits, these findings suggest that there should be limitations placed on the exposures that are known to increase the risk of concussions.

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CHAPTER 4

Title: Head injury at early ages is associated with risk of Parkinson's disease

Authors: Kathryn M. Taylor, SM[1], Marie-Helene Saint-Hilaire, MD[2], Lewis Sudarsky, MD[3], David K. Simon, MD[4], Bonnie Hersh, MD[5], David Sparrow, DSc[6,7], Howard Hu MD, ScD[8], Marc G. Weisskopf, PhD, ScD[1,9]

1) Department of Environmental Health, Harvard T.H. Chan School of Public Health, Boston, MA
2) Department of Neurology, Boston University Medical Center, Boston, MA
3) Department of Neurology, Brigham and Women's Hospital, Boston, MA
4) Department of Neurology, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA
5) Harvard Vanguard Medical Associates, Boston, MA
6) VA Boston Healthcare System, Jamaica Plain, Boston, MA
7) Boston University Schools of Public Health and Medicine, Boston, MA
8) Departments of Epidemiology, Global Health, and Environmental Health, Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada
9) Department of Epidemiology, Harvard School of Public Health, Boston, MA

4.1 Abstract

Objective: To test the hypothesis that the age at which a head injury occurs is associated with Parkinson's Disease (PD) risk.

Methods: We conducted a case-control study of 380 neurologist confirmed PD patients and 230 controls from the greater Boston, Massachusetts area with questionnaire data on history of head injury and other covariates. We used multivariable logistic regression to estimate adjusted odds ratios (OR) and their corresponding 95% confidence intervals (CI) for PD.

Results: Overall we found an increased risk of PD associated with having a head injury that resulted in a loss of consciousness more than 10 years before the questionnaire date, but it did not reach statistical significance (OR= 1.49; 95% CI= 0.83-2.66). We found a significant (p=0.03) effect of age at first head injury with injuries at earlier ages associated with greater risk of PD. For every 5 year earlier age at first head injury with loss of consciousness the OR for PD was 1.27 (95% CI: 1.03-1.58).

Conclusion: Our results suggest that head injury specifically in early life increases the risk of PD.

4.2 Introduction:

Parkinson's disease [PD] is a progressive neurodegenerative disease with an insidious onset.[1] It is the second most prevalent neurological disease and as much as 95% of cases are considered sporadic or without a genetic cause.[2] It has been suggested that brain inflammation may be a risk factor for PD.[3-5] In animal experiments, head trauma resulted in chronic brain inflammation through disturbance of the blood brain barrier and evolving white matter damage.[4, 6, 7] These findings have spurred a great interest in the impact that head injuries may have on the risk of PD.

Several studies have demonstrated an association between head injury and PD.[8-13] However, there is concern that these findings could be attributed to reverse causation or instability caused by prodromal PD resulting in a higher risk of head injuries. The few studies that have evaluated the timing of head injury have found that having a head injury closer to PD diagnosis was strongly associated with PD. This association decreased as the time between the head injury and PD diagnosis increased.[11, 14, 15] These findings suggest that reverse causation is a concern and needs to be considered in any analysis.

No studies have considered whether the age at which head injuries occur is related to PD risk. Animal experiments have found that early life brain inflammation caused by environmental exposures can result in persistent changes in the nigrostriatal pathway, accumulation of proinflammatory factors in the brain, and increased neurologic susceptibility to other environmental exposures.[3, 4, 7, 16] We examined the question of age at head injury and risk of PD in a case-control study based in Boston, Massachusetts.

4.3 Methods:

Subject recruitment:

Between 2003 and 2007, patients with PD were recruited from four movement disorder clinics in the Boston, Massachusetts area. Cases were evaluated twice by a neurologist with at least 6 months between each evaluation. Case status was confirmed using U.K. Brainbank criteria.[17] Individuals deemed eligible were enrolled and completed questionnaires that included questions about past head injuries. Controls were recruited from family, friends and in-laws of the cases, community targeted advertisements, and through recruitment of participants in the Harvard Cooperative Program on Aging study (HCPOA). HCPOA is a registry of elderly volunteers who have agreed to participate in studies. A total of 380 cases and 230 controls answered questions on head injury including the timing of those injuries.

This study was reviewed and approved by the Human Research Committees at the Harvard T.H. Chan School of Public Health, the BWH, and the VA Boston Healthcare System. All participants gave written informed consent prior to participating in the study.

Exposure and Covariate Assessment:

Head injury status was assessed via questionnaire. Both cases and controls were asked to respond to the following questions: “Have you ever lost consciousness as a result of a head injury?,” and “At what age was your first head injury that resulted in loss of consciousness.” Unless otherwise specified, we use the term head injury to refer to head injury with loss of consciousness. Those reporting a head injury were also asked about the total number of head injuries. From these responses we created a dichotomous variable for head injury. Our base analyses excluded any head injuries within the 10 years prior to the questionnaire date to attempt to avoid reverse causation. In sensitivity analyses we also conducted additional analyses after

excluding head injuries in the 15 and 20 years prior to the questionnaire date to reduce the chance of reverse causation even further. Additional data included in these analyses and obtained via questionnaire, were age, gender, race, education, and smoking status.

Statistical Analysis:

Odds ratios (OR) and their corresponding 95% confidence intervals (CI) were estimated using multivariable logistic regression. Total number of head injuries was analyzed both as a continuous variable and as a categorical variable (0, 1, >1). Age at first head injury was analyzed as a categorical variable (no head injury and tertiles of age at first head injury based on the distribution among the controls). The significance of the trend over age at first injury was assessed in models treating age at first injury as a continuous variable that included an indicator for ever having a head injury, with all those who never had a head injury assigned a constant for age, in order to keep all subjects in the analysis. To test the potential non-linearity of associations with these continuous variables, we used natural splines and selected the best model fit using the Akaike information criterion (AIC). For both age at first head injury and the total number of head injuries, better fit was obtained with linear models. Thus, only the linear results are reported.

Models were adjusted for age at the date of visit (years), its square, sex, race (white, non-white), highest level of education (high school or less, attended college, graduated college, post-graduate school), and smoking status (ever, never). In addition, we adjusted for ever having a head injury without loss of consciousness, which was available for 241 cases and 219 controls because this question was only added to the questionnaire later, so that the reference group was those who never had any head injury with or without loss of consciousness. In a sensitivity analysis for our model evaluating the effect of age at first head injury, we also controlled for

number of head injuries. We used missing indicator variables when covariate data was missing. Analyses were conducted using SAS (version 9.3; SAS, Inc. Cary, NC)[18] and R statistical software (version 3.1.1; R Development Core Team; 2013)[19] for models that utilized splines.

4.4 Results:

Patients with PD were more likely to be male, white, have a higher level of education, and less likely to have ever smoked compared with the controls (Table 4.1). On average the cases were diagnosed with Parkinson's disease 9.4 years (sd=6.8 years) prior to answering the questionnaire. There were 69 cases and 24 controls who ever had a head injury. The median age at first head injury was 15 (Interquartile range= 10-18) among the cases and 18.5 (Interquartile range= 12-44.5) among the controls (Table 4.2).

Table 4.1: Characteristics of study population by case status.

Characteristics	**Controls (N=230)**	**Cases (N=380)**
Years since diagnosis (mean ± SD)	NA	9.4±6.8
Age (years) at data of visit (mean± SD)	68.6±10.7	66.8±9.5
Gender		
Male (%)	79 (34.4)	242 (63.7)
Female (%)	151 (65.6)	138 (36.3)
Race		
White (%)	188 (81.7)	363 (95.5)
Non-White (%)	42 (18.3)	15 (4.0)
Missing	0 (0)	2 (0.5)
Education		
High School or Less (%)	35 (15.2)	56 (14.7)
Attended College (%)	53 (23.0)	58 (15.3)
Graduated College (%)	67 (29.1)	113 (29.7)
Attended Grad School (%)	73 (31.7)	149 (39.2)
Missing (%)	2 (0.9)	4 (1.1)
Smoking Status		
Never (%)	102 (44.4)	181 (47.6)
Ever (%)	111 (48.3)	158 (41.6)
Missing (%)	17 (7.4)	41 (10.8)

NA, not applicable.

Table 4.2: Characteristics of study population by head injury status

Characteristics	Never (N=517)		Ever (N=93)	
	Cases (N=311)	**Controls** (N=206)	**Cases** (N=69)	**Controls** (N=24)
Age at first head injury (years) (median)	NA	NA	15	18.5
Interquartile range of age (years) at first head injury	NA	NA	10-18	12-44.5
Number of head injuries (median)	NA	NA	1	1
Interquartile range of number of head injuries	NA	NA	1-3	1-1.5
Gender				
Male (%)	191 (61.4)	64 (31.1)	51 (73.9)	15 (62.5)
Female (%)	120 (38.6)	142 (68.9)	18 (26.1)	9 (37.5)
Race				
White (%)	296 (95.2)	166 (80.6)	67 (97.1)	22 (91.7)
Non-White (%)	13 (4.2)	40 (19.4)	2 (2.9)	2 (8.3)
Missing (%)	2 (0.6)	0 (0)	0 (0)	0 (0)
Education				
High School or Less (%)	50 (16.1)	32 (15.5)	6 (8.7)	3 (12.5)
Attended College (%)	44 (14.2)	50 (24.3)	14 (20.3)	3 (12.5)
Graduated College (%)	94 (30.2)	58 (28.2)	19 (27.5)	9 (37.5)
Attended Grad School (%)	119 (38.3)	64 (31.1)	30 (43.5)	9 (37.5)
Missing (%)	4 (1.3)	2 (1.0)	0 (0)	0 (0)
Smoking Status				
Never (%)	151 (48.6)	93 (45.2)	30 (43.5)	9 (37.5)
Ever (%)	127 (40.8)	100 (48.5)	31 (44.9)	11 (45.8)
Missing (%)	33 (10.6)	13 (6.3)	8 (11.6)	4 (16.7)

NA, not applicable

The odds ratio (OR) for PD among those with a head injury was elevated, but not significant (Table 4.3). When head injuries in the 15 or 20 years before the questionnaire date were excluded to more stringently avoid reverse causation, the OR for PD did not diminish, although none of the OR quite reached statistical significance (Table 4.3). When number of head injuries were considered, the OR for PD was 1.34 (95% CI= 0.69-2.58) for those with one head injury and 1.72 (95% CI= 0.57-5.19) for those with more than one. When treating head injuries as a continuous variable, the OR per injury was 1.21 (95% CI= 0.83-1.78). The OR for PD

increased with earlier age of injury and this association was significant in our base model (p=0.027), and in models that excluded injuries in the 15 years (p=0.047) or 20 years (p=0.016) before the questionnaire. In our base model the OR per 5 years younger age at first head injury was 1.27 (95% CI: 1.03-1.58). In the same model, when controlling for total number of head injuries, the OR increased slightly and remained significant (OR=1.34; 95% CI=1.07-1.67). The OR by categories of age at first head injury compared with those who never had a head injury (with or without loss of consciousness) from our base model are shown in figure 4.1.

Table 4.3: Adjusted* OR for PD by history of head injury with loss of consciousness, excluding injuries in different time periods before the questionnaire date.

Exposure window	Cases	Controls	OR (95% CI)	p-value
Excluding injuries within 10 years of the questionnaire				
Never having a head injury	316	209	1.00 (Ref)	
Ever having a head injury with a loss of consciousness	64	21	1.49 (0.83- 2.66)	0.18
Excluding injuries within 15 years of the questionnaire				
Never having a head injury	316	210	1.00 (Ref)	
Ever having a head injury with a loss of consciousness	64	20	1.54 (0.86-2.79)	0.15
Excluding injuries within 20 years of the questionnaire				
Never having a head injury	318	211	1.00 (Ref)	
Ever having a head injury with a loss of consciousness	62	19	1.52(0.83-2.79)	0.17

* Adjusted for ever having a head injury without loss of consciousness, gender, age, age squared, race, education, smoking status.

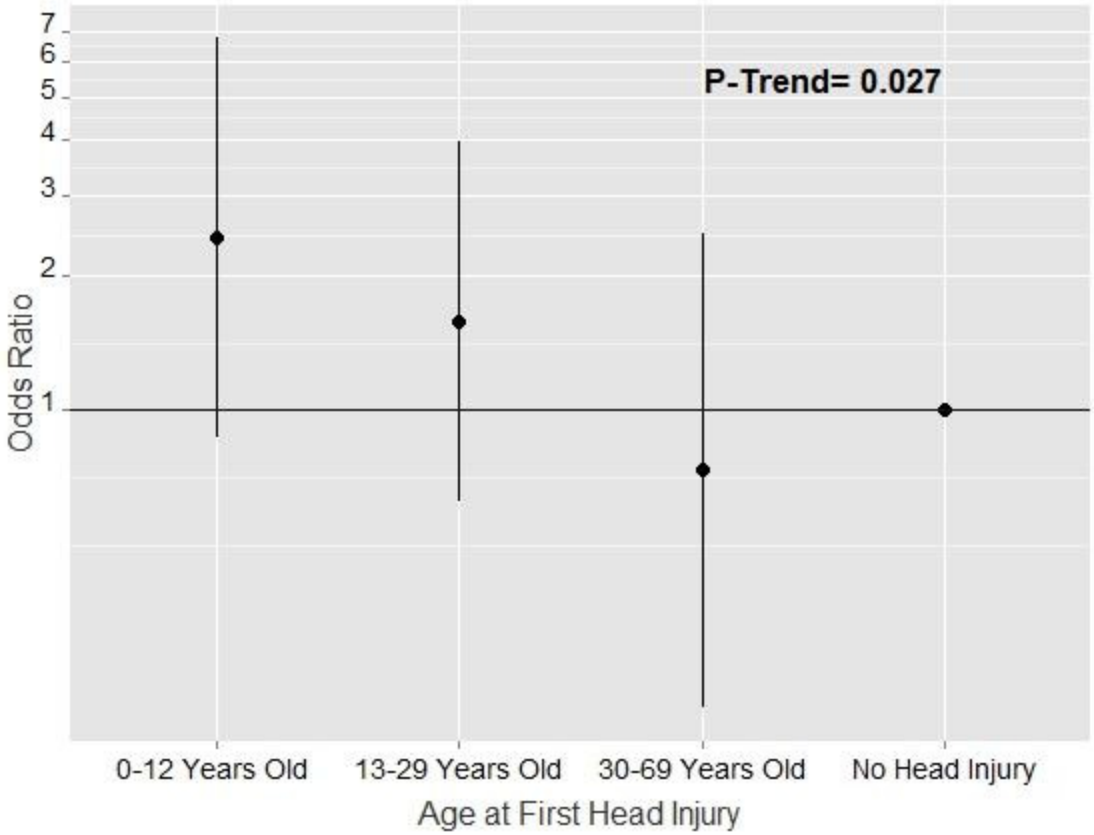

Figure 4.1: Association between head injury with loss of consciousness and Parkinson's disease by the age at which the first head injury occurred when excluding injuries occurring up to 10 years prior to the questionnaire date. The reference group is those with no head injury at all. Odds ratios are indicated by black squares and the 95% confidence intervals by the vertical lines.

4.5 Discussion:

Our study found an association between earlier age at first head injury and Parkinson's disease. The timing of head injuries relative to risk of PD has been looked at before with regard to possible reverse causation—that is that head injuries in a period prior to PD diagnosis may be the result of underlying prodromal PD rather than a cause of PD. However, to our knowledge,

the role of age at head injury has not been explored. The increasing trend in odds of PD with earlier age at first head injury cannot be explained by reverse causation since that would make head injuries at older ages—those closer to the PD diagnosis date—appear more strongly associated with PD. While the greater association with earlier age at first head injury could be related to more head injuries overall among those with an earlier age at first head injury, controlling for number of head injuries did not diminish the association seen with head injuries in early life.

The prior literature on head injury and PD is mixed. Several studies have reported relationships between head injury and PD.[10, 11] More recent studies, however, have suggested that the association between head injuries and PD is driven by head injuries in the years just before diagnosis.[11, 14, 15] While this reverse causation does appear to occur, our findings may help explain some of the discrepancy between studies. The large registry studies that demonstrated reverse causation had objectively identified occurrences of head injury, but they did not explore head injuries in early life—possibly because the data did not go back far enough. Elevated risk seen with self-report of head injury in prior studies may have been found because this exposure assessment also captured earlier life head injuries.

There are several proposed mechanisms that have been hypothesized as to how head injury could contribute to PD risk. Evidence suggests that head injuries can result in long-term microglial activation.[7, 20] When these cells are over-activated or go unregulated there can be low level chronic neurodegeneration and it is this self-perpetuating cycle which can be initiated by head injuries that has been linked to PD.[4,21] Brain inflammation as a result of head injury has been shown to produce PD-relevant pathology in animal experiments.[4, 6] Furthermore, these studies have indicated that early life is an important time window to consider when evaluating

the neurotoxicity resulting from inflammation. Early life, even in utero, exposure to lipopolysaccharide and several pesticides in animal studies have all been associated with progressive degeneration of dopaminergic neurons,[22-24] with the suggestion that the effects are caused, at least in part, by the induced inflammation.

A limitation of our study was the collection of head injury data through self-report, which raises the possibility of recall bias. However, while preferential head injury reporting by cases is possible, it is difficult to theorize why participants would specifically over report head injuries in early life, and in a way that produces a significant linear dose-response with age at first injury. Furthermore, in at least one study,[9] perfect agreement was found between self-reported head injury and medical record verification in a validation subset. An additional limitation was the recruitment of many spouse, relative, and friend controls, which skewed our controls to be more often female since the cases tended to be male. Although the gender difference can be accounted for by adjustment, spouse, relative, and friend controls are not always ideal because they tend to be more similar to the cases than the general population. This is a benefit with regard to covariates because it reduces confounding, but it can also make the main exposures of interest more similar between cases and controls. However, this would bias results towards the null, which could in part be why the association with head injury overall did not reach statistical significance, but it would not account for the significant trend we found between age at first injury and PD.

In conclusion, our findings suggest that the age at which a head injury occurs is relevant for subsequent risk of PD. This new finding could explain some of the discrepancy between prior studies of head injury and risk of PD, and suggest that the younger brain may be particularly vulnerable to traumatic insult. These findings are of particular concern, given that on average

over half a million children between the ages of 0-14 are hospitalized for traumatic brain injuries each year.[25]

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CHAPTER 5

5.1 Conclusion

The high prevalence of head injuries in the United States population and the fact that the number of reported head injuries has risen steadily over the past decade has increased media attention and public awareness of potential negative effects of these injuries. There has been a large influx of research on traumatic brain injuries in the last few years. Unfortunately as a result of this increase in publications in this relatively new field of research, there have also been conflicting findings with a lack of consensus on the ill effects of traumatic brain injury. These conflicting findings seem to be driven by small sample sizes with short-term follow-up which may not be sufficient to truly evaluate the long-term effects of head injury on any outcome.

The research presented in this dissertation suggests that having a head injury in earlier life has a greater impact on cognitive function and PD development than having a head injury in later life. This should not be surprising given the significant neurologic transformations occurring within the brain in early life. During childhood and adolescence, the brain undergoes both anatomical and functional changes that impact how the brain functions throughout the rest of life. My findings suggest that traumatic brain injuries during this important window of development can disrupt this process and have long-lasting impacts.

Of particular concern for head injuries is how the timing of these injuries may affect the outcomes measured. A component of my dissertation evaluates how the timing of concussions may impact cognitive function (Chapter 2). It appears as though there are competing effects between the timing of the last head injury and how close it is the test date and the effect of age at first head injury. This study shows how the timing of the test, in conjunction with past concussions, can impact the test scores that may not be related to long-lasting effects. These time effects need to be considered when evaluating the effect of ever having a concussion on long term impacts on cognitive function. The age at first concussion analysis demonstrates that results on each of the domain specific tests are related to the stage of an individual's development when they have a head injury.

The next step was to assess how timing of concussions may impact the change in cognitive score (Chapter 3). The findings showed that there was a rapid increase in test score following a concussion which was actually a recovery from the initial rapid decrease in cognitive function associated with acute concussion effects. This is particularly relevant the closer a concussion was to an individual's first visit. This change seems to represent acute recovery from the concussion. Not accounting for this rapid increase in score could make it appear as if having a concussion has a positive effect on cognitive growth or it could mask the effect of concussions if one exists. The age at first concussion analysis demonstrated that there was not heterogeneity across the different domain specific tests and that while a head injury in earlier in life was worse for cognitive function overall, it did not really have an impact on cognitive change.

When considering a later life outcome such as Parkinson's disease, timing of the head injuries was also important. Because Parkinson's disease has a slow progression which often results in delayed diagnosis, sometimes years after the onset of symptoms, there is the potential

for reverse causation where the instability caused by the prodromal disease increases the risk of head injury. If these injuries are not accounted for, analysis any observed association could be related to the head injuries following the disease that cannot affect disease onset. When we accounted for potential reverse causation, there was still an effect of age at first head injury on Parkinson's disease. Specifically, there was a linear effect where age at first injury was inversely associated with an increase in the likelihood of developing of Parkinson's disease.

The growing incidence of head injuries combined with the adverse associated neurological and cognitive health outcomes, mandates more focus be placed on mitigating exposures that increase risk of head injuries. Future research on the effects of head injuries should further elucidate the time and age of concussion effects presented in this dissertation. Particular focus should also be paid to evaluate potential effect modifiers of these effects so that better policies and interventions may be designed.