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Validating and testing the versatility of the cumulative head impact index

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VALIDATING AND TESTING THE VERSATILITY OF
THE CUMULATIVE HEAD IMPACT INDEX

by

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I would like to dedicate this work to the participants of the LEGEND Study, who give so much of themselves for the advancement of our understanding of chronic traumatic encephalopathy and other neurodegenerative disease. Their dedication to this research is extraordinary, and a constant source of inspiration to me.
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I would like to thank the exceptional staff of the Boston University Alzheimer’s Disease and Chronic Traumatic Encephalopathy Center for supporting this thesis in enumerable ways. In particular, I would like to thank Dr. Robert Stern for his passionate mentorship over the last year and a half, and the LEGEND Study interns for their relentless work collecting the data that makes this research possible. Thank you Chena Farhat, James Burgess, Sarah Gould, and Sam Neveu. I would also like to thank my husband, Aaron Edwards. Without your support I could not have completed this body of work.
VALIDATING AND TESTING THE VERSATILITY OF
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JOHN PARKER HAYDEN

ABSTRACT

In the study of diseases such as chronic traumatic encephalopathy (CTE), the ability to gather retrospective estimates of an individual’s total repetitive head impacts (RHI) is paramount. Although the exact mechanism responsible for the development of CTE is still unknown, it is well accepted that RHI play a critical role. Until recently, however, the methodology used to collect retrospective estimates of RHI have been very limited. In the beginning of 2016, Montenigro et al. from the Boston University’s Alzheimer’s Disease and CTE Center published a new method of RHI estimation called the Cumulative Head Impact Index (CHII). The CHII was developed by collecting self-reported football histories (years of play, positions of play and levels of play), and using that data to extrapolate the findings of short-term helmet-accelerometer studies into career-long estimates of cumulative head impacts. In addition to publishing this new method, Montenigro et al. (2016) also determined that the CHII was very successful at predicting later-life neurobehavioral and cognitive impairment, an essential ability of any RHI estimate intended to be used in CTE research. Participants in the Montenigro et al. (2016) analysis were part of an ongoing longitudinal study where individuals take yearly surveys of their neurobehavioral and cognitive well-being in addition to answering surveys about sports participation, head injuries and overall wellbeing. Participants had played football at the high school or college level, but had not played any other contact
sports. This thesis serves as an initial validation of that publication, and also tests the ability of the CHII to predict later-life impairment in a more diverse population of athletes.

Participants in this thesis were selected from the same ongoing longitudinal study according to two distinct sets of inclusion and exclusion criteria. For the purposes of conducting a validation study, the first set of criteria were identical to those used by Montenigro et al. (2016). The second experimental set allowed for participants who had participated in a secondary contact sport if it was at the high school level or below. These two sets of criteria resulted in 70 “validation” participants, and 82 “experimental” participants. Using the same methods as Montenigro et al. 2016, we calculated the CHII for all participants, and examined the ability of the CHII to predict later-life impairment. Our findings validated that the CHII was indeed successful at predicting later-life impairment from cumulative head impacts among the validation group of 70 participants. In particular, the CHII successfully predicted a threshold dose-response relationship between CHI and apathy (p >0.001), depression (p >0.001), executive function dysregulation (p >0.001), and self-reported cognitive impairment (p >0.001). We then found that the CHII was much less successful at predicting impairment in the experimental group of 82, only finding significance in measures of apathy (p=0.0502) and executive function dysregulation (p=0.0277). Overall, our findings indicate that the CHII is an excellent improvement in methods of estimating RHI in people whose only contact sport is football.
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LIST OF ABBREVIATIONS

AES ................................................................................................................. Apathy Evaluation Scale
BRI .............................................................................................................. Behavioral Regulation Index
BRIEF-A .................................. Behavioral Rating Inventory of Executive Function-Adult Version
BU ............................................................................................................. Boston University
BU AD CTE Center ...................... Boston University Alzheimer’s Disease and CTE Center
CES-D ........................................... Center for Epidemiologic Studies-Depression Scale
CHI ................................................................. Cumulative Head Impacts
CHII .............................................................. Cumulative Head Impact Index
CTE .......................................................................................... Chronic Traumatic Encephalopathy
GEC ......................................................................... Global Executive Composite
LEGEND.... Longitudinal Examination to Gather Evidence of Neurodegenerative Disease
MI ................................................................. Metacognition Index
NFL ............................................................... National Football League
RHI ............................................................. Repetitive Head Impacts
TBI ................................................................. Traumatic Brain Injury
INTRODUCTION

The Historical Antecedents of CTE and Repetitive Head Impacts: from Antiquity to Super Bowl Sunday

Today it is not uncommon to see phrases like “Concussion Crisis” splashed among the day’s headlines [1]. Indeed, worrisome stories about the long term effects of sports-related head injuries seem to have become a part of our daily lives, penetrating virtually every major news organization from the New York Times and Sports Illustrated to Buzzfeed [2-9]. While some may consider this the result of an unwarranted media frenzy, the statistics surrounding repetitive head impacts (RHI) in sports are troubling to say the least. More than 200 million Americans play organized sports, and every year those athletes experience up to 3.8 million sports-related concussions [10, 11]. Perhaps most distressing are studies indicating that as many as half of American football players at the high school and college level sustain a concussion every year, while up to 30% of those same athletes sustain more than one annually [11-13]. The issue of RHI in contact sports is one of staggering proportions that very much deserves the spotlight it currently receives. These concerns are not new, however, and while our understanding of the long term effects of RHI may be more advanced than ever before, our concerns about their consequences date as far back as antiquity.

Long before the game of American football was invented, concerns regarding trauma to the brain were considered important enough that they made their way into some of the earliest known medical documents, including the “Edwin Smith Papyrus”, which dates back to around 1550BC [14]. Contained within the lines of the papyrus are the first
appearance of the word “Brain” in medical literature, as well as the earliest known medical guidelines for diagnosing and treating brain injuries [14, 15]. By the time of Ancient Mesopotamia, medical understanding of brain trauma and its subsequent treatment had only marginally improved, with drilling into the skull, or “trepanation” still serving as the primary treatment method for those who survived injury long enough to receive medical attention [16, 17].

It wasn’t until the 20th century when substantial technical advances in clinical and research practices permitted the examination of the brain and its reaction to trauma more closely[18]. Following hundreds of years of virtual stagnation, scientists began to make headway understanding what happens in the brain following impact. Within the first few decades of the 20th century, researchers were already confident that lasting damage could occur to the brain on the microscopic level even when fracture to the skull did not occur [19]. At this point, it had become clear that the brain was far more vulnerable to impact-related damage than previously thought, and research began expanding from individuals with penetrating injuries to those who suffered other kinds of blows to the head [20].

By the 1920’s, neurologists were investigating the long term consequences resulting from brain injury in contact sports. The term “punch drunk” was first used in medical literature by Harrison Martland in 1928 to describe a collection of cognitive symptoms that seemed to result from the head impacts experienced by professional boxers or “pugilists” [20]. Around that same time, the researchers Osnato and Giliberti were conducting an examination of more than 100 cases of acute traumatic brain injury (TBI). Upon the study’s completion, the researchers concluded that “in a few instances
complete resolution does not occur, and there is a strong likelihood that secondary
degenerative changes develop” [19]. It is in this same 1927 study where we see the first
usage of the terms “traumatic encephalitis” and “post-concussion neuroses” [19].

By the year 1940, Bowman and Blau had documented the case of a 28-year old
boxer in writings that would become the first place the term Chronic Traumatic
Encephalopathy (CTE) was used in medical literature [21]. The young boxer was
described as having increasingly child-like behavior, memory difficulty, and mood
changes that included depression, and paranoia [22]. After his symptoms remained
unimproved over the course of 18 months, Bowman and Blau determined that he was
experiencing “chronic” traumatic encephalopathy and thus the term was born [23].

While these first cases were mostly focused on boxers, the possibility of the same
issues affecting American football players did not escape these earliest researchers.
Indeed Martland explicitly states his opinions on the matter in yet another publication
where he writes: “While this disease (punch drunk) is most commonly observed in
pugilists it is not entirely confined to this sport, but may be seen in wrestlers, and not
uncommonly in footballers” [24]. In fact, as is chronicled in the excellent historical
overview of CTE by Montenigro et al. 2015, many of the earliest researchers explicitly
stated their assumption that the same chronic degenerative effects could be found to
affect American football players [23].

Despite these insights, widespread acknowledgement that CTE could be found in
American football players did not come until almost half a century later in 2005, when
neuropathologist Bennet Omalu observed unusual changes in the brain of Mike Webster,
a retired National Football League (NFL) player. The strange accumulations of protein that Omalu observed in Webster’s brain were consistent with those found in cases of CTE [25]. Webster, a four-time Super Bowl champion, had been somewhat of a national hero, and the story of his descent into depression, homelessness and dementia during the final years of his life caught the nation off guard, creating a lightning rod for suspicions that Webster’s football career had caused the damage to his brain. Following the news of Webster’s posthumous diagnosis with CTE and the diagnosis of several other prominent football players shortly thereafter, the prevalence of CTE in football became solidified as an issue of national significance [23].

**The Complicated Case of CTE**

As of this writing, there is still no way to diagnose CTE in a living person. To further complicate matters, there is also extraordinary diversity among the symptoms typically associated with the disease. All of the major symptoms can also be caused by unrelated maladies, making it impossible to tell who has the disease and who doesn’t from clinical symptoms alone. A literature review of more than 200 autopsy-confirmed CTE cases found in excess of 50 commonly observed symptoms across 4 different categories [26] (Table 1).
Given the broad spectrum of clinical features that can be present, identifying the true cases of CTE among living populations has remained a major barrier to researchers. Without an in-vivo diagnosis, and without an easily distinguishable clinical picture of the disease, researchers have focused efforts on better understanding that factors that contribute to the development of CTE. Unsurprisingly, the study of repetitive head impacts is at the core of much of this research.
Cumulative Head Impacts: Understanding, and Measuring the Major Risk Factors of CTE.

Significant improvements in our understanding of CTE and its risk factors can still be made in the absence of an in-vivo diagnostic tool. To date, every neuropathologically confirmed case of CTE has had a history of RHI, but not everyone with a history of RHI gets CTE [26]. The implication is that while RHI is likely a necessary factor in the development of CTE, it is also likely not sufficient. As such, researchers must undertake a wide range of investigations to better understand what additional risk factors may exist. Consideration of other components such as genetics, BMI, age, gender and variations within head impacts could help clarify our understanding of who is most vulnerable to the disease.

Almost undeniably however, RHI are a primary contributing factor to the development of CTE, and our ability to quantify them remains essential to virtually all aspects of CTE research. Despite the incredible importance of RHI analysis. Methodology of assessing life-long history of RHI has remained somewhat primitive, relying primarily on retrospective collection of self-reported or informant-reported concussion histories[27]. These approaches are inherently challenging given that they require the accurate recall of nuanced events that may have occurred many years ago and that may have occurred countless times throughout an athlete’s career [28]. Although prospective studies will eventually provide researchers with a better measure of cumulative head impacts as they...
are reported over the course of a participant’s life, the vast majority of individuals who play contact sports are not prospectively followed, so researchers must continue to rely on retrospective analysis of cumulative head impacts.

Several validated scales exist, and are commonly used in the interpretation of retrospective head injury data [29-31]. In addition to the use of these scales, some researchers have sought to supplement retrospective concussion data with indirect measures of head injury. Studies using this approach by measuring total years of play or age of first exposure to football have successfully linked higher levels of head impact exposure to later-in-life cognitive and neurobehavioral dysfunction [32-41]. These studies collectively underscored the utility of head impact estimates in predicting the emergence of symptoms that are associated with CTE. Most importantly however, they underscore the importance of developing robust and clinically validated methods of estimating cumulative head impacts (CHI) that can become standardized within the field of research. Recently, researchers at Boston University’s Alzheimer’s Disease and Chronic Traumatic Encephalopathy Center (BU AD and CTE Center) created a new cumulative RHI metric called the Cumulative Head Impact Index (CHI index or CHII) with precisely this goal in mind [27].
The Cumulative Head Impact Index: Designing a New Approach to Measuring both Concussive and Sub-Concussive Hits in Football.

The CHI index combines aspects of previous metrics while addressing a long-debated question about the significance of concussive vs. sub-concussive hits to the head. Sub-concussive hits are impacts below the threshold needed to elicit any of the symptoms of a concussion. While they might not cause obvious symptoms, these smaller hits are certainly not harmless; imaging studies have successfully demonstrated changes in brain function following even single seasons of contact sports when no concussions were reported [23, 42, 43]. In fact, many researchers believe that the accumulation of these sub-concussive hits could be a major risk factor for CTE; approximately 16% of confirmed cases of CTE have occurred in individuals with no reported history of concussions [44]. This is not surprising when one considers how incredibly common these sub-concussive hits likely are; research has suggested that high school football players experience as many as 600 sub-concussive hits per season, and that college players experience upwards of 1000 [45]. Despite these statistics and the implication that sub-concussive hits likely contribute to the development of CTE, sub-concussive hits to the head are rarely included in research that retrospectively studies football players.

Previous research has sought to address this oversight. Using helmet-based accelerometers tuned to record impacts above a threshold of 10-15g, studies have recorded the concussive and sub-concussive hits experienced by players at different
positions and at various levels of play during a typical season [42, 46-50]. Additional studies using accelerometer data have shown that sub-concussive hits at the high-school level are associated with post-season micro-structural white matter changes, as well as reductions in neurophysiological health and cognitive functioning [42, 43, 51, 52].

The results of these studies are both disturbing and promising to those studying the connection between RHI and later in life neurological consequences. Unfortunately, these short-lived accelerometer studies do not capture cumulative head impacts over the course of an athlete’s entire career [27, 41]. Hits over the course of a career in football vs in a single season of football are considered the most important when predicting later-in-life issues such as CTE [53]. With this in mind, researcher have attempted to extrapolate career-long estimates of RHI from season long accelerometer study data.

The application of accelerometer-based data in a retrospective analysis was successfully demonstrated in 2015 by the Head Impact Exposure Estimate (HIEE), which used self-reported data from football players at the college and high school levels in conjunction with accelerometer data to estimate the number of cumulative RHI that occurred during those players’ entire high school and college careers [41]. While this method was a large step in the right direction, it still fell short in two critical ways; first, the study excluded the possibility of hits accumulated prior to high school football (i.e. at the youth level), and second the study was not clinically validated. The latter point is the more relevant one in the context of CTE. Cumulative RHI estimates should be tested for their ability to
predict later-life neurobehavioral and cognitive impairment if they are going to be of use in CTE research.

The creation of the Cumulative Head Impact Index in 2016 by researchers at the BU AD CTE Center addressed both of these shortcomings. The CHI index utilizes self-reported data about years of play, positions played, and level of play in football and uses that data to extrapolate short-term accelerometer-based RHI studies (which include hits at the youth level) into career-long estimates of cumulative head impacts [27]. The CHI index was then tested for its ability to predict later-life neurobehavioral and cognitive impairment, making it particularly applicable to the study of CTE [27].

Making the CHI Index: Explaining the Methods of Montenigro et al. 2016

Essential Components of the CHI Index

The two categories of data used in the creation of the CHI index are a). the self-reported athletic data from study participants, and b). objective measures of repetitive head impacts obtained from football helmet accelerometer studies [27]

The self-reported athletic history data was obtained as part of the ongoing Longitudinal Examination to Gather Evidence of Neurodegenerative Disease (LEGEND) study at the BU AD and CTE Center. The LEGEND Study football data included participants’
positions of play, total number of seasons played, and percent of total games played at each position for every level of play (youth through college) [27].

The remaining key CHII component, short-term accelerometer-based measures of RHI, were obtained from a literature review of helmet accelerometer studies in football players at the youth, high school and college levels. Specifically, Montenegro et al. (2016) used the key words: HITS System, 6DOF, accelerometers, helmet-sensor, football, youth, high school, and college to find appropriate papers for this review. From these results, studies were selected according to a priori inclusion criteria [27]:

1. **Head impacts were measured during every practice and game for the entire season.**
2. **Level of play (youth, high school, college) was identified.**
3. **Head impact frequencies were reported for positions of play.**
4. **Any impact event with a peak linear acceleration less than 10g was excluded for analysis. A minimum cutoff of 10g ensures the elimination of non-impact events (e.g. jumping) from the calculation of head impact frequency.**

The resulting studies provided Montenigro et al. (2016) with multiple estimates of RHI per season for each level of play and position in football[47-50, 54]. The weighted means of those estimates from each of by level of play and position are shown in Table 2.
Table 2. Summary of mean impacts per season utilized by Montenigro et al. (2016) for the CHI index. Data collected from literature review of helmet-accelerometer studies with full methods previously published [27]. DL = defensive linemen, LB = linebackers, DB = defensive backs, OL = offensive linemen, OB/RB = offensive backs or running backs, WR = wide receivers QB = quarterbacks, WR/DB = wide receivers and defensive backs (cornerbacks and safeties, DL/OL = linemen

<table>
<thead>
<tr>
<th>Level of Play</th>
<th>Position</th>
<th>Weighted mean RHI per season from all studies [47-50,54]</th>
</tr>
</thead>
<tbody>
<tr>
<td>College</td>
<td>DL</td>
<td>871</td>
</tr>
<tr>
<td></td>
<td>LB</td>
<td>685</td>
</tr>
<tr>
<td></td>
<td>DB</td>
<td>417</td>
</tr>
<tr>
<td></td>
<td>OL</td>
<td>728</td>
</tr>
<tr>
<td></td>
<td>OB/RB</td>
<td>412</td>
</tr>
<tr>
<td></td>
<td>WR</td>
<td>237</td>
</tr>
<tr>
<td></td>
<td>QB</td>
<td>206</td>
</tr>
<tr>
<td>High School</td>
<td>QB</td>
<td>467</td>
</tr>
<tr>
<td></td>
<td>WR/DB</td>
<td>372</td>
</tr>
<tr>
<td></td>
<td>RB/LB</td>
<td>619</td>
</tr>
<tr>
<td></td>
<td>DL/OL</td>
<td>868</td>
</tr>
<tr>
<td>Youth</td>
<td>All positions</td>
<td>107</td>
</tr>
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Adapted with permission from Montenigro et al. (2016).

Using mean RHI per season data from this review, Montenigro et al. (2016) then extrapolated the RHI data into career-spanning estimates using the self-reported sports histories of the LEGEND Study participants.
The athletes for the original Montenigro et al. (2016) study were selected from within the existing pool of active LEGEND participants according to a variety of strict inclusion and exclusion criteria. First, all participants needed to have played football with the highest level of competition occurring at the high school or college level [27]. This decision was based on the absence of professional-level helmet accelerometer data. It should be noted that although youth-level only players were excluded, RHI from youth-level play was accounted for in the final CHII calculations (Table 2). This is a noted improvement over the Kerr at al. (2015) HIEE method, which does not account for youth level play [27, 41]. Second, participants must have not participated in any level of other high-risk contact sports where substantial RHIs could have occurred [27]. This exclusion helped reduce the likelihood that the CHI index would under-estimate a player’s total RHI. Sports that were defined as high risk for this exclusion criteria are listed in Table 3. Finally, participants must have completed at least a full year of participation in the LEGEND Study, and must not have reported any concussive events within a year of their LEGEND Study assessment [27].
Table 3. List of high exposure sports excluded from the original Montenigro et al. (2016) study population. Participation in any of the following sports was used as an exclusion criterion in the Montenigro et al. (2016) study.

<table>
<thead>
<tr>
<th>Sport</th>
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<tbody>
<tr>
<td>Amateur Wrestling</td>
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<td>Boxing</td>
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<tr>
<td>Bull Riding</td>
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<tr>
<td>Diving</td>
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<tr>
<td>Horse Jumping</td>
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<tr>
<td>Ice Hockey</td>
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<tr>
<td>Karate</td>
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<tr>
<td>Lacrosse</td>
</tr>
<tr>
<td>Martial Arts</td>
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<tr>
<td>Mixed Martial Arts (MMA)</td>
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<tr>
<td>Entertainment Wrestling</td>
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<tr>
<td>Rugby</td>
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<tr>
<td>Soccer</td>
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</table>

*Sample CHII Calculation for a Hypothetical Athlete*

The CHI Index for each participant is calculated by combining the self-reported data with the impact frequencies estimated by level of play and position. The following example from Montenigro et al. (2016) provides a demonstration for calculating the CHI index of a hypothetical participant who played at the college, high school and youth levels.
“Player A, is a 42 year old salesman who reports having participated in football at the youth, high school and collegiate levels.

a. In college, Mr. A reported that he played for a total of 3 seasons; that he sustained a knee injury in the summer before his senior year and then quit the team. His primary position for his college team was line-backer (LB); he reported having no secondary or tertiary positions of play. Of all the games his college football team participated in during his three seasons of play, he estimated having participated in 85% percent of game downs as a line-backer. Thus, his college CHI index was: $(85\%) \times (685 \text{ impacts per season for LB from Table 5}) \times (3 \text{ seasons}) = 1,747$.

b. In high school, Mr. A reported that he played for all 4 seasons. His primary position for his high school team was also LB; he reported having a secondary position playing the offensive line (OL) as a guard. Of all the games in high school he estimated having participated in 40% percent of game downs as a LB and 30% as OL. Thus, his high school CHI index was: $[(40\%) \times (619 \text{ impacts per season for LB}) \times (4 \text{ seasons})] + [(30\%) \times (868 \text{ impacts per season for OL}) \times (4 \text{ seasons})] = 2,032$.

c. Lastly, Mr. A reported that he played 4 seasons of football prior to high school. He reported having played as an OL throughout his youth participation. Due to a limited number of players on his team, he estimated that he participated in 90% game downs for all 4 seasons. Thus, his youth CHI index was: $(90\%) \times (107 \text{ impacts per season for any position}) \times (4 \text{ seasons}) = 385$.

d. His CHI index = $1,747 + 2,032 + 385 = 4,164$.”[27]
The LEGEND Study requires participants to complete yearly phone and internet surveys that cover a variety of topics ranging from athletic history to overall cognitive functioning. Annual internet surveys are self-completed by the participants, and subsequent phone surveys are administered by members of the research team at the BU AD CTE Center. Detailed information about the LEGEND Study have been previously published [36, 55, 56]. A subset of the measures from the online survey and the phone interview were selected by Montenigro et al (2016), based on the availability of established cut-off values for clinically significant outcomes (i.e. impaired or not impaired), and established utility within RHI and CTE literature [27].

Health and Athletic History Questions

As part of the study, LEGEND Study participants are asked a set of general health and sports-history related questions. A self-reported estimate of total concussions is obtained after participants are read a modern definition of what constitutes a concussion [55]. This definition is based on a CDC statement as well as the third International Conference on Concussions in Sports held in Zurich [57, 58]. It is important to note that the number of concussions reported by participants was highly skewed, so Montenegro et al. (2016) decided to use the log of concussions for all analyses [27].
Previous research has indicated that beginning to play tackle football before the age of 12 posed a higher risk of later-in-life cognitive and structural dysfunction [38, 59]. Montenigro et al. (2016) decided to include this variable by sorting participants dichotomously into those with an age of first exposure (AFE) before 12, and those with AFE after 12 [27]. Finally, a subset of the extensive LEGEND Study athletic history was selected by Montenigro et al. (2016) for use in the appropriate extrapolation of the accelerometer data to study participants [27]. Specifically, the researchers included what sports the participants played, how many total years they played each sport, how many total seasons they played each sport, what positions they played, and what levels they participated in (youth, high school, college,) [27].

_Cognitive and Neurobehavioral Measures_

In addition to being a convenience sample, The LEGEND Study was selected for analysis because of the neurobehavioral and cognitive assessments that participants are required to complete each year. In order to see whether or not the CHI index would be a useful tool in studying the relationships between RHI and later-life neurobehavioral and cognitive impairment, the researchers performed multiple clinical validations of the CHI index using LEGEND Study Data. Several particular measures from the LEGEND Study data were selected and are described below:
The Behavioral Rating Inventory of Executive Function-Adult Version (BRIEF-A) tests executive function as it might affect an individual’s daily living [60]. The BRIEF-A is well-validated and has been used in various RHI studies previously given its relevance to one of the hallmark symptoms of CTE: executive function dysregulation [32, 60]. The measure asks a series of 75 questions which ask the participant how often they have dealt with a particular issue in the past month. They are able to respond with either “never=1”, “sometimes=2” or “often=3”. Higher scores therefore correspond with greater executive dysfunction. The 75 answers are summed into the “Global Executive Composite” (GEC), which provides an assessment of overall executive functioning. Answers may also be broken down into sub-scores which assess more specific types of executive function. The “Meta-cognition index” (MI) can be thought of as an estimate of executive function that regulate planning, organization, problem-solving, and working memory among other features. The “Behavioral Regulation Index” (BRI) can be thought of as an estimate of executive function that indicates self-monitoring of emotions and actions as well as flexibility in task-switching. Scores on the BRIEF-A are converted into standardized age-adjusted T-scores (M=50, SD=10), and those with T-scores more than 1.5 standard deviations are considered impaired [60].

The Center for Epidemiologic Studies-Depression Scale (CES-D) is a screening tool for the symptoms of depression [61]. The measure consists of 20 questions that ask participants to report how often they have experienced various symptoms over the past week. Participants may respond on a scale ranging from “none of the time = 0” to “most
or all of the time = 3”. Higher scores indicate more depression, with a cut-off score of greater than or equal to 16 generally indicating clinically significant depression [61-63].

The Apathy Evaluation Scale (AES) assesses a participant’s levels of apathy over the past 4 weeks [64]. Participants are asked how well 18 descriptors reflect their feelings over the last month, and are allowed to respond on a scale ranging from “not at all characteristic = 3” to “very characteristic = 0”. The higher the overall score, the more severely apathetic the participant is feeling. A well-accepted cutoff score of greater than or equal to 34 is considered to indicate clinically significant apathy [65].

Brief Test of Adult Cognition by Telephone (BTACT) consists of a series of objective measures to test a participant’s overall cognitive functioning [66, 67]. Taking less than 30 minutes to complete and encompassing a wide range of sub-tests, the BTACT is an ideal method for quickly assessing cognitive function during the telephone surveys [66, 68]. The BTACT is comprised of 6 sections, which measure episodic verbal memory (immediate and delayed Rey-Auditory-Verbal Learning Test), working memory (Digits Backward), verbal fluency (Animals Categorical Fluency), task-switching (red/Green Test), inductive reasoning (Number Series), and processing speed (Backward Counting)[67]. Scores for the BTACT were interpreted as is fully described in Montenigro et al. 2016 with cognitive impairment assigned as 1.5 SD below the normative mean [27]. Ultimately, the BTACT was excluded from all analysis in our own paper because of an unusually small sample of participants who registered as impaired (n=5 or 3%).
Findings of the CHII: Utility of the New Model for Measuring Cumulative RHI and Predicting Later-Life Neurobehavioral and Cognitive Impairment.

To reiterate, the CHII was created as a new way to estimate an athlete’s cumulative exposure to repetitive head impacts from participation in football [27]. Utilizing sports histories from the LEGEND Study, and objective accelerometer data, researchers calculated a CHII for each member of the study cohort, and found that the mean CHII lay within the expected range for football players at the high school and college levels [27, 69].

The CHII data was then applied to neurobehavioral and cognitive measures from the LEGEND Study to see if the CHII could be used to predict later-life clinical outcomes [27]. First, Montenigro et al. (2016) interpreted each participant’s LEGEND Study data using dichotomous outcomes (“impaired” or “not impaired”) according to the accepted cut-off scores previously discussed [27]. Researchers were then able to determine whether or not higher CHII values were predictive of impairment. What the researchers found was that the CHI index strongly predicted later-life impairment for all of the selected LEGEND Study measures (BRIEF-A, CES-D, AES, and BTACT) [27]. Furthermore, the researchers found that the CHII was more successful at predicting impairment across those measures than the single-variable metrics used previously (such as age of first exposure, total years players, or total number of concussions reported) [27].
Of particular interest was the finding that the CHI index predicted later life impairment in a threshold, dose-response manner. This kind of relationship, which is illustrated in figure 1, implies a steady baseline (BL) risk of impairment up to a certain CHII. Above that value of CHII, the risk of impairment increases in a dose-relationship. For example, the researchers found that the risk for impairment in several LEGEND Study measures nearly doubled with each 2800 CHI above the threshold. It is worth noting that this finding was perhaps unsurprising to the researchers as similar relationships have been observed in studies of both soccer and boxing [27, 70-72].

![Figure 1. Threshold dose response relationship between CHII and risk of impairment. Montenigro et al. 2016 showed that a baseline (BL) risk of impairment exists below a certain threshold CHII dose. Above these threshold doses (reported in Table 4) the risk of impairment steadily increased with increasing doses of CHII.](image)

Reproduced with permission from Montenigro et al. 2016.
For each of the LEGEND Study clinical measures, a different threshold-dose was determined (Table 4). These threshold doses were determined by Montenigro et al. (2016) using a Bayesian hierarchical model estimated by Markov Chain Monte Carlo (MCMC) method with 30,000 simulations implemented in PROC MCMS in SAS 9.4 [27, 73]. Among the clinical domains covered by the LEGEND Study measures, cognitive function had the highest dose-response threshold (Table 4) [27]. Montenigro et al. (2016) speculated that this higher threshold could be indicative of differences in the underlying mechanisms that affect cognitive changes vs. changes in mood and behavior [27, 71, 74, 75].

Table 4. **Mean Threshold CHII for Dose-Response of all LEGEND Study Measures.**

For each clinical domain covered by the LEGEND Study measures, there is a unique CHII threshold, above which the risk of impairment steadily increases with increasing CHII. It is important to note that below the threshold CHII, a constant risk of impairment still exists.

<table>
<thead>
<tr>
<th>LEGEND Study Measure</th>
<th>Clinical Domain</th>
<th>Mean Threshold CHII for Dose-Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavioral Regulation Index of the BRIEF-A</td>
<td>Behavior</td>
<td>3172</td>
</tr>
<tr>
<td>Metacognition Index of the BRIEF-A</td>
<td>Metacognition</td>
<td>2939</td>
</tr>
<tr>
<td>Global Executive Composite of the BRIEF-A</td>
<td>Executive Function</td>
<td>2723</td>
</tr>
<tr>
<td>Center for Epidemiologic Studies Depression Scale</td>
<td>Depression</td>
<td>3450</td>
</tr>
<tr>
<td>Apathy Evaluation Scale</td>
<td>Apathy</td>
<td>2948</td>
</tr>
<tr>
<td>Brief Test of Adult Cognition by Telephone</td>
<td>Cognition</td>
<td>6480</td>
</tr>
</tbody>
</table>

*Adapted with permission from Montenigro et al. 2016*
It is important to clarify that the threshold dose-response does not indicate safety below a certain CHII. Risk of later-life impairment does exist below the threshold (Figure 1). Indeed, there is a baseline risk that exists below these thresholds for all of the LEGEND Study measures[27]. Additionally, the Montenigro et al. (2016) study does not provide us with a way to determine when it is “safe” to retire from football [27]. The results instead showed the risk of impairment continuing to rise with increasing doses of CHI, and did not indicate a specific point at which risk of impairment became less severe [27]. What the index does provide is a dramatically improved tool to retrospectively quantify exposure to repetitive head impacts in the context of CTE research. The predictive power of the CHII also emphasizes the importance of considering sub-concussive hits as a major contributing factor to CTE; concussion history was less strongly predictive of later-life impairment than the CHII [27].

The Future of the CHI Index: Further Validation, and Expanded Application

The creation of the CHI index provided a major step forward in our ability to retrospectively study the effects of repetitive head impacts on later-life impairment. Given that the CHII was only published at the beginning of 2016, validation of the index is still needed to help establish it as a new standard for retrospective RHI analysis. There is also still a need for methods of retrospective RHI analysis in athletes with a more complicated history of exposure to RHI. The small sample size of the original CHII analysis was largely due to the very strict inclusion and exclusion criteria; ultimately,
many people who participate in tackle football are likely to participate in some other contact sport as well. To this end, further research should be conducted to determine whether or not secondary sources of RHI from additional contact sports significantly impede the ability of the CHII to predict later life impairment.

*Specific Aims*

This present study intends to serve as both a preliminary validation of the CHII index, and as an investigation into the versatility of the CHI index in assessing athletes with more complicated sports backgrounds (i.e. participation in a second contact sport). Using a new subset of participants from within the LEGEND Study, we have taken 70 previously un-analyzed individuals who meet the original Montenigro et al. (2016) criteria and re-run the same analyses to see if the CHII is still predictive of impairment. This study also serves as a preliminary attempt at expanding the utility of the CHII index to athletes who also participated in a secondary contact sport at a low (high school or youth) level. Our hypothesis is that the CHI index will still be able to predict late-in life decline according to the same dose-response relationship that was initially found in football-only participants, and that the CHII will have more limited predictive power with the more complicated football non-exclusive group. We hope that this study will both strengthen confidence in the ability of the CHII to retrospectively analyze the RHI of football players, and will broaden our understanding of which additional populations of athletes the CHII index might be useful for.
METHODS

LEGEND Study Overview

The LEGEND Study is an ongoing study at the Boston University Alzheimer’s Disease and CTE Center. The purpose of the study is to learn more about the long term effects of repetitive head impacts, including their relationship with CTE. The cohort is comprised of individuals who, among other requirements, meet certain minimum criteria for participation in organized athletics. The LEGEND Study is advertised to potential participants by inclusion on the BU CTE Center website, inclusion in advertising and mailing materials from the Concussion Legacy Foundation, inclusion on the website SternNeuroLab.org and by the distribution of a study flyer via social media outlets. Inclusion criteria focus primarily on participation in at least one sport that features officiated completion at the youth, high school, college, semi-professional or professional level. Complete descriptions of the LEGEND Study and its protocols have been previously published[36, 55, 56].

Inclusion and Exclusion Criteria for the Study Sample

Two new subsets of participants from the LEGEND Study were selected for this analysis. The first was a group of \((n = 70)\) participants who met the exact same inclusion and exclusion criteria utilized by Montenigro et al. (2016). These participants met all of the same criteria, described previously, but had not been included in the study at the time of the Montenigro et al. (2016) analysis.
The second group of 82 participants met the same football inclusion criteria: they had played contact football at the college or high school level. This second group of participants also played any of the additional contact sports listed in Table 3, but not above the high school level. This additional inclusion criterion was selected to test the ability of the CHII to predict later-life impairment when additional sources of RHI are present.

Finally, as was true of Montenigro et al. (2016), participants in both subsets needed to have completed at least their full first year of participation in the LEGNED study, and must not have reported any concussive events within 1 year of their annual assessment.

**LEGEND Study Measures and Cut-off Scores**

The same neurobehavioral and cognitive measures (BRIEF-A, AES, and CES-D) were selected for analysis in this validation study. As in Montenigro et al (2016), these measures were selected for their common use in TBI and CTE literature and for the existence of well-validated cut-off scores indicating impairment [27]. The BTACT was excluded from analysis because of an unusually small group of participants that registered as impaired (n=5 or 3%) that made analysis of the threshold dose-response relationship impossible.
**CHI Index Calculations**

The CHII was calculated for each of the 152 new participants as is outlined previously in the sample calculation section, and below in Table 5. In short, their football histories from the LEGEND Study (positions, levels of play, years of play) were used in conjunction with the objective RHI measures calculated from the Montenigro et al (2016) literature review of accelerometer studies. The table below, reproduced from Montenigro et al. (2016) provides a clear map of how the CHI index is calculated for any individual (Table 5).

**Table 5. Calculation of the Cumulative Head Impacts Index.** For the youth, high school and college levels of play, LEGEND Study data for top three positions played, and total number of seasons at each level were combined with the weighted average RHI per season obtained from the Montenigro et al. (2016) literature review[27].

<table>
<thead>
<tr>
<th></th>
<th>(% games played at 1st position)</th>
<th>X</th>
<th>(Position’s weighted average # impacts per season)</th>
<th>X</th>
<th>(Total # of youth seasons)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Youth</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>[A]</td>
</tr>
<tr>
<td></td>
<td>(% games played at 2nd position)</td>
<td>X</td>
<td>(Position’s weighted average # impacts per season)</td>
<td>X</td>
<td>(Total # of youth seasons)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(% games played at 3rd position)</td>
<td>X</td>
<td>(Position’s weighted average # impacts per season)</td>
<td>X</td>
<td>(Total # of youth seasons)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For the high school level of play, the same calculation applies but with data for top three positions played, and total number of seasons at the high school level obtained from the Montenigro et al. (2016) literature review.

<table>
<thead>
<tr>
<th></th>
<th>(% games played at 1st position)</th>
<th>X</th>
<th>(Position’s weighted average # impacts per season)</th>
<th>X</th>
<th>(Total # of high school seasons)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High School</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>[B]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

= [A]

= [B]
Cumulative Head Impacts Index = \[ A + B + C \]

Adapted with permission from Montenigro et al. (2016)

### Statistical Analysis

All statistical analyses were completed using the same statistical approaches of Montenigro et al. (2016). All group comparisons were made using two sample t-tests for continuous normal variables, Wilcoxon two-sample tests for non-normal continuous variables and chi-square tests for categorical or dichotomous variables [27].

For each of the selected LEGEND Study clinical measures, we modeled the dichotomous outcome (probability or impaired vs not impaired) with the participants’
CHIII. The threshold-dose for each of our present analyses was selected from the original findings of Montenigro et al. 2016 as they are outlined in Table 4. These threshold doses were initially determined by Montenigro et al. (2016) using a Bayesian hierarchical model estimated by Markov Chain Monte Carlo (MCMC) method with 30,000 simulations implemented in PROC MCMS in SAS 9.4 [27, 73].
RESULTS

Demographics of Study Sample

Participant demographics (Table 6) were compared across the two highest levels of play (high school and college) as was done in Montenigro et al. (2016). There was no significant difference in the mean ages of the former high school and college level athletes (Table 6). Unsurprisingly, the 91 college level participants had significantly more education ($p=0.024$, $p=0.045$) than high school level players in terms of years of education and highest terminal degree respectively (Table 6). Finally, among the study sample there was no significant difference in the number of high school or college athletes who participated in a second contact sport (Table 6).

Table 6. Demographics of all 152 study participants.

<table>
<thead>
<tr>
<th></th>
<th>Total Sample N=152</th>
<th>High School N=61</th>
<th>College N=91</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) Mean (SD)</td>
<td>43 (12.9)</td>
<td>44 (12.2)</td>
<td>42.8 (13.4)</td>
<td>0.503</td>
</tr>
<tr>
<td>Formal education (years)</td>
<td>17.2 (2.6)</td>
<td>16.6 (3.1)</td>
<td>17.7 (2.2)</td>
<td>0.024</td>
</tr>
<tr>
<td>Education (terminal degree)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High School / GED</td>
<td>22 (14.5)</td>
<td>14 (23)</td>
<td>8 (8.8)</td>
<td></td>
</tr>
<tr>
<td>Bachelor’s / Associates</td>
<td>79 (52)</td>
<td>30 (49.1)</td>
<td>49 (53.6)</td>
<td>0.045</td>
</tr>
<tr>
<td>etc.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Master’s or Doctorate</td>
<td>51 (33.6)</td>
<td>17 (27.9)</td>
<td>34 (34.4)</td>
<td></td>
</tr>
<tr>
<td>Played Second Contact</td>
<td>82 (53.9)</td>
<td>32 (52.5)</td>
<td>50 (54.9)</td>
<td>0.763</td>
</tr>
<tr>
<td>Sport N (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The CHII was calculated for all 152 participants in both of the subgroups (football-only validation group n=70, and football with another contact sport experimental group n=82).

The mean CHII for all 152 athletes in both subgroups are listed in Table 7. The mean CHII for the total sample is within the expected range based on previous literature [27, 69]. The mean CHII for all 61 high school level players was significantly lower than the CHII for the 91 college-level players (p < 0.001), as were the self-reported concussions (p = 0.013) and total seasons of football play (p < 0.001) (Table 7).

**Table 7. CHII, concussions and seasons of play for the entire study sample of 152 athletes.** Concussions were self-reported after participants received a modern definition of concussion (methods described previously) Numbers in parenthesis are standard deviations unless otherwise notes. IQR = inter-quartile range

<table>
<thead>
<tr>
<th>RHI Exposure Metric</th>
<th>Total Sample N=152</th>
<th>High School N=61</th>
<th>College N=91</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHI Index Mean (SD)</td>
<td>5036.7 (3335.5)</td>
<td>2745.7 (2097.6)</td>
<td>6407.7 (3116.5)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Self-Reported Concussions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (IQR)</td>
<td>48.6 (26)</td>
<td>32.0 (17)</td>
<td>59.75 (37)</td>
<td>0.013*</td>
</tr>
<tr>
<td>Total seasons of football</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>play Mean (SD)</td>
<td>3.86 (4.0)</td>
<td>2.94 (1.34)</td>
<td>4.5 (4.0)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Separate CHII calculations and exposure metrics were completed for the validation sample of 70 football players who were selected by the exact same inclusion and exclusion criteria as Montenigro et al. (2016). These individuals had only played football and denied having participated in any additional contact sports. Their CHII, self-reported concussions and seasons of football play are listed in Table 8. For the football-only
players in this validation sample, the calculated CHII were again within the expected range for high school and college football players [27, 69]. The 29 high school level players had significantly lower CHII, and total seasons of football play than the 41 college level players (p< 0.001, p=0.003), but their self-reported concussions were not significantly different (Table 8).

Table 8. CHII, concussions and seasons of play for validation sample of 70 high school and college level football players. Concussions were self-reported after participants received a modern definition of concussion (methods described previously) Numbers in parenthesis are standard deviations unless otherwise notes. IQR = inter-quartile range

<table>
<thead>
<tr>
<th>RHI Exposure Metric</th>
<th>Total Sample N=70</th>
<th>High School N=29</th>
<th>College N=41</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHI Index</td>
<td>4305.7 (3081.1)</td>
<td>2538.8 (1757.3)</td>
<td>5555.5 (4908.0)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Self-Reported Concussions (IQR)</td>
<td>40.2 (20)</td>
<td>37.0 (18)</td>
<td>37.0 (22)</td>
<td>0.702*</td>
</tr>
<tr>
<td>Total seasons of football play</td>
<td>3.65 (4.0)</td>
<td>2.8 (1.56)</td>
<td>4.23 (4.0)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

*Mann-Whitney U Test

A third set of identical calculations were completed for the experimental group of 82 athletes who had participated in other contact sports in addition to football (Table 9). The mean CHII for the 32 former high school level football non-exclusive athletes was significantly lower than the CHII for the 50 former college-level athletes (p <0.001), as were the self-reported concussions (p = 0.005) and total seasons of football played (p < 0.001) (Table 9). The calculated CHII were once again within the expected range for high school and college football players [27, 69]
Table 9. CHII, concussions and seasons of play for 82 athletes who played a secondary contact sport in addition to football. Concussions were self-reported after participants received a modern definition of concussion (methods described previously) Numbers in parenthesis are standard deviations unless otherwise indicated. IQR = interquartile range.

<table>
<thead>
<tr>
<th>RHI Exposure Metric</th>
<th>Total Sample N=82</th>
<th>High School N=32</th>
<th>College N=50</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHI Index</td>
<td>5660.7 (3434.7)</td>
<td>2933.3 (1998.5)</td>
<td>7406.3 (3001.4)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Self-Reported Concussions (IQR)</td>
<td>55.8 (39)</td>
<td>20.7 (17)</td>
<td>78.3 (46)</td>
<td>0.005*</td>
</tr>
<tr>
<td>Total seasons of football play</td>
<td>4.0 (4.0)</td>
<td>7.1 (3.1)</td>
<td>12.0 (3.1)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

*Wilcoxon two sample test

CHII and Risk of Later-Life Impairment

In the analysis of the 70 validation football players who met the original football-only Montenigro et al. (2016) criteria, there was a significant increase in probability of impairment beyond the threshold dose for all of the outcomes excluding the Behavioral sub-score of the BRIEF-A (Table 10).

Table 10. Increasing risk of impairment on LEGEND Study clinical measures for the 70 validation-group football players at increasing doses of CHII. Baseline (BL) refers to risk of impairment below the threshold dose (listed in table 4). Risk of impairment reported as probabilities with 95% confidence interval. Adjusted for age and education.

<table>
<thead>
<tr>
<th>Clinical Outcomes Validation Sample N = 70</th>
<th>BL</th>
<th>BL + 1400 CHI</th>
<th>BL + 2800 CHI</th>
<th>BL + 4200 CHI</th>
<th>BL + 5600 CHI</th>
<th>BL + 7000 CHI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavior (BRI)</td>
<td>CHII Dose</td>
<td>0-3728</td>
<td>3728-5128</td>
<td>5128-6528</td>
<td>6528-7928</td>
<td>7928-9328</td>
<td>9238-10728</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------</td>
<td>---------------------</td>
<td>---------------------</td>
<td>---------------------</td>
<td>---------------------</td>
<td>---------------------</td>
<td>---------------------</td>
<td></td>
</tr>
<tr>
<td>0-2461</td>
<td>0.34 (0.29-0.39)</td>
<td>2461-3861</td>
<td>3861-5261</td>
<td>5261-6661</td>
<td>6661-8061</td>
<td>8061-9461</td>
<td></td>
</tr>
<tr>
<td>0.26 (0.24-0.29)</td>
<td>0.39 (0.31-0.47)</td>
<td>0.53 (0.36-0.69)</td>
<td>0.67 (0.42-0.85)</td>
<td>0.78 (0.48-0.95)</td>
<td>0.87 (0.53-0.99)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHII Dose</td>
<td>0-2430</td>
<td>2430-3830</td>
<td>3830-5230</td>
<td>5230-6630</td>
<td>6630-8030</td>
<td>8030-9430</td>
<td></td>
</tr>
<tr>
<td>0.25 (0.23-0.27)</td>
<td>0.39 (0.34-0.45)</td>
<td>0.55 (0.45-0.66)</td>
<td>0.71 (0.56-0.83)</td>
<td>0.83 (0.66-0.93)</td>
<td>0.91 (0.75-0.98)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHII Dose</td>
<td>0-2766</td>
<td>2766-4166</td>
<td>4166-5566</td>
<td>5566-6966</td>
<td>6966-8366</td>
<td>8366-9766</td>
<td></td>
</tr>
<tr>
<td>0.36 (0.33-0.39)</td>
<td>0.52 (0.44-0.59)</td>
<td>0.67 (0.52-0.80)</td>
<td>0.80 (0.61-0.92)</td>
<td>0.90 (0.69-0.98)</td>
<td>0.95 (0.76-1.00)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHII Dose</td>
<td>0-4068</td>
<td>4068-5468</td>
<td>5468-6868</td>
<td>6868-8268</td>
<td>8268-9668</td>
<td>9668-11068</td>
<td></td>
</tr>
<tr>
<td>0.64 (0.62-0.66)</td>
<td>0.46 (0.41-0.51)</td>
<td>0.29 (0.21-0.39)</td>
<td>0.16 (0.08-0.27)</td>
<td>0.07 (0.03-0.18)</td>
<td>0.03 (0.01-0.10)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In the analysis of 82 experimental LEGEND Study participants who played a contact sport in addition to football, there was a significant increase in probability of impairment beyond the threshold dose for executive function (GEC) and apathy (p= 0.02, p=0.050) (Table 11). All other metrics did not reach significance (Table 11).
Table 11. Increasing risk of impairment on certain LEGEND Study clinical measures for the 82 athletes who played a second contact sport at increasing doses of CHII. Baseline (BL) refers to risk of impairment below the threshold dose (listed in table 4). Risk of impairment reported as probabilities with 95% confidence interval. Adjusted for age and education.

<table>
<thead>
<tr>
<th>Clinical Outcomes</th>
<th>Experimental Sample N=82</th>
<th>BL</th>
<th>BL + 1400 CHI</th>
<th>BL + 2800 CHI</th>
<th>BL + 4200 CHI</th>
<th>BL + 5600 CHI</th>
<th>BL + 7000 CHI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavior (BRI)</td>
<td>CHII Dose: 0-3728</td>
<td>3728-5128</td>
<td>5128-6528</td>
<td>6528-7928</td>
<td>7928-9328</td>
<td>9238-10728</td>
<td>0.79 (0.79)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Risk of Impairment: 0.40 (0.39-0.41)</td>
<td>0.42 (0.27-0.58)</td>
<td>0.44 (0.17-0.74)</td>
<td>0.46 (0.10-0.87)</td>
<td>0.48 (0.05-0.94)</td>
<td>0.50 (0.02-0.98)</td>
<td>0.58 (0.05-0.98)</td>
<td></td>
</tr>
<tr>
<td>Meta-cognition (MI)</td>
<td>CHII Dose: 0-2461</td>
<td>2461-3861</td>
<td>3861-5261</td>
<td>5261-6661</td>
<td>6661-8061</td>
<td>8061-9461</td>
<td>0.68 (0.68)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Risk of Impairment: 0.25 (0.24-0.27)</td>
<td>0.31 (0.20-0.45)</td>
<td>0.38 (0.15-0.66)</td>
<td>0.44 (0.11-0.83)</td>
<td>0.51 (0.08-0.93)</td>
<td>0.58 (0.05-0.98)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Executive Function (GEC)</td>
<td>CHII Dose: 0-2430</td>
<td>2430-3830</td>
<td>3830-5230</td>
<td>5230-6630</td>
<td>6630-8030</td>
<td>8030-9430</td>
<td>0.02 (0.02)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Risk of Impairment: 0.19 (0.17-0.21)</td>
<td>0.28 (0.20-0.37)</td>
<td>0.38 (0.21-0.58)</td>
<td>0.49 (0.22-0.76)</td>
<td>0.60 (0.23-0.89)</td>
<td>0.70 (0.24-0.96)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression (CES-D)</td>
<td>CHII Dose: 0-2766</td>
<td>2766-4166</td>
<td>4166-5566</td>
<td>5566-6966</td>
<td>6966-8366</td>
<td>8366-9766</td>
<td>0.72 (0.72)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Risk of Impairment: 0.66 (0.65-0.68)</td>
<td>0.63 (0.44-0.80)</td>
<td>0.60 (0.23-0.89)</td>
<td>0.56 (0.09-0.95)</td>
<td>0.53 (0.03-0.98)</td>
<td>0.49 (0.01-0.99)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apathy (AES)</td>
<td>CHII Dose: 0-4068</td>
<td>4068-5468</td>
<td>5468-6868</td>
<td>6868-8268</td>
<td>8268-9668</td>
<td>9668-11068</td>
<td>0.05 (0.05)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Risk of Impairment: 0.73 (0.68-0.77)</td>
<td>0.59 (0.45-0.73)</td>
<td>0.45 (0.19-0.73)</td>
<td>0.31 (0.05-0.73)</td>
<td>0.19 (0.01-0.73)</td>
<td>0.11 (0.00-0.73)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For the final impairment analysis, all 152 participants were analyzed together as group (Table 12). The metacognition (MI) and executive function (GEC) measures showed
significant increase in risk of impairment as CHII dose increased (p= 0.0315, p<0.001) (Table 12).

Table 12. Increasing risk of impairment with increasing dose of CHII for some clinical LEGEND Study measures among the entire study sample of 152 athletes.
Baseline (BL) refers to risk of impairment below the threshold dose (listed in table 4). Risk of impairment reported as probabilities with 95% confidence interval. Adjusted for age and education

<table>
<thead>
<tr>
<th>Clinical Outcomes Entire Sample N=152</th>
<th>BL BL + 1400 CHI BL + 2800 CHI BL + 4200 CHI BL + 5600 CHI BL + 7000 CHI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavior (BRI)</td>
<td>CHII Dose</td>
<td>0-3728</td>
</tr>
<tr>
<td>Risk of Impairment</td>
<td>Risk of Impairment</td>
<td>0.37 (0.35-0.38)</td>
</tr>
<tr>
<td>Meta-cognition (MI)</td>
<td>CHII Dose</td>
<td>0-2461</td>
</tr>
<tr>
<td>Risk of Impairment</td>
<td>Risk of Impairment</td>
<td>0.24 (0.22-0.25)</td>
</tr>
<tr>
<td>Executive Function (GEC)</td>
<td>CHII Dose</td>
<td>0-2430</td>
</tr>
<tr>
<td>Risk of Impairment</td>
<td>Risk of Impairment</td>
<td>0.20 (0.19-0.22)</td>
</tr>
<tr>
<td>Depression (CES-D)</td>
<td>CHII Dose</td>
<td>0-2766</td>
</tr>
<tr>
<td>Risk of Impairment</td>
<td>Risk of Impairment</td>
<td>0.41 (0.39-0.42)</td>
</tr>
<tr>
<td>Apathy (AES)</td>
<td>CHII Dose</td>
<td>0-4068</td>
</tr>
<tr>
<td>Risk of Impairment</td>
<td>Risk of Impairment</td>
<td>0.55 (0.52-0.57)</td>
</tr>
</tbody>
</table>
A final exposure comparison was made in order to see how the other RHI metrics (concussion and seasons played) compared between the validation and experimental groups (Table 13). The CHII and seasons of football played were significantly higher (p=0.013, p<0.001) in the experimental group (Table 13). The mean number of self-reported concussions was also higher among the experimental group, but did not reach significance (Table 13).

Table 13. Comparison of concussion, CHII and seasons of play between the validation and experimental samples. Concussions were self-reported after participants received a modern definition of concussion (methods described previously) Numbers in parenthesis are standard deviations unless otherwise notes. IQR = inter-quartile range

<table>
<thead>
<tr>
<th>RHI Exposure Metric</th>
<th>Validation Sample (football only)</th>
<th>Experimental Sample (football with other contact)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-Reported Concussions (IQR)</td>
<td>40.2 (20)</td>
<td>55.8 (39)</td>
<td>0.253</td>
</tr>
<tr>
<td>CHI Index</td>
<td>4305.7 (3081.1)</td>
<td>5660.7 (3434.8)</td>
<td>0.013*</td>
</tr>
<tr>
<td>Seasons of football play</td>
<td>3.65 (1.98)</td>
<td>4.03 (2.042)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

*Mann-Whitney U Test
DISCUSSION

We conducted a two-fold assessment of the CHI index by validating the findings of Montenigro et al. (2016) and testing the versatility of the CHII on athletes with more complicated histories of participation in contact sports. For the purposes of validation, we utilized a new sample of participants from the same ongoing study that Montenigro et al. (2016) used for their analysis. The selected 70 individuals played high school or college level football and denied playing any other contact sports. For the purposes of testing versatility, we assembled a group of 82 new participants from the same study who had reported playing a secondary contact sport among those listed in Table 4. The mean CHI indexes for the total group, the validation group, and the experimental group (5037, 4306, and 5661 respectively; Tables 7-9) were all within the range expected for former high school and college level players based on previous research [27, 69].

This study should be viewed as a preliminary validation of the Montenigro et al. (2016) CHI Index. Our findings support that the CHII can effectively estimate RHI among football-only athletes who played at the high school and college level. Furthermore, our findings suggest that the CHII might adequately capture cumulative RHI among individuals who have played low-level additional contact sports such as boxing, wrestling and soccer. Although the CHII was not as successful at predicting late-life impairment when applied to the experimental sample, the CHII did capture higher RHI in the college vs high school experimental group players (Table 9), and successfully predicted two measures of impairment (Table 11).
As previously discussed, one of the intended primary uses of the CHII is in the context of CTE research. Therefore, the ability of the CHII to predict later-life neurobehavioral and cognitive impairment is paramount to its success. Our study showed that the CHII was very successful at predicting later-life impairment across the majority of clinical measures originally used by Montenigro et al. (2016) when the CHII was applied to the validation sample (Table 10). Furthermore, our findings for the validation sample support the threshold dose-response model initially proposed by Montenigro et al. (2016).

Clinical validation of the CHII was much less successful when applied to the experimental group, and to the entire study sample (experimental + validation) (Table 11 and 12). A likely explanation of the weaker predictive power of the CHII in the experimental sample, and thereby in the complete sample, are the RHI from a secondary sport that are not accounted for by the CHI index. Since the CHII only accounts for RHI in football, any athlete with another significant source of RHI (from soccer or boxing for example) will likely have a CHII that underestimates their true cumulative head impacts. This could also explain why the mean concussions reported by the experimental group were higher than the validation group; although the difference did not reach significance, this could be the result of our smaller sample size. Additional research with a larger sample size could add clarification to this.
If one assumes that the experimental group had CHI indexes that underestimated their true cumulative head impacts, then it seems possible that our pre-determined threshold-doses were inappropriate for use with those athletes. Since the threshold-doses from the Montenigro et al. (2016) study created with football only players, it may be worth re-running the determinations for the experimental sample and seeing if the CHII has more predictive power with new thresholds.

Further limitations in this study should also be addressed in future research. The CHII’s predictive power should be compared against concussion history, and seasons of play for the validation and experimental groups. Although we believe that the CHII will remain the superior predictor when applied to the validation sample, it seems possible that concussion history would become the better predictor for athletes with more complicated contact sport histories. Self-reported concussion histories, though unreliable, have the ability to capture RHI from a variety of contact sports, not just football. Therefore, concussion history may remain the preferable method of RHI estimation in athletes with multiple contact sports until accelerometer data becomes available for a wider range of activities besides football.

Overall the findings of this study emphasize that the connection between RHI and later-life neurobehavioral and cognitive impairment is not a simple one. Although this study supports that the CHI index is a significant improvement in retrospective estimation of RHI in football players, we must remember that RHI and later-life impairment occur in
the context of many other factors. For example, Montenigro et al. (2016) observed that more football seasons played (when controlling for CHII) predicted less behavior impairment (BRI) [27]. Montenigro et al. (2016) point out that this significant negative correlation between total seasons played and BRI could be explained by previous research which demonstrates the neurobehavioral benefits of exercise [27, 76-78]. Additional analysis could also be done with this present study to compare the likelihood of impairment between the validation and experimental sample.

This study is limited by many of the same factors as the original Montenigro et al. (2016) study. Despite validating that the CHII is able to predict later-life impairment in football only athletes, this is still not an explicit study of a relationship between the CHII and CTE. Until the CHII can be applied to neuropathologically confirmed cases of CTE, or until in-vivo biomarkers are discovered, the application of the CHII to CTE-specific research will remain somewhat speculative. Our study also does not clarify what factors contribute to the baseline risk of impairment. There is still a need for longitudinal research that accounts for factors such as BMI, diet, exercise, and genetics in order to better understand what contributes to the underlying risk of impairment among our samples. Additional limitations exist in the methodology for obtaining RHI estimates from the accelerometer studies. As is discussed by Montenigro et al (2016), the studies have slightly different methodologies such as different thresholds of recording. Future research should constantly strive to eliminate these limitations by updating the RHI estimates used in CHII calculations with any new accelerometer studies published. The
choice of a convenience sample from the LEGEND Study also causes a degree of selection bias that limits the external validity of our findings.

As mentioned above, future research studies should determine whether the CHII is better at predicting later life impairment in non-exclusive football players when compared to other metrics such as total seasons played, or total number of concussions reported. Until accelerometer data is available from other sports, the creation of a CHI-like index for other sports will remain impossible, and in the meantime it may be beneficial to create metrics that combine information from multiple sports (for example, total seasons of football, and total seasons of soccer) in a single useful metric. Although a great deal of public media attention is payed to the incidents of CTE found among football players, real-world athletes who participate in multiple sports might also be a great risk of developing these later-life diseases and must be studied as efficaciously as possible. Longitudinal, prospective studies like the LEGEND Study will remain indispensable in the further development of this research. As the LEGEND Study continues and more longitudinal data becomes available, researcher should expand their analysis with the CHII beyond the participant’s first year in LEGEND. The co-enrollment of LEGEND Study participants in brain donation programs such as the VA-BU-CLF Brain Bank will also ensure the availability of post-mortem CTE diagnoses to further validate any link between the CHII, RHI, and neurodegenerative diseases such as CTE.
LIST OF JOURNAL ABBREVIATIONS

JAMA........................................JAMA: The Journal of the American Medical Association

OAJSM .................................................. Open Access Journal of Sports Medicine
REFERENCES


2. *BMX Legend Dave Mirra Had Brain Disease CTE - BuzzFeed News*.

3. *Here's What We Don't Know About Head Injuries And Sport - BuzzFeed News*.


CURRICULUM VITAE

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EDUCATION

Vassar College: Poughkeepsie, NY
Bachelor of Arts, May 2014

Boston University School of Medicine, Division of Graduate Medical Sciences: Boston, MA
MS of Medical Sciences, anticipated May of 2016

RELEVANT EXPERIENCE

Boston University Medical Center
Head Research Coordinator: Legend Study
CTE Center, LEGEND Study – P.I. Dr. Robert Stern
April 2015 – August 2016
• As the head research coordinator for the C.T.E. Center’s LEGEND Study (Longitudinal Examination to Gather Evidence of Neurodegenerative Disease), I work very closely with study participants, beginning with their initial enrollment, and following them through their continued participation. I also work directly with the data collected by the study, and will be writing my Masters thesis over the next 12 months. I work one-on-one with our P.I. Dr. Robert Stern, and under his direction take on a wide variety of tasks, ranging from grant writing and IRB management, to data analysis and overall project restructuring. I also oversee the CTE Center’s internship program, and am responsible for training and directing between 4 and 5 graduate and undergraduate student interns. 40H/week

Premier Medical Group
Observer
Department of Urology under Paul K. Pietrow, M.D.
Fall 2013-Spring 2014
• Observed surgery and clinical visits with Dr. Pietrow over the course of my senior year at Vassar. A large portion of the surgeries were performed robotically or laparoscopically, and as a result I had the opportunity to work first hand with the da Vinci Skills Simulator. Aprox 10H/week.

Vassar College
Research Assistant
Department of Neuroendocrinology- Lab of Dr. Kelli Duncan
Fall 2012-Spring 2014
• Tested the neuroprotective effects of progesterone following traumatic brain injury (TBI). Utilizing a bird model of vocalization patterns, I test the comparative vocal recovery among progesterone vs. vehicle treated birds. The research hopes to better inform current studies of the use of progesterone as a drug therapy for acute immune responses that follows TBI in humans. Aprox 8-10H/week