Cumulative Head Impact Exposure Predicts Later-Life Depression, Apathy, Executive Dysfunction, and Cognitive Impairment in Former High School and College Football Players

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Contributor's Statement

Philip H. Montenigro is the primary author. He was responsible for the original design and conceptualization of the study and analyses, data collection, drafting of the manuscript, and interpretation of the data. Dr. Alosco participated in drafting and revising the manuscript. Mr. Martin participated in data management and analysis, and revising the manuscript. Mr. Daneshvar participated in initial design of the LEGEND study and revising the manuscript. Dr. Mez participated in revising the manuscript. Ms. Chaisson oversaw data management for this study. Mr Nowinski participated in obtaining funding for the study and revising the manuscript.

Dr. Au participated in drafting and revising the manuscript. Dr. McKee participated in revising the manuscript. Dr. Cantu participated in initial design of the LEGEND study and revising the manuscript. Dr. McClean participated in exposure modeling, interpretation of the data, and revising the manuscript. Dr. Tripodis is co-principal author; he participated in the study design, conducted the statistical analysis, participated in interpretation of the data, and manuscript revision for this study. Dr. Stern is co-principal author and is corresponding author. He was responsible for overseeing the study and participated in the study design, analysis, interpretation, and manuscript revision. He also played a role in obtaining funding for this study.

ABSTRACT

Repetitive head impacts (RHI) refer to the cumulative exposure to concussive and subconcussive events. Although RHI is believed to increase risk for later-life neurological consequences (including chronic traumatic encephalopathy), quantitative analysis of this relationship has not yet been examined due to the lack of validated tools to quantify lifetime RHI exposure. The objectives of this study were: 1) to develop a metric to quantify cumulative RHI exposure from football, that we term the cumulative head impact index (CHII); 2) to use the CHII to examine the association between RHI exposure and long-term clinical outcomes; and (3) to evaluate its predictive properties relative to other exposure metrics (i.e., duration of play, age of first exposure, concussion history). Participants included 93 former high school and collegiate football players that completed objective cognitive and self-reported behavioral/mood tests as part of a larger ongoing longitudinal study. Using established cut-off scores, we transformed continuous outcomes into dichotomous variables (normal versus impaired). The CHII was computed for each participant and derived from a combination of self-reported athletic history (i.e., number of seasons, position(s), levels played), and impact frequencies reported in helmet accelerometer studies. A bivariate probit, instrumental variable model revealed a threshold dose-response relationship between the CHII and risk for later-life cognitive impairment ($p<0.0019$), self-reported executive dysfunction ($p<0.0003$), depression ($p<0.0009$), apathy ($p<0.0040$), and behavioral dysregulation ($p<.0001$). Ultimately, the CHII demonstrated greater predictive validity relative to other individual exposure metrics.

Key Words: Football, concussion, subconcussive impacts, cognition, behavior, long-term impairment

INTRODUCTION

Repetitive head impacts (RHI) refer to the cumulative exposure to recurrent concussive and subconcussive events.[1-6] A *concussive* event is a direct or indirect impact to the head of sufficient intensity to produce overt clinical symptoms that typically resolve within days or weeks,[5] but can persist for months[7] or more than one year.[8] The mechanisms of concussion are believed to involve shearing and tensile forces to axons that occur during the impact induced acceleration, deceleration, and rotational forces of the brain.[9] A *subconcussive* event is similar in that it also involves a transfer of mechanical energy to the brain at enough force to injure axonal integrity, but does not result in clinical symptoms.[1-4, 10, 11] However, the intensity of impact necessary to trigger this potential neuronal damage is not known and whether there are levels of impact that are benign to neuronal functioning has also not been determined.

The investigation of RHI has most commonly been in the setting of contact sports, such as American football. Over 4.5 million amateur athletes participate in tackle football each year,[12, 13] and this sport has one of the highest rates of concussion.[14, 15] Surveys of high school and college athletes show that around 50% of football players suffer a concussion each year, and more than 30% sustain multiple concussions.[14, 16, 17] Subconcussive events are likely even more frequent, as helmet-based accelerometer studies estimate that amateur football players average 600 subconcussive impacts per season in high school and over 1000 at the collegiate level.[3] The high prevalence of concussive and subconcussive events in amateur football players is concerning given their reported association with acute[18-20] and chronic[21-25] neurological consequences. Repetitive subconcussive blows (measured by helmet accelerometer sensors recording events that exceed 14.4g[10]) are associated with pre- to post-season cognitive decline,[10, 26] functional brain alterations (e.g., reduced neurophysiological health),[10, 26, 27] and microstructural white matter brain changes[28] in high school football players.

Although research on this topic still is limited, cumulative concussive as well as subconcussive impacts may be a key contributor to later-life neurological consequences, including the neurodegenerative disease, chronic traumatic encephalopathy (CTE).[29] Importantly, 16% of pathologically confirmed cases of CTE have no reported history of concussion,[30] highlighting the potential long-term risks of subconcussive injury. In addition, although CTE has been described predominantly in former professional contact sport athletes, a recent study of deceased amateur athletes and controls found that a history of contact sport involvement was the greatest risk factor for CTE neuropathology.[31] Various exposure metrics (e.g., age of first exposure to football[32-34], duration of football play[11, 35-37], concussion history[21-25]) have been linked to later-life cognitive and neurobehavioral disturbances in former football players and other contact sport athletes. These different metrics may reflect different aspects of RHI exposure, each with slightly different effects on the brain.[11, 35]

A direct relationship between RHI and long-term clinical outcomes has been difficult to formally test due to the lack of validated tools to quantify cumulative RHI exposure.[38] Quantifying RHI exposure is methodologically challenging given that it involves a self-reported assessment of multiple events that occur throughout one's athletic career. Thus far, research on RHI and long-term outcomes has relied on single, indirect metrics based on a subject's history of traumatic brain injury (TBI) that involves retrospective self-reports or proxy reports using a structured interview containing validated scales[39-41]. These scales include those recommended by the National Institute of Neurological Disorders and Stroke (NINDS) common data elements and the Center for Disease Control (CDC).[42] Despite known limitations, numerous studies have demonstrated the usefulness of retrospective report in predicting long-term consequences following multiple concussions.[21, 22, 43] While short-term head impact exposure could be quantified prospectively with the placement of accelerometers in the helmets of athletes, this approach does not estimate cumulative exposure over one's athletic career, which is

speculated to be of primary importance for predicting later-life impairments and CTE.[44, 45] In response to this need, Kerr et al. recently proposed the Head Impact Exposure Estimate (HIEE),[46] which estimates a football player's total hours of contact exposure, excluding exposure prior to high school, using self-report interview. However, the HIEE has not been validated in a model with clinical outcomes.

In our study, we developed and validated a metric to estimate an athlete's total cumulative exposure to RHI from football, referred to as the cumulative head impacts index (CHII). To derive the CHII we combined two sources of information: a) individual *self-report* measures of athletic exposure; and b) extrapolated *objective* measures based on position(s) played, obtained from published helmet-accelerometer studies. Our metric includes estimates for youth, high school and collegiate level exposure, and incorporates percentages for all positions played (i.e. primary, secondary, tertiary, etc.). The purpose of this study was to evaluate the relationship between the CHII and later-life cognitive, behavioral, and mood impairment. Additionally, we compared the predictive validity of the CHII against three other individual exposure metrics, namely total season/years played, age at first exposure, and overall concussion history.[21-23, 25, 32, 33, 43, 47] We hypothesized that cumulative head impact exposure would have a measurable threshold, above which the risk of developing later life clinically-meaningful cognitive, mood, and behavioral impairment increases significantly.

MATERIALS AND METHODS

Study Design

This present sample was part of a larger ongoing study, the Longitudinal Examination to Gather Evidence of Neurodegenerative Disease (LEGEND) study, at the Boston University Alzheimer's Disease and CTE Center. LEGEND is a longitudinal study to assess potential risk factors for short- and long-term consequences of RHI. Participation involves annual telephone-based cognitive assessments, web-based measures of mood, behavior, and cognition, and saliva sampling for APOE genotyping. The LEGEND research protocol was approved by the Institutional Review Board of Boston University Medical Campus and written consent was obtained from all LEGEND participants. Study participation was open to adults, age 18 or older, who were either active or former athletes, across all sports and levels of play. There is no active recruitment program for LEGEND. Rather, this is a convenience sample in which potential subjects learn of the study through descriptions on the investigators' websites and through word-of-mouth. Therefore, the LEGEND sample should not be viewed as being representative of all athletes. Detailed descriptions of the LEGEND protocol have been previously published.[25, 47, 48]

Participants

Of the 800 participants in the LEGEND dataset at the time of analysis, 93 former amateur football players met the following inclusion and exclusion criteria: 1) highest level of football played was at high school or college; 2) no concussion sustained in the year prior to their initial evaluation (to diminish potential effect of acute brain injuries on clinical outcome measures); and 3) no participation in another contact sport (i.e., amateur wrestling, boxing, bull riding, diving, horse jumping, ice hockey, karate, lacrosse, martial arts, mixed martial arts, entertainment wrestling, rugby, and soccer). The

final sample included 17 former high school football players and 76 former collegiate football players. Demographic characteristics of the sample are in Table 1.

[Table 1 | about here]

Health & Athletic History

Participants were administered a structured questionnaire that has been used previously,[25, 32, 47] designed to collect retrospective information about the participant's lifetime athletic experience, past medical history, and concussion history. Questions about athletic experience captured variables regarded by the literature as being potential predictors of brain trauma, such as: (1) sports played,[11, 49] (2) age at first exposure to tackle football,[32-34], (3) levels of play,[50-53] (youth, high school, college, professional), (4) number of seasons played at each level, [27, 28, 54] (5) total years played,[23, 35-37] (6) all positions[55-58] played for each sport (1st, 2nd, 3rd etc.) at each level, (7) percentage of game time played at each position,[46, 58], and (8) age at retirement from the sport.[36]

The self-reported number of concussions was obtained, after participants were read a "modern" definition of concussion, based on the CDC statement on sports-related concussion[59] and the Third International Conference on Concussion in Sport held in Zurich.[60] The concussion history characteristics of the sample are provided in Table 2. Since the distribution of self-reported concussions is highly skewed, we used the log of concussions in all subsequent analyses to normalize the distribution. Participants were also asked to report their age at first exposure (AFE) to tackle football and the total number of seasons they played (i.e., duration of football play) (Table 2). For our analysis, participant's AFE was converted into a dichotomous variable: AFE before age 12 and AFE at age 12 or above. Age 12 was selected as the cutoff based on our previous work on AFE as an exposure metric associated with later-life clinical and structural changes.[32, 33] For duration of

play, we used seasons rather than years because for some athletes a year of football involved both a fall and spring season.

[Table 2 | about here]

Cumulative Head Impact Exposure Index (CHII)

The CHII was developed as an estimate of an athlete's total cumulative exposure to RHI from football. To derive an individual's CHII we combined data from two sources of information: a) individual *self-report* measures of athletic exposure obtained from the LEGEND questionnaire at each level played (youth, high school, college), such as number of seasons played, positions played at each level (primary, secondary, and tertiary), and the proportion of the season's total game time played at each position; and b) a measure of estimated head impacts received per season, based on data from published helmet accelerometer studies that report the frequency of head impacts per season by position and level of play (See below and Table 3).[55-57 61, 62].

Published Accelerometer Studies Used to Determine Frequency of Head Impacts by Position and Level of Play.

To obtain estimates of the frequency of head impacts by position and level of play, we performed a systematic review of the literature (using Pubmed) on helmet accelerometer studies, using the following keywords/search terms: HITS system, 6DOF, accelerometers, helmet-sensor, football, youth, high school, and college. Studies that satisfied the following *a priori* inclusion criteria were selected:

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 from analysis. A minimum cutoff of 10g ensures the elimination of non-impact events (e.g., jumping) from the calculation of head impact frequency.[37, 63-65 56, 66]

Table 3 provides a summary of key data-points obtained from each accelerometer study that met our inclusion criteria. The participants in the studies summarized in Table 3 were active in both games and practices. Since most players at youth level play at multiple positions, we include a single number to reflect exposure for all seasons each player spent at youth level. There was a single high school study identified that grouped together certain positions, such as linesmen, regardless of whether they played at offensive or defensive positions. Since many players at the high school level would interchangeably play at both offense and defense, using a similar exposure metric for these positions is a realistic assumption.[61] Impact frequencies from these studies was pooled and weighted, whenever possible, to derive averages weighted by each study's sample size. These weighted averages are estimates of the impact frequencies per position at the different levels of play (youth, high school, college).

[Table 3 | about here]

The CHII was calculated from the self-report variables and weighted impact frequencies using the equations outlined in Table 4. A hypothetical case is provided to illustrate the calculation of the CHII:

1. Mr. A is a 42 year old male who reports having participated in football at the youth, high school and collegiate levels.
    a. In college, Mr. A reported that he played a total of 3 seasons. His primary position for his college team was linebacker (LB); he reported having no secondary or tertiary positions of play. He estimated having participated in 85% percent of game downs as a linebacker. Thus, his college CHII was: (85%) x (685 impacts per season for LB from Table 5) x (3 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 CHII was: [(40%) x (619 impacts per season for LB) x (4 seasons)] + [(30%) x (868 impacts per season for OL) x (4 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. He estimated that he participated in 90% game downs for all 4 seasons. Thus, his youth CHII was: (90%) x (107 impacts per season for any position) x (4 seasons) = 385.
d. His overall CHII = 1,747 + 2,032 + 385 = 4,164.

[Table 4 | about here]

Clinical Outcomes & Measures

The following set of instruments administered to LEGEND participants were selected for the current study: (1) Brief Test of Adult Cognition by Telephone (BTACT)[67]; (2) Behavior Rating Inventory of Executive Function - Adult Version (BRIEF-A)[68]; (3) Center for Epidemiologic Studies - Depression Scale (CES-D)[69]; and (4) Apathy Evaluation Scale (AES)[70]. Each of these measures were chosen *a priori* based on their previous use in studies of TBI and concussion (BRIEF-A[25, 71, 72]; AES[73-75]; CES-D[76-78]; BTACT[79]), and on the availability of validated cut-off scores suggesting clinically meaningful impairment.[68, 73, 80-82]

Brief Test of Adult Cognition by Telephone (BTACT).[67, 79] The BTACT is an objective measure of cognitive function administered by telephone. The benefits and validity of cognitive test batteries administered by telephone are well-documented.[79, 83] The BTACT requires 20 minutes to complete

and consists of 6 subtests that 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] A global composite score was derived with the bi-factor approach, which has an overall improved validity over the single-factor approach and is better able to distinguish between persons with a lifetime history of head injury.[79] Age and gender corrected scores were scaled relative to a healthy normative sample. Objective cognitive impairment was defined as 1.5 standard deviations below the normative mean.[82, 84]

The Behavior Rating Inventory of Executive Function - Adult Version (BRIEF-A).[68] Participants completed an online version of the BRIEF-A questionnaire, a well-validated 75-item measurement of executive function behavior in activities of daily living. Participants rate "*how often each of the [75] following behaviors has been a problem?"* in the past month on a three-point Likert scale (1 = never, 2 = sometimes, 3 = often); higher scores indicate a greater degree of dysfunction. We used the global measure of executive function (Global Executive Composite [GEC]), as well as two factor-based measures of cognitive regulation (Meta-cognition Index [MI]) and behavioral-emotional regulation (Behavioral Regulation Index [BRI]). Raw scores are converted into standardized age-adjusted T-scores (M=50, SD=10). T-scores ≥1.5 standard deviations of the normative mean (T-scores ≥ 65) are considered clinically impaired.[68]

The Center for Epidemiologic Studies - Depression Scale (CES-D).[69] The CES-D is a 20-item self-report measure of depression symptoms that was developed and validated by the National Institute of Mental Health.[69] Participants rate their depression symptom severity in the past week on a four-point Likert scale that ranges from "none of the time" to "all of the time." Higher scores indicate more

severe depressive symptoms, with an established total CES-D cutoff score ≥ 16 reliably indicating clinically meaningful depression.[80, 81]

Apathy Evaluation Scale (AES).[70] The AES is an 18-item self-report measure of apathy over the past four weeks. Participants rate their apathetic emotions, thoughts, and behaviors in the past 4 weeks on a four-point Likert scale that ranges from "not at all characteristic" to "very characteristic." Higher total AES scores indicate worse apathy, with an established cutoff total AES score ≥ 34 reliably indicating clinically meaningful apathy.[73]

Statistical Modeling

Group Comparisons. The former high school and collegiate football player groups were compared 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.

[Figure 1 | about here]

Regression Modeling. To test our study hypothesis we modeled each dichotomous outcome measure (probability of impairment or not) with our predictor metric (CHII). This model is illustrated in Figure 1. We first identified a point (threshold-dose) at which the magnitude of the relationship (slope) changes from a zero magnitude (B1=0) to a non-zero magnitude (B2>0). The change-point threshold shows the conversion of the relationship from a baseline risk of playing football to a dose-response relationship above which higher exposure to head impacts can lead to higher risk of impairment.[85] The change point was identified using a Bayesian hierarchical model estimated by Markov Chain Monte Carlo (MCMC) method with 30,000 simulations implemented in PROC MCMC in SAS 9.4.[85] An important contribution in modeling head impact exposure to long-term outcomes is the incorporation of concussion history into the model. Since a head impact is a necessary condition for a concussion,

we cannot estimate the effect of head impacts by controlling for concussions in a simple regression setup. This relationship between predictors where a value of one variable is directly caused by another is often described as endogenous.[86] If endogeneity exists between variables within our model, the following two problems would occur: (1) a linear regression model that includes both the CHII and concussion history would give invalid inference, and (2) the estimates of the slopes from such a regression model would be biased. To address the inference and bias problems caused by endogeneity we used an "instrumental variable model" with log concussions as the instrument.[87] The instrumental variable model can be described as a two-stage regression. In the first-stage regression, we estimate the effect of the log of the number of concussions on the CHII, while in the second-stage regression we use the predicted values from the first stage to estimate the effect of the CHII on the probabilities of impairment for each of the outcomes. Both regressions included age and education as covariates. Next, we applied the instrumental variable model using a bivariate probit model. The estimated effect of cumulative head impacts derived from this instrumental variable model is equivalent to an effect estimated among the compliers from a study where exposure was prospectively randomized.[88] Thus, an instrumental variable model allows for causal inference from observational data with large measurement error.[88, 89] Furthermore, the instrumental variable approach reduces the measurement error of the estimates of frequency of head impacts by position and level of play. Since the studies used to estimate these frequencies are independent from the LEGEND study, their measurement error is uncorrelated from the self-reported concussions in LEGEND. Therefore, in this instance, concussions become an ideal instrument to calibrate and reduce the measurement error of head impacts exposure. Similar approaches in different setting have been used in econometric and clinical therapeutic studies. [90,91]

Comparison to other exposure metrics. We also examined *total seasons played* and *age of first exposure* (AFE) as simple exposure metrics that have demonstrated a significant relationship with

clinical outcomes in other studies.[11, 32, 33, 35, 36] Total season played and AFE were independently added to our bivariate probit model with age and education as covariates. Next, we modeled clinical outcomes with concussion history in a separate univariate probit model, with age and education included as covariates.

RESULTS

Participant Demographics & Group Comparisons

[Table 5 | about here]

Participant demographics (Table 1), exposure variables (Table 2), and outcome measures (Table 5) were compared across the two highest levels of play, i.e., high school and college. The college-level group had significantly more years of education (t-test=3.58, p-value=0.0005), more seasons played (t-test=4.85, p-value<0.0001), a greater number of concussions (Wilcoxon=592.5, p-value=0.0431), and a higher CHII (t-test=2.47, p-value=0.0156. All other group comparisons were nonsignificant. Mean scores on the BTACT, an objective measure of cognitive function, indicated that the entire sample was, on average, cognitively normal (Table 5).

CHI Exposure & Risk of Impairment

The CHII was calculated for all 93 participants, and the means for former high school and collegiate football players are listed in Table 2.

[Table 6 | about here]

[Figure 2 | about here]

The CHII change-points listed in Table 6 indicate the threshold number of impacts, above which a dose-response relationship is initiated between exposure (CHII) and the risk of impairment. Figure 2 shows the predicted probabilities of impairment for different doses of exposure. The baseline risk of impairment significantly increases linearly after a change-point as exposure increases in all outcomes. (See **supplementary Table 1** for a tabular summary of the data depicted in Figure 2). Specifically, we find that the risk of impairment increases steadily every 1400 impacts, or twice the

sample's average's season number of impacts (700) above the baseline change-point. For all outcomes, the risk of developing clinically meaningful impairments in mood, behavior, and cognition increased considerably with two additional seasons worth of head impacts. For example, we found that adding 10 seasons of impacts above the baseline threshold increased a subject's risk of developing objective cognitive impairment by 25 fold.

Other Exposure Metrics & Risk of Impairment

We added alternate exposure metrics to our bivariate probit model to test whether other metrics might be better at predicting clinical outcomes and/or whether they might eliminate the predictive significance of the CHII. Total seasons of play and AFE did not add independently to our bivariate probit model, nor did they eliminate the significance of the CHII for predicting clinical outcomes. When added to the model with the CHII, participants with AFE<12 showed some increase in the risk for impairment but did not achieve significance on any outcome after adjusting for CHI: GEC (β=0.41, p-value=0.2542), MI (β=0.36, p-value=0.3456), BRI (β=0.56, p-value=0.073), CES-D (β=0.49, p-value=0.1771), AES (β=0.33, p-value=0.4170), BTACT (β=0.81, p-value=0.1427). Interestingly, when controlling for CHI, increasing the total number of seasons played reduced the risk for clinical impairment : BRI (β=-0.11, p-value=0.0183), MI (β=-0.09, p-value=0.0847), GEC (β=-0.07, p-value=0.1586), CES-D (β=-0.09, p-value=0.1224), AES (β=-0.07, p-value=0.2011), BTACT (β=-0.03, p-value=0.6390). The *significant* negative association between total seasons played and BRI is consistent with previous research demonstrating a neurobehavioral benefit from regular exercise.[92-94] The betas (β indicates the magnitude and direction of the relationship between the predictor, AFE or total seasons, and the risk for impairment in a model that also takes into account a quantitative estimate of CHI exposure. For example, positive betas indicate a positive association between

exposure and impairment, such that increasing exposure was associated with an increased probability of impairment..

Lastly, we explored the role *concussion history* had on predicting clinical outcomes and compared its predictive power to that of the CHII. Because of the endogeneity problem previously described (i.e., that head impacts are a necessary factor for both the CHII and concussions) we could not simply include concussion history as a covariate in our CHII model. The spearman correlation between concussion history and the CHII was 0.22 (p-value=0.02). Therefore, we ran a univariate probit model with age and education as covariates, in order to evaluate the predictive power of concussions on the probability of impairment. The estimates were: BRI (β =0.50, p-value=0.0109), MI (β =0.41, p-value=0.0255), GEC (β =0.48, p-value=0.0138), CES-D (β =0.48, p-value=0.0195), AES (β=0.30, p-value=0.0717), BTACT (β =0.43, p-value=0.1526). Compared to the CHII, concussion history was limited to predicting self-reported changes in behavioral regulation (BRI), cognition (MI), executive dysfunction (GEC), and depression (CES-D), but not apathy (AES), or objective cognitive dysfunction (BTACT). Even for the significant outcomes (BRI; MI; GEC; CES-D), concussion history was found to have less predictive power than the CHII.

DISCUSSION

We developed a metric of cumulative exposure to RHI from football, the CHII, a measure that includes self-reported exposure and estimated quantitation of head impacts based on published helmet accelerometer studies. The CHII was used to examine the relationship between cumulative RHI exposure and later-life cognitive, mood, and behavioral impairment in a sample of former football players whose highest level of play was either high school or college. Subjects denied having played any other contact sport at any time. The mean CHII of 7,742 total impacts for our sample is consistent with the range of cumulative impacts expected for former high school and college football players.[3] We found that the CHII strongly predicts later-life clinical outcomes, outperforming other individual metrics such as concussion history, age at first exposure to tackle football, and total duration of play, suggesting that it is a useful metric to estimate lifetime RHI exposure.

We view this study as an initial examination of the CHII and our findings of the relationship between earlier RHI exposure and later life impairments should be considered preliminary due to several limitations described below. Moreover, this was not a study of CTE or neurodegeneration; our outcome measures focused on clinically-meaningful levels of cognitive, mood, and behavior impairment and did not include any biomarkers of underlying disease or injury. This study does, however, underscore the importance of subconcussive trauma in the development of later life neurological impairment. The number of self-reported concussions predicted impairment in fewer outcomes than the CHII. Compared to the CHII, concussion history did not significantly predict apathy or objective cognitive dysfunction (BTACT). These findings are consistent with previous imaging studies of amateur athletes which demonstrated that changes in brain functional imaging occurred after a single season of cumulative asymptomatic impacts without concussion[10, 26, 27] and post-mortem studies that indicate 16% of former contact-sport athletes with pathologically verified CTE had no concussion history.[30].[36] These studies together with our current findings highlight the critical

need to evaluate prospectively the potential risk and later-life consequences of exposure to repetitive asymptomatic blows to the head (i.e., subconcussive impacts).

This study is the first in the literature to demonstrate a threshold dose-response relationship between estimated cumulative head impact exposure from football and later-life risk for cognitive and neurobehavioral impairment. We found that after a threshold, the risk for impairment increased with additional impacts. Similar findings of a threshold dose-response from RHI have been reported in studies of soccer and boxing.[35, 95-97] Specifically, our results show that the risk of developing behavioral dysregulation, executive dysfunction, depression, and apathy nearly doubled with 2800 additional impacts above the threshold. Our findings also show that increasing the CHI dose from 6500 to over 12000 increased the risk for objective cognitive impairment by a considerable twenty-five fold.

Interestingly, the dose-response threshold for cognitive function was much higher relative to other outcomes. Though speculative, it is possible that changes in mood and behavior reflect a different underlying mechanism or areas of structural impairment than cognitive changes, and that the cognitive changes reflect the evolution and progression of underlying CTE pathology.[36, 98] This is consistent with previous imaging studies in soccer players, wherein a lower threshold for detecting microstructural brain changes from soccer heading was identified compared to the threshold for memory impairment on neuropsychological evaluation.[95] Furthermore, in CTE, individuals with cognitive symptoms present later in the clinical course than behavioral impairments.[98]

Our findings indicate that below identified thresholds, accumulated impacts have no apparent effect on the risk for cognitive or neurobehavioral impairment. However, individuals had a baseline constant risk below the threshold. This baseline risk does not suggest that safety below the threshold is

assumed. Moreover, our study design does not allow us to determine a safe time to cease RHI exposure, i.e., quit football. Furthermore, the baseline risk and the threshold likely depend on several subject-specific factors such as possible genetic susceptibility, body mass index, socioeconomic status, cognitive reserve, etc.[99] Large, well-controlled, prospective, longitudinal research that distinguishes threshold effects and baseline risk in football is clearly needed to identify maximum exposure levels for each player's safety. Such research would ultimately facilitate the development of safety guidelines that could minimize the risk of adverse effects on the brain in football.

Considering the public health implications of our study, there is also a need to investigate any causal evidence between RHI exposure and clinical impairment. Establishing cause indicates the possibility of intervention. We utilized the Bradford-Hill criteria for evaluating causal inference in observational studies[100] and our findings are *suggestive* of a causal relationship between cumulative head impact exposure and later-life clinical impairment. We analyzed eight Bradford-Hill criteria in our model: strength, dose-response, consistency, plausibility, coherence, experiment, reversibility, temporality, and specificity. *Strength of association* between our predictor, the CHII, was very strong on all six measures of clinical impairment and higher than any other exposure predictor. The *dose-response criterion* is of particular importance in disorders that exhibit a latent onset, and this was supported by the present study.[101] Regarding *consistency of association,* the dose-response relationship has also been shown in boxers.[94, 102-103] The *plausibility of association* is supported by human and animal studies that show cumulative subconcussive impacts and axonal Injury and blood brain barrier damage.[10, 11, 28, 93, 104-107] Since 1928, a relationship has been hypothesized between RHI and neurological disease supporting the notion of *coherence of association*.[106] Animal models have shown reduced number of impacts results in a reduced negative consequences to support *experimentation of association and the reversibility of association*.[109-110] Lastly, exposure must

precede the disease, which conforms to observations in all previous studies and demonstrates *temporality of association*.

These findings do not suggest that every individual with a history of RHI -- even exposure above the reported thresholds -- will have later life cognitive, mood, or behavioral impairments or develop a neurodegenerative disease, such as CTE. Support of a causal relationship does not imply a universal relationship. For example, a causal relationship between smoking tobacco and subsequent lung cancer has long been accepted. However, not all smokers develop lung cancer; some develop other conditions and diseases causally linked to smoking (e.g., stroke, heart disease, emphysema), and still others remain healthy throughout their lives. We hope that the use of the CHI (and subsequent iterations of this exposure metric) will result in greater clarification and validation of the causal relationship between football-related RHI and later life clinical impairment.

The current study has clear limitations. Although all the accelerometer studies used to measure RHI discarded linear accelerations below 10g, some of the studies used a slightly higher minimum cutoff to register a hit. However, small differences in cutoff points are likely not meaningful given that the majority of recorded impacts had mean accelerations well above the minimum cutoff points (as supported by the data summarized in Table 3). For instance, the frequency of impacts per season reported by Mihalik et al.[55] was lower than the frequency reported by Crisco et al.,[57] despite having used a lower cutoff (Mihalik 10g; Crisco 14.4g). Additional research using both helmet-based and head-based accelerometers is needed to develop standardized, consensus based cutoff points.[66] In addition, within the CHII, it is assumed that players are active in both games *and* practice, and does not take into account players who do not participate in games. Participants in our study were active players in games in high school and in college. For example, former college players in our study averaged 3.6 years of play and 50% game involvement. Therefore, because of the possible

difference in RHI exposure between reserve players (who participate in all practices but limited game involvement) and starters (who participate in all practices and have extensive game involvement), and because of the potential discrepancy in the frequency and severity of RHI exposure between practices and games, our findings may not accurately reflect differences in long-term consequences between starters and reserve players. Moreover, our study evaluated only certain aspects of exposure (i.e., cumulative impacts) and did not use other possible biomechanical metrics, such as cumulative linear and rotational accelerations. The sample size of the present study was also small due to the strict inclusion and exclusion criteria. The present results will need replication in larger studies. Furthermore, despite our analytic approach, the study design is cross-sectional which limits the extent to causal inference. Our convenience sample may induce a self-selection bias limiting the external validity of our findings. However, our instrumental variable analytic approach reduced the measurement error bias and potential confounding effects.[111] Specifically, this method allowed us to provide unbiased estimates of causal effects in our nonrandomized sample[88, 89] and is increasingly utilized in clinical studies[112-113] particularly when there are obstacles to performing a randomized controlled trial.

Future studies will be necessary to validate the CHII and improve our understanding on the long-term clinical consequences of RHI exposure. Larger studies are needed to investigate the effect of CHI exposure by age and level. Studies utilizing objective fluid and neuroimaging biomarkers will allow for a better understanding of the underlying etiology associated with CHI exposure. Case-controlled postmortem studies will also be necessary to examine the association between the CHII and CTE (and other) neuropathology. There is also the need to examine additional potential risk factors that may modify the relationship between RHI exposure and later life cognitive and neurobehavioral impairment, including, but not limited to, genetics, diet, exercise, substance use (including performance enhancing drugs), and cardiovascular risk. Finally, there is a need for similar models of

cumulative RHI exposure for other contact sports, once accelerometer or some other objective measure of head impacts is more widely available.

CONCLUSION

We developed the CHII, a tool to quantify retrospective cumulative exposure to RHI, including subconcussive impacts. Using the CHII, we showed that RHI exposure among amateur football players is associated with later-life cognitive and neurobehavioral consequences. Although our findings raise safety concerns for participation in amateur football, prior to changes in policy and rules, prospective longitudinal research in larger samples is needed to validate the CHII and replicate and extend our associated findings.

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RAS is a paid consultant to Amarantus Bioscience, Biogen, and Avanir Pharmaceuticals. He also serves as an expert advisor to attorneys for cases pertaining to the long-term consequences of repetitive brain trauma. He receives royalties from Psychological Assessment Resources for the publication of neuropsychological tests. **RCC** receives compensation from the National Football League as Senior Advisor to the Head Neck and Spine Committee, from the National Operating Committee on Safety of Athletic Equipment as Chairman of the Scientific Advisory Committee and from Concussion Legacy Foundation as co-founder and Medical Director for some talks given and research conducted. He receives royalties from Houghton Mifflin Harcourt and compensation from expert legal opinion. All other authors report no competing financial interests. For all other authors, no competing financial interests exist.

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FIGURE LEGENDS

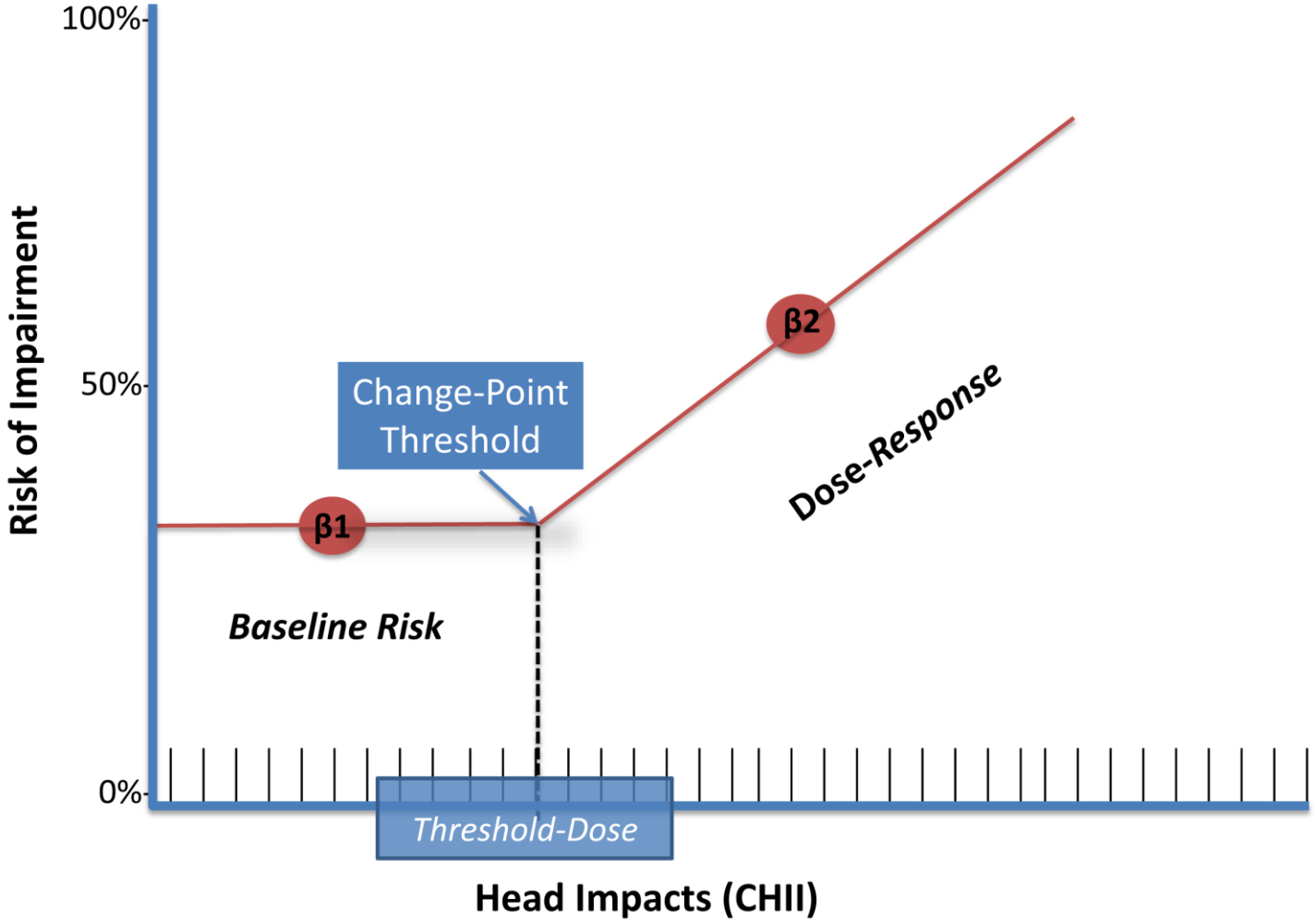

Figure 1. Schematic of the dose-response model with a constant baseline risk of later-life impairment (Baseline gradient of slope = 0) below the cumulative head impact threshold-dose and with increasing probability of impairment (Dose-Response gradient of slope > 0) above that threshold-dose.

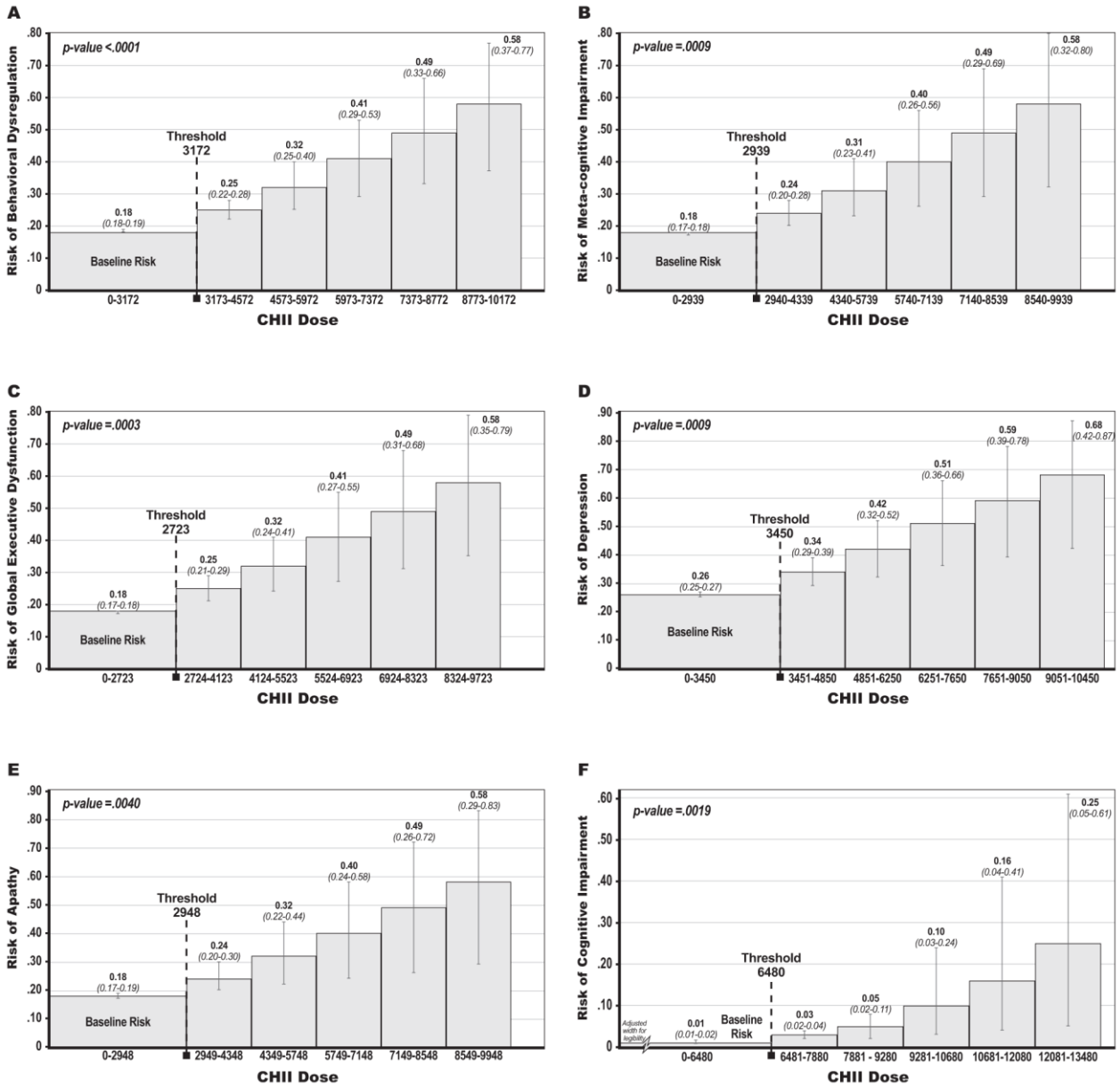

Figure 2. (A-F) Each dichotomous outcome measure (A-F; probability of impairment) was fit using a bivariate probit, instrumental variable model adjusted for both age and education as well as our predictor variable of interest (CHII). Baseline Risk refers to the risk of impairment at the CHII dose range below the thresholds identified in Table 6. Above these threshold, a significant linear dose-response relationship between CHII exposure and later-life clinical impairment was found for all outcomes. See supplemental Table 1 for tabular data.

lative Head Impact Exposure Predicts Later-Life Depression, Apathy, Executive Dysfunction, and Cognitive Impairment in Former High School and College Football Players (doi: 10.1089/neu.2016

TABLES

Table 1. Demographics

	Total Sample N=93	High School N=17	College N=76	
	Mean (SD)	Mean (SD)	Mean (SD)	*p-value
Age (years)	47.3 (13.9)	43.6 (11.6)	47.7 (14.2)	0.2760
Formal education (years)	16.9 (2.1)	15.3 (2.1)	17.2 (2.0)	0.0005
Education (terminal degree N%)				
High School / GED	11(11.8)	6 (35.3)	5 (6.6)	0.0018
Bachelor's / Associates / etc	50 (53.8)	7 (42.2)	43 (56.6)	
Master's or Doctorate	32 (34.4)	4 (23.5)	28 (36.8)	
Working Full or Part Time N(%)	63 (67.7)	10 (58.8)	53 (69.8)	0.673
Marital Status Married N(%)	39 (41.9)	5 (62.5)	34 (63.0)	0.658
Body Mass Index	31.5 (5.6)	31.5 (6.7)	31.5 (5.3)	0.994
Handedness-Right N(%)	74 (79.6)	13 (76.5)	61 (80.3)	0.484
Military history N(%)	14 (15.1)	5 (29.4)	9 (11.8)	0.0671

***Wilcoxon two sample test. Numbers in parentheses are standard deviations except when otherwise indicated.**

Table 2. Exposure variables

	Total Sample N=93	High School N=17	College N=76	
	Mean (SD)	Mean (SD)	Mean (SD)	p-value
[a]Concussion history Median (IQR)	20 (3)	10 (13)	20 (39)	0.0431*
[b]CHII	7741.5 (4547.3)	5348.8 (3600.2)	8276.7 (4583.8)	0.016
Age at first exposure (years)	10.9 (2.7)	10.8 (2.7)	11.0 (2.7)	0.884
Average years of youth football	3.3 (2.5)	3.4 (2.3)	3.3 (2.5)	0.931
Seasons of football play	11.1 (4.2)	7.1 (3.1)	12.0 (3.1)	<.0001
Time since retirement (years)	26.3 (14.2)	26.4 (12.2)	26.3 (14.4)	0.971

***Wilcoxon two sample test; [a]Interviewers read participants a current definition of concussion (methods described elsewhere[47]) and asked to estimate their concussion history based on that definition; [b]Cumulative Head Impacts Index. Numbers in parentheses are standard deviations except when otherwise indicated. IQR = inter-quartile range.**

Table 3. Summary of data collected from review of helmet-accelerometer studies

Level	Position	Study	Minimum acceleration	N	Mean/ Median	Weighted mean impacts per season
College	DL	Crisco et al 2010[57]	14.4 g	29	1086	871
		Mihalik et al 2007[55]	10.0 g	13	965	
		Crisco et al 2011[62]	10.0 g	49	718	
	LB	Crisco et al 2010[57]	14.4 g	29	846	685
		Mihalik et al 2007[55]	10.0 g	9	655	
		Crisco et al 2011[62]	10.0 g	47	592	
	DB	Crisco et al 2010[57]	14.4 g	34	487	417
		Mihalik et al 2007[55]	10.0 g	12	731	
		Crisco et al 2011[62]	10.0 g	55	306	
	OL	Crisco et al 2010[57]	14.4 g	46	960	728
		Mihalik et al 2007[55]	10.0 g	22	921	
		Crisco et al 2011[62]	10.0 g	75	543	
	OB/RB	Crisco et al 2010[57]	14.4 g	23	459	412
		Mihalik et al 2007[55]	10.0 g	12	589	
		Crisco et al 2011[62]	10.0 g	37	326	
	WR	Crisco et al 2010[57]	14.4 g	16	305	237

		Mihalik et al 2007[55]	10.0 g	5	501	
		Crisco et al 2011[62]	10.0 g	30	157	
	QB	Crisco et al 2010[57]	14.4 g	8	305	206
		Crisco et al 2011[62]	10.0 g	14	149	
High School	QB	Broglio et al 2011[61]	15 g	4	467	467
	WR/DB	Broglio et al 2011[61]	15 g	28	372	372
	RB/LB	Broglio et al 2011[61]	15 g	27	619	619
	DL/OL	Broglio et al 2011[61]	15 g	41	868	868
Youth	All positions	Daniel et al 2012[56]	10 g	7	107	107

Player positions selected by our study participants were grouped, whenever necessary, in accordance with position groups as reported in the selected helmet-accelerometer studies and cross-referenced with position groups as characterized by relevant and authoritative publications.[58,114] 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. For more detailed information see references listed in table.

Table 4. Calculation of the Cumulative Head Impacts Index

YOUTH	**% games played at 1st position**	**X**	**Position's weighted average # impacts per season**	**X**	**Total # of youth seasons**	**= [A]**
	+					
	% games played at 2nd position	**X**	**Position's weighted average # impacts per season**	**X**	**Total # of youth seasons**	
	+					
	% games played at 3rd position	**X**	**Position's weighted average # impacts per season**	**X**	**Total # of youth seasons**	
+						
HIGH SCHOOL	**% games played at 1st position**	**X**	**Position's weighted average # impacts per season**	**X**	**Total # of youth seasons**	**= [B]**
	+					
	% games played at 2nd position	**X**	**Position's weighted average # impacts per season**	**X**	**Total # of youth seasons**	
	+					
	% games played at 3rd position	**X**	**Position's weighted average # impacts per season**	**X**	**Total # of youth seasons**	
+						
COLLEGE	**% games played at 1st position**	**X**	**Position's weighted average # impacts per season**	**X**	**Total # of youth seasons**	**= [C]**
	+					
	% games played at 2nd position	**X**	**Position's weighted average # impacts per season**	**X**	**Total # of youth seasons**	
	+					
	% games played at 3rd position	**X**	**Position's weighted average # impacts per season**	**X**	**Total # of youth seasons**	

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

Table 5. Behavior, mood, and cognition outcome measures

	Total Sample N=93	High School N=17	College N=76	
	Mean (SD)	Mean (SD)	Mean (SD)	p-value
Behavioral Regulation Index of the BRIEF-A[68]	64.1 (15.9)	64.4 (16.0)	64.0 (16.0)	0.9288
Metacognition Index of the BRIEF-A[68]	64.5 (16.9)	62.2 (14.8)	65.0 (17.4)	0.5493
Global Executive Composite of the BRIEF-A[68]	65.3 (16.9)	64.2 (15.0)	65.6 (17.3)	0.7563
Center for Epidemiologic Studies Depression Scale[69]	21.7 (15.5)	21.7 (17.9)	21.7 (15.0)	0.9854
Apathy Evaluation Scale[70]	35 (11.5)	34.2 (12.5)	35.2 (11.3)	0.7455
Brief Test of Adult Cognition by Telephone[79]	0.04 (0.9)	-0.11 (1.05)	0.08 (0.90)	0.4359

BRIEF-A = Behavior Rating Inventory of Executive Function – Adult Version.

Table 6. Change point thresholds from baseline constant risk to dose-response relation between CHII and risk of impairment

Outcome Measure	Clinical Domain	Threshold *Median CHII for Dose-Response	95% CI
Behavioral Regulation Index of the BRIEF-A	Behavior	3172	1579-8726
Metacognition Index of the BRIEF-A	Metacognition	2939	1554-8715
Global Executive Composite of the BRIEF-A	Executive Function	2723	1541-9040
Center for Epidemiologic Studies Depression Scale	Depression	3450	1588-8159
Apathy Evaluation Scale	Apathy	2948	1541-6938
Brief Test of Adult Cognition by Telephone	Cognition	6480	1749-9567

***The Median and 95% CI from 30,000 Markov Chain Monte Carlo simulations. Change-point thresholds represent the median number of impacts above which there is a predictive dose-response relationship between head impacts and clinically meaningful measures of impairment. BRIEF-A = Behavior Rating Inventory of Executive Function – Adult Version.**

SUPPLEMENTAL MATERIAL

Supplemental Table 1. Predicted probabilities of impairment with 95% CI for different doses of cumulative exposure

Clinical Outcome		*Baseline	Baseline + 1400 CHI	Baseline + 2800 CHI	Baseline + 4200 CHI	Baseline + 5600 CHI	Baseline + 7000 CHI	p-value
Behavior (BRI)	CHII Dose	0-3172	3173-4572	4573-5972	5973-7372	7373-8772	8773-10172	<.0001
	Risk of Impairment	0.18(0.18-0.19)	0.25(0.22-0.28)	0.32(0.25-0.40)	0.41(0.29-0.53)	0.49(0.33-0.66)	0.58(0.37-0.77)	
Meta-cognition (MI)	CHII Dose	0-2939	2940-4339	4340-5739	5740-7139	7140-8539	8540-9939	0.0009
	Risk of Impairment	0.18(0.17-0.18)	0.24(0.20-0.28)	0.31(0.23-0.41)	0.40(0.26-0.56)	0.49(0.29-0.69)	0.58(0.32-0.80)	
Executive Function (GEC)	CHII Dose	0-2723	2724-4123	4124-5523	5524-6923	6924-8323	8324-9723	0.0003
	Risk of Impairment	0.18(0.17-0.19)	0.25(0.21-0.29)	0.32(0.24-0.41)	0.41(0.27-0.55)	0.49(0.31-0.68)	0.58(0.35-0.79)	
Depression (CES-D)	CHII Dose	0-3450	3451-4850	4851-6250	6251-7650	7651-9050	9051-10450	0.0009
	Risk of Impairment	0.26(0.25-0.27)	0.34(0.29-0.39)	0.42(0.32-0.52)	0.51(0.36-0.66)	0.59(0.39-0.78)	0.68(0.42-0.87)	
Apathy (AES)	CHII Dose	0-2948	2949-4348	4349-5748	5749-7148	7149-8548	8549-9948	0.0040
	Risk of Impairment	0.18(0.17-0.19)	0.24(0.20-0.30)	0.32(0.22-0.44)	0.40(0.24-0.58)	0.49(0.26-0.72)	0.58(0.29-0.83)	
Cognition (BTACT)	CHII Dose	0-6480	6481-7880	7881-9280	9281-10680	10681-12080	12081-13480	0.0019
	Risk of Impairment	0.01(0.01-0.02)	0.03(0.02-0.04)	0.05(0.02-0.11)	0.10(0.03-0.24)	0.16(0.04-0.41)	0.25(0.05-0.61)	

Adjusted for age and education. *Baseline refers to the risk of impairment at the CHII dose range below the change-point thresholds listed in Table 6. At and below these thresholds risk of impairment is at a constant baseline. Above the threshold, there is a dose-response relationship between increasing CHII exposure and the risk of clinical impairment. All outcome measures were transformed into dichotomous variables (impairment or not) using established cut-off points. These results identify the risk of developing clinically meaningful impairment in

later-life from exposure to impacts from amateur football.