Elevated markers of brain injury as a result of clinically asymptomatic high-acceleration head impacts in high-school football athletes

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OBJECTIVE This prospective observational cohort study of high-school football athletes was performed to determine if high-acceleration head impacts (HHIs) that do not result in clinically diagnosed concussion still lead to increases in serum levels of biomarkers indicating traumatic brain injury (TBI) in asymptomatic athletes and to determine the longitudinal profile of these biomarkers over the course of the football season.

METHODS Sixteen varsity high-school football athletes underwent baseline neurocognitive testing and blood sampling for the biomarkers tau, ubiquitin C-terminal hydrolase L1 (UCH-L1), neurofilament light protein (NF-L), glial fibrillary acidic protein (GFAP), and spectrin breakdown products (SBDPs). All athletes wore helmet-based accelerometers to measure and record head impact data during all practices and games. At various time points during the season, 6 of these athletes met the criteria for HHI (linear acceleration > 95g and rotational acceleration > 3760 rad/sec²); in these athletes a second blood sample was drawn at the end of the athletic event during which the HHI occurred. Five athletes who did not meet the criteria for HHI underwent repeat blood sampling following the final game of the season. In a separate analysis, all athletes who did not receive a diagnosis of concussion during the season (n = 12) underwent repeat neurocognitive testing and blood sampling after the end of the season.

RESULTS Total tau levels increased $492.6\% \pm 109.8\%$ from baseline to postsession values in athletes who received an HHI, compared with $164\% \pm 35\%$ in athletes who did not receive an HHI ($p = 0.03$). Similarly, UCH-L1 levels increased $738.2\% \pm 163.3\%$ in athletes following an HHI, compared with $237.7\% \pm 71.9\%$ in athletes in whom there was no HHI ($p = 0.03$). At the end of the season, researchers found that tau levels had increased 0.6 ± 0.2 pg/ml ($p = 0.003$) and UCH-L1 levels had increased 144.3 ± 56 pg/ml ($p = 0.002$). No significant elevations in serum NF-L, GFAP, or SBDPs were seen between baseline and end-of-athletic event or end-of-season sampling (for all, $p > 0.05$).

CONCLUSIONS In this pilot study on asymptomatic football athletes, an HHI was associated with increased markers of neuronal (UCH-L1) and axonal (tau) injury when compared with values in control athletes. These same markers were also increased in nonconcussed athletes following the football season.

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KEYWORDS traumatic brain injury; concussion; subconcussion; biomarker; accelerometry; pediatrics

HIGH-SPEED collision sports continue to be extremely popular among adolescents, even though the adolescent brain may be particularly sensitive to mild traumatic brain injury (mTBI), or concussion.^{5,19,46} Concussion is defined by the Concussion in Sports Group

as a “traumatic brain injury induced by biomechanical forces.”¹⁹ However, the clinical diagnosis of concussion is currently made on the basis of overt clinical symptoms such as loss of consciousness or the athlete’s self-report of symptoms. The majority of concussions are not visibly

ABBREVIATIONS BESS = Balance Error Scoring System; CCAT = Computerized Cognitive Assessment Tool; fMRI = functional magnetic resonance imaging; GFAP = glial fibrillary acidic protein; HHI = high-acceleration head impact; K-D Test = King-Devick Test; mTBI = mild traumatic brain injury; NF-L = neurofilament light protein; SAC = Standardized Assessment of Concussion; SBDP = spectrin breakdown product; SCAT3 = Sports Concussion Assessment Tool—3rd edition; UCH-L1 = ubiquitin C-terminal hydrolase L1.

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recognizable, allowing many athletes who may be experiencing subtle symptoms to elude clinical testing and continue to play.^{4,12,22,23,44} Although concussions are known to have negative effects on academic and job performance, one study in high-school football athletes showed that only 47.3% of athletes reported their concussion symptoms; reasons for this lack of reporting included the athlete's desire to continue to play, a lack of awareness about concussion or the seriousness of the injury, and the desire not to let the team down.^{18,34}

Given the difficulty in establishing the diagnosis of mTBI, blood biomarkers have been an attractive area of research because they can be objectively quantified.⁴⁵ Several studies have shown that axonal and neuronal proteins are elevated after mTBI.^{13,31} Examples of such proteins include tau, ubiquitin C-terminal hydrolase L1 (UCH-L1), neurofilament light protein (NF-L), glial fibrillary acidic protein (GFAP), and spectrin breakdown products (SBDPs). Tau is a microtubule-associated protein found abundantly in axons; previous studies have shown tau to be elevated in pediatric patients and professional hockey players who have sustained an mTBI.^{9,21,39} UCH-L1 is a highly specific neuronal protein that has been shown to be elevated in the presence of mTBI.^{15,29,43} Alpha II-spectrin is a component of the cortical membrane cytoskeleton and is found in axons and presynaptic terminals.^{7,35} The breakdown products of this protein (SBDPs) were found to be elevated in concussed hockey players.⁴¹ GFAP is an intermediate protein found in the astroglial skeleton and has proved to be a promising biomarker for mTBI, given its specificity to the brain.^{14,26,28,30,32} NF-L is a major component of the axonal skeleton and has been found to be elevated after mTBI in boxers and in patients with post-concussion syndrome.^{38,40}

Previous investigations have revealed a subset of football athletes in whom there was evidence of altered brain functionality on functional magnetic resonance imaging (fMRI) in the absence of clinically apparent symptoms.⁴² The investigators were unable to elucidate whether the athletes were not experiencing symptoms or not reporting symptoms, but their findings may represent nonclinical sequelae of head impacts without concussion. A correlation analysis indicated that the fMRI changes were related to the number of impacts sustained in the previous week of football participation, but impact severity was not evaluated.

Kinematic data of postimpact head motion, monitored using helmet-based accelerometers, have shown promise in identifying parameters that elevate the risk for concussion. However, the ability to implement the use of biomechanical data that predict concussion remains elusive.^{19,25} Nevertheless, high-acceleration head impacts (HHIs) have consistently been shown to elevate the risk of neurological injury.⁶ In a study of 54,247 head impacts captured by helmet accelerometry in high-school athletes, there was a 6.9% incidence of mTBI when the impact exceeded 5582.6 rad/sec² in rotational acceleration and 96.1g in linear acceleration, while the incidence of mTBI was 0.00004% when the impact magnitude fell below these values.³ Similar data have also been reported in both collegiate and professional athletes.^{8,33}

The goal of this study was to evaluate the relationship between HHI and serum biomarkers for mTBI in a cohort of high-school varsity football athletes. Given the known likelihood of underreporting of symptoms by athletes, we hypothesized that those athletes who experienced HHIs would demonstrate neurocognitive deficits and biomarker evidence of mTBI, despite the absence of overt clinical symptoms.

Methods

Study Population and Study Design

A prospective cohort study of high-school varsity football athletes was conducted between July and October 2016. After study approval by the University of Michigan Institutional Review Board, written assent and consent were obtained. Any athlete who was undergoing active treatment for mTBI, had a history of moderate or severe TBI, or had undergone neurosurgery was excluded. Sixteen athletes volunteered for participation. Demographic information was obtained, including age, height, weight, concussion history, and sports participation history. All athletes underwent a preseason clinical evaluation that included use of the Axon Sports Computerized Cognitive Assessment Tool (CCAT; Cogstate), King-Devick (K-D) Test (kingdevicktest.com), Balance Error Scoring System (BESS; University of North Carolina Sports Medicine Research Laboratory), Sports Concussion Assessment Tool—3rd edition (SCAT3; <http://bjism.bmj.com/content/bjsports/47/5/259.full.pdf>), and Standardized Assessment of Concussion (SAC; a component of SCAT3) for symptom evaluation. The CCAT-generated composite scores of processing speed, attention, learning, working memory speed, and working memory accuracy were used as an index for cognitive functioning. In addition, a blood sample was obtained at the same time point in all participants to establish baseline values.

Each athlete's helmet was fitted with the Riddell Head Impact Telemetry System (HITS; Simbex) encoder to measure and record head impact data during all practices and games. All athletes were monitored for concussion symptoms by the athletic training staff, and diagnoses of mTBI were made by independent physicians. A second blood sample was obtained immediately after the athletic event during which an athlete received an HHI, which was defined as an impact that simultaneously achieved a linear acceleration of > 95g and a rotational acceleration of > 3760 rad/sec². This definition was based on results of a previous investigation together with a correction to the resultant rotational acceleration value.^{3,36} In all athletes who did not meet the criteria for an HHI sometime during the course of the season, a second blood sample was obtained immediately after the final game of the season. Finally, 3–5 days after the final game of the season, a third blood sample was obtained in all athletes and all underwent repeat testing using the CCAT, K-D Test, BESS, SCAT3, and SAC.

Biochemical Procedures

All blood samples were obtained via venipuncture of the median cubital vein or dorsal metacarpal vein into

serum-separation tubes. Specimens were kept at room temperature and allowed to stand for 1 hour. The samples were then centrifuged at 1200g for 15 minutes. The supernatant was aliquoted into cryovials and immediately stored at -80°C . At the conclusion of the season, samples were sent to the Quanterix Corporation for total tau and NF-L analysis, and to Banyan Biomarkers for GFAP, UCH-L1, and SBDP analysis. The limits of detection were as follows: tau 0.01 pg/ml, NF-L 0.01 pg/ml, GFAP 8 pg/ml, UCH-L1 13 pg/ml, and SBDPs 3 pg/ml. All values found to be below the limit of detection were reported to be one-half the limit of detection. The coefficient of variation was 4% for tau, 5% for NF-L, and unreported for GFAP, UCH-L1, and SBDPs.

Statistical Analysis

Serum levels of the biomarkers of TBI and neurocognitive testing scores were obtained and analyzed pre- and postseason as well as at the end of the last game for controls and at the end of the game in which the HHI occurred for members of the HHI group. Continuous data were summarized using the mean $\pm$ standard error. Categorical data were summarized by counts and percentages. The distribution of the clinical data was examined to determine the proper statistical test. Overall comparisons of pre- and postseason data for all athletes were done by using either a paired t-test or the Wilcoxon signed-rank test. The Pearson (r) or Spearman (ρ) correlation coefficient was used to examine the magnitude of the correlation between changes in biomarker values from the pre-season measurements, together with the total number of hit impacts during the season, the cumulative linear and rotational acceleration, and the magnitude of the correlation between the percentage change in biomarkers at the end-of-game assessment and the maximal linear and rotational acceleration. A between-group analysis (HHI vs non-HHI) was performed using the percentage change at the end-of-game assessment compared with baseline data to account for baseline variability with a low sample size. Percentage-change data were analyzed by performing either a 2-sample t-test or the Wilcoxon rank-sum test. Scatterplots were produced to display the change in clinical data between groups. A p value of 0.05 or smaller was considered significant for all hypothesis tests. The aforementioned tests were all done using SAS 9.4 (SAS Institute Inc.), and the figures were produced using GraphPad Prism 7.00 (GraphPad Software).

Results

Study Population

Sixteen male athletes assented to participation in the study and consent was obtained from them or their parents as appropriate. The athletes had a mean age of 16.9 ± 0.2 years, height of 182.7 ± 1.8 cm, and weight of 94.7 ± 5.5 kg, as well as a mean of 7 years of playing football prior to the study season. Six athletes (37.5%) reported that they previously had sustained an mTBI. Two athletes were unable to participate in the accelerometry analysis during the season (one athlete was demoted from varsity football and the other had an incompatible helmet). These athletes

were not included in the HHI analysis and were not included in the correlation analysis of helmet kinematics and biomarker level changes that was performed at the end of season. Three athletes were diagnosed with an mTBI during the season and were removed from further analysis, although one of these athletes had received an HHI that preceded and was unrelated to his mTBI diagnosis. In one athlete, the baseline biomarker levels were elevated to the maximal limits of detection. This athlete was eliminated from further analysis due to our inability to reliably measure changes in biomarker levels. Data from a total of 45 athletic events (36 practices, 9 games) were captured using helmet accelerometry.

HHI Biomarker Testing

Of the 14 athletes monitored with helmet accelerometry, 3 were ineligible for analysis (one with a broken leg, one with a diagnosed mTBI, and one in whom there was a biomarker analysis discrepancy). Six athletes met the acceleration criteria for HHI and 5 athletes were identified as non-HHI controls. During the season 7756 total head impacts were recorded, of which 11 impacts (0.001%) met the criteria for HHI. No athletes received multiple HHIs in a single game or practice, and only the first incidence of HHI for any particular athlete was used for analysis. In the HHI group, the mean linear acceleration was $114.7g \pm 5.3g$, and the rotational acceleration was 5224.5 ± 260.1 rad/sec². In the non-HHI group, the mean maximal linear acceleration on the day of testing was $63.6g \pm 10.5g$ and the mean maximal rotational acceleration was 2346.8 ± 166.2 rad/sec².

In the HHI group, the mean time between the HHI and venipuncture was 87.7 ± 9.5 minutes, whereas in the non-HHI group, the mean time between the maximal impact and venipuncture was 99.6 ± 19.7 minutes. Serum levels of biomarkers in the HHI and non-HHI groups are summarized in Table 1. There were no differences in baseline values between the HHI and non-HHI (control) athletes ($p > 0.05$). There was a mean percentage increase of $492.6\% \pm 109.8\%$ in serum tau after HHI, compared with $164.0\% \pm 35.3\%$ in controls ($p = 0.03$). Serum UCH-L1 rose $738.2\% \pm 163.3\%$ after HHI, compared with $237.7\% \pm 71.9\%$ in controls ($p = 0.03$). There were no significant differences between the HHI and non-HHI groups for changes in NF-L, GFAP, or SBDPs (for all, $p > 0.05$). Biomarker level results for players with and without HHI are displayed in Fig. 1. There was a positive correlation between the maximal rotational acceleration and the percentage change in tau ($r = 0.65$, $p = 0.03$) and UCH-L1 ($r = 0.65$, $p = 0.03$). No other significant correlations between the maximal rotational acceleration or maximal linear acceleration and the percentage change in biomarkers were seen (for both, $p > 0.05$).

End-of-Season Biomarker Testing

Of the 16 athletes in the study, 4 were ineligible for postseason analysis (3 with a diagnosis of mTBI and 1 in whom there was a biomarker analysis discrepancy). The remaining 12 athletes were eligible for postseason testing. Pre- and postseason serum values of biomarkers are sum-

TABLE 1. Comparison of biomarker serum-level changes between the HHI and non-HHI groups

Biomarker	Baseline (pg/ml)	Postgame (pg/ml)	Percentage Change (%)	p Value
NF-L				
Non-HHI group	4.58 ± 1.21	7.52 ± 3.48	64.7 ± 51	1.0
HHI group	5.53 ± 1.20	8.74 ± 1.70	62.2 ± 14	
Tau				
Non-HHI group	1.05 ± 0.07	2.70 ± 0.27	164.0 ± 35.3	0.03
HHI group	0.79 ± 0.16	3.86 ± 0.35	492.6 ± 109.8	
GFAP				
Non-HHI group	32.69 ± 9.99	33.02 ± 9.07	3.2 ± 6.8	0.6
HHI group	38.02 ± 17.24	43.51 ± 18.0	36.0 ± 17.9	
SBDPs				
Non-HHI group	24.24 ± 9.40	41.42 ± 5.53	148.8 ± 64.1	0.5
HHI group	24.50 ± 4.58	44.61 ± 6.31	105.4 ± 31.9	
UCH-L1				
Non-HHI group	234.62 ± 50.59	686.56 ± 81.28	237.7 ± 71.9	0.03
HHI group	183.25 ± 92.11	945.80 ± 136.13	738.2 ± 163.3	

There were 6 athletes in the HHI group and 5 in the non-HHI (control) group. Values are expressed as means ± standard errors unless otherwise indicated. Boldface type indicates statistical significance.

marized in Table 2. A 64.8% increase in levels of tau ($p = 0.003$) and a 62.6% increase in levels of UCH-L1 ($p = 0.002$) were seen at the end of the season. There were no significant changes in levels of NF-L, GFAP, or SBDPs. The mean number of head impacts was 471.6 ± 69.4 , the mean cumulative linear acceleration was $1.25 \times 10^4 g$, and the mean cumulative rotational acceleration was $5.66 \times 10^5 \text{ rad/sec}^2$. No significant correlations were seen between accelerometry metrics and changes in pre- and postseason serum levels of tau, UCH-L1, NF-L, or GFAP. There was a negative correlation between changes in SBDPs and the number of head impacts ($r = -0.76$, $p = 0.01$), cumulative linear acceleration ($r = 0.69$, $p = 0.02$), and cumulative rotational acceleration ($r = -0.75$, $p = 0.01$).

Neurocognitive Testing

The results for pre- and postseason neurocognitive scores are summarized in Table 3. Among the 12 athletes eligible for postseason analysis, there was a significant im-

provement in the K-D Test time (-6.8 ± 1.4 seconds, $p < 0.001$) as well as in the processing speed (4.7 ± 2.0 , $p = 0.03$), likely due to a learning effect. There were no other significant changes in neurocognitive parameters.

Discussion

TBI-specific biomarkers are a promising advance in the development of an objective method of mTBI diagnosis.³¹ However, there is limited evidence regarding the effects on these biomarkers of a single large-magnitude impact in the absence of concussion and of repetitive nonconcussive impacts. To our knowledge, this study is one of the first to show direct associations between a high-magnitude head impact not resulting in concussion and brain injury in humans. Previous work has demonstrated elevated tau and NF-L following a match in boxers without a diagnosed mTBI,^{24,40} and Oliver et al. reported an increase in NF-L in asymptomatic athletes over the course of a collegiate football season.²⁷ As these markers are present in both clinically symptomatic and nonsymptomatic athletes, their diagnostic utility remains unknown, but these recent studies do provide evidence that repetitive nonconcussive impacts can affect serum biomarkers.

In the present study, tau and UCH-L1 levels significantly increased in athletes after a single HHI when compared with the levels of these markers in athletes who did not receive an HHI. These results suggest neuronal and axonal injury after HHI. An HHI was defined objectively by using helmet accelerometry based on previous work indicating that the greatest mTBI risk is with an impact having linear acceleration $> 95g$ and rotational acceleration $> 3760 \text{ rad/sec}^2$. Of the 7756 total head impacts recorded over the full season, only 11 (0.001%) met the criteria for HHI. The alterations in blood biomarkers seen in the HHI group indicate that a significant effect on blood biomarker levels may occur with only a limited number of football-

FIG. 1. Scatterplot of percentage changes in biomarkers in the HHI (triangles) and non-HHI (circles) groups. Values are displayed as means ± standard errors.

TABLE 2. Biomarker changes across the season in the 12 athletes available for postseason analysis

Biomarker	Preseason (pg/ml)	Postseason (pg/ml)	Change (%)	p Value
NF-L	5.05 ± 0.76	7.48 ± 1.3	48.1	0.09
Tau	0.88 ± 0.09	1.45 ± 0.19	64.8	0.003
GFAP	39.75 ± 10.02	41.75 ± 10.49	5.0	0.1
SBDPs	23.33 ± 4.28	28.25 ± 2.63	21.1	0.1
UCH-L1	230.30 ± 56.26	374.50 ± 66.51	62.6	0.002

Values are expressed as means ± standard errors unless otherwise indicated. Boldface type indicates statistical significance.

related impacts. A recent study by Kawata et al. supports this finding, demonstrating that a group of football athletes with higher cumulative impact kinematics had consistently greater increases in S100 β , another biomarker of brain injury, after practice than a group of athletes with lower cumulative impact kinematics.¹¹ However, the effect of a solitary HHI was not evaluated. Similarly, Marchi et al. evaluated serum S100 β in college football players before and after games.¹⁷ They determined that there was a correlation between S100 β changes and the number and severity of head impacts, which were determined by a video review and athlete report, respectively. In a subset of athletes, the authors additionally correlated the changes in S100 β with changes on diffusion tensor imaging (DTI), which were suggestive of structural changes in the brain. Again, the effect of a single HHI could not be evaluated as the head impact severity was not confirmed with helmet accelerometry.

The potential for detrimental long-term effects resulting from repeated impacts is rooted in the theory that each head impact leads to subtle damage to the neuron that accumulates to clinically meaningful changes over time.^{1,2,16} A threshold for the number of impacts has recently been proposed without accounting for impact severity.²⁰ Based on data from this pilot study, it is possible that nonconcussive HHI and mTBI are not dichotomous entities, but rather represent movement along a spectrum of injury.

Although recent guidelines of the Concussion in Sports Group do not support the use of accelerometry to diagnose mTBI, the results from our study suggest that accelerometry may have clinical utility.¹⁹ The neuronal and axonal markers of HHI may represent the low end of the spectrum of brain injury that is not captured by the current, clinically dependent definition of mTBI. Accelerometry can identify those athletes with HHIs and bring them to clinical attention. This could potentially be an actionable area for athletic trainers and physicians, as HHIs represent only 0.001% of all impacts. Finally, while it is impractical to eliminate all head contact in collision sports, it is reasonable to predict that improvements in technology and refinement of game rules may reduce the incidence of HHI.^{10,37}

Not only did the present study identify biomarker evidence of neuronal and axonal injury after HHI, but the increase in serum tau and UCH-L1 levels identified post-season suggests neuronal and axonal injury in these high-

TABLE 3. Neurocognitive performance scores across the season in the 12 athletes available for postseason analysis

Test	Preseason	Postseason	p Value
K-D Test (seconds)	48.2 ± 2.4	41.4 ± 1.7	<0.001
SAC score	26.1 ± 0.7	27.4 ± 0.5	0.1
BESS score	9.1 ± 1.1	7.8 ± 1.5	0.3
SCAT symptom inventory score	3.3 ± 1.4	3.3 ± 1.1	0.3
CCAT score			
Processing speed	100.0 ± 1.5	105.0 ± 1.5	0.03
Attention	103.0 ± 1.3	105.0 ± 1.5	0.2
Learning	104.0 ± 2.8	107.0 ± 3.3	0.3
Working memory speed	102.0 ± 2.3	105.0 ± 2.3	0.05
Working memory accuracy	105.0 ± 2.2	98.7 ± 1.5	0.05

Values are expressed as means ± standard errors unless otherwise indicated. Boldface type indicates statistical significance.

school athletes in whom mTBI was not diagnosed. To our knowledge, this is the first evidence of biomarker changes in clinically asymptomatic athletes of this age. These results are similar to those of Talavage et al., who described activation alterations in the dorsolateral prefrontal cortex in clinically asymptomatic high-school football athletes.⁴² Those authors also found evidence of neurocognitive deficits in visual and verbal composite scores, findings that differ from those of the present study in which no objective neurocognitive deficits were captured. Further, Talavage et al. noted a correlation between the number of impacts to the upper-frontal location and changes observed on fMRI, whereas the present study did not find any positive correlation between the cumulative hit total or cumulative impact kinematics and the changes in TBI biomarkers. Importantly, the lack of association between cumulative head impact burden and biomarker changes in this study suggests that there are likely other important factors that may result in the development of long-term sequelae in athletes involved in collision sports. Notably, following games there were increases in biomarker levels in athletes in the non-HHI group as well, suggesting that the routine contact experienced in football may lead to deleterious cellular effects, even though the cause and clinical significance of increased biomarker levels in athletes who did not receive an HHI remain unclear. Finally, the lack of correlation of the results of biomarker measurement with those of neurocognitive testing in our study participants may be attributable to the inherent insensitivity of those neurocognitive tests for detection of subtle changes resulting from HHI. Importantly, a formal neuropsychological assessment performed by a neuropsychologist remains the gold standard.¹⁹

Limitations to the Study

There are a number of limitations to this study. The sample size was small, potentially increasing an outlier effect and impairing the ability to control for variables such as medical history, age, weight, and other factors. The small sample size may have affected the ability to detect a correlation between kinematics and changes in serum

biomarkers. The results found here must be replicated in a larger study. Additionally, we were unable to have a control at the time of the HHI; instead, control values were obtained at the end of the last game of the season. The timing to blood draw in the non-HHI (control) group (99.6 minutes after impact) was similar to that in the HHI group (87.7 minutes after HHI), but this difference may have led to some unexpected effects. Furthermore, the clinical implications of subclinical elevations in the selected biomarkers are uncertain. Long-term effects of the elevations seen here may be insignificant. The reasons why tau and UCH-L1 levels were found to be elevated after HHI and at the end of the season, while GFAP, NF-L, and SBDPs levels were unchanged, also remain to be determined. The very early timing of the blood draw may have affected these results. Without a non-collision sport control, it is unclear why the biomarkers were elevated even in the non-HHI football control group. These elevations could be related to additional minor head impacts or peripheral nerve injury, or they may have been exercise induced. Finally, this prospective observational, nonrandomized study relied on volunteer subjects, which could potentially lead to a volunteer bias in the data.

Conclusions

In this pilot study of asymptomatic high-school football athletes, HHI was associated with increased markers of neuronal (UCH-L1) and axonal (tau) injury in athletes with HHI exposure compared to controls without HHI. These same markers were also increased among non-HHI athletes at the end of the football season. Interpretation of these findings remains unknown, as these athletes did not demonstrate clinical signs and symptoms of mTBI.

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Disclosures

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Author Contributions

Conception and design: Joseph, Park, Szerlip, Broglio. Acquisition of data: Joseph, Swallow, Willsey, Broglio. Analysis and interpretation of data: Joseph, Swallow, Broglio. Drafting the article: Joseph, Swallow, Willsey, Broglio. Critically revising the article: Joseph, Korley, Oppenlander, Park, Szerlip, Broglio. Reviewed submitted version of manuscript: Joseph, Swallow, Korley, Oppenlander, Park, Szerlip, Broglio. Approved the final version of the manuscript on behalf of all authors: Joseph. Statistical analysis: Lapointe, Khalatbari. Study supervision: Joseph, Park, Szerlip, Broglio.

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