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CLINICAL ARTICLE

Effects of repetitive head trauma on symptomatology of subsequent sport-related concussion

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OBJECTIVE Adolescent participation in athletics continues to grow, leading to an increasing incidence of sports-related concussion (SRC). The current literature suggests that a greater number of prior concussions positively correlates with a greater number of total symptoms, but the specific concussion-related symptoms are not as well defined. The current study investigated the effects of prior recurrent head injury on the symptom profiles of student-athletes after another suspected concussion.

METHODS A multicenter database consisting of 25,815 Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) results was filtered for student-athletes aged 12–22 years old who competed in 21 different sports. Patients were separated into 2 cohorts: athletes reporting a single prior concussion (SRC1) and athletes reporting 2 or more prior concussions (SRC2+). Comparisons were assessed for differences in 22 symptoms and 4 symptom clusters at baseline, first postinjury test (PI1), and second postinjury test (PI2) by using univariate and multivariate analyses.

RESULTS No differences were seen between SRC1 (n = 2253) and SRC2+ (n = 976) at baseline. At PI1, the SRC2+ group (n = 286) had lower severity of headaches (p = 0.04) but increased nervousness (p = 0.042), irritability (p = 0.028), sadness (p = 0.028), visual problems (p = 0.04), and neuropsychiatric symptoms (p = 0.009) compared with SRC1 (n = 529). Multivariate analysis revealed decreased headache severity with increased prior concussion (β = −0.27,95% CI −0.45 to −0.09, p = 0.003). Multivariate analysis at PI2 demonstrated the SRC2+ cohort (n = 130) had increased cognitive (β = 1.22, 95% CI 0.27–2.18, p = 0.012), sleep (β = 0.63, 95% CI 0.17–1.08, p = 0.007), and neuropsychiatric (β = 0.67,95% CI 0.14–1.2,0.014) symptoms compared with SRC1 (n = 292).

CONCLUSIONS At longitudinal follow-up, patients with a history of recurrent concussions reported greater symptom burden in cognitive, sleep, and neuropsychiatric symptom clusters but not migraine symptoms. This is an important distinction because migraine symptoms are often more easily distinguishable to patients, parents, and physicians. Careful assessment of specific symptoms should be considered in patients with a history of recurrent head injury prior to return to play.

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KEYWORDS traumatic brain injury; repetitive trauma; adolescent athlete; concussion

Parents often encourage their children to participate in organized sports for established physical, psychological, and sociological benefits.[1,2] Such positive outcomes speak to both the current overall increase in youth numbers within organized athletics, as well as the pragmaticism in forecasting said numbers to continue rising in the United States.[3] Extensive adolescent sport involvement is coupled with concussion incidence, and the prevalence of concussions among children serves as a considerable concern among parents and relevant governing entities.[2] Approximately 30–45 million children and adolescents participate in nonscholastic sports, and over 7 million adolescents take part in high school sports in the US annually.[4–6] Sports-related injuries are frequent,

ABBREVIATIONS ADHD = attention-deficit/hyperactivity disorder; DLD = developmental language disorder; ImPACT = Immediate Post-Concussion Assessment and Cognitive Testing; PI1 = first postinjury test; PI2 = second postinjury test; S_{diff} = standard error of difference at the 80% confidence interval; SRC = sports-related concussion; SRC1 = athletes reporting a single prior concussion; SRC2+ = athletes reporting 2 or more prior concussions.

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accounting for almost one-fourth of children and adolescents presenting to the emergency department with a head injury.[7] Additionally, the Centers for Disease Control and Prevention has reported that 20% of the estimated 1.7 million concussions that occur each year in children and adolescents are sports related.[8,9]

Heightened awareness of the potential consequences of those who engage in athletics begs the question of whether the aforementioned benefits outweigh the risks. Although most children and adolescents who endure a sports-related concussion (SRC) recover entirely from their initial symptoms, a subset of youth athletes experience more unfavorable outcomes such as cognitive, behavioral, and emotional consequences.[10,11] The sequelae of those who experience multiple concussions are even less promising, as repetitive concussions during maturation may result in both acute (e.g., recovery, return-to-play) and long-term (cognitive performance, mood dysregulation) complications.[12] Furthermore, even subtle cognitive discrepancies may have profound effects on academic and athletic performance, as well as social integration.

Although a prior study in the literature investigated differences in concussion incidence and recovery of children and adolescents with varying numbers of previous concussions, there is limited evidence on associated concussion symptomatology.[13] Understanding how symptomatology changes in young athletes who have multiple concussions could help to predict potential long-term consequences (academic, athletic, social performance), retrospectively grade severity of concussion, and/or provide better guidelines for safe return to sports and academics. We hypothesized that athletes with a history of multiple concussions would have greater neuropsychiatric and cognitive symptom burden compared with individuals with a single prior concussion.

Methods

Data Collection

Data were queried from a multicenter database supplied by ImPACT Applications, Inc., which were composed of 25,815 Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) assessments performed from 2009 to 2019. The ages of the subjects ranged from 12 to 22 years. Eligibility criteria included subjects who had an established baseline test prior to injury and then sustained an SRC in competitive play or practice. Additionally, only patients who reported their number of previous concussions, which occurred before the current suspected concussion was evaluated with ImPACT in our database, were included. A total of 11,563 subjects were included in the defined age group. All athletes without a baseline test (n = 2295), as well as those who did not report their number of prior concussions (n = 1987), were excluded.[14] Baseline tests were split into 2 cohorts: those who reported a single prior concussion (SRC1), and those who reported 2 or more previous concussions (SRC2+). Institutional Review Board approval was granted for this study, and the requirement for informed consent was waived.

Head Injury Symptom Profiles

The ImPACT test is a battery of neurocognitive assessments designed to evaluate for cognitive dysfunction after a suspected head injury. These assessments are divided into 5 broad categories (verbal memory, visual memory, processing speed, reaction time, and total symptom score). Per the ImPACT protocols, significant deviation from baseline by the standard error of difference at the 80% confidence interval (S_{diff}) in at least 2 of the 5 composite scores is an indication of concussion.[14,15] Ultimately, concussion is a clinical diagnosis that requires evaluation by physicians and athletic training staff; however, for the purposes of this investigation, we used the ImPACT criteria for our concussion diagnosis at postinjury, as previously reported in the literature.[14–16]

Head injury was defined as any insult that required evaluation by a trainer, physician, or coach at the time of injury and led to a postinjury ImPACT test being levied to further evaluate for concussion. As part of the ImPACT assessment, patients are prompted to rate the current severity of 22 symptoms on a scale from 0 to 6, with 6 indicating maximum severity. These individual symptoms are also grouped into symptom clusters (migraine, cognitive, sleep, neuropsychiatric). The full list of symptoms and symptom clusters is included in Table 1.[17] The individual symptom scores were collected at baseline and the first postinjury test (PI1). PI1 was defined as the first ImPACT test taken after a suspected head injury. If the subject met the qualifications for a concussion at PI1 (with 2 of 5 composite scores below S_{diff}), they would then proceed to take a second postinjury test (PI2) to track recovery and to determine if they still met the criteria for concussion. Symptom cluster data were also collected for subjects at PI2; individual symptom data were unavailable.

Statistical Analysis

The demographic characteristics of all those who met the inclusion criteria of the SCR1 and SCR2+ cohorts were compared, while only subjects who had ImPACT assessments that qualified as a concussion at PI1 and PI2 were included in the postinjury symptom analyses. We used the chi-square test to compare categorical variables, and the Student t-test was used to compare continuous variables.

The multivariate models controlled for age, sex, chronic headache history, diagnosed learning disability, and attention-deficit/hyperactivity disorder (ADHD) and were used to evaluate the effect of previous concussions on the symptoms experienced at PI1. PI2 controlled for all the same variables but also included the number of days between the 2 tests as an additional variable in the regression analysis. We performed 2 separate multivariate models: 1 analyzed the number of prior concussions as a categorical variable (SRC1 vs SRC2+), and 1 analyzed the number of prior concussions as a continuous variable. All statistical modeling was performed by using Prism 9.5.0 (GraphPad Software), with a confidence interval of 95% and $\alpha = 0.05$.

Results

The study population included 2253 subjects in the SRC1 cohort and 976 subjects in SRC2+. The average age

TABLE 1. Symptoms and symptom clusters

Migraine	Cognitive	Neuropsychiatric	Sleep
Headache	Feeling mentally "foggy"	Nervousness	Trouble falling asleep
Nausea	Feeling mentally "slowed down"	Sadness	Drowsiness
Vomiting	Difficulty remembering	Feeling more emotional	Sleeping too much
Balance problems	Difficulty concentrating	Irritability	Sleeping too little
Dizziness			
Visual problems			
Fatigue			
Sensitivity to light			
Sensitivity to noise			

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of SRC2+ was older than that of SRC1 (15.69 vs 15.54 years, $p = 0.012$), but no difference was seen between the proportions of subjects who were male (68.3% vs 67.5%, $p = 0.66$). The numbers of patients with ADHD and developmental language disorder (DLD) were also not statistically different between the 2 groups (137 vs 75 patients, $p = 0.09$; 80 vs 37 patients, $p = 0.74$). The mean years of experience within athletics was marginally higher in SRC2+ (2.47 vs 2.24, $p < 0.021$) (Table 2).

On univariate analysis of PI1, the SRC2+ cohort (n = 286) had lower severity of headaches (mean 1.06 vs 1.27, $p = 0.04$) than SRC1 (n = 529). However, the severity of irritability (1.13 vs 1.1, $p = 0.028$), nervousness (0.42 vs 0.285, $p = 0.042$), sadness (0.37 vs 0.27, $p = 0.028$), visual problems (0.525 vs 0.406, $p = 0.042$), and neuropsychiatric cluster (1.65 vs 1.25, $p = 0.009$) symptoms were all greater in patients who had 2 or more concussions (Fig. 1). Although statistically insignificant, SRC2+ trended toward significance for increased severity of vomiting (0.077 vs 0.038, $p < 0.088$) and sleeping more (0.451 vs 0.316, $p < 0.054$). The entirety of the univariate results for PI1 are reported in Table 3.

On univariate analysis of PI2, SRC2+ (n = 130) demonstrated greater severity in several symptom clusters, including cognitive (3.32 vs 2.12, $p = 0.011$), sleep (1.42 vs 0.84, $p = 0.011$), and neuropsychiatric (1.45 vs 0.77, $p = 0.009$) clusters, in comparison with those in SRC1 (n = 292) (Fig. 2). A complete report of the univariate analysis of PI1 is reported in Table 3.

Multivariate analysis, with the number of prior concussions at PI1 used as a categorical variable, demonstrated that the SRC2+ cohort had a decreased association with headache symptoms ($\beta = -0.27$, 95% CI −0.45 to −0.09, $p = 0.0031$). Multivariate analysis, with the number of prior concussions at PI2 used as a categorical variable, revealed that the SRC2+ cohort had an increased association with experiencing cognitive ($\beta = 1.22$, 95% CI 0.27–2.18, $p = 0.0121$), sleep ($\beta = 0.63$, 95% CI 0.17–1.08, $p = 0.0070$), and neuropsychiatric ($\beta = 0.67$, 95% CI 0.14–1.2, $p = 0.0138$) cluster symptoms (Table 4). After adjustment of our multivariate model to account for the number of prior concussions as a continuous variable, the only notable difference with the initial model that used a categorical variable was that headache symptoms were no longer signficiantly different at PI1 ($\beta = -0.09$, 95% CI −0.19 to 0.01, $p > 0.05$). There were also slight changes to the estimate coefficients, but all other statistically significant results remained significant at PI1 and PI2. The full results of this analysis are reported in Table 5.

Discussion

The present study investigated the effect of multiple concussions on the symptom profiles of young student-athletes who had a new SRC, as defined by ImPACT results, and compared these patients with their counterparts who experienced only a single prior concussion. At the initial postinjury test, PI1, there were minimal differences in symptom profiles because the only significant result of the multivariate analysis was that those subjects with repetitive concussions reported less headache symptoms. As time progressed to the next postinjury test, PI2, there were greater differences between these 2 groups. PI2 showed that athletes with recurrent head trauma were more likely to report greater severity of cognitive, sleep, and neuropsychiatric cluster symptoms but not migraine symptoms. These results are important to convey to medical providers, athletic training staff, and parents, as they should pay particular attention to certain symptoms when assessing

TABLE 2. Demographic characteristics

Characteristic	SRC1 (n = 2253)	SRC2+ (n = 976)	p Value
Age, yrs	15.54 ± 1.5	15.69 ± 1.7	0.012
Male sex	1522 (67.5)	667 (68.3)	0.66
ADHD	137 (6.1)	75 (7.7)	0.09
DLD	80 (3.6)	37 (3.8)	0.74
Athletic experience, yrs	2.24 ± 2.5	2.47 ± 2.7	0.021
Days btwn PI1 & PI2	13.3 ± 29	12.5 ± 26	0.80
Previous concussions		2.53 ± 0.88	

Values are shown as number (%) or mean ± SD unless indicated otherwise.

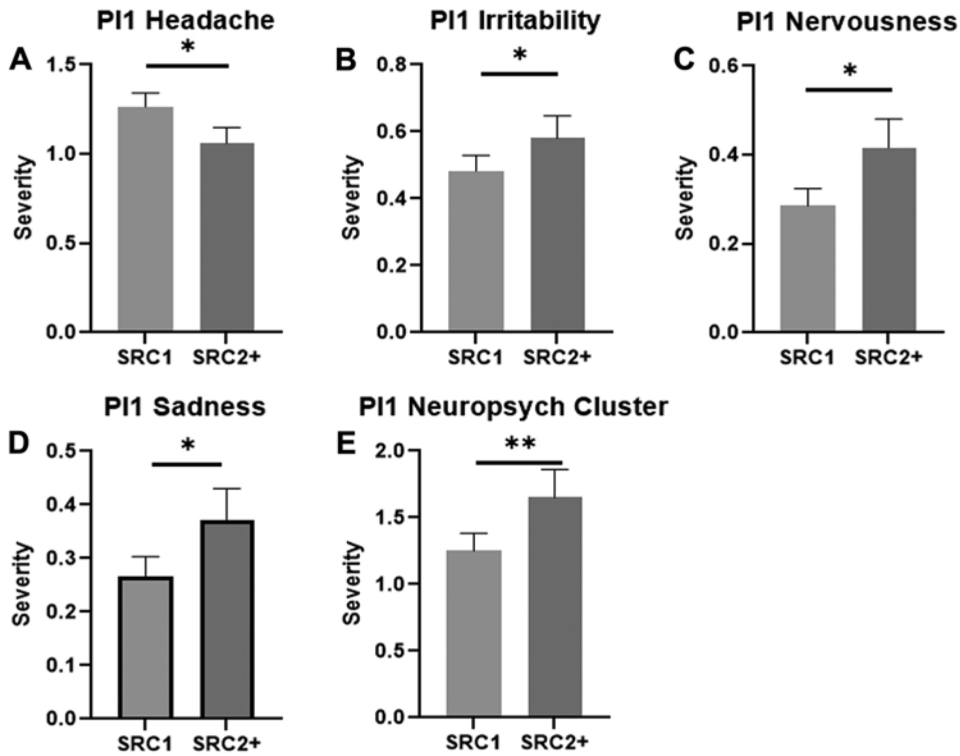

FIG. 1. Comparison of mean (*bars*) and standard deviation (*error bars*) severity scores for either symptoms (headache [**A**], irritability [**B**], nervousness [**C**], and sadness [**D**]) or symptom cluster (neuropsychiatric cluster [**E**]) associated with each panel at PI1. *p < 0.05; **p < 0.01.

the readiness to return to play of an athlete with multiple prior concussions.

There are a multitude of symptoms that occur after sustaining an SRC. These symptoms include headache, nausea, vomiting, sensitivity to light, difficulty concentrating, and sleep difficulties.[18] The ImPACT test requires athletes to self-report 22 different symptoms after a suspected concussion. A prior study showed that the test-retest reliability of the total symptom score was lower than those of the symptom clusters, suggesting that evaluation of more symptom indices besides total symptom score is necessary.[19] Although there has been research into the differences that prior concussions create in terms of incidence, severity, and recovery of future concussions, little research has investigated changes in symptomatology at a granular level.[13] Additionally, there have been mixed results in terms of how previous concussions may affect a patient's symptoms. Hannah et al. found that there was decreased severity of total symptom burden after the initial concussion in patients with prior concussions, whereas Ellis et al. found that patients with prior concussions had an increased total symptom burden after initial head injury.[13,20] Prior research has shown that concussion history may be associated with prolonged recovery, changes in total symptom burden, and prolonged recovery.[21–23] The bulk of the research that delves into the effects that repetitive trauma may have on symptom burden after a future concussion has focused on the total symptom score, which is included as one of the overall composite scores for the ImPACT test.[24,25] Furthermore, these studies routinely investigated the concussion assessments of the ImPACT test directly after head injury, which we defined as PI1, but rarely assessed the performance of subsequent tests such as PI2.[20] Follow-up testing is important to include because studies have shown that differences in symptoms occur at follow-up testing as a result of differences in initial severity and recovery.[13,26] The novelty of this study was the exploration of granular symptom data and investigation into follow-up assessments.

Assessing symptomatology coupled with neurocognition yields more comprehensive data, as opposed to assessment of symptomatology alone. A prior study by Schatz et al. investigated changes in symptomatology at a granular level; however, they only assessed for differences at baseline testing prior to injury.[27] While it is important to characterize how risk factors may impact baseline neurocognitive function, such as headaches, medications, and age, it is equally important to determine how these risk factors may affect neurocognition after a suspected SRC.[28–30] The present study provided this information because it tracked symptomatology with follow-up testing at multiple time intervals, discovering minimal differences at PI1 (headache) but larger differences in multiple symptom clusters (cognitive, neuropsychiatric, sleep) at PI2 between cohorts. An interesting finding of our study was that patients with 2 or more prior concussions had decreased severity of headache compared with the patients with only 1 prior concussion at PI1, but there were no differences in the migraine cluster at PI2. A possible explanation for this is that SRC2+ patients may have been more familiar with concussion symptoms, such as headache, and thus were less likely to report them until they became more apparent. This hypothesis aligns with the findings of Schatz et al., who found that patients with 2 or more concussions reported greater "physical" symptoms (which included headache) at baseline.[27] However, while there was a statistical difference in headache severity at PI1 (1.27 vs 1.06, p = 0.04), the clinical significance is limited because this indicates that both groups experienced a low headache burden on the 0- to 6-point scale. Additionally, when the number of prior concussions was treated as a continuous rather than a categorical variable, there was no longer a difference in headache symptoms.

The other notable finding of our study was that the SRC2+ cohort demonstrated increased cognitive, neuropsychiatric, and sleep cluster dysfunction on PI2 testing. The physical symptoms, including headache, fatigue, and dizziness, are likely to manifest early and recover first while sleep disturbances, forgetfulness, and frustration are likely to manifest later.[31] This is in line with our findings but does not explain why there was a greater effect on athletes with repetitive concussion history. Patients with a significant history of repetitive head trauma may simply take longer to return to baseline cognitive functioning, suggesting protracted recovery. Indeed, past observational cohort studies have indicated the same. Among 160 collegiate athletes, Slobounov et al. found slower neurocognitive recovery after repeat concussion as compared with after the first concussion.[32] Head injury can lead to permanent brain damage, including loss of neural connectivity and plasticity.[33,34] Those with a history of concussion may compensate over time and present without neurocognitive impairment at baseline. However, repeat head injury can further damage cognitive reserves, adding further insult to already compromised neural pathways.[33] This may explain why those with a history of 2 or more concussions remained cognitively impaired at the second postinjury test to a greater extent than those with a less burdensome history. An important point to emphasize regarding the current study is that although there were distinct differences in symptom severity between groups on PI1 and PI2, no difference was found between the 2 groups in terms of the number of days that passed between each test (p = 0.80). We also included this variable in our multivariate model to eliminate any effect it may have had on symptom severity.

Changes in symptomatology are important to recognize; however, as the current study reports, there are differences in symptom profiles depending on whether an athlete has had 1 or many prior concussions. Caregivers may be routinely aware of common concussive symptoms such as headache, sensitivity to light, and difficulty concentrating, but they may be less aware of more subtle symptoms such as sadness, trouble sleeping, numbness, or visual problems. In younger children or athletes who may not report these symptoms, it is important for healthcare providers and caregivers alike to be aware of and able to recognize these symptoms. Additionally, as athletes become more independent, they may falsely report their symptoms at a lower severity to avoid being restricted from competition.[35] Awareness of concussion symptoms and recovery is essential to prevent long-term neurological deficits.

TABLE 3. Univariate analysis of postinjury symptom burden

Symptom	SRC1 (n = 529)	SRC2+ (n = 286)	p Value
PI1			
No. of subjects	529	286	
Headache	1.27	1.06	**0.04**
Vomiting	0.038	0.077	0.088
Nausea	0.518	0.462	0.904
Balance issues	0.648	0.622	0.811
Dizziness	0.751	0.794	0.681
Trouble falling asleep	0.459	0.539	0.382
Fatigue	0.664	0.678	0.880
Sleeping more	0.316	0.451	0.054
Sleeping less	0.289	0.350	0.398
Lightheadedness	0.917	0.986	0.325
Drowsiness	0.718	0.815	0.341
Sensitivity to noise	0.815	0.902	0.409
Irritability	1.1	1.13	**0.028**
Nervousness	0.285	0.42	**0.042**
Sadness	0.27	0.37	**0.028**
Emotional	0.357	0.406	0.124
Numbness or tingling	0.147	0.213	0.187
Mentally foggy	0.754	0.734	0.603
Feeling slowed	0.645	0.759	0.112
Difficulty concentrating	0.985	1.02	0.377
Difficulty remembering	0.573	0.559	0.760
Visual problems	0.406	0.525	**0.042**
Migraine cluster	5.23	5.42	0.526
Cognitive cluster	4.14	4.39	0.406
Sleep cluster	0.934	1.16	0.152
Neuropsychiatric cluster	1.25	1.65	**0.009**
PI2			
No. of subjects	292	130	
Migraine cluster	2.33	3.15	0.12
Cognitive cluster	2.12	3.32	**0.011**
Sleep cluster	0.84	1.42	**0.011**
Neuropsychiatric cluster	0.77	1.45	**0.009**

Values are shown as mean unless indicated otherwise. Boldface type indicates statistical significance ($p < 0.05$).

Limitations

This was a retrospective study that had inherent limitations in terms of the calculations and generalizability. There is also no way of knowing whether these subjects had head trauma and had received outside treatment, which would not have been reported in our database. However, the protocols used by the organizations in-

FIG. 2. Comparison of mean (*bars*) and standard deviation (*error bars*) severity score for symptom clusters (cognitive cluster [**A**], neuropsychiatric cluster [**B**], and sleep cluster [**C**]) associated with each panel at PI2. *p < 0.05; **p < 0.01.

cluded in the database help to reduce this limitation. The symptom scores and severity were self-reported by the athletes, which may have introduced either conscious or unconscious bias because there was no definitive test to determine whether their reported symptoms were accurate. An additional source of bias was the self-reporting of the number of prior concussions that an athlete had experienced. Athletes may underreport the number of prior concussions that they have experienced in their lifetime, which would have underestimated the sample size of the SRC2+ cohort.[36] This provides the rationale for the use of only 2 groups so that the SRC2+ cohort could encompass a larger range of lifetime concussions.

Although some findings were statistically significant due to our robust sample, they may not hold weight clinically and therefore some results may be limited. There is currently no minimal clinically significant difference in individual symptom severity. Therefore, although statistical significance may have been reached, the clinical differences indicated by these values are subjective. Prior studies have shown that age, sex, and sport contact level have an effect on symptom reporting after suspected concussion.[37] In an effort to mitigate these effects, our analysis controlled for these possible confounders in the multivariate model. Although we were able to control for the number of days that passed between PI1 and PI2 tests, we do not have data on the time that passed from injury to PI1, thereby creating a limitation because there was no a standardized postinjury assessment protocol. The current database consisted of only actively participating athletes at the time of data collection, and therefore we cannot account for any athlete who may have been removed from competitive play for any reason. We assume that there are athletes who are no longer participating in sports due to their concussion history, but we do not have access to any data about this population.

Conclusions

Patients with a history of recurrent concussions appear to have a higher symptom burden in cognitive, sleep, and neuropsychiatric symptom clusters but not migraine symptoms. This is an important distinction because migraine symptoms are comparably more overt to both pa-

TABLE 4. Multivariate analysis of the prior number of concussions as a categorical variable (SRC1 vs SRC2+)

Symptom	Estimate	95% CI	p Value
PI1			
Headache	−0.27	−0.45 to −0.09	**0.003**
Nervousness	0.11	−0.02 to 0.24	0.103
Irritability	0.07	−0.08 to 0.21	0.386
Sadness	0.07	−0.05 to 0.20	0.238
Visual problems	0.08	−0.05 to 0.21	0.243
Neuropsychiatric cluster	0.29	−0.13 to 0.71	0.173
PI2			
Migraine cluster	0.89	−0.17 to 1.94	0.101
Cognitive cluster	1.22	0.27 to 2.18	**0.012**
Sleep cluster	0.63	0.17 to 1.08	**0.007**
Neuropsychiatric cluster	0.67	0.14 to 1.2	**0.014**

Boldface type indicates statistical significance (p < 0.05).

TABLE 5. Multivariate analysis of prior number of concussions as a continuous variable

Symptom	Estimate	95% CI	p Value
PI1			
Headache	−0.09	−0.19 to 0.01	0.06
Nervousness	−0.01	−0.08 to 0.07	0.86
Irritability	0.05	−0.03 to 0.13	0.22
Sadness	0.04	−0.03 to 0.10	0.26
Visual problems	0.05	−0.02 to 0.12	0.17
Neuropsychiatric cluster	0.07	−0.16 to 0.29	0.58
PI2			
Migraine cluster	0.59	−0.07 to 1.26	0.08
Cognitive cluster	0.80	0.21 to 1.40	**0.01**
Sleep cluster	0.37	0.09 to 0.66	**0.01**
Neuropsychiatric cluster	0.47	0.14 to 0.80	**0.006**

Boldface type indicates statistical significance (p < 0.05).

tients and physicians. Therefore, more careful monitoring of these cognitive, sleep, and neuropsychiatric symptoms should be considered for patients with a history of recurrent head injury.

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Disclosures

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Author Contributions

Conception and design: Quinones, Schupper, Genadry, Lovell, Choudhri. Acquisition of data: Quinones, Schupper, Hrabarchuk, Genadry, Lovell, Choudhri. Analysis and interpretation of data: Quinones, Young, Hrabarchuk, Lamb, Genadry, Kalagara, Gometz, Choudhri. Drafting the article: Quinones, Young, Schupper, Hrabarchuk, Lamb, Genadry, Kalagara. Critically revising the article: Quinones, Schupper, Ali, Hrabarchuk, Lamb, Genadry, Kalagara, Asfaw, Gometz. Reviewed submitted version of manuscript: Quinones, Schupper, Ali, Hrabarchuk, Lamb, Genadry, Kalagara, Asfaw, Choudhri. Approved the final version of the manuscript on behalf of all authors: Quinones. Statistical analysis: Quinones, Hrabarchuk, Lamb, Genadry. Administrative/technical/material support: Quinones, Lamb, Genadry. Study supervision: Quinones, Schupper, Lovell, Choudhri.

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