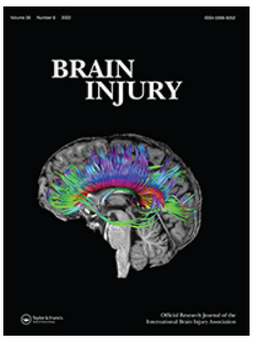

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High altitude modulates concussion incidence, severity, and recovery in young athletes

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ABSTRACT

Background: High altitude may affect concussion, but prior studies are limited . We tested whether high altitude affects sport-related concussion (SRC) incidence, severity, and recovery.

Methods: Twenty-five thousand eight hundred fifteen baseline and post-injury Immediate Post-Concussion Assessment and Cognitive Testing results were compiled from Florida and Colorado, low (27 m or 62 m) and high (1,640 m or 1,991 m) altitude locations, respectively. Incidence, severity, and recovery of injury were compared between altitudes.

Results: High altitude was associated with increased suspected concussion incidence (adjusted OR, 2.04 [95% CI, 1.86 to 2.24];$P < .0001$). However, high altitude was associated with lower concussion severity measured by Severity Index (SI) (adjusted OR, 0.42 [95% CI, 0.37 to 0.49];$P < .0001$). High altitude was associated with decreased recovery from post-concussive symptoms in the migraine (β, −2.72 [95% CI, −3.31 to −2.13]; $P < .0001$), cognitive (β, −1.88 [95% CI, −2.40 to −1.36]; $P < .0001$), and sleep symptom clusters (β, −0.30 [95% CI, −0.52 to −0.08]; $P = .007$). Athletes with initial SI≥8 showed prolonged neurocognitive dysfunction at high altitude (HR, 1.38 [95% CI, 1.06 to 1.81]; $P = .02$).

Conclusions: High altitude was associated with increased suspected concussions and prolonged recovery but less severe initial injury.

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Sports related concussion; mild traumatic brain injury; high altitude; severity index

Introduction

Youth sports are popular in the United States, and participation has been associated with physical, lifestyle, social, and cognitive benefits (1). However, sports put children at risk for injuries including sports-related concussion. Multiple factors including but not limited to sex, player position, sport type, level of play, aggressive behavior, and environmental factors are hypothesized to modulate concussion risk (2).

Previous studies have investigated altitude as a potential environmental modulator of concussion. Some have shown protective effects of high altitude attributed to the slosh effect, where high altitude associated hypoxia causes increased cerebral blood flow, increased brain volume, and decreased brain movement during trauma (3–7). Other studies have reported no significant effects or increased risk of concussion due to altitude, and there is disagreement over whether these findings are valid and applicable to wider populations (6,8–10). Additionally, previous studies have used cutoffs for high altitude below 300 m, potentially too low for meaningful physiological changes (11). Importantly, jugular vein occlusion has emerged as a strategy to reduce brain sloshing despite limited prior study, and as of 2018, 300 high school and college sports teams are using jugular vein compression devices (12). Further study is important to understand potentially significant physiologic changes at high altitude.

Our study explores effects of altitude on concussion by studying young athletes in Colorado and Florida, states with the 1st and 49th ranked mean altitudes, respectively. Due to the increased difference in altitude, we believe that altitude can be more thoroughly studied. We hypothesize that high altitude may significantly affect concussion incidence, severity, and recovery.

Materials and methods

Design and participants

We used data from 25,815 Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) results between July 2009 and June 2019 provided through a research agreement with ImPACT Applications Inc (Coralville, IA). Eligible subjects aged 12–22 years were part of athletic organizations following standardized care, which included preseason baseline testing, head injury assessment by physicians and athletic trainers, and post-injury ImPACT testing for suspected concussions. Clinical confirmation of a suspected concussion was made using examination. Follow-up post-injury ImPACT tests were conducted at different intervals depending on symptom severity and student availability. Testing occurred in Westminster, CO, Durango, CO, Orlando, FL, and Tallahassee, FL with

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altitudes of 1,640 m, 1,991 m, 27 m, and 62 m, respectively. Colorado and Florida were high and low altitude locations, respectively. This study was approved by the Mount Sinai institutional review board for human subject research. The study was deemed exempt from informed consent because the data were de-identified and previously collected for clinical use.

Demographic information and medical history

Demographic information and medical history were self-reported during ImPACT testing. Demographic data included age, sex, and sport played. Sports were categorized into contact/collision, limited contact, and noncontact sports. Medical history data included diagnosed attention deficit hyperactivity disorder (ADHD), diagnosed learning disability, autism, dyslexia, depression, anxiety, chronic headaches, chronic migraines, and previous concussion history.

ImPACT testing

ImPACT conducts a Post-Concussion Symptom Scale survey before testing neurocognitive function using a variety of tests (13). The Post-Concussion Symptom Score (PCSS) migraine, cognitive, sleep, and neuropsychiatric clusters were calculated as previously described (14,15). The range of possible scores is 0–63 for the Migraine cluster, 0–42 for the Cognitive cluster, 0–21 for the Sleep cluster, and 0–28 for the Neuropsychiatric Cluster. ImPACT evaluates changes from baseline in 5 composite scores to provide a surrogate marker for concussions. Changes from baseline that exceeded the standard error of difference at the 80% confidence interval (S_{diff}) for healthy control subjects were considered significant (13). A patient has significant neurocognitive dysfunction on ImPACT when changes from baseline meet or exceed S_{diff} in at least two of the five metrics. The composite scores are verbal memory, visual memory, reaction time, processing speed, and post-concussion symptom scale (13).

Incidence of suspected concussion

We calculated incidence rates as number of suspected concussions per person-years at risk for injury. Patients required a baseline test to be considered at risk for injury. ImPACT baseline tests are reported to be stable for 2 years, and patients with greater than 2 years between baseline tests were considered lost to follow-up (16).

Severity index

We used Severity Index (SI) to assess suspected concussion severity as previously described (17). Changes in composite scores (ΔScore) from baseline to post injury 1 test (PI1) were calculated (Equation 1). If ΔScore did not exceed $S_{diff,}$ it was assumed that there was no change from baseline (Equation 2). To estimate the severity of each suspected concussion we summed the number of S_{diff} above baseline for each composite score to create a Severity Index (Equation 3).

$$\Delta Score = |PI1Score - BaselineScore| \quad \text{(Equation1)}$$

$$f(\Delta Score) = \begin{cases} 0, \Delta Score < Sdiff \\ \Delta Score, \Delta Score \geq Sdiff \end{cases} \quad \text{(Equation2)}$$

$$SeverityIndex = \sum_{i=1}^{5} \frac{f(\Delta Score)_i}{Sdiff_i} \quad \text{(Equation3)}$$

Statistical analyses

We performed statistical analyses with Prism 8.0 (GraphPad Software, San Diego, CA) and SAS 9.4 (SAS Institute Inc., Cary, NC). Descriptive statistics described demographics and medical history. Chi-square and Fisher's Exact tests compared incidence rates between altitudes and means for patient demographics and medical history. T-tests compared SI between altitudes. Multivariable logistic regression was used to compare suspected concussion incidence and SI between altitudes while controlling for demographic differences. For analysis, patients were binned into groups based on SI: 0–4, 4–8, 8–12, and >12. Kaplan–Meier plots and Cox proportional hazards models were used to examine concussion recovery patterns in aggregate. The event in survival analyses was recovery from significant neurocognitive dysfunction on ImPACT. For these analyses, all follow-up tests conducted within 45 days of PI1 for each patient were used. Analysis was restricted to patients with significant neurocognitive dysfunction on ImPACT and at least 1 follow-up test within that window. Log-rank tests were used to evaluate significant differences between curves. Multivariable linear regression was used to evaluate symptom cluster differentials for follow-up ImPACT tests post-injury. Multivariable analyses were subject to random data sampling and variable deletion techniques to improve internal consistency. For all analyses, $\alpha = 0.05$.

Results

Demographics

Of the 25,815 ImPACT tests, 11,563 ImPACT tests were preseason baseline tests, 7,445 tests were post-injury 1 (PI1) tests conducted after suspected concussion, and 6,807 were follow-up post-injury tests (PI2-4) to measure recovery. Of those 7,445 PI1 tests, 5,216 (70.0%) tests had a corresponding baseline test for comparison. Eight thousand six hundred and sixty-seven (75.0%) baseline tests and 3,463 (73.3%) PI1 tests with baselines were conducted at low altitude, and 2,896 (25.0%) baseline tests and 1,753 PI1 (26.7%) tests were conducted at high altitude. Of the included injuries with PI1 tests, 2,304 (44.2%) had at least one follow-up test after PI1 that could be used to assess recovery. Patients were ages 12–22, and 89.4% were high-school age (14–18 years).

Comparisons of groups in analysis at low and high altitude are presented in Table 1. For baseline tests, patients at low altitude were older and had a larger proportion of male athletes. Patients at low altitude had a higher proportion with diagnosed ADHD, and lower proportions with autism,

Table 1. Demographics of study populations at low and high altitude.

	Baselines			Suspected concussions			Post-Injury analysis			Recovery from concussion on ImPACT analysis		
	Low Altitude (n = 8667)	High Altitude (n = 2896)	P value	Low Altitude (n = 3463)	High Altitude (n = 1753)	P value	Low Altitude (n = 1720)	High Altitude (n = 584)	P value	Low Altitude (n = 978)	High Altitude (n = 290)	P value
Age (SD)	15.4 (1.4)	15.2 (1.9)	<0.0001	16.0 (1.4)	15.9 (2.0)	0.25	15.9 (1.4)	15.8 (2.0)	0.18	15.9 (1.4)	15.5 (1.9)	0.0004
Male (%)	5839 (67.4)	1783 (61.6)	<0.0001	2364 (68.3)	1101 (62.8)	<0.0001	1152 (67.0)	376 (64.4)	0.25	631 (64.5)	179 (61.7)	0.38
Female (%)	2828 (32.6)	1113 (38.4)	<0.0001	1099 (31.7)	652 (37.2)	<0.0001	568 (33.0)	208 (35.6)	0.25	347 (35.5)	111 (38.3)	0.38
Diagnosed ADD/ADHD (%)	474 (5.5)	104 (3.6)	<0.0001	191 (5.5)	60 (3.4)	0.0008	99 (5.8)	20 (3.4)	0.03	54 (5.5)	8 (2.8)	0.06
Diagnosed learning disability (%)	243 (2.8)	79 (2.7)	0.90	95 (2.7)	52 (3.0)	0.66	55 (3.2)	10 (1.7)	0.06	22 (2.2)	3 (1.0)	0.24
Autism (%)	27 (0.3)	17 (0.6)	0.053	7 (0.2)	11 (0.6)	0.02	4 (0.2)	2 (0.3)	0.65	2 (0.2)	2 (0.7)	0.23
Dyslexia (%)	132 (1.5)	94 (3.2)	<0.0001	58 (1.7)	63 (3.6)	<0.0001	24 (1.4)	19 (3.2)	0.007	13 (1.3)	11 (3.8)	0.012
Depression/Anxiety/ Other psychiatric treatment (%)	276 (3.2)	155 (5.4)	<0.0001	112 (3.2)	82 (4.7)	0.009	62 (3.6)	25 (4.3)	0.46	43 (4.4)	15 (5.2)	0.58
Chronic headaches (%)	907 (10.5)	353 (12.2)	0.10	385 (11.1)	223 (12.7)	0.09	191 (11.1)	86 (14.7)	0.02	106 (10.8)	44 (15.2)	0.04
Chronic migraines (%)	607 (7.0)	275 (9.5)	<0.0001	278 (8.0)	177 (10.1)	0.01	138 (8.0)	67 (11.5)	0.01	75 (7.7)	34 (11.7)	0.03
Previous concussion history ≥2 (%)	667 (7.7)	598 (20.6)	<0.0001	398 (11.5)	450 (25.7)	0.0001	193 (11.2)	157 (26.9)	<0.0001	104 (10.6)	75 (25.9)	<0.0001
Contact/Collision Sport (%)	6279 (72.4)	1968 (68.0)	<0.0001	2772 (80.0)	1278 (72.9)	<0.0001	1396 (81.2)	431 (73.8)	0.0001	772 (78.9)	203 (70.0)	0.002
Limited contact sport (%)	1477 (17.0)	666 (23.0)	<0.0001	537 (15.5)	380 (21.7)	<0.0001	248 (14.4)	125 (21.4)	<0.0001	155 (15.8)	68 (23.4)	0.003
Noncontact sport (%)	420 (4.8)	97 (3.3)	0.007	61 (1.8)	34 (1.9)	0.66	25 (1.5)	13 (2.2)	0.26	15 (1.5)	3 (1.0)	0.78
Sport blank (%)	491 (5.7)	165 (5.7)	0.95	93 (2.7)	61 (3.5)	0.12	49 (2.8)	15 (2.6)	0.72	36 (3.7)	10 (3.4)	0.85

Abbreviations: ADD/ADHD, Attention-Deficit Disorder/Attention-Deficit/Hyperactivity Disorder; ImPACT, Immediate Post-Concussion Assessment and Cognitive Testing

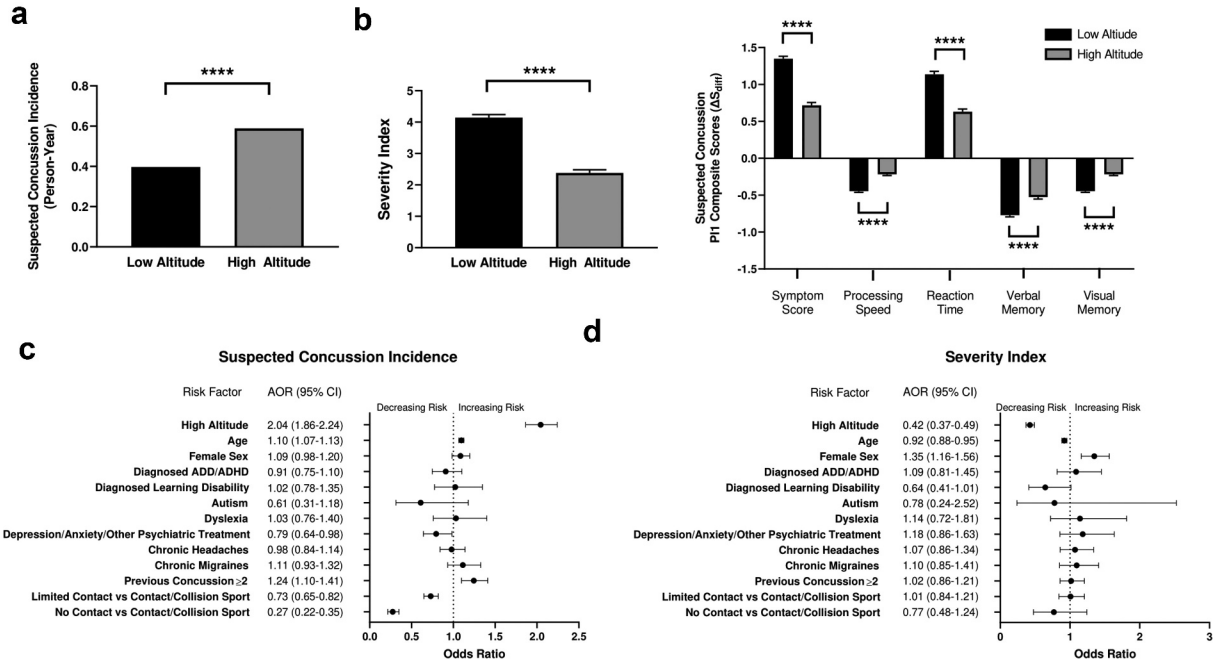

Figure 1. Univariate and multivariable analysis of concussion incidence and severity at low and high altitude. (A) Incidence of clinically suspected concussions at low and high altitude per person-year. (B) Severity Index for clinically suspected concussions at low and high altitude at the first post injury test (PI1). ImPACT composite scores for suspected concussion at PI1 expressed as 80% confidence intervals make up severity index and are presented. Error bars indicate SEM, **** = p < .0001 (C) Adjusted odds ratios for factors affecting suspected concussion incidence in multivariable logistic regression. (D) Adjusted odds ratios for factors affecting suspected concussion severity index in multivariable logistic regression. AOR indicates adjusted odds ratio. ADD/ADHD indicates attention deficit disorder/attention deficit/hyperactivity disorder. Error bars indicate 95% CIs. The dotted lines indicate an odds ratio of 1.

dyslexia, depression or anxiety, chronic migraines, and at least two prior concussions than patients at high altitude. For the category of listed sport, patients at low altitude had a higher proportion of contact or collision sports, lower proportion with limited contact sports, and a higher proportion of non-contact sports. Patients at low and high altitude were similar with regard to diagnosed learning disability, chronic headaches, and no listed sport.

Concussion incidence and severity

Incidence of suspected concussion was 0.40 per person-year at low altitude and 0.59 per person-year at high altitude (Incidence Rate Ratio 1.48 [95% CI, 1.40 to 1.57];P < .0001, Figure 1A). When analyzing differences in initial injury severity, patients at low altitude had higher Severity Index (SI) vs. patients at high altitude (SI) (4.14 [95% CI, 3.96 to 4.33] vs 2.38 [95% CI, 2.18 to 2.58];P < .0001, Figure 1B). When calculating SI for suspected concussions at PI1, patients at low altitude had larger differences from baseline in all 5 ImPACT composite scores (Figure 1B). In multivariable analysis controlling for demographic differences, odds of suspected concussion remained elevated at high altitude (adjusted OR, 2.04 [95% CI, 1.86–2.24]; P < .0001, Figure 1C). Additionally, increased age and history of ≥2 prior concussions was associated with increased odds of suspected concussion, while limited contact vs contact/collision sports, no contact vs contact/collision sports, and depression/anxiety/other psychiatric treatment were associated with decreased odds of suspected concussion (Figure 2A). Odds of increased SI bin for suspected concussion remained significantly decreased at high altitude (adjusted OR, 0.42 [95% CI, 0.37–0.49]; P < .0001, Figure 1D). Additionally, decreased age and female sex were associated with increased odds of increased SI (Figure 1D).

Recovery

In the recovery analysis, patients were binned into two groups based on SI: low severity (SI<8) and high severity (SI ≥8). The median (interquartile range) follow-up time for the low severity groups were 8 days (IQR, 5–14 days) at low altitude and 7 days (IQR, 4–13 days) at high altitude. The median (IQR) follow-up time for the high severity groups were 12 days (IQR, 7–19 days) at low altitude and 10 days (IQR, 7–19 days) at high altitude. When measuring recovery from significant neurocognitive dysfunction, Kaplan–Meier analysis showed no difference between low and high altitude recovery for low severity injuries (HR, 0.98; 95% CI, 0.82–1.18; log-rank P = .86). However, high severity injuries showed prolonged recovery at high altitude (HR, 1.34; 95% CI, 1.06–1.70, log-rank P = .02, Figure 2A). Cox proportional hazards models controlling for demographic differences showed similar results, with no difference between low and high altitude recovery for low severity injuries (aHR, 0.95; 95% CI, 0.79–1.14; log-rank P = .55). High severity injuries showed prolonged recovery at high altitude (aHR, 1.38; 95% CI, 1.06–1.81, log-rank$P$ = .02, Figure 2B).

Recovery was also measured by absolute changes in 4 post-concussion symptom clusters: migraine, cognitive, sleep, and neuropsychiatric clusters. In multivariable linear regression analysis, high altitude was associated with decreased recovery in the migraine (β, −2.72 [95% CI, −3.31 to −2.13];P < .0001), cognitive (β, −1.88 [95% CI, −2.40 to −1.36];P < .0001), and sleep symptom clusters (β, −0.30 [95% CI, −0.52 to −0.08]; P = .007). No difference was seen between altitudes for the neuropsychiatric symptom cluster (β, −0.22 [95% CI, −0.50 to −0.05];P = .12, Table 2). These findings were consistent with fitted multivariable analysis for the 4 post-concussion symptom clusters (Supplement).

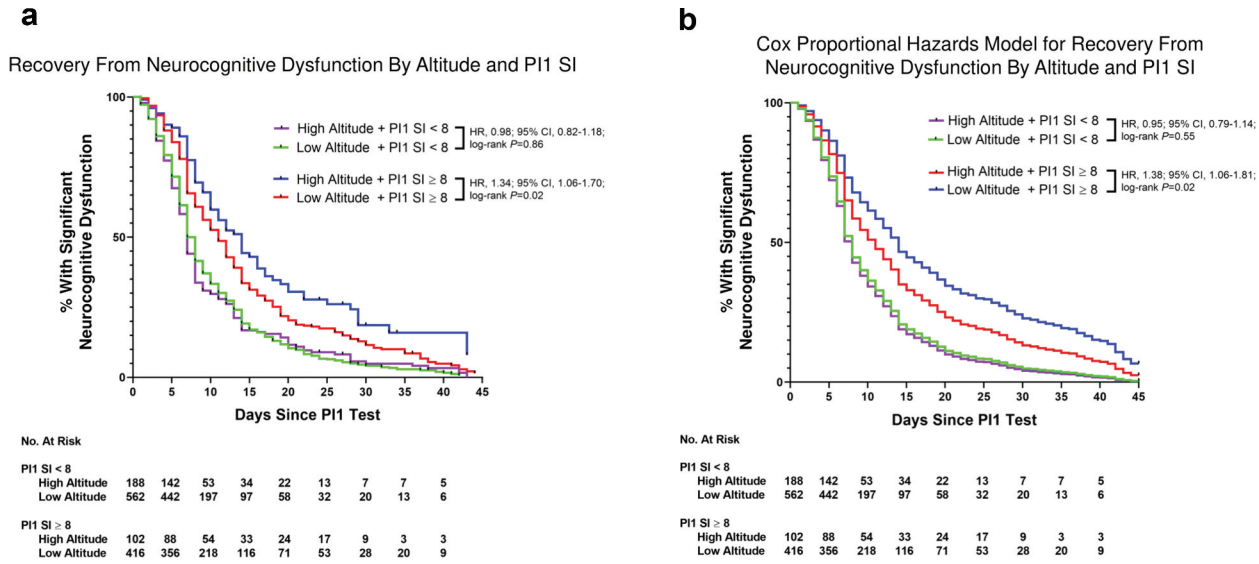

Figure 2. Recovery from neurocognitive dysfunction by altitude and concussion severity. (A) Kaplan-Meier curves measuring recovery from significant neurocognitive dysfunction for patients stratified by altitude and PI1 Severity Index. (B) Curves represent multivariable Cox proportional hazards regression analysis plotting recovery from significant neurocognitive dysfunction for patients stratified by altitude and PI1 Severity Index. Curves are adjusted for age, sex, ADD/ADHD, learning disability, autism, dyslexia, treated depression/anxiety/other psychiatric disorder, chronic headaches, chronic migraines, previous concussion, and sports type. HR indicates hazard ratio.

Table 2. Multivariable linear regression analysis of post-concussion recovery measured by absolute change in post-concussion symptom clusters.

	Migraine symptom cluster		Cognitive symptom cluster		Sleep symptom cluster		Neuropsychiatric symptom cluster	
Variable	Adjusted β (95% CI)	P Value	Adjusted β (95% CI)	P Value	Adjusted β (95% CI)	P Value	Adjusted β (95% CI)	P Value
High Altitude	−2.72 (−3.31 to −2.13)	<.0001	−1.88 (−2.40 to −1.36)	<.0001	−0.30 (−0.52 to −0.08)	0.007	−0.22 (−0.50 to 0.05)	0.12
SI ≥ 8	8.16 (7.60 to 8.71)	<.0001	6.51 (6.02 to 7.00)	<.0001	1.72 (1.51 to 1.93)	<.0001	2.53 (2.26 to 2.79)	<.0001
Age	−0.09 (−0.25 to 0.07)	0.28	0.15 (0.01 to 0.28)	0.04	0.03 (−0.03 to 0.09)	0.32	0.09 (0.01 to 0.16)	0.02
Female Sex	1.67 (1.06 to 2.27)	<.0001	1.03 (0.50 to 1.57)	0.0001	0.12 (−0.11 to 0.34)	0.32	1.11 (0.83 to 1.39)	<.0001
Diagnosed ADD/ ADHD	−0.25 (−1.38 to −.89)	0.67	0.79 (−0.21 to 1.79)	0.12	0.18 (−0.25 to 0.60)	0.42	1.05 (0.52 to 1.58)	0.0001
Diagnosed learning disability	2.74 (1.09 to 4.40)	0.0012	1.23 (−0.23 to −2.69)	0.1	0.05 (−0.58 to 0.67)	0.89	0.29 (−0.49 to 1.07)	0.47
Autism	1.21 (−4.18 to 6.6.0)	0.66	1.05 (−3.70 to 5.80)	0.67	−0.25 (−2.27 to 1.77)	0.81	0.43 (−2.10 to 2.95)	0.74
Dyslexia	−0.62 (−2.49 to 1.25)	0.52	−1.11 (−2.75 to 0.54)	0.19	0.09 (−0.61 to 0.79)	0.8	−0.58 (−1.45 to 0.30)	0.20
Depression/Anxiety/Other psychiatric treatment	1.06 (−0.22 to 2.34)	0.1	1.72 (0.59 to 2.85)	0.003	0.24 (−0.24 to −0.72)	0.33	0.58 (−0.02 to 1.18)	0.06
Chronic headaches	−0.25 (−1.18 to 0.67)	0.59	−0.18 (−0.99 to 0.63)	0.67	0.24 (−0.11 to 0.58)	0.18	−0.35 (−0.78 to 0.09)	0.12
Chronic migraines	1.38 (0.36 to 2.41)	0.008	0.67 (−0.23 to 1.58)	0.14	0.22 (−0.17 to 0.60)	0.28	1.08 (0.60 to 1.56)	<.0001
Previous concussion history ≥2	0.74 (0.03 to 1.44)	0.04	0.87 (0.25 to 1.50)	0.006	0.11 (−0.15 to 0.38)	0.41	0.13 (−0.20 to 0.46)	0.45
Limited contact vs. contact/collision sport	0.62 (−0.16 to 1.41)	0.12	−0.11 (−0.80 to 0.59)	0.77	−0.05 (−0.34 to 0.25)	0.76	−0.22 (−0.59 to 0.15)	0.24
No contact vs. contact/collision sport	−2.00 (−4.05 to 0.03)	0.054	−0.45 (−2.25 to 1.35)	0.63	0.06 (−0.71 to 0.82)	0.88	−0.29 (−1.25 to 0.67)	0.55
Days after PI1	−0.006 (−0.010 to −0.001)	0.02	−0.007 (−0.011 to −0.003)	0.002	−0.003 (−0.004 to −0.001)	0.004	−0.001 (−0.003 to 0.001)	0.28

Abbreviations: ADD/ADHD, Attention-Deficit Disorder/Attention-Deficit/Hyperactivity Disorder; PI1, Post-Injury 1 Test; SI, Severity Index

Discussion

We found that young athletes at high altitude have an increased incidence of suspected concussion. However, suspected concussions at high altitude initially had less severe symptoms. High altitude athletes reported prolonged recovery from migraine, cognitive, and sleep cluster symptoms and prolonged recovery from significant neurocognitive dysfunction for severe injuries.

Our findings agree with one study showing a 77% increase in concussion risk in college football at high altitude, but disagrees with others showing no effect or decreased concussion at high altitude (3–8,10). The prior study showing increased concussion at high altitude suggested that altitude did not contribute to risk due to differences between acute and chronic exposure. Since college athletes traveled to games within 24 hours, this acute exposure may not allow time for physiologic changes to occur (8). In our study, only 5.6% were above the age of 18, so athletes are more likely to have chronic exposure to high altitude with significant effects. However, the mechanism for increased suspected concussion remains unclear. Long term exposure to high altitude has been associated with cognitive deficits, altered expression of synaptic proteins, and modified functional and structural connectivity within the brain (18,19). It is possible that this neuroadaptation response at high altitude may increase risk of concussion.

In studies finding decreased concussion at high altitude, protective effects may be caused by the "slosh" or "tighter fit" theory where hypoxia induced cerebral edema decreases cranial movement upon impact. Further study of the slosh effect is important because jugular vein occlusion has emerged as a strategy to potentially induce the slosh effect and protect against concussion (12,20). Inspiration has been drawn from woodpeckers, which may prevent cerebral injury by limiting intracranial space (20). Criticism of previous studies is largely due to low cutoffs for high altitude, all less than or equal to 284 m, far below altitudes where notable physiological differences begin. Some physiologists hypothesize that changes in aerobic events begin at ~1000 m or 3,300 ft and changes in anaerobic events begin at 2,134 m or 7,000 ft (21). High altitude locations in the study (1640 m and 1991 m) are above the threshold for aerobic sports and slightly below the threshold for anaerobic sports. Additional criticism is pointed at weak physiologic and epidemiologic basis for associating altitude with decreased concussion incidence. One study using the same NFL database as prior studies found that animal team logo was equally as protective as altitude (10). Comparing slight increases in cranial fluid volume to woodpecker's complicated macroscopic and microscopic adaptations has been called inaccurate (20).

To the best of our knowledge, no prior studies have investigated whether altitude affects concussion severity. Surprisingly, our study found that high altitude athletes suffer less severe injuries as measured by SI despite having more suspected concussions. It is possible that the proposed slosh effect may help decrease concussion severity. On a cellular level, increased concussion severity has been associated with decreased cerebral blood flow, Aβ plaques, microhemorrhages, and unchecked neurotransmitter release causing lactic acid accumulation (22). Other factors associated with increased concussion severity include female sex and gender, lack of helmet use, and premature return to sports following concussion (23–25). Other than sex which was controlled for in the multivariate analysis, it is unclear whether these or

unknown factors are contributing to decreased injury severity at high altitude. As mentioned before, complex neuroadaptation response at high altitude may be affecting concussion severity (18,19). Additionally, high altitude may have deleterious effects on cognitive function, which could elevate baseline deficits and lead to decreased change from baseline after injury (26).

Our study found that athletes at high altitude had slower recovery measured by migraine, cognition, and sleep post-concussion symptom clusters. Athletes at high altitude with severe concussion injuries (SI ≥8), but not mild ones (SI<8), had prolonged recovery from significant neurocognitive dysfunction. This finding aligns with a prior study showing 60% of athletes returned to full activity within 1 week at low altitude compared to 37% high altitude (8). Recovery from concussion typically takes 7–10 days, and delayed recovery has been associated with postconcussion syndrome, severe acute symptoms, prior concussion, younger age, female gender, history of migraines, psychiatric conditions, and post-traumatic amnesia (22,27,28). Many of these variables were controlled for in multivariable analysis. Since differences between altitudes persisted past 10 days for most patients with severe injuries, increased postconcussion syndrome could be contributing to delayed recovery at high altitude although no potential causes of postconcussion syndrome have been proven or accepted (27). One area of active study is inflammation; studies have shown that exercise at high altitude causes increased oxidative stress, and new studies are beginning to link oxidative stress to inflammation and inflammatory responses (29). However, it is still unknown whether neuroinflammation improves or impedes recovery (22).

Our study has limitations. Concussion due to trauma and non-sports-related accidents were not included. ImPACT may be available at schools with increased resources, which may bias the study population. While concussion was suspected after examination by physicians or athletic trainers, it is not known whether athletes were officially diagnosed with a concussion by a physician. However, diagnosis of concussion by athletic trainers has been shown to be up to 98.5% concordant with physician diagnoses (30). For recovery analysis, treatment protocols and timing of post injury testing were not standardized, which could impact results. We believe differences in timing did not significantly affect results because timing of post-injury tests was not statistically different between cohorts, and time of testing was controlled for in post-concussive symptom analysis. However, this does not give the exact duration of concussion on ImPACT since they could have recovered in the days prior to the test. Thus, Kaplan–Meier analysis may overestimate recovery time. Lead time bias between clinical concussion and neurocognitive testing may affect results of ImPACT. ImPACT protocol dictates that initial post-injury testing should be done within 48 hours of injury, but many athletes did not report the date of initial injury. Analysis was limited to 2 states, potentially limiting external validity. Colorado and Florida may not adequately represent high and low altitude regions throughout the country and the world. Lastly, unaccounted variation in level of participation, athlete skill level, and other environmental factors may have affected results.

Conclusion

High altitude was associated with increased incidence of suspected concussion but less severe initial injury overall. High altitude was also be associated with prolonged recovery, especially for severe injuries. Effects of high altitude on concussion appear complex, and it is unclear whether physiologic responses are protective or harmful.

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