




## Research Article

# Posttraumatic headache and clinical recovery after pediatric concussion

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## Abstract

**Objective:** To examine the association of posttraumatic headache (PTH) type with postconcussive symptoms (PCS), pain intensity, and fluid cognitive function across recovery after pediatric concussion. **Methods:** This prospective, longitudinal study recruited children (aged 8–16.99 years) within 24 hours of sustaining a concussion or mild orthopedic injury (OI) from two pediatric hospital emergency departments. Based on parent-proxy ratings of pre- and postinjury headache, children were classified as concussion with no PTH ( $n = 18$ ), new PTH ( $n = 43$ ), worse PTH ( $n = 58$ ), or non-worsening chronic PTH ( $n = 19$ ), and children with OI with no PTH ( $n = 58$ ). Children and parents rated PCS and children rated pain intensity weekly up to 6 months. Children completed computerized testing of fluid cognition 10 days, 3 months, and 6-months postinjury. Mixed effects models compared groups across time on PCS, pain intensity, and cognition, controlling for preinjury scores and covariates. **Results:** Group differences in PCS decreased over time. Cognitive and somatic PCS were higher in new, chronic, and worse PTH relative to no PTH (up to 8 weeks postinjury;  $d = 0.34$  to  $0.87$  when significant) and OI (up to 5 weeks postinjury;  $d = 0.30$  to  $1.28$  when significant). Pain intensity did not differ by group but declined with time postinjury. Fluid cognition was lower across time in chronic PTH versus no PTH ( $d = -0.76$ ) and OI ( $d = -0.61$ ) and in new PTH versus no PTH ( $d = -0.51$ ). **Conclusions:** Onset of PTH was associated with worse PCS up to 8 weeks after pediatric concussion. Chronic PTH and new PTH were associated with moderately poorer fluid cognitive functioning up to 6 months postinjury. Pain declined over time regardless of PTH type.

**Keywords:** Pediatric concussion; mild traumatic brain injury; posttraumatic headache; cognition; pediatric pain; mild orthopedic injury

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## Statement of Research Significance

**Research Question or Topic:** Does posttraumatic headache (PTH) onset influence clinical symptoms or cognition in pediatric concussion?

**Main Findings:** Relative to children without PTH, children who had PTH in the first 10 days after concussion had worse child- and parent-reported symptoms and lower fluid cognition.

**Study Contributions:** Findings suggest that children who develop PTH after concussion may benefit from interventions to help mitigate PTH.

## Introduction

Concussion, a form of mild traumatic brain injury (TBI), affects over one million North American children annually (Bryan et al., 2016). Common postconcussive symptoms (PCS) include somatic (e.g., fatigue, headache), affective (e.g., sadness, anxiety), and cognitive (e.g., inattention, forgetfulness) difficulties (Ayr et al., 2009). Although PCS typically resolve by 1 month, roughly 15 to 25% of children experience persisting PCS (Chadwick et al., 2022; Ledoux et al., 2019; Mayer et al., 2020). The most common PCS is

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posttraumatic headache (PTH), which can occur acutely in up to 85 to 96% of cases (Irwin et al., 2020), irrespective of children's preinjury headache history, and may persist longer than other common PCS (Marbil et al., 2023).

PTH risk is greater up to 3 months after concussion relative to mild orthopedic injury (OI), especially for children with no preinjury headache, suggesting that it may be specific to the effects of concussion (Marbil et al., 2023). In the context of pediatric concussion, PTH can present as (i) new headache (i.e., posttraumatic onset with no preinjury headache), (ii) worse headache (i.e., increased frequency or severity relative to preinjury headache; Headache Classification Committee of the International Headache Society (IHS), 2018), or (iii) chronic (non-worsening headache relative to preinjury headache; Marbil et al., 2023). Compared to other forms of pain, headache pain has been most strongly associated with disability in children (van Gessel et al., 2011). However, little research has specifically investigated whether PTH is associated with poorer clinical outcomes after concussion in children (Kwan et al., 2017).

Differences in the development and presentation of PTH may influence clinical outcomes and recovery after concussion in children, but prospective and longitudinal research is needed (Babcock et al., 2013; Blinman et al., 2009; Eisenberg et al., 2014; Heyer et al., 2016). Children who have preinjury headaches (Blume, 2015) or who develop PTH early after concussion are at risk of prolonged recovery, including persisting PCS (Babcock et al., 2013) and cognitive difficulties (Kwan et al., 2020; McConnell et al., 2020), which could negatively interfere with their daily activities (Barlow, 2016; Rabinowitz et al., 2015). This is problematic because pain that recurs or persists for more than three months, including headache-related pain, is associated with negative outcomes (Treede et al., 2015, 2019). These include poor health-related quality of life (Gold et al., 2009) and long-term functioning, including into adulthood (Murray et al., 2020). Headache pain intensity is associated with increased self-reported cognitive symptoms in youth with concussion (Kwan et al., 2020). Still, little is currently known about the relationship between PTH and pain intensity in pediatric concussion (Kwan et al., 2017), especially more than three months after injury (Kwan et al., 2020).

Identifying predictors of poor clinical outcomes after pediatric concussion is imperative for optimal clinical decision-making and attenuating the negative effects of persisting symptoms on children's quality of life (Moran et al., 2012; Novak et al., 2016). Thus, this prospective, longitudinal study aimed to examine whether different presentations of PTH are related to PCS, pain intensity, and fluid cognitive functioning up to 6 months after pediatric concussion relative to mild OI. Children with concussion with (i) no PTH, (ii) new PTH, (iii) worse PTH, or (iv) chronic headache were compared to children with mild OI without postinjury headache on PCS, pain intensity, and fluid cognition up to 6 months postinjury. Based on previous research, children with worse PTH or chronic headache were expected to demonstrate more severe PCS, higher pain intensity, and worse cognitive function than those with new or no PTH after concussion and OI (Babcock et al., 2013; Blume, 2015; Kwan et al., 2020; McConnell et al., 2020). Type of PTH was expected to predict clinical outcomes after controlling for other factors that can increase risk of prolonged recovery, including female sex, older age, lower socioeconomic status (SES), and greater preinjury symptoms (Marbil et al., 2023).

## Methods

### General procedure

Data were drawn from a larger prospective, longitudinal cohort study of concussion outcomes in children, as previously described (Marbil et al., 2023; Yeates et al., 2021). Children aged 8 to 16.99 years were recruited within 24 hours of sustaining a concussion or a mild OI during initial emergency department visits at two children's hospitals in Ohio, United States, between 2014 and 2017. Information about the injury and acute signs and symptoms were collected by medical personnel using a standard injury case report form during the emergency department visit. Participants returned for 10-day, 3-month, and 6-month postinjury assessments. Written informed parent consent and child assent were obtained in accordance with Helsinki Declaration and institutional review board ethical standards, and with approval at Nationwide Children's Hospital and Rainbow Babies & Children's Hospital. Study data were collected and managed using Research Electronic Data Capture (REDCap) tools hosted at Nationwide Children's Hospital (Harris et al., 2009, 2019).

### Participants

Detailed inclusion and exclusion criteria for both injury groups are published (Marbil et al., 2023; Yeates et al., 2021). Briefly, children with concussion were included if they sustained head trauma and met at least one criterion of the World Health Organization definition of mild TBI (Carroll et al., 2004): (1) observed loss of consciousness <30 minutes; (2) Glasgow Coma Scale score of 13 or 14 (Teasdale et al., 2014; Teasdale & Jennett, 1974); or (3)  $\geq 2$  acute signs or symptoms of concussion (e.g., posttraumatic amnesia, focal neurological deficits, vomiting, headache, dizziness, or other changes in mental status). Children with OI were included if they had an upper or lower extremity extracranial fracture that resulted in an Abbreviated Injury Scale score  $\leq 4$  (Committee on Injury Scaling, 1998). As previously published (Marbil et al., 2023; Yeates et al., 2021), several exclusion criteria applied to both injury groups: (1) severe injury (i.e., AIS score  $\geq 4$ ); (2) injury that would hinder neuropsychological testing; (3) postinjury hypoxia, hypotension, or shock postinjury; (4) involvement of alcohol or drugs during the injury; (5) prior TBI or psychiatric disorder requiring hospitalization; (6) premorbid neurological disorder (apart from migraine) or intellectual impairment; (7) current injury due to abuse or assault; or (8) MRI contraindication.

In this study, only children with concussion or mild OI with information on preinjury headache and PTH at the 10-day follow-up visit were eligible for inclusion.

### Measures

#### Socioeconomic status (SES)

An SES composite (z-score) was derived from standardized measures of total years of maternal education, median family income for the family census tract, and parent occupational status that were completed by parents at the 10-day follow-up assessment (Yeates et al., 2021).

#### Intellectual functioning

Full Scale IQ was assessed at the 10-day follow-up visit using the two-subtest version of the Wechsler Abbreviated Scale of Intelligence, Second Edition (WASI-II; Wechsler, 2011). Results for IQ in this sample have been published (Ware et al., 2023).

### Headache questionnaire

As detailed in a previous study of headache onset and characteristics in this sample (Marbil et al., 2023), parents completed a standardized headache questionnaire at the initial emergency department visit and all three follow-up visits to assess pre- and postinjury headache, respectively. The questionnaire contains: (1) 25 items assessing headache characteristics, such as nature (e.g., throbbing), location, functional interference, frequency, duration, and severity; and (2) 3 items on current headache treatment, including pain medication usage (i.e., yes/no; Hershey, 2005; Palermo et al., 2005). Preinjury headache ratings described the 12 months preceding the injury. Postinjury (PTH) ratings described the first 10 days after injury, the period from 10 days to 3 months postinjury, and the period from 3 to 6 months postinjury. Questionnaire results were used to determine: (1) preinjury headache status (i.e., present, absent); (2) the presence, duration, severity, frequency, and worsening of PTH; and (3) classification of headaches into distinct phenotypes (i.e., migraine, tension-type, and not otherwise classified).

For this study, children with concussion were classified based on their preinjury and 10 day postinjury headache (PTH) ratings as having: (1) No PTH (no PTH, irrespective of preinjury headache); (2) New PTH (PTH with no preinjury headache); (3) Worse PTH (positive preinjury headache history and PTH that reflected at least a twofold increase in headache frequency or a 2-point increase on a 10-point pain rating scale for headache severity as compared with preinjury levels; Headache Classification Committee of the International Headache Society (IHS), 2018); and (4) Chronic PTH (positive preinjury headache history and PTH that did not meet criteria for worsening headache). We did not examine the impact of phenotype (e.g., migraine, tension-type, or not otherwise classified) on outcomes due to the limited number of participants with each classification type (see Marbil et al., 2023) and associated lack of power to assess those effects.

### Postconcussive symptoms (PCS)

The Health and Behavior Inventory (Ayr et al., 2009) was completed by parents at the initial emergency department visit to assess preinjury symptoms, by parents and children at each postinjury follow-up, as well as weekly via REDCap or phone app, to assess postinjury symptoms (Yeates et al., 2021). The 20-item measure assesses cognitive (11 items) and somatic PCS (9 items) on a 4-point scale of symptom frequency (i.e., never, rarely, sometimes, often), and is validated for use in concussion (O'Brien et al., 2021; Zhang et al., 2022). Given the focus on headache in this study, item 12 (i.e., "Has headaches") from the somatic subscale was not included in score calculations for both parent and child ratings.

### Pain intensity

Intensity of pain, including but not limited to headache, was reported by children at each postinjury visit and weekly via remote assessment in response to a question about current pain (i.e., "How much pain do you currently have?"). Ratings were made on an 11-point numerical scale (0 to 10, with 0 indicating no pain). This scale provides a reliable and valid measure of pain intensity in pediatric populations (Birnie et al., 2019; Castarlenas et al., 2017; von Baeyer et al., 2009), including concussion (Kwan et al., 2020).

### Cognitive function

Children completed the computerized National Institutes of Health Toolbox Cognition Battery subtests (Weintraub et al.,

2013) at each postinjury assessment. The measure includes subtests assessing attention and inhibitory control, cognitive flexibility, episodic and working memory, and processing speed, and is validated for assessing cognitive abilities in pediatric populations, including concussion (Chadwick et al., 2021; Weintraub et al., 2013). The Fluid Cognition Composite was used as a measure of fluid cognitive functioning. We only examined fluid cognition in this study given prior findings, including in the current sample, that concussion negatively impacts fluid cognitive processes but not crystallized cognition (Chadwick et al., 2021).

### Performance validity

The Medical Symptom Validity Test (MSVT; Green, 2004) was completed by children at each postinjury visit to account for performance validity. It provides thresholds for invalid performance.

### Statistical analysis

Group differences on demographic variables were examined using  $\chi^2$  or Fisher's Exact test, Mann-Whitney U test, and one-way analyses of variance with Tukey's Honestly Significant Difference or Kruskal-Wallis test with pairwise comparisons in IBM SPSS Statistics for Windows version 29.0 (IBM Corp., 2022) and SAS software version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Mixed effects linear regression modeling was conducted using Stata version 18.0 (StataCorp, 2021) to compare groups on weekly cognitive and somatic PCS (based on parent and child report), weekly pain intensity (based on child report), and fluid cognitive performance at each follow-up assessment. For PCS and pain ratings, restricted cubic splines were used to test for the nonlinear effects of time, with five knots placed at the default percentiles for time (weeks) postinjury (i.e., 5<sup>th</sup> percentile = week 1, 27.5<sup>th</sup> percentile = week 6, 50<sup>th</sup> percentile = week 12, 72.5<sup>th</sup> percentile = week 18, 95<sup>th</sup> percentile = week 26; Harrell, 2015). A model with a group by time postinjury interaction term was tested against a main effects model using a likelihood ratio test, and the interaction term was retained in final models when  $p < .10$ . Covariates sex and SES composite were included in all models. Age at injury was included as a covariate in models for PCS and pain intensity, but not for fluid cognition because the Fluid Cognition Composite scores are age-standardized. Preinjury cognitive and somatic PCS scores (based on parent report) were included in respective models for PCS. Models tested for both a random intercept and slope, as well as nonlinearity using restricted cubic splines, with unrestricted covariance matrices at the participant level. All main effect and interaction models were bootstrapped 1,000 times before likelihood ratio tests were conducted to minimize any outlier effects and to produce error terms around estimated random effects. Post-hoc pairwise comparisons were computed to decompose significant main or interaction effects involving group. Standardized effect size of pairwise comparisons was assessed using model estimates for Cohen's  $d$ , with  $|0.20| \leq d < |0.50|$ ,  $|0.50| \leq d < |0.80|$ , and  $d \geq |0.80|$  signifying small, medium, and large effects, respectively (Cohen, 1988).

## Results

### Sample

An overview of the study sample and attrition is presented in our previous study of PTH (Marbil et al., 2023). Of 315 children who consented for the study, 217 (68%; 143 concussion/74 OI) returned

**Table 1.** Demographic data for final sample of children in each headache group

Variable	Concussion (n = 138)					p-value*
	No PTH (n = 18)	New PTH (n = 43)	Worse PTH (n = 58)	Chronic PTH (n = 19)	OI (no PTH) (n = 58)	
Preinjury headache, n (%)	9 (50.0)	0 (0.0)	58 (100.0)	19 (100.0)	21 (36.2)	–
<b>Age at injury, mean (SD) years</b>	<b>12.04 (2.43)</b>	<b>11.88 (2.72)</b>	<b>13.53 (2.46)</b>	<b>11.88 (2.27)</b>	<b>12.18 (2.32)</b>	<b>.004</b>
Sex, n (%) male	13 (72.2)	31 (72.1)	33 (56.9)	15 (78.9)	41 (70.7)	.288
Race, n (%)						.198**
American Indian/Alaskan	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.3)	0 (0.0)	
Asian	0 (0.0)	1 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)	
Black	5 (27.8)	18 (41.9)	17 (29.3)	9 (47.4)	26 (44.8)	
Multi-racial	2 (11.1)	2 (4.7)	9 (15.5)	0 (0.0)	12 (20.7)	
Pacific Islander	1 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
White	10 (55.6)	22 (51.2)	32 (55.2)	9 (47.4)	20 (34.5)	
SES composite, mean (SD) z-score	0.24 (1.29)	-0.04 (0.93)	0.29 (1.06)	0.01 (0.92)	-0.20 (0.89)	.099
Full Scale IQ, mean (SD) <sup>a</sup>	103.83 (12.54)	95.93 (14.74)	101.09 (15.57)	94.00 (15.75)	98.50 (15.84)	.159
Definite or suspected loss of consciousness, n (%) <sup>b</sup>	5 (27.8)	16 (40.0)	16 (27.6)	5 (26.3)	–	.550
Glasgow Coma Scale score <15, n (%) <sup>c</sup>	3 (17.6)	5 (12.5)	6 (11.5)	1 (6.7)	–	.839
<b>Injury mechanism, n (%) <sup>d</sup></b>						<b>&lt;.001</b>
Fall	8 (44.4)	15 (35.7)	14 (24.6)	9 (47.4)	28 (49.1)	
Struck object	3 (16.7)	5 (11.9)	21 (36.8)	7 (36.8)	11 (19.3)	
Struck person	3 (16.7)	12 (28.6)	16 (28.1)	3 (15.8)	5 (8.8)	
Bicycle- or motor vehicle-related	4 (22.2)	10 (23.8)	6 (10.5)	0 (0.0)	5 (8.8)	
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	8 (14.0)	
Injury context, n (%) sport or recreational setting <sup>e</sup>	16 (88.9)	32 (78.0)	45 (78.9)	13 (68.4)	41 (78.8)	.678
Validity test, n (%) failure	2 (11.1)	5 (11.6)	1 (1.7)	1 (5.3)	1 (1.7)	.063
Headache medication, n (%) usage <sup>f</sup>						
Preinjury	4 (22.2)	0 (0.0)	34 (58.6)	9 (47.4)	6 (10.3)	<.001
10 days postinjury	0 (0.0)	25 (58.1)	41 (70.7)	16 (84.2)	0 (0.0)	<.001
3 months postinjury <sup>g</sup>	4/15 (26.7)	10/33 (30.3)	22/42 (52.4)	9/11 (81.8)	6/44 (13.6)	<.001
6 months postinjury <sup>h</sup>	3/15 (20.0)	8/32 (25.0)	17/41 (41.5)	5/8 (62.5)	5/38 (13.2)	.011
Preinjury PCS (parent), median (IQR)						
Cognitive	7 (2,11)	9 (2,16)	11 (5,15)	12 (5,20)	7 (1,15)	.269
Somatic	3 (0,5)	1 (0,3)	4 (2,7)	2 (0,7)	1 (0,4)	<.001

Note. **Bolded and italicized** =  $p < .05$ .

\*Fisher's Exact or  $\chi^2$  test for group (i.e., concussion with No PTH, concussion with New PTH, concussion with Worse PTH, concussion with Chronic PTH, and OI with no headache).

\*\*This refers to the comparison between the proportion of children who are White to children who are not White.

<sup>a</sup>Full Scale IQ based on the Wechsler Abbreviated Scale of Intelligence, Second Edition (WASI-II) 2 subtest version (Wechsler, 2011). Data available for 195 participants.

<sup>b</sup>Data available for 135 of 138 participants.

<sup>c</sup>Glasgow Coma Scale score (Teasdale et al., 2014) available for 124 of 138 participants.

<sup>d</sup>Data available for 193 participants.

<sup>e</sup>Data available for 187 participants.

<sup>f</sup>Based on parent report.

<sup>g</sup>Data available for 145 participants.

<sup>h</sup>Data available for 134 participants.

for the 10-day follow-up. Children who returned did not differ from children who did not return in terms of age at injury, sex, mechanism of injury, or whether the injury occurred during sport/recreational play, but did differ in distribution of race, with White children more likely than non-White children to return ( $\chi^2(1) = 12.24$ ,  $p < .001$ ), and area-based SES (i.e., 2010 census tract median family income), which was higher for the children who returned relative to those only seen in the emergency department ( $U = 12851.00$ ,  $p = .003$ ). Of the 217 children who returned for the 10-day follow-up, 211 children had both preinjury and 10-day postinjury headache questionnaire data. Children with concussion were included irrespective of preinjury headache or PTH status. However, we excluded 15 children with OI who had PTH (1 with new PTH; 11 with worse PTH; 3 with chronic PTH) because the small cell sizes resulted in very low statistical power to examine subgroup differences (Marbil et al., 2023). After excluding children with OI who had PTH, the final sample included 196 children (138 concussion/58 OI without PTH). The children included in final analyses did not differ from those who were

excluded in age at injury, sex, race, SES, mechanism of injury, or whether the injury occurred in a sport/recreational setting.

### Demographic and injury characteristics

Table 1 reports sociodemographic and injury characteristics for the final sample. Of the 138 children with concussion, 18 were classified with No PTH, 43 with New PTH, 58 with Worse PTH, and 19 with Chronic PTH. Preinjury headache was reported by 50% of children with No PTH after concussion and in 36% of children with OI with no PTH.

The concussion PTH subgroups and the OI (no PTH) group did not differ in sex, race, SES composite, Full Scale IQ, injury context (e.g., sport/recreational), or preinjury cognitive PCS scores, but did differ in age at injury, mechanism of injury, headache medication usage, and preinjury somatic PCS scores. Children with Worse PTH were older than those with New PTH and OI. Preinjury somatic PCS scores were higher for concussion with Worse PTH relative to concussion with New PTH and OI (no PTH).



**Table 2.** Statistical results for cognitive and somatic postconcussive symptom (PCS), pain intensity, and fluid cognition

Outcome	Model predictor	$\beta$	SE	95% CI		<i>p</i> -value
				Lower	Upper	
Cognitive PCS (Parent)	<b>Group</b>	-	-	-	-	< .001 <sup>†</sup>
	Time postinjury (weekly) <sup>†</sup>	-	-	-	-	.676 <sup>‡</sup>
	<b>Group × Time<sup>†</sup></b>	-	-	-	-	.019 <sup>††</sup>
	Sex (Female – Male)	-0.93	0.86	-2.62	0.77	.283
	Age at injury (years)	0.25	0.18	-0.10	0.60	.168
	SES (z-score)	-0.49	0.40	-1.27	0.29	.220
	<b>Preinjury score</b>	<b>0.67</b>	<b>0.05</b>	<b>0.58</b>	<b>0.76</b>	< .001
	<b>Group</b>	-	-	-	-	< .001 <sup>†</sup>
Cognitive PCS (Child)	Time (weekly) <sup>†</sup>	-	-	-	-	.070 <sup>‡</sup>
	<b>Group × Time<sup>†</sup></b>	-	-	-	-	< .001 <sup>††</sup>
	Sex (Female – Male)	-1.60	1.11	-3.77	0.56	.147
	Age at injury (years)	0.21	0.18	-0.15	0.56	.263
	<b>SES (z-score)</b>	<b>-1.39</b>	<b>0.56</b>	<b>-2.48</b>	<b>-0.29</b>	.013
	<b>Preinjury score</b>	<b>0.20</b>	<b>0.08</b>	<b>0.05</b>	<b>0.35</b>	.011
	<b>Group</b>	-	-	-	-	< .001 <sup>†</sup>
	Time (weekly) <sup>†</sup>	-	-	-	-	.893 <sup>‡</sup>
Somatic PCS (Parent)	<b>Group × Time<sup>†</sup></b>	-	-	-	-	< .001 <sup>†</sup>
	Sex (Female – Male)	-0.07	0.12	-0.30	0.16	.550
	Age at injury (years)	0.05	0.03	-0.00	0.10	.052
	SES (z-score)	-0.08	0.06	-0.20	0.03	.160
	<b>Preinjury score</b>	<b>0.36</b>	<b>0.06</b>	<b>0.24</b>	<b>0.48</b>	< .001
	<b>Group</b>	-	-	-	-	< .001 <sup>†</sup>
	Time (weekly) <sup>†</sup>	-	-	-	-	.027 <sup>‡</sup>
	<b>Group × Time<sup>†</sup></b>	-	-	-	-	< .001 <sup>††</sup>
Somatic PCS (Child)	Sex (Female – Male)	-0.28	0.16	-0.58	0.03	.074
	Age at injury (years)	0.02	0.03	-0.03	0.08	.355
	SES (z-score)	-0.14	0.08	-0.28	0.01	.074
	<b>Preinjury score</b>	<b>0.16</b>	<b>0.06</b>	<b>0.04</b>	<b>0.27</b>	.008
	<b>Group</b>	-	-	-	-	.124
	Time (weekly) <sup>†</sup>	-	-	-	-	< .001 <sup>†</sup>
	<b>Sex (Female – Male)</b>	<b>-0.33</b>	<b>0.11</b>	<b>-0.54</b>	<b>-0.11</b>	.003
	<b>Age at injury (years)</b>	<b>0.04</b>	<b>0.02</b>	<b>0.01</b>	<b>0.07</b>	.011
Pain intensity (Child)	SES (z-score)	-0.01	0.04	-0.09	0.07	.797
	<b>Group</b>	-	-	-	-	.026
	Time (visit) <sup>††</sup>	-	-	-	-	< .001
	Sex (Female – Male)	2.98	2.53	-1.98	7.93	.239
Fluid cognition <sup>a*</sup>	<b>SES (z-score)</b>	<b>4.14</b>	<b>1.31</b>	<b>1.57</b>	<b>6.72</b>	.002

Note: Bolded and italicized =  $p < .05$ .

<sup>†</sup>Restricted cubic spline (5 knots)

<sup>††</sup>Categorical variable (10 days, 3 months, and 6 months postinjury)

<sup>\*</sup>Overall test using Wald  $\chi^2$

<sup>††</sup>Likelihood ratio test

<sup>a</sup>Age standardized score.

<sup>b</sup>Data available for 195 participants.

### Clinical outcomes

At 10 days postinjury, pain intensity scale scores were missing for 2 (3.4%) children with OI (with no PTH), and Fluid Cognition scores were missing for 3 (5.2%) children with concussion with Worse PTH. One (1.7%) child with OI (with no PTH) did not have Fluid Cognition scores at any postinjury follow-up. Statistical results for cognitive and somatic PCS, pain intensity, and fluid cognition are reported in Table 2. Significant pairwise comparisons, conducted to decompose main or interaction effects involving group, and standardized effect sizes (i.e., Cohen's  $d$ ) are reported in Table 3.

### Postconcussive symptoms

Group differences in PCS based on both parent and child report varied by time postinjury, after controlling for sex, age at injury, SES, and preinjury PCS score.

Results for cognitive PCS scores are shown in Figure 1. Relative to OI, cognitive PCS scores were higher in the New PTH group for weeks 1–4 per parent and child report, in the Chronic PTH group for week 1 (parent report) and weeks 1–2 (child report), and in the Worse

PTH group for weeks 1–3 (parent report) and week 1 (child report). Relative to No PTH, cognitive PCS scores were higher in the New PTH group for weeks 1–2 (parent report) and 1–8 (child report), in the Chronic PTH group for week 27 (parent report) and weeks 1–5 (child report), and in the Worse PTH group for weeks 1–3 (child report).

Results for somatic PCS (excluding headache) are shown in Figure 2. Somatic PCS scores were higher relative to OI in the New PTH group for weeks 1–5 per parent report and weeks 1–4 per child report, in the Chronic PTH group for weeks 1–2 per parent and child report, and in the Worse PTH group for weeks 1–5 (parent report) and 1–3 (child report). Relative to No PTH, somatic PCS scores were higher in the New PTH group for weeks 1–4 (parent report) and weeks 1–8 (child report), in the Chronic PTH group for week 1 (parent report) and weeks 1–3 (child report), and in the Worse PTH group for weeks 1–4 (parent report) and 1–6 (child report).

Among the covariates, higher SES was associated with lower cognitive PCS scores based on child report. Higher preinjury cognitive and somatic PCS scores predicted higher postinjury cognitive and somatic PCS scores per parent and child report, respectively.

**Table 3.** Significant pairwise comparison results to follow up significant main or interaction effects involving group for cognitive and somatic postconcussive symptoms (PCS) and fluid cognition. Pain intensity did not differ by group.

Outcome	Group comparison	Week	Marginal mean difference (95% CI)	Cohen's <i>d</i> (95% CI)	<i>p</i> -value
Cognitive PCS (Parent)	New PTH vs OI (no PTH)	1	5.05 (2.36, 7.75)	0.65 (0.30, 0.99)	< .001
		2	4.30 (1.86, 6.75)	0.55 (0.24, 0.86)	< .001
		3	3.58 (1.16, 5.99)	0.46 (0.15, 0.76)	.004
		4	2.91 (0.36, 5.46)	0.37 (0.05, 0.70)	.026
	Chronic PTH vs OI	1	3.20 (0.34, 6.06)	0.41 (0.04, 0.77)	.028
		2	3.32 (1.17, 5.47)	0.42 (0.15, 0.70)	.002
	Worse PTH vs OI	1	4.29 (1.93, 6.66)	0.55 (0.25, 0.85)	< .001
		2	2.38 (0.27, 4.50)	0.30 (0.03, 0.57)	.027
	New PTH vs No PTH	1	3.54 (0.20, 6.88)	0.45 (0.03, 0.88)	.038
		2	3.16 (0.01, 6.30)	0.40 (0.00, 0.80)	.049
	Chronic PTH vs No PTH	27	4.89 (0.03, 9.76)	0.62 (0.00, 1.25)	.049
Cognitive PCS (Child)	New PTH vs OI	1	4.61 (1.41, 7.81)	0.43 (0.13, 0.73)	.005
		2	4.19 (1.20, 7.18)	0.39 (0.11, 0.67)	.006
		3	3.78 (0.71, 6.85)	0.35 (0.07, 0.64)	.016
		4	3.38 (0.05, 6.71)	0.31 (0.00, 0.62)	.046
	Chronic PTH vs OI	1	5.12 (1.51, 8.72)	0.47 (0.14, 0.81)	.005
		2	4.47 (0.72, 8.22)	0.41 (0.07, 0.76)	.020
	Worse PTH vs OI	1	3.91 (1.05, 6.76)	0.36 (0.10, 0.63)	.007
	New PTH vs No PTH	1	6.18 (2.48, 9.88)	0.57 (0.23, 0.92)	.001
		2	6.17 (2.68, 9.66)	0.57 (0.25, 0.90)	< .001
		3	6.14 (2.57, 9.71)	0.57 (0.24, 0.90)	< .001
		4	6.06 (2.22, 9.90)	0.56 (0.21, 0.92)	.002
		5	5.90 (1.75, 10.05)	0.55 (0.16, 0.93)	.005
		6	5.63 (1.25, 10.01)	0.52 (0.12, 0.93)	.012
	Chronic PTH vs No PTH	7	5.24 (0.80, 9.68)	0.49 (0.07, 0.90)	.021
		8	4.77 (0.38, 9.15)	0.44 (0.04, 0.85)	.033
		1	6.68 (2.58, 10.79)	0.62 (0.24, 1.00)	.001
		2	6.45 (2.24, 10.65)	0.60 (0.21, 0.99)	.003
	Worse PTH vs No PTH	3	6.21 (1.60, 10.81)	0.58 (0.15, 1.00)	.008
		4	5.95 (0.82, 11.09)	0.55 (0.08, 1.03)	.023
		5	5.67 (0.05, 11.30)	0.53 (0.00, 1.05)	.048
		1	5.47 (1.82, 9.12)	0.51 (0.17, 0.85)	.003
		2	4.56 (1.11, 8.01)	0.42 (0.10, 0.74)	.010
		3	3.69 (0.25, 7.14)	0.34 (0.02, 0.66)	.036
Somatic PCS (Parent)	New PTH vs OI	1	1.16 (0.77, 1.55)	1.23 (0.82, 1.65)	< .001
		2	0.97 (0.62, 1.32)	1.03 (0.66, 1.40)	< .001
		3	0.78 (0.42, 1.14)	0.83 (0.45, 1.21)	< .001
		4	0.61 (0.21, 1.00)	0.65 (0.23, 1.07)	.002
	Chronic PTH vs OI	5	0.46 (0.02, 0.90)	0.49 (0.02, 0.96)	.040
		1	1.01 (0.52, 1.51)	1.08 (0.55, 1.61)	< .001
	Worse PTH vs OI	2	0.73 (0.29, 1.18)	0.78 (0.30, 1.26)	.001
		1	1.20 (0.84, 1.55)	1.28 (0.90, 1.66)	< .001
		2	1.00 (0.66, 1.34)	1.06 (0.70, 1.42)	< .001
		3	0.80 (0.45, 1.16)	0.86 (0.48, 1.24)	< .001
		4	0.62 (0.23, 1.01)	0.66 (0.24, 1.08)	.002
		5	0.46 (0.03, 0.89)	0.49 (0.03, 0.95)	.004
	New PTH vs No PTH	1	0.78 (0.25, 1.31)	0.83 (0.27, 1.40)	.004
		2	0.68 (0.21, 1.15)	0.72 (0.22, 1.23)	.005
		3	0.58 (0.13, 1.03)	0.62 (0.14, 1.10)	.012
		4	0.48 (0.02, 0.95)	0.52 (0.02, 1.02)	.042
	Chronic PTH vs No PTH	1	0.64 (0.01, 1.26)	0.68 (0.01, 1.35)	.047
	Worse PTH vs No PTH	1	0.82 (0.29, 1.35)	0.87 (0.31, 1.44)	.002
		2	0.71 (0.23, 1.19)	0.76 (0.25, 1.27)	.004
		3	0.60 (0.14, 1.06)	0.64 (0.15, 1.13)	.011
		4	0.50 (0.02, 0.97)	0.53 (0.02, 1.04)	.022
Somatic PCS (Child)	New PTH vs OI	1	0.83 (0.39, 1.28)	0.64 (0.30, 0.98)	< .001
		2	0.76 (0.36, 1.16)	0.58 (0.27, 0.89)	< .001
		3	0.68 (0.26, 1.10)	0.52 (0.20, 0.84)	.002
		4	0.60 (0.12, 1.08)	0.46 (0.09, 0.83)	.014
	Chronic PTH vs OI	1	0.83 (0.35, 1.31)	0.63 (0.26, 1.00)	< .001
		2	0.67 (0.17, 1.18)	0.51 (0.13, 0.90)	.009
	Worse PTH vs OI	1	0.88 (0.46, 1.29)	0.67 (0.35, 0.99)	< .001
		2	0.71 (0.32, 1.10)	0.55 (0.25, 0.84)	< .001
	New PTH vs No PTH	3	0.55 (0.15, 0.96)	0.42 (0.11, 0.74)	.008
		1	0.88 (0.26, 1.49)	0.67 (0.20, 1.14)	.006
		2	0.88 (0.33, 1.44)	0.68 (0.25, 1.10)	.002
		3	0.89 (0.35, 1.42)	0.68 (0.27, 1.09)	.001
		4	0.88 (0.33, 1.42)	0.67 (0.26, 1.09)	.002

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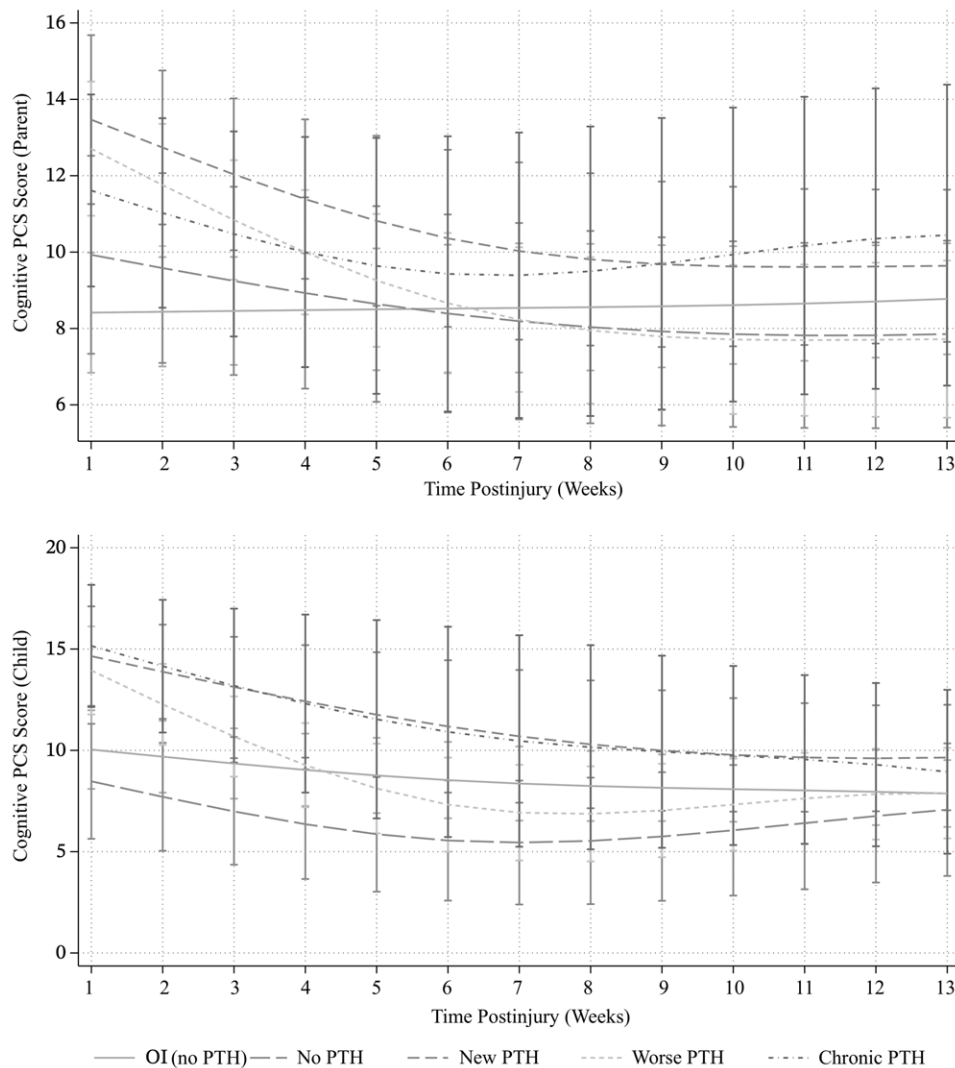
**Table 3.** (Continued)

Outcome	Group comparison	Week	Marginal mean difference (95% CI)	Cohen's <i>d</i> (95% CI)	<i>p</i> -value
Fluid cognition <sup>a</sup>	Chronic PTH vs No PTH	5	0.85 (0.28, 1.42)	0.65 (0.22, 1.08)	.003
		6	0.80 (0.22, 1.38)	0.61 (0.17, 1.06)	.007
		7	0.72 (0.14, 1.29)	0.55 (0.11, 1.00)	.014
		8	0.62 (0.06, 1.18)	0.47 (0.05, 0.90)	.030
		1	0.87 (0.28, 1.47)	0.67 (0.21, 1.12)	.004
	Worse PTH vs No PTH	2	0.80 (0.21, 1.39)	0.61 (0.16, 1.07)	.008
		3	0.73 (0.06, 1.40)	0.56 (0.05, 1.07)	.033
		1	0.92 (0.35, 1.49)	0.71 (0.27, 1.14)	.001
		2	0.84 (0.31, 1.37)	0.64 (0.24, 1.05)	.002
		3	0.76 (0.25, 1.27)	0.58 (0.19, 0.97)	.004
	Chronic PTH vs OI	4	0.69 (0.16, 1.21)	0.52 (0.13, 0.92)	.010
		5	0.62 (0.08, 1.15)	0.47 (0.06, 0.88)	.024
		6	0.56 (0.01, 1.10)	0.42 (0.01, 0.84)	.046
Fluid cognition <sup>a</sup>	Chronic PTH vs OI	–	–11.19 (–19.54, –2.85)	–0.61 (–1.06, –0.15)	.009
	New PTH vs No PTH	–	–9.40 (–18.04, –0.76)	–0.51 (–0.98, –0.04)	.033
	Chronic PTH vs No PTH	–	–13.96 (–24.06, –3.86)	–0.76 (1.30, –0.21)	.007

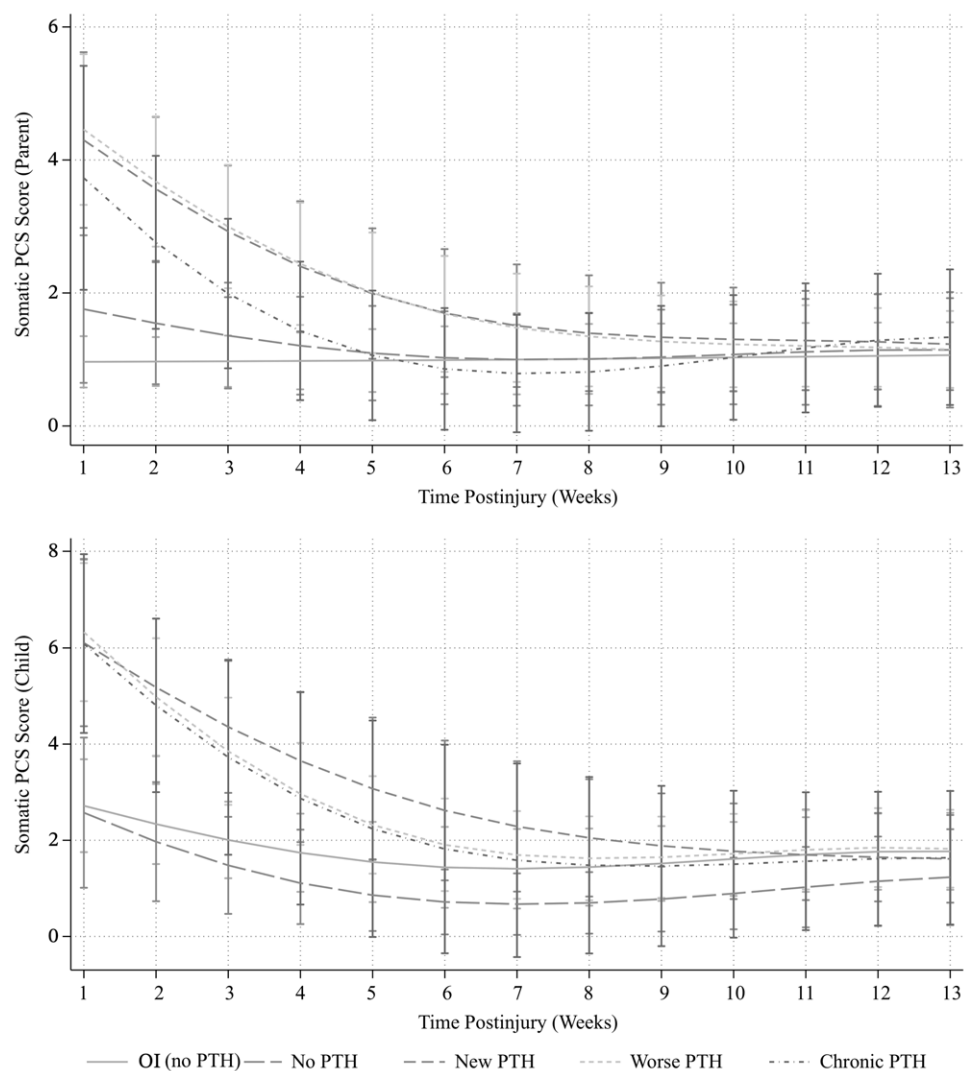
Note: Significance defined as  $p < .05$ .

CI = confidence interval, OI = orthopedic injury, PTH = posttraumatic headache.

<sup>a</sup>Data available for 195 participants.



**Figure 1.** Cognitive postconcussive symptom scores based on parent (top) and child (bottom) report by group over time.



**Figure 2.** Somatic postconcussive symptom scores based on parent (top) and child (bottom) report by group over time.

### Pain intensity

Results for pain intensity are shown in Figure 3. Groups did not differ in pain intensity across time postinjury after controlling for sex, age at injury, and SES. Across groups, increasing time postinjury was associated with decreasing pain intensity. Among the covariates, pain intensity was lower in males relative to females and positively associated with older age at injury.

### Fluid cognition

Results for fluid cognition scores are shown in Figure 4. Fluid cognition scores differed by group, across time postinjury, after controlling for sex and SES. Scores were lower in the Chronic PTH group versus the No PTH and OI groups, and in the New PTH group versus the No PTH group. Across groups, greater time postinjury was associated with increasing scores. Among the covariates, higher SES was associated with higher fluid cognition scores.

### Influence of validity testing

Ten children (5% of the total sample) had  $\geq 1$  validity test score below cutoffs for valid performance (i.e., “failure”; Table 1). After excluding children who scored below cutoffs on any validity

testing, results were similar to those for the final sample for all clinical outcomes (Supplemental Table 1). One exception was that fluid cognition scores no longer differed significantly by group, although the direction of the effect was similar. For covariates, somatic PCS per child report was lower in females than males.

### Influence of trauma-related lesions

Children completed an MRI at 10 days postinjury as part of the larger study (Ware, Goodrich-Hunsaker, et al., 2020; Ware, Shukla, et al., 2020). Among children with concussion with New PTH, six (14%) had trauma-related findings identified on radiological review of the images (i.e., complicated mild TBI). One child with trauma-related lesions on MRI also failed validity testing. Among children with New PTH, those with trauma-related lesions did not differ from those without ( $n = 37$ ) on any clinical outcome at any time postinjury,  $.116 \leq p \leq .903$ . After excluding the 6 children with complicated mild TBI with New PTH, results were similar to those for the final sample for all clinical outcomes (Supplemental Table 2). However, higher SES predicted lower somatic PCS scores per parent report and females had lower somatic PCS scores than males per child report.



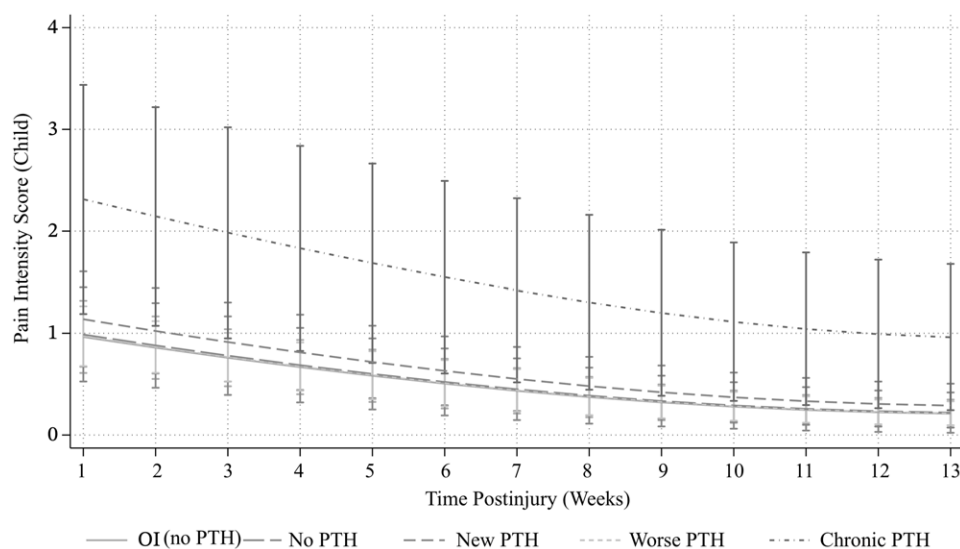


Figure 3. Pain intensity by group over time.

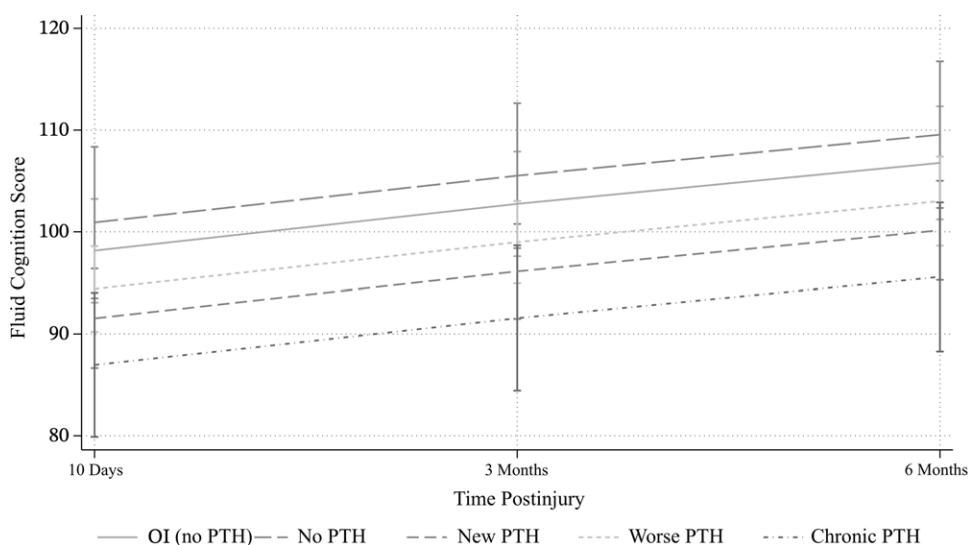


Figure 4. Fluid cognition standard scores by group at 10 days, 3 months, and 6 months postinjury.

## Discussion

This longitudinal, prospective cohort study investigated whether PTH presentation was associated with cognitive and somatic PCS, pain intensity, and fluid cognition up to 6 months postinjury after concussion. Overall, PTH presentation was indeed associated with clinical outcomes after concussion, as found previously (Babcock et al., 2013; Novak et al., 2016). Children with PTH 10 days after concussion (i.e., New, Worse, and Chronic PTH groups) had more severe cognitive and somatic PCS and more prolonged recovery than children with no PTH or OI, consistent with previous studies (Kwan et al., 2020; McConnell et al., 2020). Children with new and chronic PTH also demonstrated lower fluid cognition across time postinjury relative to children with no PTH. Children with new, chronic, and worse PTH did not differ from one another on any outcomes, suggesting that the presence of PTH of any type, regardless of preinjury headache history, increases children's risk of persisting PCS and poorer fluid cognitive functioning. Lastly, pain intensity decreased over time, but did not differ across groups, suggesting that it is a ubiquitous experience after mild traumatic

injury in children. Importantly, findings related to group were not strongly influenced by performance on validity testing or the presence of trauma-related lesions 10 days after concussion (i.e., complicated mild TBI).

The presence of PTH was an important risk factor for more severe and persisting problems after concussion. Preinjury headache and early PTH are both associated with prolonged recovery from PCS (Babcock et al., 2013; Blume, 2015), and preinjury headache can increase risk of PTH (Heyer et al., 2016; Kuczynski et al., 2013; Marbil et al., 2023). However, we previously found an increased risk of PTH up to 3 months after concussion relative to mild OI regardless of preinjury headache (Marbil et al., 2023), suggesting that PTH may be secondary to concussion in some children. The current findings suggest that the presence of PTH can contribute to worse clinical outcomes after pediatric concussion beyond the influence of preinjury headache, sex, SES, and age at injury.

Differences in PCS were especially pronounced in children with PTH compared to those with OI without PTH in the first 5 weeks

postinjury, when recovery typically occurs in pediatric concussion (Ledoux et al., 2019; Mayer et al., 2020). However, higher PCS relative to children without PTH (No PTH) were self-reported by children with new PTH up to 8 weeks postinjury and by those with worse PTH up to 5 weeks postinjury, whereas differences based on parent ratings were only reported up to 4 weeks postinjury. Headache is the most common type of pain reported during childhood, with recurrent and persistent headache estimated to occur in roughly 26 to 58% of children (Abu-Arafeh et al., 2010; Chambers et al., 2024; King et al., 2011). Children with headache prior to their injury (e.g., concussion with Chronic PTH or Worse PTH) might have established effective pain management strategies or headache care that helped mitigate prolonged symptoms after concussion. Therefore, the presence of new onset (New PTH) or worse headache (Worse PTH) after concussion could represent an additional burden for children struggling with PCS. Future research on other specific domains or types of PCS will help to determine whether PCS profiles are specific to PTH types.

Fluid cognitive functioning was poorer in children with PTH than in those without PTH after concussion and OI, regardless of PTH type. Fluid cognitive functioning can be diminished up to 3 months following pediatric concussion (Chadwick et al., 2021; Hou et al., 2023). The current findings suggest that PTH is associated with greater cognitive impairment in children, regardless of their preinjury headache history. However, group differences did not change over time, suggesting that differences in fluid cognition could be caused by pre-injury functioning or a long-term effect of PTH. Childhood headache is associated with cognitive impairment (van Gessel et al., 2011). There is a paucity of research regarding PTH and cognition after concussion in children. Further research is warranted to better understand specific characteristics of PTH that might directly result from or be exacerbated by a concussion and influence cognitive outcomes. Regardless, time postinjury had a significant main effect on cognitive functioning, which improved over time in all groups. This is consistent with our previous findings in this sample (Chadwick et al., 2022), although cognition has not always differed between children with concussion relative to OI in other studies (Babikian et al., 2011).

Interestingly, PTH was not associated with children's pain intensity ratings. This suggests that the children with OI, who did not have PTH, likely had pain in other areas (e.g., at the site of injury) that was comparable to the pain reported by children with concussion, across headache groups. The pain intensity measure might not have captured all aspects of pain. For example, although a self-report numerical pain rating scale has been demonstrated as acceptable for pediatric populations (Castarlenas et al., 2017), it does not reflect the effects of pain localization or functional impairment, which could impact recovery from concussion (Kwan et al., 2017). Future research could incorporate more detailed pain measures, given the implications that widespread or multiple-location pain could have for outcomes and treatment of chronic pain in children (Foxen-Craft et al., 2023).

We included several covariates in our models to account for their potential association with clinical outcomes. PCS and fluid cognitive functioning were associated with SES, and pain intensity varied by sex and age at injury. The relation of SES to PCS and fluid cognition scores, found across groups and time postinjury, was expected (White, 1982; von Stumm & Plomin, 2015). Children from families of greater social disadvantage are at risk of worse clinical outcomes and reduced cognitive functioning (Gaudet et al., 2024; Last et al., 2018; von Stumm & Plomin, 2015; Ware et al., 2023). Risk factors for pain overlap with those of PTH. For

example, the risk of PTH is greater for children who are older (i.e., adolescents) and female (Babcock et al., 2013; Ledoux et al., 2019; Marbil et al., 2023; Mayer et al., 2020). Across groups and time postinjury, females and older children reported worse pain severity, consistent with patterns observed in pediatric chronic pain more generally (Chambers et al., 2024; King et al., 2011).

Finally, our results remained similar after excluding children whose performance did not meet cutoffs on validity testing, as well as children with trauma-related findings on neuroimaging (i.e., complicated mild TBI). The current rate (5%) of failed validity testing is consistent with published research in another larger Canadian sample (Ware et al., 2023), but is somewhat lower than previously published rates of failure in children with persistent PCS after mild TBI, typically drawn from clinic settings (i.e., 12 to 20%; Kirkwood, 2015). We previously did not find cognitive deficits to be strongly associated with validity test performance in this sample (Chadwick et al., 2021). Additional research is needed to better understand the implications and significance of validity testing among children with concussion (Bigler, 2012; Kirkwood & Kirk, 2010; Kirkwood, 2015). All children with complicated mild TBI developed PTH 10 days after concussion (i.e., were in the New PTH group). However, results did not substantially differ after their exclusion. Understanding the pathophysiology of PTH after pediatric concussion is an important direction of future research (Fan et al., 2024). More research is particularly needed to understand whether risk of developing PTH differs for children with concussion as compared with complicated mild TBI (Rausa et al., 2020; Schmidt et al., 2018).

This study has several notable strengths. First, we used a standardized questionnaire to measure headache characteristics and conducted a novel comparison of subgroups based on headache presentations (i.e., New PTH, Worse PTH, Chronic PTH). Second, we included a comparable injury group of children with OI without PTH to better isolate the effects of concussion as opposed to traumatic injury more generally (Babikian et al., 2011). Additionally, although the onset and presentation of headache, and thus subsequent classification of children into headache groups, were determined based solely on parent report, we assessed somatic and cognitive PCS based on both parent and child report. Parent and child symptom reports are only moderately correlated (Hajek et al., 2010). The validity of child versus parent ratings is not well understood but may vary by children's age. Parents may better account for symptoms in younger children (i.e., 8 years old), whereas older children (i.e., adolescent) may provide more accurate ratings than parents. Future research on the reasons for discrepancies between parent and child ratings is needed to address this issue. For now, our use of multi-informant ratings provides a more comprehensive understanding of the relationship of post-traumatic headache to PCS severity after pediatric concussion.

This study also has limitations. We only recruited children from pediatric hospital emergency departments, so the findings may not generalize to children who present in other settings or who do not seek medical care (Arbogast et al., 2016). Further, although our study included children from diverse racial backgrounds, attrition was higher for non-White children. Thus, results may not generalize to children of racialized groups. Some research has shown lower rates of presentation to emergency departments and of receiving a diagnosis of concussion among Black children (Lyons et al., 2019; Pate et al., 2022; Wallace & Mannix, 2021). However, pediatric concussion research that includes and focuses on racialized individuals is lacking, precluding more comprehensive understanding of whether and how racial identity influences

postconcussive outcomes (Cook et al., 2023). Additional research is needed to identify important factors, including those associated with marginalized identities and social determinants of health, that moderate outcomes after pediatric concussion. While attrition and data loss rates in the larger study parallel those of other studies of concussion in children (Babikian et al., 2011; Taylor et al., 2010), statistical power might have limited our ability to detect subtle group differences across recovery. The sample size and low rates of migraine and tension-type headache in our sample prevented us from examining the influence of those PTH phenotypes on clinical outcomes. Migraine headache could result in higher PCS severity (van Ierssel et al., 2023) and prolonged recovery (Klein et al., 2022) after concussion, and needs to be examined in relation to outcomes in future research. Psychiatric functioning also could moderate outcomes after concussion. Children who sustain concussion can develop mood problems (Sabir & Malhi, 2023), and chronic pain can increase mental health difficulties (Vinall et al., 2016). Future research should examine the interrelationships among concussion, PTH, pain, and mood. Lastly, information about headache medication usage was limited, precluding any examination of the association of medication usage with outcomes (Russo et al., 2022). Future research should examine the influence of common over-the-counter and prescription headache medications on clinical outcomes following pediatric concussion.

## Conclusions

This prospective longitudinal study examined PTH presentation in relation to clinical outcomes, including PCS, pain intensity, and fluid cognition, in children with concussion versus mild OI. Relative to children without PTH, children who had PTH in the first 10 days after concussion had worse child- and parent-reported PCS and lower fluid cognition. Children who develop PTH, particularly those without a history of preinjury headache, may benefit from interventions, such as learning pain management strategies, to help mitigate PTH. However, clinical trials focused on the treatment of PTH are needed to optimize clinical management of pediatric concussion. Future research that examines distinct PTH characteristics and phenotypes in a larger sample could help inform interventions to reduce PTH and ameliorate symptom burden following pediatric concussion.

**Supplementary material.** The supplementary material for this article can be found at <https://doi.org/10.1017/S1355617725000128>

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**Author contribution.** Ms. Marbil and Dr Ware wrote the manuscript.

Dr Galarneau and Ms. Minich performed the statistical analyses and revised the manuscript.

Drs. Hershey, Orr, Taylor, Bigler, and Cohen revised the manuscript.

Dr Yeates was the principal investigator of the study and reviewed and revised the manuscript.

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