## ORIGINAL RESEARCH

# Trajectories of Persistent Postconcussion Symptoms and Factors Associated With Symptom Reporting After Mild Traumatic Brain Injury

Check for updates

Linda Fordal, MSc,[a,b] Jonas Stenberg, PhD,[a,c] Grant L. Iverson, PhD,[d,e,f]
Simen B. Saksvik, PhD,[b,g] Migle Karaliute, MSc,[g,h] Anne Vik, PhD,[a,c]
Alexander Olsen, PhD,[b,g,1] Toril Skandsen, PhD[a,b1]

From the [a]Department of Neuromedicine and Movement Science, Norwegian University of Science and Technology (NTNU), Trondheim, Norway;
[b]Department of Physical Medicine and Rehabilitation, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway; [c]Department of
Neurosurgery, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway; [d]Department of Physical Medicine and Rehabilitation,
Harvard Medical School, Boston, Massachusetts, United States; [e]Spaulding Rehabilitation Hospital and Spaulding Research Institute,
Charlestown, Massachusetts, United States; [f]Home Base, A Red Sox Foundation and Massachusetts General Hospital Program, Charlestown,
Massachusetts, United States; [g]Department of Psychology, Norwegian University of Science and Technology (NTNU), Trondheim, Norway; and
[h]Department of Neurology and Clinical Neurophysiology, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway.

### Abstract

**Objective:** To examine the trajectories of persistent postconcussion symptoms (PPCS) after mild traumatic brain injury (MTBI) and to investigate which injury-related and personal factors are associated with symptom reporting.

**Design:** Prospective longitudinal cohort study. Follow-up at 3 and 12 months postinjury.

**Setting:** A level 1 trauma center and an emergency outpatient clinic.

**Participants:** Patients with MTBI (n=358), trauma controls (n=75), and community controls (n=78).

**Main outcome measures:** Symptoms were assessed with the British Columbia Postconcussion Symptom Inventory (BC-PSI). Participants were categorized as having moderate to severe PPCS (msPPCS) when reporting ≥3 moderate/severe symptoms or a BC-PSI total score of ≥13. BC-PSI total scores were compared between the groups and were further used to create cutoffs for reliable change by identifying uncommon and very uncommon change in symptoms in the community control group. Associations between symptom reporting and 25 injury-related and personal factors were examined.

**Results:** The MTBI group had a similar prevalence of msPPCS at 3 and 12 months (21%) and reported more symptoms than the control groups. Analyses of individual trajectories, however, revealed considerable change in both msPPCS and BC-PSI total scores in the MTBI group, where both worsening and improvement was common. Intracranial lesions on computed tomography were associated with a greater likelihood of improving from 3 to 12 months. Those with msPPCS at both assessments were more likely to be women and to have these personal preinjury factors: reduced employment, pain, poor sleep, low resilience, high neuroticism and pessimism, and a psychiatric history.

**Conclusions:** Group analyses suggest a stable prevalence of msPPCS the first year postinjury. However, there was considerable intraindividual change. Several personal factors were associated with maintaining symptoms throughout the first year.

Archives of Physical Medicine and Rehabilitation 2022;103:313—22

© 2021 Published by Elsevier Inc. on behalf of The American Congress of Rehabilitation Medicine.

The majority of people who sustain a mild traumatic brain injury (MTBI) experience a period of days or weeks with somatic, emotional, or cognitive symptoms, such as headaches, irritability, or attention problems, followed by a return to their normal function.[1] These symptoms are called postconcussion symptoms (PCS). A considerable minority, however, will suffer from PCS for months or years,[1,2] henceforth called persistent postconcussion symptoms (PPCS) when referring to their presence at 3 months postinjury or later. The nature and prevalence of PPCS after MTBI have been reported in numerous cross-sectional studies and in some longitudinal studies.[3-11] However, surprisingly few have examined the individual trajectories of PPCS in adults recruited from the time of injury.[6,8] Postconcussion-like symptoms are common in other conditions, such as depression and chronic pain, and are even common in community controls.[2,12,13] Thus, to obtain a more complete understanding of the dynamic course of PPCS, it is important to compare change in symptoms over time after MTBI to the typical change in people who have not sustained a brain injury.

The risk of developing PPCS varies between individuals, and several personal factors, such as employment status, sex, preinjury health, and personality traits, are associated with symptom reporting,[14-21] though the literature related to injury-related factors, such as intracranial lesions on computed tomography (CT), remains largely inconclusive.[22] Further, it has not been determined how the different factors are associated with the stability and change of PPCS reporting throughout the first year after MTBI. Our research group has previously published an article on the association between personal factors and PPCS at 3 months.[19] We now extend this study with a longitudinal examination of symptoms. The present study examined the trajectories of PPCS in a large sample of persons with MTBI, trauma controls (TCs), and community controls (CCs) at 3 and 12 months postinjury. Additionally, we examined how injury-related factors and personal factors were associated with PPCS reporting from 3 to 12 months postinjury.

## Methods

### Participants

The participants were part of the Trondheim MTBI follow-up study, a population-based study consisting of 378 patients with MTBI, recruited between April of 2014 and January of 2015.[23] The study recruitment procedure identified all patients with MTBI in the catchment area who were seeking acute care after head trauma during the inclusion period (n=732), and the differences

between the 378 enrolled and those not enrolled were small; hence, the patients in the follow-up study have been shown to be fairly representative of all patients seeking health care for an MTBI.[23] The inclusion criteria were to have sustained a traumatic brain injury (TBI)[24] and to be 16-59 years of age. The TBI was further defined as mild based on the criteria set by the WHO Collaborating Centre Task Force: (1) loss of consciousness (LOC) of <30 minutes; (2) Glasgow Coma Scale score of 13-15 when assessed in the emergency department; and (3) posttraumatic amnesia (PTA) lasting <24 hours.[25] LOC had to be witnessed to be classified as present, whereas PTA was based on self-report. The radiology reports from acute head CTs were used for information about intracranial lesions. The exclusion criteria were (1) ongoing substance abuse or severe medical or psychiatric problems (eg, bipolar disorder, psychosis, cancer) deemed severe enough to interfere with follow-up; (2) a previous complicated mild, moderate, or severe TBI or a severe neurologic disorder (eg, multiple sclerosis, stroke); or (3) nonfluency in Norwegian.

For the present study, 75 TCs and 78 CCs were included. Recruitment of patients with MTBI and the TCs took place at 2 emergency departments: (1) a level 1 trauma center in Trondheim, Norway, and (2) the outpatient clinic Trondheim Municipal Emergency Clinic. The CCs were recruited among staff and acquaintances/family of staff and patients. The TCs were matched on age and sex on a group level, and the CCs were matched on age, sex, and education, a strategy that resulted in groups comparable on most characteristics.[19] The TCs had suffered orthopedic injuries not involving the head, neck, or dominant upper extremity. The CCs and TCs had the same exclusion criteria as the patients with MTBI. The CCs did not receive treatment for any psychiatric disorder at the time of inclusion. The study was approved by the regional committee for research ethics (REK 2013/754). All participants gave informed consent, as did parents of participants younger than 18 years of age.

### Study procedures

Patients were consecutively identified based on lists of emergency department visits and CT referrals and approached and enrolled as previously described.[23] Data on injury-related and personal characteristics were collected shortly after the injury, through a structured interview and questionnaires. Interviews were conducted by telephone and the questionnaires were either completed at the hospital or sent and returned by mail. At 3 and 12 months postinjury, all participants underwent an outcome evaluation interview by telephone or at the hospital.

### Personal preinjury factors

Details on the 22 personal factors analyzed in the present study are presented in table 1. Information on age, sex, years of completed education, school marks, reading difficulties, work status, previous MTBIs, pain, psychiatric history, sleep quality, and substance use was obtained by interview. Information regarding preinjury headache, alcohol use, attention deficit hyperactivity disorder symptoms, personality traits, life orientation (optimism/pessimism), threatening events, and resilience was obtained through questionnaires.

---

**List of abbreviations:**

| | |
|---|---|
| BC-PSI | British Columbia Postconcussion Symptom Inventory |
| CCs | community controls |
| CT | computed tomography |
| LOC | loss of consciousness |
| msPPCS | moderate to severe persistent postconcussion symptoms |
| MTBI | mild traumatic brain injury |
| PCS | postconcussion symptoms |
| PPCS | persistent postconcussion symptoms |
| PTA | posttraumatic amnesia |
| TCs | trauma controls |
| TBI | traumatic brain injury |

**Table 1** Measurement of 22 personal preinjury factors

| Variable | Measures and Categorization | Collection Method and Measure Details |
|---|---|---|
| Age | Years | Medical records |
| Sex | Woman or man | Medical records |
| Education | Years of completed education. Starting from the first year of school (6 years of age) | Self-report, interview |
| School marks | Average high school marks (1-6 scale) | Self-report, interview |
| Reading difficulties | Recorded as "yes" if the person had been diagnosed with reading difficulties | Self-report, interview |
| Reduced work/studies | Recorded "yes" if the person had worked/studied <80% (of a 37.5-h week) | Self-report, interview |
| Previous MTBI | Recorded as "yes" if the person had sustained 1 or more head traumas likely to have fulfilled the MTBI criteria in the present study | Self-report, interview |
| Pain | Recorded as "yes" if the person had non-headache pain in any part of the body graded ≥3 on a 0-10 numeric rating scale | Pain map and numeric rating scale |
| Headache | Recorded as "yes" or "no" | Item from self-report questionnaire. "Have you suffered from headache during the last year?" |
| Psychiatric history | Recorded "yes" if the person reported having sought health care for a psychiatric illness | Self-report, interview |
| Substance use | Recorded "yes" if the person reported using drugs other than alcohol | Self-report, interview |
| Poor sleep quality | Insomnia Severity Index.[26] The mean of the first 3 items: difficulties falling asleep, staying asleep, and waking up too early, was used | Self-report questionnaire, with a 5-point Likert scale. Higher scores indicate greater sleep problems. The first 3 questions were administered as an interview |
| ADHD symptoms | Adult ADHD Self-Report Scale version 1.1. The total score was calculated for the full scale (all 18 items)[27-29] | Self-report questionnaire. Higher scores indicate more attention/hyperactivity problems. 2 missing items accepted |
| Alcohol use | The Alcohol Use Disorders Identification Test.[30] The total score of the 10 items | Self-report questionnaire. Higher scores indicate higher consumption. 2 missing items accepted |
| Personality traits | Big Five Inventory (BFI-44).[31,32] A short form of the Big Five Inventory including 44 items. The mean score for each scale was calculated | Self-report questionnaire yielding scores on extroversion, agreeableness, conscientiousness, neuroticism, and openness. Higher scores indicate higher levels of the personality trait. At least 50% of the items in each personality domain had to be answered for that scale to be calculated |
| Pessimism | Life Orientation Test-Revised.[33,34] The mean score was used | Self-report questionnaire with 10 items, 6 of them measuring optimism/pessimism, and 4 fillers (not scored items). Lower scores indicate higher optimism and the variable is therefore referred to as "pessimism." 2 missing items accepted |
| Threatening life events | List of Threatening Events Questionnaire.[35,36] The total number of events was calculated | Self-report questionnaire measuring experience of environmental stressful events during the last year. The Norwegian version comprised 13 items. 2 missing items were accepted |
| Resilience | Resilience Scale for Adults. This study used the total resilience score, which was the mean of all item scores[37-39] | Self-report questionnaire with 33 items measuring 6 dimensions (perception of self, planned future, social competence, family cohesion, social resources, and structured style) and a score of total resilience. Higher scores indicate higher resilience. 3 missing items accepted |

NOTE. Adapted from Skandsen et al.[19]
Abbreviation: ADHD, attention deficit hyperactivity disorder.

## Persistent postconcussion symptoms

PPCS were measured with the British Columbia Postconcussion Symptom Inventory (BC-PSI). The BC-PSI consists of items measuring 13 core symptoms: headache, dizziness, nausea, fatigue, noise sensitivity, irritability, sadness, nervousness, temper problems, poor concentration, memory problems, reading disability, and sleep problems.[12] The frequency and intensity of symptoms are reported on a 0-5 scale. These scores are converted to a combined score between 0 and 4, with higher scores indicating greater severity and frequency. Two outcome measures were calculated from the BC-PSI. First, we made a variable representing PPCS as a binary outcome (having moderate to severe PPCS or not), referred to as msPPCS. We categorized participants as having msPPCS if at least 1 of the following 2 criteria was met: (1) reporting ≥3 moderate to severe symptoms, that is, a score of 3 or 4; or (2) having a total score of ≥13 points. Second, we also investigated the symptom severity load as a continuous variable; thus, the second outcome variable is the BC-PSI total score (range, 0-52).

## Statistical analyses

Chi-square tests were used to calculate whether the proportion of participants fulfilling the msPPCS criteria differed between the patients with MTBI, TCs, and CCs. Kruskal-Wallis tests were used to examine differences between the 3 groups on the BC-PSI total score.

Several methods to calculate reliable change exist.[40] However, most assume a reasonably normal distribution of scores. In PCS scales, this assumption is often violated. We therefore used the natural distribution of change scores to calculate reliable change.[41,42] First, data from the CCs were used to create cutoffs for reliable change for the BC-PSI total score. The change scores were calculated by subtracting the 3-month assessment score from the 12-month assessment score. By examining the natural distribution of change scores in the CCs, uncommon and very uncommon change scores (ie, cutoffs) were identified. These represent improvement or worsening in symptoms reported by ≤10% (uncommon change) and ≤5% (very uncommon change), respectively. That is, in this study we predefined the percentages and not the actual cutoffs. The cutoffs were utilized to identify the percentage of patients with MTBI and TCs who had an improvement or worsening that was uncommon, or very uncommon, among CCs.

Chi-square and Kruskal-Wallis tests were used to compare 4 groups of patients with MTBI on injury-related and personal factors: (1) stable msPPCS (fulfilled the msPPCS criteria at both assessments), (2) stable no msPPCS (did not fulfill the msPPCS criteria at either assessment), (3) msPPCS worseners (fulfilled the criteria at 12 months only), and (4) msPPCS improvers (fulfilled the criteria at 3 months only). The unadjusted P values are reported along with the comparisons still significant after Bonferroni correction for multiple comparisons. Post hoc comparisons were performed on factors significant after Bonferroni correction.

# Results

## Participant characteristics

Of the 378 patients with MTBI in the Trondheim MTBI follow-up study, 358 completed the BC-PSI at least once and were included in the present analyses. The mean age in the sample was 31.5 years, 34.1% were women, and 69% were not admitted to the hospital. There were 75 TCs and 78 CCs who completed the BC-PSI at least once. No statistically significant differences were found between the patients with MTBI, TCs, and CCs in age, sex, or level of education. However, the patients with MTBI reported significantly more prior MTBIs (table 2).

**Table 2** Characteristics of the MTBI group, TCs, and CCs

| Variables | MTBI Group | Trauma Controls | Community Controls | P |
|---|---|---|---|---|
| n | 358 | 75 | 78 | |
| Age, years | | | | .375 |
|   Mean (SD) | 31.5 (13.0) | 32.5 (13.3) | 33.2 (13.0) | |
|   Median (IQR) | 25.5 (20.9-41.3) | 27.5 (21.0-46.2) | 28.5 (23.0-44.0) | |
| Sex female, n (%) | 122 (34.1) | 30 (40.0) | 31 (39.7) | .457 |
| Education years, median (IQR) | 13 (12.0-16.0) | 14 (12.0-16.0) | 13 (12.0-16.0) | .057 |
| Previous MTBI yes, n (%) | 76 (21.4) | 6 (8.0) | 9 (11.5) | **.006** |
| Cause of injury,* n (%) | | | | |
|   Fall | 129 (36.0) | 23 (30.7) | — | — |
|   Violence | 59 (16.5) | 1 (1.3) | — | — |
|   Bicycle | 57 (15.9) | 7 (9.3) | — | — |
|   Sports accident | 50 (14.0) | 27 (36.0) | — | — |
|   Motor vehicle accident | 40 (11.2) | 3 (4.0) | — | — |
|   Struck object | 17 (4.7) | 5 (6.7) | — | — |
|   Other /unknown | 6 (1.7) | 9 (12.0) | — | — |
| LOC yes/missing, n (%) | 167 (46.6)/130 (36.3) | — | — | — |
| PTA long, 1-24 h, n (%) | 98 (27.4) | — | — | — |
| CT Findings yes/not performed n (%) | 20 (5.6)/77 (21.5) | — | — | — |
| GCS, n (%) | | | | |
|   13 | 5 (1.4) | — | — | — |
|   14 | 50 (14.0) | — | — | — |
|   15 | 264 (73.7) | — | — | — |
|   Unknown | 39 (10.9) | — | — | — |
| Fractures (any), yes, n (%) | 56 (15.6) | 44 (58.6) | — | — |
| Level of care, n (%) | | | | |
|   Not admitted | 247 (69) | 64 (85.3) | — | — |
|   Observed <24 h | 57 (15.9) | — | — | — |
|   Admitted neurosurgery | 37 (10.3) | — | — | — |
|   Admitted other | 17 (4.7) | 11 (14.7) | — | — |

Bold values equal P<.05.
Abbreviations: GCS, Glasgow Coma Scale; IQR, interquartile range.
* Each patient was registered within 1 category, reflecting the primary cause of injury.
Bold values equal P<.05.

**Table 3** Differences between groups in msPPCS (total score ≥13 or ≥3 moderate/severe symptoms on the BC-PSI) and BC-PSI total score at 3 and 12 months

| | MTBI Group | Trauma Controls | Community Controls | P | Post hoc |
|---|---|---|---|---|---|
| 3 months, n | 337 | 75 | 77 | | |
| msPPCS, n (%) | 70 (20.8) | 6 (8.0) | 1 (1.3) | **<.001** | MTBI>TC,CC |
| BC-PSI total score | | | | **.041** | MTBI>TC,CC |
| Mean (SD) | 6.5 (8.2) | 3.8 (5.5) | 3.1 (3.2) | | |
| Median (IQR) | 3.0 (0.0-10.0) | 1.0 (0.0-6.0) | 2.0 (0.5-4.5) | | |
| 12 months, n | 323 | 71 | 68 | | |
| msPPCS, n (%) | 67 (20.7) | 9 (12.7) | 2 (2.9) | **.001** | MTBI>CC |
| BC-PSI total score | | | | **.010** | MTB>TC,CC |
| Mean (SD) | 6.6 (8.0) | 4.8 (7.7) | 3.0 (3.1) | | |
| Median (IQR) | 4.0 (0.0-10.0) | 1.0 (0.0-7.0) | 2.0 (1.0-4.0) | | |

Bold values equal *P*<.05.
Abbreviation: IQR, interquartile range.
Bold values equal p <.05.

## Group differences in msPPCS and the BC-PSI total score at 3 and 12 months

There were significant differences between the groups in prevalence of msPPCS at both 3 months (*P*<.001) and 12 months (*P*=.001). At 3 months, 20.8% of the MTBI group met the classification criteria for msPPCS, significantly more than among TCs (8.0%) and CCs (1.3%). At 12 months, 20.7% of the MTBI group met the criteria, significantly more than the CCs (2.9%) but not the TCs (12.7%). The patients with MTBI had a significantly higher BC-PSI total score than both the TCs and CCs at 3 and 12 months (table 3).

## Trajectories of msPPCS from 3 to 12 months

Of the patients with MTBI who completed both assessments (n=302), 11.6% met the criteria for msPPCS both times (n=35; stable msPPCS), 70.2% at neither assessment (n=212; stable no msPPSC), 8.9% at 3 months only (n=27; msPPCS improvers), and 9.3% at 12 months only (n=28; msPPCS worseners). From these

data it follows that 55.6% of patients with msPPCS at 3 months still met the criteria at 12 months (35/63) and that 88.7% who did not have msPPCS at 3 months also did not have msPPCS at 12 months (212/239; figure 1). Descriptive statistics for the msPPCS groups on the BC-PSI total score showed considerable change in msPPCS improvers and worseners from 3 to 12 months (table 4).

## Trajectories of the BC-PSI total score from 3 to 12 months

Cutoffs for reliable uncommon and very uncommon improvement and worsening in BC-PSI total scores among CCs are presented in table 5. For example, in the CCs, improving ≥5 points (uncommon change) occurred in fewer than 10%, and improving ≥8 points (very uncommon change) occurred in fewer than 5%. The percentage of patients with MTBI and TCs whose BC-PSI total score improved or worsened reliably from 3 to 12 months, based on the cutoffs derived from the CCs, are also presented in table 5. An uncommon improvement was observed in 20.9% of the MTBI
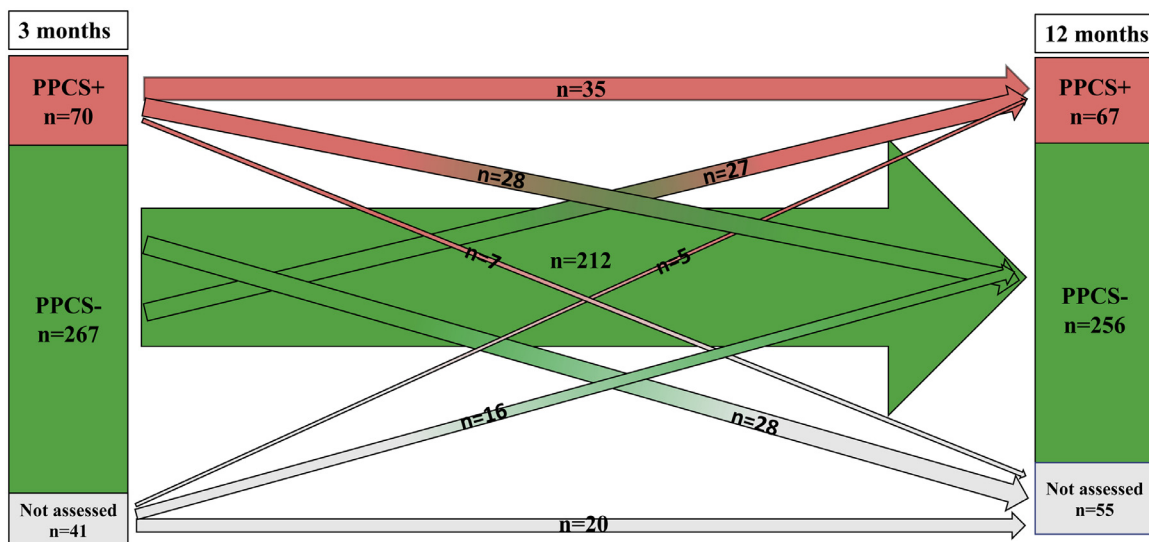


**Fig 1** Illustration of the change in msPPCS in patients with MTBI between 3 and 12 months after injury. PPCS+, meets the criteria for msPPCS; PPCS−, does not meet the criteria for msPPCS.

**Table 4**   BC-PSI total score in the msPPCS groups at 3 and 12 months

| | Stable msPPCS n=35 | Stable No msPPCS n=212 | msPPCS Worseners n=27 | msPPCS Improvers n=28 |
|---|---|---|---|---|
| **3 months** | | | | |
| Mean (SD) | 22.9 (8.0) | 2.6 (3.4) | 5.2 (3.3) | 17.7 (3.4) |
| Median(IQR) | 22.0 (16.0-29.0) | 1.0 (0.0-5.0) | 6.0 (3.0-8.0) | 17.5 (15.3-19.0) |
| **12 months** | | | | |
| Mean (SD) | 21.2 (6.5) | 2.8 (3.3) | 17.1 (5.6) | 5.4 (3.2) |
| Median (IQR) | 22.0 (16.0-25.0) | 1.0 (0.0-5.0) | 16.0 (13.0-20.0) | 5.5 (3.0-7.0) |

Abbreviation: IQR, interquartile range.

**Table 5**   Cutoffs and reliable change estimates in BC-PSI total score

| | Reliable Worsening | | Broadly Normal Change | | | Reliable Improvement | |
|---|---|---|---|---|---|---|---|
| | Very Uncommon <5% | Uncommon <10% | Worse | No Change | Better | Uncommon <10% | Very Uncommon <5% |
| Δ Total score | ≥6 | ≥4 | 1-3 | 0 | 1-4 | ≥5 | ≥8 |
| Community controls, n (%), n=67 | 2 (3.0) | 6 (9.0) | 24 (35.8) | 13 (19.4) | 18 (26.9) | 6 (9.0) | 3 (4.5) |
| Trauma controls, n (%), n=71 | 9 (12.7) | 11 (15.5) | 19 (26.8) | 16 (22.5) | 20 (28.2) | 5 (7.0) | 2 (2.8) |
| MTBI group, n (%), n=302 | 46 (15.2) | 67 (22.2) | 51 (16.9) | 64 (21.2) | 57 (18.9) | 63 (20.9) | 36 (11.9) |

NOTE. If an individual in the community control group's change score is the same or greater than the ones presented in the table, the change is greater than the change experienced by 5% or 10% of the sample. Because many individuals have the same change score, the *actual* percentage of the sample having a score as extreme as the cutoffs presented is always smaller than the *intended* percentage. For example, the cutoff for very uncommon worsening in total symptoms is ≥6. A worsening of 6 or greater is experienced by 3% of the community controls (and not 5, which was intended). However, replacing 6 with the next less extreme change score (ie, 5) would mean that *more* than 5% experienced this change. Patients with mild traumatic brain injury and trauma controls were classified as having a very uncommon or uncommon improvement or worsening, or broadly normal change, based on cutoffs derived from change scores in the community control group (top row).

**Table 6**   Injury-related and personal preinjury factors associated with stability and change in msPPCS status from 3 to 12 months in patients with MTBI

| Variables | n | Stable msPPCS (++) | n | Stable No msPPCS (−−) | n | msPPCS Worseners (−+) | n | msPPCS Improvers (+−) | P | Post hoc Adj. |
|---|---|---|---|---|---|---|---|---|---|---|
| Age, M, MD, IQR | 35 | 31.7/23.8/20.2-48.7 | 212 | 31.7/25.9/21.1-41.6 | 27 | 31.6/23.8/20.6-46.7 | 28 | 34.7/33.8/21.8-46.6 | .603 | |
| Sex female, n (%) | 35 | 20 (57.1) | 212 | 53 (25.0) | 27 | 14 (51.9) | 28 | 12 (42.9) | **<.001*** | PPCS−−<PPCS++ and PPCS−+ |
| CT findings | 35 | | 212 | | 27 | | 28 | | **<.001*** | |
| Findings, yes, n (%) | | 3 (8.6) | | 6 (2.8) | | 1 (3.7) | | 7 (25.0) | | PPCS−−<PPCS+− |
| No findings, yes, n (%) | | 28 (80.0) | | 154 (72.6) | | 20 (74.1) | | 19 (67.9) | | |
| Not performed, yes, n (%) | | 4 (11.4) | | 52 (24.5) | | 6 (22.2) | | 2 (7.1) | | |
| PTA long, 1-24 h, n (%) | 35 | 16 (45.7) | 212 | 53 (25.0) | 27 | 5 (18.5) | 28 | 10 (35.7) | **.038** | |
| Fractures, (any), yes, n (%) | 35 | 7 (20.0) | 212 | 32 (15.1) | 27 | 3 (11.1) | 28 | 6 (21.4) | .649 | |
| Education years, M, MD (IQR) | 35 | 12.7/12.0/11.0-13.0 | 210 | 14.0/13.0/12.0-16.0 | 27 | 13.2/12.0/12.0-15.0 | 28 | 14.3/13.0/12.0-16.8 | **.009** | |
| School marks, M, MD (IQR) | 32 | 4.1/4.5/3.5-4.5 | 205 | 4.5/4.5/3.5-5.5 | 27 | 4.2/4.5/3.5-4.5 | 27 | 4.4/4.5/3.5-5.5 | .083 | |
| Reading difficulties, yes, n (%) | 35 | 7 (20.0) | 210 | 16 (7.6) | 26 | 6 (23.0) | 28 | 2 (7.1) | **.022** | |
| Reduced work, yes, n (%) | 35 | 15 (42.9) | 211 | 11 (5.2) | 27 | 2 (7.4) | 28 | 6 (21.4) | **<.001*** | PPCS−−<PPCS++ and PPCS+− PPCS−+<PPCS++ |
| Previous MTBI, yes, n (%) | 35 | 13 (37.1) | 211 | 38 (18.0) | 27 | 10 (37.0) | 28 | 4 (14.3) | **.010** | |
| Pain, yes, n (%) | 35 | 17 (48.6) | 211 | 24 (11.4) | 27 | 8 (29.6) | 28 | 10 (35.7) | **<.001*** | PPCS−−<PPCS++ and PPCS+− |
| Headache, yes, n (%) | 24 | 13 (54.2) | 175 | 45 (25.7) | 21 | 8 (38.1) | 23 | 10 (43.5) | **.015** | |
| Psychiatric history, yes, n (%) | 35 | 13 (37.1) | 211 | 24 (11.4) | 27 | 8 (29.6) | 28 | 9 (32.1) | **<.001*** | PPCS−− < PPCS++ & PPCS+- |
| Substance use, yes, n (%) | 34 | 2 (5.9) | 209 | 16 (7.7) | 27 | 1 (3.7) | 28 | 2 (7.1) | .885 | |
| Poor sleep quality (ISI), M, MD (IQR) | 35 | 0.8/0.7/0.0-1.3 | 210 | 0.3/0.0/0.0-0.3 | 27 | 0.4/0.0/0.0-0.7 | 27 | 0.6/0.3/0.0-0.7 | **<.001*** | PPCS−−<PPCS++ and PPCS+− |
| ADHD symptoms (ASRS), M, MD (IQR) | 24 | 26.6/26.0/22.0-33.0 | 168 | 21.3/21.5/17.0-26.0 | 21 | 25.1/25.0/16.5-29.0 | 22 | 23.4/22.5/18.0-28.3 | **.032** | |
| Alcohol use (AUDIT), M, MD (IQR) | 24 | 7.3/6.5/3.0-11.0 | 175 | 7.3/7.0/4.0-10.0 | 21 | 7.8/6.0/3.0-13.0 | 23 | 6.0/5.0/3.0-9.0 | .580 | |
| Personality (BFI), M, MD (IQR) | | | | | | | | | | |
| Extroversion | 24 | 4.3/4.4/3.7-5.0 | 175 | 4.7/4.8/4.1-5.5 | 20 | 4.7/4.9/3.8-5.4 | 23 | 4.5/4.6/3.8-5.3 | .188 | |
| Agreeableness | 24 | 5.2/5.3/4.7-5.9 | 175 | 5.4/5.4/4.9-5.9 | 20 | 5.2/5.1/4.6-5.9 | 23 | 5.4/5.4/4.9-6.0 | .513 | |
| Conscientiousness | 24 | 4.8/4.8/3.9-5.4 | 175 | 5.1/5.1/4.4-5.8 | 20 | 4.8/4.8/4.0-5.5 | 23 | 5.0/5.3/4.4-5.7 | .194 | |
| Neuroticism | 24 | 3.9/3.9/2.9-5.2 | 175 | 3.0/2.9/2.1-3.6 | 20 | 3.6/3.4/3.0-4.1 | 23 | 3.2/3.3/2.8-3.8 | **<.001*** | PPCS−−<PPCS−+ and PPCS++ |
| Openness | 24 | 4.4/4.3/3.7-5.3 | 175 | 4.7/4.6/4.1-5.4 | 20 | 4.5/4.4/3.9-4.9 | 23 | 5.1/5.2/4.6-5.5 | **.029** | — |
| Pessimism (LOT-R) M, MD (IQR) | 24 | 1.9/1.8/1.5-2.5 | 174 | 1.1/1.0/0.7-1.5 | 20 | 1.5/1.6 /1.0-2.0 | 23 | 1.0/1.0/0.7-1.4 | **<.001*** | PPCS++>PPCS+− and PPCS−− |
| Threatening life events (LTE-Q) M, MD (IQR) | 24 | 2.8/2.5/1.0-4.0 | 174 | 1.3/1.0/0.0-2.0 | 19 | 1.6/1.0/1.0-2.0 | 23 | 1.0/1.0/0.0-1.0 | **.004** | |
| Resilience (RSA) M, MD (IQR) | 24 | 4.8/5.1/3.7-5.5 | 173 | 5.6/5.6/5.1-6.0 | 20 | 5.2/5.3/4.6-5.8 | 23 | 5.4/5.4/5.2-6.0 | **.002*** | PPCS−−>PPCS++ |

Bold values equal P<.05.
Abbreviations: ASRS, Adult ADHD (Attention Deficit-Hyperactivity Disorder) Self-Report Scale; AUDIT, Alcohol Use Disorders Identification Test; BFI, Big Five Inventory; IQR, interquartile range; ISI, Insomnia Severity Index; LOT-R, Life Orientation Test-Revised; LTE-Q, List of Threatening Events Questionnaire; M, mean; MD, Median; PPCS+, meets the criteria for msPPCS. PPCS−, does not meet the criteria for msPPCS; RSA, Resilience Scale for Adults.
*   Statistically significant after Bonferroni correction for multiple comparisons (critical *P*-value=.002).
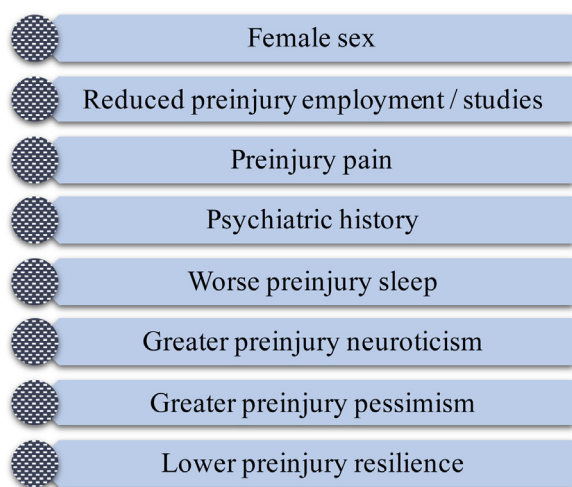Bold values equal p <.05.

Fig 2   Personal factors significantly associated with reporting msPPCS throughout the first year after injury (stable msPPCS; ie, msPPCS at both 3 and 12 months postinjury). All variables differed significantly between those who had stable msPPCS (n=35) compared with those who had stable no msPPCS (n=212).

group and in 7% of the TCs, whereas 22.2% of the MTBI group and 15.5% of the TCs had an uncommon worsening.

## Factors associated with msPPCS

Nine factors (1 injury-related and 8 personal preinjury factors) differed significantly between the msPPCS groups after Bonferroni correction (table 6 and figure 2). The stable msPPCS group and the stable no msPPCS group had the highest and the lowest numbers, respectively, in the following categories: women (57% vs 25%), reduced work/studies (ie, working or studying less than 80%, 43% vs 5%), preinjury pain (49% vs 11%), and a psychiatric history (37% vs 11%). The worst preinjury sleep quality, most neuroticism, and lowest resilience were reported in the stable msPPCS group, whereas the opposite was the case for the stable no msPPCS group. Pessimism was highest in the stable msPPCS group and lowest among msPPCS improvers. Intracranial lesions on CT were most common among msPPCS improvers (25%) and least common in the stable no msPPCS group (2.8%).

## Discussion

This population-based study followed a large representative sample of mainly nonhospitalized patients with MTBI[23] from the time of injury and compared them to TCs and CCs over the first year after injury. Unlike most studies, we complemented the group-level analyses by examining individual trajectories of PPCS reporting from 3 to 12 months postinjury. There are 4 main findings. First, the prevalence of self-reported PPCS was higher in patients with MTBI compared with the TCs and CCs, measured by both msPPCS and the BC-PSI total score, at both 3 and 12 months. This finding is in line with several other studies reporting higher PPCS in patients with MTBI compared with both TCs[4,8,10,43] and healthy controls.[5,6,43] It is well-known that post-concussion-like symptoms are common in the general population and in TCs.[2,12,13] That said, given that the MTBI group had greater symptom reporting than the control groups at both assessments,

this suggests that MTBI, in and of itself, might be associated with persistent symptom reporting at both 3 and 12 months after MTBI. Second, the group-level prevalence of msPPCS was nearly identical in the MTBI group at 3 and 12 months (21%). Third, despite the similar prevalence, individual trajectories revealed considerable change regarding which individuals met the criteria at each time point, where both worsening and improvement was common. Finally, 8 personal preinjury factors were associated with high PPCS reporting throughout the first year (table 6, figure 2), and 1 injury-related factor, intracranial lesions on CT, was related to symptom reporting at 3 months but not at 12 months (table 6).

The analyses of change in msPPCS uncovered distinct individual trajectories that might be obscured by a seemingly stable group-level prevalence of msPPCS from 3 to 12 months. The prevalence of msPPCS was similar at 3 and 12 months, which is in line with findings from some other studies reporting the prevalence of PCS in cohorts assessed at 2 or several time points postinjury.[7-10] The stable group-level prevalence of msPPCS from 3 months onward (21%) might leave the impression that the chances of a recovery after 3 months are small. However, almost half of the patients with msPPCS at 3 months improved by 12 months (44%). In contrast, only a small proportion of patients who did not have msPPCS at 3 months developed it by 12 months (11%). Nonetheless, this minority comprised 40% of the msPPCS group at 12 months (figure 1), demonstrating that some patients are at risk of delayed clinical worsening, a course that potentially could be modified through early identification and intervention.

Analyzing the BC-PSI total scores as a continuous variable also revealed substantial individual-level change from 3 to 12 months after injury (table 5). The patients with MTBI had a less stable BC-PSI total score than the control groups, where both symptom worsening (22.2%) and improvement (20.9%) were common from 3 to 12 months. This finding highlights that symptom reporting tends to fluctuate, a common observation in clinical practice and also reported in a recent study on military personnel[9] and in children.[44] To our knowledge, data on typical change on the BC-PSI in healthy controls have not been published. In this article, we provide information to future researchers and clinicians for how to interpret reliable change on the BC-PSI (table 5).

In patients with MTBI, the stable msPPCS and stable no msPPCS groups differed on a variety of personal factors. Eight personal preinjury factors were associated with high PPCS reporting throughout the first year after injury: being a woman, having reduced employment/studies, pain, poor sleep, low resilience, high neuroticism and pessimism, and a psychiatric history (stable msPPCS, figure 2), whereas 1 injury-related factor, intracranial lesions on CT, was related to symptom reporting at 3 months but not at 12 months (msPPCS improvers, table 6). It is well-established that personal preinjury factors, such as poor health, female sex, reduced employment, and poor sleep quality,[16,18,19,45] are associated with PPCS, and our findings are in line with this. Less is known about the role of injury-related and personal factors on improvement and worsening of PPCS the first year after injury. Sex is a variable of particular interest in contemporary literature, and we found that female sex was a risk factor for maintained PPCS. Sex and gender are known to modify health and disease because of distinct genetic, anatomic, behavioral, and physiological traits and characteristics.[46] Interestingly, and perhaps relevant for headache observed after MTBI, is that signaling mechanisms underlying pain hypersensitivity (eg, glial cell activation) are sexually dimorphic.[47,48] Further adding to the complexity, not only gender but also perceptions of gender inequality are associated

with psychological distress.[49] Future studies should further target how sex and gender influence outcome after MTBI.

Interestingly, we found that intracranial lesions were most common in msPPCS improvers. Thus, their symptoms at 3 months might have been influenced by a more severe initial injury, and their improvement could partly reflect ongoing neurobiological recovery. Our results indicate that intracranial lesions may predict early, more time-limited msPPCS, whereas individuals with stable msPPCS have personal factors putting them at risk for developing and, moreover, maintaining the condition. The msPPCS improvers were also the least pessimistic of the groups, which could suggest that PPCS patients' thoughts and attitudes toward their injury may affect their symptom reporting and thus their outcome. A review of psychological factors and PPCS found that cognitive biases may contribute to the development of PPCS and that cognitive behavioral therapy might lead to a swifter recovery.[50] A recent systematic review found cognitive behavioral therapy promising in some aspects,[51] although others highlight the methodological limitations in the literature,[52] revealing a need for more high-quality studies. The findings in the current and other studies, that patients with PPCS more often have a psychiatric history[15,19] and are less resilient[19,53] than the general population, along with the fact that experiencing a MTBI may contribute to developing depression and anxiety,[50] add to the picture of PPCS as a complex condition with both neurobiological, social, and psychological aspects.

## Study limitations

This study has several limitations. First, information about the personal preinjury factors was collected retrospectively. However, the information was collected shortly after the injury and the participants were specifically asked to base their responses on their situation before the injury, hence increasing the likelihood that it was not biased by the outcome of this particular injury. Second, it is inherently challenging to examine change when a cutoff is used (eg, msPPCS). It is difficult to know whether most change marginally exceeds the cutoff or whether there is larger and more meaningful change. To account for the limitations associated with cutoffs, we added analyses of change in BC-PSI total scores. Further, the median change in BC-PSI total score in msPPCS improvers and msPPCS worseners from 3 to 12 months was considerable, indicating that most change was not just across the cutoff (table 4). Third, even though the present study had a large sample size, some subgroups were inevitably small; for example, the number of patients with intracranial lesions among the msPPCS improvers was 7, which reduces confidence in our finding relating to intracranial lesions and outcome. Finally, some patients could be seeking litigation, known to affect PCS reporting.[54,55] In Norway, however, the government provides free health care, as well as sickness and disability benefits. A possible additional litigation process is relevant for the minority who have been injured in motor vehicle collisions or have sustained work-related injury, but the medico-legal evaluation, in these contexts, is performed at least 2 years after the injury. Therefore, we considered it unnecessary to control for litigation in this study.

## Conclusions

The present study revealed that apparent group-level stability in persistent postconcussion symptom reporting, from 3 to 12 months

after injury, masks significant intraindividual change. Furthermore, we observed a possible pattern in need of more research; having a more severe injury, characterized by a visible lesion on acute head CT, was associated with improvement from 3 to 12 months, suggesting ongoing neurobiological recovery. In addition, several personal preinjury factors were associated with maintaining high PPCS reporting throughout the first year after injury: being a woman, working/studying less than full time, having a psychiatric history, and having worse self-reported health, characterized by bodily pain and poorer sleep quality. In addition, personality factors, such as lower resilience, greater neuroticism, and greater pessimism, were associated with persistent symptom reporting. However, considering that the prevalence of PPCS was much higher in the MTBI group compared with the control groups, it does not seem to be the personal factors alone that contribute to PPCS. Indeed, these factors likely interact in a dynamic way with biological, psychological, and psychosocial factors that are more proximally related to the injury and to other biopsychosocial factors that evolve during the subacute, persistent, and chronic phases of recovery, all through mechanisms that are not well understood. The complexity of PPCS, for many people, necessitates a holistic assessment approach, followed by multidisciplinary care. The results of this study support the importance of using effective psychosocial and psychological interventions over the course of the first year after MTBI to facilitate recovery and to improve patients' quality of life.

## Keywords

## Corresponding author

Toril Skandsen, NTNU, Faculty of Medicine and Health Sciences, N-7491 Trondheim, Norway. *E-mail address:* toril.skandsen@ntnu.no.

## References

1. Williams WH, Potter S, Ryland H. Mild traumatic brain injury and postconcussion syndrome: a neuropsychological perspective. J Neurol Neurosurg Psychiatry 2010(81):1116–22.
2. Cassidy JD, Cancelliere C, Carroll LJ, et al. Systematic review of self-reported prognosis in adults after mild traumatic brain injury: results of the international collaboration on mild traumatic brain injury prognosis. Arch Phys Med Rehabil 2014;95(Suppl):132–51.
3. Chiang CC, Guo SE, Huang KC, Lee BO, Fan JY. Trajectories and associated factors of quality of life, global outcome, and post-concussion symptoms in the first year following mild traumatic brain injury. Qual Life Res 2016;25:2009–19.
4. Dikmen S, Machamer J, Temkin N. Mild traumatic brain injury: longitudinal study of cognition, functional status, and post-traumatic symptoms. J Neurotrauma 2017;34:1524–30.
5. Stein MB, Ursano RJ, Campbell-Sills L, et al. Prognostic indicators of persistent post-concussive symptoms after deployment-related mild traumatic brain injury: a prospective longitudinal study in US Army soldiers. J Neurotrauma 2016;33:2125–32.
6. Wäljas M, Iverson GL, Lange RT, et al. A prospective biopsychosocial study of the persistent post-concussion symptoms following mild traumatic brain injury. J Neurotrauma 2015;32:534–47.

7. Ferdosi H, Schwab KA, Metti A, et al. Trajectory of postconcussive symptoms 12 months after deployment in soldiers with and without mild traumatic brain injury: Warrior Strong Study. Am J Epidemiol 2019;188:77–86.

8. Kraus JF, Hsu P, Schafer K, Afifi AA. Sustained outcomes following mild traumatic brain injury: results of a five-emergency department longitudinal study. Brain Inj 2014;28:1248–56.

9. Lange RT, Lippa SM, Bailie JM, et al. Longitudinal trajectories and risk factors for persistent postconcussion symptom reporting following uncomplicated mild traumatic brain injury in US military service members. Clin Neuropsychol 2020;34:1134–55.

10. Losoi H, Silverberg ND, Wäljas M, et al. Recovery from mild traumatic brain injury in previously healthy adults. J Neurotrauma 2016;33:766–76.

11. Hiploylee C, Dufort PA, Davis HS, et al. Longitudinal study of postconcussion syndrome: not everyone recovers. J Neurotrauma 2017;34:1511–23.

12. Iverson GL, Lange RT. Examination of "postconcussion-like" symptoms in a healthy sample. Appl Neuropsychol 2003;10:137–44.

13. Voormolen DC, Cnossen MC, Polinder S, et al. Prevalence of postconcussion-like symptoms in the general population in Italy, The Netherlands and the United Kingdom. Brain Inj 2019;33:1078–86.

14. Silverberg ND, Gardner AJ, Brubacher JR, Panenka WJ, Li JJ, Iverson GL. Systematic review of multivariable prognostic models for mild traumatic brain injury. J Neurotrauma 2015;32:517–26.

15. Iverson GL, Gardner AJ, Terry DP, et al. Predictors of clinical recovery from concussion: a systematic review. Br J Sports Med 2017;51:941–8.

16. van der Naalt J, Timmerman ME, de Koning ME, et al. Early predictors of outcome after mild traumatic brain injury (UPFRONT): an observational cohort study. Lancet Neurol 2017;16:532–40.

17. Cnossen MC, Winkler EA, Yue JK, et al. Development of a prediction model for post-concussive symptoms following mild traumatic brain injury: a TRACK-TBI pilot study. J Neurotrauma 2017;34:2396–408.

18. Yue JK, Rick JW, Morrissey MR, et al. Preinjury employment status as a risk factor for symptomatology and disability in mild traumatic brain injury: a TRACK-TBI analysis. NeuroRehabilitation 2018;43:169–82.

19. Skandsen T, Stenberg J, Follestad T, et al. Personal factors associated with postconcussion symptoms three months after mild traumatic brain injury. Arch Phys Med Rehabil 2021;102:1102–12.

20. Wojcik SM. Predicting mild traumatic brain injury patients at risk of persistent symptoms in the emergency department. Brain Inj 2014;28:422–30.

21. Morgan CD, Zuckerman SL, Lee YM, et al. Predictors of postconcussion syndrome after sports-related concussion in young athletes: a matched case-control study. J Neurosurg Pediatr 2015;15:589–98.

22. Panenka WJ, Lange RT, Bouix S, et al. Neuropsychological outcome and diffusion tensor imaging in complicated versus uncomplicated mild traumatic brain injury. PLoS One 2015;10:e0122746.

23. Skandsen T, Einarsen CE, Normann I, et al. The epidemiology of mild traumatic brain injury: the Trondheim MTBI follow-up study. Scand J Trauma Resusc Emerg Med 2018;26:34.

24. Menon DK, Schwab K, Wright DW, Maas AI. Position statement: definition of traumatic brain injury. Arch Phys Med Rehabil 2010;91:1637–40.

25. Carroll LJ, Cassidy JD, Holm L, Kraus J, Coronado VG. Methodological issues and research recommendations for mild traumatic brain injury: the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. J Rehabil Med 2004;43:113–25.

26. Bastien CH, Vallières A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. Sleep Med 2001;2:297–307.

27. Kessler RC, Adler L, Ames M, et al. The World Health Organization adult ADHD Self-Report Scale (ASRS): a short screening scale for use in the general population. Psychol Med 2005;35:245–56.

28. Kessler RC, Adler LA, Gruber MJ, Sarawate CA, Spencer T, Van Brunt DL. Validity of the World Health Organization Adult ADHD Self-Report Scale (ASRS) screener in a representative sample og health plan members. Int J Methods Psychiatr Res 2007;16:52–65.

29. Able SL, Johnston JA, Adler LA, Swindle RW. Functional and psychosocial impairment in adults with undiagnosed ADHD. Psychol Med 2007;37:97–107.

30. Saunders JB, Aasland OG, Babor TF, De La Fuente JR, Grant M. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption-II. Addiction 1993;88:791–804.

31. John OP, Srivastava S, John OP, Pervin LA. The big five trait taxonomy: history, measurement, and theoretical perspectives. Handbook of personality: theory and research. p 102, 2nd ed. New York: Guilford Press; 1999. p. 102–38.

32. John OP, Naumann LP, Soto CJ, John OP, Robins RW, Pervin LA. Paradigm shift to the integrative big-five trait taxonomy: History, measurement, and conceptual issues. Handbook of personality: theory and research. p 114, 3rd ed. New York: Guilford Press; 2008. p. 114–58.

33. Scheier MF, Carver CS, Bridges MW. Distinguishing optimism from neuroticism (and trait anxiety, self-mastery, and self-esteem): a reevaluation of the Life Orientation Test. J Pers Soc Psychol 1994;67:1063–78.

34. Carver CS, Scheier MF, Segerstrom SC. Optimism. Clin Psychol Rev 2010;30:879–89.

35. Brugha TS, Cragg D. The List of Threatening Experiences: the reliability and validity of a brief life events questionnaire. Acta Psychiatr Scand 1990;82:77–81.

36. Rosmalen JGM, Bos EH, De Jonge P. Validation of the Long-term Difficulties Inventory (LDI) and the List of Threatening Experiences (LTE) as measures of stress in epidemiological population-based cohort studies. Psychol Med 2012;42:2599–608.

37. Friborg O, Hjemdal O, Rosenvinge JH, Martinussen M. A new rating scale for adult resilience: what are the central protective resources behind healthy adjustment? Int J Methods Psychiatr Res 2003;12:65–76.

38. Friborg O, Hjemdal O, Martinussen M, Rosenvinge JH. Empirical support for resilience as more than the counterpart and absence of vulnerability and symptoms of mental disorder. J Individ Differ 2009;30:138–51.

39. Friborg O, Barlaug D, Martinussen M, Rosenvinge JH, Hjemdal O. Resilience in relation to personality and intelligence. Int J Methods Psychiatr Res 2005;14:29–42.

40. Duff K. Current topics in science and practice evidence-based indicators of neuropsychological change in the individual patient: relevant concepts and methods. Arch Clin Neuropsychol 2012;27:248–61.

41. Stenberg J, Karr JE, Karlsen RH, Skandsen T, Silverberg ND, Iverson GL. Examining test-retest reliability and reliable change for cognition endpoints for the CENTER-TBI Neuropsychological Test Battery. Front Neurol 2020;11:541533.

42. Karlsen RH, Karr JE, Saksvik SB, et al. Examining 3-month test-retest reliability and reliable change using the Cambridge Neuropsychological Test Automated Battery. Appl Neuropsychol 2020 Feb 21. [Epub ahead of print]. https://doi.org/10.1080/23279095.2020.1722126. Accessed.

43. Rabinowitz AR, Li X, Mccauley SR, et al. Prevalence and predictors of poor recovery from mild traumatic brain injury. J Neurotrauma 2015;32:1488–96.

44. Silverberg ND, Iverson GL, McCrea M, Apps JN, Hammeke TA, Thomas DG. Activity-related symptom exacerbations after pediatric concussion. JAMA Pediatr 2016;170:946–53.

45. Theadom A, Cropley M, Parmar P, et al. Sleep difficulties one year following mild traumatic brain injury in a population-based study. Sleep Med 2015;16:926–32.

46. Mauvais-Jarvis F, Bairey Merz N, Barnes PJ, et al. Sex and gender: modifiers of health, disease, and medicine. Lancet 2020;396:565–82.

47. Midavaine É, Côté J, Marchand S, Sarret P. Glial and neuroimmune cell choreography in sexually dimorphic pain signaling. Neurosci Biobehav Rev 2021;125:168–92.

48. Doust YV, King AE, Ziebell JM. Implications for microglial sex differences in tau-related neurodegenerative diseases. Neurobiol Aging 2021;105:340–8.

49. Harryson L, Novo M, Hammarström A. Is gender inequality in the domestic sphere associated with psychological distress among women and men? Results from the Northern Swedish Cohort. J Epidemiol Community Health 2012;66:271–6.

50. Broshek DK, De Marco AP, Freeman JR. A review of post-concussion syndrome and psychological factors associated with concussion. Brain Inj 2015;29:228–37.

51. Chen CL, Lin MY, Huda MH, Tsai PS. Effects of cognitive behavioral therapy for adults with post-concussion syndrome: a systematic review and meta-analysis of randomized controlled trials. J Psychosom Res 2020;136:110190.

52. Bergersen K, Halvorsen JØ, Tryti EA, Taylor SI, Olsen A. A systematic literature review of psychotherapeutic treatment of prolonged symptoms after mild traumatic brain injury. Brain Inj 2017;31:279–89.

53. Oldenburg C, Lundin A, Edman G, Deboussard CN, Bartfai A. Emotional reserve and prolonged post-concussive symptoms and disability: a Swedish prospective 1-year mild traumatic brain injury cohort study. BMJ Open 2018;8:e020884.

54. Hanks RA, Rapport LJ, Seagly K, Millis SR, Scott C, Pearson C. Outcomes after concussion recovery education: effects of litigation and disability status on maintenance of symptoms. J Neurotrauma 2019;36:554–8.

55. Lange RT, Iverson GL, Rose A. Post-concussion symptom reporting and the "good-old-days" bias following mild traumatic brain injury. Arch Clin Neuropsychol 2010;25:442–50.