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Emotional reserve and prolonged post-concussion symptoms and disability

A prospective one-year mild traumatic brain injury cohort study

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Abstract

Objective: Prolonged post-concussion symptoms (PCS) affect a significant minority of mild traumatic brain injury (mTBI) patients. The aetiology is multi-factorial depending on pre-injury as well as peri- and post-injury factors. In this study, we examine outcome from an emotional reserve perspective.

Design: Prospective cohort study.

Setting: Patients were recruited from three emergency departments in major university hospitals in the same city. Follow-up data were collected in an outpatient setting at one of the recruiting hospitals.

Participants: 122 patients with a history of blunt head trauma (aged 15-65 years; male/female 57/37) admitted for mTBI within 24 hours after trauma, (Glasgow Coma Scale score of 14 – 15, loss of consciousness <30 minutes, and/or posttraumatic amnesia < 24 hours). Exclusion criteria were other significant physical injury, other major neurological disorder, including previous significant head injury.

Procedure: Recruitment in three emergency departments. Initial assessments were made one week after the injury. Patients were mailed the follow-up questionnaires one year post-injury.

Outcome measures: At one-week follow-up, the participants received a psychiatric assessment, completed a personality inventory, measures of psychological resilience, depression, anxiety, and post-traumatic symptoms. One-year outcome was measured by the Rivermead Post Concussion Symptoms and the Rivermead Head Injury Follow-Up questionnaires.

Results: The psychiatric examination revealed more symptoms of anxiety, depression and post-traumatic symptoms in the acute stage for patients who later developed PCS. After one year 12% matched the extended criteria for PCS (>=3 symptoms and >=2 disabilities). PCS patients reported more preinjury and concurrent psychiatric problems, lower level of functioning before the injury, and experienced more stress. They showed, higher somatic trait anxiety, embitterment, mistrust and lower level of psychological resilience, than, recovered participants.

Conclusion: PCS was associated with less adaptive emotional functioning already at the time of injury, which exacerbated after the mTBI.

Keywords

concussion, cognitive reserve, coping-style, brain injury

Strengths and limitations of this study

- Prospective design including relatively homogeneous consecutive patients (GCS 14-15), selected by injury criteria, not for post concussive complaints, within the first 24 hours after the trauma
- Individual standardized psychiatric assessment for the screening of current and preinjury psychiatric problems minimizing recall bias by early follow-up (< 1 week after injury)
- Assessment of preinjury factors performed without knowledge of late outcome
- Data collection includes a large number of preinjury as well as injury related variables, which in previous studies have been reported to be relevant for outcome
- Limited generalizability due to relatively high attrition rate (23 percent) where patients with shorter formal education were more likely to drop out.

Introduction

The prognosis after a mild traumatic brain injury (mTBI) in general is beneficial [1 2]. However, a noteworthy proportion of individuals continue to report post-concussive symptoms (PCS) for months [3 4], years, [5] or even decades [6]. The reason for the chronicity of the state is unclear. The hypothesis that PCS may be associated with acquired long-term cognitive deficits following mTBI has not been corroborated in meta-analyses [7-11]. Instead, some research points to the possibility that PCS is linked to lower *pre-injury* cognitive functioning, so called cognitive reserve [12-15]. In other words: the conditions in the brain at the time of injury may be more important than previously assumed for the outcome and suggest an individual pre-injury vulnerability for developing PCS.

Cognitive reserve is part of the larger construct *brain reserve capacity,* which was suggested by Paul Satz [16] as a threshold model for understanding different clinical outcomes after seemingly similar brain insults or pathologies. But, while brain reserve is typically concerned with anatomical features of the brain (e.g., brain volume, synaptic count, dendritic branching), cognitive reserve relates specifically to the active processes of the brain [17]. Individuals with higher cognitive reserve might be better to cope with brain injury by using pre-existing, more efficient, cognitive processing abilities, or by recruiting more unaffected networks in the brain in a compensatory manner [18]. Variables that have been used as estimates of cognitive reserve are those associated with life-time experiences [18], such as educational and occupational attainment. These variables also relates heavily to socioeconomic status (SES), which has repeatedly been shown to influence health, regardless of whether the individual has suffered an injury or not [19].

Gallo and Matthews [20] suggested a Reserve-Capacity Model where the relation between low SES and health is explained. The model posits that people with lower SES are at a disadvantage in two ways: first they are likely to experience more stress, both daily hassles, and major stressors; secondly, they also have fewer reserves to cope with that stress. Importantly, the authors suggest that the individual's intra-personal reserves can act as a moderator and partly explain differences in health outcome, and they present evidence that a negative emotional state is linked to adverse health effects. In this perspective, we may think of an *intra-personal emotional reserve* that, like the cognitive reserve, act as a buffer against adverse subjective outcome and partly explain individual differences in outcome.

Emotional reserve is a hypothetical construct, and good proxies for measurement might be measures of disadvantageous personality traits and psychological resilience. Life circumstances that could be indicative of lower levels of emotional reserve could also include previous exposure to psychiatric conditions.

Kay et al. [21] in an early descriptive clinical study of vulnerability for PCS suggested personality traits such as overachievement, dependency, insecurity, grandiosity, and borderline personality characteristics. Few studies have however systematically investigated the association between personality and PCS. Rush and co-workers [22] using consecutive patients from an emergency care unit found that mTBI patients had scored in the normal range of a personality inventory (NEO-PI-R), and were not significantly different from a control group. They did not find any association between reported PCS symptoms and personality variables. However, they did not examine a PCS group separately.

In a cross-sectional study of healthy participants with no prior brain injury (n=93), Garden et al. [23] found that depressive, dependent, sadistic, negativistic,

borderline, anxiety, somatic, dysthymia and major depression characteristics, as measured by the Millon Clinical Multiaxial Inventory–III were associated with a higher number of postconcussion-like symptoms. In a recent prospective cohort study, Yuen et al. [24] found a positive association between depressive and anxious personality traits and heightened PCS reporting after mTBI.

Psychological resilience has been described as an ability to recover from different adverse experiences [25]. According to a recent review, there were only a few studies, with conflicting results, concerning resilience as a moderating factor for outcome after mTBI [26]. In general, there was an association between higher resilience and less PCS. A Finnish prospective cohort study found that higher levels of resilience were associated with lower symptom reporting [25]. Cross-sectional studies have found that lower levels of resilience are associated with higher symptom-reporting in participants who report having had a mTBI between 1-6 months ago [27]. Similar results have been found in a military veterans sample [28]. However, in a prospective cohort study of emergency department patients, McCauley and colleagues [29] found that higher levels of resilience at baseline (<24 hours) was associated with *higher* symptom reporting. In this study though, PCS-like symptoms were collected earlier (one month) post injury, before the onset of the more chronic stages of PCS [30].

There are various results regarding the influence of previous psychiatric conditions as a predictor of PCS. Luis, Vanderploeg, and Curtiss [13] used a psychiatric interview in their sample of randomly selected Vietnam war veterans and found that a pre-combat history of psychiatric problems was more common for developing PCS. In a consecutive sample of emergency department visitors with mTBI, Meares et al [31 32] found that a preinjury depressive or anxiety disorder had an increased risk for PCS. Ponsford et al. [33] also found that individuals with PCS, defined as highly distressed,

tended to have more previous neurological or psychiatric problems. Stulemeijer et al. [15] studied a prospective sample of emergency department visitors with mTBI. Premorbid emotional problems were not significantly associated with PCS although close (p=.059). In this sample, 32 percent reported a history of treatment with a psychologist, social worker or psychiatrist, or current use of psychotropic medication, or both, and supposedly broader inclusion criteria were applied. Snell et al. [34]reported no association between preinjury psychiatric problems and worse outcome in a mixed sample of prospectively followed emergency department mTBI patients as well as referred patients to a concussion clinic.

To conclude, there is a lack of research or conflicting results on the effect of pre-injury emotional factors on outcome after mTBI. Vakil and his group [35] examined several personality and emotional factors as components of reserve capacity in a group of moderate to severe TBI patients. They found moderating effects of these factors on outcome in addition to effects of injury severity.

We have previously reported [12] an association between cognitive reserve and the development of post-concussion symptoms in a prospectively followed cohort of mTBI patients. The aim of the present study was to investigate aspects of emotional reserve, both psychological variables and psychiatric experiences and its association with prolonged PCS, at one-year post-injury in the same study group.

Method

Participants

This study reports data from a larger mTBI-study where participants were recruited from three emergency departments during the period from January 2000 to December 2001. The study size was determined based on power calculations for differences on bio-medical variables for mTBI patients versus healthy controls. This have been reported previously [36]. This study reports a sub-set of the data concerning one-year outcome for mTBI-patients split into two outcome groups.

Inclusion required a history of blunt head trauma with admission to hospital emergency wards within 24 hours, with loss of consciousness (LOC) and/or posttraumatic amnesia (PTA), and a Glasgow Coma Scale (GCS) score of 14 – 15 at first assessment. Inclusion criteria were limited to GCS of 14–15 to create a more homogenous group since previous studies have suggested that patients with GCS 13 should be considered as a moderate severity [37 38]. Age range allowed for inclusion was 15 to 65. Exclusion criteria were any of the following: LOC > 30 minutes, PTA > 24 hours, other significant physical injury or other major neurological disorder, including a previous significant brain injury. Patients with high-velocity traumas were managed according to a regional trauma protocol and were not available for the study. No financial incentives were offered for participants, and no particular intervention was attached to the study. The study was approved by the regional ethical board.

PCS was defined as having three or more remaining symptoms on The Rivermead Post Concussion Symptoms Questionnaire (RPQ), and two or more disabilities on The Rivermead head injury follow up questionnaire (RHFUQ) at the

one-year follow-up. Patients who did not match the criteria for PCS was defined as recovered.

Procedure

Participants were recruited in the emergency department after having suffered an mTBI. Eligible participants were approached by the physician on duty. Daily visits of the research staff were aimed to decrease selections bias. After information about the study, informed consent was obtained from all participating patients. The emergency ward staff recorded GCS, duration of LOC, PTA and retrograde amnesia, and the result of a blood alcohol test. CT scan of the brain was performed within 24 hours after admission and an MRI scan of the brain was performed within one week. The data collection was exhaustive and included questionnaires, cognitive testing, psychiatric assessment and blood samples to test several hypotheses. However, data collection was distributed during several days to minimize fatigue. This report focuses on the following assessments: at day one, The RPQ was administered to measure initial symptom severity. A multiaxial psychiatric assessment (see below) and questionnaires were completed by the participants at one week post injury. Finally, at one year post injury, the participants were mailed the RPQ and RHFUQ and were instructed to complete and mail them back to the hospital. To maximize participation at follow-up, participants were reminded through a telephone call by the research-nurse

Measures

Psychiatric assessment

Current and previous psychiatric diagnosis on Axis I and II according to DSM-IV were established in the clinical interview, performed by an experienced

neuropsychiatrist (AL) taking also in consideration the risk for participators' bias and fatigue one week after the injury. General medical condition (Axis III) was assessed by a checklist survey, combined with a neurological examination to detect sequelae from the recent injury and to exclude other neurological disorders. Axis IV, psychosocial and environmental factors, was assessed by use of the *Severity of Psychosocial Stressors scale*. The scale addresses eleven potential areas of stress during the last year (e.g., financial problems, marital problems, loss of a relative), and comprises eleven "yes" or "no" questions. The experienced level of distress was rated on a graded scale with six options: none, mild, moderate, severe, extreme, catastrophic, as recommended in DSM-III-R [39]. Axis V, Global Assessment of Function (GAF), was assessed by use of a self-report version of the Global Assessment of Functioning Scale from 0 to 100. Two GAF measures were collected, one for the last year ("GAF-1") and one for the final two weeks ("GAF-2") before the injury.

Measures of post injury symptoms

The Rivermead Post Concussion Symptoms Questionnaire (RPQ)

This questionnaire, developed by King and co-workers consists of sixteen items to rate changes in subjective symptoms after a mild traumatic brain injury [40]. The scale uses five numerical categories, where 0 = not experienced at all, 1 = it is no longer a problem, 2 = a mild problem, 3 = a moderate problem, and 4 = a severe problem. The RPQ score is then calculated as the sum of all the symptom scores excluding ratings of 1 (as they indicate resolved symptoms).

The Rivermead head injury follow up questionnaire (RHFUQ)

This self-report questionnaire contains ten items and covers a perceived change in ability in social and home activities. The scale uses five numerical categories, where 0 = no change, 1 = no change, but more difficult, 2 = a mild change, 3 = a moderate change, 4 = a very marked change [41].

The Hospital Anxiety and Depression Scale (HADS)

HADS [42] was used to measure symptoms of anxiety and depression. It is a brief self-report test with 14 items (seven each for depression and anxiety). It was developed specifically to be used with non-psychiatric patients in medical and somatic settings. The respondent marks the most suitable alternative for each item on a four point Likert scale and the responses are scored from 0 to 3. The HADS has been extensively used, and its psychometric properties have been found to be good [43 44].

The Impact of Event Scale – Revised (IES-R)

IES-R is a widely used self-report scale for assessing stress reactions after traumatic events [45]. It contains 22 items where the respondent rates the frequency of stress reactions during the last week, with the following options: 0 (not at all), 1 (rarely), 3 (sometimes) and 5 (often). The scale is composed of three subscales associated with posttraumatic stress disorder (PTSD): intrusion, avoidance, and hyper arousal. The IES-R has good psychometric properties [46].

Preinjury behavioural and personality measures

The Swedish Universities Scales of Personality (SSP)

SSP is a personality inventory standardized on a representative sample (n = 741) from the general Swedish population [47]. The SSP is designed to measure only traits commonly associated with psychopathology (e.g., anxiety proneness, extraversion,

and aggression-hostility). It consists of 91 items, divided into 13 subscales. Each item is expressed as a statement to which the respondent has four answers to choose from, ranging from "Does not apply at all" to "Applies completely." Scores are summed and transformed to T scores (mean = 50, SD = 10) for men and women separately.

The Sense of Coherence Scale (SOC)

The SOC measures psychological resilience to stressful events and was developed by Antonovsky [48]. The SOC scale contains three subcomponents: comprehensibility, manageability, and meaningfulness. The scale consists of twenty-nine statements, and the respondent marks his/her agreement on a seven point Likert scale. It has been used previously in traumatic brain injury research [49] who found that SOC-score was similar in a group of individuals with TBI many years post-injury when compared to nondisabled people. In patients with orthopaedic injuries, a high SOC score predicted a better outcome after surgery after one year [50].

Alcohol Use Disorders Identification Test (AUDIT)

Screening for hazardous alcohol use was made by use of the Alcohol Use Disorders Identification Test (AUDIT) [51]. The AUDIT consists of 10 items and measures alcohol consumption, drinking behaviour, adverse reactions and alcohol related problems during the last twelve months. Each item is scored from 0 to 4. A cut-off score of 8 or higher has been shown to have s sensitivity and specificity over 90 % for hazardous alcohol use [51]. It has been used in previous TBI-research [52 53].

Statistics

All data were entered and analysed with IBM's SPSS. Categorical variables were summed into frequencies for each group and then analysed with $\chi 2$. For tables with small expected cell counts the Fisher exact test was used. For larger contingency

tables with ordered data (e.g., length of PTA), the linear-by-linear association test was used.

Numerical variables were first summarized with standard descriptives and checked for skewness. Variables with skewness exceeding significantly above one were subsequently analysed with a non-parametric method (Mann-Whitney). Otherwise, the student's t-test was chosen for comparisons between the two outcome groups. If the Levene's test for equality of variances was found to be violated, a t-statistic not assuming homogeneity of variance was computed. Statistical significance was set at $p<.05$, and all tests were two-tailed.

Results

Recruitment and one-year outcome

A total of 122 patients accepted the invitation and were included in the study. The initial recruitment process, including analysis of acceptance rate and differences between participating and the non-participating patients, is described in previous publications [12 54].

At the one-year follow up, 94 participants were still in the program (attrition rate 23 percent). The patients who dropped out (n=28) did not differ from remaining patients with respect to sex ($\chi 2$ (1) = 1.00, p = .316), age (t (120) = 0.41, p = .967) or initial level of experienced symptoms as reported in RPQ (t (116) = 1.14, p = .257. However, the patients who dropped out had fewer years of education (M = 10.8, SD 3.6) than remaining patients (M = 12.6, SD = 2.6), t (110) =2.46, p = .015.

Data on RPQ and RHFUQ at one-year post-injury was analyzed to create the two outcome groups. In RPQ, fifty patients (53 %) reported having no remaining symptoms at all, an additional twenty-six patients (28 %) reported just one or two

remaining symptoms, and eighteen (19 %) reported three or more remaining symptoms. In RHFUQ seventy-eight patients (83%) reported no disability, an additional three patients (3 %) reported just one disability, and the remaining thirteen patients (14 %) reported two or more disabilities. Eleven patients (12 %) matched the combined criteria for PCS which required three or remaining symptoms and two or more remaining disabilities. Remaining patients (n=83) formed the recovered group.

Sociodemographics

There was a significant association between sex and outcome, $\chi 2$ (1) = 5.81, p = .022. Based on the odds ratio, women were 4.97 times more likely to end up in the PCS group, 95 % CI [1.22 – 20.17]. There were no significant differences between the two groups with regard to age (t (92) = -1.08, p =.281), years of education (t (92) = 1.24, p = .218) or marital status ($\chi 2$ (1) = 0.53, p = 1.00). The details are presented in Table 1, along with occupational status. Occupational status at the time of injury showed significant differences between the two groups ($\chi 2$ (5) = 33.24, p = <.001) and was further analysed by visual inspection. A distinct difference between the two groups was that all students recovered by one year. Patients on sick leave at the time of the injury tended to develop PCS, while those on a pension (both retirement and disability) recovered.

Medical data

Data regarding acute injury characteristics for the two outcome groups at the one-year follow-up are presented in Table 2. The type of injury did not affect outcome ($\chi 2$ (4) =6.91, p = .141), nor did a lower GCS score ($\chi 2$ (1) = 0.82, p = 1.00). Both loss of consciousness and PTA were divided into manageable time frames and cross-tabulated. No effect was found for loss of consciousness (linear-by-linear association = 0.66, p = .417), but longer duration of PTA was associated with recovery (linear-by-

linear association = 4.54, p = .033). Eleven participants reported retrograde amnesia, four of them longer than five minutes. All of those who reported retrograde amnesia belonged to the recovered group, but it did not reach significance ($\chi2(1)$ =1.65, p = .351). No effect for alcohol intoxication $\chi2(1)$ = 1.47, p=.449. Further, alcohol intoxication at the time of injury was not associated with PTA ($\chi2(3)$ = 0.77, p =.857), LOC ($\chi2(2)$ = 2.69, p = .261), or retrograde amnesia ($\chi2(1)$ = 0.25, p = .696). Injury related changes on CT or MRI was evident in eight participants and not related to outcome ($\chi2$ (1) =1.50, p = .235), but to a lower initial GCS ($\chi2$ (1) =5.63, p = .049). Initial symptom severity, as measured by the RPQ the day after the trauma, showed excessive skewness and was analysed with Mann-Whitney. The result showed that the PCS group (Mdn = 68.32) initially experienced significantly more symptoms than the recovered group (Mdn = 44.14), U = 685,50, p = .005, r = 0.29.

Psychiatric assessment

The psychiatric assessment found previous or concurrent psychiatric disorders in 29 of the participants (31 percent). Nine out eleven PCS patients (83 percent) had a previous or concurrent psychiatric disorder, established at the psychiatric assessment one-week post injury. This was significantly higher than in the recovered group where only twenty out of 83 participants (24 percent) had a previous or concurrent disorder. Forty-two of the recovered patients and ten of the PCS patients reported psychosocial stress of at least moderate severity during the year before the injury, ($\chi2(1)$ = 6.38, p = .020). Total number of psychosocial stressors showed excessive skewness and was analysed with Mann-Whitney. The result showed that the PCS group also reported more stressors (Mdn = 73.55) than the recovered group (Mdn = 44.05), U = 743.00, p = .001, r = 0.36. The two self-rated GAF measures showed a negative skewness exceeding -1 and were consequently analysed with non-parametric analysis (Mann-

Whitney). Patients with PCS had significantly lower self-rated global functioning (*Mdn* = 35.61) than patients who had recovered (*Mdn* = 50.32) for the year before the injury, U = 470.0, *z* = -2.11, *p* = .035, *r* = -0.22. For the two weeks before the injury similar results were obtained with lower scores for patients with PCS (*Mdn* = 37.44) than patients who had recovered (*Mdn* = 49.88), but just short of being significant, *U* = 503.0, *z* = -1.77, *p* = .076, *r* = -0.18. The results for the actual ratings are shown in Table 3.

Preinjury behavioral and personality measures

Participants who developed PCS reported significantly less resilience for stressful events in the Sense of Coherence Scale than those participants who recovered *(t* (91) = 2.44, *p* = .018, *r* = 0.25). When breaking down the results in the three subcomponents of the scale, no significant differences were found concerning experienced comprehensibility or meaningfulness, but in manageability (*t* (91) = 2.79, *p* = .006, *r* = 0.28, see Table 3.

To see if personality traits, as measured by the SSP, were associated with outcome, independent samples t-tests were performed. Levene's test for equality of variances was found to be violated for somatic trait anxiety (*F* (92) = 4.61, *p* = .034), embitterment (*F* (92) = 10.98, *p* = .001), and physical trait aggressivity (*F* (92) = 4.34, p=0.40). For these traits, a t-statistic not assuming homogeneity of variance was computed. As can be seen in Table 4, results indicate that patients with PCS had elevated somatic trait anxiety, embitterment, and mistrust when compared with the group who had recovered. Previous alcohol consumption pattern did not differ between the two groups, see Table 3.

Post-injury symptoms

Both Impact of Event Scale and Hospital Anxiety and Depression Scale showed excessive skewness (>1) and was analysed using non-parametric methods (Mann-Whitney). The results showed that patients who developed PCS (*Mdn* = 68.45) reported more initial post-traumatic stress than patients who later recovered (*Mdn* = 44.72), $U = 687.00$, $z = 2.72$, $p = .007$, $r = 0.28$. Looking further at the subscales revealed that the two groups differed significantly only in hyperarousal, with the PCS group (*Mdn* = 75.91) reporting more distress than the recovered group (*Mdn* = 43.73), $U = 769.00$, $z = 3.74$, $p = .000$, $r = 0.39$. There were highly significant differences between the two groups on emotional distress as measured by HADS. One-week post injury, the PCS group (*Mdn* = 72.41) experienced higher levels of anxiety than the recovered group (*Mdn* = 44.20), $U = 730.50$, $z = 3.30$, $p = .001$, $r = 0.34$. The PCS group (*Mdn* = 72.77) also experienced more symptoms of depression than the recovered group (*Mdn* = 44.15), $U = 734.50$, $z = 3.32$, $p = .001$, $r = 0.34$. The parametric mean and standard deviation for both scales are shown in table 5.

Discussion

The main purpose of this study was to examine if aspects of emotional reserve capacity were associated with the development of PCS symptoms after mTBI, to complete our previous findings regarding cognitive reserve in the same cohort [12]. At the one-year follow-up, twelve percent of this cohort fulfilled our extended criteria for PCS, including both symptoms and disability.

Factors related to the actual injury, so called peri-injury factors, were in general not related to outcome. On the other hand, the weight of preinjury factors emerged markedly. The PCS-group reported a greater number of psychosocial

stressors for the year preceding the injury, corroborating previous findings [55]. We found that individuals with a previous or concurrent psychiatric disorder, or with a family history of such disorder were more likely to develop PCS. Both GAF ratings were significantly lower, corroborating and extending earlier findings [13 32 33]. Despite the elevated frequency of 15 percent of alcohol abuse in the cohort, there were no differences in the number of intoxicated patients or alcohol abuse between PCS- and recovered patients. Among the post-injury factors, higher levels of PTSD symptoms as assessed by the IES-R, in particular the subscale of hyper-arousal showed a clear association to PCS. Also, both anxiety and depression was higher in PCS patients one week after trauma. The findings are further supported by the design of the study, since data was obtained within a week after the mTBI, minimizing recall bias and before the development of PCS symptoms, minimizing the risk for confirmation bias.

We used the Swedish Scales of Personality, the SSP, to measure different aspects of personality and found in the PCS group elevated level of somatic anxiety, but not psychic anxiety, compared to the recovered group. The SSP divides trait anxiety into a psychic and a somatic component [47 56]. This division of anxiety was first suggested by Eysenck [57]where the somatic component reflects autonomous over-reactivity, and the mental component reflects brooding and worrying behaviour. Further, the PCS group had significantly higher levels of mistrust. This SSP-scale has its origins in the subscale suspicion in the Buss-Durkee Hostility Inventory [58] and measures traits of being suspicious and distrusting of other people's motives. The elevated level of embitterment in the PCS group may be linked to coping responses during stressful life events. The SSP scale can be illustrated by the following item: "I had often gotten into trouble even when it was not my fault.". Blaming others has previously been found to influence symptom reporting in mTBI patients [59]. To sum it

up, a pattern of higher reactivity in the autonomic nervous system, and some personality traits (embitterment and suspiciousness) may lead to more stress in everyday life, and an increased sensitivity when encountering and managing traumatic events, such as a brain injury.

We used a different measure of psychological resilience in connection with mTBI than other studies [26], but the findings were similar; lower levels were linked to PCS development. The three-factor construction of the SOC allows further analysis of different aspects of resilience: comprehensibility, manageability, and meaningfulness. We found that it was only manageability was significantly lower in the PCS group. This subscale is tapping into an underlying construct of being in control of one's life and a sense of mastery. To our knowledge, this finding has not been reported before. Thus, the outcome differed despite seemingly similar brain insult, highlighting the importance of biopsychosocial factors for the development of PCS [60], such as the extent of cognitive [17] and emotional reserve [35].

As mentioned before, the peri-injury factors were hardly related to outcome in this study. Injury related changes found on MRI or CT scan and initial lower GCS-score were not related to PCS, which is in line with previous findings [61 62]. However, PCS-patients reported a shorter duration of PTA. One should mention though that there were few individuals with imaging findings and the GCS score was restricted to just 14 or 15, so one cannot rule out that the study was under powered to detect differences.

To conclude, the present findings fit and extend Gallo and Matthews'[20] Reserve-Capacity Model demonstrating a link between psychosocial adjustment and specific symptom development after an injury. The results demonstrate the meaning of intra-personal emotional reserve for symptom development along with cognitive

reserve, complementing our previous findings. Thus, the variations seen in outcome after mTBI may to a considerable degree reflect individual differences in emotional and cognitive coping ability. The results highlight the importance of considering psychiatric history when identifying patients at risk of developing PCS and emphasize the value of considering these pre-injury factors in clinical management.

Author Statement

CO, AL and AB conceived of the present study. AL, GE, CNB and AB initiated the study design. AL and CNB contributed to data collection. GE provided statistical expertise. All authors contributed to the interpretation of the study results as well as the writing of the manuscript. All authors have read and agree with the manuscript's final content.

Competing interests

The authors report no competing interest.

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Data sharing statement

There are no unpublished data available.

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Table 1: Sociodemographic characteristics of mTBI patients split into recovered by one year and those who reported both symptoms and disability (PCS).

Characteristic	Recovered (n = 83)	PCS (n = 11)
Age, Mean (SD)	36.7 (15.2)	41.9 (13.2)
Sex, n (%)		
Male	54 (65)	3 (27)
Female	29 (35)	8 (73)
Marital status, n (%)		
Unmarried, living alone	20 (24)	3 (27)
Married, living together	63 (76)	8 (73)
Years of education, Mean (SD)	12.7 (2.6)	11.6 (2.7)
Occupational status, n (%)		
Working	63 (76)	6 (55)
Studying	15 (18)	0 (0)
Unemployed	0 (0)	1 (9)
Sick leave	1 (1)	4 (36)
Disability pension	2 (2)	0 (0)
Retirement pension	2 (2)	0 (0)

Table 2: Peri-injury data for the those who had recovered by one year, and those who still reported post concussive symptoms (PCS).

Characteristics	Recovered (n=83)	PCS (n=11)
Type of injury, n (%)		
Fall from height	31 (37)	3 (27)
Fall from the same level	17 (20)	1 (9)
Traffic	17 (20)	3 (27)
Assaults	9 (11)	0 (0)
Other	9 (11)	4 (36)
Loss of Consciousness, n (%)		
< 1 minute	37 (45)	5 (45)
1-5 minutes	31 (37)	6 (55)
6-30 minutes	15 (18)	0 (0)
Post-traumatic amnesia, n (%)		
< 1 minute	10 (12)	4 (36)
1-5 minutes	19 (23)	4 (36)
6-45 minutes	34 (41)	1 (9)
> 45 minutes	20 (24)	2 (18)
GCS Score, n (%)		
15	73 (88)	10 (91)
14	10 (12)	1 (9)
Retrograde amnesia	11 (13)	0 (0)
Injury related changes on CT or MRI	6 (7)	2 (18)
Intoxicated by alcohol, n (%)	22 (27)	1 (9)
Initial symptom severity*, Mean (SD)	10.4 (9.3)	23.8 (17.0)

Note: Initial symptom severity was measured by the Rivermead Post Concussion Symptoms Questionnaire (RPQ). There was one missing protocol from the recovered group. The variable showed excessive skewness and Mann-Whitney was used as statistical method. However, here the values are shown since they are considered more informative.

Table 3: Pre-injury variables for mTBI patients split into those who had recovered by one year and those who reported both symptoms and disability (PCS)

Variables	Recovered (*n*=83)	PCS (*n*=11)	p
Previous or concurrent psych disorder, n (%)	20 (24)	9 (82)	.000
Previous psych disorder	16 (19)	7 (64)	.004
Concurrent psych. disorder	8 (10)	7 (64)	.000
Family history of psych disorder	17 (20)	4 (36)	.257
Self-assessed GAF, Mean (SD)			
The year before the injury	86.2 (11.5)	67.3 (21.5)	.015
The two weeks before the injury	87.1 (11.1)	73.2 (20.3)	.048
Previous mild traumatic brain injury	4 (5)	2 (18)	.147
Alcohol consumption (Audit)			
Mean (SD)	4.99 (4.22)	5.50 (8.07)	.751
Eight or above, n (%)	13 (17)	1 (10)	1.00
Sense of Coherence Scale, Mean (SD)			
Coherence	54,0 (8,2)	51,0 (6,6)	.240
Manageability	57,1 (8,0)	49,5 (11,6)	.006
Meaningfulness	46,8 (6,0)	41,5 (10,7)	.135
Total	53,1 (11,3)	44,1 (14,4)	.018
Number of psychosocial stressors, Mean (SD)	1.30 (1.40)	3.73 (2.15)	.004

Note: There were eight missing questionnaires for Audit (seven for the recovered and one for the PCS group). There was one missing questionnaire for Sense of Coherence Scale.

Table 4: Mean T-scores for the Swedish universities scales of personality completed one week post injury, split into those who had recovered by one year and those who reported both symptoms and disability (PCS).

	Recovered (*n*=83)		PCS (*n*=11)			
Personality variable	*M*	*SD*	*M*	*SD*	*p*	Cohen's *d*
Anxiety proneness						
Somatic trait anxiety	45,3	7,8	53,8	11,0	.030	0.89
Psychic trait anxiety	45,4	9,1	49,8	11,6	.156	0.42
Stress susceptibility	46,9	10,4	52,1	15,1	.145	0.40
Low assertiveness	46,8	9,7	43,9	10,5	.362	-0.04
Extraversion						
Impulsivity	51,8	9,4	54,5	12,6	.400	0.23
Adventure seeking	54,1	9,3	55,9	7,7	.558	0.21
Detachment	44,2	8,7	47,7	8,9	.216	0.40
Embitterment	46,7	8,4	59,3	15,3	.022	1.02
Social desirability	54,4	9,7	51,3	9,6	.311	-0.32
Aggression-Hostility						
Verbal trait aggressivity	50,4	8,4	51,0	11,1	.823	0.06
Physical trait aggressivity	47,2	9,0	53,6	14,6	.185	0.53
Trait irritability	46,2	10,9	52,0	14,6	.112	0.45
Mistrust	44,5	10,7	55,1	13,2	.004	0.88

Table 5: The results from measures of post-traumatic and emotional symptoms at one week post injury for the two outcome groups: recovered and those who still reported symptoms and disability (PCS) at one year post injury.

	Recovered (n=83)		PCS (n=11)		
Variable	*M*	*SD*	*M*	*SD*	p
Impact of Event Scale					
Intrusions	6,2	5,4	15,2	14,7	.132
Avoidance	4,8	6,7	9,3	10,2	.223
Hyper-arousal	3,5	4,3	12,4	8,7	.000
Total	14.5	14.5	36,8	30,0	.007
Hospital Anxiety and Depression Scale					
Anxiety	2.7	3.3	8.4	5.7	.001
Depression	2.2	2.6	6.7	4.7	.001

Note: Both scales showed excessive skewness (>1) and was analyzed with non-parametric method (Mann-Whitney). The actual parametric scores are shown here for being more informative.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **Page 1**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **Page 2**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **Pages 4-7**
Objectives	3	State specific objectives, including any prespecified hypotheses **Page 7**
Methods		
Study design	4	Present key elements of study design early in the paper **Page 8**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **Page 8-9**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **Page 8-9**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **Page 8**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **Pages 9-12**
Bias	9	Describe any efforts to address potential sources of bias **Participant bias:** **Recall bias – page 3** **Confirmation bias, social desirability and fatigue page 9** **Selection bias –** **participation, representativity page 9** **analysis of differences between participating and nonparticipating patients and between participants and drop – outs – page 13** **Researcher bias: Early data collection minimizes bias – study design – page 18**
Study size	10	Explain how the study size was arrived at **Page 8**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **Page 12**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding

Page 12
(*b*) Describe any methods used to examine subgroups and interactions **N/A**
(*c*) Explain how missing data were addressed **We used an unbiased approach, and stated where there were missing data in the tables, see table 2 and 3.**
(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed **Page 13**
(*e*) Describe any sensitivity analyses **N/A**

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **Page 13**
		(b) Give reasons for non-participation at each stage **Page 13**
		(c) Consider use of a flow diagram **N/A**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **Page 14, Table 1.**
		(b) Indicate number of participants with missing data for each variable of interest **See Table 2 and 3.**
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) **Page 9**
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time **Page 15**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **We have only included unadjusted estimates.**
		(*b*) Report category boundaries when continuous variables were categorized **Pages 12-13**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **N/A**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **N/A**
Discussion		
Key results	18	Summarise key results with reference to study objectives **Pages 17-18**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **Page 19**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **Pages 17-19**
Generalisability	21	Discuss the generalisability (external validity) of the study results **Page 19**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **Page 20**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Emotional reserve and prolonged post-concussion symptoms and disability: A Swedish prospective one-year mild traumatic brain injury cohort study

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Emotional reserve and prolonged post-concussion symptoms and disability

A Swedish prospective one-year mild traumatic brain injury cohort study

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Abstract

Objective: Prolonged post-concussion symptoms (PCS) affect a significant minority of mild traumatic brain injury (mTBI) patients. The aetiology is multi-factorial depending on pre-injury as well as peri- and post-injury factors. In this study, we examine outcome from an emotional reserve perspective.

Design: Prospective cohort study.

Setting: Patients were recruited from three emergency departments in major university hospitals in Stockholm, Sweden. Follow-up data were collected in an outpatient setting at one of the recruiting hospitals.

Participants: 122 patients with a history of blunt head trauma (aged 15-65 years; admitted for mTBI within 24 hours after trauma, (Glasgow Coma Scale score of 14 – 15, loss of consciousness <30 minutes, and/or posttraumatic amnesia < 24 hours). Exclusion criteria were other significant physical injury, other major neurological disorder, including previous significant head injury.

Procedure: Recruitment in three emergency departments. Initial assessments were made within one week after the injury. Patients were mailed the follow-up questionnaires one year post-injury.

Outcome measures: A psychiatric assessment was performed at one week post-injury. The participants also completed a personality inventory, measures of psychological resilience, depression, anxiety, and post-traumatic symptoms. One-year outcome was measured by the Rivermead Post Concussion Symptoms and the Rivermead Head Injury Follow-Up questionnaires.

Results: The psychiatric assessment revealed more symptoms of anxiety, depression and post-traumatic symptoms in the acute stage for patients who later developed PCS. After one year, 94 participants were still in the program (male/female 57/37) and 12% matched the extended criteria for PCS (>=3 symptoms and >=2 disabilities). PCS patients reported more preinjury and concurrent psychiatric problems, lower level of functioning before the injury, and experienced more stress. They showed higher somatic trait anxiety, embitterment, mistrust and lower level of psychological resilience, than, recovered participants.

Conclusion: Intra-personal emotional reserve shape the emergence and persistence of PCS after mTBI.

Keywords

concussion, cognitive reserve, coping-style, brain injury, emotional reserve

Strengths and limitations of this study

- Prospective design including relatively homogeneous consecutive patients (GCS 14-15), selected by injury criteria, not for post concussive complaints, within the first 24 hours after the trauma
- Individual standardized psychiatric assessment for the screening of current and preinjury psychiatric problems minimizing recall bias by early follow-up (< 1 week after injury)
- Assessment of preinjury factors was performed without knowledge of late outcome
- The number of patients with prolonged post-concussion symptoms and disability (PCS) were few (n=11), implying reduced power to detect differences when compared to recovered patients.
- Limited generalizability due to relatively high attrition rate (23 percent) where patients with shorter formal education were more likely to drop out.

Introduction

The prognosis after a mild traumatic brain injury (mTBI) in general is beneficial [1 2]. However, a noteworthy proportion of individuals continue to report post-concussive symptoms (PCS) for months [3 4], years, [5] or even decades [6]. The reason for the chronicity of the state is unclear. The hypothesis that PCS may be associated with acquired long-term cognitive deficits following mTBI has not been corroborated in meta-analyses [7-11]. Instead, some research points to the possibility that PCS is linked to lower *pre-injury* cognitive functioning, so called cognitive reserve [12-15]. In other words: the conditions in the brain at the time of injury may be more important than previously assumed for the outcome and suggest an individual pre-injury vulnerability for developing PCS.

Cognitive reserve is part of the larger construct *brain reserve capacity,* which was suggested by Paul Satz [16] as a threshold model for understanding different clinical outcomes after seemingly similar brain insults or pathologies. But, while brain reserve is typically concerned with anatomical features of the brain (e.g., brain volume, synaptic count, dendritic branching), cognitive reserve relates specifically to the active processes of the brain [17]. Individuals with higher cognitive reserve might be better to cope with brain injury by using pre-existing, more efficient, cognitive processing abilities, or by recruiting more unaffected networks in the brain in a compensatory manner [18]. Variables that have been used as estimates of cognitive reserve are those associated with life-time experiences [18], such as educational and occupational attainment. These variables also relates heavily to socioeconomic status (SES), which has repeatedly been shown to influence health, regardless of whether the individual has suffered an injury or not [19].

Gallo and Matthews [20] suggested a Reserve-Capacity Model where the relation between low SES and health is explained. The model posits that people with lower SES are at a disadvantage in two ways: firstly they are likely to experience more stress, both daily hassles, and major stressors; secondly, they also have fewer reserves to cope with that stress. Importantly, the authors suggest that the individual's intra-personal reserves can act as a moderator and partly explain differences in health outcome, and they present evidence that a negative emotional state is linked to adverse health effects. In this perspective, we may think of an *intra-personal emotional reserve* that, like the cognitive reserve, act as a buffer against adverse subjective outcome and partly explain individual differences in outcome.

Emotional reserve is a hypothetical construct, and good proxies for measurement might be measures of disadvantageous personality traits and psychological resilience. Life circumstances that could be indicative of lower levels of emotional reserve could also include previous mental health problems.

Kay et al. [21] in an early descriptive clinical study of vulnerability for PCS suggested personality traits such as overachievement, dependency, insecurity, grandiosity, and borderline personality characteristics. Few studies have however systematically investigated the association between personality and PCS. Rush and co-workers [22] using consecutive patients from an emergency care unit found that mTBI patients had scored in the normal range of a personality inventory (NEO-PI-R), and were not significantly different from a control group. They did not find any association between reported PCS symptoms and personality variables. However, they did not examine a PCS group separately.

In a cross-sectional study of healthy participants with no prior brain injury (n=93), Garden et al. [23] found that depressive, dependent, sadistic, negativistic,

borderline, anxiety, somatic, dysthymia and major depression characteristics, as measured by the Millon Clinical Multiaxial Inventory–III were associated with a higher number of postconcussion-like symptoms. In a recent prospective cohort study, Yuen et al. [24] found a positive association between depressive and anxious personality traits and heightened PCS reporting after mTBI.

Psychological resilience has been described as an ability to recover from different adverse experiences [25]. According to a recent review, there were only a few studies, with conflicting results, concerning resilience as a moderating factor for outcome after mTBI [26]. In general, there was an association between higher resilience and less PCS. A Finnish prospective cohort study found that higher levels of resilience were associated with lower symptom reporting [25]. Cross-sectional studies have found that lower levels of resilience are associated with higher symptom-reporting in participants who report having had a mTBI between 1-6 months ago [27]. Similar results have been found in a military veterans sample [28]. However, in a prospective cohort study of emergency department patients, McCauley and colleagues [29] found that higher levels of resilience at baseline (<24 hours) was associated with *higher* symptom reporting. In this study though, PCS-like symptoms were collected earlier (one month) post injury, before the onset of the more chronic stages of PCS [30].

There are various results regarding the influence of previous psychiatric conditions as a predictor of PCS. Luis, Vanderploeg, and Curtiss [13] used a psychiatric interview in their sample of randomly selected Vietnam war veterans and found that a pre-combat history of psychiatric problems was more common for developing PCS. In a consecutive sample of emergency department visitors with mTBI, Meares et al [31 32] found that a preinjury depressive or anxiety disorder had an increased risk for PCS. Ponsford et al. [33] also found that individuals with PCS, defined as highly distressed,

tended to have more previous neurological or psychiatric problems. Stulemeijer et al. [15] studied a prospective sample of emergency department visitors with mTBI. Premorbid emotional problems were not significantly associated with PCS although close (p=.059). In this sample, 32 percent reported a history of treatment with a psychologist, social worker or psychiatrist, or current use of psychotropic medication, or both, and supposedly broader inclusion criteria were applied. Snell et al. [34]reported no association between preinjury psychiatric problems and worse outcome in a mixed sample of prospectively followed emergency department mTBI patients as well as referred patients to a concussion clinic.

One reason for conflicting results in studies of PCS, is different inclusion criteria, creating diverse prevalence rates in different studies. Some of the more usual symptoms (e.g headache, fatigue and memory problems) after mTBI are also common in other diagnostic groups, and even in people who reports to be healthy. It is thus possible that criteria based only on symptom reporting is too lenient. We suggest that one way to sharpen PCS criteria is to require, in addition to symptoms, reporting of disability, in line with the DSM-IV provisional diagnosis of post-concussive disorder requiring disability in at least two different areas in life [35].

To conclude, there is a lack of research or conflicting results on the effect of pre-injury emotional factors on outcome after mTBI. Vakil and his group [36] examined several personality and emotional factors as components of reserve capacity in a group of moderate to severe TBI patients. They found moderating effects of these factors on outcome in addition to effects of injury severity.

We have previously reported [12] an association between cognitive reserve and the development of post-concussion symptoms in a prospectively followed cohort of mTBI patients. The aim of the present study was to investigate aspects of emotional

reserve, psychological variables and psychiatric vulnerability and their association with a restrictively defined PCS group, at one-year post-injury in the same study group.

Method

Participants

This study reports data from a larger mTBI-study where participants were recruited from three emergency departments during the period from January 2000 to December 2001. The study size was determined based on power calculations for differences on bio-medical variables for mTBI patients versus healthy controls. This have been reported previously [37]. This study reports a sub-set of the data concerning one-year outcome for mTBI-patients split into two outcome groups.

Inclusion criteria required visit to emergency ward within 24 hours after blunt head trauma, with loss of consciousness (LOC) and/or posttraumatic amnesia (PTA), and a Glasgow Coma Scale (GCS) score of 14 – 15 at first assessment. Inclusion criteria were limited to GCS of 14–15 to create a more homogenous group since previous studies have suggested that patients with GCS 13 should be considered as a moderate severity [38 39]. Age range allowed for inclusion was 15 to 65. Exclusion criteria were any of the following: LOC > 30 minutes, PTA > 24 hours, other significant physical injury or other major neurological disorder, including a previous significant brain injury. Patients with high-velocity traumas were managed according to a regional trauma protocol and were not available for the study. No financial incentives were offered for participants, and no particular intervention was attached to the study. The study was approved by the regional ethical board.

PCS was defined as having three or more remaining symptoms on The Rivermead Post Concussion Symptoms Questionnaire (RPQ), and two or more disabilities on The Rivermead head injury follow up questionnaire (RHFUQ) at the one-year follow-up. Patients who did not match the criteria for PCS was defined as recovered.

Procedure

Participants were recruited in the emergency department when they sought care for having suffered a blunt head trauma. Eligible participants were approached by the physician on duty. Daily visits of the research staff were aimed to decrease selection bias. After information about the study, informed consent was obtained from all participating patients. The emergency ward staff recorded GCS, duration of LOC, PTA and retrograde amnesia, and the result of a blood alcohol test. CT scan of the brain was performed within 24 hours after admission and an MRI scan of the brain was performed within one week. Scans were evaluated according to standard hospital routines by experienced radiologists. The data collection was exhaustive and included questionnaires, cognitive testing, psychiatric assessment and blood samples to test several hypotheses. However, data collection was distributed during several days to minimize fatigue. This report focuses on the following assessments: at day one, The RPQ was administered to measure initial symptom severity. A multiaxial psychiatric assessment (see below) and questionnaires were completed by the participants within one week post injury. Finally, at one year post injury, the participants were mailed the RPQ and RHFUQ and were instructed to complete and mail them back to the hospital. To maximize participation at follow-up, participants were reminded through a telephone call by the research-nurse

Measures

Psychiatric assessment

Current and previous psychiatric diagnosis on Axis I and II according to DSM-IV were established in a semi-structured clinical interview, performed by an experienced neuropsychiatrist (AL) taking also in consideration the risk for participators' bias and fatigue one week after the injury. General medical condition (Axis III) was assessed by a checklist survey, combined with a neurological examination to detect sequelae from the recent injury and to exclude other neurological disorders. Axis IV, psychosocial and environmental factors, was assessed by use of the *Severity of Psychosocial Stressors scale,* completed by the participant. The scale addresses eleven potential areas of stress during the last year (e.g., financial problems, marital problems, loss of a relative), and comprises eleven "yes" or "no" questions. The experienced level of distress was rated on a graded scale with six options: none, mild, moderate, severe, extreme, catastrophic, as recommended in DSM-III-R [40]. Axis V, Global Assessment of Function (GAF), was assessed by use of a self-report version of the Global Assessment of Functioning Scale from 0 to 100. Two GAF measures were collected, one for the last year ("GAF-1") and one for the two weeks ("GAF-2") preceeding the injury.

Measures of post injury symptoms

The Rivermead Post Concussion Symptoms Questionnaire (RPQ)

This questionnaire, developed by King and co-workers consists of sixteen items to rate changes in subjective symptoms after a mild traumatic brain injury [41]. The scale uses five numerical categories, where 0 = not experienced at all, 1 = it is no longer a problem, 2 = a mild problem, 3 = a moderate problem, and 4 = a severe problem. The

RPQ score is then calculated as the sum of all the symptom scores excluding ratings of 1 (as they indicate resolved symptoms).

The Rivermead head injury follow up questionnaire (RHFUQ)

This self-report questionnaire contains ten items and covers a perceived change in ability in social and home activities. The scale uses five numerical categories, where 0 = no change, 1 = no change, but more difficult, 2 = a mild change, 3 = a moderate change, 4 = a very marked change [42].

The Hospital Anxiety and Depression Scale (HADS)

HADS [43] was used to measure symptoms of anxiety and depression. It is a brief self-report test with 14 items (seven each for depression and anxiety). It was developed specifically to be used with non-psychiatric patients in medical and somatic settings. The respondent marks the most suitable alternative for each item on a four point Likert scale and the responses are scored from 0 to 3. The HADS has been extensively used, and its psychometric properties have been found to be good [44 45].

The Impact of Event Scale – Revised (IES-R)

IES-R is a widely used self-report scale for assessing stress reactions after traumatic events [46]. It contains 22 items where the respondent rates the frequency of stress reactions during the last week, with the following options: 0 (not at all), 1 (rarely), 3 (sometimes) and 5 (often). The scale is composed of three subscales associated with posttraumatic stress disorder (PTSD): intrusion, avoidance, and hyperarousal. The IES-R has good psychometric properties [47].

Preinjury behavioural and personality measures

The Swedish Universities Scales of Personality (SSP)

SSP is a personality inventory standardized on a representative sample (n = 741) from the general Swedish population [48]. The SSP is designed to measure only traits commonly associated with psychopathology (e.g., anxiety proneness, extraversion, and aggression-hostility). It consists of 91 items, divided into 13 subscales. Each item is expressed as a statement to which the respondent has four answers to choose from, ranging from "Does not apply at all" to "Applies completely." Scores are summed and transformed to T scores (mean = 50, SD = 10) for men and women separately.

The Sense of Coherence Scale (SOC)

The SOC measures psychological resilience to stressful events and was developed by Antonovsky [49]. The SOC scale contains three subcomponents: comprehensibility, manageability, and meaningfulness. The scale consists of twenty-nine statements, and the respondent marks his/her agreement on a seven point Likert scale. It has been used previously in traumatic brain injury research [50] who found that SOC-score was similar in a group of individuals with TBI many years post-injury when compared to nondisabled people. In patients with orthopaedic injuries, a high SOC score predicted a better outcome after surgery after one year [51].

Alcohol Use Disorders Identification Test (AUDIT)

Screening for hazardous alcohol use was made by use of the Alcohol Use Disorders Identification Test (AUDIT) [52]. The AUDIT consists of 10 items and measures alcohol consumption, drinking behaviour, adverse reactions and alcohol related problems during the last twelve months. Each item is scored from 0 to 4. A cut-off score of 8 or higher has been shown to have s sensitivity and specificity over 90 % for hazardous alcohol use [52]. It has been used in previous TBI-research [53 54].

Patient and public involvement

The design of the study, the choice of research question and outcome measures, and the recruitment to and conduct of the study was performed by health care professionals with extensive professional experience of work with this group of patients and robust knowledge of previous research in the field. Patients were not involved in this process.

Statistics

All data were entered and analysed with IBM's SPSS. Categorical variables were summed into frequencies for each group and then analysed with $\chi 2$. For tables with small expected cell counts the Fisher exact test was used. For larger contingency tables with ordered data (e.g., length of PTA), the linear-by-linear association test was used.

Numerical variables were first summarized with standard descriptives and checked for skewness. Variables with skewness exceeding significantly above one were subsequently analysed with a non-parametric method (Mann-Whitney). Otherwise, the student's t-test was chosen for comparisons between the two outcome groups. If the Levene's test for equality of variances was found to be violated, a t-statistic not assuming homogeneity of variance was computed. Odds ratios (OR) with confidence intervals (CI) and p-values were calculated using logistic regression. Statistical significance was set at $p<.05$, and all tests were two-tailed.

Results

Recruitment and one-year outcome

A total of 122 patients accepted the invitation and were included in the study. The initial recruitment process, including analysis of acceptance rate and differences between participating and the non-participating patients, is described in previous publications [12 55].

At the one-year follow up, 94 participants were still in the program (attrition rate 23 percent). The patients who dropped out (n=28) did not differ from remaining patients with respect to sex ($\chi 2$ (1) = 1.00, p = .316), age (t (120) = 0.41, p = .967) or initial level of experienced symptoms as reported in RPQ (t (116) = 1.14, p = .257. However, the patients who dropped out had fewer years of education (M = 10.8, SD 3.6) than remaining patients (M = 12.6, SD = 2.6), t (110) =2.46, p = .015.

Data on RPQ and RHFUQ at one-year post-injury were analysed to create the two outcome groups. In RPQ, fifty patients (53 %) reported having no remaining symptoms at all, an additional twenty-six patients (28 %) reported just one or two remaining symptoms, and eighteen (19 %) reported three or more remaining symptoms. This last number shows a decrease in this cohort from 33 percent PCS-cases at three months post injury[12], using symptom only criteria. In RHFUQ seventy-eight patients (83%) reported no disability, three patients (3 %) reported just one disability, and the remaining thirteen patients (14 %) reported two or more disabilities. Eleven patients (12 %) matched the combined criteria for PCS which required three or remaining symptoms and two or more remaining disabilities. Remaining patients (n=83) formed the recovered group.

Sociodemographics

There was a significant association between sex and outcome, $\chi 2$ (1) = 5.81, p = .022. Based on the odds ratio, women were 4.97 times more likely to end up in the PCS group, 95 % CI [1.22 – 20.17]. There were no significant differences between the two groups with regard to age (t (92) = -1.08, p =.281), years of education (t (92) = 1.24, p = .218) or marital status ($\chi 2$ (1) = 0.53, p = 1.00). The details are presented in Table 1, along with occupational status. Occupational status at the time of injury showed significant differences between the two groups ($\chi 2$ (5) = 33.24, p = <.001) and was further analysed by visual inspection. A distinct difference between the two groups was that all students recovered by one year. Patients on sick leave at the time of the injury tended to develop PCS, while those on a pension (both retirement and disability) recovered.

Medical data

Data regarding acute injury characteristics for the two outcome groups at the one-year follow-up are presented in Table 2. The type of injury event did not affect outcome ($\chi 2$ (4) =6.91, p = .141), nor did a lower GCS score ($\chi 2$ (1) = 0.82, p = 1.00). Both loss of consciousness and PTA were divided into manageable time frames and cross-tabulated. No effect was found for loss of consciousness (linear-by-linear association = 0.66, p = .417), but longer duration of PTA was associated with recovery (linear-by-linear association = 4.54, p = .033). Eleven participants reported retrograde amnesia, four of them longer than five minutes. All of those who reported retrograde amnesia belonged to the recovered group, but it did not reach significance ($\chi 2(1)$ =1.65, p = .351). No effect for alcohol intoxication $\chi 2(1)$ = 1.47, p=.449. Further, alcohol intoxication at the time of injury was not associated with PTA ($\chi 2(3)$ = 0.77, p =.857), LOC ($\chi 2(2)$ = 2.69, p = .261), or retrograde amnesia ($\chi 2(1)$ = 0.25, p = .696). Injury

related changes on CT or MRI was evident in eight participants and not related to outcome ($\chi 2$ (1) =1.50, p = .235), but to a lower initial GCS ($\chi 2$ (1) =5.63, p = .049). Initial symptom severity, as measured by the RPQ the day after the trauma, showed excessive skewness and was analysed with Mann-Whitney. The result showed that the PCS group (Mdn = 68.32) initially experienced significantly more symptoms than the recovered group (Mdn = 44.14), U = 685,50, p = .005, r = 0.29.

Psychiatric assessment

Nine out of eleven PCS patients (83 percent) had a previous or concurrent psychiatric disorder, established at the psychiatric assessment one-week post injury. This was significantly higher than in the recovered group where only twenty out of 83 participants (24 percent) had a previous or concurrent disorder.

Forty-two of the recovered patients and ten of the PCS patients reported psychosocial stress of at least moderate severity during the year before the injury, ($\chi 2(1) = 6.38$, p = .020). Total number of psychosocial stressors showed excessive skewness and was analysed with Mann-Whitney. The result showed that the PCS group also reported more stressors (Mdn = 73.55) than the recovered group (Mdn = 44.05), U = 743.00, p = .001, r = 0.36. The two self-rated GAF measures showed a negative skewness exceeding -1 and were consequently analysed with non-parametric analysis (Mann-Whitney). Patients with PCS had significantly lower self-rated global functioning (*Mdn* = 35.61) than patients who had recovered (*Mdn* = 50.32) for the year before the injury, U = 470.0, z = -2.11, p = .035, r = -0.22. For the two weeks before the injury similar results were obtained with lower scores for patients with PCS (*Mdn* = 37.44) than patients who had recovered (*Mdn* = 49.88), but just short of being significant, U = 503.0, z = -1.77, p = .076, r = -0.18. The results for the actual ratings are shown in Table 3.

Preinjury behavioral and personality measures

Participants who developed PCS reported significantly less resilience for stressful events in the Sense of Coherence Scale than those participants who recovered *(t* (91) = 2.44, p = .018, r = 0.25). When breaking down the results in the three subcomponents of the scale, no significant differences were found concerning experienced comprehensibility or meaningfulness, but in manageability (t (91) = 2.79, p = .006, r = 0.28.

To see if personality traits, as measured by the SSP, were associated with outcome, independent samples t-tests were performed. Levene's test for equality of variances was found to be violated for somatic trait anxiety (F (92) = 4.61, p = .034), embitterment (F (92) = 10.98, p = .001), and physical trait aggressivity (F (92) = 4.34, p=0.40). For these traits, a t-statistic not assuming homogeneity of variance was computed. As can be seen in Table 4, results indicate that patients with PCS had elevated somatic trait anxiety, embitterment, and mistrust when compared with the group who had recovered. Previous alcohol consumption pattern did not differ between the two groups, see Table 3.

Post-injury symptoms

Both Impact of Event Scale and Hospital Anxiety and Depression Scale showed excessive skewness (>1) and was analysed using non-parametric methods (Mann-Whitney). The results showed that patients who developed PCS (Mdn = 68.45) reported more initial post-traumatic stress than patients who later recovered (Mdn = 44.72), U = 687.00, z = 2.72, p = .007, r = 0.28. Looking further at the subscales revealed that the two groups differed significantly only in hyperarousal, with the PCS group (Mdn = 75.91) reporting more distress than the recovered group (Mdn = 43.73), U = 769.00, z = 3.74, p = .000, r = 0.39. There were highly significant differences

between the two groups on emotional distress as measured by HADS. One-week post injury, the PCS group (*Mdn* = 72.41) experienced higher levels of anxiety than the recovered group (*Mdn* = 44.20), $U = 730.50$, $z = 3.30$, $p = .001$, $r = 0.34$. The PCS group (*Mdn* = 72.77) also experienced more symptoms of depression than the recovered group (*Mdn* = 44.15), $U = 734.50$, $z = 3.32$, $p = .001$, $r = 0.34$. The parametric mean and standard deviation for both scales are shown in table 5.

Discussion

The main purpose of this study was to examine if aspects of emotional reserve were associated with the development of PCS after mTBI, to complete our previous findings regarding cognitive reserve in the same cohort [12]. At the one-year follow-up, twelve percent of this cohort fulfilled our extended criteria for PCS, including both symptoms and disability.

Factors related to the actual injury, so called peri-injury factors, were in general not related to outcome, with one notable exception: the PCS-group reported more initial injury symptoms. This could theoretically be interpreted as a sign of severity of the underlying injury. However, most evidence suggests that objective acute injury factors are not related to late outcome, so it is unlikely that the actual injury was more serious. A more feasible view is that the reporting of a large number of initial symptoms after a mTBI is merely another marker for the pre-injury psychological vulnerability in the PCS-group, that already at a very early stage after the injury shapes the emergence and later on the persistence of symptoms and disability.

The weight of preinjury factors emerged markedly. The PCS-group reported a greater number of psychosocial stressors for the year preceding the injury, corroborating previous findings [56]. We found that individuals with a previous or

concurrent psychiatric disorder, or with a family history of such disorder were more likely to develop PCS. Both GAF ratings were significantly lower, corroborating and extending earlier findings [13 32 33]. Despite the elevated frequency of 15 percent of alcohol abuse in the cohort, there were no differences in the number of intoxicated patients or alcohol abuse between PCS- and recovered patients. Among the post-injury factors, higher levels of PTSD symptoms as assessed by the IES-R, in particular the subscale of hyperarousal showed a clear association to PCS. Also, both anxiety and depression were higher in PCS patients one week after trauma. The findings are further supported by the design of the study, since data were obtained within a week after the mTBI, minimizing recall bias and before the development of prolonged PCS symptoms, minimizing the risk for confirmation bias.

We used the Swedish Scales of Personality, the SSP, to measure different aspects of personality and found in the PCS group elevated level of somatic anxiety, but not psychic anxiety, compared to the recovered group. The SSP divides trait anxiety into a psychic and a somatic component [48 57]. This division of anxiety was first suggested by Eysenck [58]where the somatic component reflects autonomous over-reactivity, and the mental component reflects brooding and worrying behaviour. Further, the PCS group had significantly higher levels of mistrust. This SSP-scale has its origins in the subscale suspicion in the Buss-Durkee Hostility Inventory [59] and measures traits of being suspicious and distrusting of other people's motives. The elevated level of embitterment in the PCS group may be linked to coping responses during stressful life events. The SSP scale can be illustrated by the following item: "I had often gotten into trouble even when it was not my fault.". Blaming others has previously been found to influence symptom reporting in mTBI patients [60]. To sum it up, a pattern of higher reactivity in the autonomic nervous system, and some

personality traits (embitterment and suspiciousness) may lead to more stress in everyday life, and an increased sensitivity when encountering and managing traumatic events, such as a brain injury.

We used a different measure of psychological resilience in connection with mTBI than other studies [26], but the findings were similar; lower levels were linked to PCS development. The three-factor construction of the SOC allows further analysis of different aspects of resilience: comprehensibility, manageability, and meaningfulness. We found that only manageability was significantly lower in the PCS group. This subscale is tapping into an underlying construct of being in control of one's life and a sense of mastery. To our knowledge, this finding has not been reported before. Thus, the outcome differed despite seemingly similar brain trauma, highlighting the importance of biopsychosocial factors for the development of PCS [61], such as the extent of cognitive [17] and emotional reserve [36].

As mentioned before, the peri-injury factors were hardly related to outcome in this study. Injury related changes found on MRI or CT scan and initial lower GCS-score were not related to PCS, which is in line with previous findings [62 63]. However, PCS-patients reported a shorter duration of PTA. However, there were only few individuals with imaging findings and the GCS score was restricted to 14 or 15, so the sample was too small to enable the detection of differences.

Strengths and limitations

The study had a prospective design and included all patients within the first 24 hours after the trauma when injury related factors could be reliably assessed. Preinjury factors were thoroughly assessed soon after injury, minimizing recall bias [64]. A further strength is the comprehensive psychiatric assessment by a senior psychiatrist, instead of solely relying on self-report questionnaires. In previous studies [13 32], psychiatric

assessments have yielded decreased estimates of PCS. The assessment of preinjury factors was performed without knowledge of late outcome.

The small size of the PCS group is a limitation and relevant findings may have remained undetected due to low power. There is also a substantial lack of precision, which can be seen in the wide confidence intervals. Larger prospective samples are thus required to corroborate the present results. Further, the association between attrition and limited education is problematic, causing restricted generalizability. Finally, the symptoms and disabilities in the PCS-definition show some overlap with psychiatric conditions, and previous as well as concurrent psychiatric disorders turned out to be risk factors for PCS. Given the many other psychosocial determinants for PCS found in our study, a biopsychosocial approach, taking the psychiatric comorbidities into account, is likely to yield the most thorough understanding of the emergence and persistence of symptoms and disability after mTBI.

In conclusion, the present findings fit and extend Gallo and Matthews'[20] Reserve-Capacity Model demonstrating a link between psychosocial adjustment and specific symptom development after an injury. The results demonstrate the importance of intra-personal emotional reserve for symptom development along with cognitive reserve, complementing our previous findings. Thus, the variations seen in outcome after mTBI may to a considerable degree reflect individual differences in emotional and cognitive coping ability. The results highlight the importance of considering psychiatric history when identifying patients at risk of developing PCS and emphasize the value of considering these pre-injury factors in clinical management.

Author Statement

CO, AL and AB conceived of the present study. AL, GE, CNDB and AB initiated the study design. AL and CNDB contributed to data collection. GE provided statistical expertise. All authors contributed to the interpretation of the study results as well as the writing of the manuscript. All authors have read and agree with the manuscript's final content.

Competing interests

The authors report no competing interest.

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Data sharing statement

There are no unpublished data available.

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Table 1: Sociodemographic characteristics of mTBI patients split into recovered by one year and those who reported both symptoms and disability (PCS).

Characteristic	Recovered (*n* = 83)	PCS (*n* = 11)
Age, Mean (SD)	36.7 (15.2)	41.9 (13.2)
Sex, n (%)		
Male	54 (65)	3 (27)
Female	29 (35)	8 (73)
Marital status, n (%)		
Unmarried, living alone	20 (24)	3 (27)
Married, living together	63 (76)	8 (73)
Years of education, Mean (SD)	12.7 (2.6)	11.6 (2.7)
Occupational status, n (%)		
Working	63 (76)	6 (55)
Studying	15 (18)	0 (0)
Unemployed	0 (0)	1 (9)
Sick leave	1 (1)	4 (36)
Disability pension	2 (2)	0 (0)
Retirement pension	2 (2)	0 (0)

Table 2: Peri-injury data for the those who had recovered by one year, and those who still reported post concussive symptoms (PCS).

Characteristics	Recovered (n=83)	PCS (n=11)
Type of injury event, n (%)		
Fall from height	31 (37)	3 (27)
Fall from the same level	17 (20)	1 (9)
Traffic	17 (20)	3 (27)
Assaults	9 (11)	0 (0)
Other	9 (11)	4 (36)
Loss of Consciousness, n (%)		
< 1 minute	37 (45)	5 (45)
1-5 minutes	31 (37)	6 (55)
6-30 minutes	15 (18)	0 (0)
Post-traumatic amnesia, n (%)		
< 1 minute	10 (12)	4 (36)
1-5 minutes	19 (23)	4 (36)
6-45 minutes	34 (41)	1 (9)
> 45 minutes	20 (24)	2 (18)
GCS Score, n (%)		
15	73 (88)	10 (91)
14	10 (12)	1 (9)
Retrograde amnesia	11 (13)	0 (0)
Injury related changes on CT or MRI	6 (7)	2 (18)
Intoxicated by alcohol, n (%)	22 (27)	1 (9)
Initial symptom severity*, Mean (SD)	10.4 (9.3)	23.8 (17.0)

Note: Initial symptom severity was measured by the Rivermead Post Concussion Symptoms Questionnaire (RPQ). There was one missing protocol from the recovered group. The variable showed excessive skewness and Mann-Whitney was used as statistical method. However, here the values are shown since they are considered more informative.

Table 3: Pre-injury variables for mTBI patients split into those who had recovered by one year and those who reported both symptoms and disability (PCS). Odds ratios (OR) with confidence intervals (CI) and p-values are calculated using logistic regression.

Variables	Recovered (*n*=83)	PCS (*n*=11)	OR (CI)	p
Previous or concurrent psych disorder, n (%)	20 (24)	9 (82)	14.2 (2.8 – 71.1)	.001
Previous psych disorder	16 (19)	7 (64)	7.3 (1.9 – 28.1)	.004
Concurrent psych. disorder	8 (10)	7 (64)	16.4 (3.9 – 68.5)	<.001
Family history of psych disorder	17 (20)	4 (36)	2.4 (0.9 – 6.3)	.077
Self-assessed GAF, Mean (SD)				
The year before the injury	86.2 (11.5)	67.3 (21.5)	0.9 (0.8 – 1.0)	<.001
The two weeks before the injury	87.1 (11.1)	73.2 (20.3)	0.9 (0.8 – 1.0)	.003
Previous mild traumatic brain injury	4 (5)	2 (18)	4.3 (0.6 – 27.1)	.117
Alcohol consumption (Audit)				
Mean (SD)	5.0 (4.2)	5.5 (8.1)	1.0 (0.8 -1.2)	.748
Eight or above, n (%)	13 (17)	1 (10)	0.5 (0.0 – 4.7)	.573
Number of psychosocial stressors, Mean (SD)	1.30 (1.40)	3.73 (2.15)	2.1 (1.4 – 3.1)	<.001

Note: There were eight missing questionnaires for Audit (seven for the recovered and one for the PCS group). There was one missing questionnaire for Sense of Coherence Scale.

Table 4: Mean T-scores for the Swedish universities scales of personality completed one week post injury, split into those who had recovered by one year and those who reported both symptoms and disability (PCS).

	Recovered (*n*=83)		PCS (*n*=11)			
Personality variable	*M*	*SD*	*M*	*SD*	*p*	Cohen's *d*
Anxiety proneness						
Somatic trait anxiety	45,3	7,8	53,8	11,0	.030	0.89
Psychic trait anxiety	45,4	9,1	49,8	11,6	.156	0.42
Stress susceptibility	46,9	10,4	52,1	15,1	.145	0.40
Low assertiveness	46,8	9,7	43,9	10,5	.362	-0.04
Extraversion						
Impulsivity	51,8	9,4	54,5	12,6	.400	0.23
Adventure seeking	54,1	9,3	55,9	7,7	.558	0.21
Detachment	44,2	8,7	47,7	8,9	.216	0.40
Embitterment	46,7	8,4	59,3	15,3	.022	1.02
Social desirability	54,4	9,7	51,3	9,6	.311	-0.32
Aggression-Hostility						
Verbal trait aggressivity	50,4	8,4	51,0	11,1	.823	0.06
Physical trait aggressivity	47,2	9,0	53,6	14,6	.185	0.53
Trait irritability	46,2	10,9	52,0	14,6	.112	0.45
Mistrust	44,5	10,7	55,1	13,2	.004	0.88

Table 5: The results from measures of post-traumatic and emotional symptoms at one week post injury for the two outcome groups: recovered and those who still reported symptoms and disability (PCS) at one year post injury. Odds ratios (OR) with confidence intervals (CI) and p-values are calculated using logistic regression.

	Recovered (n=83)		PCS (n=11)			
Variable	*M*	*SD*	*M*	*SD*	OR (CI)	p
Impact of Event Scale						
Intrusions	6.2	5.4	15.2	14.7	1.1 (1.0 – 1.2)	.002
Avoidance	4.8	6.7	9.3	10.2	1.1 (1.0 – 1.2)	.070
Hyper-arousal	3.5	4.3	12.4	8.7	1.2 (1.1 - 1.4)	<.001
Total	14.5	14.5	36.8	30.0	1.1 (1.0 – 1.1)	.001
Hospital Anxiety and Depression Scale						
Anxiety	2.7	3.3	8.4	5.7	1.3 (1.1 – 1.6)	<.001
Depression	2.2	2.6	6.7	4.7	1.4 (1.1 – 1.7)	<.001

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **Page 1**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **Page 2**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **Pages 4-7**
Objectives	3	State specific objectives, including any prespecified hypotheses **Page 7**
Methods		
Study design	4	Present key elements of study design early in the paper **Page 8**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **Page 8-9**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **Page 8-9**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **Page 8**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **Pages 9-12**
Bias	9	Describe any efforts to address potential sources of bias **Participant bias:** **Recall bias – page 3** **Confirmation bias, social desirability and fatigue page 9** **Selection bias –** **participation, representativity page 9** **analysis of differences between participating and nonparticipating patients and between participants and drop – outs – page 13** **Researcher bias: Early data collection minimizes bias – study design – page 18**
Study size	10	Explain how the study size was arrived at **Page 8**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **Page 12**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding

Page 12
(*b*) Describe any methods used to examine subgroups and interactions **N/A**
(*c*) Explain how missing data were addressed **We used an unbiased approach, and stated where there were missing data in the tables, see table 2 and 3.**
(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed **Page 13**
(*e*) Describe any sensitivity analyses **N/A**

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **Page 13**
		(b) Give reasons for non-participation at each stage **Page 13**
		(c) Consider use of a flow diagram **N/A**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **Page 14, Table 1.**
		(b) Indicate number of participants with missing data for each variable of interest **See Table 2 and 3.**
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) **Page 9**
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time **Page 15**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **We have only included unadjusted estimates.**
		(*b*) Report category boundaries when continuous variables were categorized **Pages 12-13**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **N/A**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **N/A**
Discussion		
Key results	18	Summarise key results with reference to study objectives **Pages 17-18**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **Page 19**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **Pages 17-19**
Generalisability	21	Discuss the generalisability (external validity) of the study results **Page 19**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **Page 20**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.