PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Emotional reserve and prolonged post-concussion symptoms and disability: A Swedish prospective one-year mild traumatic brain injury cohort study
AUTHORS	Oldenburg, Christian; Lundin, Anders; Edman, Gunnar; Deboussard, Catharina; Bartfai, Aniko

VERSION 1 – REVIEW

REVIEWER	Keith Yeates University of Calgary, Canada
REVIEW RETURNED	20-Dec-2017

GENERAL COMMENTS	This study examines the role of premorbid psychiatric and personality factors in the prediction of persistent postconcussive symptoms and disability in a sample of 94 adults with mild traumatic brain injury (TBI). The results showed that individuals with persistent poor outcomes at 1 year post-injury, as compared to those without such difficulties, reported more anxiety, depression, and post-traumatic symptoms acutely, more preinjury and concurrent psychiatric problems, lower overall functioning prior to injury, and more stress. They also reported personality features such as more somatic trait anxiety, embitterment, and mistrust, and less psychological resilience, compared to adults who recovered. The study has several strengths, including the prospective design, clear inclusion criteria, and a comprehensive assessment of "emotional reserve." Moreover, the results are generally consistent with previous research suggesting that pre-existing psychiatric and psychological factors account for more variability in the long-term outcomes after mild TBI than do injury factors. The paper could be improved if the authors addressed two major issues, as well as several other points: Major concerns 1) A central methodological decision in this study was the choice to define postconcussive syndrome (PCS) as having three or more symptoms on the RPQ and two or more disabilities on the RHFUQ. The authors offer no conceptual or empirical rationale for this classification, or for the cutoffs used for each instrument, which therefore seem rather arbitrary. The basis for combining the two instruments and for the specific cutoffs on both needs to be better justified. Would slightly different cutoffs, or the use of only one rather than two instruments, lead to different results? Sensitivity analyses could address this concern. 2) The sample size of the group with PCS is very small (n = 11),

	raising concerns about whether the group is representative of the larger population of individuals with PCS, and hence about whether the study's results are generalizable. The authors cannot increase the sample size, but they could acknowledge that the small size of the PCS group is a concern. Changes in the criteria for PCS (see #1 above) might also lead to increases in the size of the PCS group. Other concerns 1) The age range of the participants is quite large, but the authors do not explore or consider whether any of the relationships of their measures of "emotional reserve" to PCS vary by age. Given the small size of the PCS group, that group is unlikely to adequately represent the range of ages of the recovered group (and in fact the PCS group is older on average). 2) The authors state that all participants were admitted to hospital emergency wards. This is likely a language issue, but does that mean only that patients were seen in emergency settings, or that they were actually admitted as hospital inpatients? If the latter, they would be unrepresentative of individuals with mild TBI, who generally are seen in emergency settings and then sent home. 3) The participants apparently all completed both CT and MRI scans. The authors do not state how the imaging was evaluated, although they report that "injury related changes" were not related to PCS. Much more information is needed about how "injury related changes" were defined and evaluated. 4) The psychiatric assessment apparently was based on a clinical interview. Was it a standardized, validated, structured interview? If not, was the reliability of the assessment established in any way? 5) Who completed the Psychosocial Stressors scale as part of the psychiatric assessment? The physician or the participant? 6) The finding that acute symptom levels were higher in the PCS group than the recovered group warrants somewhat more mention in the Discussion. Acute level of symptoms is consistently identified as one of the best predictors of persistent symptoms, and may reflect the underlying injury given the frequent association of acute symptoms with injury factors. Thus, in this sample, the injury itself may have played some role in the occurrence of PCS, despite the lack of association with specific injury factors.

REVIEWER	DR Bryan G Garber Directorate of Mental Health, Canadian Forces Health Services Group Headquarters, Department of National Defence, Canada
REVIEW RETURNED	17-Jan-2018

GENERAL COMMENTS	Peer Review of Paper Titled: Emotional reserve and prolonged post-concussion symptoms and disability. A prospective one-year mild traumatic brain injury cohort study. Authors: Oldenburg et al The paper reports findings from a one year prospective cohort study. The primary objective was to determine if emotional reserve at or before the time of injury could predict the presence of persistent

	post-concussive syndrome at one year post-injury. The construct of emotional reserve is rather ill defined in this paper and a clearer operational definition would have been helpful. Indeed the study found evidence to support their thesis. Persistent post-concussive cases had more preinjury and concurrent psychiatric problems, lower levels of functioning before injury, and experienced more stress. There was also certain personality traits and lower levels of psychological resilience that were correlated. This study had a number of strengths as the authors point out. It was a prospective design and used individualized psychiatric assessment. The large amount of data collected was both a strength and a flaw because the small number of cases of persistent post-concussive syndrome (n=11) really limited their ability to do any statistical modelling that would have controlled for confounding of so many covariates. Indeed the authors need to acknowledge that this small number of cases is what really limits generalizability of their results to all individuals with persistent post-concussive symptoms. The authors do not report any estimate of the effect sizes for any of the variables that they report as significant. The one time that they do (females have OR PCS 4.97 [95% CI 1.22-20.17]) one can see that the confidence intervals are quite wide. Consequently statements made in the discussion that certain variables had no effect on outcome are misleading. These variables may had an association to outcome but the study design had insufficient power to detect those effects. It may be advisable for the authors to limit analysis to key variables and use modelling such as Poisson Regression to provide estimates of the effects and their confidence intervals. This would allow the reader to get a better sense of both the strength of the association and how sample size truly limited the ability to thoroughly mine the large quantity of data that they have available to them and control for the effects of confounding. I suspect they will find that they run out of power very quickly. Persistent post-concussive syndrome is a complex entity and disentangling the effect of brain injury from psychological trauma is challenging. The authors did have a non-brain injured control group in their original biomarker study and this would have been a novel opportunity to conduct a prospective longitudinal comparison. Why did the authors not evaluate the control group for evidence of PCS at follow up? I am confident that some of the controls would have manifested PCS and this would have enabled them to evaluate the effect of injury factors on PCS far more thoroughly. I believe this was a missed opportunity. There is the potential for misclassification of outcomes that are not addressed as a limitation. The authors used a questionnaire at follow up and defined the presence of PCS symptom as persistent PCS. Given the strong correlation to psychiatric diagnoses at injury, could these cases have been psychiatric illnesses diagnosed as PCS? A final point I wish to raise is that most experts would define persistent PCS as symptoms persisting beyond 3 months. By one year most have resolved. I suspect that individuals with PCS at one year represent a somewhat different part of the PCS spectrum. Given the prospective nature of the study design. The authors could have evaluated subjects at 3 months, 6 months and one year post-injury. This would have provided a crucial insight into the recovery

	trajectory. It is also likely that they would have found more cases in the earlier time period to work with thereby addressing the power issue. I wonder if such an approach might also have revealed that some of the factors correlated with persistent symptoms change over time. In summary, the authors need to do more to address issues of low power, misclassification and inability to control for confounding in their study design.

VERSION 1 – AUTHOR RESPONSE

To reviewer 1
Thank you for the positive response!

About your major concerns:

- We are glad that you pointed out the central question about the definition of PCS. It is something we had elaborated on in earlier drafts of the manuscript but that was cut out due to the word limit. In our earlier publication from this cohort we used the "three or more" symptoms definition, which is rather common, and in part is coming from the ICD-10 criteria. It is our belief that this definition may be too lenient, and due to suggestions from other experts here in Sweden we wanted to include some measure of actual experienced disabilities in daily life, which in fact was required in the former definition of post-concussion disorder from DSM-IV. We have now added a paragraph about the rationale for the extra disability criteria in the introduction.
o See page 7.

- Your other major concern was related to low power given the small size of the PCS-group. This is of course related to our stricter inclusion criteria, and as you have pointed out we cannot increase the size of the study at this time. We have acknowledged this as a limitation of the study.
o See page 20

About your other concerns:

- The age range of the participants was large, as you have pointed out. There were however no statistically significant differences between the groups even though the mean age of the PCS group was somewhat higher. Thus, possible age related changes in personality might affect similarly both the pcs and non-pcs groups. The relationship between emotional reserve measures with age is an interesting point. Obviously, risk of lifetime exposure for psychiatric experiences is higher with increasing age. There have also been reports of age-related changes in personality, but since the two groups are comparable with regard to age we have reasoned that it is unlikely that the present results are influenced by the large age range in our cohort.

- About the "admitted to hospital wards" sentence. Thanks for pointing that out! Indeed, we did not mean that the patients were hospitalized, but that they came to the hospital emergency ward within 24 hours of a trauma. So, the patients are in fact representative of those seeking care, and not the patients seeking care and becoming hospitalized. To make this as clear as possible we have changed two sentences in the method section.
o See page 8 and 9.

- The evaluation of CT and MRI scans were according to standard hospital routines, and were done by experienced radiologists. There were no particular research protocol followed. We have clarified

that in the manuscript.
o See page 9.

- The psychiatric interview was semi-structured and conducted by an experienced neuro-psychiatrist, author AL. We have added the word semi-structured in the description.
o See page 10.

- The Psychosocial Stressors scale was completed by the participant and was used in the psychiatric interview. We have added a sentence for clarification.
o See page 10.

- Finally, we have added three sentences to the discussion to highlight your observation that the PCS-group was more affected in the acute phase. If this reflects the seriousness of the underlying injury or lesser ability to cope with that injury is a very tough research question. Our findings of this groups pre-injury status has led us to hypothesize that it is the latter explanation that is correct.
o See page 18.

To reviewer 2

We thank you for the positive response and constructive feedback!

- Your initial comment that "emotional reserve" is rather ill defined is noted, and we certainly want to develop a clear operational definition in the future. At this moment we only have an exploratory approach and have reasoned that emotional reserve draws its content from three overall sources: personality, emotional coping abilities, and exposure to psychopathological conditions.

- Your major concern is the low number of PCS-cases in this cohort, and you propose that we could use another statistical model. We have consulted with our statistician about poisson regression but he suggested we should use logistic regression instead, due to our dichotomous outcome. Following his advice, we have recalculated the results for table 3 and 5 and now provide odds ratios with confidence intervals. P-values were mostly consistent with prior calculations but changed slightly in a few cases (in the direction of being more significant). What is evident in the tables are the wide confidence intervals due to the small sample size. We think this adds valuable information, and highlights your point about the limitation that the small size of the PCS group (n=11) consitutes. This is now mentioned in the limitation section in the discussion.
o See page 20

- Your next major point is about the potential for misclassification of PCS due to the large overlap of symptoms with common psychiatric conditions is highly relevant. There is a large literature that suggests that symptoms in the aftermath of an mTBI is almost undistinguishable from a general effect of having suffered any bodily trauma, and also from other symptom-based illnesses (e.g. depression). Bu the issue of misclassification is problematic. The word "misclassification" implicates that of the two diagnoses "post-concussional disorder" and, for example "depression", one of the two is correct and the other one is false. Hence, the individual could have a diagnosis of depression which turns out to be wrong and should be replaced by post-concussional disorder or vice versa. Our study challenge this view of two mutually exclusive conditions. Both depression and postconcussional disorder are symptom based conditions with overlapping symptomatology, a feature shared also with several other diagnostic entities. No biomedical marker is at hand to prove or disprove either diagnosis. Postconcussional disorder is preceded by an mTBI and in medical settings this order of events often justifies the use of this term. But our study shows that the causal link between the medical consequenses of the brain injury (PTA, LOC, hemorraghe) and the subsequent development of

symptoms is weak or, in a number of cases, possibly non-existent. In summary, there is no way of reliably disentangling these two conditions. Accordingly, we think that the term "misclassification" is not applicable in this context. We have added a rather lengthy paragraph to express our view on this issue.
o See page 21

- In line with the above problem for misclassification you raise the question about the healthy controls, and whether any of them could have been classified as PCS. Given the relatively high frequency of reported symptoms even in healthy samples that is a very relevant and intriguing question. In fact, the healthy controls did complete the RPQ and RHFUQ questionnaires. However, we have left out that data because the questionnaires are not worded in the same way. The mTBI patients were asked (as is the common practice when using RPQ) to rate changes in their experienced symptoms in relation to their pre-injury baseline. The healthy controls were just requested to rate their current symptom level. In our opinion this procedure makes the two ratings uncomparable, but perhaps not uninteresting? I quickly looked in our dataset, and saw that approximately 20 percent of the healthy controls reported three or more current symptoms in RPQ. This is obviously a possible confounder, and also have bearing on the well-known hypothesis of a "good-old-days"-bias that may be in play when mTBI patients try to compare their current symptom level to a distant past. However, given the large amount of data already in the manuscript we have decided to leave this information out.

- Your final point regards PCS prevalence at different time intervals after injury. You suspect that we would have found more PCS cases earlier post injury. This is in fact the case. Our previous publication from this cohort study used data from the three months follow-up and is referenced in the manuscript. Indeed, 33 percent fulfilled the symptom-only criteria at three months post injury, versus 19 percent at one year. For clarity we have added a sentence in the results section to highlight this observation.
o See page 14.

VERSION 2 – REVIEW

REVIEWER	Keith Yeates University of Calgary, Canada
REVIEW RETURNED	13-Mar-2018

GENERAL COMMENTS	The authors have addressed my concerns. I appreciate their responsiveness to the previous reviews.