Author’s response to reviews

Title: Longitudinal Trajectories of Comorbid PTSD and Depression Symptoms Among U.S. Service Members and Veterans

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Version: 1 Date: 04 Oct 2019

Author’s response to reviews:

To: BMC Psychiatry Editor, Samuel Harris, PhD
From: Richard Armenta, Assistant Professor
RE: Manuscript Re-Submission

October 4, 2019

Dear Dr. Harris,

Enclosed please find our revised manuscript titled “Longitudinal Trajectories of Comorbid Posttraumatic Stress Disorder and Depression Symptoms Among US Service Members and Veterans.” We continue to believe that BMC Psychiatry is a good fit for this research. We appreciate the opportunity to respond to the editors and reviewer’s comments and agree this revision has improved the clarity of our manuscript. Our responses to each of the editor’s and reviewer’s comments (in bold) follow this letter and we also include the manuscript with track changes to indicate the edits made based on the editors and reviewers comments.

Thank you for considering our work for potential publication in BMC Psychiatry. As corresponding author, please contact me if I may be of assistance in providing additional information.

Very Respectfully,
Response to Editor and Reviewer’s Comments

Editor Comments:

1. Of course, the focus of the paper is on how PTSD and MDD trajectories move together. Nonetheless, in line with the need to optimise parsimony in mixture models, could the authors please confirm that the simultaneous growth model fitted the data better than each of the separate PHQ and PCL growth models? In other words, was there greater explanatory value in having a dual growth model when compared to either considered individually? If not, that’s fine: It would presumably suggest that the course of depression symptoms might be sufficiently well understood from PTSD alone, or vice versa.

This is an interesting suggestion. We are not aware of a method to compare the explanatory value in separate mixture models to one that is combined. However, when examined separately, the models produce very similar looking trajectories that are highly correlated. What you suggest does appear to be the case on average in that changes in depression symptoms largely correspond to changes in PTSD symptoms and they change with relatively the same magnitude. However, we are hesitant to suggest that only measuring symptoms of one condition is sufficient to understand change in both, particularly due to the clinical ramifications and individual exceptions to the above rule.

2. Given that simultaneous trajectory models are not often used in the literature, and given that a variety of terminology is used to describe similar sorts of models (e.g., “dual growth models”, “multiple trajectory models” etc), could the authors please provide a SEM-style growth modelling diagram to help readers visualise the model.

We appreciate this suggestion and agree that there could be confusion about the type of modelling used. We created a SEM-style growth modelling diagram (below), however, we do not think it would be appropriate to include in the manuscript and may add to additional confusion given that figures of this nature are not typically included for the type of analysis we conducted. We made changes throughout the methods of the paper to help clarify the analyses used for this manuscript and feel that the clarifications in the methods along with the figures already included in the manuscript should help the reader understand the type of modelling used to examine trajectories of comorbid PTSD/MDD. We are happy to revisit this issue if the editor feels that more clarification is needed.

3. The model fit indices and relative fit tests have produced somewhat ambiguous results: For instance, BIC values continue to fall with successive classes beyond 4 and BMLRT tests continue to remain significant up to and including 7 classes. In this situation, other factors such
as parsimony, theoretical coherence etc are especially important in favoring one solution over another. With this in mind, could the authors please state in precisely what way the four-class solution was more “interpretable” than the other solutions?

We agree that more clarity was needed on how we decided on a 4-class model given the ambiguous results of the fit indices. Parsimony was largely the major concern for selecting the four-class solution over the others. Further, the significant LMR test indicates that the 5-class solution did not significantly improve model fit beyond the 4-class model. In terms of interpretability, the 4 class was favorable to the three-class model given the addition of a distinct class that followed a very different trajectory than the other three classes. However, with the addition of the fifth class, two of the trajectories followed a similar pattern. Taken together with the entropy values continuing to decline with more classes, and the non-significant LMR we decided on a 4 class model instead of a 5 class model.

4. Yes, the authors are most interested in “what happens” to people with high PTSD and MDD symptoms. Nonetheless, by selecting only those who met the screening threshold for both PTSD and MDD at baseline, there is a restriction in the range of scores for the trajectories at baseline, but less so at other timepoints. The authors need to comment on this in the paper and consider the implications for the trajectory results. For instance, a deteriorating/worsening trajectory (who may have gone on to develop high PTSD+MDD symptoms) may not be identifiable from this sample given that all symptoms were necessarily prominent for study inclusion.

Previous studies looking at trajectories of PTSD and depression among service members have demonstrated that a small proportion of service members have high symptoms at a given time. Given that this is such a small proportion, including the entire sample in a mixture analysis would be unlikely to produce multiple trajectories describing the change in service members with high symptoms. We agree that the current analysis does not describe individuals who go on to develop high PTSD+MDD symptoms, but it does presumably include participants that had low or subthreshold PTSD and MDD symptoms pre-baseline which worsened by the baseline assessment.

5. Further to the previous point, given that the authors can only rely on proxy diagnoses derived from self-report measures, one wonders why the overall sample was restricted in this way when an analysis of the overall sample could have been used to determine the trajectories and outcomes for those with high levels of both PTSD and MDD, but also allow inclusion of participants who started with lower levels, but who then developed high levels of both PTSD and MDD symptoms. Yes, there’s value in focusing on those who have both high levels of PTSD symptoms and MDD symptoms (as outlined in the Introduction). However, there’s presumably participants from the larger study who would have for all intents and purposes had a trajectory of high PTSD/high MDD for much of the time if they hadn’t been excluded at baseline.

We agree that it is possible that participants who were excluded from the study may have developed high co-morbid PTSD/MDD symptoms after the initiation of the study period. It is also possible those who started out with only one condition developed comorbid conditions after the start of the study, which would have meant they were excluded from this analysis. While
those are both interesting questions that should be addressed, for this initial study we wanted to focus on those with existing comorbid PTSD/MDD to understand how the symptoms change together over time among this high-risk group. Now that we have a better understand of the trajectories, further studies will allow inclusion of those who started at lower levels but then develop high symptoms for both conditions, or those who only screen positive for one condition and later develop symptoms for the other to have comorbid PTSD/MDD.

6. The authors need to address the issue of overlapping symptoms between PTSD and MDD and how these may have influenced the results. For instance, could part of the reason for the relatively indistinguishable trajectories between PTSD and MDD symptoms be that item 9 of the PCL-C, for instance, is “Loss of interest in activities you used to enjoy?”, while item 1 of the PHQ-8 is “Loss of interest or pleasure in doing things”. There is similar item overlap for sleep and concentration, such that three of the eight PHQ-8 items (almost half) have almost complete overlap with the PCL-C. The authors should either run a sensitivity analysis of sorts (whereby overlapping items are removed from one or both scales) or otherwise take steps to determine whether/to what extent the overlapping trajectories are an artefact of item overlap. The results of any additional analyses in this respect may only be provided as supplementary information or similar, but the ability to provide some (ideally data-driven) comment regarding this in the paper is important.

We appreciate this suggestion and agree that the overlapping symptoms could be an issue. We have run a sensitivity analysis to exclude the similar items from the scales. We excluded the overlapping items from the scales and reran the analysis to determine to what extent the similar trajectories for PTSD and MDD were a result of the overlap. The excluded items from the PHQ (Little interest or pleasure in doing things; Trouble falling or staying asleep, or sleeping too much; Trouble concentrating on things, such as reading the newspaper or watching television) and for PCL-C (Loss of interest in things that you used to enjoy; Having difficulty concentrating; Trouble falling or staying asleep). To run the sensitivity analysis we kept the same study population that met criteria for co-morbid PTSD and MDD and removed the overlapping items and rescored PCL-C and PHQ-8 with the smaller number of items. Once we rescored both scales we reran the adjusted trajectory models to determine whether we would identify the same number of classes and whether the trajectories followed a similar pattern to our original analysis. Based on this analysis, we found that the rescaled trajectories followed a nearly identical pattern to the original trajectories that included all of the items. This suggests that the similar trajectories of PTSD/MDD are not a result of the overlapping items. We have included the following sentences in the manuscript.

Methods (Page 7): “To ensure that related PTSD and MDD trajectories were not a result of the overlapping items on the two scales, we ran a sensitivity analysis that removed the overlapping items before scoring (i.e., items on sleep, loss of interest, and trouble concentrating). The scales with removed items were rescored and mixture modeling was conducting following the same methods described above.”

Results (Pages 8 and 9): “Further, in the sensitivity analysis that removed overlapping items from the scale, the trajectories were nearly identical to the original trajectories with no items removed (supplementary figure 1).”
7. On page 7, the authors justify a four class solution based partly on: “significant Lo-Mendell-Rubin adjusted likelihood ratio test of the 5-class solution” – do they mean 4 or 5 here?

We have clarified that the significant LRM test of the 5-class solution indicates that more complex model did not improve fit enough to justify the reduction in parsimony.

8. Could the authors please provide additional detail regarding the analyses from which Table 2’s results are derived? Were the “adjusted models” SEM models which included these variables? Or were they logistic or multinomial regression models predicting trajectory class(es)? How were assumptions of multicollinearity and the like examined? Presumably many of the predictor variables would have been strongly associated with each other.

Covariates were entered directly into the model as predictors of the latent class (see recommended SEM-style diagram). Given that the latent class had four categories, this is analogous to the multinomial regression model, but continues to take into account the uncertainty of individuals class assignment which makes the estimates more accurate than doing the analysis in two steps. The text in the statistical analysis section has been modified to make this clearer. Multicollinearity was assessed using variance inflation factors (VIF). Variables with a VIF value of greater than 4 were considered to be potentially collinear. In our sample we did not find any of the variables over this threshold.

We added the following sentence to the statistical analysis section of the manuscript (Page 7): “Multicollinearity was assessed using variance inflation factors (VIF) with a VIF >4 indicating collinearity between covariates; no covariates were above this threshold.”

Responses to Reviewer 1:
This study uses a large, longitudinal data set of service members and veterans to describe symptom trajectory among those with comorbid (probable) PTSD and MDD. I believe the study provides a meaningful contribution to the literature, particularly in understanding the prevalence of various trajectories of comorbid PTSD/MDD, as well as correlates of unremitting symptoms. The prospective nature of the study (with several correlates of trajectory measured at baseline) and size of the sample are notable strengths. However, I think the manuscript could be strengthened in a few key ways (comments on each section included below).

1. “Among the psychiatric disorder, major depressive disorder is the most frequently comorbid with PTSD.”
-Please provide a reference for this statement. I believe the rates of depression comorbidity are comparable to substance use disorder comorbidity.

We thank the reviewer for this and agree that more clarity in our statements was needed. The rates of depression comorbidity are comparable to substance use disorder comorbidity for civilians with DSM-III criteria (47.9% MDE vs 51.9% AUD; Kessler et al., 1995); however, in service members, MDD was the most common diagnosis comorbid with PTSD (49.0%; AUD
was 26.9% [which was still less than Adjustment and GAD], Walter et al., 2018). Also, a RAND study showed that depression was the most commonly comorbid disorder with PTSD among active duty service members (56%; although it was technically behind "sleep disorders/symptoms" at 61.8%, but this was a very general category; AUD was at 16%; Hepner et al., 2016). Finally, meta-analytic findings from civilian and veteran data showed that 52% of individuals with PTSD had co-occurring depression (Rytwinski et al., 2013).

We have updated the introduction (please see page 2) to clarify this point and have updated the references. The manuscript now read as follows: "Among the psychiatric disorders, major depressive disorder is highly comorbid with PTSD (52%; Rytwinski et al., 2013) and the disorder most frequently comorbid with PTSD among active duty service members (Hepner et al., 2016; Walter et al., 2018).

2. "Those with persistent PTSD were more likely to have comorbid PTSD"
-I suggest you revise to say "comorbidities in addition to PTSD"

We have updated the manuscript to clarify this point (please see page 2).

3. "However, they do not directly address symptom change among individuals with comorbid PTSD and MDD"
-In addition to highlighting the gap in knowledge that you are trying to fill, please elaborate briefly on its importance. For example, what are the clinical implications of looking at a sample selected specifically for comorbid PTSD and MDD? What additional information will you get, over and above prior studies, which have already assessed trajectory of PTSD symptoms, and bi-directional PTSD/MDD relationships. For example, are there compelling reasons to think that PTSD trajectories should be different for those with comorbid PTSD/MDD as opposed to PTSD alone?

This is an interesting point and it is possible that trajectories for PTSD may serve as a proxy for symptom change. However, evidence suggests that those with comorbid PTSD/MDD may be different than those with only a single disorder and that impairments are greater for comorbid symptoms compared to a singular disorder alone. Given this, we were very interested in examining the pattern of symptoms among those with comorbid PTSD/MDD and have added a related statement to the introduction (please see pages 2-3):

“This is a critical limitation given that research shows the high prevalence of and greater impairment associated with comorbid PTSD and MDD, using a sample with this probable comorbidity can more accurately address fluctuations of these symptoms in this content.”

Additionally, there are only few studies that have examined the treatment of PTSD with comorbid depression among military populations (Meyer, Kimbrel, Tull, and Morissette (2011) and Stander, Thomsen, Highfill-McRoy (2014)), which suggested future efforts should focus on developing more integrated treatment approaches for comorbid PTSD/MDD and evaluating their efficacy. An interesting future question would be to examine how PTSD symptoms alone can account for the trajectory of comorbid symptoms over time.
4. You have an extensive list of covariates in your methods section. In your introduction, consider including some background describing why you selected the covariates you did for your analyses.

We chose covariates for this study based on previous research on factors associated with PTSD and MDD and have added a related statement on page 4. For the sake of brevity in the introduction, and to focus on the importance of studying PTSD/MDD we chose not to describe why we selected all of the covariates that we did. In addition to typical demographic and military characteristics, we included trauma-related factors that are predictors for PTSD and/or MDD, such as deployment/combat, childhood trauma, sexual assault, and disabling injury/illness. We also decided to adjust for numerous behavioral and physical factors that have been shown to be associated with PTSD and/or MDD, such as BMI, smoking, alcohol, sleep, social support, and bodily pain. Most of the previous work using Millennium Cohort Study data on PTSD and MDD has found associations with these same covariates, so we believed it was important to include them in this study to better understand the trajectories.

5. Were all subjects enrolled in this study when active duty? Or are some active duty and others veterans? Consider exploring possible differences in trajectories between active duty service members and veterans. If the pattern of findings is the same across both groups, I would recommend including this as a footnote.

All participants were either active duty or in Reserves/National Guard when enrolled. As would be expected, many participants separated from service during the study period. However, how to incorporate time-varying covariates (like subsequent veteran status) into LGMM models is an ongoing debate without clear, validated methods. Current methods would remove variance attributed to veteran status, rather than examine it as suggested. Prior research has used known class analyses to compare trajectories of PTSD between Millennium Cohort participants who separated from service and those that remained in service and found highly comparable trajectory shapes with an increased proportion of veterans in negative trajectories (Porter, Bonanno, Frasco, Dursa, & Boyko, 2017). Such comparisons, although interesting, are outside of the scope of the current analysis although we have included this in future directions for research.

The following sentence has been added to the discussion: “We were not able to fully assess differences in trajectories between active duty, Reservist/National Guardsmen, and veterans given changes in status over time. Given this, future studies should explore differences in trajectories between these groups.”

6. Please include some additional information on the validity of using the PCL and PHQ-8 to assess PTSD and depression diagnosis in the manner used in the present study.

We have included several references on the validity of the PCL-C and the PHQ-8 to assess diagnostic PTSD and depression. The new references included are as follows:

7. Life events - please provide the rationale for combining physical harassment, divorce, and financial stress into one categorical variable. Why was this done differently than other items for this questionnaire? Please provide rationale and/or evidence for scoring the questionnaire in this manner.

This is a good point. In our previous research of this Cohort, we have included a summary measure for stressful life events. Our use of these items is broadly based on a modified version of the Social Readjustment Rating Scale-Revised (Hobson et al. 1998), but for this paper we pulled out the traumatic items that may be considered Criterion A (“The person was exposed to: death, threatened death, actual or threatened serious injury, or actual or threatened sexual violence”) for PTSD (e.g. sexual assault, violent assault and disabling injury). The other items included in the summary life stressors measure (i.e., sexual harassment, divorce, and financial stress) that do not meet Criterion A, were then collapsed in one variable to assess and adjust for other life events that may cause life stress (as demonstrated by Hobson et al 1998).

We added the following sentences to the manuscript on page 5: “Stressful life events are broadly based on a modified version of the Social Readjustment Rating Scale-Revised [1] with items that were considered criterion A kept as separate items and those items not considered criterion A collapsed into one variable as demonstrated by others [1].”

8. You mention the PHQ alcohol abuse scale. Please spell out the full name of the scale the first time you mention it.

Thank you for catching this, we have spelled out the full name of the scale in its first use.

9. You use the PHQ and PCL as indicators of two separate diagnoses. However, some studies suggest that certain items of the PCL are non-specific and tap into general dysphoria (e.g., Marshall, Schell, &amp; Miles, 2010; Grubaugh et al., 2010). Please comment on this
limitation in your discussion, and consider describing what this might mean for the interrelation of your findings. For example, consider the possibility that these disorders move in tandem because they might represent or tap into the same underlying construct.

We appreciate the reviewer pointing this out and agree that there are many overlapping symptoms between the PCL and PHQ. Given this, we have conducted a sensitivity analysis to exclude the overlapping items and found that even with the overlapping items removed that the two trajectories move in tandem and are very similar to the trajectories with all items included. We have included more information about this sensitivity analysis in the manuscript as well as a supplementary figure to demonstrate these findings.

Furthermore, a recent study among veterans demonstrated moderate-to-high correlations between two PHQ-9 symptom clusters and four PCL-5 symptom clusters (r’s=.46-.92; Hurlocker, Vidaaurri, Cuccurullo, Maieritsch, & Franklin, 2018) which highlights the strong correlation between aspects of depression and PTSD, including those that are less topically linked than others (e.g., affective symptoms and avoidance behaviors).


10. You briefly mention the use of integrative medicine (line 38, p. 9) and multidisciplinary treatment (line 4, pg. 10), but provide no references supporting the benefits of these techniques to prevent chronicity in those with comorbid psychological conditions. Please briefly elaborate on your rationale for suggesting these as future directions of research/promising intervention techniques for this specific population, including references to prior research as needed. For example, you can provide references to support the idea that physical factors are highly modifiable with multidisciplinary treatment.

Thank you for pointing out that we did not include a reference to support our statements. There have been several studies that demonstrate the benefit of integrative medicine and multidisciplinary approaches for working with patients with comorbid PTSD/depression including research by Flory et al in 2015, Luberto et al in 2013, Libretto et al in 2015, Strachan et al in 2012, and Sornborger et al in 2017. We have included a couple of these references in the manuscript to support our statements.


11. I appreciate the thoroughness of your limitations section. For lines 4-6 (pg. 12), where you state that "both tools… have demonstrated high validity," please include references. Also ensure that the references code the measures (PHQ, PCL) in the manner you used in the present study (e.g., coding by diagnostic criteria, rather than overall cutoff scores).

We have included the following references on this statement:

12. In the strengths section, consider including the prospective nature of your design as a strength for causal inference (e.g., social support, as measured at baseline, predicts trajectory of symptoms over 15 years).

We appreciate this suggestion and state in the manuscript that the long follow up period of our study is a notable strength. We did not include statements regarding causality as that was not the main focus of the study and we feel that discussing causality in this study was not appropriate at this time given the exploratory nature of this study. However, future studies should further examine causality associated with comorbid PTSD/MDD.

Reviewer 2:
This paper addresses an important topic in the field of traumatic stress studies: longitudinal trajectories of symptom development in prospectively followed trauma-exposed patient populations. Overall, the methods are sound with the sampling frame well explicated/referenced. The choice of the PCL and PHQ-8 as screening measures for PTSD and depressive symptoms are well justified. The manuscript could benefit from some enhancements, however.
1. The literature review could be expanded to a broader discussion of the current manuscript findings in the context of the now sizable body of work relating to PTSD trajectory assessments (see Galatzer-Levy et al., Clinical Psychology Review, 2018).

Thank you for this comment. We have expanded the literature review to discuss previous work that has been done describing trajectories of PTSD over time. Specifically, we highlight the high prevalence of resilient trajectories and how this may limit the generalizability of these studies to clinical populations.

Below is what we included in the introduction on page 2:
“A growing literature has detailed heterogeneous trajectories of PTSD over time following traumatic exposure [2]. Generally, these studies have found four separate trajectories describing resilience, chronicity, recovery, and delayed onset. Resilience is the most common trajectory, particularly among military members. Previous studies have found fewer than 20% of service members categorized in all other trajectories combined [3-5]. Results from these previous studies, which include such a large proportion of resilient individuals, may mask important heterogeneity among individuals with high symptomatology. For example, in these studies, typically only one trajectory includes individuals with high symptomology at baseline. Therefore, limited information is available about potential heterogeneity among clinical populations.”

2. Specifically, the discussion could better address how the identified trajectories in the current investigation provide corroborative or discriminant trajectory classification when compared to prior prospective cohort investigations.

We have included an additional paragraph comparing and contrasting the trajectories found in the current investigation with those of previous investigations. In brief, the chronic and steady recovery trajectories from the current investigation mirror those of prior work. However, the prevalence of these trajectories was much higher and the level of symptoms across the study were higher than most prior studies. The modal trajectory in the current study was the rapid recovery trajectory which is similar to studies where the modal trajectory is resilience. Below is what was included in the discussion on pages 10 and 11 to address this comment:

“Restriction of the sample to individuals meeting criteria for probable PTSD and MDD precluded the formation of many typical classes (e.g., delayed onset, resilience) found in prior studies [2]. Rather than two trajectories (chronicity and recovery) describing individuals with high symptoms, the current study identified four different trajectories of change among individuals with probable comorbid PTSD/MDD. Additionally, even for trajectories that are similar to those found previously (i.e., chronic and gradual recovery trajectories), the level of symptoms reported in the current study was higher than in prior studies [3-5]. This suggests poorer prognoses of individuals with probable comorbid PTSD/MDD. Even within the rapid recovery trajectory, which is most comparable to resilience trajectories, participants continued to report a moderate level of symptoms across the study period. However, similar to prior studies, the proportion exhibiting this optimal trajectory was most prevalent, however, the prevalence (32%) was much lower than those exhibiting resilience in prior investigations (80%-90%) among those with and without mental health symptoms.”
3. Also, the discussion might productively be expanded to include reflection on cutting edge investigations that incorporate trajectory analyses into the secondary assessment of randomized clinical trials (see Galantzer Levy et al., PLoS One, 2013 & Osenbach et al., Psychiatry Interpersonal and Biological Processes, 2014).

Thank you for pointing us to these interesting studies. We agree that our paper benefits from including a short discussion of these findings in relation to our own. We have added a couple sentences to the discussion to incorporate these studies. In paragraph two of the discussion on page 10 we added the following sentence:

“Further, previous PTSD trajectory work has highlighted the benefit of tailoring interventions and treatment for PTSD based on the specific trajectory patterns of the individual [47, 48]. Specifically, Galantzer et al 2013 found that early treatment affected symptom remittance for those who were in the slow recovery class, but not for those in a rapid remittance trajectory [47].”

4. Finally, it appears that a major formatting error has occurred that needs to be addressed in a large subgroup of the endnote citations such that journal names have been replaced by acronyms.

Thank you for catching this mistake, we have updated the endnote citations to ensure they are all correct.