Author's response to reviews

Title: Functional and Self-Rated Health Mediate the Association between Physical Indicators of Diabetes and Depressive Symptoms

Authors:

Sylvia Boehme (sylvia.boehme@fu-berlin.de)
Christian Geiser (christian.geiser@usu.edu)
Babette Renneberg (b.renneberg@fu-berlin.de)

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Author's response to reviews: see over
Dear Prof. Margaret Maxwell,

Thank you for your evaluation and your constructive comments on our manuscript: Functional and Self-Rated Health Mediate the Association between Physical Indicators of Diabetes and Depressive Symptoms. We very much appreciated your comments. As both reviewers rated the quality of written English only as acceptable we had the language checked again. Responses are given point-by-point below in blue color and Times New Roman italics.

Editorial comments:

Reviewer 1 questions the authors evaluation of the strength and direction of the proposed relationship between Diabetes and Depression and the authors might like to clarify this (or acknowledge the literature shows a variable pattern in the direction and strength of these associations?). The comments by Reviewer 2 on the introduction might also help in this case.

Thank you for emphasizing this point. In response to your and the reviewers’ comments we are now more careful with the interpretation of the previously published work on that topic and have clarified this in the manuscript.

Reviewer:
Bhautesh Dinesh Jani

1. Background (2nd Paragraph, 4th line): Authors' state that "It has been hypothesized that depression may constitute a risk factor [e.g.,7], but there is more and stronger evidence for depression as a consequence of diabetes [e.g.,8]. Reference 7 is meta-analysis by Mezuk et al. based on 13 studies and more than 6000 patients showing 60% increased of development of type 2 Diabetes in patients with depression, so there is substantial evidence supporting this relationship. Reference 8 is another meta-analysis based on 11 studies and more than 48,000 patients showing 24% increased risk of development of depression in patients with Diabetes. Based on the references which the authors have quoted, I do not agree with authors' observation that there is more and stronger evidence for depression as a consequence of diabetes.

Thank you for this remark. We agree and are now expressing the matter more carefully. We state that the causal direction remains unclear as large meta-analyses found contradictory evidence (on page 3).

2. Background (2nd Paragraph, last line): Authors state that "While some found significant associations between depression and glycemic control [e.g., 9,10] other found no such relationship [11,12]. Reference 11 is a review by Markowitz et al. examining the efficacy of various treatment options in treatment of depression in patients with diabetes. This review does not examine the relationship between glycemic control and prevalent depressive symptoms in patients with diabetes.

This issue has been clarified in the manuscript on page 3. The review by Markowitz found mixed effects of antidepressive therapy on glycemic control in patients with diabetes and depression. Although the review does not explicitly examine the relationship between glycemic control and depressive symptoms it reports treatment effects on glycemic control in
patients with diabetes and depression. Therefore, we think it is worth citing this article on the relationship of depressive symptoms and glycemic control.

3. Methods
Depressive Symptoms: Authors state that a WHO score of < 28 is regarded as an indicator of a major depressive disorder. The authors should quote that the accuracy of the suggested cut-off i.e. <28 is 80% against SCID based on the study they have referenced. Thank you for bringing up the study from Löwe et al. (2004) that has compared three short screening instruments for depression and could show very good properties of the WHO-5. We added a statement concerning the psychometric characteristics of the WHO-5 scale found by Löwe et al. (2004) on page 6.

4. Methods
Physical Health Measures: It is unclear from the manuscript, whether authors have used HbA1C as a binary variable or a continuous variable. This needs to be clarified. In the measures’ description we now explain that HbA1c was used as a continuous variable. The path analyses, however, have been performed with HbA1c as a continuous variable.

5. Results Section: A flow chart explaining the total number of patients at the beginning of the study and patient drop-outs at various stages is required as per the STROBE statement. We added a Participants’ Flow Diagram according to the CONSORT Statement in Figure 2 and describe the analyses in the text on pages 4-5.

Minor Revisions
1. Discussion Section: This section could be potentially divided into "Summary of Findings", "Comparison with Existing Literature" and "Limitations" sub-headings. We adopted your recommendation and structured the discussion section according to your suggestion.

2. The implications of various patient drop outs should be discussed in Limitations.
In response to your suggestion we added a comment on the drop-outs and the implications on the analyses/results. We now mention that although the drop-out in our study was relatively high, this should not have affected the analyses much. This is because we used full information maximum likelihood estimation (FIML) to include all available data points. FIML is currently the state-of-the art in missing data analysis, as it allows retaining high statistical power in the presence of missing data. Furthermore, by including auxiliary variables in the analyses (e.g., the Time 1 variables in the case of longitudinal analyses), bias is reduced relative to listwise deletion or other ad hoc missing data handling strategies (see, e.g., Enders, 2011, Applied Missing Data Analysis; Guilford). In the case of our longitudinal analyses, the covariance coverage remained relatively high (most covariance coverage values in terms of the proportion of data present to estimate a given variance or covariance were in the 60 to 70% range, with only a few values falling below 50% and no values falling below 40%, indicating that there was enough information available to estimate the path coefficients reliably in our longitudinal model.

Reviewer:
Lindsay S Mayberry

Reviewer's report:
Summary
In this manuscript, the authors postulate that perceptions of health may mediate the associations between objective physical health indicators and depressive symptoms among adults with diabetes. They apply an existing conceptual framework to a large data set using path analysis to examine
associations with individual indicators of each construct and between the constructs themselves. Findings suggest that perceived health status is more strongly associated with depressive symptoms, cross-sectionally and longitudinally, and mediates the association between objective physical health and depressive symptoms. This manuscript has several substantial strengths, including the use of a theoretical framework, the analytic techniques (multiple measures and cross-sectional and longitudinal analyses), and the consistency and strength of the effects. I am especially impressed by the sensitivity analyses done on missing HbA1c values (pg. 5). This is a very strong manuscript that makes a substantial contribution. However, several areas require clarification before it is suitable for publication. My major concerns focus on the organization of the introduction and the presentation of the results. Each of these issues is described in detail below.

Major Compulsory Revisions
1. The introduction requires some reorganization and clarification. As written, the constructs are presented somewhat randomly. I recommend the authors present the framework earlier in the introduction (i.e., third paragraph) and go into more detail on the study/framework by Whitelaw & Liang (population, constructs, outcomes, findings). Then the subsequent paragraphs can focus on each construct/relationship in the proposed framework. This will help clarify why these constructs were selected for inquiry and how, specifically, your work extends Whitelaw & Liang’s. Be clearer about what problem your paper is seeking to address.

We have restructured the background section according to the suggestions of the reviewer and moved the introduction of the framework to the 3rd paragraph, so the reader learns earlier about the underlying and to be tested framework. We also added a short statement to clarify the aims of our study.

2. The analyses are one of the clear strengths of this work. However, the presentation of the analyses and results needs to be clarified in the following ways:
   a. This is my most substantial concern about the manuscript: It is unclear if the “separate indicators” of PH, FH, or depressive symptoms are loaded onto latent variables in your path models (in which case you are running structural equation models) or if you are running multiple path models in which you switch out the indicators. It should be and seems like it is the former, but there in some places it seems that you are switching the variables and running multiple models. For instance, “for predicting each of the four FH outcomes” (pg. 8) and similar sentences using “each” imply you are running several models and switching out the constructs rather than using a latent construct. I think the authors should use latent constructs and describe the loadings of each individual indicator. It is standard notation to depict latent variables with circles and the indicator variables (measured variables) with rectangles in all figures. (Note: I think it makes sense to run two models – one for each of the outcome measures because of the differences between them – but still load the PH & FH indicators onto latent variables).

Thank you for that comment. In our modeling approach, we included all measured variables (indicators/observed variables of the constructs) simultaneously in a single path analytic model (that is, we did not run separate models for different variables; we only ran separate models for the cross-sectional and longitudinal data, respectively). We did not use latent variables in the models, but instead estimated all individual paths between the measured variables separately (in a single model). Our rationale for this decision was that the indicators for the same facet (e.g., physical health) could not be assumed to be congeneric measures of a single dimension in the factor analytic sense (i.e., the measures did not show perfectly correlated true scores). Each indicator represented a distinct facet of the constructs (measured something different), thus adding incremental information and increasing the content validity and generalizability of our study. Furthermore, by analyzing all individual paths separately, we were able to show that different facets related differently to outcome measures—another indication that it would not have been reasonable to have the indicators load onto common factors/latent variables.
b. Pg. 6: Are the cross-sectional path models using only data from time 1 only or aggregated across time points. The former is preferable. This needs clarification in the first sentence of the analyses section.

Yes, the cross-sectional model used time 1 data only. This is now clarified in the manuscript on page 6.

c. On Pg. 7 there are results from ANOVAs (?) comparing all the constructs on insulin dependence. This is not described in the analyses and it is unclear why only insulin use was explored this way (why not the other covariates)?

Thanks for bringing up this matter. We found the differences between insulin- and non-insulin-dependent persons on the key measures worth reporting. You are right to indicate they may not fit into the proposed framework. We therefore removed this paragraph.

d. If the main hypothesis is that FH & SRH mediate the association between PH & depressive symptoms, indirect effects and associated confidence intervals are needed. One of the primary strengths of path analysis/structural equation modeling is deriving bootstrapped confidence intervals for indirect effects—especially for latent constructs. These should be reported.

We agree and now report the bias-corrected bootstrapped CIs for all indirect effects in Table 4.

e. The longitudinal results are too dense and difficult to read. I recommend only highlighting how these results were consistent with/diverged from your main hypotheses and associated findings from the cross-sectional analysis. Possible the other results could be featured in an online appendix for those who are interested.

We’ve shortened the longitudinal results section and added a document for the appendix containing a table and presentation of the longitudinal results.

Minor Essential Revisions

3. I recommend changing the title to “Depressive Symptoms” instead of “Depression” to be more accurate.

We’ve changed the title to depressive symptoms as this matches the terminology within the manuscript.

4. Please avoid describing patients as “suffering from diabetes” but rather simply state “persons with diabetes.”

We’ve also changed that.

5. Pg. 4 – the German health company randomly selected participants from what pool?

The participants have been selected from a pool of all insurants meeting the mentioned criteria. We’ve clarified that in the manuscript on page 4.

6. Move this sentence (pg. 8 “In terms of the measures of PH, the path coefficients...”) up to the paragraph under “Insert Fig. 2a here.” This supports the assertion that the indicators of FH were the strongest predictors of SRH—as written, there is no evidence to support that claim in the referenced figure or the paragraph.

The sentence describes the non-significant associations of the PH indicators with the final outcome measures (depressive symptoms) that are only displayed in figure 2c. We therefore left this sentence beyond figure 2c to explain the figure to the reader. And we added a short comment on page 9 to interpret this finding.

7. The figure names do not match between the text and figures for 2b and 2c.
We thank the reviewer for her careful reading. The mistakes have been corrected.

8. Sentences/paragraphs that need revision:
   a. Pg. 5, “Furthermore, participants insulin-dependence...height.”
   We have corrected the sentence as follows: “Furthermore, participants reported their insulin-dependence, weight and height.”
   
   b. What is meant by these sentences? Can they be deleted? Pg. 6, “According to the proposed model depressive symptoms are regarded as a distal outcome. Therefore anxiety/depression was used as an outcome variable.”
   We want to make clear that anxiety/depression is originally a subscale of the EQ-5D (that is used as a FH indicator in the analyses). But we used this specific subscale not as predictor but as outcome to avoid predicting depressive symptoms with depressive symptoms. We’ve revised the sentence and clarified its meaning as follows: “According to the proposed model depressive symptoms are regarded as the distal outcome. Therefore the anxiety/depression subscale of the EQ-5D was used as an outcome variable instead of a predictor variable in terms of functional health.”
   
   c. The ethical approval paragraph needs revision for clear language and grammar.
   We have revised grammar in this paragraph.
   
   d. This paragraph is very unclear, pg. 11-12 “There have been few approaches...”
   This paragraph aims at presenting approaches originated in health and clinical psychology to address perceived impairment in patients with diabetes. Goal is to give ideas on the contents of future programs for persons with diabetes or practitioners in this field. We have revised the paragraph and clarified the objective.

9. Why is there a discrepancy in this notation: sometimes “beta = coefficient” and sometimes “beta > coefficient”?
   If more than one beta is referred to, we report only the smallest value by writing $\beta_x$. If only one beta is referred to we report the exact value $\beta=x$.

10. Some of the limitations mentioned seem tangential/unrelated to the findings (e.g., results not applying to non-clinically diagnosed diabetics—why might that matter?), whereas other more substantial issues are not mentioned. For instance, what about the disproportional number of men in the sample? What about using self-reported HbA1C levels—might results be different with lab values? The authors made great points about the potential for shared method bias.
   We refer to whether the diabetes diagnosis is known or not because persons with diagnosed diabetes know about their diagnosis, are consequently more likely to be treated for their diabetes and might therefore differ in the health aspects (SRH, FH, depressive symptoms) that have been analyzed in our study. We can only suspect how much knowing about a certain disease affects health behavior and perception. This is now elaborated in the manuscript.

11. Pg. 10 “As expected, the participants in our study showed a significantly higher level of depressive symptoms as compared to the general population.” This needs citations and comparisons—what is the rate in the general population vs. the sample rate?
   We added the general population rate of the WHO-5 reported by Bech et al. (2003).

Discretionary Revisions
12. Personally, I would have preferred to see the entire model in a single figure instead of broken into three separate figures.
   See Point 2 of the Major Revisions Section.