Author’s response to reviews

Title: Type D personality is a predictor of prolonged acute brain dysfunction (delirium/coma) after cardiovascular surgery

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Responses to reviewers

REVIEWERS’ COMMENTS and RESPONSES:

Editor Comments:

You will see from the reviewers' comments that they welcome the changes you made in your revised manuscript and feel the manuscript is improved, but some important issues do remain. The reviewers have provided extremely thorough and useful comments on your manuscript. I look forward to receiving a revised version of the manuscript which addresses these comments.
In my view, one issue that still needs to be resolved is highlighted by Reviewer 1 and concerns conducting an analysis based on the continuous conceptualisation of Type D, using interaction of NA x SI (note that this is different to the additive approach that you presented in your previous manuscript). For completeness, and in line with some recently conducted studies, I would recommend that this continuous analysis would be a useful addition to your results section. Please ensure that you address this and the reviewers other comments in a revision.

To the Editor

Thank you for your continuous help for this study. We have revised the manuscript in accordance with reviewer suggestions.

To Reviewer #1

Dear Dr. Michael Smith

I appreciate your kind response and my response to each comment is below.

Reviewer reports:

Michael Smith (Reviewer 1): Thank you for once again giving me the opportunity to review this manuscript. As previously stated, and in agreement with the other reviewer, I find the premise of the paper to be a very good. It makes a novel contribution to the literature, and appears to be methodologically sound in terms of the thoroughness of the data collection.

In my first review of the manuscript, I requested that the authors undertake an analysis based upon the continuous conceptualisation of Type D personality (and provided this reference for guidance: Stevenson & Williams, 2014, Psychology & Health). In a subsequent revision, the authors did this, but chose to use a conceptualisation which involved summing together NA and SI (as suggested by Horwood & Anglim, 2017), rather than the NAxSI interaction. While, in my view, the 'additive' approach is a is a less satisfactory approach to conceptualising Type D personality than the 'interaction' approach (for the reasons highlighted by the other reviewer in the most recent round of revisions), I was content with the approach taken, given that it was based upon a recently published suggestion as to how this construct should be conceptualised. However, I now note that the authors have abandoned all analyses based on the continuous Type D construct, and instead just include NA and SI in separate regression models. Perhaps this is because of the other reviewer's suggestion to delete Table 3 from the manuscript. I don't want to provide any advice which is contradictory to suggestions from the other reviewer, but I am of the view that it is important to include an analysis based upon the continuous conceptualisation of
Type D personality (preferably the NA×SI interaction term, which would also allay the concerns of the other reviewer regarding the 'additive' conceptualisation).

Answer for the comment: I really appreciate your insightful comment. As per your recommendation, we have added the analysis of NA×SI interaction modeling (Table 4).

Another concern I have with the latest version is with the incorporation of the mediation analyses. In the last round of reviews when I stated "Page 20, lines 5-6 should be reworded, as they imply that mediation was observed, when no such analysis was performed" - I didn't necessarily intend that the authors conduct and include mediation analyses in the manuscript. I was just requesting that the authors modify their interpretation of the findings, which incorrectly implied mediation. The mediation analysis now comes as a bit of a surprise in the Results section, as seemingly no rationale for conducting such an analysis is provided in the Introduction. The authors should therefore either remove the mediation analysis and reconsider their interpretation of the findings in the Discussion, or provide a rationale for including a mediation analysis in the Introduction. If the latter, it needs to be very clear how and why depression should be considered both a mediator and a moderator of the relationship between Type D personality and DCDs.

Answer for the comment: Thank you for your comment about this issue. We have added parts to the introduction about interaction modeling.

One of my comments on the previous version of the manuscript has still not been fully resolved: "Throughout the Discussion, including in the Conclusions paragraph the authors refer to 'Type D personality-associated depressive symptoms'. I'm not sure that this accurately captures what the data are telling us. The interaction between Type D and depression is indicating that the effect of Type D personality on DCFDs is being moderated by depressive symptoms, whereby, depressive symptoms in the presence of Type D personality inflate the Type D effect on DCFDs." This finding is interpreted correctly in the Results section: "Depressive symptoms can therefore be said to have an additive deleterious effect on DCFDs when combined with Type D personality." However, on several occasions this finding is still not correctly described/interpreted in the Discussion section - please rectify.

Answer for the comment: Thank you for your insightful comment for this part. We agree with your opinion that depressive symptoms in the presence of Type D personality inflate the Type D effect on DCDs. We rechecked the discussion part and modified the discussion and conclusion to better reflect this.
Johan Denollet (Reviewer 3): The authors have been very responsive to the reviewers' comments, and the paper has been much improved. However, there still is some room for further improvement, as indicated by my comments and suggestions.

Abstract, paragraph on Results.

On p. 2, last line, the authors state that: "Based on multivariate analysis, Type D personality significantly increase DCDs …". I think it is important to make clear to the reader which variables were included in the multivariate model. Perhaps, the authors could change this sentence as follows:

"Multivariate analysis showed that Type D personality was significantly associated with increased DCDs (OR:2.8, 95%CI:1.3–6.1), after adjustment for depressive symptoms and clinical variables."

Also, I would suggest the authors to slightly rephrase the last 4 lines in the results section of the Abstract as follows:

"Additionally, there was a significant Type D x depression interaction effect (OR:1.7, 95% CI:1.2–2.2), and depressive symptoms were associated with DCDs in Type D patients, but not in non-Type D patients. Mediation modeling showed that depressive symptoms partially mediated the association of Type D personality with DCDs (Aroian test =0.04)."

Answer for the comment: Thank you so much for your kind comment and showing each step. We rephrased the results within the abstract.

Text, Results, Regression model, page 14 (lines 2-7).

The authors state that Type D personality, depression, mSOFA, benzodiazepine and propofol were associated with significantly decreased DCDs (Table 2). However, all of these factors were associated with INCREASED (not decreased) DCDs. Please correct.

Also, they mention in the next sentence that: "Increase in DCDs would have indicated that the factors alone would worsen conscious states in the 7-day post-operative period." This line doesn't run, please rephrase as follows:

"This indicates that these factors were independently associated with prolonged acute brain dysfunction in the 7-day post-operative period."

Results, Table 2, p. 15

In the title of Table 2, the word 'free' needs to be removed:
"Regression model for prolonged delirium/coma [free] days".

In Table 2, the authors report that the 95% CI for Type D personality in model 2 was (1.5-1.0). However, the upper CI cannot be 1.0, and should at least be >2.4. Please correct.

Answer for the comment: Thank you for pointing out this mistake. We corrected the sentence.

Results, Interaction, p. 17

I would suggest to change the heading "Interaction" (p. 17, first line) by the heading "Moderator model".

The significant Type D X depression interaction effect indicates that Type D personality, as a stable disposition, moderated the association of depressive symptoms with prolonged brain dysfunction. This is also clearly presented in Figure 3: depressive symptoms were only associated with prolonged brain dysfunction in Type D patients, but depressive symptoms were not associated with brain dysfunction in non-Type D patients.

The authors now state that: "The presence of depressive symptoms therefore had a significant effect on DCDs between Type D personality patients versus non-Type D personality (Figure 3). Depressive symptoms can therefore be said to have an additive deleterious effect on DCFDs when combined with Type D personality" (page 17, lines 5-8).

I would like to suggest to modify this statement as follows:

"This interaction effect indicates that Type D personality moderated the association of depressive symptoms with DCFDs; i.e., depressive symptoms had a deleterious effect in terms of prolonged brain dysfunction among Type D patients, but depressive symptoms were not associated with DCFDs in non-Type D patients (Figure 3)."

Answer for the comment: Thank you for showing the modifications so clearly. We have changed this part of the manuscript in accordance with the suggestion.

Figure 3.

The title of Figure 3 (Depressive symptom's interaction for delirium/coma days) is not very informative. Consider changing the title to:

"Association of depressive symptoms with prolonged brain dysfunction, stratified by Type D personality".
The labels on the left side of this figure are a bit misleading. Now it looks like the first two graphs in the forest plot represent the effects of Type D personality. However, what they actually do represent is the effect of depressive symptoms, stratified by Type D personality.

Hence, the following labels would be more informative:

"Depressive symptoms in Type D patients"
"Depressive symptoms in non-Type D patients"
"Depressive symptoms in the total sample"

Figure 4 legends, p. 19 (lines 1-2).

What the figure 4 shows is the mediation effect of depressive symptoms, but not the mediation effect of Type D personality. Hence, the legend of Figure 4 could be something like:

"The mediation effect of depressive symptoms regarding the association of Type D personality with DCDs, adjusted for the same covariates used in regression modeling."

Answer for the comment: Thank you for your suggestion. Your advised explanation is more informative, so we changed the title and labels.

Discussion.

Please discuss the finding that depressive symptoms were associated with prolonged brain dysfunction among Type D patients, but not among non-Type D patients.

Answer for the comment: Thank you for pointing out for this part, we added a discussion of the association of depressive symptoms and prolonged brain dysfunction among Type D patients.

Discussion, page 21 (lines 11-13).

The author state that: "… has reported that Type D personality is associated with decreased endothelial progenitor cells in a large, population-based study [52] and a recent study showed that this association was robust across time[53]." However, reference [52] reports findings of a study in patients with heart failure (and not a large, population-based study), and reference [53] reports on the association of Type D personality with endothelial dysfunction (and not endothelial progenitor cells) in patients with coronary artery disease. Hence, this statement should be corrected along these lines:
"… has reported that Type D personality is associated with decreased endothelial progenitor cells in patients with heart failure [52] and a recent study in patients with coronary artery disease showed that the association of Type D personality with endothelial dysfunction was robust across time[53]."

Answer for the comment: Thank you for showing the way of thinking. We changed part of the manuscript.

References

I still noticed some inaccuracies in the reference list.

Ref. #16. The correct authorship of this paper is: Denollet J, Sys SU, Stroobant N, Rombouts H, Gillebert TC, Brutsaert DL.

Ref. #33 does not include the Journal name.

Answer for the comment: Thank you for pointing out these mistakes and we apologize for them. They have been corrected.