Author's response to reviews

Title: Personality dimensions of schizophrenia patients compared to control subjects by gender and the relationship with illness severity

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Author's response to reviews: see over
Alice Murray,
Executive Editor of BMC Psychiatry

Dear editor,

Please find, attached, the revised manuscript Ref. MS: 1246219175110940, “Personality dimensions of schizophrenia patients compared to control subjects by gender and the relationship with illness severity,” by Carmen Miralles et al.

In this revised version, we have taken into account all of the comments suggested by the reviewers. Our responses are itemized on the accompanying sheets, and where necessary, we have made the appropriate changes in the text.

We hope that the revised version of the manuscript meets the requirements for inclusion in BMC Psychiatry.

Sincerely yours,

Lourdes Martorell, PhD
Responses to the reviewers’ comments

Reviewer #4 (Jen Vohs) Comments to Author

Summary
The present investigation aimed to identify the differences between personality dimensions of schizophrenia patients and healthy control subjects by gender. Miralles et al. also sought to explore the gender-dependent relationships between personality dimensions and illness severity variables. Temperament and Character Inventory-Revised dimensions were compared by gender between 161 schizophrenia patients and 214 healthy controls from a population-based sample. Correlations and regression analysis was then implemented in order to examine the relationships among personality dimensions and illness severity variables. The findings suggested that male and female schizophrenia patients have specific personality profiles and that the relationship between personality dimensions and illness severity depends on gender.

General Comments: This study addresses the unique issue of characterizing personality characteristics and gender effects in psychotic illness. The authors of this study have been generally thoughtful in the design and execution of this study. It is this reviewer’s impression that the study is of value and should be considered for publication in BMC Psychiatry, with Revisions (see below).

MINOR REVISIONS

1. Are the data sound and well controlled?
Data seem well controlled as persons in the patient and control groups were selected carefully. The way in which diagnoses were determined seems rather ‘loose’ at first glance. While diagnoses were determined based on DSM IV criteria, a diagnostic instrument (SCAN) was only used on those patients who had been admitted for shorter than a six-month duration. While this makes sense (given you can clinically gain a great deal of dx info about a patient over a 6 mo period), further explanation for this decision may be helpful to make this decision seem more sound to less clinically sophisticated readers.

Response to the reviewer: We considered clinical judgment by two independent psychiatrists after a six-month period of being admitted to the hospital as appropriate to ensure that patients had a reliable diagnosis of schizophrenia. However, for those
patients who were admitted for only a short period of time, including those who had their first contact with our institution, we considered it better to confirm the diagnosis using a validated diagnostic instrument. This is now better explained on page 8, lines 14-19.

2. **Can the writing, organization, tables and figures be improved?**

The present manuscript is well written, with adequate grammar, spelling, and organization. There are a few typos that need to be corrected. The authors should review carefully and correct. The authors should ensure their formatting is appropriate for BMC Psychiatry.

**Response to the reviewer:** We have reviewed the typographic errors throughout the manuscript and have also made some minor changes to ensure that the format is appropriate for *BMC Psychiatry*; for example: 1) we removed the shaded areas in Table 1 (page 20); 2) we added the volumes and page numbers to references 7 and 8, and 3) we removed incorrect information provided in reference 27.

Table 1. Would it make more sense to spell out the reference / citation rather than use the number, in order to improve the ease for the reader?

**Response to the reviewer:** We agree with the reviewer, and in the revised version of the manuscript, the first author of the reference and year of publication have been added to the citation number; see page 20.

Table 2/Figure 1. It seems that Table 2 and Figure 1 provide very similar information. Is the figure really necessary?

**Response to the reviewer:** We agree with your observation that Table 2 (corresponding to Table 3 in the new version of the manuscript) and Figure 1 provide similar information. However, the figure, in addition to graphically depicting the differences, further demonstrates differences between male and female subjects in the control group that would be difficult to capture in the table. We feel that these differences are very interesting and are important to highlight for readers. In fact, the differences according to gender in the control group are the reason for stratifying the sample by gender. Therefore, Figure 1 is maintained in the new version of the manuscript. We have slightly moved the bars corresponding to significant differences between male and female control subjects to better display the results.
Furthermore, we now emphasize that the differences in HA, RD, and C between male and female controls are statistically significant; see page 11, lines 6-8 in the results section and page 13, lines 3-5 in the discussion.

In the abstract – further comment on the importance of the conclusions should be considered. The reader is left wondering, “what about this profile would be meaningful to anyone except a personality researcher?”

Response to the reviewer: In the new version, we describe the main characteristics of the personality profiles for schizophrenia patients, emphasizing those that are more prominent in male patients and those that are more prominent in female patients. Page 3 and 4, lines 23-26 and 1-2, respectively.

A few of the reference (11, 12 for example) are more than a decade old. While these were clearly valuable additions to the lit – if available please list more recent data backing your arguments in the introduction.

Response to the reviewer: We replaced the previous references to Salem and Kring 1998 and Leng and Chue 2000, regarding gender differences in schizophrenia, with the following more recent references:


Accordingly, some minor changes have been introduced in the text; see page 6, lines 19-24.

From the introduction – the reader is left wondering why he should continue reading? May consider revision such that the reasons (besides that simply “studies considering gender differences are scarce”) are clearly and concretely spelled out to the reader.

Response to the reviewer: We now clarify the reasons for conducting the study and the objectives; see page 7, lines 19-24.
MAJOR REVISIONS

3. Are the methods appropriate and well described, and are sufficient details provided to allow others to evaluate and/or replicate the work?
Something that really seems problematic throughout this article is that lack of articulation of what we’re actually testing. Careful definition of each personality characteristic (described briefly in the discussion only?) would enable the reader to not only be more interested, but also better understand the importance of the study. In its present form – this paper is written for personality researchers whom are very familiar with that specific focus. To satisfy the scope of BMC Psychiatry – a more broad and thorough approach would be helpful.

Response to the reviewer: In the revised manuscript, we now define the nature of each personality dimension in the introduction. We have also attempted to articulate the results of the study explaining the personality characteristics of the subjects depending on their high or low scores in the TCI-R dimensions. See page 3, lines 23-26 and page 4, lines 1-2 in the abstract; page 5, lines 25-26 and page 6 lines 1-9 in the background section; and page 13, lines 16-20; page 14, lines 23-25; page 15, lines 6-9.

4. Is the interpretation (discussion and conclusion) well balanced and supported by the data?
The discussion provided a nice summary of the study. Generally, the interpretation of the results was reasonable. However, an exception to this falls toward the end of the discussion when the authors make the argument that the findings are important separately due to gender and personality (relating this to other clinical condition) but fail to integrate how exactly this would be useful given the way the data were analyzed here. Further explanation is needed if the authors wish to maintain this argument. Generally speaking, the discussion lacks context and does not highlight why this finding should be clinically exciting to anyone outside the field of study related to psychosis and personality. It was not explicitly put forth how this ms. will serve to move the general study of schizophrenia forward. It is this reviewer’s impression the discussion can be made stronger through revision – specifically widening the discussion of ‘how this fits into what is already known’ and most importantly, ‘how this will be useful for moving the field and clinical care forward’.
Response to the reviewer: We agree that this part was confusing, and we now mention that we stratified the sample by gender because the male and female control subjects differed in some of the personality dimensions. We now note that our results support the consideration of gender in future studies of personality dimensions; however, we do not advocate that future studies should always stratify the sample, as the appropriateness of such a strategy will depend on the objectives of each study. Moreover, we have added a new reference regarding gender differences in the implication of personality in depression; see page 16, lines 9-14.

5. Is the question posed original, important and well defined?
While the authors have clearly identified a niche within the literature, their question is not clearly defined because the personality constructs that are the focus (dependent variables) of the study are not operationally defined. This makes it difficult to determine the value of the study overall.

Response to the reviewer: In the revised manuscript, we have defined the characteristics of the personality dimensions and the clinical implications that relate personality dimensions to the severity of illness according to gender. We believe that the value of the study has been improved; see page 5, lines 25-26 and page 6, lines 1-9 in the background section, and page 17, lines 7-15.

6. What are the strengths and weaknesses of the methods?
A strength of the methods as written is the use of a well established tool. However, validity and reliability need to be clarified. Also - only one method of data collection on personality was collected, despite the clear focus on personality in this ms. This should, at minimum, be mentioned as a limitation in the discussion. May want to comment in the introduction or methods about choosing the dimensional rather that categorical approach: It seems to be a strength.

Response to the reviewer: We agree with the reviewer that the psychometric properties of the TCI-R should be clarified. They are now discussed on page 10, lines 4-5. We also now describe as a limitation the use of only one questionnaire; however, we emphasize that the TCI-R presents a strong correlation with the PSY-5, page 16, lines 19-21. As the reviewer suggested, we now comment on the dimensional models versus the categorical models, and we have noted that dimensional models are the
7. **Statistical Consideration?**

In looking at Table 2, it seems possible that the same information from your multiple t-test comparisons could be gained with a GLM Multivariate Analysis of Variance? If you did choose this method, you could get not only main effects of Diagnosis and Gender but also determine any possible interaction effects as well. Then a series of post-hoc (Bonferroni perhaps) tests could further distinguish groups. This analysis could potentially provide a much more thorough characterization of your data.

**Response to the reviewer:** Because we determined that male and female control subjects differ in HA, RD, and C, we decided to stratify the sample by gender. Because of this reviewer suggested conducting a General Linear Model Multivariate Analysis of Variance, we performed these analyses for HA and RD. However, the model failed to identify any interaction between diagnosis and gender; further, gender differences were not identified, likely because four distinct groups in the comparisons are established.

8. **Are there any ethical or competing interests issues you would like to raise?**

No
Reviewer #2 (Bethany Leonhardt) Comments to Author

Major Compulsory revisions:
1. The authors name what each of the personality dimensions are in the beginning, but do not offer explanations of what each facet is. While it may seem obvious what each component is referring to, there are numerous ways these titles could be interpreted, and if readers are unfamiliar with the TCI they may not know what each scale is really measuring and be able to imagine how these factors impact outcomes for individuals with schizophrenia. It would be helpful to include such descriptions in the beginning of the article.

Response to the reviewer: We agree with the comment of this reviewer (coinciding with the other reviewers). It is better to provide a brief explanation for each personality dimension in the introduction section to provide a better description of what they refer to and to meet the scope of BMC Psychiatry. Page 5 lines 25-26 and page 6 lines 1-9.

2. On a similar note to point 1, it would be helpful to summarize the profiles the authors found for each sex in the discussion section. It would be helpful for clinicians working with individuals with schizophrenia if each profile were described and then the different correlational items noted. For example, including something such as "males with schizophrenia tend to be high in (trait), which describes someone who is .... this has also been shown to be correlated with higher rates of hospitalization, etc.

Response to the reviewer: The new version of the manuscript incorporates a paragraph including information about the personality profiles for male and female schizophrenia patients in the abstract, page 3 lines 23-26 and page 4 lines 1-2, and throughout the discussion, page 13 lines 16-20, page 14 lines 23-25, and page 15 lines 6-9.

3. The authors use the term "gender" throughout the article, however, gender is often thought to be a social construct or identity that individuals make for and identify themselves. It seems that the authors are looking at differences amongst the sexes (a more biological concept than gender) and thus language should be changed accordingly or the authors need to identify earlier on in the paper what they are meaning by using the term gender.
**Response to the reviewer:** We agree that gender concept refers to the complex interaction between biological, psychological, and social variables, and therefore, in the new version of the manuscript, we have clarified that the meaning of gender in the study is male or female sex; see page 9, line 19.

**Minor Essential Revisions:**

1. I would suggest making a second paragraph toward the end of page 12 that deals specifically with treatment outcomes and these personality profiles the authors have identified. This seems like a particularly important element of the paper and should be highlighted and easy to identify. It may be helpful to include a heading.

**Response to the reviewer:** We have divided the discussion into four sections in the new version of the manuscript. In the conclusion section, clinical implications regarding the personality traits in schizophrenia patients are mentioned.

**No Discretionary Revisions noted.**
Reviewer #3 (Lindy-Lou N Boyette) Comments to Author

Review of ‘Personality dimensions of schizophrenia patients compared to control subjects by gender and the relationship with illness severity. This manuscript addresses two interesting subjects: personality and gender in schizophrenia. Both subjects, and their combination, merit greater attention in schizophrenia research. However, I have some concerns and questions, mainly regarding the choice of analyses and the support of the current data to the conclusions.

Major Compulsory Revisions:

The authors declare that male and female schizophrenia patients may have specific personality profiles. If I understand correctly, they base this on their findings that differences with controls ‘were more significant’ for HA for males and for RD for females. This is confusing because of several reasons. 1) How does this fit with the authors’ conclusion that no differences in personality dimensions were found between males and females within the patient group?

Response to the reviewer: We do not agree that a conclusion of the study is that no differences in personality dimensions were found between males and females within the patient group because the objective of the study was to compare schizophrenia patients and control subjects by gender. This sentence was included at the end of the results section to provide complementary descriptive information to readers, however the results section has been restructured for clarity.

2) Did the authors test their finding that differences in HA and RD are ‘more significant’? If so, in what manner? I assume that the authors are aware that simply saying that a p level is more or less significant than another p level in another group cannot lead to any conclusions regarding differences between the groups. For instance, simply different number of subjects might influence a p level.

Response to the reviewer: We agree with this comment, and we now note that the differences in HA and RD were larger and more significant in males and females, respectively, because of the large differences between the means. This information is now provided in Table 3 (page 23). These large differences coincide with the most significant p values. Notably, higher RD mean differences were identified in female
group, although the number of female subjects compared was lower than the number of males compared.

3) If tested, -based on Figure 1- why did they conclude this for HA and RD, but not for C?

Response to the reviewer: We reached this conclusion because the mean differences between the controls and schizophrenia subjects were similar in the male and female groups (9.1 and 9.3, respectively), as shown in Table 3; see page 23.

4) Finally, whether or not the authors acknowledge statistical significance of differences in HA for males and RD for females remains unclear. First, they declare (correctly since they set alpha level at 0.05, see Statistics paragraph) that for both genders differences in HA and RD between patients and controls are statistically significant (HA females p=0.015 and RD males p=0.011, Table 2). They then, summarizing, state that males have high scores for HA and ST and low scores for SD and C, whereas females have high scores for ST and low scores for RD, SD and C, by which I assume they actually mean higher/lower scores compared to the control counterparts, and by which the authors suddenly seem to suggest that male patients do not have different scores for RD and female patients do not have different scores for HA compared to their control counterparts, since these scales are not mentioned. This, however, does not match with their earlier statements and with the results presented in Table 2. Please explain.

Response to the reviewer: We have modified the first paragraph of the results to provide a better explanation. Additionally, Table 3 (previously Table 2) highlights the greater differences identified in the study; see page 23.

The authors should elaborate in the Background paragraph on what they see as the advantages of independent analyses for gender compared to treating gender as a covariate. It’s not clear to me what the advantages could be; and, also, it seems to me that some of the conclusions from the present study are more fitting for analyses in which gender is entered as a covariate. F.e. the conclusion that ‘the relation between personality dimensions and illness severity depends on gender’ would be more robust if the authors had conducted, depending on their hypothesis, mediation analyses or moderation analyses. The latter would also be more in concurrence with the meta-
analysis reference, cited in the Discussion, which found gender to be a moderator of HA (reference number 7).

**Response to the reviewer:** We conducted stratified analyses by gender because the male and female control subjects differed in HA (91.8 in males versus 98.1 in females), RD (104.0 in males versus 113.8 in females), and C (141.0 in males versus 136.6 in females). We agree that gender could be considered either as a main factor or a moderating factor. However, we wanted the present study to reflect that personality dimensions in male and female schizophrenia patients are different from those of healthy male and female subjects; the large differences that we identified were due to the independent analyses performed by gender because the healthy male and female controls indeed presented differences in three of the seven personality dimensions. Either mediation or moderation analysis could have been conducted, but the objective of the study was not to moderate the effect of gender but to enhance its effect.

No information was given on the psychometric properties of the TCI-R in schizophrenia patients. F.e. are the reliability and factor structure of the TCI-R in schizophrenia patients comparable to healthy controls? Are the TCI-R scales stable over time, despite fluctuations in psychotic symptom severity?

**Response to the reviewer:** Reliability and the factor structure of the TCI-R have not been assessed in schizophrenia patients, and therefore, we cannot affirm that it is comparable to healthy controls. However, the TCI-R has been used in distinct populations and distinct clinical conditions, and its factor structure has been replicated. Ideally, the stability of the TCI-R over time should be assessed to determine whether fluctuations in symptomatology involve changes in personality dimensions; however we mentioned that only clinically stable patients participated in the study.

Was psychotic symptom severity (positive symptoms, negative symptoms and cognitive deficits/disorganization) assessed in patients? The authors state in the Background paragraph that ‘... males consistently have more negative symptoms and cognitive deficits ...’. In the Participants paragraph they state the patients to be ‘clinically stable’. Does that mean that all participating patients have no positive or negative symptoms and no cognitive deficits? This is relevant, since symptom severity may influence the relation between gender and clinical outcome- and also perhaps the TCI-R scores.
Response to the reviewer: Unfortunately, symptom severity was not assessed in the present study. This is now mentioned as a limitation of the study; see page 16, lines 21-24. In the new version of the manuscript, the references regarding gender differences in schizophrenia have been changed, we now only note that males consistently present more negative symptoms than females, as the new references did not discuss regarding cognitive deficits.

When we wrote “clinically stable”, we meant to refer to patients who are in the stable phase of the disease. They could present psychotic symptoms but to a lesser extent than those observed in the acute phase. Therefore, patients presenting major psychopathological symptoms or severe cognitive deficits were not able to take part in the study. This is mentioned at page 9 lines 1-2.

What would be the clinical relevance of assessing the TCI-R in patients who are (already) frequently admitted to a psychiatric hospital and male patients who attempt suicide?

Response to the reviewer: We now note that male and female patients who are frequently admitted to psychiatric hospitals and male patients who attempt suicide should be evaluated regarding their personality traits to focus efforts on educating and supporting patients presenting this high risk. Furthermore, exploring personality traits in male and female schizophrenia patients may be helpful in identifying at-risk patients for hospital admission or attempted suicide. See page 17, lines 9-15.

-No limitations of the current study are mentioned.

Response to the reviewer: In the new version of the manuscript, a section corresponding to the limitations of the study has been included; see page 16, lines 16-24.

Minor Essential Revisions:

In general, more specifics in the text regarding who is being compared to who would help greatly in readability.

Response to the reviewer: We now better described the subjects that are being compared, particularly in the results section.
Clinical outcome in this study is age of disease onset, number of suicide attempts and number of admissions to a psychiatric hospital. What period of time was set for the assessment of the latter two variables? Previous year, lifetime?

**Response to the reviewer:** The number of suicide attempts and the number of admissions to psychiatric hospitals were lifetime variables. This is now mentioned; see page 9, lines 20-24.

**Discretionary Revisions:**

The TCI-R was administered by clinical psychologists to the patients and was self-administered for controls. What was the exact involvement of the clinical psychologists?

**Response to the reviewer:** Clinical psychologists administered the TCI-R to avoid comprehension problems or attention bias during completion of the questionnaire. This is now mentioned; see page 10, lines 5-7.
Reviewer #1 (Sune Bo) Comments to Author

Generally:
A very interesting study focusing on the role of personality in schizophrenia, and furthermore with a focus on gender-differences.
The article is well written and displays some very interesting findings for the field. However, there needs to be done some (primarily) structural changes before the publication of the article:

Background:
In the introduction it should be stated more clearly, that personality and personality traits are both used to underline precursors for later development of schizophrenia, as well as how certain personality traits and personality pathology influence the development of the illness.

Response to the reviewer: We agree with the reviewer, and in the new version of the manuscript, we indicate that personality can modulate both the expression and course of illness as well as influence the onset of illness. Page 5 lines 2-5.

(Minor Essential Revisions)
It is stated that: “Most of the alternative models...”. What is meant by alternative models? Section three of the DSM-5 uses the PID-5 instrument as a way to measure personality pathology, and is not considered alternative.

Response to the reviewer: We agree that the DSM-5 clearly indicates the use of the PID-5. Consequently, we have removed the concept of alternative models and now mention only the PID-5 instrument in the background section. Page 5 lines 16-19.

(Minor Essential Revisions)
It would be appropriate with a short distinction between the categorically based personality pathology diagnostics inherit in the DSM-system and the more dimensional way of operationalizing personality as represented in the different trait-models used in the literature (including the TCI).

Response to the reviewer: We now briefly mention the distinct aspects of categorical versus dimensional models. Page 5 lines 12-16.
In the section describing differences between males and females, do mention the study by Abu-Akel, Ahmad (2013) (Superior Mentalizing Abilities of Female Patients with Schizophrenia.” Psychiatry research) to highlight gender differences in relation to more functional measures.

**Response to the reviewer:** We now mention this interesting study of Abu-Akel 2013. Page 6 line 24.

It is mentioned towards the end of the section that no prior studies have looked at personality traits in schizophrenia and hospital admission. That is correct (to my knowledge), but the subject hospital admission has not been introduced elsewhere in the background section and needs further introduction.

**Response to reviewers:** We now provide more information regarding the hospital admission due to schizophrenia in the background section. Page 7 lines 11-16.

Methods

Study design:
This section needs to be better structured (Major Compulsory Revisions). Inclusion and exclusion criteria. Is it cross-sectional study design/naturalistic etc.?

**Response to the reviewer:** We now include more information regarding the inclusion criteria for both the patient and the control groups; see page 8 line 26 and page 9 lines 1-12. We also now mention that the study was cross-sectional; see page 8, line 3.

Participants:
How was the recruitment procedure? (Major Compulsory Revisions)

**Response to the reviewer:** Information about the recruitment procedure for patients and controls is included; see page 9 lines 4-6 and lines 12-15.

After the section describing the participants, I recommend a measure section, describing ALL the measures used in this study (Minor Essential Revisions)
Response to the reviewer: We have introduced the section “Study variables” after the “Participants” section; see page 9, lines 18-26.

Statistics
This section can be reduced – it most be taken for granted that most readers are familiar with the statistics used in this study (Minor Essential Revisions)

Response to the reviewer: We have removed the phrase “We tested for variable normality using the Kolmogorov-Smirnoff test”, as this is the obvious test for assessing normality. We also introduced minor changes to reduce the length of the section. When doing so, however, we considered that readers could be interested in knowing whether the variables were normally distributed.

Basic socio- and clinical demographic results lack (age, mean scores for clinical measures etc.) (Major Compulsory Revisions)

Response to the reviewer: We have introduced Table 2, which presents the basic socio- and clinical demographic data of the participants. See page 22.

Discussion
Generally, this section needs to be better structured. First, results regarding gender differences in the control group are mentioned and then the results looking at gender differences between the control and the patient group. It would provide a better overview of the results from this study if a clearer distinction was made between the different results found. (Minor Essential Revisions). Most importantly, it seems there is a general lack of intending to explain these findings, why is it that male and female have different profiles? (Major Compulsory Revisions)

Response to the reviewer: We agree with the reviewer and believe it is better to present first the differences between patient and control subjects by gender and then follow with the differences within the controls. Therefore, we have restructured the paragraphs in the results section.
In the new version of the manuscript, we have attempted to explain why male and female have different profiles; see page 15, lines 16-26. Also, we tried to better explain our findings and their potential impact on clinical practice; see page 17 lines 7-15.