Author's response to reviews

Title: Determining the Impact of Medical Co-morbidity on Subjective and Objective Cognitive Performance in an Inner City Memory Disorders Clinic: A Retrospective Chart Review

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Author's response to reviews: see over
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Dear Editor-in-Chief:

Re: Manuscript 9213588704094178

Determining the impact of medical co-morbidity on subjective and objective cognitive performance in an inner city memory disorders clinic: a retrospective review

Thanks very much to both you and the reviewers for the excellent feedback on the article. I will attempt to address each reviewer’s concerns in turn:

With respect to the comments from the editor in chief:

(1) Include context information within the background section of your abstract.
I included the context information in the background section of the abstract, page 2.

(2) Document, within your manuscript, the name of the ethics committee which approved your study.
In the methods section, first paragraph, page 5, I have given the name of the ethics board that approved the study (the St. Michaels Hospital Research Ethics Board).

With respect to comments from reviewer number one:

Thanks for the excellent feedback.

The introduction should be shortened substantially and maybe organised to lead up to the hypotheses, tightly documenting every prediction made.
As suggested by the reviewer I have significantly shortened the introduction by eliminating redundant material and clarifying the hypotheses.

The sample needs to be defined in terms of diagnoses, medication, other relevant clinical factors to be interpretable. (The paragraph: "The present study was conducted in a Memory Disorders Clinic located in a large urban centre..." may fit better in the results or even methods section?)
I agree with the reviewers comment. In response to the reviewer’s feedback I have included more detail about the memory clinic sample in the first paragraph of the methods, page 5. "Our clinic is located in an Inner City neighbourhood where patients typically have low SES" - how does that make it suitable to examine the effects of SES? I agree with the reviewer’s observation. The sample recruited did have mixed SES and therefore is ideal for studying the effects of SES. I have clarified this in the back ground section, second paragraph, page 5.

In the methods section the difficulties associated with multiple comparisons and confounding, and the solutions of these problems employed in this study should be described.
I concur with the reviewers comment and have expanded on how confounders were dealt with in the results section, first paragraph, page 9.

The discussion should provide a systematic description of study limitations due to cross-sectional design, clinical rather than epidemiological sample, subject number etc... The self-selection to attend a memory clinic may have played a role in the correlations observed? General applicability of the results to the population, different patient groups should be discussed.
In response to the reviewer’s feedback I have expanded on the limitations of the study in the last paragraph of the discussion, page 12. Specifically, I have included more information about the nature and size of the sample and how this may limit generalizability to other clinical populations.

**How was depression defined?**
Depression was defined according to DSMIV criteria and diagnosed following comprehensive assessment by a geriatric psychiatrist. I have included this information in the methods section, first paragraph, page 8

**Define the abbreviation SES before using it (does it include education? [Abstract]).**
Thanks for pointing this out. In the background of the abstract page 2 I have defined the abbreviation and have also clarified that education and residential SES are studied as separate variables. I re-iterated this in the methods section, first paragraph, page 6.

**How does "residential SES" differ from personal SES, as employed in other studies in its effects on cognition and why?**
Thanks for the comment. We chose to use residential SES as opposed to personal SES in order to maximize our patient sample, realizing this could potentially be a limitation. I have elaborated on this in the methods section, page 6, first paragraph.

**the CIRS score correlated positively with the MMSE score... are you sure?**
The reviewer is correct and thanks for pointing out the error. CIRS scores correlated negatively not positively with the MMSE. In the results section, second paragraph, page 8, I have corrected this.

With respect to comments from reviewer number two:
Thanks very much for the excellent feedback.

1. **(Major Compulsory Revision) The authors must provide greater detail about the procedures used to diagnose depression.**
I agree with the reviewer’s observation and thanks very much for pointing this out. Depression was defined according to DSMIV criteria following comprehensive assessment by a geriatric psychiatrist. This information is now provided in the methods, first paragraph, page 8.

2. **(Minor Essential Revision) In results, authors stated that “depression correlated with all measures of objective cognitive function” but the table indicates that it correlated with subjective complaints only. This may be a typographical error.**
The author is correct and thanks very much for pointing this out. Depression did not correlate with any objective measure of brain function. I have corrected this statement on page 9, first paragraph, results.

3. **(Major Compulsory Revision) In results, age may be a significant covariate or suppressor variable. MMSE is known to be affected by both age and education level. In the results reported, it is possible that either depression or subjective memory complaint may be associated with objective memory/cognitive performance after the effects of medical comorbidity are removed. In other word, medical comorbidity may have the most pronounced effect on memory/cognitive performance, but there may be some residual association to depression, or to subjective complaints. This could be tested statistically, although it might require**
using parametric statistical methods. 
The reviewer raises an excellent point. We agree with reviewer that age may be a covariate or suppressor variable in the correlation analysis. To examine whether it makes a difference if we adjusted for the effect of age, Spearman rank correlation analyses were conducted to partial out the effect of age. We found that almost all the conclusions were the same except for a slight change in the magnitude of correlations. We also conducted multivariable linear regression analysis to examine whether depression or subjective memory complaint may be associated with objective memory/cognitive performance after the effects of medical comorbidity are removed. We found that the correlation between the depression (or subjective general complaints) and BNA total score was not statistically significant after adjusting for the effects of age and medical comorbidity. We are not sure whether this is a power issue (small sample size). That is why we just conducted bivariate correlation analysis in this paper. The details of these analyses are reported in the results section, first paragraph, page 9.

4. (Minor Essential Revision) In discussion, authors state that medical comorbidities may affect functioning of the frontal lobes, and cite the correlation with BNA executive function as supporting evidence. This is a bit of a stretch, however, since it is more likely that significant medical comorbidities are likely to affect a variety of functional capacities. Authors should remove or qualify this. We agree with the reviewer that inferring the BNA explains the link between medical co-morbidity and frontal lobe function is beyond the scope of this paper. We have deleted this comment from the discussion.

5. (Major Compulsory Revision) The authors correctly conclude that elderly subjects with medical comorbidities and memory impairment are at risk because they do not accurately report, or may not be aware of, the extent of their memory difficulties. However, this is not surprising because study after study after study has shown that subjective memory complaint is more strongly correlated with mood disturbance than it is with objective memory performance. The data in this study is interesting because it reveals that this association holds even in the context of significant medical illness. This should be highlighted in the discussion. The author makes an excellent point regarding how our findings contribute to the literature. I have highlighted this in the discussion, first paragraph, page 11.

With respect to comments from reviewer number three:
Thanks very much for the excellent feedback.

Major Compulsory Revisions
1. More information is needed about the Memory Disorders Clinic through which the subjects are recruited. For example, are patients referred to this clinic by their family doctor or specialist or self-referred? What is the base rate of subjective memory complaints amongst all patients coming to the clinic, it seems to me that this might be high. The reviewer makes an excellent point. I have provided more information about the Memory Clinic and patterns of referral in the background section, second paragraph, page 5.

2. More information is needed about the subjects in this study. For example, it would be helpful to know the MMSE scores, the authors state that a score of 26 or below is used to identify dementia but do not tell us what proportion of the
sample was within the dementia range. Also, it would be helpful to see the scores from the cognitive tests that form the Behavioural Neurology Assessment. The authors mention, in the Discussion section (last paragraph) that they did not stratify by diagnosis which is understandable but nevertheless it would be useful to know what percentage of their population was Normal, MCI or Demented and how this was determined given that this was a Memory Disorders Clinic. Finally, in the first paragraph of the Results section the authors state that “over 50% had symptoms compatible with major depression”. This seems an extremely high of major depression in this sample and I wonder if what they really mean is that over 50% endorsed one or more symptom of depression. Also, this is not consistent with Table 1 which shows that 44.7% of subjects were depressed.

The reviewer raises a number of important issues. I have included mean scores for the BNA and MMSE as well as given a breakdown of the different diagnoses made in table 1 and in the results section, first paragraph, page 8. Unfortunately, the individual BNA subscores are unavailable. I have also provided more information about how dementia was diagnosed in the methods section, page 7, last paragraph. I have also corrected the percentage of patients diagnosed with depression, 45%, in the results section, first paragraph, page 8. Although this is somewhat high it is not uncommon for depressed patients to present to Memory Clinics as a result of increased memory complaints.

3. As mentioned above, the rate of Normal, MCI and Dementia among this sample is not provided, but the authors should consider what impact diagnosis may have on ratings of subjective memory impairment. For example, more severely demented patients may tend to under-recognize memory loss in everyday life whereas Normal elderly who are concerned enough about their memory to attend a Memory Clinic may over-state their deficits, the so-called “worried well”.

The reviewer makes a valid comment. I have now specified the percentage of patients with different diagnoses as previously specified and have provided more information about the impact of diagnosis on the rating of subjective memory complaints which I have included in the discussion, third paragraph, page 11.

4. Is there any evidence that the PAOF has been validated with patients with dementia?

The reviewer makes an excellent point. While the PAOF has not been validated in the elderly and I have alluded to this as a limitation of this study it has been validated in patients with chronic medical illnesses who are often older. I have referenced this in the methods section, first paragraph, page 7.

5. A citation should be added to the paragraph describing the BNA following the statement “and has been demonstrated to be superior to the MMSE in detecting dementia.”

I agree with the reviewer’s comment. In response I have added a citation as suggested by the reviewer with respect to the BNA being superior to the MMSE in the methods section, first paragraph, page 7.

6. Given that the subjects in this study are recruited through a Memory Disorders clinic, the authors should discuss the lack of generalizability of their findings to the family practice setting.
We concur with the reviewer’s comment that because of the specialized nature of the patient sample the findings are not generalizable to other clinical settings. I have elaborated on this in the discussion, second paragraph, page 12.
7. Finally, the authors offer a number of limitations to their study, which are reasonable, however they may wish to also consider how they deal with the limitations. For example, although the BNA has not been validated with other neuropsychological tests they do earlier in the manuscript suggest that it has been validated with patients with dementia used as a cognitive outcome measure in multiple clinical trials.

The reviewer makes a valid point regarding how we chose to address the study limitations. I have addressed this in the discussion section, page 12, second paragraph.

**Minor Essential Revisions**
1. The label on Table 2 refers to correlations between “SES and outcome variables” isn’t SES also an outcome variable should it be “Correlations between outcome measures”?
I have revised the title of table 2 as suggested by the reviewer.
2. There are a few typos that should be corrected throughout the manuscript
I have corrected all typographical errors as suggested by the reviewer.

**Discretionary Revisions**
1. The manuscript is quite repetitive, specifically the first couple of paragraphs in the Discussion section repeat information from the Introduction. Good editing would tighten up the paper and make it easier for the reader.

The reviewer makes an excellent point regarding the repetitive nature of the manuscript. In response to this feedback we have tightened up both the introduction and discussion.

In conclusion, I thank the editor and chief and reviewers very much for their excellent feedback. Let me know if you have any questions in regards to my revisions and I look forward to your feedback.

Sincerely,

Corinne Fischer MD FRCPC