Author's response to reviews

Title: The accuracy of the MMSE in detecting cognitive impairment when administered by general practitioners: A prospective observational study

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Author's response to reviews: see over
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Dr. Lolu da-Silva  
Senior Assistant Editor  
BMC-series journals

RE: MS: 5841473815470627; “The accuracy of the MMSE in detecting cognitive impairment when administered by general practitioners”; Patrizio Pezzotti, Silvia Scalmana, Antonio Mastromattei and Domenico Di Lallo

Dear Dr. da-Silva:

We have revised the above-specified manuscript to take into account the reviewers’ additional comments (below we have provided a point-by-point response). The manuscript has also been entirely revised for the English style.

Overall, two reviewers feel that our manuscript is acceptable whereas the other (Hein van Hout) is still unsatisfied. Although we found some of this latter reviewer’s comments to be useful in further improving the manuscript (particularly the title, the Abstract, the Introduction, and the Discussion), we do not agree with the reviewer’s suggestion to eliminate the results relative to the outpatient centres for dementia (referred to as “UVA” in the manuscript), for two reasons. The first is that these results provide an immediate comparison for the performance of the GPs in applying the MMSE. The second reason is that, although the UVAs were unblinded to the MMSE score of the GPs and to the other measured used for the clinical diagnosis, in actual clinical practice it is unlikely that the MMSE scores of the UVAs were influenced by the score given by the GP. Furthermore, in clinical practice, the MMSE is likely to be used independently of all other instruments for making the diagnosis of cognitive impairment, even if in disagreement with the result of the MMSE. We thus feel that it is unlikely that the unblinded condition of the UVAs when performing the MMSE influenced the results.

Thank you for your consideration.

Sincerely,

Patrizio Pezzotti
List of answers and changes made to the manuscript and responses to the reviewers’ comments

Reviewer: Hein van Hout
However, I strongly feel that the authors unjustly disagreed with two methodological issues I made. These issues strongly influence the interpretation of the results.
Maybe I have not explained my points clearly enough in the first review. My concerns are based on official evaluation criteria for diagnostic studies (STARD).

The authors may want to check the official STARD criteria of the consort statement on: http://www.consort-statement.org/mod_product/uploads/STARD%202003%20checklist.pdf
As you will understand points 5 and 11 remain insufficiently addressed in this revised paper.
Point 5 of the STARD statement concerns the sampling procedure. The GPs in the study purposefully sampled patients they suspected or diagnosed already. The problem that arises here is that we do not know the magnitude of missed patients. In my earlier review I referred to this point as verification bias. This a major methodological limitation which was not discussed at all and has consequences for the main interpretation. For example the abstract's conclusion could be rewritten to:
'the MMSE could be used in general medicine for the early detection of cognitive impairment IN SUSPECTED PATIENTS'. Consequently the interpretation in the discussion part should be rearranged to take this point into account.

We agree with the CONSORT statement about the STARD criteria and are aware that our study was limited for the sampling procedure. Although we felt that this had already been reported as a limitation in the previous Discussion, we further revised this section to better take into account the reviewer’s comment. We have also revised the title and the abstract, specifying that this was an observational study and that the objective was to evaluate the performance of the MMSE in an actual public-health setting and not to validate it. As suggested by the reviewer, we have completely rewritten the Conclusions of the Abstract, as follows: “In a public-health setting involving patients with symptoms of cognitive disturbances, the MMSE used by the GPs was sufficiently accurate to detect patients with cognitive impairment, particularly those with dementia.” We have also revised the last sentence of the Introduction, as follows: The objective of the present study was to determine in an actual public-health setting whether GPs can accurately detect a cognitive deficit using the MMSE in patients with suspected cognitive impairment. To this end, we compared the results of the MMSE applied by GPs to those of the MMSE applied by specialized neuropsychologists.”

To get a feel of the 'missed portion' one could think further analyses i.e. compare the portion the GPs detected with official prevalence statistics. Also it is possible to compare detection portions across the GPs. Likely some will do 'better' than others. In addition, if measured, the detected portion could be related to GPs characteristics.
At the beginning of the Results, we have added a sentence that provides the estimated prevalence of dementia and of AD in persons of 65 years of age or older followed by our sample of GPs. The estimated prevalence was 3.5%. This prevalence varied by GPs, and we cannot exclude the possibility that some GPs did “better” than others. However, it was not possible to evaluate if there was a relationship between the prevalence of dementia and the GP’s characteristics because this information was not collected.

Point 11. STARD concerns the blindness or independency of index and reference test. However, it is bizarre to evaluate the UVA derived MMSE score, which completely unblinded, to the UVA's own clinical diagnosis. Obviously their own MMSE scores perform better than those of the GPs. Moreover, in my opinion this part of the paper does not contribute to the objectives of the study at all and should be omitted. Despite being problematic, a reader may accept the limited influence of GPs derived MMSE scores on the UVA's clinical diagnosis. So this part could be preserved.

Although we agree that the blindness or independency of scores is important, we believe that is also important to provide the results of the MMSE of the UVAs and that these cannot be eliminated from the manuscript. In fact, UVAs are an important reference group and the comparison will help the reader to better evaluate the performance of the GPs. Furthermore, we feel that the potential bias related to the unblinded conditions is in this case of limited importance. In fact, the UVAs were interested in an accurate diagnosis (based mainly on many other diagnostic instruments) and not in evaluating the performance of the MMSE score administered by the GPs. Furthermore, in the normal clinical practice of the UVAs, the MMSE is administered and scored without taking into account the results of the other instruments used for making the clinical diagnosis. Thus it is unlikely that the unblinded conditions of the UVAs when performing the MMSE biased the results. In any case, to take into account this criticism we have further revised the paragraph on limitations in the Discussion section.

Below we report the entire paragraph on the limitations of our study, also focussing on the sampling procedure and the unblinded conditions.

“The major limitation of our study is that the GPs were asked to identify only those patients who they suspected to have a cognitive deficit (see selection criteria in the “Methods” section), and only those patients who scored 24 or less were evaluated by the UVAs. Thus we do not know how accurate the MMSE used by GPs would be in detecting cognitive impairment in patients not suspected to have a deficit (i.e., not sampled) or in patients with a suspected deficit yet with a score greater than 24. With regard to the latter patients, we feel that it is reasonable to assume that there were very few missed cases with cognitive impairment, as suggested by the results shown in Figure 2; furthermore, for patients who scored more than 24 yet whose symptoms were extremely serious, it was suggested that the GPs refer them to the UVA, and no cases of suspected cognitive impairment were confirmed. Another limit of our study is that the single items of the MMSE were not
collected, so that we were not able to evaluate more in-depth whether or not disagreement between paired scores was due to specific aspects of the examination. Moreover, patients with borderline scores (23 or 24) according to the GPs had a greater probability of receiving higher UVA scores than patients with scores far below the cut off, simply because of measurement error and daily variation. In particular, we cannot exclude the possibility that some of the GPs may have assigned a score of 24 to persons who, in their opinion, based on clinical observation or information provided by family members, were affected by cognitive impairment. Another limit that should be taken into account is that the GPs were not randomly selected and they underwent a training session, limiting the representativeness with respect to the general community. Furthermore, the UVAs were not blinded to the GPs’ MMSE scores, because patients were invited to go to the UVA based on the MMSE score. However, it is unlikely that the UVAs were conditioned by the score given by the GP. Finally, in this observational study, those who administered the MMSE in the UVAs were not blinded to the cognitive and familial anamnesis, the neurological and blood examinations, neuroimaging, and the neuropsychological, functional and behavioural evaluations. However, in the UVAs’ normal clinical practice, the MMSE is administered and scored without taking into account the results of the other measurements for making the clinical diagnosis. Thus it is unlikely that this would have biased the results."

**Reviewer: Barton Palmer**

The authors have been appropriately responsive to my prior suggestions. Limitations of the study include the lack of counter-balanced administration, and the absence of information on the responses and scores provided for individual items (whereby the investigators might verify and clarify the tendency for patients to obtain slightly lower MMSE scores from the GPs.) These limitations have been appropriately addressed in the Discussion sections (although should also be explicitly mentioned in the Abstract), and do not appear to distract from the broader point of the potential utility of the MMSE in general practice.

*The Abstract has been revised to specify that this was an observational study (specified also in the title) of non-randomly selected GPs and that the UVAs were not blinded to the GPs’ MMSE. We have also revised the Discussion, adding a sentence that provides a hypothetical explanation for the tendency of the MMSE scores obtained by the GPs to be slightly lower.*

**Reviewer: Howard Fillit**

I am okay with the reviewers responses. I believe the manuscript should now be published.

*We thank the reviewer.*