Author's response to reviews

Title: Informant-Reported Cognitive Symptoms That Predict Amnestic Mild Cognitive Impairment

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Author's response to reviews: see over
June 27, 2010

Dear Dr. Patel,

Enclosed are our point-by-point responses to the reviewers’ comments for the article entitled “Informant-Reported Cognitive Symptoms That Predict Amnestic Mild Cognitive Impairment”. We have attempted to address each concern as thoroughly and accurately as possible and we hope that they are found to be satisfactory. Every effort has been made to conform to editorial parameters. In the present draft, we incorporated the editorial suggestions. They are highlighted in red.

All authors have contributed substantially to the manuscript, have read its final version, and agree with the presented findings. Mr. Malek-Ahmadi and Dr. Sabbagh take responsibility for the integrity of the data and the accuracy of the data analysis. We feel that this contribution is timely, current, and relevant to the literature. We look forward to a seeing it in press in the near future.

Sincerely,

Michael Malek-Ahmadi, MSPH
Marwan Sabbagh, MD, FAAN
Reviewer 1

The methods are appropriate but not clearly defined; in particular (see Method – Study Sample) it should be needed to better describe the neuropsychological protocol adopted to diagnose aMCI.

The following has been added to the Methods section:

Individuals whose performance was 1.5 standard deviations (SD) below age- and education-corrected means on a delayed recall measure of verbal memory were classified as aMCI. Individuals with both single and multiple domain aMCI were included in the analysis. Multiple domain aMCI cases were classified as those with memory performance 1.5 SD below age- and education-corrected means with performance in another cognitive domain (e.g., executive functions) also falling 1.5 SD below age- and education-corrected means.

Furthermore, I have some concerns about the criteria to define CN participants. In fact, the absence of cognitively-based limitation of activities of daily living is enough to exclude dementia, not to rule out subjects with aMCI or subjective cognitive complaints.

The following has been added to the Methods section:

In addition, all CN participants scored above 1.5 SD on age- and education-corrected means on a battery of neuropsychological tests and received global CDR rating of 0 [13].

Finally, it should be mentioned the package supporting statistical analysis.

The following has been added to the end of the Statistical Analysis subsection:

Systat 13.0 was used to carry out all analyses.

The data are sound. However, describing in Results the same items always reported in Table 3 seems little redundant.

The items listed in Table 3 have been removed from the text of the Results section.
Reviewer 2

First, it is very important to this reviewer that a more detailed description regarding the diagnostic process for aMCI is provided. Since there is no general consensus on how the Petersen criteria should be implemented, the authors are requested to specify in detail how the Petersen criteria were implemented in their study.

The following has been added to the Methods section:

Individuals whose performance was 1.5 standard deviations (SD) below age- and education-corrected means on a delayed recall measure of verbal memory were classified as aMCI. Individuals with both single and multiple domain aMCI were included in the analysis. Multiple domain aMCI cases were classified as those with memory performance 1.5 SD below age- and education-corrected means with performance in another cognitive domain (e.g., executive functions) also falling 1.5 SD below age- and education-corrected means.

The authors mention that results of neuropsychological tests were used as part of the diagnostic process. Which tests were included in the neuropsychological battery?

A sub-section entitled “Neuropsychological Tests” has been added to the Methods section and describes the individual tests.

Was the AQ questionnaire taken into consideration when the clinician made the diagnosis? If so, then it’s not surprising that items from the AQ questionnaire are predictive of the group membership (whether aMCI or NC).

The following has been added to the Methods section:

The AQ was not utilized in the differential diagnosis for aMCI individuals and was not utilized in the consensus diagnosis for CN individuals.

Similarly, what were the exact criteria to characterize a person as CN? “Having no demonstrable cognitively-based limitations of activities of daily living” may exclude the diagnosis of dementia but this does not mean that these persons could not be characterized as MCI. Once again the authors are requested to describe in detail what were the specific procedures used by the neurologist, psychiatrist and neuropsychologist to define someone as CN.

The following has been added to the Methods section, study sample subsection:

In addition, all CN participants scored above 1.5 SD on age- and education-corrected means on a battery of neuropsychological tests and received global CDR rating of 0 [13].
The authors found that the responses on certain items of the AQ questionnaire statistically distinguish the two groups of interest and also predict group membership. My major concern is what is the utility of these findings on the individual level. As can be seen from table 2, 14 out of 47 persons (approximately 30%) would be misclassified as CN based on their informant’s response to item no. 3; more than half aMCI would be misclassified as NC according to their informant’s responses on the questions regarding knowing the date or ability to manage finances etc.

The chi-square analyses presented in Table 2 are utilized in order to demonstrate differences in response frequency for aMCI and CN individuals. As with any screening or diagnostic test, some degree of misclassification is inherent in the measure or tool. However, Chi-square analyses are typically not used for clinical group classification and are not usually intended to measure diagnostic and group classification accuracy. The logistic regression analysis was carried out (Table 3) to address this as it is a more appropriate and accepted method for determining the ability a particular measure to differentiate between clinical groups.

The authors argue that the AQ contributes to the accurate identification of those in need for further assessment. However, based on the individual responses of informants to those 4 items most aMCI persons would not be identified. Also, if the combination of these 4 items is what predicts group membership, is there a mathematical equation (resulting from the regression analysis) that a clinician can use to better identify aMCI based on the responses on the four items of this questionnaire?

The four items found to be significant in the logistic analyses are not necessarily intended to be used in combination with each other. Rather, these individual items had higher discriminatory power than the others. It is possible that a mathematical equation could be derived using these four items, but this might actually limit the AQ’s diagnostic ability given that aMCI is a very heterogenous diagnostic entity. Furthermore, the use of such an equation may not have great practical significance as the original intent of the AQ is that primary care and geriatric clinicians with limited face-to-face patient time would have a brief and accurate assessment of cognitive status available to use.

It is not clear to this reader how clinicians can incorporate these findings into their daily practice, so they can better identify persons with possible MCI.

The following has been added to the end of the Discussion section:

These data indicate that problems with orientation to time, repeating statements and questions, difficulty managing finances, and trouble with visuospatial orientation may accompany memory deficits in aMCI. From a clinical standpoint, these findings are important as it will allow clinicians to more easily and accurately determine which individuals require further assessment of cognitive problems.
I have a slight concern about the fact the authors own copyright to this new questionnaire. Does this mean they have any financial interests in this questionnaire? If so they should just declare this and it is not a major issue.

It should be noted that the authors’ institution, Banner Health, holds the copyright for the AQ. However, the AQ is given out at no charge to those who request it from the authors so there is no financial interest in the AQ. This has been noted in the Competing Interests section.

Other Editorial Review

Manuscript body has been edited to BMC Geriatrics Format.

Conclusion section clearly states the findings and implications of the study.

Author contributions have been edited to the suggested format.

Requesting Consent Statement has been added in the Acknowledgements and Funding section. Also included are the sources of financial support for the study.