Author’s response to reviews

Title: Differential diagnosis of depression and Alzheimer's disease with the Addenbrooke Cognitive Examination-Revised

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Author's response to reviews: see over
Dear Editors,

We greatly appreciate the consideration of our manuscript (MS: 1586445401458159) entitled "Differential diagnosis of depression and Alzheimer's disease with the Addenbrooke Cognitive Examination-Revised (ACE-R)".

We greatly appreciate the review of our manuscript by prof. Larner and prof. Schmand, and we are thankful for providing us with many valuable recommendations, which made it possible to improve the quality of our manuscript. As you will see below, we have provided our responses to the comments provided by prof. Larner and prof. Schmand and we have made the changes in the revised manuscript. All the authors have reviewed the revised manuscript and have approved its resubmission.

Many thanks for allowing us to revise our manuscript. Please let us know if additional changes are necessary for acceptance.

Please take into consideration that the manuscript is submitted by other person on our behalf because Vilnius University Faculty of Medicine has a Prepay Membership Contract with BioMed Central Ltd, and therefore manuscript submissions are managed by one appointed institutional person - Dr. Tomas Kacergius (tomas.kacergius@mf.vu.lt).

Respectfully,

Augustinas Rotomskis

On behalf of authors: Ramunė Margevičiūtė, Arūnas Germanavičius, Gintaras Kaubrys, Valmantas Budrys, Albinas Bagdonas
We addressed the questions and comments in the following ways:

1. I wonder why you excluded depressed patients and control subjects who had MMSE scores below 27. People who score a few points below 27 may have perfectly normal cognitive functions, especially when they are relatively old and less educated. By excluding them, you undoubtedly embellished the diagnostic accuracy of the ACE-R. This is my main objection. In case you collected data in these subjects and excluded them only for this paper, I would suggest to include them again and to redo all analyses.

RESPONSE: Indeed this exclusion of depression patients below 27 on MMSE could embellish the diagnostic accuracy of the ACE-R. We reincluded 17 depression patients, which fell below 27 on MMSE, and redone all the analyses. We changed the data information in Tables 1-5 (lines 503-541).

2. You were very brief on the diagnostic work-up of the patients. Probably both recruitment centers had different diagnostic routines. In Table 1 you gave the ICD-10 code of the depressed patients, which is fine, but you might elaborate a bit more in the methods section on issues like who made the diagnosis, and how dementia or neurodegenerative diseases were excluded. This would give the readers some idea of the likelihood of misclassified MCI or AD cases in the depressed group. Similarly, how was AD diagnosed, and how were other causes of cognitive impairment excluded? Were any neuroimaging or amyloid assays done? According to Table 1 the patients satisfied the NINCDS-ADRDA criteria (McKhann et al. 1984). Would it be possible for you to apply more recent criteria (McKhann et al. Alzheimers Dement 2011)?
RESPONSE: We expanded the description, how patients with AD were diagnosed (lines 499-500, Table 1. Inclusion criteria for the participant recruitment). Alzheimer's disease was diagnosed according to the standards laid out by Lithuanian Ministry of Health (the standards are the same for all health care institutions in Lithuania). All patients with AD had a neurologist's consultation, psychiatrist's consultation, were tested with MMSE, neuroimaging was done with a computerized tomography or a magnetic resonance tomography at the time of diagnosis establishment. Hematology including ESR, basic biochemistry, thyroid function tests were performed for all AD participants. We selected NINCDS-ADRDA diagnostic criteria, because these are the mandatory criteria of the diagnosis of AD in Lithuanian by the decision of the Lithuanian Ministry of Health. All patients with suspected depression were interviewed by experienced psychiatrist, standard procedure of differential diagnosis was used (instrumental, non-instrumental tests and psychological assessment battery). All diagnoses were made using ICD-10-Australian modification (ICD-10-AM) using definition of severe major depression episode. Also, concomitant mental and physical disorders were specified.

3. You concluded the abstract by stating: “Diagnostic accuracy may be improved by analyzing the neuropsychological profiles and using lower cutoffs for different age groups.” So, I wonder why you didn’t do that yourself? You looked at the profiles and statistically tested group differences, but you didn’t take this one step further using the information to improve diagnostic accuracy. For example, you might do two logistic regression analyses, one to find the best discriminating variables to distinguish between AD and healthy aging, and the other to distinguish between AD and depression. Similarly, you propagated using lower cutoffs for older age groups. So, why didn’t you do that? You might use the control group to calculate age corrections (and corrections for education, I would suggest), and apply these corrections to all subjects. The beta’s are substantive
(in the order of \(|.4|\), so this strategy seems worthwhile. At least in theory, this should lead to higher diagnostic accuracy.

**RESPONSE:** To further support our notion that differential diagnosis of AD and depression may be based on the analysis of neuropsychological profiles provided by ACE-R, we conducted a logistic regression analyses to find the best discriminating variables to distinguish between AD and depression. A description of the analysis was added (lines 294-299). Regarding the age adjusted cutoffs: unfortunately, we are unable to develop different cutoffs for different age groups, because the study sample is too small for this task. As we laid out in the discussion the development of different cutoffs for different age groups could be the objective of future research.

4. The rationale for your study is the difficulty that clinicians experience in distinguishing between dementia and depression. You based this rationale on rather old references. However, aren’t we better equipped these days to make this distinction than 20-30 years ago? In other words, can you support the rationale with more recent studies showing that it still is a problem?

**RESPONSE:** We have rewritten the introduction to the study establishing more clearly that there is a shortage of studies on cognitive screening tests for differential diagnosis of dementia and depression (lines 66-122). Based on current evidence, there are no screening measures that are sufficiently valid for distinguishing among depression and AD in a clinical setting, and this is even more of an issue when depression and cognitive impairment occur together.

5. The sensitivity and specificity figures given on page 9 do not seem to correspond to the figures given on the next page, nor to the ROC curve. The legend of the ROC curve does not state to what group comparison it refers. Please clarify.
RESPONSE: We acknowledge that the formulation of the paragraph as it was provided was confusing, so we separated the logistic regression from ROC analysis to clarify the results (lines 194-204).


RESPONSE: Indeed it wasn’t clearly explained how and why the cutoff scores for Lithuanian version were established. We expanded the description of this topic (lines 107-122).

7. Reference citations are not continuously numbered (e.g. p4-5, ref 23 follows ref 13), and the round brackets used to denote references are also used to denote subscores on ACE-R (p6, lines 118-120) which is extremely confusing. Then at p13, line 307 and page 14, lines 308, 311 and 312, reference numbering is abandoned altogether for author names! Referencing system needs to be consistent.

RESPONSE: We are sorry for this oversight. Reference system was corrected to be consistent.
Other minor revisions suggested by the Reviewer were corrected:

Line 67: “Are the most successful” to read “are likely to be the most successful”.

Line 225: “Lower the control” to read “lower than the control”.

Line 309: “In our study age had a significant influence on ACE-R performance in depression and control groups”.

Line 331: “Qualitatively” is removed from the text.

Line 341: “Memories are most”.

Line 345: “Mild” instead of “mild occasionally”.

Please kindly keep in mind that the numbering of the corrected lines differ from those indicated in the Review due to the changes made in the article text above the corrected lines.