Author's response to reviews

Title: Comorbidity of dementia: a cross-sectional study of primary care older patients.

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Author's response to reviews: see over
To the BMC Psychiatry Editorial Team,

We thank you and the reviewers for your feedback. We have been able to respond to each of the thoughtful remarks of the reviewers, as stated below, and we believe the original manuscript has been substantially improved. All modifications have been highlighted in yellow in the manuscript.

Reviewer #1:

Major compulsory revisions:

- The authors indicate at introduction end that epidemiological knowledge on comorbidities associated with dementia and the presence of patterns is scarce if nonexistent. However at discussion they mention studies by Zuliani et al, Newcorner et al, Sanderson et al, Marengoni et al, Schäfer et al, approaching the simultaneous presence of chronic ailments and dementia. I find such asserts contradictory and not compatible with the title where a NEW APPROACH is announced. I suggest authors recognise such prior work at the introduction and discuss the present study results instead of merely listing results of prior work.

  The title and the paragraph at the end of the introduction have been modified according to the suggestions of the reviewer.

- The epidemiologic study of comorbidities of an index diagnosis (dementia in this case) is complex since, as Ording and Sørensen recently indicated, concepts such as morbidity, comorbidity, and complications have been confusing, and some of them are used interchangeably. Furthermore, the different potential approaches (cross-sectional, lifecourse) and reasons for methodological choices have to be made explicit not only in methods but also in discussing results. For instance, Benito-Leon et al Neurology 2006, observed an association of essential tremors with dementia in a prevalence study and Bermejo-Pareja F et al Mov Dis 2007 show a high incidence of dementia in a cohort of patients with essential tremor. I suggest authors focus at the introduction their main interest and state-of-art in studying comorbidity in dementia and define alternative potential approaches. I guess the cross-sectional one is one of them; perhaps the most immediate to provide a perspective to build a longitudinal and more specific approaches.

  The introduction has been modified in order to focus our interest in studying comorbidity of dementia by means of alternative methodological approaches. All references cited by the reviewer have been included.

- The DISCUSSION section requires structure and elimination of speculative recommendations.

  The discussion section was re-structured and speculative recommendations were omitted. The discussion has now the following parts: 1) summary of the findings, 2) strengths and limitations, 3) clinical discussion of comorbidities of dementia, 3) discussion about methods, 4) clinical applicability of findings, 5) conclusions.
Minor essential revisions:

INTRODUCTION

• First paragraph. “its prevalence has increased continuously over the past decades” constitutes a misleading statement. In recent door-to-door studies prevalence of dementia among a Swedish population (Qiu C, von Strauss E, Bäckman L, Winblad B, Fratiglioni L. Neurology. 2013) remained stable (with longer duration of disease an likely decreasing incidence – as shown at the Rotterdam cohort). Changes in crude prevalence due to aging populations is a different issue or should be specified. The World Alzheimer Report is quoted using a reference (Phelan et al JAMA 2012) on high increase of hospital use and not the original one.

The first paragraph has been modified and the mentioned references have been included. The quotation to the World Alzheimer Report has been corrected.

• First paragraph. Phelan at el JAMA 2012 a paper on a high OR 1.45 hospital admission is used to quote a statement of the fraction of health care costs attributed to the elderly population. A different data source should be provided.

A new reference has been included instead of the old one, which had been erroneously inserted.

RESULTS

• First paragraph. Dementia is referred to “12.34% had dementia as the only disease”. Since at introduction authors properly state that dementia “is a syndrome”, perhaps the use of a different term “coded diagnosis” or “diagnosis” at RESULTS may be preferred “.

The term disease was substituted by diagnosis in the mentioned sentence of the Results Section.

• Negative associations are not reported. Were they found in logistic regression? Those with neoplasms would perhaps be expected. A more complete report of results in table 3 including negative associations would be needed. Competing risks and the role of survival bias may have to be discussed.

Negative associations are shown in the table attached at the end of the document. Given that our focus is on comorbidities of dementia, we prefer not to divert readers’ attention with negative associations. Moreover, we do not see a clear take-away message from these new results.

DISCUSSION

• First paragraph. The discussion of the association of dementia (assuming it mainly refers to Alzheimer’s Disease) with Type II Diabetes requires inclusion of recent knowledge on shared molecular mechanisms (see as an example Götz J et al Frontiers in AGING NEUROSCIENCE, 2013).

The coexistence of dementia and diabetes was further developed and the suggested reference was included.

• First and second paragraphs. First page is devoted to discuss associations with hypertension, diabetes, and entities denoted as “new chronic diseases” (first line second paragraph). The term “new” is not motivated. Should be erased.

The term new was substituted by different in the mentioned sentence.

• Reference 22 is incomplete, lacks editors, authors, chapter and pages and likely peer review.
It has been substituted by more a peer reviewed journal article.

- Second page. Largely devoted to methodology, I do not see a clear message. The term “spontaneous” in the expressions “visualization of spontaneous associations between...” is unclear.

The 6th paragraph of the discussion section now talks about the impact of applied methodologies, in a more extended manner. Clear take-away messages have now been incorporated.

- The two last paragraphs constitute unmotivated proposals, suggestions and recommendations which should be preceded by a rationale or suppressed.

These paragraphs have been deleted. The 7th paragraph of the discussion now talks about the clinical applicability of findings, based on our analyses.

- Section Comparison to other studies. Findings in other studies should be structured, compared to own study results and perhaps not a list of each study results deprived from criticisms. I suggest they are mentioned when single associations are first discussed.

The different studies under the older “Comparison to other studies” section have been incorporated to the part where disease associations are discussed.

- Section Limitations. Should be early described in DISCUSSION and useful for interpreting results. Those due to the cross-sectional design are crucial and authors are well aware of them.

The limitations section was moved to the beginning of the discussion.

CONCLUSION

- The paper lacks conclusions a part from the 12 reported associations. An explicit text, free from speculative considerations or recommendations, should be provided after interpretation of study results.

Done.

Other revisions:

- Part of the CONCLUSION might be elaborated and moved to discussion after suggesting how a longitudinal study of the dementia cohort may be approached using causal or predictive models.

Done.

Reviewer #2:

Essential / compulsory revisions:

- The end of the introduction is not very clear to me. Why do studies on the comorbidity of dementia need new methodological approaches? How does this related to “… using the statistical methods most frequently applied in current research.”? Is the focus on new methodology or on the comorbidity of dementia?

The introduction has been modified in order to focus our interest in studying comorbidity of dementia by means of alternative methodological approaches.

- For me, figure 1 is not very helpful, because it is hard to understand it. I assume one figure represents the males and the other the females (which is which)? One figure includes 21 diseases, the other 23; probably those have factor scores >.25? (please add a foot note or
something similar in the figure) What does it mean when disease names are underlined? What should I learn from the fact that most factor scores are <.40?

Further information has been added in the foot note in order to make it more understandable.

• The abstract does not give any results of the factor analysis.

In the abstract, results from the logistic and regression analyses are given together.

**Discretionary revisions:**

• If the focus is on methodology the authors might want to extend their discussion beyond the specific example of comorbidity of dementia.

The 6th paragraph of the discussion section now talks about the impact of applied methodologies, in a more extended manner. Clear take-away messages have now been incorporated.

• The authors have access to an impressive database holding information on over 70 thousands patients aged 65 years and older. The authors do hardly give any explicit comments on the quality of the data(base) used.

The limitations and strengths of the data source used were highlighted.

• I think the authors could give an explanation as to why they use exploratory factor analysis and e.g. not hierarchical cluster analysis (Vu T, Finch CF, Day L. Patterns of comorbidity in community-dwelling older people hospitalised for fall-related injury: a cluster analysis. BMC Geriatr. 2011 Aug 18;11:45. doi: 10.1186/1471-2318-11-45.) or other available statistical methods.

This issue has been incorporated into the 6th paragraph of the discussion section.

• In their discussion the authors have not yet convinced me that their methods of quantifying the comorbidity of dementia (with analyzing specific diseases) is more useful than calculating a comorbidity index to trace to patients with dementia who are at high risk for hospitalization or mortality. Can the authors formulate recommendations for clinical practice based on their analysis?

This issue has been incorporated into the 6th paragraph of the discussion section.

**Reviewer #3:**

**Minor essential revisions:**

• The term “physiopathology” should be replaced by the term "pathophysiology".

The suggested modification was carried out.

**Discretionary revisions:**

• I think that the described limitations related to claims data does not only apply to the dementia diagnosis, as it was clearly discussed by the authors. Moreover, there might be some imprecision, ambiguities or incompleteness in the comorbid diagnosis as well (due to under- and over-reporting, or misclassification). But the benefit (the non-selective character of the sample) may outweigh this disadvantage. Maybe, this point could be strengthening in discussion.

The limitations and strengths of the data source used were highlighted.
Table 3. The odds ratios of dementia-associated diseases in men and women

<table>
<thead>
<tr>
<th>Men</th>
<th>OR</th>
<th>CI 95%</th>
<th>Women</th>
<th>OR</th>
<th>CI 95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety, neuroses</td>
<td>2.19</td>
<td>(1.84 - 2.60)</td>
<td>Chronic skin ulcers</td>
<td>2.89</td>
<td>(2.38 - 3.53)</td>
</tr>
<tr>
<td>Parkinson's disease</td>
<td>2.13</td>
<td>(1.49 - 3.06)</td>
<td>Anxiety, neuroses</td>
<td>1.79</td>
<td>(1.63 - 1.96)</td>
</tr>
<tr>
<td>Chronic skin ulcers</td>
<td>2.05</td>
<td>(1.41 - 2.96)</td>
<td>Anemia</td>
<td>1.57</td>
<td>(1.37 - 1.79)</td>
</tr>
<tr>
<td>Anemia</td>
<td>1.95</td>
<td>(1.58 - 2.41)</td>
<td>Cerebrovascular disease</td>
<td>1.57</td>
<td>(1.29 - 1.90)</td>
</tr>
<tr>
<td>Retinal disorders</td>
<td>1.72</td>
<td>(1.03 - 2.87)</td>
<td>Behavior problems</td>
<td>1.53</td>
<td>(1.22 - 1.92)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>1.63</td>
<td>(1.28 - 2.07)</td>
<td>Congestive heart failure</td>
<td>1.42</td>
<td>(1.15 - 1.75)</td>
</tr>
<tr>
<td>Cardiac arrhythmia</td>
<td>1.53</td>
<td>(1.25 - 1.88)</td>
<td>Parkinson’s disease</td>
<td>1.41</td>
<td>(1.02 - 1.94)</td>
</tr>
<tr>
<td>Thyroid disease</td>
<td>1.43</td>
<td>(1.07 - 1.91)</td>
<td>Cardiac arrhythmia</td>
<td>1.24</td>
<td>(1.06 - 1.45)</td>
</tr>
<tr>
<td>Prostatic hypertrophy</td>
<td>1.29</td>
<td>(1.11 - 1.50)</td>
<td>Thyroid disease</td>
<td>1.17</td>
<td>(1.02 - 1.35)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.87</td>
<td>(0.77 - 0.98)</td>
<td>Disorders of lipid metabolism</td>
<td>0.90</td>
<td>(0.81 - 0.99)</td>
</tr>
<tr>
<td>Disorders of lipid metabolism</td>
<td>0.82</td>
<td>(0.70 - 0.97)</td>
<td>Low back pain</td>
<td>0.89</td>
<td>(0.80 - 0.99)</td>
</tr>
<tr>
<td>Cardiovascular disorders, other</td>
<td>0.63</td>
<td>(0.40 - 0.98)</td>
<td>Osteoporosis</td>
<td>0.79</td>
<td>(0.70 - 0.90)</td>
</tr>
<tr>
<td>Obesity</td>
<td>0.60</td>
<td>(0.39 - 0.93)</td>
<td>Cervical pain syndromes</td>
<td>0.78</td>
<td>(0.63 - 0.98)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Obesity</td>
<td>0.50</td>
<td>(0.40 - 0.64)</td>
</tr>
</tbody>
</table>