Author's response to reviews

Title: Reducing complexity: A visualization of multimorbidity by combining disease clusters and triads

Authors:

Ingmar Schäfer (in.schaefer@uke.de)
Hanna Kaduszkiewicz (kaduszkiewicz@allgemeinmedizin.uni-kiel.de)
Hans-Otto Wagner (h.wagner@uke.de)
Gerhard Schön (g.schoen@uke.de)
Martin Scherer (m.scherer@uke.de)
Hendrik van den Bussche (bussche@uke.de)

Version: 3
Date: 25 November 2014

Author's response to reviews: see over
The Editor

BMC Public Health

Manuscript resubmission: Reducing complexity: A visualization of multimorbidity by combining disease clusters and triads

4th of November 2014

Dear Editor

Thank you very much for the report of the reviewers and for the opportunity to resubmit a revised version of this paper. We highly appreciate the constructive criticism and have revised the paper carefully. We hope to have met all the suggestions satisfactorily and think that the paper has improved due to this revision.

On the following pages you will find answers to each comment. To facilitate reading, the original comments of the reviewers were copied into this letter. Comments were numbered and provided with a "C"-prefix and our answers to the comments with an "A"-prefix. Changes in the cited sections of the manuscript have been underlined.

Reviewer 1:

Major Compulsory Revisions

C1.1) This is an interesting study that uses network analyses to identify clusters of diseases within those with multimorbidity and visually presents the results of the multimorbidity clusters. Whilst the authors describe this method as providing increased information on the complexity of multimorbidity, it seems the results are in concordance with the prevalence of the conditions in the older population, i.e. metabolic syndrome and musculoskeletal conditions are both highly prevalent in the older population, I think it needs to be emphasized by the authors of what additional and novel information is provided here in this study and how the results of this study will facilitate the improvement of multimorbidity in clinical guidelines is unclear.

A1.1) Thank you for pointing out that we should clarify the novel aspects of the study, which we now describe in a paragraph at the beginning of the discussion section. However, the results of this study show that the number of associations of a disease does not necessarily follow the prevalence of the condition as stated by the reviewer. This is already discussed in our article ("It should be noted that diseases with a higher prevalence do not necessarily have a higher degree or betweenness centrality than diseases with a lower prevalence (e.g. in the male population hyperuricemia/gout has only half the prevalence of lipid metabolism disorders, but 50% more edges and a much higher betweenness centrality."). The study confirms many other studies that identified multimorbidity patterns (cf. review on multimorbidity patterns by Prados-Torres et al. in JCE 2014), but does this with a more systematic and appropriate approach than the studies published before. Our study also gives more detailed information as it is the first study on multimorbidity that describes the association between single diseases on person-level and does this in a graphical way.
Abstract

C1.2) Include the aim of the study at the end of the background. Include the name of the data source. In the methods section only include the current method used, ie the network analyses of disease triads identified from previous study. Include total number of patients included in study.

A1.2) We did as suggested.

Background.

C1.3) The background section is too long and includes a lot of superfluous information.

A1.3) We shortened the section where possible.

C1.4) Line 101, use the correct definition of multimorbidity. ‘Multimorbidity is the presence of two or more conditions’ that can include any type of disease combinations.

A1.4) We changed the sentence as suggested, but deviated in two points from the suggestion. First, the definition of multimorbidity includes either at least two diseases or at least three diseases (cf. review by Marengoni et al. 2011) and we therefore did not choose a cut off value in our sentence. Second, most definitions of multimorbidity include only chronic conditions and so we also did not include acute illnesses.

C1.5) “over the last decade many research groups have tried to understand the complexity of multimorbidity, due to it’s high prevalence estimated between 50 and 99% in the older population and its association with adverse health outcomes such as decline in functional status....

A1.5) We changed the paragraph as suggested.

C1.6) Delete sentences starting with out team until reference 5.

A1.6) We deleted the sentences as suggested.

C1.7) Line 112 Question: how will analysis of associations of diseases reduce the complexity of multimorbidity exactly?

A1.7) In an epidemiological sense complexity in multimorbidity means that every disease can be combined with every other disease. If we analyse the distribution of diseases in order to only consider highly prevalent and statistically associated combinations, we can disregard a large part of combinations (those that are not prevalent and/or not associated) and therefore we reduce complexity.

C1.8) Paragraph starting 115-140 needs to be summarized in a more succinct manner.

A1.8) We shortened the paragraph.

C1.9) Delete from line 141, this is not needed and simply state the aims of the current study. In this study we conducted a network analysis to ..... 

A1.9) We deleted most of the paragraph and stated the aim of the study.
Methods

C1.10) Include subject headers where possible to help readability.

A1.10) We added the subject headers “data set” and “ethics statement” and kept the subject header “statistical analyses”.

C1.11) Given previous publications I think line182-199 could be summarized. The methodology of the current paper begins on line 202.

A1.11) We think this is an essential information needed to understand the analyses and we wish to keep it for this reason in the way it is even if it has been published before.

C1.12) It would be helpful to explain what exactly is meant by the terms numbers of edges and betweenness centrality and what this means for the observed multimorbidity clusters, in the methods (I see this is clearer in the results section).

A1.12) We now give more information concerning “edgelist” and “betweenness centrality” in the methods section and we also included a list of frequently used terms at the end of the manuscript (cf. our answer A2.5).

Discussion

C1.13) It needs to be emphasized about the importance of using the network analysis approach to identifying multimorbidity clusters and what what additional and novel information is provided here in this study. How will the results of this study facilitate the improvement of multimorbidity in clinical guidelines is unclear, over and above what is already known?

A1.13) We now included a paragraph at the beginning of the discussion section in which the novel aspects of the study are described (cf. our answer A.1.1)

Conclusion

C1.14) Delete sentence starting line 465 to end of sentence line 470 ending in academic vault. Simply present conclusions of current study and its implications for improving care / understanding of multimorbidity and potential to improve clinical guidelines.

A1.14) We deleted the metaphor and simply stated the conclusions of the study.

Reviewer 2:

Major Compulsory Revisions

C2.1) The wording “significantly associated combinations” (Abstract), even with significantly in quotation marks, is somewhat misleading since it suggests but does not seem to refer to any statistical hypothesis testing. Similarly, the claim “We were able to show which diseases are statistically associated” seems strong given the nature of the data and the applied methods. Alternatively, something like “This study provides evidence on joined occurrences of diseases in elderly population, ...” may be more appropriate. I would suggest to carefully review and reconsider, first, the wording in all instances where it is referred to “significance”, and, second, the general claims made in the conclusions.

A2.1) Thank you for this very helpful comment. We deleted the word “significant” from our manuscript as we agree that most readers would expect significance due to a statistical test for significance and this is not what we did. We also agree that the claim of “statistical association” might be misleading
and we also deleted the word “statistical” in this context. However, we kept the word “associated” (without “significantly” or “statistically”), because the observed-expected-ratio shows the degree of association between two conditions even if it gives no information about the statistical significance of this association. Furthermore, we limited the claim of the study on the associations in our data set.

**Minor Essential Revisions**

C2.2) The authors should state the purpose of the study in the abstract, see BMC Public Health submission guideline.

A2.2) We did as suggested.

C2.3) It would be helpful if the authors highlighted already in the abstract that their study population was 65 years and older.

A2.3) We referred to the age group.

C2.4) Although, this might have been included in previous publications by the authors, a table on the characteristics of the study population for both males and females in 2006 and 2004 could be added, e.g. showing the age distributions, numbers of prevalent diseases, etc...

A2.4) As suggested we included a table with patient characteristics of 2006 and 2004.

C2.5) Many readers who are unfamiliar to network analyses may not be aware of terms such as “edgelist” used in the abstract (line 61). These terms should very briefly be explained when used first. Also, it might be helpful to prepare a box or a table that very briefly explains frequently used terms that many readers of BMC Public Health might not be familiar with, e.g. “edge”, “bridge”, ...

A2.5) We now explained all frequently used terms related to the network analysis in a section at the end of the manuscript (before the references).

C2.6) The authors state at the end of the background section: “This work is done for both genders separately”. This sentence could be moved into to methods section and a brief justification for the separate analysis could be added.

A2.6) As suggested we moved this sentence into the methods section and provided a brief justification.

C2.7) More details on the network analysis could be given in the statistical analysis subsection.

A2.7) We amended further information about the network analysis (cf. our answer A1.12).

C2.8) Some discussion of the fact that data are from 2006 (and 2004) would be useful. Although this might be difficult to say: what would be likely differences (if there are any) if more up-to-date data had been used?

A2.8) The most likely differences would be higher prevalence rates of most chronic conditions which might result in the need of increasing the prevalence cut-off for triad inclusion in order to keep results comparable. We provided this discussion in the strengths and weaknesses section.

C2.9) Please replace "tetrachoric factors analysis" by "tetrachoric factor analysis".
A2.9) We corrected this spelling mistake.

C2.10) A list of the ICD codes used to define each condition or a reference to such a list in a previous publication anywhere in the paper would be useful.

A2.10) In the methods section we already provided this reference (“Prevalence, gender-specific rank order and ICD-10 codes of the diagnosis groups have been published in another study [9].”). However, if the reviewers think that additional information is necessary we will be glad to provide it.

C2.11) Results, line 292-296, “circle”: More appropriately, an “ellipse”. How is the size of these ellipses in Figures 1 and 2 determined?

A2.11) Thank you for this helpful remark. We replaced “circle” by “ellipse” in the manuscript. For calculating the relative size of the ellipses we used the formula “A = \pi a b” (with “A” being the surface area and “a” and “b” each being a semi-axis) and defined “a = 3 b”.

Discretionary Revisions

C2.12) The “metaphor from Greek methodology” at the end of the background section and in the conclusion seems dispensable.

A2.12) As suggested we deleted the metaphor.

Additional Editorial Request:

C3.1) Copyediting: We recommend that you copyedit the paper to improve the style of written English.

A3.1) We sent the paper to copyediting as suggested.

Kind regards

Ingmar Schäfer