

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Comparative analysis of methods for identifying multimorbidity patterns in a South Mediterranean European Region: a cross-sectional study.
AUTHORS	Roso-Llorach, Albert Violan-Fors, Concepción Foguet-Boreu, Quintí Rodríguez-Blanco, Teresa Pons-Vigués, Mariona Pujol-Ribera, Enriqueta Valderas, Jose

VERSION 1 - REVIEW

REVIEWER	Pietro Ferrari
REVIEW RETURNED	31-Aug-2017

GENERAL COMMENTS	<p>This work uses a very interesting and informative data resource, the Catalan SIDIAP database. The Authors intended to explore the occurrence of patterns of multi-morbidity across the study population, where clinical information was recorded through electronic health records. Despite the research idea being interesting, the study fails to convey relevant information in a useful way. The Authors decided to focus the work on a quasi-methodological comparison of hierarchical cluster analysis (HCA) and exploratory factor analysis (EFA). This is a debatable choice as the SIDIAP database has great potential to disclose useful information on the occurrence of multi-morbidity among the same individuals. HCA and EFA are very different tools, and the fact that they provide differential evidence is to be expected. Occurrence of a specific morbid condition is a discrete state. In this respect application of HCA seems a very natural choice to appreciate the level of clustering of such conditions, thus producing informative findings. On the other hand, with EFA one usually measures propensity towards adherence to specific conditions/states that individuals tend to show with various degrees of consistency, such as high physical activity or large intake of dietary fibres. The application of such scores to something that either exists or does not exist can still provide information on the propensity towards the simultaneous occurrence of multiple morbid conditions. However, the interpretation is less obvious, letting aside the methodological complications that scores are by definition orthogonal (at least before further stretching of results via rotation), and despite the technique does not really fit discrete data, as clearly pointed out by the Authors. In this respect I find it difficult to agree with the sentence in the conclusions of the Abstract as, while acknowledging the methodological challenges, these multi-morbidity patterns likely exist irrespectively of the analytical method used to identify them. It</p>
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	<p>is up to a careful research plan and a sensible use of statistical technique to observe them. The manuscript could be substantially improved if the aims of the work were better defined.</p> <p>Detailed comments.</p> <p>Abstract. Please use more appropriate description of the "...263 bocks (ICD-10)".</p> <p>This is a cross-sectional analysis that seems to refer to information in 2010. What was the time span the multi-morbidity referred to approximately? In other words, how far in time were morbid conditions retrospectively assessed for individuals in the SIDIAP database?</p> <p>Abstract, results and following. As the analysis included some 408K individuals with at least two conditions, what is the meaning of the sentence "... the 12 clusters with at least diagnoses"?</p> <p>Introduction, line 40. What distance do the Authors refer to, mathematical (Euclidean) or chronological distance?</p> <p>Lines 44-5. Unclear statements, please consider revision.</p> <p>Line 457. Conditionally, please clarify on what.</p> <p>Page 2, lines 2-6: this type of statements pertains to the discussion, rather than the Introduction.</p>
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REVIEWER	Chenkai Wu
REVIEW RETURNED	23-Oct-2017

GENERAL COMMENTS	<p>In this study, the authors compared two different statistical approaches in identifying multimorbidity patterns in a Spanish cohort and concluded the different approaches produced different results. The paper is nicely written and the quantitative analyses are very rigorous and thorough. However, I did not clearly see the clinical and scientific contributions this paper could bring to the literature. It is not surprising to me that two methods, developed for different purposes, produced different results; maybe these two methods would produce similar results in a different population. Also, the authors did not explore, in what circumstances, these two approaches would produce similar or different results, is it because of sample size, number of diseases, combination of diseases, sample characteristics or something else? In my opinion, a simulation study maybe more valuable because it allows us to test the main hypothesis—whether the approaches produce the same results—in all kinds of situations. Please find my other specific comments and suggestions below:</p> <ol style="list-style-type: none"> 1. A table describing the demographic, lifestyle, and health characteristics of the study participants is helpful. 2. The authors wrote "... EFA is not designed for clustering purposes and it is essentially used for (visual) exploratory purposes, dimensionality reduction purposes or variables transformation." I think principle component analysis is more like a dimension reduction approach, while EFA alone with confirmatory factor analysis are primarily used for testing hypothesized
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	<p>relationships between observed measures and latent constructs.</p> <p>3. Because all study participants are from Catalonia, Spain, a more specific title might be more appropriate, e.g., replace “South Mediterranean European Region” with “in Spain”</p> <p>4. Please spell out ICD-10 in the Abstract.</p> <p>5. There are a few typos and grammatical errors that need to be corrected. For example, “results compared for each method” should be “results were compared for each method” (p. 2, lines 19-21)</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

First of all, we wish to express our gratitude to the reviewer for his constructive comments, which have helped to improve the revised version of the manuscript.

In order to facilitate understanding, we have set the changes that have been made to the paper with simple quotes.

This work uses a very interesting and informative data resource, the Catalan SIDIAP database. The Authors intended to explore the occurrence of patterns of multi-morbidity across the study population, where clinical information was recorded through electronic health records.

ANSWER

Many thanks for the comments. We are grateful for the reviewer’s attention to our work.

Despite the research idea be interesting, the study fails to convey relevant information in a useful way. They Authors decided to focus the work on a quasi -methodological comparison of hierarchical cluster analysis (HCA) and exploratory factor analysis (EFA). This is a debatable choice as the SIDIAP database has great potential to disclose useful information on the occurrence of multi-morbidity among the same individuals. HCA and EFA are very different tools, and the fact that they provide differential evidence is to be expected. Occurrence of a specific morbid condition is a discrete state. In this respect application of HCA seems a very natural choice to appreciate the level of clustering of such conditions, thus producing informative findings. On the other hand, with EFA one usually measures propensity towards adherence to specific conditions/states that individuals tend to show with various degree of consistency, such as high physical activity or large intake of dietary fibres. The application of such scores to something that either exists or does not exist can still provide information on the propensity towards the simultaneous occurrence of multiple morbid conditions. However, the interpretation is less obvious, letting aside the methodological complications that scores are by definition orthogonal (at least before further stretching of results via rotation), and despite the technique does not really fit discrete data, as clearly pointed out by the Authors. In this respect I find it difficult to agree with the sentence in the conclusions of the Abstract as, while acknowledging the methodological challenges, these multi-morbidity patterns likely exists irrespectively of the analytical method used to identify them. It is up to a careful research plan and a sensible use of statistical technique to observe them. The manuscript could be substantially improved if the aims of the work were better defined.

ANSWER

As the reviewer suggested, we have rewritten some parts of the introduction:

‘These studies highlight the lack of consensus to measure patterns of comorbidity and multimorbidity. In recent years, the number of studies based on real-world data (RWD) [5] has increased significantly, which makes it even more difficult to establish a consensus on how to measure comorbidity and multimorbidity patterns. Although much more information is available, the different databases may not

be comparable, making it difficult to arrive at observations and draw firm conclusions. It also limits our ability to compare analyses using RWD and to evaluate whether one approach may be better suited to the purpose. Therefore, it is difficult to identify multimorbidity patterns and provide adequate health services according to the population needs.'

We also revised the last paragraph in the introduction, as follows:

'For all these reasons, the aim was to compare multimorbidity patterns identified with the two most commonly used methods: hierarchical cluster analysis (HCA) and exploratory factor analysis (EFA) in a large primary care database. Specific objectives were 1) to determine how the choice of method may affect the composition of these patterns and 2) to consider the potential application of each method in the clinical setting.'

As a result of changes in the introduction and discussion sections, we modified the statement of our research aim in the abstract:

'The aim was to compare multimorbidity patterns identified with the two most commonly used methods: hierarchical cluster analysis (HCA) and exploratory factor analysis (EFA) in a large primary care database. Specific objectives were 1) to determine how the choice of method may affect the composition of these patterns and 2) to consider the potential application of each method in the clinical setting.'

And also the conclusions in the abstract:

'Conclusions. This study showed that multimorbidity patterns vary depending on the method of analysis used (HCA vs EFA) and provided new evidence about the known limitations of attempts to compare multimorbidity patterns between RWD studies. We found that EFA was useful in describing comorbidity relationships and HCA could be useful for in-depth study of multimorbidity. Our results suggest possible applications for each of these methods and add information about some aspects that must be considered in standardization of future studies: spectrum of diseases, data utilization, and methods of analysis.'

Furthermore, we added this paragraph in the discussion section to clarify some aspects:

'The multimorbidity patterns obtained with EFA show a main factor (a disease) that has a correlation with another disease, either coexisting or that may occur during the patient's clinical course. [20] Thus, EFA could be more useful for analyzing comorbidity and for describing the correlation between diseases that have a pathophysiological relationship. This approach also may help to answer the question of which condition should be considered the main disease and which the comorbidity.'

Finally, we have rewritten the final conclusion in the text:

'The multimorbidity patterns obtained with EFA show a main factor (i.e., a disease) that has some correlation with the additional diseases in the pattern, suggesting a comorbidity relationship. Meanwhile, the HCA would be useful for in-depth study of multimorbidity. We introduced new evidence about the known limitations of attempts to compare multimorbidity or comorbidity patterns between RWD studies, as our results add information about aspects that must be considered in standardization of future studies: spectrum of diseases, data utilization, and methods of analysis.'

Abstract. Please use more appropriate description of the "...263 blocks (ICD-10)".

ANSWER

We have added the description of ICD in the abstract of the revised manuscript.

'Cross-sectional study. Diagnoses were based on the 263 corresponding blocks of the International Classification of Diseases (ICD-10).'

This is a cross-sectional analysis that seems to refer to information in 2010. What was the time span the multi-morbidity referred to approximately? In other words, how far in time were morbid conditions retrospectively assessed for individuals in the SIDIAP database?

ANSWER

We appreciate this question. A cross-sectional design (based on patient status on 31 December 2010) precludes calculation of a time span. Therefore, duration of the coded diseases was not collected. The analysis focused on the clusters observed in active diagnoses at the study date.

Abstract, results and following. As the analysis included some 408K individuals with at least two conditions, what is the meaning of the sentence "... the 12 clusters with at least 2 diagnoses"?

ANSWER

It is important to remember that the analysis clustered diseases, not individuals; therefore it is possible to obtain clusters with only one disease (i.e., a disease that has no frequent co-occurring conditions in the 408K records analyzed). Twelve out of 53 clusters contained 2 or more diagnoses. Of course, the remaining 41 "single-disease clusters" are not informative and we didn't show them. We have more space to explain this in the Results, where we said, on page 11: 'Using HCA with the Ward method, we obtained 53 clusters, with just 12 clusters grouping at least two diagnoses for women and 15 clusters for men (Table 1).'

Introduction, line 40. What distance do the Authors refer to, mathematical (Euclidean) or chronological distance?

ANSWER

We refer to mathematical (Euclidean) distance, which is the most common distance used in cluster analysis. In our study, we used the Jaccard distance between binary variables.

We added this clarification in the introduction:

The HCA clusters tend to contain diagnoses that are similar to each other (in terms of 'Euclidean' distance), but dissimilar from the diagnoses in other clusters; no diagnosis can be included in more than one cluster.

Lines 44-5. Unclear statements, please consider revision.

ANSWER

We appreciate this observation and the opportunity to improve clarity in the revised introduction:

'In contrast, EFA along with confirmatory factor analysis are primarily used to test hypothesized relationships between observed measures and latent constructs.'

Line 457. Conditionally, please clarify on what.

We have eliminated this controversial word and have tried to better explain the method by reformulating the paragraph as shown in the next response.

Page 2, lines 2-6: this type of statements pertains to the discussion, rather than the Introduction.

ANSWER

We appreciate this observation. We have deleted the entire paragraph from the Introduction and moved this point to the discussion section, revised as follows:

'In addition, EFA is problematic for binary data, which can be grouped because of having similar distributions rather than any common underlying feature. On the other hand, in factor analysis the measure of association incorporates information on both positive and negative concordances [8]. In

contrast, the analysis of clusters allows us to show that the occurrence of one or more health conditions can be conditioned by their co-occurrence, without considering negative concordances. [7]

Reviewer: 2

In this study, the authors compared two different statistical approaches in identifying multimorbidity patterns in a Spanish cohort and concluded the different approaches produced different results. The paper is nicely written and the quantitative analyses are very rigorous and thorough. However, I did not clearly see the clinical and scientific contributions this paper could bring to the literature. It is not surprising to me that two methods, developed for different purposes, produced different results; maybe these two methods would produce similar results in a different population. Also, the authors did not explore, in what circumstances, these two approaches would produce similar or different results, is it because of sample size, number of diseases, combination of diseases, sample characteristics or something else? In my opinion, a simulation study maybe more valuable because it allows us to test the main hypothesis—whether the approaches produce the same results—in all kinds of situations. Please find my other specific comments and suggestions below:

ANSWER

Thank you for this comment. We sought to elucidate what each method adds to the study of multimorbidity/comorbidity and in which circumstances each could be more applicable in clinical practice. On the other hand, we take note of the reviewer's suggestion of a simulation analysis for a possible future study. We have slightly revised our statement of the aims of the study, as follows:

'The aim was to compare multimorbidity patterns identified with the two most commonly used methods: hierarchical cluster analysis (HCA) and exploratory factor analysis (EFA) in a large primary care database. Specific objectives were 1) to determine how the choice of method may affect the composition of these patterns and 2) to consider the potential application of each method in the clinical setting.'

Furthermore, we added this paragraph in the discussion section:

'The multimorbidity patterns obtained with EFA show a main factor (a disease) that has a correlation with another disease, either coexisting or that may occur during the patient's clinical course. [20] Thus, EFA could be more useful for analyzing comorbidity and for describing the correlation between diseases that have a pathophysiological relationship. This approach also may help to answer the question of which condition should be considered the main disease and which the comorbidity.'

Finally, we have rewritten the final conclusion:

'The multimorbidity patterns obtained with EFA show a main factor (i.e., a disease) that has some correlation with the additional diseases in the pattern, suggesting a comorbidity relationship. Meanwhile, the HCA would be useful for in-depth study of multimorbidity pattern. We introduced new evidence about the known limitations of attempts to compare multimorbidity or comorbidity patterns between RWD studies, as our results add information about aspects that must be considered in standardization of future studies: spectrum of diseases, data utilization, and methods of analysis.'

1. A table describing the demographic, lifestyle, and health characteristics of the study participants is helpful.

ANSWER

The authors agree that this could have added some interesting background. The SIDIAP database has a lot of information, but not at all of it was accessible for our study. The study protocol submitted to the Committee on the Ethics of Clinical Research included only 3 variables: diagnosis, age, and sex.

2. The authors wrote "... EFA is not designed for clustering purposes and it is essentially used for (visual) exploratory purposes, dimensionality reduction purposes or variables transformation." I think principle component analysis is more like a dimension reduction approach, while EFA alone with confirmatory factor analysis are primarily used for testing hypothesized relationships between observed measures and latent constructs.

ANSWER

The reviewer is correct. We apologize for using an improper definition and have rewritten the paragraph using the concise language provided by the reviewer:

'In contrast, EFA along with confirmatory factor analysis are primarily used to test hypothesized relationships between observed measures and latent constructs. In addition, EFA allows for inclusion of any diagnosis in multiple factors as they can present significant correlations with more than one factor. [5-8]'

3. Because all study participants are from Catalonia, Spain, a more specific title might be more appropriate, e.g., replace "South Mediterranean European Region" with "in Spain"

ANSWER

In response to your suggestion, we have changed the title, omitting the geographic reference to focus more clearly on the key elements of our study (comparative analysis of multimorbidity patterns and use of real-world data):

'Comparative analysis methods for identifying multimorbidity patterns: A study of 'real world' data.'

4. Please spell out ICD-10 in the Abstract.

ANSWER

Thank you for pointing out this oversight. We have revised the sentence as follows:

'Cross-sectional study. Diagnoses were based on 263 blocks of the International Classification of Diseases (ICD-10).'

5. There are a few typos and grammatical errors that need to be corrected. For example, "results compared for each method" should be "results were compared for each method" (p. 2, lines 19-21)

ANSWER

We have reviewed the text and corrected typos and grammatical errors.

VERSION 2 – REVIEW

REVIEWER	Chenkai Wu
REVIEW RETURNED	12-Dec-2017

GENERAL COMMENTS	<p>Most of my comments have been addressed. There are some lingering issues I would encourage the authors to consider.</p> <p>Major: The first aim of the paper is to "determine how the choice of method may affect the composition of these patterns". However, I think "whether choice of method affects the composition of these patterns" may be more appropriate as the conclusion is "This study showed that multimorbidity patterns vary depending on the method of analysis used (HCA vs EFA)". Again, to determine how the choice of</p>
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	<p>method may affect the comorbidity patterns, a simulation study is needed.</p> <p>Another aim is to "consider the potential application of each method in the clinical setting." However, in the Conclusion, there is only a very vague/general statement, "We found that EFA was useful in describing comorbidity relationships and HCA could be useful for in-depth study of multimorbidity". In addition, I assume that the second last paragraph in the Discussion discusses the clinical utility of the two methods; however, in my opinion, these nuances between the two methods matter much more in research setting than in a bust clinical setting. Therefore, I am not convinced that this methodological paper has many applications in the clinical setting.</p> <p>Minor:</p> <p>In the Abstract, please spell out RWD. Also, because only one data set was used, I am not sure why the authors said, " xxx compare multimorbidity patterns between RWD studies".</p>
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VERSION 2 – AUTHOR RESPONSE

Reviewer: 2

Most of my comments have been addressed. There are some lingering issues I would encourage the authors to consider.

First of all, we wish to express our gratitude to the reviewer for his constructive comments, which have helped us to improve the revised version of the manuscript.

In order to facilitate we highlighted the words or paragraphs in grey in the answers

Major:

The first aim of the paper is to "determine how the choice of method may affect the composition of these patterns". However, I think "whether choice of method affects the composition of these patterns" may be more appropriate as the conclusion is "This study showed that multimorbidity patterns vary depending on the method of analysis used (HCA vs EFA)". Again, to determine how the choice of method may affect the comorbidity patterns, a simulation study is needed.

ANSWER

Thank you for this comment; we have changed the aim in the abstract and in the introduction section:

Specific objectives were 1) to determine how the choice of method may affect the composition of these patterns whether choice of method affects the composition of these patterns and 2) to consider the potential application of each method in the clinical setting.

We also added these lines in the discussion section:

Nevertheless, it would be necessary to carry out a simulation study to determine how the choice of method may affect the patterns, as it allows us to test the obtained patterns in all kinds of situations.

Another aim is to "consider the potential application of each method in the clinical setting." However, in the Conclusion, there is only a very vague/general statement, "We found that EFA was useful in describing comorbidity relationships and HCA could be useful for in-depth study of multimorbidity". In addition, I assume that the second last paragraph in the Discussion discusses the clinical utility of the two methods; however, in my opinion, these nuances between the two methods matter much more in

research setting than in a bust clinical setting. Therefore, I am not convinced that this methodological paper has many applications in the clinical setting.

ANSWER

We appreciate this observation, but we only wanted to explain potential applications of these methods and which might be useful for future investigation in the clinical setting. We added these words in the conclusion section of the abstract:

Our results suggest possible applications for each of these methods in clinical and research settings and add information about some aspects that must be considered in standardization of future studies: spectrum of diseases, data utilization, and methods of analysis.

Minor:

In the Abstract, please spell out RWD. Also, because only one data set was used, I am not sure why the authors said, " xxx compare multimorbidity patterns between RWD studies".

ANSWER

We have changed the sentence in the abstract:

to compare multimorbidity patterns between in Real World Data studies