PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Prevalence and patterns of multimorbidity in Amazon Region of Brazil and associated determinants: a cross-sectional study
AUTHORS	Araujo, Elizete; Silva, Marcus; Galvao, Tais; Nunes, BP; Pereira, Mauricio

VERSION 1 – REVIEW

REVIEWER	Caroline Jackson University of Edinburgh, Usher Institute of Population Health Sciences & Informatics
REVIEW RETURNED	30-Apr-2018

GENERAL COMMENTS	The authors report the findings of a cross-section study investigating the prevalence of multimorbidity in the metropolitan area of Manaus in north Brazil. They also report on associated determinants and health service factors. They found that a third reported having two or more chronic conditions and that, in adjusted analyses, multimorbidity was associated with female sex, older age and having a worse health perception. Multimorbidity was also associated with more health service use. The authors also sought to identify multimorbidity patterns, identifying one pattern in women and two in men. This study addresses the important topic of multimorbidity and reports some interesting findings from a geographical area which has been somewhat less studied in terms of multimorbidity prevalence, patterns and determinants. Whilst the findings are interesting and generally well-presented, the rationale for the current study requires clarification in the introduction. The discussion does not flow well, is very fragmented and does not adequately discuss the study findings within the context of previous studies. Major comments Introduction 1. The rationale for the current study is not entirely clear. The authors mention the findings on multimorbidity from the National Health Survey in 2013, but do not indicate whether this is the only/best estimate of multimorbidity in the country. No other previous studies of multimorbidity in Brazil or similar countries are referenced. Clearer justification for the current study is needed. Methods 1. The authors do not justify why they included the stated 12 chronic conditions. How were these conditions chosen for inclusion? 2. How did you decide how to categorise age in the analyses? Results 1. The authors report that multimorbidity is associated with being

	elderly, yet they (quite correctly) highlight the extent of multimorbidity in those aged under 60 years. I would recommend rephrasing the comments on age to reflect the fact that multimorbidity prevalence increases with increasing age, but that in terms of burden of disease, the burden of multimorbidity is actually highest in the 35-59 age-group categories. When looking in detail at those with multimorbidity to examine the prevalence of individual chronic diseases, the authors highlight specific diseases among women and women in the youngest age categories. Whilst these diseases have high prevlance, the absolute numbers are low in comparison to disease frequencies in other age-groups, so I'm not convinced of the usefulness of highlighting these findings in the text (and especially not in the first paragraph of the discussion section) 2. In table 2, it would be helpful to include the total N for each column in the top row. It seems rather odd that the percentages for heart disease, asthma and depression in those aged 60 or over is 100? Is this an error? Discussion 1. The discussion section is rather fragmented and doesn't flow very well. The authors need to follow a more ordered and coherent structure. The authors jump from summarising the findings, to mentioning the limitations and then proceed to referring to previous studies in a bit of a random order, sometimes without reference to their own findings (e.g. page 15, paragraph 2). 2. In their limitations section, the authors mostly discuss the issue of self-reporting. I would use the term recall bias instead of memory bias here. Other limitations to highlight include the cross-sectional nature of the study, which means that temporal associations cannot be investigated (and the authors should therefore be careful not to over-interpret health service use as a determinant of multimorbidity, since it could be a consequence of multimorbidity). Another limitation is the short list of conditions included (and the broad categories of conditions), which will have impacted the results (see comments below). 3. The authors refer to previous literature which indicates that multimorbidity prevalence estimates are lower the fewer the number of conditions that are included (page 13 paragraph 2. Yet they don't make any reference to their own study here. They included 12 conditions, some of which are very broad categories of diseases (e.g. all respiratory diseases were grouped together). They have also omitted various diseases (such as liver disease, osteoporosis, other mental health disorders apart from depression). This is likely to have impacted on their findings, especially the analysis of multimorbidity patterns. The authors need to acknowledge the limitations of their choice of conditions and the groupings used. 4. There is no real discussion about the identified multimorbidity patterns with reference to how these findings compare/contrast with previous studies of multimorbidity patterns. This study is odd in that only one pattern was found in women and two in men. Most previous studies have identified at least three and generally four-five multimorbidity patterns. The authors need to consider explanations for their findings and highlight the limitations of their methods, which might explain the lack of observed patterns. One might also question whether raised cholesterol (and possibly even hypertension) should be considered a chronic disease and not a risk factor for disease. 5. In the second paragraph of page 14, the authors comment on the

	'higher frequency of multimorbidity in younger adults'. This should be rephrased since it is a bit misleading, given the authors findings that multimorbidity increases with increasing age. 6. In paragraph 2 of page 14, the authors also comment that they didn't find an association between income and multimorbidity. However, I think it's important to note that there is an association in the unadjusted analyses (as shown in table 1) and that adjusting for other factors, especially other socioeconomic factors, has removed the association. 7. I'm not convinced that the final sentence (and reference) given on paragraph 2 of page 14 fits in well with the discussion here. 8. In paragraph 4 of page 14, the authors refer to the age characteristics of the observed clusters in men. It's not entirely clear if they performed these analyses or if these comments are based on assumptions. If they did perform the analyses, these should be reported in the results (and methods included in the methods section) and not the discussion. 9. On page 15, the authors discuss the difference in multimorbidity prevalence in the north and south of Brazil and also refer to health service provision/use in these areas. They make a rather conflicting point that a reduction in health service use leads to increased multimorbidity. Yet, they also comment in the paper that multimorbidity levels are higher in the south than the north, where there is greater access to health services. 10. On page 9, paragraph 3, the authors refer to other studies of multimorbidity, in terms of prevalence. It would be sensible to mention this earlier in the discussion, within the context of their own findings. Again, the fragmented structure of the discussion affects the readability and flow. 11. Finally, the conclusion section mentions that further work on physical and psychic disorders is needed. This statement appears suddenly, since this particular point is not touched upon anywhere else in the article. Minor comments: Results 1. The authors that they included 4001 participants, yet the abstracts indicates 4000. 2. Please clarify the highest education category – does this represent those with a tertiary education or higher (i.e. degree/college education or higher?)

REVIEWER	Carl D'Arcy University of Saskatchewan, Canada
REVIEW RETURNED	01-May-2018

GENERAL COMMENTS	This is solid manuscript but I would have liked some additional information. For example since the comparison is of a region within Brazil to Brazil as a whole I would have like more regional context on Manaus and Amazonas. Briefly, how does this area currently differ from the rest of Brazil, economically, socially and in terms of population composition. Is Portuguese the common language for all groups in this area of Brazil? Indigenous populations? What kind of health care system is there? How is health care and health insurance organized and delivered?

	I would also like to know how representative is the study sample? How does the sample surveyed compare to the census data for the area. If the researchers used the same or essentially similar questionnaire as used in the national survey they should clearly say so. The English in the manuscript was very good, I only notice one word error on Page 3, line 40 the word I think should be “physician visits” instead of “physical visits”.

REVIEWER	Changgui Kou School of Public Health, Jilin University, China
REVIEW RETURNED	02-May-2018

GENERAL COMMENTS	1. How and why do you choose the investigation places you mentioned in the article? Can Manaus and the surrounding 7 citied represent North Brazil? 2. There are 12 chronic diseases in your survey? How and why you choose these 12 chronic diseases? Is there any basis? 3. The prevalence of diabetes and hypertension is rising in parallel with that of excess weight, why don’t you include obesity in your study? (Reference: Schmidt M I, Duncan B B, Azevedo e S G, et al. Chronic non-communicable diseases in Brazil: burden and current challenges. [J]. Lancet, 2011, 377(9781):1949-1961.) 4. Cardiovascular diseases, diabetes, cancer, and chronic respiratory disease are be infected by tobacco use, physical inactivity, unhealthy diets, and harmful use of alcohol, why don’t authors explore the association between these habits with multimorbidity? 5. In results, numbers you described in the article are not consistent with those in table 2 and 3.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Caroline Jackson

Institution and Country: Chancellor's Fellow, Usher Institute of Population Health Sciences & Informatics, University of Edinburgh, Scotland, UK

Please state any competing interests or state ‘None declared’: None declared
Please leave your comments for the authors below

The authors report the findings of a cross-section study investigating the prevalence of multimorbidity in the metropolitan area of Manaus in north Brazil. They also report on associated determinants and health service factors. They found that a third reported having two or more

chronic conditions and that, in adjusted analyses, multimorbidity was associated with female sex, older age and having a worse health perception. Multimorbidity was also associated with more health service use. The authors also sought to identify multimorbidity patterns, identifying one pattern in women and two in men. This study addresses the important topic of multimorbidity and reports some interesting findings from a geographical area which has been somewhat less studied in terms of multimorbidity prevalence, patterns and determinants. Whilst the findings are interesting and generally well-presented, the rationale for the current study requires clarification in the introduction. The discussion does not flow well, is very fragmented and does not adequately discuss the study findings within the context of previous studies.

Major comments

REVIEWER COMMENT:

INTRODUCTION

1.The rationale for the current study is not entirely clear. The authors mention the findings on multimorbidity from the National Health Survey in 2013, but do not indicate whether this is the only/best estimate of multimorbidity in the country. No other previous studies of multimorbidity in Brazil or similar countries are referenced. Clearer justification for the current study is needed.

OUR RESPONSE: A we accept the suggestions and correct the justification and added other researches realized in Brazil. *In Brazil, the 2013 National Health Survey ……."and the most*

extensive evidence on population multimorbidity, has identified that the prevalence of multimorbidity was 26-29% in the southern region and 14-19% in the northern region.[14] The differences found suggest heterogeneity in socioeconomic development. Studies in specific populations conducted on the south and southeast regions identified higher multimorbidity prevalence in women and elderly.[15] [16] The differences found suggest heterogeneity in socioeconomic development.[17] However, there is a lack of studies on the north region to identify more susceptible groups and expand our knowledge about multimorbidity at the local level."

METHODS

REVIEWER COMMENT:

1. The authors do not justify why they included the stated 12 chronic conditions. How were these conditions chosen for inclusion?

OUR RESPONSE: The list of diseases followed a national standard, used in several national surveys (National Health Survey- PNS and National Survey and Household Sample Survey - PNAD). Allows comparability with other regions of the country

REVIEWER COMMENT:

2. How did you decide how to categorise age in the analyses?

OUR RESPONSE: We adjust the age groups according to previous publications in Brazil, in order to allow better comparability. We added the information in the method "age (18 to 24; 25 to 34; 35 to 44; 45 to 59 and ≥ 60 years)[21]"

RESULTS

REVIEWER COMMENT:

1.The authors report that multimorbidity is associated with being elderly, yet they (quite correctly) highlight the extent of multimorbidity in those aged under 60 years. I would recommend rephrasing the comments on age to reflect the fact that multimorbidity prevalence increases with increasing age, but that in terms of burden of disease, the burden of multimorbidity is actually highest in the 35-59 age-group categories. When looking in detail at those with multimorbidity to examine the prevalence of individual chronic diseases, the authors highlight specific diseases among women and women in the youngest age categories. Whilst these diseases have high prevlance, the absolute numbers are low in comparison to disease frequencies in other age-groups, so I'm not convinced of the usefulness of highlighting these findings in the text (and especially not in the first paragraph of the discussion section)

OUR RESPONSE: We appreciate the comment and made corrections in the text. "*The mean of any chronic disease and the multimorbidity increased with age (0.5 ± 0.8 in the 18 to 24 year-old group and 2.5 ± 1.9 in those 60 years or above)"* Our data do not allow inference in terms of disease burden, higher in the categories of age groups 35 to 59.

REVIEWER COMMENT:

2. In table 2, it would be helpful to include the total N for each column in the top row. It seems rather odd that the percentages for heart disease, asthma and depression in those aged 60 or over is 100? Is this an error?

OUR RESPONSE: We accepted the suggestion, in table 2. We include the total N for each column in the top row and we add to the results. Yes, the percentages for heart disease, asthma and depression in those aged 60, they are correct, justified by the small "N"

REVIEWER COMMENT:

Discussion

1.The discussion section is rather fragmented and doesn't flow very well. The authors need to follow a more ordered and coherent structure. The authors jump from summarising the findings, to mentioning the limitations and then proceed to referring to previous studies in a bit of a random order, sometimes without reference to their own findings (e.g. page 15, paragraph 2).

OUR RESPONSE: We appreciate the comment. The text was better structured. We used checklist STROBE (attached to scholarOne) as directed by the journal, STROBE defines the following structure for the discussion (key results, limitations and strengths, interpretation, and generalization).

REVIEWER COMMENT:

2.In their limitations section, the authors mostly discuss the issue of self-reporting. I would use the term recall bias instead of memory bias here. Other limitations to highlight include the cross-sectional nature of the study, which means that temporal associations cannot be investigated (and the authors should therefore be careful not to over-interpret health service use as a determinant of multimorbidity, since it could be a consequence of multimorbidity). Another limitation is the short list of conditions included (and the broad categories of conditions), which will have impacted the results (see comments below).

OUR RESPONSE: We accepted the suggestion. We use the term " *recall bias*". The text was better structured.

REVIEWER COMMENT:

3. The authors refer to previous literature which indicates that multimorbidity prevalence

estimates are lower the fewer the number of conditions that are included (page 13 paragraph 2. Yet they don't make any reference to their own study here.

OUR RESPONSE: We appreciate the comment. The text was better structured.

REVIEWER COMMENT:

3.They included 12 conditions, some of which are very broad categories of diseases (e.g. all respiratory diseases were grouped together). They have also omitted various diseases (such as liver

disease, osteoporosis, other mental health disorders apart from depression). This is likely to have impacted on their findings, especially the analysis of multimorbidity patterns. The authors need to acknowledge the limitations of their choice of conditions and the groupings used.

OUR RESPONSE: We followed the methodology used in the great inquiries of the country, this allows us comparability to identify inequalities, and generate evidence for health policies at the local level. Although it was omitted such as liver disease (osteoporosis, other mental health disorders). Page 14, third paragraph. "*We used a cut-off point of ≥2 and ≥3 chronic diseases, as previous studies did.*[3 5] *We identified the most vulnerable multimorbidity groups were women and the elderly. The multimorbidity was higher in older people and it increases with age, this outcome was observed in previous studies.*[5 9 20] *The National Health Survey conducted in Brazil in 2013 reported that women are most affected in all socioeconomic groups, especially the elderly.*[36]*"*

REVIEWER COMMENT:

4. There is no real discussion about the identified multimorbidity patterns with reference to how these findings compare/contrast with previous studies of multimorbidity patterns. This study is odd in that only one pattern was found in women and two in men. Most previous studies have identified at least three and generally four-five multimorbidity patterns. The authors need to consider explanations for their findings and highlight the limitations of their methods, which might explain the lack of observed patterns. One might also question whether raised cholesterol (and possibly even hypertension) should be considered a chronic disease and not a risk factor for disease.

OUR RESPONSE: We adjusted the text, page 16, third paragraph "*A single multimorbidity pattern was identified in women, which included the 12 researched diseases. The factor loading the most strength of association in women was heart disease. In previous studies conducted in Brazil with similar questions, up to three multimorbidity pattern have been identified, and hypertension had the most strength of association, but no stratification by sex was done.*[20] *It is possible that the lowest number of pattern for women in our research may be due to stratification or to the broad categories of diseases. In men, lung disease was disease with higher factorial loading, comparable to a Spanish population-based cross-sectional study.*[51] *Based on assumptions, elderly men could be*

clustered in factor 1, since they had worse outcomes. Factor 2 would include younger men with diseases developed from risk factors such as sedentary lifestyle and obesity."

REVIEWER COMMENT:

5.In the second paragraph of page 14, the authors comment on the 'higher frequency of multimorbidity in younger adults'. This should be rephrased since it is a bit misleading, given the authors findings that multimorbidity increases with increasing age.

OUR RESPONSE: We adjusted the text, page 16, third paragraph. "*Two findings of our research are rarely described in previous studies: the higher frequency of multimorbidity in younger ages and the lack of association with economic status. One-half of adults aged 25 to 34 years and almost two-thirds of interviewees aged 35 to 44 years reported any chronic condition, and almost one-third had multimorbidity. The development of multimorbidity in young adults is agreement with previous data from Brazil.*[20 36 37]*"*

REVIEWER COMMENT:

6.In paragraph 2 of page 14, the authors also comment that they didn't find an association between income and multimorbidity. However, I think it's important to note that there is an association in the unadjusted analyses (as shown in table 1) and that adjusting for other factors, especially other socioeconomic factors, has removed the association.

OUR RESPONSE: We adjusted the text Page 16 third paragraph. *We identified lack of association after adjusting for socioeconomic block"*

REVIEWER COMMENT:

7.I'm not convinced that the final sentence (and reference) given on paragraph 2 of page 14 fits in well with the discussion here.

OUR RESPONSE:. We adjusted the text page 15 third paragraph. "*This effect was observed in other austerity scenarios, in which this type of policy reduced jobs, education and use of health services, resulting in an increase of chronic diseases.*[43 44] *High-income countries has found that 3,6 more years of education reduces the risk of cardiovascular disease by one third.*[45]*"*

REVIEWER COMMENT:

8. In paragraph 4 of page 14, the authors refer to the age characteristics of the observed clusters in men. It's not entirely clear if they performed these analyses or if these comments are based on assumptions. If they did perform the analyses, these should be reported in the results (and methods included in the methods section) and not the discussion.

OUR RESPONSE: We adjusted the text. Page 16, third paragraph*." Based on assumptions, elderly men could be clustered in factor 1, since they had worse outcomes. Factor 2 would include younger men with diseases developed from risk factors such as sedentary lifestyle and obesity."*

REVIEWER COMMENT:

9. On page 15, the authors discuss the difference in multimorbidity prevalence in the north and south of Brazil and also refer to health service provision/use in these areas. They make a rather conflicting point that a reduction in health service use leads to increased multimorbidity. Yet, they also comment in the paper that multimorbidity levels are higher in the south than the north, where there is greater access to health services.

OUR RESPONSE: We adjusted the text. "*Our results showed similarities to a cross-sectional study conducted in 2012 in Pelotas city in the southern region of Brazil with 2 927 subjects, in which 29.1% of the interviewees had more than two chronic diseases and*

14% had three or more.[37] The 2013 National Health Survey also confirmed these findings: 22% of Brazilians reported two or more chronic diseases, and 10% were affected by more than three.[14] The highest prevalence was observed in the south (26 to 29%),[14] which is more economically developed and have greater access to health services.[17 38] Any chronic disease occurred in 45% of Brazilians, with a lower prevalence in the north region.[39]"

REVIEWER COMMENT:

10.On page 9, paragraph 3, the authors refer to other studies of multimorbidity, in terms of prevalence. It would be sensible to mention this earlier in the discussion, within the context of their own findings. Again, the fragmented structure of the discussion affects the readability and flow.

OUR RESPONSE: We appreciate the comment. We adjusted the text.

REVIEWER COMMENT:

11.Finally, the conclusion section mentions that further work on physical and psychic disorders is needed. This statement appears suddenly, since this particular point is not touched upon anywhere else in the article.

OUR RESPONSE: We appreciate the comment. "*Future analyses should investigate the relationship between multimorbidity and use and costs of health services in the region"*

REVIEWER COMMENT

Minor comments:

Results

1.The authors that they included 4001 participants, yet the abstracts indicates 4000.

OUR RESPONSE: We appreciate the comment. In our sample calculation we obtained 4000 participants, at the end of the data count, 4001 had been interviewed, it was administratively decided to incorporate this "one" interviewee in the results.

2.Please clarify the highest education category – does this represent those with a tertiary education or higher (i.e. degree/college education or higher?)

OUR RESPONSE: We appreciate the comment. The highest education category is High education or above. (table 1, note: § tertiary education or higher

Reviewer: 2

Reviewer Name: Carl D'Arcy

Institution and Country: University of Saskatchewan, Canada

Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below

REVIEWER COMMENT:

1.This is a solid manuscript, but I would have liked some additional information. For example, since the comparison is of a region within Brazil to Brazil as a whole I would have like more regional context on Manaus and Amazonas. Briefly, how does this area currently differ from the rest of Brazil, economically, socially and in terms of population composition. Is Portuguese the common language for all groups in this area of Brazil? Indigenous populations? What kind of health care system is there? How is health care and health insurance organized and delivered?

OUR RESPONSE: Thank you for your comments. This is the first study in the Amazon Region, and there are also few studies in Brazil on the subject, and most of the publications are referring to the National Health Survey. The aim of the comparison was to identify inequalities between regions. Manaus (Amazonas) has the 7th largest gross domestic product in the country, is economically less developed than the region South. The language spoken in the Brazil is Portuguese, including in Amazonas. Isolated indigenous groups that speak their own dialect were not included in the research, we investigated only the residents of the urban area of the metropolitan region of

Manaus. We added one note in the end of the table 1. (‡ People who use the public health service). Health service are offered in public, private and by health insurance.

REVIEWER COMMENT:

2. I would also like to know how representative is the study sample? How does the sample surveyed compare to the census data for the area. If the researchers used the same or essentially similar questionnaire as used in the national survey they should clearly say so.

OUR RESPONSE: We used probabilistic sampling, with data from the 2010 census (2 106 322 residents ≥ 18 years old in 2647 urban census tracts) stratified by age and sex quotas. This ensures representativeness. Details of the sampling process are described in the research protocol http://www.scielo.br/scielo.php?pid=S2237-96222017005002103&script=sci_arttext&tlng=en

REVIEWER COMMENT:

3. The English in the manuscript was very good, I only notice one word error on Page 3, line 40 the word I think should be “physician visits” instead of “physical visits”.

OUR RESPONSE: We appreciate the comment The word has been corrected “physician visits”

Reviewer: 3

Reviewer Name: Changgui Kou

Institution and Country: School of Public Health, Jilin University, China

Please state any competing interests or state ‘None declared’: None

REVIEWER COMMENT:

1.How and why do you choose the investigation places you mentioned in the article? Can Manaus and the surrounding 7 citied represent North Brazil?

OUR RESPONSE: The choice of the metropolitan region aims to investigate the health of the population in a larger area that represents the population of the State. Metropolitan Region in Brazil is an area composed of a set of contiguous cities and with socioeconomic integration to a large city (in this case, Manaus the capital) where it has greater infrastructure, variety of health services, large labor market and high resident population, the metropolitan region representing more than 60% of the population of the state.

REVIEWER COMMENT:

2.There are 12 chronic diseases in your survey? How and why you choose these 12 chronic diseases? Is there any basis?

OUR RESPONSE: Thank you for your comments. The list of diseases followed a national standard, used in several national surveys (National Health Survey- PNS and National Survey and Household Sample Survey - PNAD). Allows comparability with other regions of the country.

REVIEWER COMMENT:

3. The prevalence of diabetes and hypertension is rising in parallel with that of excess weight, why don't you include obesity in your study? (Reference: Schmidt M I, Duncan B B, Azevedo e S G, et al. Chronic non-communicable diseases in Brazil: burden and current challenges. [J]. Lancet, 2011, 377(9781):1949-1961.)

OUR RESPONSE. We appreciate the comment. We are adapting our questionnaire to the second wave of research

REVIEWER COMMENT:

4.Cardiovascular diseases, diabetes, cancer, and chronic respiratory disease are be infected by tobacco use, physical inactivity, unhealthy diets, and harmful use of alcohol, why don't authors explore the association between these habits with multimorbidity?

OUR RESPONSE: That's an excellent observation. This association will be investigated in another study.

REVIEWER COMMENT:

5.In results, numbers you described in the article are not consistent with those in table 2 and

OUR RESPONSE: We appreciate the comment, and we reviewed all text and table.

VERSION 2 – REVIEW

REVIEWER	Dr Caroline Jackson Usher Institute for Population Health Sciences & Informatics, University of Edinburgh
REVIEW RETURNED	03-Jul-2018

GENERAL COMMENTS	The authors have addressed most of the comments satisfactorily. However, a few areas require further clarification. I also think the findings on multimorbidity patterns are not adequately discussed. There are some grammatical errors, with some sentences require rephrasing. 1. Please explain in the methods what is meant by the phrase 'using a reference health service' 2. Background section; third paragraph – the first sentence does not read well. I recommend cutting this into two sentences to improve clarity. 3. Methods section; penultimate paragraph – sentences beginning "This technique allowed us to…" also doesn't read well. In particular, the phrase '…identify the tendency of coexisting diseases…' doesn't makes sense. The sentence is overly long and could be cut into two sentences to improve clarity. 4. Results – paragraph headed "Prevalence of multimorbidity". The revised sentence doesn't really make sense – it doesn't make sense to say 'The mean of any chronic disease…' and it's not clear whether the numbers given in brackets both refer to the mean number of conditions (given the reference to multimorbidity). The sentence requires rephrasing 5. Table 2 would benefit from further description in the text. Also, it's a bit odd to present the % followed by the 'n' in brackets – the convention is to report the n and the % in brackets. 6. Reporting of the multimorbidity patterns in results section: The authors focus on describing which disease loads on to the factor with the highest loading, which isn't especially informative and is not the purpose of doing a factor analysis. They could characterise the first pattern identified in men as essentially being cardiometabolic. It's very odd that no clear pattern was identified in women, with all 12 included conditions loading on to the factor with a loading of more than 0.3. I think this is only partially explained by broad definitions of diseases being included, since quite a few specific diseases were in fact included, particularly the cardiometabolic conditions. The authors don't sufficiently refer to the published literature on multimorbidity patterns and need to acknowledge more explicitly their somewhat odd, even if inexplicable, finding. 7. Page 16 – second paragraph – the sentence "The cross-sectional nature of the study does not allow temporal associations investigations" should be rephrased to "The….does not allow investigation of temporal associations" 8. Page 17 – paragraph beginning "This is the first local study…" – the sentence "The multimorbidity was higher in older people…" doesn't make sense. Suggest rephrase to "Multimorbidity was higher…, as observed in previous studies."

	9. On page 18, please be explicit that you found no association between income and multimorbidity after adjusting for SES. 10. Page 18 – sentence beginning “High-income countries has found…” uses incorrect English. This should read “Studies in high-income countries have found…” 11. Page 19 – you indicate that factor one would comprise younger men and factor two older men, based on assumptions – which assumptions? Why can you assume this?

REVIEWER	Carl D'Arcy University of Saskatchewan, Canada
REVIEW RETURNED	09-Jul-2018

GENERAL COMMENTS	While the authors have responded to my review comments and suggestions in the separate document most of those responses have not been reflected in the text of the manuscript. In my initial review I asked for the inclusion of some contextual information about Manaus and Amazonas in terms of language, indigenous population, health care system etc., this was not provided. In asking my question about the representativeness of the study sample I expect to see a table column that lists both study sample and census characteristics for the region, so the readers could themselves could judge for themselves whether or not the study sample was representative of the regions’ population. I would also add an additional comments that if the authors wish to make comparisons in chronic diseases prevalence and multi-morbidity to Brazil as a whole, to other regions of Brazil or other countries then they should age/gender standardize their comparisons so that differences reported are a function of differences in prevalence and no just a reflection of the age/gender characteristics of the populations of the areas compared.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

REVIEWER COMMENT: The authors have addressed most of the comments satisfactorily. However, a few areas require further clarification. I also think the findings on multimorbidity patterns are not adequately discussed. There are some grammatical errors, with some sentences require rephrasing.

OUR RESPONSE: We thank the reviewer for dedicating her time to helping us improve our manuscript. We addressed all the comments, and the manuscript was fully reviewed by AJE, a recognized scientific English editing company.

REVIEWER COMMENT: 1. Please explain in the methods what is meant by the phrase ‘using a reference health service’

OUR RESPONSE: We clarified the expression in the text and added a footnote in each table it is mentioned. In the Methods, the text was changed as follows: *"seeking the same healthcare service when in need of attendance (health reference; yes, no)"*

REVIEWER COMMENT: 2. Background section; third paragraph – the first sentence does not read well. I recommend cutting this into two sentences to improve clarity.

OUR RESPONSE: We rephrased the third paragraph to improve clarity:

"In Brazil, multimorbidity ranged from 26% to 29% in adults living in the southern—and more developed—region and from 14% to 19% in the northern region. Studies in specific populations conducted in the south and southeast Brazilian regions identified higher prevalence of multimorbidity in women and the elderly than in other groups. Differences detected suggest heterogeneity due to socioeconomic development. In northern Brazil, there is a lack of studies identifying more susceptible groups and studies that expand our knowledge about multimorbidity at the local level."

REVIEWER COMMENT: 3. Methods section; penultimate paragraph – sentences beginning "This technique allowed us to…" also doesn't read well. In particular, the phrase '…identify the tendency of coexisting diseases…' doesn't makes sense. The sentence is overly long and could be cut into two sentences to improve clarity.

OUR RESPONSE: We appreciate the comment and changed the sentence for clarity and brevity:

"Exploratory factor analysis stratified by sex was performed to identify multimorbidity patterns, i.e., to identify associations, selecting variables with potentially common causal factors, such as interaction between diseases and/or common risk factors."

REVIEWER COMMENT: 4. Results – paragraph headed "Prevalence of multimorbidity". The revised sentence doesn't really make sense – it doesn't make sense to say 'The mean of any chronic disease…' and it's not clear whether the numbers given in brackets both refer to the mean number of conditions (given the reference to multimorbidity). The sentence requires rephrasing

OUR RESPONSE: We thank the reviewer for this comment. We have moved this information to the "Participant's characteristics" subsection and revised it to improve clarity:

"The prevalence of any chronic disease was 57.2% (95% CI 56.6 to 58.7%), with a mean ± standard deviation of 1.2 ± 1.5 chronic disease per person. This average increased with age (0.5 ± 0.8 in the 18 to 24-year-old group and 2.5 ± 1.9 in those 60 years or above)."

REVIEWER COMMENT: 5. Table 2 would benefit from further description in the text. Also, it's a bit odd to present the % followed by the 'n' in brackets – the convention is to report the n and the % in brackets.

OUR RESPONSE: We changed the presentation of Tables 1 and 2 to the convention "n (%)" and expanded the description of Table 2 in the text:

"Approximately half of women aged 35 to 59 years reported ≥2 morbidities (Table 2). Back pain was the most frequently reported health problem in both women and men, followed by hypertension. Women ≥60 years with two or more morbidities reported more hypertension (92.0%) than men did in the same age group (79.5%)."

REVIEWER COMMENT: 6. Reporting of the multimorbidity patterns in results section: The authors focus on describing which disease loads on to the factor with the highest loading, which isn't especially informative and is not the purpose of doing a factor analysis. They could characterise the first pattern identified in men as essentially being cardiometabolic. It's very odd that no clear pattern was identified in

women, with all 12 included conditions loading on to the factor with a loading of more than 0.3. I think this is only partially explained by broad definitions of diseases being included, since quite a few specific diseases were in fact included, particularly the cardiometabolic conditions. The authors don't sufficiently refer to the published literature on multimorbidity patterns and need to acknowledge more explicitly their somewhat odd, even if inexplicable, finding.

REVIEWER COMMENT: We believe that the reviewer is referring to the second factor identified for men (cardiometabolic diseases) and included this description in the Results section. We added more references to reduce and clarify the discussion of our findings on multimorbidity patterns in the Discussion section:

"A single multimorbidity pattern with all investigated diseases was identified in women. Heart disease presented the highest factor loading, but disease patterns are poorly explained due to the wide range of diseases included in one factor. This finding may be due to our measurement and analytical approach, including sex stratification, broad categories of diseases, and the number of chronic conditions investigated. In previous studies conducted in Brazil involving similar questions, up to three multimorbidity patterns have been identified: cardiometabolic, musculoskeletal-mental and respiratory. Such studies did not stratify by sex when investigating the multimorbidity pattern. An Australian longitudinal cohort with women born between 1946-51 identified five multimorbidity patterns (psychosomatic, musculoskeletal, cardiometabolic, cancer and respiratory) after investigating 18 chronic diseases and 13 symptoms. The greater number of diseases and symptoms may explain the number of clustering factors in women relative to our analysis (31 versus 12)."

REVIEWER COMMENT: 7. Page 16 – second paragraph – the sentence "The cross-sectional nature of the study does not allow temporal associations investigations" should be rephrased to "The….does not allow investigation of temporal associations"

OUR RESPONSE: We appreciate the comment and revised the sentence as suggested:

"The cross-sectional nature of the study does not allow for investigation of temporal associations."

REVIEWER COMMENT: 8. Page 17 – paragraph beginning "This is the first local study…" – the sentence "The multimorbidity was higher in older people…" doesn't make sense. Suggest rephrase to "Multimorbidity was higher…, as observed in previous studies."

OUR RESPONSE: We appreciate the comment and revised the sentence as suggested:

"Multimorbidity was higher in older people and increased with age; this finding has been observed in previous studies"

REVIEWER COMMENT: 9. On page 18, please be explicit that you found no association between income and multimorbidity after adjusting for SES.

OUR RESPONSE: We appreciate the comment and revised the sentence as suggested:

"No association was found between income and multimorbidity after adjusting for socioeconomic variables."

REVIEWER COMMENT: 10. Page 18 – sentence beginning "High-income countries has found…" uses incorrect English. This should read "Studies in high-income countries have found…"

OUR RESPONSE: We appreciate the comment and revised the sentence as suggested:

"An analysis of high-income countries found that 3.6 more years of education reduces the risk of cardiovascular disease by one-third."

REVIEWER COMMENT: 11. Page 19 – you indicate that factor one would comprise younger men and factor two older men, based on assumptions – which assumptions? Why can you assume this?

OUR RESPONSE: Thank you for your comments. We clarified the discussion of multimorbidity patterns and removed speculative assumptions:

"In men, lung disease was the disease with the highest factorial loading on factor 1, but no clear pattern of diseases was found in the clustering of this factor. Factor 2 included cardiometabolic diseases, which could be explained by similar risk factors such as sedentary lifestyle and obesity. An analysis of 2 008 electronic medical records from the Spanish National Health System identified cardiometabolic patterns in both men and women in different age ranges."

Reviewer: 2

REVIEWER COMMENT: While the authors have responded to my review comments and suggestions in the separate document most of those responses have not been reflected in the text of the manuscript. In my initial review I asked for the inclusion of some contextual information about Manaus and Amazonas in terms of language, indigenous population, health care system, etc., this was not provided.

OUR RESPONSE: We apologize for not addressing this suggestion previously. We have now made corresponding revisions in the Introduction section:

"To obtain evidence of the health status and usage of health services, a large survey was performed in 2015 in the Manaus metropolitan region,[18 19] the most populated region and largest economic cluster in northern Brazil. This region comprises more than 60% of the 3.5 million people of Amazonas, which has the largest land area, the lowest population density, and the highest population of indigenous people (4.7%) in Brazil.[20] Health coverage is mainly public (Unified Health System), and this region had the lowest coverage of health insurance in the country in 2013 (13.0%).[21]"

REVIEWER COMMENT: In asking my question about the representativeness of the study sample I expect to see a table column that lists both study sample and census characteristics for the region, so the readers could themselves could judge for themselves whether or not the study sample was representative of the regions' population.

OUR RESPONSE: As mentioned in the previous round of responses, this table was published in another paper, and we chose not to duplicate this information based on *ICMJE* and *BMJ Open* recommendations. For this round of peer review, we have uploaded this table as a supplementary file so that the editor can decide whether it would be suitable to reprint the table in the present manuscript. We have clarified in the Methods section that this information is available in a previous open-access publication:

"Details of the study design and the representativeness of the sample are available elsewhere.[18]"

REVIEWER COMMENT: I would also add an additional comments that if the authors wish to make comparisons in chronic diseases prevalence and multi-morbidity to Brazil as a whole, to other regions of Brazil or other countries then they should age/gender standardize their comparisons so that differences

reported are a function of differences in prevalence and no just a reflection of the age/gender characteristics of the populations of the areas compared.

OUR RESPONSE: We appreciate the comment and agree that this analysis would provide valuable evidence. Standardized comparisons were not the objective of the present study. In the Discussion section, all comparisons with previous studies were contextualized to allow for better interpretation of the results by the readers.

VERSION 3 – REVIEW

REVIEWER	Caroline Jackson Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, Scotland, UK
REVIEW RETURNED	10-Sep-2018

GENERAL COMMENTS	The authors have satisfactorily addressed my remaining comments.