PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Multimorbidity as an Important Issue among Women: Results of Gender Difference Investigation in a Large Population-Based Cross-Sectional Study in West Asia
AUTHORS	Alimohammadian, Masoomeh; Majidi, Azam; Yaseri, Mehdi; Ahmadi, Batoul; Islami, Farhad; Derakhshan, Mohammad; Delavari, Alireza; Amani, Mohammad; Feyz-Sani, Akbar; Poustchi, Hossein; Pourshams, Akram; Sadjadi, Amir Mahdi; Khoshnia, Masoud; Qaravi, Samad; Abnet, Christian; Dawsey, Sanford; Brennan, Paul; Kamangar, Farin; Boffetta, Paolo; Sadjadi, Alireza; Malekzadeh, Reza

VERSION 1 - REVIEW

REVIEWER	Ana Quiñones Oregon Health & Science University, United States
REVIEW RETURNED	10-Aug-2016

GENERAL COMMENTS	The objective of this manuscript is to assess gender and age strata differences in multimorbidity in northern Iran. While this represents a new contribution to the epidemiology of multimorbidity in a rapidly evolving literature, as currently written, the paper lacks methodological detail and clarity. The following concerns reduce my enthusiasm for the paper: <u>General comments:</u> 1. Abstract is unclearly written: a. the "objectives" section instead provides the study background; the objective of the study is listed in the "main outcome measures" section b. the "study population" section should provide details of the number of included individuals and the age ranges, which is instead provided in the "results" section. c. it is also critical that the authors define multimorbidity in the "main outcome measures" section. Is this operationalized as 2+ co-occurring chronic conditions? This needs to be explicitly stated from the outset. d. under the "strengths and limitations of this study," is this large population-based cohort a representative cohort? If so, this should be stated and brief details and/or citations documenting the sampling frame and weighting procedures to account for non-response should be provided in the Methods section. If not, use of a convenience sample needs to be listed as a limitation of the study.

	2. The Introduction section is missing some important context, particularly at the end of paragraph two. What is often cited here are contraindications between medications used to treat separate chronic conditions, and provider confusion about adherence to best-practices and disease-specific practice guidelines that are developed without considering simultaneously occurring chronic conditions. Individuals with multimorbidity face health care system-wide difficulties: at worst, clinical practice risks ignoring other complicating medical conditions; at best, there is uncertainty about adhering to clinical practice guidelines in the face of multimorbidity. These issues should be acknowledged. 3. The sample size for the study population is very unclearly specified throughout the manuscript. The manuscript is very unclear about the study population and the criteria for inclusion in the study. The numbers reported in the Abstract, Methods, Results, and Tables all vary, and it is not immediately clear how these numbers are produced. Suggest the authors report the study population that reflects exclusions (and report those), and that they are consistent about reporting these numbers throughout the manuscript. For example, it is very unclear why in the narrative text of the manuscript the study population is reported as n=49,946 however in the tables the total number is reported as n=10,035. 4. Related to point 1c, multimorbidity is defined on pg. 6 as "self-reported occurrence of two or more chronic diseases (mostly related to aging)." Are the authors differentiating between acute and chronic conditions? Are included conditions only age-related and not occurring earlier in the lifecourse even if chronic? Is type I diabetes included, or only type II diabetes? 5. There is a cryptic reference to accounting for "design effects" using GEE methods on pg. 6 (lines 40-42). Please provide additional detail on what is meant here along with a citation(s) supporting the approach taken. 6. Discussion of the relationship between gender and multimorbidity (and any hypothesized differences by gender) is underdeveloped in the manuscript. As a result, it is a bit of a surprise to see Table 1 reporting individual chronic disease differences by gender for people with multimorbidity. Why are these reported? Are the authors hypothesizing differences by gender in individual disease prevalence that might influence the prevalence and composition of multimorbidity in this population? Strongly suggest that this table should be made a supplemental table and some brief motivation and discussion be provided in text. 7. Table 2 is presented in a very confusing way: a. It is unclear why age categories are bottom- and top-coded to include ages below 49 and above 61 when elsewhere in the text the study age range inclusion is reported as 40-75. b. It is unclear why the numbers for each of the variables do not sum to the column totals and the percentages do not add to 100. I believe this is attributable to the fact that the total number of individuals with multimorbidity in the cohort is ~10k, however the column reports ~49k. Again, the manuscript would benefit from some consistency in

	how the sample size is reported and logically presented to readers. 8. The discussion of the results on pg. 9 is overly brief and unclearly presented. Were the main effects also included in the interaction models? Were these main effects also significant in addition to the interaction effects that are reported as being significantly different by gender? 9. Like Table 2, Table 3 is also presented in a confusing manner. The age categories are also presented inconsistently with the text, and baseline variables used for the adjusted models should be explicitly listed in the footnote. 10. The outset of the Discussion (pg. 11, lines 9-14) is unclearly written. This statement at the end of the paragraph is overly general and would benefit from further specification and highlighting the 2-3 main findings from the interaction models. 11. Pg. 11, lines 41-45 in the Discussion would benefit from a more nuanced discussion of the Poisson model findings. Here and throughout, given the model specification, something can be said here about the level or counts of multimorbidity in the interpretation of the Poisson models to provide more specification and interpretive detail of the direction of the findings. 12. Pg. 13, line 3: it is not clear how the authors came to the conclusion that these findings “confirm that multimorbidity is an important neglected health issue.” It is very tenuous and very unclear how this claim is supported by the analyses. The authors will have to connect more logical dots to make this statement convincing to readers. Relatedly, the authors may want to consider revising the manuscript title. It is very unclear why this assertion is made given the many studies, systematic reviews, and working groups publishing on multimorbidity epidemiology, time trends, and methodological approaches to standardize its measurement as well as efforts to develop coherent practice guidelines. It is unclear how this can be characterized as “neglected” even if that may be the case in one specific national setting. Specific comments: 1. Pg. 3, line 19: “effect” should be changed to “associations” 2. Pg. 4, lines 22-23: change “significant” to “significantly associated with” 3. Pg. 12, line 5: delete “is”

REVIEWER	Dragana Jovic Institute of Public Health of Serbia "Dr Milan Jovanovic Batut", Serbia
REVIEW RETURNED	03-Oct-2016

GENERAL COMMENTS	Abstract is not complete and should be revised. Outcomes could be more clear. Table 1 should be more clear. Discussion should be enriched, conclusions should be softened. If I saw well, manuscript does not contain strenghts and limitations. Paper needs professional editing for English language.

VERSION 1 – AUTHOR RESPONSE

General comments:
1. Abstract is unclearly written:
a. the "objectives" section instead provides the study background; the objective of the study is listed in the "main outcome measures" section
Response: done
b. The "study population" section should provide details of the number of included individuals and the age ranges, which is instead provided in the "results" section.
Response: done
c. It is also critical that the authors define multimorbidity in the "main outcome measures" section. Is this operationalized as 2+ co-occurring chronic conditions? This needs to be explicitly stated from the outset.
Response: done
d. Under the "strengths and limitations of this study," is this large population-based cohort a representative cohort? If so, this should be stated and brief details and/or citations documenting the sampling frame and weighting procedures to account for non-response should be provided in the Methods section. If not, use of a convenience sample needs to be listed as a limitation of the study.
Response: We agree with the reviewer's assessment. Required information was added to method section as suggested.
2. The Introduction section is missing some important context, particularly at the end of paragraph two. What is often cited here are contraindications between medications used to treat separate chronic conditions, and provider confusion about adherence to best-practices and disease-specific practice guidelines that are developed without considering simultaneously occurring chronic conditions. Individuals with multimorbidity face health care system-wide difficulties: at worst, clinical practice risks ignoring other complicating medical conditions; at best, there is uncertainty about adhering to clinical practice guidelines in the face of multimorbidity. These issues should be acknowledged.
Response: In regards to the assessment made by the reviewer we added a sentence to explain the importance of targeting the complication and specific care related to multimorbidity in introduction.
3. The sample size for the study population is very unclearly specified throughout the manuscript. The manuscript is very unclear about the study population and the criteria for inclusion in the study. The numbers reported in the Abstract, Methods, Results, and Tables all vary, and it is not immediately clear how these numbers are produced. Suggest the authors report the study population that reflects exclusions (and report those), and that they are consistent about reporting these numbers throughout the manuscript. For example, it is very unclear why in the narrative text of the manuscript the study population is reported as n=49,946 however in the tables the total number is reported as n=10,035.
Response: In response to the request made by the distinguished reviewer, in order to clarify the sample size, we combined the two sentences explaining this point together in the first paragraph of methods section.
4. Related to point 1c, multimorbidity is defined on pg. 6 as "self-reported occurrence of two or more chronic diseases (mostly related to aging)." Are the authors differentiating between acute and chronic conditions? Are included conditions only age-related and not occurring earlier in the life course even if chronic? Is type I diabetes included, or only type II diabetes?
Response: "chronic conditions" in this study is defined as: conditions that cause individual to pursue long term (maybe lifelong) medical help, and/or they require to consume specific medications in order to maintain their health status. As long as the condition is, or expected to be prolonged it is considered chronic condition. As we added in the manuscript's new revision both Diabetes Type I and Type II were considered.
5. There is a cryptic reference to accounting for "design effects" using GEE methods on pg. 6 (lines 40-42). Please provide additional detail on what is meant here along with a citation(s) supporting the approach taken.
Response: To further explain the details as requested by the reviewer, a paragraph explaining this

part was added to methods.
6. Discussion of the relationship between gender and multimorbidity (and any hypothesized differences by gender) is underdeveloped in the manuscript. As a result, it is a bit of a surprise to see Table 1 reporting individual chronic disease differences by gender for people with multimorbidity. Why are these reported? Are the authors hypothesizing differences by gender in individual disease prevalence that might influence the prevalence and composition of multimorbidity in this population? Strongly suggest that this table should be made a supplemental table and some brief motivation and discussion be provided in text.
Response: As suggested by respected reviewer Table 1 removed from main text and was brought as supplemental table instead.
7. Table 2 is presented in a very confusing way:
a. It is unclear why age categories are bottom- and top-coded to include ages below 49 and above 61 when elsewhere in the text the study age range inclusion is reported as 40-75.
Response: To clarify the mentioned issue, we made some changes to Table 2 to clarify these missing or vague points.
b. It is unclear why the numbers for each of the variables do not sum to the column totals and the percentages do not add to 100. I believe this is attributable to the fact that the total number of individuals with multimorbidity in the cohort is ~10k, however the column reports ~49k. Again, the manuscript would benefit from some consistency in how the sample size is reported and logically presented to readers.
Response: Thanks to the meticulous concern of the respected reviewer for this comment. We considered this point in new version of table.
8. The discussion of the results on pg. 9 is overly brief and unclearly presented. Were the main effects also included in the interaction models? Were these main effects also significant in addition to the interaction effects that are reported as being significantly different by gender?
Response: We have included the main effect in our model in addition to the interaction term. But the significance of the main effect is not considered (and should not considered) to be the reason for the effect of some level of gender in the RR. However the statistically significant interaction effect demonstrates that the effect of variation would be different in gender levels. Based on these findings, it seems reasonable to fit the model separately for men and women the effect interpreted for them separately. It is possible to have a statistically significant relation between variable in a level of gender when it is no statistically significant on the other level.
9. Like Table 2, Table 3 is also presented in a confusing manner. The age categories are also presented inconsistently with the text, and baseline variables used for the adjusted models should be explicitly listed in the footnote.
Response: done
10. The outset of the Discussion (pg. 11, lines 9-14) is unclearly written. This statement at the end of the paragraph is overly general and would benefit from further specification and highlighting the 2-3 main findings from the interaction models.
Response: We brought more details in this regards as distinguished reviewer mentioned.
11. Pg. 11, lines 41-45 in the Discussion would benefit from a more nuanced discussion of the Poisson model findings. Here and throughout, given the model specification, something can be said here about the level or counts of multimorbidity in the interpretation of the Poisson models to provide more specification and interpretive detail of the direction of the findings.
Response: We used the Poisson model to obtain the Relative risk in our observational model. There are some occasions in which odds ratio could be misleading, so we used a model that can provide the odds ratio. The detail about the rationale of this could be found in Alternatives for logistic regression in cross-sectional studies: an empirical comparison of models that directly estimate the prevalence ratio. BMC Med Res Method 2003;3:21.
12. Pg. 13, line 3: it is not clear how the authors came to the conclusion that these findings “confirm that multimorbidity is an important neglected health issue.” It is very tenuous and very unclear how this claim is supported by the analyses. The authors will have to connect more logical dots to make

this statement convincing to readers. Relatedly, the authors may want to consider revising the manuscript title. It is very unclear why this assertion is made given the many studies, systematic reviews, and working groups publishing on multimorbidity epidemiology, time trends, and methodological approaches to standardize its measurement as well as efforts to develop coherent practice guidelines. It is unclear how this can be characterized as "neglected" even if that may be the case in one specific national setting.
Response: Both in discussion and title what we meant as "neglected" is not the high prevalence of multimorbidity among all age-groups. Our focus was the relatively high prevalence of multimorbidity among middle-age people.
Specific comments:
1. Pg. 3, line 19: "effect" should be changed to "associations"
Response: done
2. Pg. 4, lines 22-23: change "significant" to "significantly associated with"
Response: done
3. Pg. 12, line 5: delete "is"
Response: done

VERSION 2 – REVIEW

REVIEWER	Ana Quinones Oregon Health & Science University, USA
REVIEW RETURNED	15-Dec-2016

GENERAL COMMENTS	The authors have sufficiently addressed concerns. Only minor issues remain: 1. The manuscript would benefit from additional proofreading. 2. There are more appropriate citations for uncertainty regarding clinical guideline adherence in the face of multimorbidity than citation #11. The authors may want to consider any of the following suggestions: Uhlig, K., Leff, B., Kent, D., Dy, S., Brunnhuber, K., Burgers, J. S., ... & Mulrow, C. (2014). A framework for crafting clinical practice guidelines that are relevant to the care and management of people with multimorbidity. Journal of general internal medicine, 29(4), 670-679. Guthrie, B., Payne, K., Alderson, P., McMurdo, M. E., & Mercer, S. W. (2012). Adapting clinical guidelines to take account of multimorbidity. British Medical Journal, 345(oct04), e6341-e6341. Hughes, L. D., McMurdo, M. E., & Guthrie, B. (2013). Guidelines for people not for diseases: the challenges of applying UK clinical guidelines to people with multimorbidity. Age and ageing, 42(1), 62-69. Boyd, C. M., & Martin Fortin, M. D. (2010). Future of multimorbidity research: how should understanding of multimorbidity inform health system design?. Public Health Reviews, 32(2), 1.

REVIEWER	Dragana Jovic Institute of Public Health of Serbia
REVIEW RETURNED	15-Dec-2016

GENERAL COMMENTS	This is second review of the above mentioned article. After careful reading I would like to give several major remarks: 1. Pg.21 line 7: Authors state that the objective of the study is “Investigating the impact of gender and age-groups upon multimorbidity in northern Iran”. This can only partly be claimed (be valid for gender) because statistical analyses are not stratified by age groups. In regard to this claim, part of the title of the study “Multimorbidity: A Neglected Issue **among Middle-Age people**…” is not appropriate, unless the authors reformulate their statistical analyses. 2. Pg.21 line 9: Authors wrote that their study represents cross-sectional analysis of Golestan cohort data. Later in the manuscript two statements appears: first that data were collected at the beginning of a representative cohort study during 2003-2004 (49,946 respondents); second that a total of 50,045 adults aged 40-75 years residing in Golestan province in northeastern Iran were enrolled in a cohort study from 2004 to 2008. This creates quite confusion and can put under question Method suitability. According to my opinion this study is a secondary analysis of data based on a sample used for cohort study. If I am not right and it is cross-sectional analysis, authors must state whether they used the same sample size as cohort study for conducting cross-sectional study. 3. Pg.21 line 21: I don`t see in abstract and manuscript prevalence of multimorbidity calculated for whole study population. In such circumstances how authors may state that multimorbidity is neglected issue? Which comparisons authors made to show that multimorbidity is neglected? In the Discussion section these two points (overall prevalence and neglected issue) are not enough described. Also, authors answer in General comments “Our focus was the relatively high prevalence of multimorbidity among middle-age people.” on this point is not strong. 4. Pg.21 line 14: Authors defines multimorbidity as comorbidity of 2 or more chronic diseases, which is completely incorrect. Having regard that the numbers in table 1 and table 2 are now different from those given at first submission, that the numbers in supplementary table are unchanged, the light of presented definition of multimorbidity may cast shadow on correctness of performed analyses. 5. Pg.21 line 25: Authors retain term “younger” for respondents <50y in whole manuscript, even after first revision. I cannot agree with retained term. 6. Pg.21 line 41: Conclusion presented in abstract is too wide and not supported by data and discussion provided in the manuscript. 7. The Introduction section is missing the most important context mentioned as objective of the study i.e. gender i.e. what is known about gender differences in the prevalence of multimorbidity. This section demands improvement.

	8. Pg. 23 line 10: Authors state “This issue could be further amplified by co-occurrence of two or more chronic diseases in one person, **a condition** that is known as multimorbidity.” Here, I am not sure whether this statement is a matter of knowledge of the authors or a matter of poor level of English. In line 25 of the same page, this statement is repeated. 9. Pg. 23 line 54: In General comments authors are kindly asked to improve description of the Method section. According to my opinion, authors did not completely follow this recommendation. It seems that they start to describe method of cohort study, but do not continue to describe the method used in their study i.e. from which period of time data originates, what were inclusion/exclusion criteria, which chronic diseases entered statistical analyses etc. These must be clearly stated. 10. I am worried about several matters in the Method. First is the number of chronic diseases which served as the basis for calculating the prevalence of multimorbidity (7 in total?). Second is the data on GERD presented in supplement table and in table 1 (Authors stated that interviewers were trained, results show that almost 70% of respondents were illiterate and 76.6 of the study population with multimorbidity reported to have GERD. Did respondents know what is GERD?). The third: pg. 24 line 7 - authors states “In this mainly rural population …” Results presented in table 1 show that about 23% of the total number of respondents reported to live in rural areas. Can authors please explain all these observation? 11. Pg 24 line 9: Authors should explicitly explain definition of being physically active/inactive. 12. Pg. 24 line 29: Authors state :” In order to evaluate the differences in distribution of factors between genders …”. Can authors rephrase this into: In order to evaluate differences in the distribution of respondents according to socio-demographic and lifestyle factors and gender … 13. Table 1: In the Method section authors should highlight definition of Light and Heavy smoker/Usage of alcohol. In the last column of this table simple difference is presented (for example: for age group 40-49 difference is calculated > 17.3% -8.6 % = 8,7%). I believe that it would be valuable to put *p* values in the column and explain in the Results section how many times the prevalence of multimorbidity in women is higher than in men. 14. Discussion section is improved but not enough to stress importance of the differences in the prevalence of multimorbidity between men and women. This may be due to the fact that the prevalence of multimorbidity is appraised

	on the basis of "part of sampling frame" (province vs. nationally representative sample i.e. not enough references for such case) and that data belong to the period before 2009. 15. Pg. 30 line 57: It seems that the reference indicated after the name of the World Health organization (no. 46) is not aligned with the number given in the References section. Could this be the reference no. 48 ? 16. Strengths and limitations are missing in the manuscript. 17. I get the impression that there are suggestive sentences and conclusions in the manuscript: pg.21 line 41; pg. 31 lines 10-12, lines 15-22 and some other. I am very sorry for saying that indicated sentences/conclusions may not be support by 2+1 tables presented in the manuscript.

VERSION 2 – AUTHOR RESPONSE

Responses to reviewer 1:

1. The manuscript would benefit from additional proofreading.
Response: We performed a comprehensive language editing by a native English editor in this revision.

2. There are more appropriate citations for uncertainty regarding clinical guideline adherence in the face of multimorbidity than citation #11. The authors may want to consider any of the following suggestions:
Response: We express our appreciation to this reviewer for mentioning these references. The new references have been replaced the previous reference.

Responses to Reviewer 2:
We performed a comprehensive language editing in this revision

1. Pg.21 line 7: Authors state that the objective of the study is "Investigating the impact of gender and age-groups upon multimorbidity in northern Iran". This can only partly be claimed (be valid for gender) because statistical analyses are not stratified by age groups. In regard to this claim, part of the title of the study "Multimorbidity: A Neglected Issue among Middle-Age people…" is not appropriate, unless the authors reformulate their statistical analyses.
Response: We modified the objectives per your request. Based on this change we also revised the title and body of the manuscript.

2. Pg.21 line 9: Authors wrote that their study represents cross-sectional analysis of Golestan cohort data. Later in the manuscript two statements appears: first that data were collected at the beginning of a representative cohort study during 2003-2004 (49,946 respondents); second that a total of 50,045 adults aged 40-75 years residing in Golestan province in northeastern Iran were enrolled in a cohort study from 2004 to 2008. This creates quite confusion and can put under question Method suitability.

According to my opinion this study is a secondary analysis of data based on a sample used for cohort study. If I am not right and it is cross-sectional analysis, authors must state whether they used the same sample size as cohort study for conducting cross-sectional study.
Response: Thank you for your meticulous attention to detail. Regarding your comment, we revised our typing mistake. The correct date of sampling recruitment was 2004-2008. We believe this point clarifies the obscurity about the type of study (i.e., cross-sectional vs. cohort design). This study used the basic information obtained from the Golestan Cohort Study as a cross-sectional sample.

3. Pg.21 line 21: I don`t see in abstract and manuscript prevalence of multimorbidity calculated for whole study population. In such circumstances how authors may state that multimorbidity is neglected issue? Which comparisons authors made to show that multimorbidity is neglected? In the Discussion section these two points (overall prevalence and neglected issue) are not enough described. Also, authors answer in General comments "Our focus was the relatively high prevalence of multimorbidity among middle-age people." on this point is not strong.
Response: We changed the title and removed the word "neglected". Since we had discussed the overall prevalence of multimorbidity in our previous article we did not discuss the overall prevalence of multimorbidity in this manuscript. As recommended, we added brief information about the prevalence of multimorbidity to this article.

4. Pg.21 line 14: Authors defines multimorbidity as comorbidity of 2 or more chronic diseases, which is completely incorrect. Having regard that the numbers in table 1 and table 2 are now different from those given at first submission, that the numbers in supplementary table are unchanged, the light of presented definition of multimorbidity may cast shadow on correctness of performed analyses.
Response: Per your request, we corrected the definition of multimorbidity in the abstract and introduction.

5. Pg.21 line 25: Authors retain term "younger" for respondents <50y in whole manuscript, even after first revision. I cannot agree with retained term.
Response: We changed this term in the manuscript.

6. Pg.21 line 41: Conclusion presented in abstract is too wide and not supported by data and discussion provided in the manuscript.
Response: Done.

7. The Introduction section is missing the most important context mentioned as objective of the study i.e. gender i.e. what is known about gender differences in the prevalence of multimorbidity. This section demands improvement.
Response: In the introduction we tried to provide additional clarification for gender difference in the prevalence of multimorbidity.

8. Pg. 23 line 10: Authors state "This issue could be further amplified by co-occurrence of two or more chronic diseases in one person, a condition that is known as multimorbidity." Here, I am not sure whether this statement is a matter of knowledge of the authors or a matter of poor level of English. In line 25 of the same page, this statement is repeated.
Response: In order to avoid any misunderstanding in the mentioned sentence, we changed the structure.

9. Pg. 23 line 54: In General comments authors are kindly asked to improve description of the Method section. According to my opinion, authors did not completely follow this recommendation. It seems that they start to describe method of cohort study, but do not continue to describe the method used in their study i.e. from which period of time data originates, what were inclusion/exclusion criteria, which chronic diseases entered statistical analyses etc. These must be clearly stated.

Response: Considering the recommendations of this reviewer we tried to clarify and explain our methodology in greater detail and eliminate those mainly related to the cohort study.
Information about inclusion/exclusion criteria and the list of chronic diseases considered in the multimorbidity classification were added or changed.

10. I am worried about several matters in the Method. First is the number of chronic diseases which served as the basis for calculating the prevalence of multimorbidity (7 in total?). Second is the data on GERD presented in supplement table and in table 1 (Authors stated that interviewers were trained, results show that almost 70% of respondents were illiterate and 76.6 of the study population with multimorbidity reported to have GERD. Did respondents know what is GERD?). The third: pg. 24 line 7 - authors states "In this mainly rural population …" Results presented in table 1 show that about 23% of the total number of respondents reported to live in rural areas. Can authors please explain all these observation?
Response: We respect the meticulous insight of this reviewer. We corrected the information in Table 1, in which the numbers that represented the proportions of rural and urban participants were mistakenly switched. Regarding the reviewer's concern about the validity of data for GERD, we stated in the current revision of the manuscript that a standard questionnaire had been used to evaluate participants' GERD.

11. Pg 24 line 9: Authors should explicitly explain definition of being physically active/inactive.
Response: This part was added to the new revision.

12. Pg. 24 line 29: Authors state:" In order to evaluate the differences in distribution of factors between genders …". Can authors rephrase this into: In order to evaluate differences in the distribution of respondents according to socio-demographic and lifestyle factors and gender …
Response: Done.

13. Table 1: In the Method section authors should highlight definition of Light and Heavy smoker/Usage of alcohol. In the last column of this table simple difference is presented (for example: for age group 40-49 difference is calculated > 17.3% -8.6 % = 8,7%). I believe that it would be valuable to put p values in the column and explain in the Results section how many times the prevalence of multimorbidity in women is higher than in men.
Response: As recommended, we clarified the classifications for smoking, alcohol consumption, etc. in Tables 1 and 2. We added the definition of smoker vs. nonsmoker below Table 1.
Regarding the concern of this reviewer, we must say that we had already reported significant p-values as demonstrated by an "*".We also added a column to report p-values individually.

14. Discussion section is improved but not enough to stress importance of the differences in the prevalence of multimorbidity between men and women. This may be due to the fact that the prevalence of multimorbidity is appraised on the basis of "part of sampling frame" (province vs. nationally representative sample i.e. not enough references for such case) and that data belong to the period before 2009.
Response: We mentioned in the discussion the points about the sampling frame and time period. Also we suggested future studies on more representative samples.

15. Pg. 30 line 57: It seems that the reference indicated after the name of the World Health organization (no. 46) is not aligned with the number given in the References section. Could this be the reference no. 48 ?
Response: Corrected.

16. Strengths and limitations are missing in the manuscript.
Response: These points were brought following the abstract according to the journal's policy.

17. I get the impression that there are suggestive sentences and conclusions in the manuscript: Pg.21 line 41; pg. 31 lines 10-12, lines 15-22 and some other. I am very sorry for saying that indicated sentences/conclusions may not be support by 2+1 tables presented in the manuscript.
Response: We tried to modify these parts to support the findings and results.

VERSION 3 – REVIEW

REVIEWER	Dragana Jovic Institute of Public Health of Serbia "Dr Milan Jovanovic Batut", Serbia
REVIEW RETURNED	02-Mar-2017

GENERAL COMMENTS	I don`t have comments.