

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Prevalence of anxiety and depressive symptoms and their association with multimorbidity and demographic factors: A community- based cross sectional survey in Karachi, Pakistan
AUTHORS	Farooq, Salima; Khan, Tahir; Zaheer, Sidra; Shafique, Kashif

VERSION 1 – REVIEW

REVIEWER	Dr Mohammad Akhtar Hussain Western Australia Centre for Rural Health, University of Western Australia, Geraldton, Western Australia
REVIEW RETURNED	22-Apr-2019

GENERAL COMMENTS	<p>General Comments: The authors have raised very pertinent question about the burden of anxiety and depression and its association with multimorbidity. Multimorbidity has been linked to decrease quality of life and thereby also to anxiety and depression.</p> <p>The article should be considered for publication but only after some major revision. My comments are as follows:</p> <ol style="list-style-type: none">1. The article needs careful editing particularly for English language.2. Introduction: Authors started with the definition of multimorbidity and continued with the burden of multimorbidity in developed countries. Pakistan being a developing country it would have been better to reference articles from developing countries with the multimorbidity prevalence both from primary care setting and community based survey. There are quite a few article published from developing countries.3. Methods: a) The being a cross sectional survey, it is not clear how the sample size was calculated. The justification of power calculation should be added in the method section. b) Author's mentioned that individuals who met eligibility criteria were included for the study. Please describe: what was the eligibility criteria?c) Analysis and results: The authors have used a multivariate model to adjust the variables. The results shows only a limited number of variables to be significantly associated with anxiety and depression. I would recommend to perform a step-wise logistic regression rather than including all variables in the model and including only those with statistically significant results in univariate analysis.d) The article highlights the association between multimorbidity and anxiety/depression. I would suggest authors to reanalyse their data and investigate if there are any specific combination of morbidities which had maximum impact on anxiety/depression; also it would be worth exploring the association between number of chronic conditions and anxiety/depression. <p>Table-3. It is better to remove the P values from the table. Presenting results with confidence intervals is sufficient enough to</p>
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	interpret the significance. References: References should be carefully checked and formatted as per journal style.
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REVIEWER	Lydia Poole Research Fellow UCL UK
REVIEW RETURNED	30-Apr-2019

GENERAL COMMENTS	<p>This paper examines the prevalence of depressive and anxiety symptoms in the general population in a town in Pakistan. It examines cross-sectional sociodemographic and clinical (i.e. multimorbidity) factors associated with this prevalence. I have made some suggestions for improvements to the manuscript, which the authors may wish to consider.</p> <p>Abstract</p> <ul style="list-style-type: none"> - Rather than 'analytical' perhaps write 'observational' under design. - The N is needed for the study sample. - It is not clear whether depression and anxiety were measured as continuous or dichotomous variables. - I would suggest to remove the word 'alarmingly'. - Conclusion: these factors are not 'predictors' since they were measured at the same time as the outcome; please reword. <p>Introduction</p> <ul style="list-style-type: none"> - I can't see your hypotheses anywhere. <p>Methods</p> <ul style="list-style-type: none"> - Subheadings would be useful. - When was data collected? - From your wording, the question on multimorbidity sounds like it was a binary question, but I assume participants had to tick all those illnesses that applied. Please clarify. - It would be useful to see a description of how your sociodemographic variables were measured. - By whom were height and weight and blood pressure measured? - I'm not familiar with your depression measure. Please could you provide some example items? <p>Results</p> <ul style="list-style-type: none"> - It is usual to present the mean age and SD and proportion fe/male very early on in the results section. - Details of how you derived your sample size would probably fit better in a 'Participants' section in the Methods. - I'm not sure what Table 2 adds. Table 3 shows the adjusted results and is therefore of greater value. I would consider cutting table 2, to avoid repetition for what are largely the same results. - When referring to odds ratios the correct phrasing is 'increased odds' as opposed to 'more likely'. <p>Discussion</p> <ul style="list-style-type: none"> - When discussing prevalence rates (para.1) I think you need to make the distinction between clinical depression and depressive symptoms as measured using a questionnaire. - More attention could be paid to the role of cultural differences that might account for some of the differences observed in the study
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	<p>would be useful. For example, how might income (socioeconomic status) interact with factors such as ethnicity and child-bearing? - The results for the effect of children is indeed puzzling. More justification/explanation is needed here.</p> <p>Other - I couldn't see the STROBE check-list, but perhaps it has been submitted separately.</p>
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REVIEWER	Wai-Kai Hou The Education University of Hong Kong, Hong Kong SAR, China
REVIEW RETURNED	08-May-2019

GENERAL COMMENTS	<p>Comments to author</p> <p>This study aims to examine the prevalence of anxiety and depressive symptoms, and its association with multimorbidity and demographic correlates in a random sample of 2,867 people aged 30 years or above in Karachi, Pakistan. The results showed that around 27% of the participants report clinically significant combined anxiety and depressive symptoms. About 50% reported multiple chronic conditions on a list of common chronic diseases or presented high blood pressure (i.e., hypertension), high BMI (i.e., obesity), or high blood glucose levels (i.e., type 2 diabetes). Significant anxiety/depression was more common in multimorbid individuals. Females, those without formal education, those without children, those who visited faith healers were more likely to report clinical levels of anxiety/depressive symptoms. Several merits of the study should be noted. First, the sample size was large and the population was understudied in the current literature. Second, appropriate statistical procedure was carried out. Third, methodology and results were presented very clearly. Fourth, the discussion was able to show the implication of the findings with reference to previous evidence. However, some limitations diminish the contribution of the findings.</p> <p>First, the introduction can be more organized. The importance of studying anxiety and depression should be stated at the outset, followed by a section that highlights the need for more empirical evidence on affective symptoms in low-income populations. Then multimorbidity can be introduced as an additional condition for studying affective disorders among those people.</p> <p>Second, although it is clear that “comorbid” anxiety/depression and multimorbidity can complicate health care service delivery, the underlying mechanism(s) linking anxiety/depression/affective disorders and multimorbidity was/were not explained. For example, recent relevant studies on the causality between affective symptoms and multimorbidity should be noted and discussed (e.g., Birk et al., 2019; Lai, Ma, & Hou, 2018; Read, Sharpe, Modini, & Dear, 2017).</p> <p>Third, a clear knowledge base on the demographic predictors of anxiety and/or depression should be included. This is essential for hypothesis testing, which is missing in the current study. Particularly, behavioral correlates, namely smoking and visit of faith healer and their potential associations with higher/lower symptoms should be explained clearly. What do people do in faith healing? What are the possible reasons for its association with higher affective symptoms? What are the implications of seeing faith healer, such as delay in seeking proper assessment/treatment? Why did smoking relate to</p>
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	<p>lower symptoms in the current sample? Is there difference on this between low-income and high-income countries? These are essential findings that make the current findings unique and applicable to other similar populations.</p> <p>Fourth, were there specific rationales for studying the prevalence of combined anxiety and depression in the current population? If not, then prevalence of anxiety and depressive symptoms would best be studied separately. Anxiety and depressive symptoms could have shared as well as distinct demographic correlates, which can be very useful evidence for clinical research and practice in the study population.</p> <p>Some limitations can be addressed or explained. Why is the cutoff age 30 years? What is the possible missing information on affective disorders in the emerging adults? The use of objective measures of comorbid conditions is appreciated, but the diagnostic procedure and criteria are questionable. Analyses should be conducted to show whether the results are different after excluding the information from objective measures.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Dr Mohammad Akhtar Hussain

Institution and Country: Western Australia Centre for Rural Health, University of Western Australia, Geraldton, Western Australia

1. Comment: The article needs careful editing particularly for English language.

Response: Point taken. The manuscript has been thoroughly reviewed and efforts have been made to improve the quality of English and remove grammatical errors.

2. Comment: Introduction: Authors started with the definition of multimorbidity and continued with the burden of multimorbidity in developed countries. Pakistan being a developing country it would have been better to reference articles from developing countries with the multimorbidity prevalence both from primary care setting and community based survey. There are quite a few articles published from developing countries.

Response

Thank you for the comment, we have now added references from developing countries like Bangladesh and India's multimorbidity data in the introduction section see page no 5-6. Please see track changes in introduction part.

3. Comment: Methods: a) The being a cross sectional survey, it is not clear how the sample size was calculated. The justification of power calculation should be added in the method section.

Response:

Thank you for this comment. This manuscript is originated from larger research project which included several other primary and secondary objectives, so the size of the original survey was larger than the desired sample size for this particular objective.

Thank you for pointing out important point for this manuscript. Following changes have been made in methodology part under sample size heading page no 8.

“For the objective of this study, the sample size was calculated using an online version of Open Epi calculator. The prevalence of anxiety and depression is reported to be 30% to 50% among adults in Pakistan (B. Ali & Amanullah, 2000; Waheed, Hameed, Khan, Syed, & Mirza, 2006). With 2% margin of error, 80% power and 95% confidence level, the required sample size was 2401 participants. Similarly, for secondary objective (association of anxiety and depressive symptoms with multimorbidity), keeping the confidence interval of 95%, 90% power, 1:1 ratio of non-depressed and depressed individuals with odds ratio of 1.55, and proportion of multimorbidity among non-depressed was taken as 0.1 (Smith et al., 2014), the required sample size was 2148 individuals. In order to account for missing values, a higher sample size (2401) was chosen. Assuming an attrition rate of 10%, the final sample size turned out to be 2642 participants.”

4. **Comment: Author's mentioned that individuals who met eligibility criteria were included for the study. Please describe: what was the eligibility criteria?**

Response:

Thank you for your comments. Feedback has been incorporated in the methodology page no 8, wherein we have stated that,

“All Participants who were aged 30 years and above and who were the residents of Gulshan-e-Iqbal town, Karachi Pakistan and signed the consent form to take part in the study.”

5. **Comment: Analysis and results: The authors have used a multivariate model to adjust the variables. The results shows only a limited number of variables to be significantly associated with anxiety and depression. I would recommend to perform a step-wise logistic regression rather than including all variables in the model and including only those with statistically significant results in univariate analysis.**

Response: Suggestion has been well taken. As per the reviewer's suggestion we have re-analyzed the data and performed a step wise regression. The findings of the re-analysis are presented in table 2 on page 26-27 and relevant changes are also made in the result section accordingly.

6. **Comment: The article highlights the association between multimorbidity and anxiety/depression. I would suggest authors to reanalyze their data and investigate if there are any specific combination of morbidities which had maximum impact on anxiety/depression; also it would be worth exploring the association between number of chronic conditions and anxiety/depression.**

Response:

Thank you for this point. Considering the significance of number of morbidities and their relationship with anxiety and depressive symptoms, we have re-analyzed the data as per reviewer suggestions. Analysis was re-ran to examination association between number of chronic medical condition with anxiety and depressive symptoms. Furthermore, the findings of this analysis are now added in table 3 (page 28) and relevant results are incorporated in results section of this manuscript.

- 7. Comment: Table-3. It is better to remove the P values from the table. Presenting results with confidence intervals is sufficient enough to interpret the significance.**

Response: Feedback incorporated, P-values are removed from Table 3 (now Table 2), and changes have been made in manuscript.

- 8. Comment: References: References should be carefully checked and formatted as per journal style**

Response: Thank you for your suggestion, references rechecked and formatted as per journal requirement. Please highlighted changes in references

Reviewer: 2

Reviewer Name: Lydia Poole

Institution and Country: Research Fellow UCL,UK

Abstract

- 1. Comment: Rather than 'analytical' perhaps write 'observational' under design.**

Response: Thank you for your suggestion. The feedback has been incorporated i.e. "Analytic" replaced with "observational" study design. Please see the revised abstract on page 2

- 2. Comment: The N is needed for the study sample.**

Response: Point well taken, we have mentioned the N in abstract now.

- 3. Comment: It is not clear whether depression and anxiety were measured as continuous or dichotomous variables.**

Response: Anxiety and depressive symptoms were assessed initially on continuous scale; however, we then generated a dichotomous variable using cutoff value of 20 and above were labeled as having anxiety and depressive symptoms. Literature suggested that at a score of 20 it has a sensitivity of 66%, a specificity of 79%, a positive predictive value of 83% and a negative predictive value of 60%. Description has been added in Methodology page no 9.

- 4. Comment: I would suggest removing the word 'alarmingly'**

Response: Thank you for your suggestion, feedback well taken; Word alarming has been deleted from abstract.

- 5. Comment: Conclusion: these factors are not 'predictors' since they were measured at the same time as the outcome; please reword.**

Response: Point well taken, Predictor was replaced with associated factors, see changes in page 3 track change in conclusion section.

Introduction:

- 6. Comment: I can't see your hypotheses anywhere**

Response: Thank you for feedback, following hypothesis has been added in introduction part page 7.

“It was hypothesized that there might be an association between anxiety and depressive symptoms and multimorbidity among Pakistani population aged 30 years and above.”

Methods

7. Comment: Subheadings would be useful.

Response: Thank you for your feedback. Methodology section has been divided into subheadings as per feedback. Please see page 8-12.

8. Comment: When was data collected?

Response: Data was collected from 2015-2016.

9. Comment: from your wording, the question on multimorbidity sounds like it was a binary question, but I assume participants had to tick all those illnesses that applied. Please clarify.

Response: Thank you for the comment. Patients were asked separate questions for each of the chronic illness included in the study. The multimorbidity variable was then generated at the analysis stage using all those reported chronic conditions. This now has been clarified in

Aga Khan University Anxiety and Depression Scale	0) Never	1) Some Time	2) Often	3) Always
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methodology section of the study on page # 10.

10. Comment: It would be useful to see a description of how your socio demographic variables were measured.

Response: Thank you for highlighting this important point. We have provided the description of those variables on page # 10-11 now.

11. Comment: By whom were height and weight and blood pressure measured?

Response: Thank you for this point. The anthropometric measurements as well as Blood Pressure were measured by trained health professionals mainly included doctors and Nurses who were involved in data collection. This now has been clarified in methodology section of the study on page # 9.

12. Comment: I'm not familiar with your depression measure. Please could you provide some example items?

Response: Thank you for this important comment. We have now provided the description of the tool on page # 9. For your ready reference, here is the copy of the tool.

1	Have you been sleeping less?				
2	Have you had lack of interest in your daily activities?				
3	Have you lost interest in your hobbies?				
4	Have you been anxious				
5	Have you had a sensation of impending doom?				
6	Have you had difficulty in thinking clearly?				
7	Have you preferred to be alone?				
8	Have you felt unhappy?				
9	Have you felt hopeless?				
10	Have you felt helpless?				
11	Have you been worried?				
12	Have you cried?				
13	Have you thought of taking your life?				
14	Have you had loss of appetite?				
15	Have you had retrosternal burning?				
16	Have you had indigestion?				
17	Have you had nausea?				
18	Have you had constipation?				
19	Have you felt difficulty in breathing?				
20	Have you felt tremulous?				
21	Have you felt numbness of hands and feet?				
22	Have you felt a sensation of tension in your neck and shoulders?				
23	Have you had headaches?				
24	Have you felt pain all over your body?				
25	Have you passed urine more frequently?				

Results

- 13. Comment:** It is usual to present the mean age and SD and proportion fe/male very early on in the results section,

Response: Thank you so much. Mean age and SD and proportion of female and male mention in results as per feedback. See page 13.

- 14. Comment:** Details of how you derived your sample size would probably fit better in a 'Participants' section in the Methods.

Response: Thank you for pointing out an important component. Changes have been made in the methodology part under the sub-heading of sample size calculation. Please see page # 8.

- 15. Comment:** I'm not sure what Table 2 adds. Table 3 shows the adjusted results and is therefore of greater value. I would consider cutting table 2, to avoid repetition for what are largely the same results.

Response: Thank you for highlighting this, we have made the changes as per your suggestion and table 2 now has been removed

- 16. Comment:** When referring to odds ratios the correct phrasing is 'increased odds' as opposed to 'more likely'

Response: Point is well taken: We have now made modifications as per your suggestion. "more likely" rephrase with "increased odds" please see result section page 13-14.

Discussion

- 17. Comment:** When discussing prevalence rates (para.1) I think you need to make the distinction between clinical depression and depressive symptoms as measured using a questionnaire.

Response: Thank you for highlighting this important aspect. We have made following changes in discussion section considering your positive feedback. Please see page # 15.

"Current study used a screening tool (AKUADS) to assess the presence of anxiety and depressive symptoms."

- 18. Comment:** More attention could be paid to the role of cultural differences that might account for some of the differences observed in the study would be useful. For

example, how might income (socioeconomic status) interact with factors such as ethnicity and child-bearing?

Response: Thank you the point is well taken. We have made attempts to explain and speculate on these factors in discussion section now, page # 15-16.

19. Comment: The results for the effect of children is indeed puzzling. More justification/explanation is needed here.

Response: Thank you and point is well taken. We have added following response on page 17 under discussion section.

“In our study, participants who bear more children were less likely to develop anxiety and depressive symptoms. The plausible reason could be that parents tend to positively engage and bind to their children’s lives by giving continuous love, time, support and commitment, which can all be coping strategies against distress. In contrast, other studies found that having more children is a risk factor for anxiety and depression among women (Husain et al., 2000; Nisar, Billoo, & Gadit, 2004). This could be due to the extra burden of responsibilities that woman has to fulfill in our society; whereas, as per societal norms, males are not expected to take part in household chores and traditional child care”.

Other

20. Comments: I couldn't see the STROBE check-list, but perhaps it has been submitted separately.

Response: Yes, **STROBE** checklist uploaded separately

Reviewer: 3

Reviewer Name: Wai-Kai Hou

Institution and Country: The Education University of Hong Kong, Hong Kong SAR, China

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

Comments: The importance of studying anxiety and depression should be stated at the outset, followed by a section that highlights the need for more empirical evidence on affective symptoms in low-income populations. Then multimorbidity can be introduced as an additional condition for studying affective disorders among those people.

Response: Thank you for the suggestion, feedback was incorporated see revised introduction part according to the comment.

Following changes have been made:

“Mental illness, anxiety and depressive symptoms are major public health issues. Globally 14% people suffer from mental illness (Yatham, Sivathasan, Yoon, da Silva, & Ravindran, 2018). More than three quarter of these population were linked with low and middle income countries (Jordans et al., 2014)”

Comments Third, a clear knowledge base on the demographic predictors of anxiety and/or depression should be included. This is essential for hypothesis testing, which is missing in the current study. Particularly, behavioral correlates, namely smoking and visit of faith healer and their potential associations with higher/lower symptoms should be explained clearly. What do people do in faith healing? What are the possible reasons for its association with higher affective symptoms? What are the implications of seeing faith healer, such as delay in seeking proper assessment/treatment? Why did smoking relate to lower symptoms in the current sample? Is there difference on this between low-income and high-income countries? These are essential findings that make the current findings unique and applicable to other similar populations.

Response: Point well taken, we have added following part on page 17 under the discussion section.

“probable reasons for visiting faith healers could be due to easy accessibility, availability and affordability, cultural beliefs and, the predominant stigma attached to the notion of mental illness, (Mishra, Nagpal, Chadda, & Sood, 2011; Nisar et al., 2004). Moreover, in our culture many people believe that mental illnesses are due to wrongdoings, possession of jinn, witchcraft and spirit; hence the affected consults with these faith healers rather than doctors. Our result is consistent with a past study, where it was reported that sixteen percent of the Pakistani population first approach to faith healer for their illness (Mubbashar & Saeed, 2001). Therefore, there is a dire need to create awareness regarding identification of symptoms of mental illness and to develop proper referral system for essential treatment on early stage of disease to avoid delayed presentation with more advanced disease”.

Comments: fourth, were there specific rationales for studying the prevalence of combined anxiety and depression in the current population? If not, then prevalence of anxiety and depressive symptoms would best be studied separately. Anxiety and depressive symptoms could have shared as well as distinct demographic correlates, which can be very useful evidence for clinical research and practice in the study population.

Response: We are indebted to the reviewer for pointing out this important issue and giving us the opportunity to explain why we used single tool to measure both anxiety and depressive symptoms in our population based study.

Accurate diagnosis and distinction between anxiety and depression requires expert psychiatrists' and psychologists' assessments which is, in most instances, impractical while conducting population based epidemiological studies, hence questionnaire based screening tools are employed. Although not ideal, such inventories and questionnaires can give fairly accurate estimates of the psychiatric disease burden in the general population, major bulk of which is anxiety and depression alone. Furthermore due to the co-occurrence of anxiety and depression in majority of the cases, most clinicians and researchers prefer a single scale to screen for both anxiety and depression (1, 2). AKUADS was developed in such a manner that it labels the presence of anxiety and depressive symptoms using the cut-off of 20, and, as its inherent limitation, cannot distinguish between anxiety and depression.

References

1. Goldberg D. Identifying psychiatric illness among general medical patients. *British medical journal (Clinical research ed)*. 1985;291(6489):161.
2. Pini S, Cassano GB, Simonini E, Savino M, Russo A, Montgomery SA. Prevalence of anxiety disorders comorbidity in bipolar depression, unipolar depression and dysthymia. *Journal of affective disorders*. 1997;42(2-3):145-53.

Comments: Some limitations can be addressed or explained. Why is the cutoff age 30 years? What is the possible missing information on affective disorders in the emerging adults? The use of objective measures of comorbid conditions is appreciated, but the diagnostic procedure and criteria are questionable. Analyses should be conducted to show whether the results are different after excluding the information from objective measures.

Response: The age group 30 years and above was particularly selected for this study as chronic medical conditions are on rise in this age group and we intended to estimate the burden of these chronic conditions in high risk population and how they influence the health and wellbeing of adults in our population.

Regarding a separate analysis based on excluding measurements from objective assessments is a doable option but perhaps that is not the main objective of this current manuscript. If we exclude measurements from objective assessment, the whole definition of several conditions will change. For instance to label individuals as “hypertensive” - internationally accepted approach to label individuals hypertensive is whether the individual has been told by a health professional that he/she is hypertensive, or positive history of anti-hypertensive drugs or objectively assessed impaired values of blood pressure. Now if we exclude those who are labelled hypertensive based on objective assessments and only label those as “hypertensive” who were told by health professional or with history of anti-hypertensive drugs then we will be clearly underestimating the burden of hypertension. The same will be true for other conditions like Diabetes Mellitus or Dyslipidemias. By altering this definition, this will clearly affect the definition of multimorbidity and ultimately burden of multimorbidity.

Although, this is doable but that will be a completely new analysis based purely on subjective assessment of chronic conditions. As this was not the main objective of this current study, therefore we have kept the analysis similar in this manuscript. We can consider this option in a separate manuscript, where we will be happy to incorporate the approach suggested by the reviewer.

Once again, we are unequivocally grateful to the positive and thorough comments of editor and reviewers, which we have dealt to the best of our capability and hope that this manuscript with additional analysis would be appropriate for publication. I shall be looking forward for your kind response in due course.

VERSION 2 – REVIEW

REVIEWER	Dr Lydia Poole UCL, UK
REVIEW RETURNED	10-Jul-2019

GENERAL COMMENTS	<p>Thank you for all your changes to the manuscript. I feel it is much improved. However, I still have a few minor points the author's may wish to consider.</p> <ul style="list-style-type: none"> - I recommend the document is thoroughly proof read for English language. - The Cronbach's alpha for the depression scale refers to the continuous measure - I would move this sentence so it comes before your description of the binary cut-off (p.10). - Obesity has been deleted from your list of independent variables (p.10) but is still included in the subsequent paragraph. - I am not clear why you included covariates with a p-value <.250? What is your justification for this? - You have correctly changed some of your results to describe the increased odds of an event occurring for most of your results. However, a few results are written as 'less likely..' (p.14). This
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	<p>should be changed to 'reduced odds' for accuracy.</p> <p>-In the Table footnotes, please include a list of all covariates included in the fully adjusted model.</p> <p>- Unless the journal guidelines state otherwise, I would prefer the p-values to be left in table 2 and 3.</p> <p>- I don't know if you have checked, but you may wish to use 'currently married' as the reference group for marital status as I would expect this to be the group with the least dep/anxiety? Along the same lines, why are the Sindhi group the reference as opposed to one of the others?</p> <p>- Minor comment - two of your tables seem to be labelled as Table 3.</p> <p>- In your discussion of child bearing (p.16) a reference would be useful to back-up your ideas. I am not convinced your justification fully accounts for the findings. I suspect that either there may be a non-linear association between number of children and depression/anxiety causing a measurement error in your current model or having more children acts as a buffer in that older siblings help to take care of younger ones and/or may contribute to family finances through employment. In order to test for the linear association I suggest you enter number of children as a continuous variable in your regression model and test the effect.</p>
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REVIEWER	Wai-Kai Hou Centre for Psychosocial Health, Department of Psychology, Education University of Hong Kong, Hong Kong SAR, China
REVIEW RETURNED	02-Jul-2019

GENERAL COMMENTS	The authors are to be congratulated on publishing this important study.
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VERSION 2 – AUTHOR RESPONSE

Reviewer: 2

Reviewer Name: Lydia Poole

Institution and Country: Research Fellow UCL, UK

1. Comment: I recommend the document is thoroughly proof read for English language.

Response: Thank you very much for your feedback. The manuscript has now been thoroughly reviewed and efforts have been made to improve the quality of English and remove grammatical errors

2. Comment: - The Cronbach's alpha for the depression scale refers to the continuous measure - I would move this sentence so it comes before your description of the binary cut-off (p.10).

Response: Point well taken, we have shifted the Cronbach's alpha binary cutoff

3. Comment: Obesity has been deleted from your list of independent variables (p.9) but is still included in the subsequent paragraph.

Response: Thank you for highlighting this point. Obesity is considered as a part of the chronic conditions and included in the multimorbidity definition. Detail explanation of this variable is mentioned in methodology page # 10.

4. Comment: I am not clear why you included covariates with a p-value <.250? What is your justification for this?

Response: Point taken, P-value<0.250 criteria with reference has been added in the methodology page # 12. Researchers recommended this is a screening criterion for initial variable selection, also the use of more traditional level (alpha =0.05) may fail to identify variables known to be important. ((1)

5. Comment:- You have correctly changed some of your results to describe the increased odds of an event occurring for most of your results. However, a few results are written as 'less likely..' (p.14). This

should be changed to 'reduced odds' for accuracy

Response: Point is well taken: We have now made modifications as per your suggestion. As 'less likely.. .'Rephrase with 'reduced odds' page # 14.

6. Comment: In the Table footnotes, please include a list of all covariates included in the fully adjusted model.

Response: Thank you for highlighting this important point. We have added list of covariate see incorporated changes in table page # 30.

7. Comment: Unless the journal guidelines state otherwise, I would prefer the p-values to be left

Response: Thank you for your comment, as per journal guideline and reviewer 1 suggestion, we have deleted p values.

8. Comment: I don't know if you have checked, but you may wish to use 'currently married' as the reference group for marital status as I would expect this to be the group with the least dep/anxiety?

Along the same lines, why are the Sindhi group the reference as opposed to one of the others?

Response: Thank you for your valuable suggestion. We have taken your point in consideration and reanalysis data using currently married as reference category. Changes are highlighted in table and text of result session.

Regarding taking Sindhi ethnicity as reference group, the decision was made arbitrarily as the study was conducted in Sindh province.

9. Comment: Minor comment - two of your tables seem to be labelled as Table 3.

Response: Point taken, correction has been made.

10. Comment: In your discussion of child bearing (p.16) a reference would be useful to back-up your ideas. I am not convinced your justification fully accounts for the findings. I suspect that either there may be a non-linear association between number of children and depression/anxiety causing a measurement error in your current model or having more children acts as a buffer in that older siblings help to take care of younger ones and/or may contribute to family finances through employment. In order to test for the linear association I suggest you enter number of children as a continuous variable in your regression model and test the effect.

Response: Thank you for your enlightening comment, our thoughts are well align with your point of view. However, we have analyzed that data using number of children in number of ways (continues as well as categorical) and it did not change the results (Data not shown). The reason for our justification of the result was the underline cultural dynamic of south Asian population, where even young children start working and financially supporting their families, an observation highlighted in literature and number of media sources (2). Following points were added in discussion.

“More number of children can also act as a buffer, considering the cultural dimension of the south Asian population where older children serve as a financial security for the family. Moreover, they also perform the role of caretaker, and/or may contribute to family house hold chores. This provides positive hope to the family that their future financial and social security is warranted and, thus , decreases anxiety and depression” see page # 17.