PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Anxiety and depression among people with type 2 diabetes visiting diabetes clinics of Pokhara Metropolitan, Nepal: a cross-sectional study
AUTHORS	Paudel, Shishir; Khanal, Shankar; Gautam, Sujan; Chalise, Anisha; Koirala, Tara; Marahatta, Sujan

VERSION 1 – REVIEW

REVIEWER	Sunny, Avinash Golden Community, Lalitpur, Nepal
REVIEW RETURNED	14-Oct-2022

GENERAL COMMENTS	This is an interesting research done in the midst of COVID, and highlights the need of continuous assessment and care of diabetes patient with respect to their mental wellbeing.

REVIEWER	Ganasegeran, Kurubaran Ministry of Health Malaysia, Clinical Research Center
REVIEW RETURNED	10-Nov-2022

GENERAL COMMENTS	The authors have estimated the prevalence of anxiety and depression among type 2 diabetes patients in Pokhara Metropolitan and determined their associated risk factors. While the work is well structured, I have few comments as listed below. Major revisions 1. The introduction part could be further enhanced. While the authors have described the magnitude of the problem substantially, they failed to link the highlighted problem magnitude with the mechanisms that could accelerate psychological repercussions among individuals with diabetes. On another note, the diagnosis of COVID-19 was also one of the variable explored in this study - which I believe that the authors would like to postulate the effect of "syndemicity" with those psychological repercussions. Authors should further explore on these aspects. 2. Please do not use the term "diabetic" referring to a noun. Instead authors can use terms like individuals with diabetes, people with diabetes, etc. This should be revised throughout the manuscript. 3. In the methodology, please include the formula for sample size calculation for prevalence studies. 4. The HADS has 14 items, 7 of which measures anxiety and another 7 measures depression. So why would the authors only want to measure anxiety component using HADS? Why use a different measure for depression?

	5. What are the internal consistency measures for each sub-domain of the main measure used in your population? Currently, authors just cite the Cronbach's alpha values from previous Nepali studies. 6. What was the cut-off value for VIFs that authors determined as non multi-collinearity? This should be described in the methods part as well. 7. What cut-offs were used to determined categories of anxiety and depression level? Why categorize them rather than using the measure as a continuous variable. Desperate categorization only reduces the statistical power. 8. The methodology part doesn't fully describe the data type, data source for each independent variable used in the analyses. Probably a table to describe this should be included in the methods part. Minor revisions 1. Your 95% CIs in the multivariate analysis shows wide gaps. This may refer to the circumstance that sample size is not sufficient. It may be because you have calculated the sample size for the overall prevalence, but not for each individual objective. Kindly highlight this issue in the limitations part. 2. In the discussion, the authors made consistency comparisons of the literature within the same region as of Nepal, or within the populations of the same culture. We could not appreciate diversity of results here, whereby inconsistencies of results could be appreciated among different culture and settings, which could be further discussed and debated in this section. Have a look at this paper where focus of exploration was from three different major ethnic groups (http://dx.doi.org/10.1136/bmjopen-2014-004794) 3. Further limitations of the study such as recall bias, generalizability of the study findings should be noted. 4. The manuscript requires English language check.

REVIEWER	SALINERO-FORT, MIGUEL Servicio Madrileño de Salud, Gerencia de Atención Primaria
REVIEW RETURNED	12-Nov-2022

GENERAL COMMENTS	The study is interesting and well done, but it needs attention on the points that I point out below. The introduction is too long, and part of it can be moved to the discussion section, especially lines 37 to 55. On the other hand, from my point of view, the need to carry out the study is not well explained, given the clear evidence of a higher prevalence of anxiety and depression in the population with type 2 diabetes. Although the study's methodology is solid, there may be a selection bias as these patients come to the hospital. In addition, one of them is highly specialized in diabetes. The authors could better explain whether, given the conditions of the Nepalese health system, this form of hospital care of patients is the usual one or it may be exceptional and, therefore, constitute a bias. The independent variables that show an association with the two dependent variables (anxiety and depression) are not predictor variables, since being a cross-sectional study there is no directionality. This expression (predictor) needs to be corrected. The tables 2 and 3 are hard to read and should be simplified. It is not necessary to put the percentages of the two categories of a dichotomous variable but of the most crucial category (for

	example, living alone). In addition, it is preferable to condition the percentages on columns, that is, depression vs. no depression (anxiety vs. no anxiety). In summary, what is interesting is to know the proportion of patients with anxiety who live alone (14.6%) vs. those without anxiety who live alone (5.7%). If the difference between what is observed and expected (total percentage of patients living alone -8.54%-) is large, the chi-square test will be greater than 3.84 and the p-value less than 0.05. The chi-square is 6.135, and the p-value is 0.01325 (not 0.012) for living alone between anxiety and no anxiety. On the other hand, the correct sum of 76 subjects living alone with anxiety and 181 subjects without anxiety is 257 (not 259). Therefore, the authors must revise the calculations in the tables. Having carried out the fieldwork during the COVID-19 pandemic period, an overestimation of anxiety and depression may have occurred, so this bias makes it difficult to compare the results with other studies carried out outside that context. Therefore, in the discussion section, it should be compared with a study carried out in similar circumstances (1) The presence of the COVID-19 pandemic does not invalidate the study of the associated factors, which are also consistent with previous studies in other physical and temporal scenarios. It also allows us to know the contribution of the affectation of COVID-19 on anxiety and depression, respectively. In the limitations section, the probable overestimation of anxiety and depression as a consequence of the COVID-19 pandemic should be noted. My final conclusion is major changes (1) Moradian S, Teufel M, Jahre L, Musche V, Fink M, Dinse H, Schweda A, Weismüller B, Dörrie N, Tan S, Skoda EM, Bäuerle A. Mental health burden of patients with diabetes before and after the initial outbreak of COVID-19: predictors of mental health impairment. BMC Public Health. 2021 Nov 11;21(1):2068. doi: 10.1186/s12889-021-12101-z. PMID: 34763688; PMCID: PMC8582238

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Avinash Sunny, Golden Community, Lalitpur, Nepal
Comments to the Author:
This is an interesting research done in the midst of COVID, and highlights the need of continuous assessment and care of diabetes patient with respect to their mental wellbeing.
¬ Thank you for your time and appreciation.

Reviewer: 2
Dr. Kurubaran Ganasegeran, Ministry of Health Malaysia
Comments to the Author:
The authors have estimated the prevalence of anxiety and depression among type 2 diabetes patients in Pokhara Metropolitan and determined their associated risk factors. While the work is well structured, I have few comments as listed below.
Major revisions
1. The introduction part could be further enhanced. While the authors have described the magnitude

of the problem substantially, they failed to link the highlighted problem magnitude with the mechanisms that could accelerate psychological repercussions among individuals with diabetes. On another note, the diagnosis of COVID-19 was also one of the variable explored in this study - which I believe that the authors would like to postulate the effect of "syndemicity" with those psychological repercussions. Authors should further explore on these aspects.
¬ Thank you for the valuable suggestion, we have tried to look into it and have made few changes in the manuscript in its reflection.

2. Please do not use the term "diabetic" referring to a noun. Instead authors can use terms like individuals with diabetes, people with diabetes, etc. This should be revised throughout the manuscript.
¬ Thank you for the feedback. The term ‘diabetic’ has been replaced with ‘people with diabetes’ throughout the manuscript.

3. In the methodology, please include the formula for sample size calculation for prevalence studies.
¬ Thank you for your comment. The formula used for the calculation of sample size in the present study has been included in the ‘Sample size determination’ under ‘Methods and materials’ section.

4. The HADS has 14 items, 7 of which measures anxiety and another 7 measures depression. So why would the authors only want to measure anxiety component using HADS? Why use a different measure for depression?
¬ Thank you for highlighting this context. For this research all the tools were used in Nepali language including the tool for the assessment of Depression and Anxiety. The HADS tools validated in Nepali version suggested a lower Cronbach’s alpha of 0.68 for Depression sub-scale and a fine Cronbach’s alpha of 0.76 for Anxiety sub-scale. (https://pubmed.ncbi.nlm.nih.gov/26657079/) whereas the PHQ-9 validated in Nepali version revealed a good tradeoff of sensitivity and specificity of 0.94 and 0.80. (https://pubmed.ncbi.nlm.nih.gov/26951403/). The team also looked for GAD-7 to assess Anxiety but there is no validation study conducted so far for its validation in Nepali Language. Thus to ensure the proper screening, the team went for HADS-Anxiety subscale and PHQ-9 which were the available best options in Nepali language.

5. What are the internal consistency measures for each sub-domain of the main measure used in your population? Currently, authors just cite the Cronbach's alpha values from previous Nepali studies.
¬ Thank you for the comment. We have calculated the Cronbach’s alpha of HADS-Anxiety subscale and PHQ-9 in our data as well. We didn’t administer HADS-Depression subscale in the data collection process as we had used PHQ-9 and using HADS-Depression scale would have made the interview lengthy and uneasy for the participants. We can add the Cronbach’s alpha of HADS-Anxiety subscale and PHQ-9 of our data if required in the methodology section.

6. What was the cut-off value for VIFs that authors determined as non multi-collinearity? This should be described in the methods part as well.
¬ Thank you for the comment. The cut-off value for VIF has been mentioned in the ‘Methods and materials’ section. A VIF greater than five is taken as an indication of multi-collinearity between independent variables. (Neter J, Kutner MH, Nachtsheim CJ, Wasserman W. Applied linear statistical models. Fifth edition ed2005.)
¬ In this study, the highest reported VIF was 1.610 (which is mentioned in the result section)

7. What cut-offs were used to determined categories of anxiety and depression level? Why categorize them rather than using the measure as a continuous variable. Desperate categorization only reduces the statistical power.
¬ Thank you for the comment. We had used the standard cut-offs provided by the original HADS-Anxiety subscale and PHQ-9 scale to categorize anxiety and depression level. It is mentioned in the ‘Data collection’ part under ‘Methods and materials’ section. We agree with your remarks that

categorizing the continuous variable might reduce the statistical power, but we still made the categories as to make our study more comparable with other studies which is mostly a general practice in our country context.

8. The methodology part doesn't fully describe the data type, data source for each independent variable used in the analyses. Probably a table to describe this should be included in the methods part.
¬ Thank you for the feedback. As the editor requested us to provide the Questionnaire (in English version) as a supplementary file which we have now added to the manuscript submission, we wonder if it will solve the issue of illustrating the data type and data source for independent variables, as we already have a large number of tables. We are fine to add the table if having the questionnaire does not solve this issues and it is required.
Minor revisions
9. Your 95% CIs in the multivariate analysis shows wide gaps. This may refer to the circumstance that sample size is not sufficient. It may be because you have calculated the sample size for the overall prevalence, but not for each individual objective. Kindly highlight this issue in the limitations part.
¬ Thank you for this crucial suggestion, we have added it into our limitations.

10. In the discussion, the authors made consistency comparisons of the literature within the same region as of Nepal, or within the populations of the same culture. We could not appreciate diversity of results here, whereby inconsistencies of results could be appreciated among different culture and settings, which could be further discussed and debated in this section. Have a look at this paper where focus of exploration was from three different major ethnic groups (http://dx.doi.org/10.1136/bmjopen-2014-004794)
¬ Thank you for providing this valuable literature, we have added it to our discussion section with its appropriate citation.

11. Further limitations of the study such as recall bias; generalizability of the study findings should be noted.
¬ Thank you

12. The manuscript requires English language check.
¬ Thank you, we have made several changes throughout the manuscript correcting the spelling and grammatical errors

Reviewer: 3
Dr. MIGUEL SALINERO-FORT, Servicio Madrileño de Salud
Comments to the Author:
The study is interesting and well done, but it needs attention on the points that I point out below.
1. The introduction is too long, and part of it can be moved to the discussion section, especially lines 37 to 55. On the other hand, from my point of view, the need to carry out the study is not well explained, given the clear evidence of a higher prevalence of anxiety and depression in the population with type 2 diabetes.
¬ Thank you for your suggestion. We have made slight changes in the introduction section. Although evidences suggest high prevalence of anxiety and depression, this study further highlights the mental health problems in this population and explores its relationship with factors such as social support, health insurance and public health emergencies such as COVID-19 pandemic.

2. Although the study's methodology is solid, there may be a selection bias as these patients come to the hospital. In addition, one of them is highly specialized in diabetes. The authors could better explain whether, given the conditions of the Nepalese health system, this form of hospital care of

patients is the usual one or it may be exceptional and, therefore, constitute a bias.
¬ Thank you for highlighting the potential risk of selection bias, we acknowledge it as our limitation. In regards to the Pokhara Super Speciality Health Clinic it is one among many private endocrine centers of Nepal. There are many endocrine clinics and centers in Nepal that look after the endocrine-related health problems including diabetes.

3. The independent variables that show an association with the two dependent variables (anxiety and depression) are not predictor variables, since being a cross-sectional study there is no directionality. This expression (predictor) needs to be corrected.
¬ Thank you for the feedback. The use of 'predictors' in such cases have been revised and corrected in the manuscript.

4. The tables 2 and 3 are hard to read and should be simplified. It is not necessary to put the percentages of the two categories of a dichotomous variable but of the most crucial category (for example, living alone). In addition, it is preferable to condition the percentages on columns, that is, depression vs. no depression (anxiety vs. no anxiety). In summary, what is interesting is to know the proportion of patients with anxiety who live alone (14.6%) vs. those without anxiety who live alone (5.7%). If the difference between what is observed and expected (total percentage of patients living alone -8.54%-) is large, the chi-square test will be greater than 3.84 and the p-value less than 0.05. The chi-square is 6.135, and the p-value is 0.01325 (not 0.012) for living alone between anxiety and no anxiety. On the other hand, the correct sum of 76 subjects living alone with anxiety and 181 subjects without anxiety is 257 (not 259). Therefore, the authors must revise the calculations in the tables.
¬ To simplify the tables, we have broken down the descriptive profile of the participants into two new tables.
¬ Thank you for pointing out this error in the calculation. We have rechecked all the calculations in SPSS and have revised the tables accordingly. Thank you.
¬ We tried to compare the presence or absence of Anxiety based on the nature of living companionship i.e. is anxiety more prevalent among those living alone or those living with their family?

5. Having carried out the fieldwork during the COVID-19 pandemic period, an overestimation of anxiety and depression may have occurred, so this bias makes it difficult to compare the results with other studies carried out outside that context. Therefore, in the discussion section, it should be compared with a study (1) carried out in similar circumstances.
(1) Moradian S, Teufel M, Jahre L, Musche V, Fink M, Dinse H, Schweda A, Weismüller B, Dörrie N, Tan S, Skoda EM, Bäuerle A. Mental health burden of patients with diabetes before and after the initial outbreak of COVID-19: predictors of mental health impairment. BMC Public Health. 2021 Nov 11;21(1):2068. doi: 10.1186/s12889-021-12101-z. PMID: 34763688; PMCID: PMC8582238
¬ Thank you for suggesting this literature. We have added its reflection in the manuscript with provided citation.

6. The presence of the COVID-19 pandemic does not invalidate the study of the associated factors, which are also consistent with previous studies in other physical and temporal scenarios. It also allows us to know the contribution of the affectation of COVID-19 on anxiety and depression, respectively.
¬ Thank you for suggesting this context, we have tried to add its reflection in our manuscript.

7. In the limitations section, the probable overestimation of anxiety and depression as a consequence of the COVID-19 pandemic should be noted.
¬ Thank you. We have added it to our limitation.

VERSION 2 – REVIEW

REVIEWER	Ganasegeran, Kurubaran Ministry of Health Malaysia, Clinical Research Center
REVIEW RETURNED	12-Dec-2022

GENERAL COMMENTS	The authors have made the editions as suggested.

REVIEWER	SALINERO-FORT, MIGUEL Servicio Madrileño de Salud, Gerencia de Atención Primaria
REVIEW RETURNED	21-Dec-2022

GENERAL COMMENTS	The authors have substantially improved the manuscript and responded to all my suggestions except the following: Tables 4 and 5 are still hard to read. To better explain what I want to express, I have copied the output of SPSS of the analysis between the variable's anxiety (yes/no) and the nuclear family (dichotomous variable), indicating percentages to row (as expressed in the manuscript) and to columns, respectively. If this last possibility is used, the table can be described more simply, as I propose in the last table. Usually, studies such as this indicate the percentages of each variable to columns (anxiety or depression). However, in the present study, the results are indicated to rows. For example, the male gender includes 161 subjects, 33.5% (n=54) with anxiety and 66.5% (n=107) without anxiety (sum = 100%, total value of row). Please, look at the steps included in pdf attach file

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2

The authors have made the editions as suggested.

- We would like to thank you for your valuable time and suggestion for the improvement in our manuscript

Reviewer: 3

The authors have substantially improved the manuscript and responded to all my suggestions except the following:

Tables 4 and 5 are still hard to read. To better explain what I want to express, I have copied the output of SPSS of the analysis between the variable's anxiety (yes/no) and the nuclear family (dichotomous variable), indicating percentages to row (as expressed in the manuscript) and to columns, respectively. If this last possibility is used, the table can be described more simply, as I propose in the last table. Usually, studies such as this indicate the percentages of each variable to columns (anxiety or depression). However, in the present study, the results are indicated to rows. For example, the male gender includes 161 subjects33.5% (n=54) with anxiety and 66.5% (n=107) without anxiety (sum = 100%, total value of row).

➢ We would like to thank you for your valuable time and suggestion for the improvement in our manuscript and for the pdf document to make it more clear for us to understand your comments. We have changed table 4 and 5 using Column total instead of Row total as per your suggestion.

VERSION 3 – REVIEW

REVIEWER	SALINERO-FORT, MIGUEL Servicio Madrileño de Salud, Gerencia de Atención Primaria
REVIEW RETURNED	18-Jan-2023

GENERAL COMMENTS	The authors have substantially improved the manuscript and responded to all my suggestions.