PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Prevalence and factors associated with preoperative anxiety among patients undergoing surgery in low and middle-income countries: A systematic review and meta-analysis
AUTHORS	Bedaso, Asres; Mekonnen, Nibretie; Duko, Bereket

VERSION 1 – REVIEW

REVIEWER	Sanfilippo, Katie Rose Goldsmiths University of London, Psychology
REVIEW RETURNED	15-Nov-2021

GENERAL COMMENTS	Thank you for allowing me to read and review this article. This study, which looks at the prevalence and correlates of preoperative anxiety among patients in LMICs, investigates an area in need of more exploration. Therefore, I believe this article fills an important gap in understanding which could lead to further innovation and formulate recommendations for future health care services. Below are my suggestions by section 1. Abstract • It would be helpful to be clearer about the number of countries included. After counting I believe it is 13 countries across three different continents. • It would also be helpful to name the most common scales used across the studies to measure preoperative anxiety. 2. Strengths and limitations • The second bullet point has a grammatical error (“needs cautions”). It would be clearer for this point to highlight the limitation in the generalizability of these findings to all LMICs. • The third bullet point could be split into two different points. 3. Introduction • It would be helpful to include more discussion around research that has been done to look at the prevalence of preoperative anxiety in specifically LMICs. • It would also be helpful to include research that discusses the potential effect of resources, health systems, and culture on rates of preoperative anxiety. This might help the reader understand why you are focusing on LMICs. • Some more information around the number of surgeries that happen across various LMICs (especially those which are included in this meta-analysis (e.g. Ethiopia)) and differences in surgical outcomes and recourses across countries would help the reader better understand the context for this work.

	4. Methods • I am not an expert in meta-analysis methods and therefore recommend this be reviewed by someone with this expertise. • Within the analysis section, more detail around the exact sub-group analyses which were conducted need to be included. It does not state for example that a sub-group analysis was also done based on the type of anxiety tool used. • There are significant differences in culture, resources, and health systems across the included countries, regions, and continents. I would recommend also including a sub-analysis looking at differences in pooled prevalence rates across continents or regions. 5. Results • Within the results (in the meta-analysis section) and in fact throughout the results section, it would be more accurate to report the results as “The pooled prevalence of preoperative anxiety among patients undergoing surgery within the LMICs included within this study was…”. 6. Discussion and Conclusion • Within the discussion it states that “socio-cultural aspects may partly explain the observed difference in the pooled estimates”. More discussion, based on previous research in the area, should be included to better explain what kind of “socio-cultural aspects” you might be referring to. • There should be some discussion within this section regarding the limitations of the study o While the results talk about prevalence and correlates in LMICs, in reality, it only covers 13 different countries. Also, the countries included are different in terms of their culture, resources, and health systems. Therefore, this should be recognized as a limitation in the generalizability of these findings to all LMICs. • Within the conclusion it states that preoperative anxiety was “significantly high (55%)”. Significantly higher than in HICs? This statement is not clear. • At the end of the introduction, you discuss how this work might formulate recommendations for future health care services. It might be helpful to briefly discuss within the conclusion this potential impact of the work. Overall: • There are quite a few grammatical errors throughout the article and some of the sentences were unclear or difficult to follow. I believe these could be addressed with another edit of the paper by the authors and the help of some trusted colleagues. Thanks you for all the work you have done to prepare this piece of work.

REVIEWER	Shin, Seungwon Kyung Hee University
REVIEW RETURNED	27-Dec-2021

GENERAL COMMENTS	I reviewed this manuscript, focused on the statistical methods and analyses, as the editorial office asked me. I could not find any siginificant defects in statistical methods. However, I recommend that the author could consider the following comments to enhance the quality of the manuscript.

	1. The eligibility criteria of this SR/MA should specify the low- and middle-income countries. Do they have any references for those countries? Or do they have any own definitions for those countries? 2. The authors repeatedly used the word 'correlates' including the title. Also, they sometimes used the words 'risk' or 'risk factor' in the manuscript. Precisely speaking, correlates, risk factors, or associated factors have different meanings in statistics. This SR/MA included only cross-sectional studies and the cross-sectional studies can tell the association, not the risk. I recommend the authors should consider this aspect and revise the words. 3. I guess that the authors can re-organize Table 3 more systematically to enhance the readers' understandability. 4. Table 3 shows us that there are many factors to affect the prevalence of pre-operative anxiety. Even though they are not consistent across the studies, the authors take it into consideration that they need to show more sub-group analysis, in which those factors are used for group categorization (e.g. male vs female).

REVIEWER	Alvarez-Villalobos, Neri Universidad Autonoma de Nuevo Leon, Subdireccion de Investigación
REVIEW RETURNED	27-Dec-2021

GENERAL COMMENTS	Bedaso et al. carried out a systematic review with the objective of determining the pooled prevalence of preoperative anxiety and its correlation among patients undergoing surgery in low and middle-income countries. The study's aim is interesting, as it is important to be aware of this situation in order to approach patients within this context in the best way possible. However, there are some points that can be clarified to improve the project. Here are some observations: 1. In the Search strategy section, the terms used and some term combinations are shortly described. However, this strategy is not visible in the text nor as a supplementary file, so is not possible to evaluate it. It is suggested to add the search strategy as a supplementary file. 2. In the Eligibility criteria section, the inclusion and exclusion criteria are mentioned. However, it is not explained if and how the phases of abstract and full-text screening were performed. On the other hand, it is not described if a pilot test was performed in order to reach an agreement between the reviewers. This must be clarified. 3. In the Eligibility criteria section, it is described, as an inclusion criteria, that the measurement of anxiety needs to be validated by a screening tool, but it is not clear which ones were taken into account to participate in the study. Additionally, another inclusion criteria was that the preoperative anxiety prevalence needs to be mensurated at a low or middle-income country. However, it is not clear which classification was used to classify the countries. It is suggested to define them. 4. In the Sub-group and sensitivity analysis, it is mentioned at the sub-group analysis based on the country that the higher pooled prevalence of preoperative anxiety was in a study conducted in Srilanka but having conducted only one study at that country there is not possible to match up. The same situation is reported in the sub-group analysis based on the anxiety tool used. It is important

	to recognize the limitations and do not report that a pool was made when it was not.

VERSION 1 – AUTHOR RESPONSE

1. Please revise the 'Strengths and limitations' section of your manuscript (after the abstract). This section should contain up to five short bullet points, no longer than one sentence each, that relate specifically to the methods. The novelty, aims, results or expected impact of the study should not be summarised here.
Response: First we would like to thank you for the critical comments. We have now revised the "strengths and limitations" of our review as indicated below by incorporating the suggested comments.

Strengths and limitations

¬ Conducting abroad literature search, independent screening, quality appraisal, and data extraction by two investigators represent the main strength of the current review.
¬ The absence of significant publication bias increases the reliability of our findings.
¬ The significant heterogeneity among studies and the restriction applied to include studies published only in English language are among the major limitations of the current review in generalizing these findings to all LMICs.

2. Please ensure that you have fully discussed the methodological limitations of the study in the discussion section of the main text.
Response: Now, we have revised the discussion section of our manuscript by including all the methodological limitations of our review. See the yellow highlighted changes made.

"It is worth noting the following potential limitations of our review in generalizing the findings. First, there is significant heterogeneity among studies included in the current review. Second, the restriction to include studies published only in English language could introduce possible selection bias and limit the generalizability to all LMICs."

3. Please include, as a supplementary file, the precise, full search strategy (or strategies) for all databases, registers and websites, including any filters and limits used.
Response: We have accepted the suggestion. The full search strategy is included in the revised manuscript as a supplementary file 2.
Reviewer 1
Thank you for allowing me to read and review this article. This study, which looks at the prevalence and correlates of preoperative anxiety among patients in LMICs, investigates an area in need of more exploration. Therefore, I believe this article fills an important gap in understanding which could lead to further innovation and formulate recommendations for future health care services. Below are my suggestions by section

Abstract
1. It would be helpful to be clearer about the number of countries included. After counting I believe it is 13 countries across three different continents. It would also be helpful to name the most common scales used across the studies to measure preoperative anxiety.
Response: We would like to thank the reviewer for the constructive comments. Now, we have included the number of countries and the most commonly used tool in the result section of the abstract. See the yellow highlighted changes in the abstract (result section) and result section of the

revised manuscript (Paragraph 2 of the result section, Italics font). See also, the specific included section below.
From result section of the abstract:
“Our search identified 2110 studies, of which 27 studies from 12 countries with 5,575 participants were included in the final meta-analysis.”
From paragraph 2 of the result section:
“Of the total 27 studies (5,575 population), all (100%) studies employed cross-sectional study design, and 9 (81.2%) studies published in the past five years (21, 22, 30, 43-48). Also, six studies were conducted in Ethiopia (5, 21, 22, 43-45), five studies were from Brazil (49-53), and three studies were from each of the following countries; Nigeria (30, 48, 54), Pakistan (11, 12, 55) and India (55-57).”

Strengths and limitations
2. The second bullet point has a grammatical error (“needs cautions”). It would be clearer for this point to highlight the limitation in the generalizability of these findings to all LMICs. The third bullet point could be split into two different points.
Response: Now, we have amended the strengths and limitations of our review in the revised manuscript as indicated below.

Strengths and limitations
¬ Conducting abroad literature search, independent screening, quality appraisal, and data extraction by two investigators represent the main strength of the current review.
¬ We have conducted a leave-one-out sensitivity analysis to examine the influence of a single study on the overall pooled estimates.
¬ The absence of significant publication bias increases the reliability of our findings.
¬ The significant heterogeneity among studies and the restriction applied to include studies published only in the English language are the major limitations of the current review in generalizing these findings to all LMICs.
Introduction
3. It would be helpful to include more discussion around research that has been done to look at the prevalence of preoperative anxiety in specifically LMICs.
Response: We have accepted the comment and more epidemiological studies reporting the magnitude of POA were included in the introduction section of revised manuscript (Paragraph 2). See the yellow highlighted changes made in the introduction section. Here indicated below is the included statement.
“Epidemiological studies conducted in low and middle-income countries found that the prevalence of preoperative anxiety ranges from 47 to 70.3% in India (9, 10), 62 to 97% in Pakistan (11-13), and 39.8 to70% in Ethiopia (5, 14-18).”

4. It would also be helpful to include research that discusses the potential effect of resources, health systems, and culture on rates of preoperative anxiety. This might help the reader understand why you are focusing on LMICs.
Response: Now, we have included the suggested comment in paragraph three of the introduction section (Yellow highlighted). Also, the specific included statement is indicated below.

“Furthermore, evidence also indicated that in many low and middle-income countries, the potential effect of scarce resources at health facilities, weak health systems, and culture of a given community could play a paramount role in the increased rates of preoperative anxiety among surgical patients. For example, studies demonstrated that waiting for a longer duration for surgery (24, 25), inadequate information about the procedure, disrespect by the clinician, and lacking empathy (26), and receiving less inpatient care (25) could increase the risk of preoperative anxiety. ”

5. Some more information around the number of surgeries that happen across various LMICs (especially those which are included in this meta-analysis (e.g. Ethiopia)) and differences in surgical outcomes and recourses across countries would help the reader better understand the context for this work.
Response: The suggested comment was incorporated in paragraph three of the introduction section. Also, see the indicated below changes made.

"…Furthermore, evidence also indicated that in many low and middle-income countries, the potential effect of scarce resources at health facilities, weak health systems, and culture of a given community could play a paramount role in the increased rates of preoperative anxiety among surgical patients. For example, studies demonstrated that waiting for a longer duration for surgery (27, 28), inadequate information about the procedure, disrespect by the clinician, lacking empathy (29), and receiving less inpatient care (28) could increase the risk of preoperative anxiety. Globally, the surgery rate ranges from 295 operations per 100,000 population in Ethiopia to 23,369 per 100,000 in Hungary, indicating a considerable difference in surgical service provision between low-income countries (LIC) and high-income countries (HIC) despite a growing unmet need (30). Despite the small number of surgical service in LMICs, it is compounded by the burden of managing postoperative complications such as delayed complications which mainly caused by inadequate inpatient care and low rates of follow-up service (31).

Methods

6. Within the analysis section, more detail around the exact sub-group analyses which were conducted need to be included. It does not state for example that a sub-group analysis was also done based on the type of anxiety tool used.
Response: We have conducted a subgroup analysis based on the tool used to screen anxiety. A total of 7 screening tools (Table 2 & 3) were used by all 27 studies. Therefore, we did a subgroup analysis considering each of the seven anxiety screening tools as a moderator. To make the concept clearer, we made more elaboration in the analysis sub-section of the method and subgroup analysis sub-section of the result in the revised manuscript.

NB: All the changes made were yellow highlighted in the specified section of the revised manuscript.

7. There are significant differences in culture, resources, and health systems across the included countries, regions, and continents. I would recommend also including a sub-analysis looking at differences in pooled prevalence rates across continents or regions.
Response: We agree with the suggestion and the subgroup analysis across continent (Africa, Asia, South America) was conducted. See the findings in the subgroup analysis sub-section of the result and Table 2.
Results
8. Within the results (in the meta-analysis section) and in fact throughout the results section, it would be more accurate to report the results as "The pooled prevalence of preoperative anxiety among patients undergoing surgery within the LMICs included within this study was…"
Response: We agree with the reviewer's suggestion. As indicated below (Italics font and yellow highlighted) revision was made in the revised manuscript.

"The pooled prevalence of preoperative anxiety among patients undergoing surgery within the LMICs included within this study was estimated to be 55.7% (95% CI: 48.60-62.93) with considerable heterogeneity between studies (I2= 97%; P<0.001). Consequently, a random-effects meta-analysis model was employed to estimate the overall pooled prevalence"

Discussion and Conclusion

9. Within the discussion it states that “socio-cultural aspects may partly explain the observed difference in the pooled estimates”. More discussion, based on previous research in the area, should be included to better explain what kind of “socio-cultural aspects” you might be referring to.
Response: Rather than mentioning the term “socio-cultural aspects” we made change and used the term “demographic aspect” and we gave detailed explanation of how demographic factors of participants related to the discrepancy in magnitude of preoperative anxiety. See the changes made on page 16, paragraph 1of the revised manuscript.

10. There should be some discussion within this section regarding the limitations of the study
o while the results talk about prevalence and correlates in LMICs, in reality, it only covers 13 different countries. Also, the countries included are different in terms of their culture, resources, and health systems. Therefore, this should be recognized as a limitation in the generalizability of these findings to all LMICs.
Response: Now, we have included limitations of our review in the last paragraph of the discussion. The included statement is also indicated below.
“It is worth noting the following potential limitations of our review in generalizing the findings. First, there is significant heterogeneity among studies included in the current review. Second, the restriction to include studies published only in English language could introduce possible selection bias and limit the generalizability to all LMICs.”

11. Within the conclusion it states that preoperative anxiety was “significantly high (55%)”. Significantly higher than in HICs? This statement is not clear.
Response: We have accepted the reviewer comment. Therefore, to avoid confusion we have revised the statement as indicated below (Italics font). See the changes made in the conclusion section of the abstract and main manuscript.

“Our meta-analysis indicated that around one in two patients undergoing surgery in low and middle-income countries suffer from preoperative anxiety, which needs due attention.”

12. At the end of the introduction, you discuss how this work might formulate recommendations for future health care services. It might be helpful to briefly discuss within the conclusion this potential impact of the work.
Response: Per the suggestion of the reviewer we have incorporated the recommendation of our review in the conclusion section of the revised manuscript. The specific revision is indicated below.

“….Therefore, routine screening of preoperative anxiety among patients scheduled for surgery is vital. In addition, providing preoperative education on the effect of anesthesia, surgical procedure, and possible postoperative pain management options is highly warranted.
Due to the significant heterogeneity across the studies, future studies should examine preparative anxiety for a specific group of surgical patients by stratifying the possible independent associated factors. Besides, since all the included studies employed a cross-sectional study design, the findings didn’t show a temporal relationship between preoperative anxiety and its associated factors. Therefore, future longitudinal studies and randomized controlled trials are recommended. ”
13. There are quite a few grammatical errors throughout the article and some of the sentences were unclear or difficult to follow. I believe these could be addressed with another edit of the paper by the authors and the help of some trusted colleagues.
Response: We have revised the spelling and grammar errors using online grammar and spelling checker software. Also, all authors critically revised the manuscript to avoid spelling and grammar

errors.
Reviewer 2
I reviewed this manuscript, focused on the statistical methods and analyses, as the editorial office asked me. I could not find any significant defects in statistical methods. However, I recommend that the author could consider the following comments to enhance the quality of the manuscript.
1. The eligibility criteria of this SR/MA should specify the low- and middle-income countries. Do they have any references for those countries? Or do they have any own definitions for those countries?
Response: We have included criteria we used to classify countries. The eligibility criteria was amended and additional fourth criteria was included. See paragraph 3 of the method section (eligibility criteria). Also, see the indicated below specific change made in the revised manuscript.

"…Fourth, the studies should be from a low-income or middle income country. World Bank Atlas classified countries as low-income and middle-income for those with the Gross National Income(GNI) per capita of ≤$1025 and between $1026 to 12,375, respectively (https://data.worldbank.org/indicator/NY.GNP.PCAP.CD)."

2. The authors repeatedly used the word 'correlates' including the title. Also, they sometimes used the words 'risk' or 'risk factor' in the manuscript. Precisely speaking, correlates, risk factors, or associated factors have different meanings in statistics. This SR/MA included only cross-sectional studies and the cross-sectional studies can tell the association, not the risk. I recommend the authors should consider this aspect and revise the words.
Response: We have accepted the suggested comment. Now, throughout the manuscript we used the term "associated factors" consistently and avoided terms such as "Correlates" and "Risk factors".

3. I guess that the authors can re-organize Table 3 more systematically to enhance the readers' understandability.
Response: We have now explicitly presented significant factors associated with preoperative anxiety in each study. We have also included the reported measure of association in each study. However, since the Table 3 takes more than 2 page, we have included it as a supplementary file 5.

4. Table 3 shows us that there are many factors to affect the prevalence of pre-operative anxiety. Even though they are not consistent across the studies, the authors take it into consideration that they need to show more sub-group analysis, in which those factors are used for group categorization (e.g. male vs female).
Response: Now, we have conducted a sub-group analysis using gender as a moderator (Male vs Female). See the result section of the revised manuscript (Sub-group analysis sub-section) (Page 13, paragraph 2).

"…..Furthermore, a pooled estimate of preoperative anxiety among female surgical patients (59.36%, 95%CI: 48.16-70.52, I2= 95.43, P<0.001) was higher than their male counterparts (45.95%, 95%CI: 31.69-60.21, I2= 96.67, P<0.001)."

Reviewer 3
Bedaso et al. carried out a systematic review with the objective of determining the pooled prevalence of preoperative anxiety and its correlation among patients undergoing surgery in low and middle-income countries. The study's aim is interesting, as it is important to be aware of this situation in order to approach patients within this context in the best way possible. However, there are some points that can be clarified to improve the project. Here are some observations:

1. In the Search strategy section, the terms used and some term combinations are shortly described. However, this strategy is not visible in the text nor as a supplementary file, so is not possible to evaluate it. It is suggested to add the search strategy as a supplementary file.

Response: Now, we have included the search strategy as a supplementary file 2.

2. In the Eligibility criteria section, the inclusion and exclusion criteria are mentioned. However, it is not explained if and how the phases of abstract and full-text screening were performed. On the other hand, it is not described if a pilot test was performed in order to reach an agreement between the reviewers. This must be clarified.
Response: We have now provided explanation on the abstract and full-text screening. Detail of the screening process is indicated in Identification of studies in Figure 1 of the revised manuscript which is found in paragraph 1 of the result section on Page 8. It is worth noting that screening of studies, quality appraisal and data extraction were conducted independently by two investigators (AB and NM). Disagreement were resolved through table wide discussion with the third author (BD).

However, we did a pilot test only to see the degree of difference on our quality appraisal of included studies between the two independent investigators. We have provided the inter-rater agreement in supplementary file 3. Additional clarification was provided in the Eligibility criteria and Quality appraisal sub-section of the method.

3. In the Eligibility criteria section, it is described, as an inclusion criterion, that the measurement of anxiety needs to be validated by a screening tool, but it is not clear which ones were taken into account to participate in the study. Additionally, another inclusion criterion was that the preoperative anxiety prevalence needs to be measured in a low or middle-income country. However, it is not clear which classification was used to classify the countries. It is suggested to define them.
Response: As a criterion for the studies to be included in the current review, the study should report a tool employed to assess anxiety. Basically, the tools are classified into two. The first one is a diagnostic tool such as ICD 10 (International Classification of Disease, the current updated version is ICD 10) developed by WHO. The other diagnostic tool is DSM (i.e., Diagnostic Statistical Manual Version, DSM V is the updated version) which was developed by the American Psychiatric Association. The diagnostic tool is mainly used to diagnose and treat psychiatric patients and is mostly used in the clinical setup. A second category is a screening tool, which primarily examines anxiety symptoms or probable anxiety. Most of the time, each country has its own validated tool suitable to the culture and demography of the population. Nevertheless, all the tools reported in our review are screening tools.

Therefore, any anxiety screening tool which has its validity (specificity and sensitivity) or reliability report (Cronbach's alpha)) can be included in the review.

We have now included the criteria used to classify countries based on their economic level, which is the World Bank Atlas economic classification of countries, using Gross National Income Per capita. See the revision made in Paragraph three of the method section. For the reviewer's reference, we have indicated the changes made below.

"…….Fourth, the studies should be from a low-income or middle-income country. World Bank Atlas classified countries as low-income and middle-income for those with the Gross National Income(GNI) per capita of ≤$1025 and between $1026 to 12,375, respectively (https://data.worldbank.org/indicator/NY.GNP.PCAP.CD)."

4. In the Sub-group and sensitivity analysis, it is mentioned at the sub-group analysis based on the country that the higher pooled prevalence of preoperative anxiety was in a study conducted in Srilanka but having conducted only one study in that country there is not possible to match up. The same situation is reported in the sub-group analysis based on the anxiety tool used. It is important to recognize the limitations and do not report that a pool was made when it was not.

Response: Now, we have revised the statement in the revised manuscript both in the abstract and main document. See the changes made on Page 12-14, the Result section, sub-section of sub-group and the sensitivity analysis.

VERSION 2 – REVIEW

REVIEWER	Sanfilippo, Katie Rose Goldsmiths University of London, Psychology
REVIEW RETURNED	12-Feb-2022

GENERAL COMMENTS	Thank you for all your hard work in responding to the reviewers' comments. I feel the authors have done an adequate job of responding to all the reviewers' comments and I do not have any more comments to add. I look forward to seeing this work in print.

REVIEWER	Shin, Seungwon Kyung Hee University
REVIEW RETURNED	01-Feb-2022

GENERAL COMMENTS	I appreciate for the authors' effort to amend the manuscript. I do not have any other comments. (There is a typo in the title of the table in the supplement file 5.)

REVIEWER	Alvarez-Villalobos, Neri Universidad Autonoma de Nuevo Leon, Subdireccion de Investigación
REVIEW RETURNED	01-Feb-2022

GENERAL COMMENTS	Dear Bedaso et al. Thank you very much for reading the comments. The corrections made have helped to enrich your work and have clarified ambiguities in it. However, it is suggested, if it is possible, to describe a little more in detail the methodology used in the phases of the systematic review. On the other hand, the work is adequate and sufficient, so I think it should be accepted.

VERSION 2 – AUTHOR RESPONSE

Reviewer 2

1. There is a typo in the title of the table in supplement file 5.

   Response: As indicated below we have revised the title in supplementary file 5.

   “Supplementary file 5: Factors associated with pre-operative among patients undergoing surgery”.

Reviewer 3

2. If it is possible, to describe a little more in detail the methodology used in the phases of the systematic review.

Response: We believe have already described the phases of the systematic review in the method section of the manuscript and followed the PRISMA gideline while writing the review report. Therefore, phases such database specific study search, identifying studies per eligibility criteria, quality appraisal, data extraction, data analysis and reporting is described in the method and result section of the revised manuscript.

However, as indicated in the yellow highlighted changes made in the revised manuscript, we made further detail description, specilally in the data analysis sub-section of the method.