PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Parental stress, depression, anxiety and participation to care in Neonatal Intensive Care Units: results of a prospective study in Italy, Brazil, and Tanzania
AUTHORS	Lazzerini, Marzia Barcala Coutinho do Amaral Gomez, Dafne Azzimonti, Gaetano Bua, Jenny Brandão Neto, Waldemar Brasili, Luca Travan, Laura Barradas de Souza, Juliana D'Alessandro, Michele Plet, Sabrina de Souza Lima, Geisy Maria Ndile, Emmanuel Abraham Ermacora, Maddalena Valente, Emanuelle Pessa Dalena, Paolo Mariani, Ilaria

VERSION 1 – REVIEW

REVIEWER	Dr. Anirudha Das Cleveland Clinic Children's Hospital Neonatology 9500 Euclid Ave M-31 Cleveland Ohio 44195-0001 United States
REVIEW RETURNED	26-Feb-2024

GENERAL COMMENTS	I want to thank the journal for allowing me to review such an intriguing paper. Such studies done over three countries are rare and of great importance. It was exciting to see the barriers faced by the authors in surveying three completely different settings. The study has been done well, but there is still room for improvement. Therefore, here are my comments/suggestions: First and foremost, I could not see any figures except Figure 2. Please upload the figures and make sure they are visible in the PDF. Key Message: Page 7, line 3: I think the first line should be: Immediate action should be taken to screen parents in the NICU for depression, anxiety, and stress, followed by the two current lines. I suggest not

using the word "immediate." The second sentence could be: "Mechanisms should be put in place to provide rapid access to mental health providers to the parents whose screening for psychological distress was found to be present."

Methods:
Page 10, Page 25: I disagree with the cross-sectional study design. It should be a "multicenter prospective observational cohort study."

Was there a plan for follow-up of the mothers who were found to be severely depressed or suicidal? Did the researchers have a plan for how those parents will be managed – seen by a psychologist/Psychiatrist within an acceptable period after the screening?

Page 10, lines 44-50: Why is hospitalization short in Brazil and Tanzania? Please explain.

Page 10, line 51: Please add to the limitation section that parents with previously diagnosed mental health issues were excluded. The reason is that some parents may have stress and could also start having depression after their infant is admitted to the NICU.

Page 10, exclusion criteria: Add to the limitation that parents not fluent in the language in which the questionnaire was provided were excluded. This will introduce bias as the parents who are minorities may have a higher rate of psychological distress. Also, who and how the fluency of parents in a language was determined? Please provide specifics.

Page 10, line 55: Exclusion criteria is 24 hours hospitalization or 48 hours? Your earlier statement said that the "newborns who were hospitalized in the NICU or semi-intensive care for at least 24 hours in Brazil and Tanzania". This is contradictory. Suggest clarification.

Please provide a flow diagram showing how the recruitment of subjects was done. This should include how many parents met the criteria and in what time frame, how many were approached, consented, did not consent, and how many were finally included in the study at each site. I cannot access Figure 1, which may have this information.

Please clarify if there was a point in time when the screening for psychological distress was done.

-Figures 1,3,4,5,6 were not available to me. The figures said, "Unable to convert image."

Results:
Page 21, line 6: Change to "In no country…."

Page 21, line 35: Please explain "stress significantly negatively associated with twin birth" to say something like "analyses showed parents of twin infants had less stress."

Page 22, line 3: Please change the sentence "none significant association" to "non-significant association".

Discussion:

	The discussion section needs clarification. The authors should explain the plausible reasons for the findings in the result section but some of the explanations of the findings still need to be included. Below, I have mentioned a few of them. I suggest the authors should go through the results section and try to explain all their findings while comparing and contrasting to previous research.
	Authors may also consider explaining the wide variability of stress, depression and anxiety. Is there previous research that demonstrates the difference in maternal psychological distress in low, middle, and high-income countries? I feel that the authors should highlight this point even in the conclusion because it is important.
	The first paragraph should summarize the study rather than comparing with other studies. Please rewrite the first paragraph. You may consider starting with lines 29,30, and 31 on page 22.
	Why is stress significantly negatively associated with twin birth? Please explain.
	Why did mothers from Brazil's interior/rural areas have significantly lower odds for stress than those from the city? Please explain.
	"In Tanzania… while being the parent of newborns with length of stay higher than seven days associated with lower odds of parental anxiety…" This doesn't seem easy to explain. What was the timing of the screening test? Do the authors mean that over time, the anxiety of the parents decreased?
	Why did Tanzanian parents have the highest participation scores?
	How did reading out the screening tests in Tanzania affect the scores? This is a study limitation and should be included in the limitation section if not explainable.
	Conclusion: Please add a conclusion section that should summarize the study's findings in a way that the reader can understand the implications in simple terms. Please consider stating that the main finding of the study is that screening for psychological distress in the parents of infants admitted to the NICU should be routinely done with
	Tables: Table 2: Suggest yearly births rather than monthly. Table 3: Explain the meaning of lower secondary and upper secondary education – in Grade level for better understanding of the reader (Grades 7-9, grades 10-12).

REVIEWER	Dr. Jeremy Miles Google Inc 340 Main St Venice California 90291 United States
REVIEW RETURNED	09-May-2024

GENERAL COMMENTS	Statistical Reviewer
	Abstract Comparing the frequency of symptoms across countries with a significance test makes an awful lot of assumptions, about, for example, the equivalence of measures. It also treats country as a fixed factor, where country should be treated as a random factor (these are not the only counties we might be interested in, they are a sample of countries from a larger population of countries). Putting percentages to 1 decimal place of accuracy is giving us accuracy to 1 in 1000 people - this is unnecessary when the sample is smaller than that.. Minor: I prefer to avoid using 'respectively' - it puts a lot of work on the reader, to work out which value is associated with which country. I'm not sure that saying something like "median IPP-NICU=24' when most readers won't know how to interpret a score of 24. The results section of the abstract does a lot of comparison of countries. The conclusion ignores that and says "it's high everywhere". What was the point of comparing the countries to say it was less high in some places? The statistical tests, in particular, don't match the conclusions. Introduction The introduction makes a clear case for the importance of carrying out this study. I have some minor comments: " 2.3 million die after birth, while 1.9 are stillbirths" - presumably 1.9 million? Is the 1.9 million included in the 2.3 million, or in addition? We need a denominator for the 98% to interpret it - 98% of deaths are in low and middle-income countries, what proportion of births are in these countries? Method The method section is clear. The choice of Mood's median test is unusual - this test is less powerful than either something like a Wilcoxon test or (my preference) a t-test. Were both mothers and fathers of the same infant interviewed and included in the sample? The paper doesn't seem to clearly state whether both parents were included. If they were this violates the independence assumption - typically this results in standard errors that are too low, and therefore p-values that are too low. If this is the case, the authors should use appropriate statistical methods that adjust the standard errors appropriately (most commonly generalized estimating equations, mixed (random) effects models, or sandwich estimators). Results I don't think it's necessary to report p-values as < 0.0001, they are usually reported as < 0.001.

	Why is no p-value reported for intubation in Supp Table 4. Newborns' characteristics
	Presumably when assessing age differences across the three countries, the proportion of mothers / fathers interviewed will have had an effect. But I don't see number of mothers / fathers (parental gender) in that table.
	In Supp. Table 9 Logistic regression models (and later), I think univariate and multivariate, rather than univariable, multivariable.
	The study flow diagram is not in the document - there seems to have been an error of some sort.
	Figure 3-6 are also not available.

VERSION 1 – AUTHOR RESPONSE

POINT BY POINT ANSWER TO REVIEWERS – EPINICU 3 COUNTRIES

Thank you for the comments. Please find our answers in blue.

Formatting Amendments (where applicable):

1) Missing Grant Number

You have indicated a funder/s for your paper. Please ensure to provide an award/grant number for your funder/s in the submission system. If the funder cannot provide an award/grant number, you can indicate N/A for the award/grant number.

- Thank you, this has been added

2) Collaborators (group authorship)

The collaborator group name(s) should be the one included in the main author list on ScholarOne. This means that we would recommend creating an "account" for the author group and registering this for the submission instead of the individual author names. The collaborator group name(s) followed by the individual names may be listed instead in the 'Collaborator' field on ScholarOne. BMJ will list the author group name(s) in the author byline, with the full list of individual names included in a collaborator statement at the end of the article. Details of the group's contributions should also be listed in the 'Contributorship statement' field on ScholarOne.

Further information may be found on our resource at https://authors.bmj.com/policies/bmj-policy-on-authorship/.

- Thank you, this has been revised.

Editor(s)' Comments to Author (if any):

This is a really important study, and we are keen to publish it. Please respond to the reviewer's comments adequately.

Associate Editor
Comments to the Author:
Thank you for submitting your manuscript to BMJPO.

Apologies that it has spent some time in review - we asked a lot of reviewers but it was tricky to find individuals with time to review it.

This is an interesting study and we would like to offer you the opportunity to respond to the comments raised in a major revision.

Each point will need to be responded to fully.

Overall the introduction and discussion are lengthy and each could be made more concise without losing any of the key messages.

Please carefully proof read your revised submission, especially the revised Discussion section to check that the language flows and is easy to read.

The reference formatting also needs to be looked at.

- Thank you for your appreciation, we have revised the paper accordingly, and reduced the length of the introduction and discussion section.

Reviewer: 1
Dr. Anirudha Das, Cleveland Clinic Children's Hospital
Comments to the Author
I want to thank the journal for allowing me to review such an intriguing paper. Such studies done over three countries are rare and of great importance. It was exciting to see the barriers faced by the authors in surveying three completely different settings.

The study has been done well, but there is still room for improvement.

Therefore, here are my comments/suggestions:

First and foremost, I could not see any figures except Figure 2. Please upload the figures and make sure they are visible in the PDF.

- Thank you. We submitted high quality figures, that the submitting tool had problems in rendering; we have now uploaded lower quality figures which should be visible in the PDF provided to you by the journal.

Key Message:
Page 7, line 3: I think the first line should be: Immediate action should be taken to screen parents in the NICU for depression, anxiety, and stress, followed by the two current lines. I suggest not using the word "immediate." The second sentence could be: "Mechanisms should be put in place to provide rapid access to mental health providers to the parents whose screening for psychological distress was found to be present."

- Thank you, this has been revised accordingly

Methods:

Page 10, Page 25: I disagree with the cross-sectional study design. It should be a "multicenter prospective observational cohort study."

-Thank you, this was not a cohort study, as patients were evaluated at a single time point.

Was there a plan for follow-up of the mothers who were found to be severely depressed or suicidal? Did the researchers have a plan for how those parents will be managed – seen by a psychologist/Psychiatrist within an acceptable period after the screening?

-Thank you, this is a very relevant point: management varied based on the setting, and followed local protocols. In general, mothers were referred to mental health care professional in Italy and Brazil, while at the time of the study mental health services were absent in Tanzania, sadly. As a results of this study, within the EPINICU study we are discussing how to support care on mothers with mental health disorders in Tanzania.

Page 10, lines 44-50: Why is hospitalization short in Brazil and Tanzania? Please explain.

- This data is aligned with usual practices, due to overcrowding in the Brazilian and Tanzania setting compared to the Italian setting, where natality is pretty low.

Page 10, line 51: Please add to the limitation section that parents with previously diagnosed mental health issues were excluded. The reason is that some parents may have stress and could also start having depression after their infant is admitted to the NICU.

- Thank you, very good point, we have added this in the limitation section.

Page 10, exclusion criteria: Add to the limitation that parents not fluent in the language in which the questionnaire was provided were excluded. This will introduce bias as the parents who are minorities may have a higher rate of psychological distress. Also, who and how the fluency of parents in a language was determined? Please provide specifics.

- Thank you, very good point. Fluency was assessed by the clinicians in charge, we have added this

Page 10, line 55: Exclusion criteria is 24 hours hospitalization or 48 hours? Your earlier statement said that the "newborns who were hospitalized in the NICU or semi-intensive care for at least 24 hours in Brazil and Tanzania". This is contradictory. Suggest clarification.

- We have clarified this, the criteria varied by country.

Please provide a flow diagram showing how the recruitment of subjects was done. This should include how many parents met the criteria and in what time frame, how many were approached, consented, did not consent, and how many were finally included in the study at each site. I cannot access Figure 1, which may have this information.

- Figure 1 is a flow diagram and contains this information.

Please clarify if there was a point in time when the screening for psychological distress was done.

- Thank you for your comment. This was usually done in the days before discharge as described in the Data collection procedures section.

-Figures 1,3,4,5,6 were not available to me. The figures said, "Unable to convert image."

- Thank you. We submitted high quality figures, that the submitting tool had problems in rendering; we have now uploaded lower quality figures which should be visible in the PDF provided to you by the journal.

Results:
Page 21, line 6: Change to "In no country…."
- Thank you, this has been corrected.

Page 21, line 35: Please explain "stress significantly negatively associated with twin birth" to say something like "analyses showed parents of twin infants had less stress."
- Thank you, this has been corrected.

Page 22, line 3: Please change the sentence "none significant association" to "non-significant association".
- Thank you, this has been corrected.

Discussion:
The discussion section needs clarification. The authors should explain the plausible reasons for the findings in the result section but some of the explanations of the findings still need to be included. Below, I have mentioned a few of them. I suggest the authors should go through the results section and try to explain all their findings while comparing and contrasting to previous research.

Authors may also consider explaining the wide variability of stress, depression and anxiety. Is there previous research that demonstrates the difference in maternal psychological distress in low, middle, and high-income countries? I feel that the authors should highlight this point even in the conclusion because it is important.
- Thank you, previously existing studies did not directly compare three major outcomes related to mental health - NICU related stress, depression and anxiety (both state and trait) - along with participation in newborn care, and in this sense this study is filling a research gap. this has been added.

The first paragraph should summarize the study rather than comparing with other studies. Please rewrite the first paragraph. You may consider starting with lines 29,30, and 31 on page 22.
- Thank you, the first paragraph has been edited as suggested.

Why is stress significantly negatively associated with twin birth? Please explain.
- Thank you, we agree with you that results is odd, and contradicts previous research, such as:
• 10.1007/s00737-014-0484-x
• 10.1016/j.wombi.2017.09.003
• https://doi.org/10.1016/j.rbmo.2016.04.009
• https://doi.org/10.1016/j.wombi.2015.04.001
• https://doi.org/10.1590/0104-07072014002950013
We have added this comment in the discussion.

Why did mothers from Brazil's interior/rural areas have significantly lower odds for stress than those from the city? Please explain.
- This may be due to several factors, including lower maternal awareness.

"In Tanzania… while being the parent of newborns with length of stay higher than seven days associated with lower odds of parental anxiety…" This doesn't seem easy to explain. What was the timing of the screening test? Do the authors mean that over time, the anxiety of the parents decreased?
- we agree with you that this is difficult to explain, even in multivariate analyses results may be due to chance.

Why did Tanzanian parents have the highest participation scores?
- Thank you for your comment, Higher participation in care in Tanzania may be explained by staff shortage, we clarified this point in the text.

How did reading out the screening tests in Tanzania affect the scores? This is a study limitation and should be included in the limitation section if not explainable.
- Thank you, this has been added in limitations as suggested.

Conclusion:
Please add a conclusion section that should summarize the study's findings in a way that the reader can understand the implications in simple terms. Please consider stating that the main finding of the study is that screening for psychological distress in the parents of infants admitted to the NICU should be routinely done with

- Thank you, this has been added.

Tables:

Table 2: Suggest yearly births rather than monthly.

- We have included the monthly information to allow a more accurate estimate

Table 3: Explain the meaning of lower secondary and upper secondary education – in Grade level for better understanding of the reader (Grades 7-9, grades 10-12).
- We have used ISCED (International Standard Classification of Education) for a general understanding.

Reviewer: 2
Dr. Jeremy Miles, Google Inc
Comments to the Author
Statistical Reviewer

Abstract

Comparing the frequency of symptoms across countries with a significance test makes an awful lot of assumptions, about, for example, the equivalence of measures. It also treats country as a fixed factor, where country should be treated as a random factor (these are not

the only counties we might be interested in, they are a sample of countries from a larger population of countries).

- Thank you for your comment, we understand and agree with your point. On the other side:
• this is just a descriptive observational study
• we utilized the most widely validated and used tools (no better tools are available)
• the same approach has been used by previous systematic reviews

Putting percentages to 1 decimal place of accuracy is giving us accuracy to 1 in 1000 people - this is unnecessary when the sample is smaller than that..

- Thank you for your comment, we have corrected this for samples below 100, for larger samples we will follow editorial indication on this point

Minor: I prefer to avoid using 'respectively' - it puts a lot of work on the reader, to work out which value is associated with which country.

- Thank you for your comment, this has been corrected.

I'm not sure that saying something like "median IPP-NICU=24' when most readers won't know how to interpret a score of 24.

- Thank you for your comment, please notice that how to interpret the score is explained in the method section, and in Table 1.

The results section of the abstract does a lot of comparison of countries. The conclusion ignores that and says "it's high everywhere". What was the point of comparing the countries to say it was less high in some places? The statistical tests, in particular, don't match the conclusions.
- This has been revised.

Introduction
The introduction makes a clear case for the importance of carrying out this study. I have some minor comments: " 2.3 million die after birth, while 1.9 are stillbirths" - presumably 1.9 million? Is the 1.9 million included in the 2.3 million, or in addition?
- It's in addition, we have correct this as "additionally..".

We need a denominator for the 98% to interpret it - 98% of deaths are in low and middle-income countries, what proportion of births are in these countries?
- Thank you for your comment, the denominator is the number of deaths, please notice that it was reported in the previous sentence.

Method

The method section is clear.
- Thank you for the appreciation.

The choice of Mood's median test is unusual - this test is less powerful than either something like a Wilcoxon test or (my preference) a t-test.

- We used the Mood's median test test because we were interested in observing differences between medians and not between means or distributions, as the data were not normally distributed (which is why we also presented the medians in the results).

Were both mothers and fathers of the same infant interviewed and included in the sample? The paper doesn't seem to clearly state whether both parents were included. If they were this violates the independence assumption - typically this results in standard errors that are too low, and therefore p-values that are too low. If this is the case, the authors should use appropriate statistical methods that adjust the standard errors appropriately (most commonly generalized estimating equations, mixed (random) effects models, or sandwich estimators).

- Thank you for your comment that allowed to clarify that only 70 (9.4%) of the included parents had the same baby. Among those parents, there was low to moderate Pearson correlation for IPP (rho=0.43), PSS (sol rho= 0.35), EPDS (rho=0.38) and STAI (rho=0.02). We believe that the independence assumption is not affected by this low correlation among a subset of parents. Furthermore, systematic reviews state that there is a different emotional response of male and female parents of newborns during NICU admission regardless the health conditions of the baby (Shetty A, Halemani K, Issac A, Thimmappa L, Dhiraaj S, K R, Mishra P, Upadhyaya VD. Prevalence of anxiety, depression, and stress among parents of neonates admitted to neonatal intensive care unit: a systematic review and Meta-analysis. Clin Exp Pediatr. 2023 Nov 14. doi: 10.3345/cep.2023.00486. Epub ahead of print. PMID: 37986569; Roque ATF, Lasiuk GC, Radünz V, Hegadoren K. Scoping Review of the Mental Health of Parents of Infants in the NICU. J Obstet Gynecol Neonatal Nurs. 2017 Jul-Aug;46(4):576-587. doi: 10.1016/j.jogn.2017.02.005. Epub 2017 May 12. PMID: 28506679.). Differences between mothers versus fathers in stress, depression, anxiety and participation in care were further explored in a different publication (Bua J, Dalena P, Mariani I, Girardelli M, Ermacora M, Manzon U, Plet S, Travan L, Lazzerini M. Parental stress, depression, anxiety and participation in care in neonatal intensive care unit: a cross-sectional study in Italy comparing mothers versus fathers. BMJ Paediatr Open. 2024 Apr 8;8(Suppl 2):e002429. doi: 10.1136/bmjpo-2023-002429).

Results

I don't think it's necessary to report p-values as < 0.0001, they are usually reported as < 0.001.

- Thank you, we have updated both in the text and in the tables.

Why is no p-value reported for intubation in Supp Table 4. Newborns' characteristics

- That's because we have zero for a category, so it is impossible to run a chi-squared test.

Presumably when assessing age differences across the three countries, the proportion of mothers / fathers interviewed will have had an effect. But I don't see number of mothers / fathers (parental gender) in that table.

- This information could be found in the text under population characteristics.

In Supp. Table 9 Logistic regression models (and later), I think univariate and multivariate, rather than univariable, multivariable.

Thank you, we have updated.

The study flow diagram is not in the document - there seems to have been an error of some sort.

Figure 3-6 are also not available.

- Thank you. We submitted high quality figures, that the submitting tool had problems in rendering; we have now uploaded lower quality figures which should be visible in the PDF provided to you by the journal.
. We confirm that Figure 1 is the flow diagram.

VERSION 2 – REVIEW

REVIEWER	Dr. Jeremy Miles Google Inc 340 Main St Venice California 90291 United States
REVIEW RETURNED	24-Jun-2024

GENERAL COMMENTS	I would like to thank the authors for addressing my comments on the previous draft.

VERSION 2 – AUTHOR RESPONSE

None