Peer-review Comments and Author Responses

Reviewer 1

1. *The title, "Experiences of discrimination and its impact on the intensity of pain: A study in the elderly Brazilian population". It is:*

   - *Descriptive and informative: It clearly states the main research topic and the target population.*
   - *Accurate and truthful: It reflects the study's design and findings without exaggeration or misleading claims.*
   - *Engaging and concise: It captures the reader's attention without being overly technical.*

However, using title case would improve the readability and professionalism of the article title. Here's the title in title case:

Experiences of Discrimination and Its Impact on the Intensity of Pain: A Study in the Elderly Brazilian Population

This format capitalizes the first word of each major word, including nouns, verbs, adjectives, and adverbs, except for articles like "a," "an," and "the" and certain coordinating conjunctions like "and" and "but."

Thank you for your comments. As per the suggestions, we have amended the title of the study as seen on page 1 line 3-5 of the document.

2. *Please mention who is the corresponding author?*

Addition of corresponding author as seen on page 1 line 33.

3. *Clarity in the Background:*

   - *Instead of "Pain is a multifaceted issue," consider "Pain can be complex and have many influences."*
   - *Explain how discrimination relates to incomplete symptom relief.*
   - *Instead of "deters good prognosis," consider "can make managing pain more difficult."*

Conciseness in the Results:

   - *Instead of "Thus, it's imperative..." consider "This finding emphasizes the need..."*

Active voice and simpler language:

o *Throughout the abstract, consider replacing passive voice with active voice for better clarity.*
o *Use simpler synonyms for some jargon (e.g., "multifaceted" with "complex," "perceived stress" with "feeling stressed").*

Overall: The abstract is a good starting point, but it could be improved by making it more concise, clear, and using simpler language.

Here are some suggestions for improvement in the abstract:

Clarity in the Background section:

- *Consider rephrasing or elaborating on the sentence "Pain is a multifaceted issue that can exacerbate due to external stressors like discrimination in everyday life to a poor quality of life." to more explicitly state the link between discrimination and pain.*

Here is an example of revised sentence, without jargon, simple to understand, in active voice, and parallel: Pain can be complex, and everyday experiences of discrimination can make it worse. This can lead to a lower quality of life for people who face discrimination. The elderly, in particular, may be more vulnerable to these effects due to the presence of other challenges.

Thank you. There were comments on this sentence from different reviewers. We edited this sentence in a way that all comments were addressed in lines 43-49

Abstract word count limits the explanation of this concept, but the association of discrimination and pain has been thoroughly addressed in lines 85-97 in the manuscript background.

There were comments on this sentence from different reviewers. We edited this sentence in a way that all comments were addressed in lines 63-69.

The text was amended for clarity in line 67 of the abstract.

We have replaced passive voice usage through the abstract.

With all due respect, we believe the word "perceived" is widely used in the literature that relates to stress and discrimination. It emphasizes the subjective nature of the experience. So we are respectfully keeping the word "perceived stress".
Additionally, since this is a replication study, and the "perceived stress scale" was used In the original study (Terry et al) we also used perceived stress as the scale.

There were comments on this sentence from different reviewers. We edited this sentence in a way that all comments were addressed in lines 43-49.

4. Major and Minor Issues in the Introduction:

Major:

- *Limited discussion of mechanisms: While mentioning the association between discrimination and pain, the introduction could delve deeper into potential explanations. Discussing how discrimination might lead to pain through pathways like chronic stress, psychological distress, or even biological changes would strengthen the argument.*
- *Vague reference to "general pain conditions": Specifying the types of pain investigated (e.g., chronic pain, specific conditions) would add valuable context and allow for more targeted comparisons with existing research.*
- *Limited engagement with Brazilian context: Briefly mentioning the study's focus on Brazil is good, but further exploration of relevant aspects of Brazilian society or cultural factors related to discrimination and pain could enhance the introduction's depth and relevance.*

Minor:

- o *Redundant sentences: Sentences like "It can be a source of stress since it involves experiencing..." and "Existing literature has established that..." could be condensed for conciseness.*
- o *Mentioning OA without explanation can be confusing for readers unfamiliar with the term.*
- o *Turn passive sentences like "It is revealed..." to active sentences like "Studies show..."*

- *Instead of summarizing the Terry et al. study in detail, briefly state its findings about discrimination and pain in knee OA.*

- *Emphasize how your study expands on this research by focusing on a wider age range and general pain conditions.*

    - o *Instead of listing data analysis goals, highlight the broader implications of understanding the link between discrimination, stress, and pain.*

- *End with a strong statement about the potential impact of your research on healthcare practices and inclusivity.*

Overall: The introduction provides a solid foundation for the research paper. Addressing the major issues by elaborating on potential mechanisms, specifying pain types, and engaging more with the Brazilian context, will further strengthen its impact and clarity.

Thank you for the comment. We have added potential pathways and explanations in lines 85-103 in the manuscript background to expand the discussion of the mechanism.

We aimed to evaluate the effect of discrimination and stress in overall pain. Since this article was a replication study based on a specific database, we can only assess the pain variable that was evaluated in the registry. Therefore, no specific pain conditions were assessed, but an overall subjective pain scale.

Cultural context to discrimination in Latin America and Brazil has been added in lines 127-132.

The introduction paragraphs have been modified to improve clarity and readability in this aspect in lines 85-97.

The paragraph has been edited for more clarity. The OA abbreviation is explained in the context of the previous study, and the final paragraph of the introduction emphasizes that we will broadened to any pain experience, and not to a specific disease.

Sentences have been edited as suggested.

Thank you for your suggestion. We have modified this paragraph. Terry et al study is briefly explained in line 112-115 and its findings in lines 116-119.

Final paragraph has been modified as suggested in line 134-144.

Final paragraph of the introduction was edited to expand on the wider age and general pain conditions of the population, in lines 134-144.

Final paragraph of the introduction was edited to expand on the wider age and general pain conditions of the population, in lines 134-144, including the potential impact of the research on health practices.

5. *Here are some minor suggestions for improvement:*

Conciseness:

- *You could combine the first two sentences by saying something like "We analysed data from the second wave (2019-2021) of the Brazilian Longitudinal Study of Aging (ELSI-Brazil)".*
- *Consider summarizing the reference for ELSI-Brazil by citing the key point: "a study funded by the Brazilian Ministry of Health that assesses social determinants of aging in adults 50+ residing in Brazil."*

Clarity:

- *Instead of "the from the second wave," just say "from the second wave."*

- *In the explanation of the Revised-Everyday Discrimination Scale, you could rephrase "In your day-to-day life" to "Have you ever experienced the following in your daily life?" for better flow.*

Structure:

- *You could separate the explanation of the pain intensity variables into its own paragraph for better organization.*

Here's an example of a revised version incorporating these suggestions:

For example, first paragraph :

We analysed data from the second wave (2019-2021) of the Brazilian Longitudinal Study of Aging (ELSI-Brazil), a study funded by the Brazilian Ministry of Health that assesses social determinants of aging in adults 50+ residing in Brazil (Lima-Costa et al., 2023). Data from 9,949 participants was available, including variables on sociodemographic characteristics, urban environment, discrimination, life and health history, health behaviours, general health and diseases, frailty, pain, disability, and activities of daily living.

And here an example of revised last paragraph:

The database included two variables measuring pain: one for presence/absence and another for intensity (1 = "Soft/weak", 2 = "Moderate", 3 = "Intense/strong"). Participants with no pain were assigned a score of 0.

Amended for conciseness as per lines 149-156.
Changes have been made as suggested in lines 149-152.

Changes have been made as suggested in lines – 149
The question, 'In your day-to-day life how often have any of the following things happened to you?' is as per the EOD scale, a validated scale to assess the incidence of discrimination in ones lives. Therefore, we respectfully keep the question to be consistent with the scale.

Thank you for the suggested amendment. The paragraph was edited as suggested in line 157-160.

Thank you for the suggested amendments. The paragraph was edited as suggested in line 149-154.

The paragraph was edited as suggested in line 157-160.

6. *Clarity:*

- *In the first sentence, you could rephrase "depending on the scale and distribution of the outcome variable presented" to something simpler like "based on the type and spread of data for each variable."*

- *The explanation of the survey data analysis design could be condensed by saying something like "Since the study population was divided into groups and individuals were randomly selected within each group, a multi-stage survey analysis was used."*

Additional details:

- *You could mention the software used for the statistical analysis (e.g., Stata, R).*
- *Briefly explain the rationale for choosing "multiple imputation" and the specific method used (chained equations).*
- *Specify the type of outcome variable used in the ordered logistic regression (e.g., ordinal …).*

We amended the sentence as seen on line 188-191.

We have edited this paragraph for more clarity. See lines 193-197. Nevertheless, other reviewers also asked for more details on the complex survey design, with more specifications on the stratification. Therefore, we included more details. We hope we were able to give a clear explanation.

Addition of the line: 'All data was analysed using STATA 18.0 BE' in line 188.
The rationale for choosing MI and a detailed explanation of the methods used is described in lines 208-221.

For ordinal logistic regression, the outcome variable was pain intensity. This clarification was added in line 200.

Areas for improvement:

- *Explain pain intensity levels: Specify the number and definitions of pain intensity levels (e.g., 1-3: weak, moderate, strong).*
- *Interpret interaction term: Briefly explain the rationale for investigating and reporting the interaction between race and gender, even if not significant.*
- *It would be interesting to know about the decision to include specific variables in the statistical analysis, such as race, sex, age, BMI, and region. Understanding the rationale behind these choices can provide valuable insights into the study's approach.*

The pain intensity levels have been clarified in line 157-160.

The interaction term race#sex was included in the model since group differences based on race and sex were found in the Terry et al, 2020 study.' This clarification was added in line 204. Covariates were selected based on the model used by Terry et al., since this is a replication study. The rationale for the selection of covariates was added in line 201.

7. *Areas for improvement:*

- *Explain pain intensity levels: Briefly define the pain intensity levels used in the study (e.g., 1-3: weak, moderate, strong) for clearer interpretations.*
- *Expand on Terry et al. differences: Consider discussing the potential influence of specific ethnic/racial compositions and pain types in Terry's study compared to yours.*
- *Strengthen limitations discussion: While geographical limitations are mentioned, consider addressing potential sampling limitations and potential alternative explanations for findings beyond just methodological differences.*
- *While multiple imputation was used to account for missing data, it's important to acknowledge the potential impact of this missing data on the interpretation of results.*
- *Other limitations of the study may include:*

Self-Reported Data: The study relies on self-reported data, which may be subject to recall bias and social desirability bias. Participants' responses to questions about experiences of discrimination and pain intensity may be influenced by their subjective perceptions and memory.

Sampling Bias: The study's sample may not be fully representative of the entire population of aging adults in Brazil, potentially leading to sampling bias. This could affect the generalizability of the findings to the broader population.

Missing Variables: There may be important variables that were not included in the analysis, which could potentially confound the relationship between perceived discrimination and pain intensity.

Potential Confounding Factors: The study may not have accounted for all potential confounding factors that could influence the relationship between perceived discrimination and pain intensity, such as comorbidities, access to healthcare, or socioeconomic status.

- *Suggest specific intervention targets: While advocating for interventions, consider suggesting specific areas (e.g., anti-discrimination policies, pain management protocols) to provide more tangible research directions.*

Overall, the Discussion section effectively presents the study's significance and implications. Addressing the minor points above could further enhance its clarity, depth, and actionable recommendations for future research and practice.

The pain intensity levels have been clarified in line 157-160.

Differences with the Terry et al study are described in detail in line 288 to 322 of the discussion. In lines 288-300 discussing racial composition differences between studies.

Thank you for your suggestion. Limitations on sampling were complemented in lines 325-329.

The potential impact of missing data in the findings was added in line 333-340.

Thank you for your valuable input. This limitation was added in line 345-348.

Thank you for your suggestion. Limitations on sampling were complemented in lines 325-329

Thank you for your valuable input. This limitation was added in line 329-333.

Thank you for your valuable input. This limitation was added in line 341-348.

Thank you for your valuable input. This limitation was added in line 349-359.

8. *To write a concise conclusion:*

- *Briefly summarize the main findings and their significance.*
- *Emphasize the potential impact of the research on healthcare practices and policy.*
- *Acknowledge limitations and suggest future research directions.*

Please add if any Funding received?

Any Acknowledgments ?

Any Conflicts of Interest ?

Please arrange the references in an Alphabetical order.

Funding statement was included in line 383.
Acknowledgments were included in lines 375-370.
Conflict of interest was added in line 381.
Thank you for the suggestion, the references have been arranged in an alphabetical order.

Reviewer 2

9. *The main outcome (intensity of pain), main exposure (experiences of discrimination-EOD) and covariates are not well described. I suggest defining them with separate subheadings and providing some details on how you created, managed, and/or measured it.*

We would like to thank Reviewer 2 for their thorough review of our research. Thank you.

Thanks for the excellent suggestion. The main outcome and definition of exposures are now clearly defined in individual paragraphs, in lines 157-183.

10. *Your objective is "To explore the influence of discrimination and <u>stress</u> on pain intensity in an elderly Brazilian population". However, stress is not defined in the methodology, nor mentioned before the results, where you state that "Stress was also significantly associated with the intensity of pain (OR 1.05, 95%CI 1.05 - 1.06) as described in the study by Terry et al." I suggest stating previously if stress was considered a mediator variable as in the Terry study, if stress was measured as a variable itself from the dataset, or if you meant experience of discrimination as stress? Please detail, if possible.*

Thank you for the feedback. Although stress was assessed as a mediator variable in the Terry study, we did not conduct a mediator analysis, but did include Stress as a covariate in the multivariable model to assess its effect on the intensity of pain. Stress was assessed by a variable in the database that asked the following question: 'In the last 30 days, for how many days would you say your mental health was not good, for example, you felt stressed out or with other emotional issues'. Participants answer this question with a number from 0 (None) to 30 (all days).

This variable resembles one of the 10 items from the validated Perceived Stress Scale in which participants are asked how often have they felt stressed in the last month, and they answer in a scale from 0-4 (0:never, 4: very often).

We included stress in the overall description of Terry's study in the manuscript line 192 and . we also included stress in our methods section with the definition in line 179-183.

11.

1. *Page 3, line 93: OA has not been abbreviated before.*
2. *Page 4, line 124: erase "acting", as it is followed by "act".*
3. *Page 4, line 135: erase "the", which is followed by "from".*
4. *Page 4, line 149: I suggest modifying into a paragraph.*
5. *Page 4, line 157: "each" question instead of "this" question as it refers to five different domains.*
6. *Page 4, line 162: "If" is with capital letter.*
7. *Page 5, line 208: "Mean variation was 27.77", detail of what, please.*
8. *Page 6, line 222: Choose "however" or "on the contrary".*
9. *Page 9, line 290: I suggest changing "statistical" for "statistically" significant.*
10. *Review in text citation of Terry et al. vs. Terry et al., 2020 vs. Terry et al (2020).*

Reviewer 3

12. *The abstract the beginning of the article is different to the abstract attached as a separate file. Please correct it. I review the one in the separate file because the one included in the manuscript didn't appear to be complete.*

The last line of background is similar to the Objective. I would recommend delete it.

I suggest changing the abbreviation EOD in the abstract for the complete name of the scale, because it is confusing.

Thanks for all the suggestions. Amended for grammatical conciseness.

Thank you for bringing this to our attention. The abstract has been updated in the manuscript.

The last line of the background is amended and is no longer similar to the objective.
We have removed EOD abbreviation from the abstract.

13. *Introduction:*

- *Knee OA: use of abbreviation without defining it. Please correct.*

- *In the introduction, you talked about discrimination the first 2 paragraphs. Then, the 3rd paragraph it switches to pain in osteoarthritis and psychological factors. This seems a little confusing, especially because you already talked about the association of pain and discrimination in the precious paragraph. Maybe you need to rearrange the order of the information, especially because in the 4th paragraph you talked about discrimination again, and then in the 5th again about pain and osteoarthritis.*
- *I suggest rearranging the order of the paragraph and information of the introduction. The gap should be before the objective of the trial. You can talk about the gap when you talk about the Terry study you are replicating. And can add the strengths of your analysis as part of the objectives of your trial.*

A definition for OA has been added.

Thanks for the valuable feedback. We have rearranged the introduction for more clarity and conciseness.

Thanks for the valuable feedback. We have rearranged the introduction for more clarity and conciseness.

14. Methods:

- *I would detail a little more the Brazilian Longitudinal Study of Aging. What type of study is? I imagine it´s a cohort, but prospective or retrospective? What was the original purpose of the study? Just add a couple of sentences regarding the original trial.*
- *In the statistical analysis, I don´t understand when you talk about the survey data analysis according to strata. First, I don´t know if you are referring to the original trial sample method, and how they performed it, in which case, I would include this in the part where you describe the original trial if it is important for your analysis. Second, you said the population was divided according to stratas, but I don´t know what strata they considered (was according to location, age, socioeconomic, etc?). I think you need to explain this in more detail if it´s needed in your manuscript.*

The ELSI study design is explained in 1st paragraph of the Methods section. The prospective cohort design and the purpose of the study have been added for clarity in lines 149-156.

We have added details on the ELSI complex study design, with specifications on the strata and clustering in lines 157-160.

15. Results:

- *About Table 1, I don´t understand why you decided to divide the sample by race. You considered this in your analysis adjusting your regression according to race. If you are considering this factor as an important one, I think you should add some information regarding it in the introduction, about the association of race and discrimination (or at least mention it).*

  If you are not dividing you analysis/results according to race, I don´t see the

> *importance of dividing your table 1 according to race.*
> *I would appreciate if you can explain it to me, or if you decide to present the results this way because this way was presented in the original study, etc.*
> *Another option might be to start with the total of participants in the table and then divide them by race in the table.*
> - *First paragraph, it says " Mean variation was 27.77". I don't understand what you are referring to. Variation of what? You are talking about the sex distribution, and there is no important variation in groups regarding sex distribution. Please clarify.*

Since this is a replication study, its objective is to simulate the analysis conducted by Terry et al, which was analysed according to race.
Table 1 in the Terry et al study is divided by race. That is the main reason behind this Table 1 presentation. Therefore, we have included race in the our last paragraph (aim) of the introduction to provide more information and background on race and discrimination, line 139-144.

Thanks for your valuable feedback. This error is noted and corrected as follows: 'Mean BMI was 27.77' in line 230.

> *16. Discussion:*

> - *In the limitations, you talk about differences in the sampling of the two studies. I don't know if you are referring to the Terry study and your dataset or not. Please clarify.*

> *Others:*

> - *The table S1 was not in a separate file.*

Thank you for your comment. Limitations have been expanded greatly to include sampling bias and further limitations. Lines 324-340.
Thank you. We have added Table S1 as a separate file.

> *16. Abstract:*

> *I would reorganize the sentences to improve the clarity of the text. There are 2 different abstracts, one in a separate document and one in the main manuscript text. Please, choose the most accurate and clear one.*

> *All sections need work, and I would also check if the results presented in the abstract are compatible with the methods described before.*

> *For example:*

> *Results: "In the elderly Brazilian population, discrimination and perceived stress had a significant association to pain intensity."*

However, the methods did not mention "perceived stress" as a parameter to be investigated.

Thanks for the feedback. The abstract has been revised.

Thanks for the feedback. The abstract has been revised

Perceived stress has been included in the Methods section in line 179.

17. Introduction:

I recommend reorganizing the introduction.

The paragraphs are disconnected. Based on your text, I think you should start with the relevance of pain in the older population and then describe the influence of discrimination and stress on pain intensity. Later, describe the article you planned to replicate (Terry et al., 2020). And end with a paragraph explaining your research objective to address the knowledge gap.

Thanks for your valuable feedback. The introduction has been reorganised for more clarity , and a final paragraph added with the knowledge gap in line 134-144.

18. Methods:

I recommend adding subheadings like: Study Population; Exposure; Outcome; Covariates. This will help with the fast identification of the exposure and the outcome.

I also suggest improving the description of exposure and outcome in the text.

Regarding the covariates, you added race to the model. I noticed that there were 27 Asian descendants and 38 Indigenous, representing a small proportion of the complete cohort. Does it affect the model's performance?

Regarding the interaction term added to the model, I made two comments in the manuscript. I recommend a justification for testing the interaction term between two covariates and not between one covariate and the main exposure (discrimination).

We have reorganised the methods section for more clarity on the outcome and exposure variables.

A more detailed description of EOD (lines 161-177) and stress (lines 179-183) have been added to the methods section.

In the original Terry study, only non-Hispanic white and non-Hispanic blacks cohort was used for group comparisons. Our cohort (ELSI) encompassed a diverse group. Though, as you rightly mentioned, the Asian and Indigenous group had a smaller population, and this might affect the model performance, which was included in the limitations in line 299-300.

The justification for the inclusion of the interaction term has been included in line 204-206.

19. Results:

The table one presented in the results section is described by race; I would like to ask the motivation for it. Your exposure is discrimination; is there any strategy to categorize the "Experiences of Discrimination Scale" and create two groups—discrimination (yes or no)—and prepare a table comparing the two groups?

Table 1 also has the continuous data presented as median and IQR (age) and mean and SD (BMI). Why is it necessary? Probably, in a large sample, you do not have an issue with skewed data. In addition, your report of median and IQR does not present the first and third quartiles as regularly presented in scientific journals.

I recommend adding the mean and SD for the EOD scale and the proportion of pain intensity in Table 1. Stress level should also be included; it is not clear if stress level is a continuous or categorical variable.

The stress variable was included in the model, but it was not described in the method of how you will assess and define stress in the ELSI questionnaire. Are the authors assessing stress as an exposure or a covariate? This needs to be clarified.

I would be very careful when interpreting the covariate coefficients. I understood that the main exposure of this research project was discrimination, and the other factors included in the model were covariates. Am I correct?

Thank you for your insight. As previously mentioned, only non-Hispanic white and non-Hispanic blacks cohort was used for group comparisons. Therefore, comparisons were drawn as per race.
The mere objective to replicate the data analysis as per the study by Terry et al is vehemently mentioned across the paper.

Although it is a large sample, we did not find a normal distribution for age , and therefore we chose to present it in median and IQR. The IQR has been modified in Table 1 to present Q1 and Q3 as usual.

EOD, stress and Pain intensity have been added to Table 1.

Stress variable description has been included in the Methods section in lines 179-183.

Yes, for further clarity, the methods section has been edited to clearly discern between the variables. The interpretation of the effect of discrimination has been revised and we believe is important to include it since provides clarification of the results of ordinal regression and not just logistic regression, to avoid misinterpretation from readers.

20. Discussion:

In this section, the authors describe their main findings and present previous literature that supports them.

One point that is not clear is the health equity implications of the study results.

The authors concluded that the study "underscores the detrimental health consequences associated with perceived discrimination, emphasizing the urgency for societal, systemic, and healthcare reforms to mitigate these inequities." This is a very important conclusion for this manuscript, but it would be interesting to understand which group of patients experienced discrimination to mitigate the inequities. I would elaborate on this statement.

Implications for health research and practice have been added to the discussion, based on the study findings, in lines 349-359.

The study was conducted to replicate Terry et al study. Therefore, covariates used in the model as well as the effect of race and gender were assessed. Other possible factors associated with discrimination like social-economic status , which may be very important in the context of Latin American countries as described in the introduction, were not assessed. Future studies would need to address this associations. Limitations in the associations of other important factors have been added to the discussion in lines 341-344.