

Peer-Review comments and authors responses

Reviewer 1

Comments:

1. **METHODS:** *The hypothesis presented is unclear. The authors state that regular moderate to vigorous exercise was hypothesized to reduce NSAID dependence due to its anti-inflammatory effects (Introduction). The conclusion claims that this study supports regular moderate to vigorous exercise as a viable non-pharmacological strategy to reduce NSAID use (Abstract – Results, Conclusion).*

However:

- a. *As this is a cross-sectional study, causation cannot be inferred. The manuscript occasionally acknowledges this but, in other sections, appears to discuss causation. The authors propose that physical activity reduces inflammation, leading to lower NSAID use. However, could the reverse also be true; patients without pain (and consequently not using NSAIDs) may exercise more. The interpretation of the analysis should address this more carefully.*

Response: We appreciate your comments/suggestions: **1.1** - We fixed the mention of causation in those sections to association in the abstract and conclusion

- b. *Do the authors assume that all NSAID use for any pain should be reduced due to associated risks? While reducing NSAID use for muscle pain after exercise (Background, paragraph 2; Discussion, paragraph 1) appears beneficial, I wonder if we can discuss it for any other indications since the risk-benefit profile of NSAIDs vary depending on the pain mechanism.*

Response: The aim of this study is only to investigate the use of NSAIDs for pain as the only indication, we do not have enough information to investigate what pain medications or the dose at which they were used, for this 3 reasons we can not expand the use to other indications for NSAIDs that might be beneficial. Also, the beneficial effects of some NSAID's like low-dose aspirin have not been associated with the same adverse effect profile due to the different dosing.

- c. *If the authors believe causality (maybe not) can be inferred from this cross-sectional analysis, the hypothesis and justification must be clearly articulated. Otherwise, the question of whether regular exercise reduces future NSAID use could be better answered through a prospective cohort or retrospective cohort study with data on exercise duration/ frequency (e.g., daily, monthly, or weekly over the past few years).*

Response: As nicely stated by you, we can not prove causality with this cross-sectional study, it is for sure, one of the limitations, no changes were made to the hypothesis.

d. *A reference for the NHANES 2017–2018 dataset is needed.*

Response: The reference was added as the following:

Centers for Disease Control and Prevention. (2021, June). *2017-March 2020 Data Documentation, Codebook, and Frequencies. National Health and Nutrition Examination Survey*. https://wwwn.cdc.gov/Nchs/Nhanes/2017-2018/P_PAQ.htm

Centers for Disease Control and Prevention. (2024). *NHANES 2017-2018 laboratory data overview*. Centers for Disease Control and Prevention. <https://wwwn.cdc.gov/nchs/nhanes/continuousnhanes/overviewlab.aspx?BeginYear=2017>

2. *Variables need clearer definitions. Some are unclear.*

- *What does it mean by "recreational exercise"? If a type of exercise is specified, provide the definition.*

Response: We appreciate your comments/suggestions: 3.1 - the definition of "recreational exercise" has been added to the manuscript as well as examples of the definition provided by the NHANES criteria.

- *What is the definition of exercise? Especially regular exercise mentioned in the conclusion. Related to the comment 1-3) this variable cross-sectional data? Or include longitudinal information, such as last year, an average of several months, etc. It affects the design, which is a cross-sectional or retrospective cohort, and the results may also be different, exploratory causation or association.*

Response: apologies for the mistake in terminology, we have replaced "regular" to "recreational exercise" throughout the document.

- *What is "regular exercise" as mentioned in the discussion and conclusion? Does this variable include longitudinal information, for example, including several observation points or asking past exercise habits over the last year or several months?*

Response: apologies for the mistake in terminology, we have replaced "regular" to "recreational exercise" throughout the document.

- *In the Introduction, the author mentioned that long-term NSAID use may cause EAs. This could be a motivation for conducting this study to provide exploratory information on appropriate NSAID use, more precisely, to reduce unnecessary NSAID use. I wonder if the dataset of past 30-day NSAID use sufficiently addresses this issue. If not, it should be stated as a limitation.*

Response: we double check the information from the dataset but unfortunately it does not address this question.

- *Does "At least one comorbidity" include arthritis or goat? Please define it more clearly.*

Response: unfortunately it is a limitation of the dataset that we can't know if arthritis and gout are included in the at least one comorbidity category.

- *The author mentioned there are no data for NSAID indication, however, are there any variables that implicate the indication? For example, variables related to pain intensity or difference of acute/ chronic pain?*

Response: Unfortunately this is another limitation of the dataset as we do not have any information that can point us towards an indication/reason for taking NSAIDs.

DISCUSSION: *Please explain the rationale for the selected covariates: especially,*

- a. *Could you please provide the medical rationale for why the author included sleep disorder for adjustment? While Murphy et al. (1994) suggested NSAIDs affect sleep, but seemed not to discuss the sleeping disorder can affect NSAID use.*
- b. *I understand that factors such as arthritis and gout are already included in the model as separate variables, given their impact on NSAID use and exercise. However, it is unclear why 'comorbidities' as a broader factor is also included in the model. Could the author clarify the rationale for adding 'comorbidities' in addition to these specific conditions? This comment could be answered by comments 3-5),*

Response: New reference and explanation (Korabelnikova et al (2020) explain that sleep disorders and headaches cause and/or exacerbate each other in a complex, bidirectional manner that makes necessary pharmacological approaches including NSAIDs.) paragraph 2 in discussion. Unfortunately it is a limitation of the dataset that we can't know if arthritis and gout are included in the at least one comorbidity category, we decided to include "at least one comorbidity" as an additional category because with this we think we include patients taking polypharmacy.

- 3. **RESULTS:** *Looking at the goodness of fit and Pseudo R2, the model can well explain the relationships between variables. However, given the relatively low Pseudo R2 values, has the author considered any potential interactions, such as the possible synergistic or antagonistic exercise effects on NSAID use in the presence of complications or sleep disorders?*

Response: Thank you for your feedback. We have performed the analysis with the interaction terms and we have obtained the following results:

The interaction between physical activity levels (atleast_mod) and trouble sleeping did not yield statistically significant results. None of the interaction terms ("Only Moderate#Yes," "Only Vigorous#Yes," "Moderate and Vigorous#Yes") were significant ($p > 0.192$ for all). The model fit improved slightly with the inclusion of interaction terms (log-likelihood increased from -1107.25 to -1105.99; pseudo-R² increased from 0.1195 to 0.1205). However, the improvement in predictive power was minimal.

The interaction between physical activity levels (atleast_mod) and comorbidities (Atleastonecomorbidity) showed one significant interaction term: "Only Vigorous#Yes" (OR=0.21, $p=0.011$). This suggests that vigorous physical activity reduces NSAID use among individuals with comorbidities. However, other interaction terms ("Only Moderate#Yes," "Moderate and Vigorous#Yes") were not significant ($p > 0.117$). Model fit improved slightly with the interaction term (log-likelihood increased from -1107.25 to -1103.30; pseudo-R² increased from 0.1195 to 0.1226). The improvement was marginal for this case as well.

While the inclusion of interaction terms marginally improved the model fit, the improvement was not meaningful in terms of predictive power or explanatory value. The pseudo-R² increased only slightly (by 0.001-0.003 across models), and likelihood ratio tests did not justify the added complexity. Most interaction terms were not statistically significant, indicating that the combined effects of physical activity and other variables (trouble sleeping or comorbidities) do not meaningfully alter NSAID use beyond their individual effects.

For these reasons, we opted to exclude the interaction analysis from the paper. Instead, the final analysis focuses on the robust and interpretable main effects that are more relevant to the study's objectives.

4. *Confirm whether all first authors listed contributed equally, in accordance with guidelines.*

Response: Thank you, we have confirmed that all authors contributed equally on the first page

5. Word count should be provided.

Response: Word count was provided at the end of the document

6. *Check whether the appendix containing data analysis aligns with the journal's submission guidelines.*

Response: We agreed and renamed the supplemental STATA code, table 1, table 2, figure 1 and figure 2 and appendix A to E respectively.

7. *The figure legends are not included. Did the author provide them?*

Response: Legends were included to the figures and are now part of the figure and submitted as a TIFF

Reviewer 2:

Comments:

ABSTRACT

1. *In the summary section, it is suggested to indicate what NSAID means to ensure adequate understanding of the content.*

Response: Thank you for your feedback. We agree that the information about the variable NSAID is missing in the abstract, that is why we have now included and specifies that NSAID use is considered as consumption for at least the last 30 days. The revised text reads as follows: "The variable NSAID includes its use for at least 30 days"

2. *Also in the abstract conclusions, it is described that factors such as sleep can influence pain management; however, this point is not mentioned in the key findings.*

Response: Thank you for your comment. We agree with your comment, that is why we included the association between trouble sleeping and NSAID use. The revised text reads as follows: "Additionally, having no trouble sleeping showed less likelihood of NSAID use (OR 0.34, 95% CI: 0.27, 0.41)."

3. *Regarding the keywords, chronic pain is mentioned, but the manuscript does not indicate that this is the focus of the study. Please clarify.*

Response: Thank you for your feedback, we decided to eliminate chronic pain, since our study evaluates the role of physical activity and how it can affect NSAID use.

INTRODUCTION

4. *In the introduction of the manuscript, the second paragraph is repeated with the third paragraph, at least in the initial part. It is recommended to merge both paragraphs with the corresponding information.*

Response: Thank you for your comment. The second paragraph shows the literature findings: exercise has well established anti-inflammatory effects. However, in the third paragraph we hypothesized that the exercise can also reduce NSAID consumption.

CONCLUSION

5. *In the penultimate paragraph of the conclusions, the word "varía" is mentioned, I imagine it is referring to the variables. Please review.*

Response: Thank you, we reread the text and adjusted the word to variables.

6. *In the last paragraph, it is mentioned that the study has great generalizability. However, it would be interesting to know what a representative population of the United States would*

really be to conclude that really around 5000 people included in the study can truly represent this population. Please review.

Response: Thank you, we agree we don't have enough information to generalize. The revised text reads as follows: "The strengths of this study include the large, nationally representative sample from the NHANES 2017-2018 dataset, enhancing the generalizability of our findings to the broader U.S. population. "

Reviewer 3:

ABSTRACT:

1. In the "Methods Section", I would write at the beginning: " We performed a cross-sectional design study evaluating..."

Response: Thank you, we reread the text and adjusted the beginning and added your suggestion

2. I would not mention the 5,145 adults in the Methods section, I would put in the "Key Findings"

Response: Thank you, we agree that it would be more clear and adjusted the text.

3. At the end of the "Method Section,"I would mention that the confounders were adjusted following a multivariate analysis.

Response: Thank you, we reread the text and added your suggestion

4. In the results section, I would mention some important baseline characteristics of the included population and if these results are before or after the multivariate analysis.

Response: Thank you, we added mean age, sex proportion and BMI as some important baseline characteristics

METHODS:

1. In the methods section, I would not mention here this statement "In total, 5,145 observations were included in the analysis." I would leave it to the Results section, explaining that you initially had 9,254 patients and after exclusions following the eligibility criteria you arrived at the 5,145 included patients in this analysis.

Response: We agree and have moved the information to the results

RESULTS:

1. "A total of 5,846 participants were included, with 5,145 analyzed; the remainder excluded due to missing data." Here was quite confusing, I did not understand how you got this number from the initial 9,254. It would be nice to include how many patients were excluded following each criterion from your eligibility criteria.

Response: We rewrote that phrase so it would make more sense as: "A total of 5,846 participants were included in the study. Of these, 701 were excluded due to missing data, resulting in 5,145 participants analyzed in the final dataset." As for the original 9,254 participants to the 5145 participants it was explained in the first paragraph of the methods section with the inclusion criteria of: "aged 18 and older, with complete data for moderate or vigorous recreational exercise and NSAID use"

2. “The following characteristics were seen in the 375 participants that used NSAIDs:” I would include the percentage(%) of the patients using NSAIDs.

Response: Dear review, thank you for your observation. We appreciated the comment and we added the percentage.

3. “The level of exercise: participants that didn't engage in moderate or vigorous exercise (67.7%), only moderate (21.6%), only vigorous (3.7%), and in both (6.9%). The comorbidities were arthritis (63.5%), gout (1.9%), and both (6.3%). Baseline characteristics are described further in Table 1.” It is not so clear if you are referring to the overall population or just the patients taking NSAIDs.

Response: Dear reviewer, we agree with your comments and we specified the population we are referred to avoid confusion.

4. “had higher odds for NSAID use compared to those who had none, 1.75 OR (95% CI: 1.15, 2.65).” Do not forget to input the p-value to maintain the consistency on the results reporting.

Response: Dear reviewer, we agree and we added the P value to better interpretation

DISCUSSION:

1. The authors should discuss further the main result of the NSAIDs reduction in patients with the other findings in the current literature. Give some insights and hypotheses why your results are different from Davis et al. and why they are consistent with the results in Gleeson et al., 2011; Ribeiro et al., 2022.

Response: We agreed and opted to change the references to explain better our findings with the current literature. Changes were made in paragraph 1 in discussion.

2. The authors have an excellent analysis with a well-elaborated causal pathway; you should focus on the implications that identifying the possible mediators and confounders may help future research and the impact of these results in the clinical scenario of these patients.

Response: Thank you, we added recommendations to future studies in the second and last paragraph of discussion.

CONCLUSION:

1. Great Conclusion section, it summarizes very well the whole study; I would not include this line:” This would help to better understand the underlying mechanism and its relation to chronic conditions.” As it does not add new information to the overall summary of your findings.

Response: We agreed and deleted the sentence

Additional tips:

1. In Table 1, please report the binary data that was reported in events and frequency. Also, I suggest I always put an Abbreviation section.

Response: Thank you, we added an * in table 1 to refer when mean and standard deviation was used the rest was presented as frequency with percentage and abbreviation section added at the end of the manuscript

