Peer-Review comments and authors responses

"Association Between Caffeine Intake and Depressive Symptoms: A Cross-sectional Analysis Using the NHANES 2017-2018 Database"

Reviewer 1:

Recommendation: Revisions Required

Comments for authors: Thanks for the opportunity to review this manuscript. The study examines the association between caffeine intake (three categories: 0–100 mg/day [reference], 101–200, 201–400) and PHQ-9 depressive-symptom severity (five ordered categories) using an ordinal (proportional-odds) logistic model. Crude estimates suggest lower odds at moderate intake, but adjusted results are largely null. Conclusions should be aligned with the cross-sectional design and the observed precision.

Major comments:

> **Comment 1:** NHANES complex survey design. Please re-analyze using NHANES weights, strata, and PSUs for both descriptive statistics and regression. Unweighted analyses can bias point estimates and understate standard errors. Report weighted means/percentages (with 95% CIs) and survey-adjusted model outputs.

Response: We thank the reviewer for these suggestions. We considered your suggestion and we did a thorough reassessment of our data with NHANES weights, strata, and PSUs. In Table 1 of our paper, you can find reported percentages for most of the categories and reported means for the continuous age and sedentary activity variables.

> **Comment 2:** Ordinal model — assumption and interpretation: Proportional odds assumed. State it and its consequence (one OR per predictor across thresholds), report the check (test and result), and if it fails, use partial proportional-odds or sensitivity models; temper conclusions accordingly.

Response: We thank the reviewer for these suggestions. After the weighted analysis, we tested for the proportionality of odds. This analysis gave a Chi2 = 36.3 and a p-value of 0.86. Therefore, we comply with the ordinal regression analysis.

> **Comment 3:** Caffeine exposure handling
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> **Comment 3.1:** Please also clarify how intakes >400 mg/day were handled (separate category, merged, or excluded) and show counts so readers can see cell sizes.

Response: We thank the reviewers for this comment. We excluded caffeine intake over 400 mg from the analysis. We added a paragraph in the Methods section clarifying this point.

> **Comment 3.2:** Consider a sensitivity treating caffeine as continuous (e.g., per 100 mg/day) to assess dose–response beyond the categories.

Response: We thank you for this observation. We run a sensitivity analysis using caffeine as a continuous variable in a univariable and multivariable analysis. In both scenarios, we found that OR = 1.00, 95% CI 1.00 - 1.00, and with a p-value of 0.002 and 0.001 for the univariable and multivariable analysis, respectively. We added these findings to the results section.

Comment 4: Conclusions and claims. Please align the conclusions with a cross-sectional design and largely null-adjusted results. Remove therapeutic or causal implications (e.g., caffeine as co-adjuvant or initial treatment) and frame findings as hypothesis-generating pending longitudinal/experimental evidence.

Response: Thanks for this valuable comment. We have reviewed our Conclusions section to align with the cross-sectional nature of the study. All causal language has been removed, and the identification of independent predictors was stated as complementary results. Conclusions emphasize now that results are exploratory and in search of a hypothesis that will need further confirmation in longitudinal or interventional studies.

Comment 5: Tables, figures, and reporting: - Make Table 1 survey-weighted; define all abbreviations; keep significant digits consistent; state the base for percentages.
- Ensure terminology is accurate (NHANES is a complex cross-sectional survey, not a cohort).

Response: We thank the reviewer for this suggestion. As stated earlier, we reworked the analysis with survey weights, keeping digits consistent, and stating the base for percentages. We corrected our language to match the cross-sectional nature of the survey.

Minor comments:

Comment 6: Tighten long sentences in the Introduction and Discussion; remove redundancy.

Response: We thank the reviewer for these suggestions. We have made the changes suggested.

Comment 7: Specify software and package versions used for survey design analyses.

Response: We have added the software and package version in the "Statistical Analysis" section.

Comment 8: Check references for duplicates and formatting consistency.

Response: We have double-checked references for duplicates, and they have been excluded from the reference list.

Reviewer 2:

Recommendation: Resubmission required

Comments for authors: Hello, dear authors, I'm happy to be able to review your manuscript.
Caffeine is something I'm very passionate about, since it's my number one choice of drink. Its effects, which are widely studied in cardiovascular medicine, need to be expanded to other areas, and I'm delighted to see your enthusiasm for doing just that. Having said that, the manuscript's idea, while thoroughly explained, lacks novelty. These associations have been extensively tested; therefore, I believe that when a reviewer reads your title, they will expect a more novel approach to the analysis proposed here.
Since it is a cross-sectional study, the article also lacks a certain level of reporting quality. If you adhere to the STROBE guidelines for reporting observational studies, the manuscript itself could benefit from better writing and reporting.
I'm not endorsing the current version for publication. Still, if published, it could be a stepping stone for cross-sectional studies that can control for the several factors you mentioned that were not controlled for in the analysis or in the data you worked with.
As of now, please work on my comments and suggestions to make your work more appealing for publication.

Response: We thank the reviewer for the comments and suggestions. We have reanalyzed the data using weights and included possible confounders that were not considered in the previous analysis. We are resubmitting our initial paper with a new analysis for the reviewers to revise.

Reviewer 3:

Recommendation: Accept Submission

Comments for authors:

This study addresses an important and timely topic, as depression remains a major global public health concern, and lifestyle factors such as caffeine consumption continue to attract scientific and clinical interest. By exploring the association between caffeine intake and depressive symptoms using nationally representative data from NHANES, the authors are contributing with valuable evidence to a field where previous findings have been inconsistent and sometimes contradictory. The use of a large, well-characterized dataset and the attempt to account for multiple potential confounders strengthen the relevance of this research and its potential to inform future epidemiological and clinical investigations.

The introduction provides a solid foundation for the study, offering relevant background information and effectively justifying the research objective. The authors clearly summarize existing evidence on the relationship between caffeine consumption and depression, acknowledging both studies that suggest a protective association and those reporting null or even adverse effects. This balanced overview helps to clearly delineate the existing knowledge gap. By emphasizing the inconsistencies in prior findings and the role of confounding factors such as age, sex, socioeconomic status, BMI, marital status, and smoking, the authors convincingly establish the rationale for conducting a more comprehensive analysis. Overall, the introduction is well structured and appropriately contextualizes the study within the broader literature.

The methodological approach is generally sound and appropriate for the research objective. The use of NHANES 2017–2018 data provides a large, nationally representative sample and enhances the generalizability of the findings. The categorization of caffeine intake and depressive symptoms, as well as the use of an ordered logistic regression model, are suitable choices for exploring this type of association. Importantly, the authors adjusted for multiple potential confounders, which strengthens the internal validity of the analysis. And the authors acknowledge that the cross-sectional design limits causal inference.

The results are presented clearly and align with the stated objectives. The authors appropriately report both crude and adjusted analyses, which allows readers to understand how confounding factors influence the observed associations. The finding that the initially significant association between moderate caffeine intake and depressive symptoms lost significance after adjustment underscores the complexity of this relationship and highlights the importance of controlling for sociodemographic and behavioral factors.

Comment 1: The description of confounding variables associated with PHQ-9 scores appears to refer to their overall association with depressive symptom severity, rather than with a specific PHQ-9 level (Table 3 presents the "Odds of being in a higher PHQ-9 category", but the text is saying "Confounding variables associated with PHQ-9"). For clarity, the sentence could be aligned with the table, as Table 3 shows only for the higher categories. I only suggest this minor revision to improve the clarity of Table 3, so that readers can more easily interpret the associations presented.

Response: We thank the reviewer for highlighting this. We have re-analyzed our data, and the original Table 3 is no longer in the manuscript. Instead, the reviewer can find a Forest Plot with the results of the multivariable analysis (Figure 1).

Comment 2: The discussion is coherent and effectively relates the findings to existing literature. The authors acknowledge the limitations inherent to the study design and appropriately avoid overstating causal inferences. Overall, this study adds valuable evidence to the ongoing discussion about caffeine and mental health, and its methodological rigor supports its contribution to the field.

Reviewer 4:

Recommendation: Revisions Required

Comments for authors:

Dear Author, I am thankful for the opportunity to review the manuscript titled " Association Between Caffeine Intake and Depressive Symptoms: A Cross-sectional Analysis Using the NHANES 2017-2018 Database." I congratulate you and the co-authors for the great work and efforts to put this manuscript together

Based on my peer review, here are my comments:

Comment 1: COVARIATES: "Potential confounders were identified a priori using a directed acyclic graph (DAG) and evidence from the literature" – Kindly mention clearly what evidence from the literature was sought to limit the confounders chosen, and that these should be the set of considered confounders for this manuscript.

Response: We thank the reviewer for this comment. Regarding the covariates, we have analyzed the possible confounders and cited the corresponding literature. A weighted analysis of the data was performed for the resubmission of this article, and the new included covariates are properly mentioned in the manuscript.

Comment 2: The section on covariates is not explained well enough regarding the logic/understanding behind selecting this set of variables as potential confounders.

Response: We deepened on understanding and selection of confounding variables.

Comment 3: Why wasn't annual income considered as a potential confounder? as a low income could be a possible confounder for both depression and amounts of caffeine intake & a high income person could be a target of addictive amounts of caffeine and be having depression as well due to lifestyle issues.

Response: We thank the reviewer for this comment. Income was analyzed as family monthly income and was included as a confounder.

Comment 4: What about underlying other health conditions/ co morbid conditions as a confounder ? (considering the mean age is generally in the 40 and above age group) which influence a person's consumption of caffeine- directly / indirectly which could affect the mental health of a person as well?

Response: Given the insightful comments of the reviewers, we have included three comorbidities in the analysis. This includes cardiovascular disease, thyroid disease, and diabetes, finding the first two to be independent predictors of the outcome.

Comment 5: Doesn't race / ethnicity become an important factor here to be a confounder? certain ethnic1 origins have more inclination to caffeine consumption as their normal lifestyle practices , some don't, also being prone to mental health issues

Response: We have addressed ethnicity as a confounder as the reviewer suggested.

Comment 6: I am not sure if the data set had number of hours working- that becomes a very important confounder for both caffeine intake and depression as this is responsible for people to have caffeine to work long hours leading to burn out and depression/ even if the data set had number of average hours in front of the computer screen would also add to the same.

Response: We identified working hours as a confounding factor for caffeine intake and depression, especially in relation to long working hours. The NHANES dataset on total working hours per week includes responses from 3,067 participants, a 32% of missing data, so this variable was not included in our study. Screen time was not assessed in the adults, only in the 2 to 17-year-old subgroup.

Comment 7: "Our findings reinforce the idea that obesity and lack of social support are significant risk factors for depression"- based on this line from the discussion was any form of social support considered as a separate variable, was such a kind of variable available or was it just based on being married / unmarried as that doesn't amount to lack of social support as an unmarried person can still be having the best community of family and friends compared to a person with not such a good marital relationship, based on what was this finding concluded when clearly only form of social support here is reflection of just marital status.

Response: Our findings reinforce the idea that obesity and the condition of being unmarried or without out partner are significant risk factors for depression. We used marital status as a proxy for social support, the best community of family and friends compared to a person with not such a good marital relationship based on what was this finding was clearly only form of social support here is reflection of just marital status.

Comment 8: PHQ-9 CATEGORIZATION : Please help me understand , if in each section of the caffeine intake – mild / moderate and severe – the outcome variable of depression of PHQ-9 scale of only severe/ severe + moderately severe + moderate was considered ? (was there a dichotomization of all severe symptoms together vs mild symptoms?) and multivariate model with results table 2 – reflects the association of these group with moderate & high caffeine intake only?

Response: PHQ-9 is an ordinal categorical variable for which the proportionality of odds test was used to ensure the effects of any independent variable on the odds of being in a higher PHQ-9 category are consistent across all categories of our independent PHQ-9 variable.

Comment 9: If the above is in accordance to my understanding- then please explain as per the numbers of the people who had moderate + moderately severe + severe symptoms were very less in each category compared to the number of participants (thousand to few early hundreds?) – doesn't it really have a very strong imbalance of covariates ? – are the associations really authentic considering this discrepancy ? -"In total, 8.5% of the population presented moderate-to-severe depressive symptoms (PHQ-9 score ≥10)." – as per your population description

Response: We are aware that higher categories will have a different amount of participants. However, with the weighted analysis, these differences were not statistically meaningful.

Comment 10: STRENGTHS & LIMITATIONS : the data set has included as per your analysis only age group of people from 49.4 (in general > 40 years) years as the mean age , which is not the case with caffeine intake and depression when in the united states , even a younger age group would be habitual coffee consumers and targets of mental health issues such as depression as well , so the data set lacks the diversity of age group as well to claim robust results as per previous analysis done before.

Response: We have resubmitted our statistical data with a weighted analysis, so we have addressed the concerns of the reviewer.

Comment 11: Lack of ethnically diverse population since race & ethnicity is not taken into account would be another shortcoming – as this indirectly reflects the external validity of the study

Response: We thank the reviewer for this comment. We have included ethnicity as a confounder for our analysis.

> **Comment 12:** The number of participants in each subgroup of caffeine intake being in hundreds compared to the participants being in thousands is clear imbalance in the covariates (main variables) – which definitely adds to external validity of the study- to claim that this data set analysis would have a potentially strong association to suggest for further research to be conducted etc.

Response: We have resubmitted our statistical data with a weighted analysis, so we have addressed the concerns of the reviewer.