Peer-review Comments and Author Responses

Reviewer 1

1. Overall, a good summary of the related research. Some questions related to the method of study selection and the resultant set. You begin by stating that "filters were applied for RCT (randomized clinical trials), meta-analysis, systematic reviews, and observational studies" but later you state the selection was limited to observational studies alone. RCTs would be an issue for exposure of pregnant people to air pollutants, which begs the question of inclusion in the initial search.

Initially, we were uncertain about the amount of evidence available on this topic, so we conducted a comprehensive search. We even included reviews to cover their references. Following the search, we identified only one Randomized Controlled Trial (RCT) that did not meet our inclusion criteria. Therefore, we were left with only observational studies.

2. Secondly, in the inclusion criteria you state you included "exposure of any outdoor air pollutant during pregnancy and early childhood" but later you state "Included studies focused on evaluating the impact of air pollutants during pregnancy and its correlation with NDD" which does not include exposure during early childhood.

We have considered your comment and we have agreed to remove the phrase "and early childhood" from the beginning of the text.

3. Third, and probably most concerning, is that you specified you started with 675 references and eliminated 165 duplicates, leaving 510 entries. 431 were then excluded based on the pre-defined criteria, which should leave 79 but you report only 35 were retrieved without explanation. What happened to the rest? Without a clear explanation, it is difficult to assess whether the process led to significant selection bias.

You are correct. After reviewing the Prisma flow diagram, we identified a mistake. The diagram, generated by Rayyan, did not include a few remaining excluded articles.

4. Finally, performing a meta-analysis along with the systematic review would significantly strengthen the paper and conclusions as it would reflect not just the analysis of the findings of the papers included, but more importantly, a measurement of the combined effect size of the pollutants on NDD.

I agree that conducting a meta-analysis would be an interesting approach. However, our program's goal was to conduct a review only. Although we attempted to gather data for a meta-analysis, the articles we assessed examined different pollutants, used different methods, measured different domains and scales, and studied different pregnancy stages. Therefore, to

conduct a meta-analysis, we would need to narrow down our research question and focus on only a few selected articles.

5. Other issues include minor grammatical issues and confusing statements that need to be addressed. For example, you state "the maximum age was eight years..." but then state "...and 10 years in the study of Guxens et al.,(2018)";

We have rectified the issue as per your observation. Thank you for bringing it to our attention.

6. You include "statistical prediction models based on regression analyses" in the discussion of measurement, but that is an inferential method, not a measurement method.

We have resolved the issue based on your feedback. Thank you for bringing it to our attention.

7. In the conclusion, you discuss macro ways to reduce pollution but nothing about ways to reduce the immediate exposure of pregnant people to pollution.

We agreed with the suggestion and resolved the issue.

Reviewer 2

8. The introduction presents 3 clear paragraphs that relate to each other giving the general concept of world statistics, the 2nd paragraph talks about the other factor of interest which is neurodevelopment defining it, and classifying it and the last paragraph details the knowledge gap that exists between the association of these 2 variables in prenatal stage and the concern to evaluate it at 10 years (neurodevelopment evaluation) making clear which the objective of the article, it is supported with bibliography. The introduction is precise and attractive, making clear the objective of the article. Very good.

We appreciate your feedback.

9. Clear methodology with a search strategy for various existing search engines. Well-defined search keywords using the PRISMA model for order and detailed inclusion/exclusion. Clear inclusion/exclusion criteria with no room for doubt.
Bias evaluation using STROBE is good!

We revised the assessment tool for quality and bias based on other reviewers' feedback.

10. *In the first paragraph the results are presented clearly, in a logical order according to the methodology proposed, there is a correlation which makes it easy to read.*

Thank you, we appreciate your feedback. Things that can be improved.

11. *In the table of studies there are 2 retrospective cohort-type articles and one cross-sectional study, the rest are all prospective with, a high rate of bias, in addition, one of the retrospective articles measures neurodevelopment in children with structural MRI, not with*

functional scales like all the others.... these studies may provide more bias in the type of studies and analysis of the results since they are far from the majority.

Thank you for your feedback. We conducted a re-assessment of bias and quality using the NOS tool, to standardize this issue among the included articles. The MRI study was included because the researchers also tested for cognitive performance and looked for associations between exposure, MRI findings, and cognitive assessments.

12. The dependent variable; the outcome was functional scales that in one-third of the studies the BSID III was used, which has better validity and reliability...and the others????? What about 66% of the studies?

We appreciate your feedback on this issue. We found several methods to assess neurodevelopment like BSID, including ASQ, specific cognitive or language tests, and validated and non-validated questionnaires, which are described in the results section under the heading "Neurodevelopmental delay measurement and scales used".

13. The item "Main associations found in relation to air pollution and NDD" gives a lot of information with authors and variables, I suggest organizing it better so that when reading it, it is not a bomb of information and the important thing that they want to transmit is lost.

Thank you for your feedback. We have improved that section to enhance readability.

14. There are more prenatal than postnatal evaluations....another confounding factor.

Thank you for bringing this issue to our attention. We have identified that this issue, along with other factors, can increase variability in the studies.

15. Very well-written discussion and very accurate imitations!!!!!

Thank you for your kind words of appreciation.

16. *The conclusion is very long and misses the real contribution of the study and its main result... This conclusion is closer to a discussion.*

Thank you, this suggestion was addressed. We rewrote this section.

Reviewer 3

Overall, you have an interesting topic with some minor adjustments to improve the reading and comprehension of the research.

Reviewer 4

17. *We did our best to address the comments and you can find our responses to your suggestions below. "You should consider a more attractive title, maybe indicating the*

existing association between air pollution and neurodevelopment delay that you found in your work."

Answer: We considered and changed the title to make it more attractive. Previous title: Effects of Prenatal Outdoor Air Pollution Exposure on Cognitive and Neurological Development in Offspring: A Systematic Review. Current title: Breathing in the Future: Unraveling the Link Between Prenatal Outdoor Air Pollution and Neurodevelopment in Offspring: A Systematic Review.

18. *Also, using "a mini-review" could be a better description of the work.*

Dear Reviewer: Thank you for your comment regarding the use of the term "mini-review". We consulted with our professors and decided to conduct a systematic review by PRISMA guidelines. We made sure to meet the main criteria of a systematic review.

19. *Manuscript: Although it is well written, it has more than 3,700 words (from Background through Conclusion, excluding Authorship, Abstract, Acknowledgments, References, and all the Appendix). Remember that mini-reviews should have up to 2,000 words as previously established.*

Answer: As we opted for a systematic review instead of a mini-review, we adhered to the word limit of 5,000 words for full reviews in accordance with the PPCR Journal Guidelines. (https://journal.ppcr.org/index.php/ppcrjournal/authors-center)

20. Abstract: *The sentence "The analysis showed a negative association between air pollution exposure during pregnancy and neurodevelopmental delay in the offspring" needs to be checked. It is the main finding of your study but is wrong as you properly present your results. Your results show that more air pollution exposure is associated with more neurodevelopment delays in offspring, so it is positively associated with it (or negatively associated with the neurodevelopment itself). Although it can be a wording problem, it is your main finding statement, and such a mistake can have important implications for readers.*

Answer: We have rewritten this sentence as: "This comprehensive review presents evidence suggesting that prenatal exposure to air pollution hurts cognitive and neurological development in offspring. However, future studies are needed to corroborate these results."

21. Background: *The section is well written, but it is too long. Usually, it should have three paragraphs: first, contextualize the importance of the issue you are studying; second, what is already known about it and its potential; third, clearly present your research question and the objective of your study (if possible, emphasizing what is innovative in the present work). Your research question and the objective of the review need to be clearer and easily identified in the last paragraph of your introduction.*

Answer: We followed your advice and rewrote this section into three paragraphs. The first paragraph highlights the significance of the issue, the second paragraph summarizes what is

already known, and the third paragraph presents the research question and objective of our study. This new version is also shorter than the previous one, making it easier to read.

21. *Methods: In data extraction, you should mention the authors who did it (the independent pair and the third reviewer).*

Answer: We followed your advice and mentioned the authors who did the data extraction, considering the independent pair and the third reviewer.

22. *Please clarify that you only considered full text available for your review and excluded abstracts available only from it.*

Answer: We followed your advice and mentioned this issue in the methods section, only full-text articles were included.

23. *You must reconsider using STROBE as a quality assessment tool. It was designed to guide authors on how to report observational studies (Elm et al., 2007) and can also be useful for designing and conducting such studies, but some authors consider that its use as a quality assessment tool is inadequate (Costa et al., 2011). The references you cited for using STROBE ("Quality Assessment - Systematic Review Toolbox - JABSOM Library at John A. Burns School of Medicine, n.d.; Taylor et al., 2013; Young & Solomon, 2009" and "Saleh et al., 2020") do not support its use. For example, how do you define the 68% (15/22) as your cutoff for quality? Does each STROBE item have the same importance in the quality of the study? A more appropriate tool for it is ROBINS-I (Sterne et al., 2016). I believe it is a major issue that should be addressed for publication. Please visit https://www.riskofbias.info/welcome/home/current-version-of-robins-i and check how to use the tool.''*

Answer: Since ROBINS-I is a tool for assessing observational studies assessing interventions, we considered using its equivalent ROBINS-E for the risk of bias assessment. However, we found evidence in the literature that raised some issues with this tool. We agree that STROBE was not designed for this purpose, which is why we decided to use a different, well-established tool – the Newcastle-Ottawa Scale. This tool is specifically designed for this purpose and has been widely used in the literature (Wells, 2014).

Wells, G.A., Wells, G., Shea, B., Shea, B., O'Connell, D., Peterson, J., Welch, Losos, M., Tugwell, P., Ga, S.W., Zello, G.A., & Petersen, J.A. (2014). The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-Analyses.

24. *Results: Your PRISMA flow diagram must be reviewed. First, you used "Databases (n = 4)" to indicate that you searched in four databases. I suggest excluding "(n = 4)" because the following text is clear about the four databases you used and it can confound the reader (I thought in the first reading that you identified 679 records, not 675). After excluding duplicates, you got 510 records and mentioned excluding 431: well, it is not possible to get only 35 records. In the sequence another mistake: 35 records, 1 excluded for wrong population, and only 24 included in the review. Please review it and specify the reasons for excluding so many papers (e.g., full text not available, no English language, etc.). The*

PRISMA flow diagram talks a lot about the quality of your work. Please review and check each number so they match your result.

Answer: The PRISMA flow diagram was edited and corrected to address your comments about the number of studies. These numbers are automatically delivered by Rayyan, the application used for the screening process, but the number of excluded articles was wrong and corrected accordingly. Fortunately, all the selected titles and abstracts were retrieved as full text for the full-text screening.

25. *You mentioned before that you used STROBE 68% cutoff for quality assessment which is shown in Table 1. It is not clear what is presented in Table 2. It looks like ROB-2 quality assessment, but you need to remember it is designed for RCT, not observational studies (for example, you mentioned "Assessment of intervention" but in observational studies, there is no intervention but exposure). You need to use ROBINS-I or another validated tool (there is also an electronic tool in Excel that is available on the website mentioned above).*

Answer: Thank you for this useful comment. This suggestion was also addressed when we switched the tool from STROBE to NOS. Finally, we didn't use a quality cutoff.

26. Discussion: *Check for the cohesion and fluency of your text – maybe the subheadings organization makes the text not flow.*

Answer: We have checked for the cohesion and fluency of our text, and several changes were made, making it more fluent and without subheadings.

27. *The section "Limitations of analyzed studies" needs to be rewritten using a topic structure that is not usual nor formal for scientific papers discussion section.*

Answer: Thank you, this section was rewritten accordingly.

28. Conclusion: Here you should have, generally, only one or two paragraphs of your main findings and future directions for research. It should not be a summary of your manuscript or its discussion section – it is almost another discussion of your work. Please, review it and consider if some content can be useful in the discussion.

Answer: Thank you, we rewrote the conclusion based on this suggestion.

29. *As I pointed out as a major issue of the abstract, the direction of the association is not clear in the conclusion too: "Our systematic review supports the idea that there is an association between prenatal outdoor air pollution exposure and offspring neurological development".*

Answer: We have rewritten it more clearly: "This comprehensive review presents evidence suggesting that prenatal exposure to air pollution has a harmful impact on cognitive and neurological development in offspring. However, future studies are needed to corroborate these results.''

30. References list: *You should review your references list because they are not listed according to APA style. I strongly recommend that you use a reference manager. There are some free excellent options like Zotero or Mendeley and tutorials on their websites or YouTube. Additionally, this learning is not restricted to the present work, but I consider it a game changer for those who work with scientific writing.*

Answer: Thank you very much for these suggestions. We included the references formatted in APA 7 with Zotero, initially, we worked on a shared drive file, and we couldn't use Zotero properly, for the corrected manuscript we reviewed references each by one using Zotero in a desktop Word file.

31. *Authorship: Only the first author's title is mentioned (MD). Please provide the titles of other authors.*

Answer: We have decided not to include the titles of authors alongside their names since it is not mandatory as per the PPCR Journal guidelines.

32. *There is a # symbol in the first two authors. It is not clear if it is a symbol for the first co-authorship. Please clarify it.*

Answer: The symbol '#' is placed next to the names of the first two authors to comply with the journal's co-authorship policy.

33. *Abstract: "The abstract is the first impression of your work and, in most cases, the only part of the paper that will be read. So, it needs to be clear and provide the full information for the readers. Please explain what "PM10, NO2, and PM2.5" means. This comment applies to all the manuscripts – it needs to be checked for text consistency."*

Answer: These terms were removed from the abstract, in which we only used the broader concept of air pollution. We left this explanation for the full text.

34. *"If possible, quantify the association observed between maternal exposure to air pollution and neurodevelopment delay in the offspring in the results section.''*

Answer: A meta-analysis was not possible as the results from each study were reported in very heterogeneous measurements. Alternatively, we decided to synthesize the results qualitatively.

35. Background: *"BC" is used for the first time here but is not defined (black carbon)."*

Dear Reviewer: Thank you, we addressed this issue.
36. Methods: You cited you used a broad range of study designs ("RCT (randomized clinical trials), meta-analysis, systematic reviews, and observational studies") in the search strategy, but in the eligibility criteria you only included "observational studies". I do agree with the selection you made, but it is not clear why you used a broad strategy before.''

Answer: When it comes to the eligibility criteria of our search strategy, Randomized Controlled Trials (RCTs) could potentially be problematic for studying the exposure of pregnant individuals to air pollutants. This raises the question of whether or not to include them in our initial search. Initially, we were unsure about the amount of available evidence on this topic, so we conducted a comprehensive search. We even looked at reviews to examine their references. However, after conducting the search, we discovered only one RCT that did not meet our inclusion criteria. Therefore, we were left with only observational studies for our analysis.

37. *''Table 1: Try to classify the included records into some pattern: year of publication, author (last) name in alphabetical order. Also, try to summarize the "main findings" and "limitations of study" columns because they are too long.''*

Answer: Your suggestions about the classification and organization of Table 1 were considered and modified. We also divide the information into three tables, table 1 for study characteristics, table 2 for quality assessment, and table 3 for exposure, outcome, and association summary.

38. *Table 1: The papers included in Table 1 are not enumerated (1-24). Although it seems logical, it is difficult for the readers to find any article there. Also, you are using numerical identifiers to discuss the papers in the discussion section.*
We followed your advice and enumerated the articles in Table 1.

Reviewer 5

39. *The authors are commended for conducting a comprehensive review on such an important topic. Presenting new evidence about the potential consequences of pollution on offspring neurocognitive development is relevant nowadays. Even though the research concept seemed suitable, I had several reservations while reading the manuscript. Overall, information is not clear in several points of the manuscript. I strongly recommend that you review and edit the writing and English language of the manuscript with someone certified so that the reading flows better.*

Dear Reviewer, we thank you for your comment. We recognize the importance of clear and coherent writing to effectively communicate our research findings. We appreciate your recommendation and we are committed to addressing this concern.

40. *Abstract: I suggest unifying the background and objective as an introduction.*

Thank you for your valuable feedback. According to your comment, we unified the manuscript to improve the flow of the abstract.

42. "*Objective: Evaluate the effects of prenatal outdoor air pollution exposure on cognitive and neurological development in children up to 10 years old." In the eligibility criteria, the age of the study ranges from 0-18 years.*

Thank you for your comment. We included articles with no age limit during childhood.

43. In methods, besides the STROBE checklist, the quality of the methodology and risk of bias should be assessed using the Cochrane risk-of-bias tool ROBINS-I for non-randomized studies.

Thank you for your suggestion regarding the use of the ROBINS-I tool from Cochrane for assessing the risk of bias in non-randomized studies. We appreciate the recommendation and understand the robustness and credibility the ROBINS-I tool offers. However, after careful consideration, we opted for the Newcastle-Ottawa Scale (NOS) to assess the quality of non-randomized studies included in our research. We believe that the NOS provided us with a comprehensive framework that aligned well with the specific nuances and requirements of our study. Nonetheless, we acknowledge the value of the ROBINS-I tool and will consider its utilization in future research endeavors.

44. The results lack some important information about the study population. What is the total number of study participants? What is the average participant's age found? What is the average age of the mother in studies? What pollutants were reported in the studies? The negative effect of air pollution during pregnancy has been observed in how many percent of studies? What are these abbreviations PM10, NO2, and PM2.5?

Thank you for addressing the need for additional information about the study population and pollutants studied, we reviewed as requested.

45. *There are many limitations in the study that may invalidate the results. I suggest putting it this way: This comprehensive review presents evidence suggesting that prenatal exposure to air pollution may have a harmful impact on cognitive and neurological development in offspring. However, future studies are needed to corroborate these results.*

Thank you for highlighting this sentence, we change it accordingly.

46. Introduction: I suggest using Introduction instead of Background as it is a broader term. Second paragraph: "Neurodevelopmental delay (NDD) is defined as an impairment of the developmental stage of the nervous system of children (Choo et al., 2019).". Please correct: "central nervous system".

Thank you for the suggestion, we already changed what you mentioned. Thank you, we address the commentary.

47. *Second paragraph: "The main domains include motor skills (gross and fine), language, cognition, social activities of daily living as well as the performance of the children (Bellman et al., 2013)." I suggest removing "as well as children's performance" unless you explain what this performance would be.*
Thank you for your comments, we decided to erase the part of 'main domains'
including motor skills, in this way, we remove children's performance.

48. *Third paragraph: "Previous reviews to summarize the evidence on the neurological effect of prenatal exposure to air pollution also show an inclusive association (Clifford et al., 2016; Johnson et al., 2021; Payne-Scurrent et al., 2019)." This phrase is confusing. You*

have to address previous research that supports your hypothesis in the introduction. You should include the studies, systematic reviews, and meta-analyses that were conducted on the topic, as well as why this systematic review is relevant. What new knowledge will it contribute to science? I suggest writing about this in the last paragraph of the introduction.

Dear Reviewer: Thank you for your comment. We address that issue.

49. Third paragraph: "These pollutants were included in the synthesis due to their relevance to real-world exposure, potential health impacts, documented mechanisms of harm, regulatory importance, and the desire to address research gaps. These pollutants are pervasive in outdoor air, making them suitable representatives of daily exposure scenarios. Their associations with oxidative stress, inflammation, and adverse health effects, along with regulatory scrutiny, underscore their significance. The inclusion of pollutants with distinct characteristics and sources allows for a comprehensive evaluation of exposure complexities. By investigating both extensively studied pollutants like PM2.5 and NO2 and less-explored ones like BC, the review aims to provide a detailed understanding of how prenatal exposure to various outdoor air pollutants could influence cognitive and neurological development in offspring." I highly recommend you summarize all this information. I also recommended that you include references.

Thank you for the comment. We already summarized the information and included references.

50. *Material and Methods: I suggest not using subtitles in this section of materials and methods. The reading will flow better this way, in my opinion.*

Thank you for the suggestion, we believe that subtitles will work.

51. *"We included references from the last 10 years, in the English language, with a broad range of study designs to maintain a high sensitivity, filters were applied for RCT (randomized clinical trials), meta-analysis, systematic reviews, and observational studies." Based on the eligibility criteria, this systematic review included only observational studies. Please clarify why you used filters for meta-analyses, systematic reviews, RCTs, and observational studies.*

Thank you for the comment, we did not use filters to exclude RCTs.

52. *"Observational studies with a population of pregnant women (any trimester) and their children (0-18 years), with no age limit for the outcome assessment, exposure of any outdoor air pollutant during pregnancy and early childhood, outcomes related to overall neurodevelopment or its psychomotor, cognitive, language, or behavioral domains." The age of pregnant women may represent a confounding variable for the study. It is important to include the average age of pregnant women and address this in the study's limitations. Please make it clear what early childhood is as well. Would only children under the age of eight be considered for exposure?*

Thank you for the comment, we included the average age of pregnant women and we mentioned the confounding factors in the limitation section.

53. "*The search was done between July 15th and July 28th, 2023. The reference lists of selected and recent systematic review reports were manually examined during August 2023 to identify potentially relevant studies that meet the inclusion criteria and were not achieved within the search strategy." This paragraph appears to be in the incorrect place. It must be part of the search strategy.*

Thanks for your comment, we've moved this paragraph to the search strategy section as you suggested.

54. "Only observational studies were included in the systematic review. The risk of bias was assessed using the STROBE checklist (von Elm et al., 2014). Each of the 22 items was scored as follows: 1 for compliance with STROBE recommendations, 0.5 for partial description, and 0 for not addressed at all. A STROBE score of 15/22 (68%) was considered to be satisfactory compliance (Quality Assessment - Systematic Review Toolbox - JABSOM Library at John A. Burns School of Medicine, n.d.; Taylor et al., 2013; Young & Solomon, 2009). A qualitative bias assessment using the STROBE main bias-assessment criteria was done, where the assessment of intervention, missing outcome data, measurement of outcome, selection of reported results, and overall bias were shown for each study (Saleh et al., 2020)." In addition to the STROBE checklist, you must describe ROBINS-I for risk of bias and quality assessment for non-randomized research, such as observational studies.

We appreciate your suggestion to use the ROBINS-E tool to assess the bias of our included observational studies. However, we have decided not to use ROBINS-E because it is based on the premise of comparing observational studies to randomized controlled trials (RCTs). Further, ROBINS-E assesses seven domains of bias but does not include relevant questions related to some critical sources of bias, such as exposure and funding sources, and it fails to discriminate between studies with a single risk of bias or multiple risks of bias. Moreover, the tool is severely limited in determining whether confounders will bias study outcomes. These concerns are supported by the article "The Risk of Bias in Observational Studies of Exposures (ROBINS-E) Tool: Concerns Arising from Application to Observational Studies of Exposures" by Bero et al. (2018). However, we recognize that a more appropriate tool for our review will be the Newcastle-Ottawa scale, the currently most commonly used quality assessment tool for observational studies according to Ma et al., 2020 (1) and Stang et al., 2010. (2)

(1) Ma, L.-L., Wang, Y.-Y., Yang, Z.-H., Huang, D., Weng, H., & Zeng, X.-T. (2020). Methodological quality (risk of bias) assessment tools for primary and secondary medical studies: what are they and which is better? Military Medical Research, 7(1). https://doi.org/10.1186/s40779-020-00238-8

(2) Stang A. (2010). Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. European journal of epidemiology, 25(9), 603–605. https://doi.org/10.1007/s10654-010-9491-z\

55. *Results: I suggest not using subtitles in this section of results. The reading will flow better this way, in my opinion.*

Thank you for the suggestion, we believe that subtitles will work.

56. "Risk of bias was evaluated in all studies by the assessment of air pollution interventions including the diversity of air pollutants measured, handling and reporting of missing outcome data, methods measuring outcomes as well reporting and generalizability of outcome data. Only 25 percent of all included articles have a low overall risk of bias while the rest raised some concerns mainly due to limited generalizability, less diversification in the intervention/outcome measurement methods, and missing data handling (Appendix 4, Table 2)." When analyzing Table 2, we noticed that the quality and risk of bias assessment applied was Rob 2, which is used for randomized clinical trials. Instead, you should use ROBINS-I, designed for non-randomized clinical trials such as observational studies.

Thank you for your suggestion, we used the Newcastle Ottawa scale instead of ROBINS-I.

57. More population information should be reported at the study's characteristics session, such as the total number of participants (n), the average age of participants, the average age of pregnant women, and all pollutants identified in the studies. In addition, to establish the number/percentage of studies that demonstrated that air pollution during pregnancy had a deleterious influence on the child's neurocognitive development.

Thank you for your comment. We included that information in the study's characteristics section.

58. *"Air pollutant exposure levels during pregnancy were measured using a variety of methods, including air quality monitoring data from stations located in cities, states, or countries; statistical prediction models based on regression analyses; geolocation data to determine proximity to major roadways; spatiotemporal methods that combine air quality data from monitoring stations with additional measurements, such as aerosol optical depth (AOD) data collected from satellites; and data from environmental databases or networks. " Please try dividing this sentence into two parts. It's lengthy and hard to read.*

Thanks for the suggestion we have adhered to it and made the text more fluid to read

59. *"All analyzed studies assessed the effect of air pollutants during pregnancy and NDD on their offspring. Air pollution exposure was measured during the prenatal period in all the included studies and postnatal period in seven of them." Please specify the age range for which exposure was measured.*

Thank you for your comment, but studies did not include that information.

60. *Discussion: I suggest not using subtitles in this section of results. The reading will flow better this way, in my opinion. I recommend keeping the discussion section in a logical order and minimizing the repetition of information. I suggest restructuring the discussion. The Interpretation and Synthesis of Results section simply outlined the findings. It is critical to interpret and discuss the data from the results session throughout the discussion. I suggest summarizing the data in one paragraph and starting the discussion.*

Dear reviewer, we thank you for the insights regarding the removal of the subtitles. We have removed them while restructuring the logical order of the paragraph and summarizing the data. We hope to achieve a clearer text now.

61. *Limitations of analyzed studies, Discussion of inconsistencies and heterogeneity among the results of the included studies, and Examination of potential bias or confounding should be summarized in one topic. These three topics address the potential limitations of the included studies and the systematic review itself. I recommend summarizing all limitations and pointing out possible solutions and strengths of the study at the end of the discussion, on the topic "Strengths and limitations of our review".*

We have changed our approach to addressing the limitations and hope to have made it easier to understand where the limitations for each study stand and how we have dealt with them.

62. *"Confounding: Many studies did not control for factors potentially related to both air pollution exposure and neurodevelopment, making it difficult to determine a true association between the two (Appendix 3, Table 1, studies 1-15, 17-24)." Please explain this sentence better. What are the factors potentially related to both air pollution exposure and neurodevelopment?*

We have incorporated these insights to make our study easier to understand and more comprehensive.

63. "Small sample size: Statistically significant associations were difficult to detect as several studies had small sample sizes (Appendix 3, Table 1, studies 1-7, 9-15, 17-23). Additionally, some studies included a specific population, which might not be generalizable to all pregnant women (Appendix 3, Table 1, studies 1-3, 6, 12)." The limiting aspect of studies is not only the sample size but also the characteristics of the sample utilized. Is this sample representative of the target population, and does it have external validity and generalizability? Why not? Please explain better.

We have incorporated these insights to make our study easier to understand and more comprehensive.

64. *"Possible mechanisms of developmental delay secondary to air pollution exposure." Consider including this information in the introduction section only. "Comparison with previous research" should be included in the introduction section as background information. In the discussion section, I suggest writing this information in summary form.*

Regarding the insights about moving it to the introduction, we have adhered to these suggestions, which have made the text clearer.

65. *Conclusion: I recommend that you summarize the conclusion because it is extensive. Remember this is the final session, this is your conclusion. What can I objectively conclude from the findings of this study? What can I suggest to readers? I suggest something like this Observational research published in the last 10 years supports the hypothesis... Given the*

(limitation of studies)..... caution is advised in interpreting the results presented. Future research is needed...

Thank you for the valuable feedback on condensing our conclusion for clarity and directness. We have revised the conclusion to succinctly summarize our findings, implications, and suggestions for future research, as you recommended.

66. *References: References are not in accordance with the journal guidelines. The Principles and Practice of Clinical Research Journal uses the reference format of APA 7h (please see the tutorial from APA: http://www.apastyle.org/learn/tutorials/basics-tutorial.aspx).*

Thank you for pointing out the discrepancy in the reference formatting. We have now revised and formatted all the references in accordance with the APA format.

67. *Tables and Figures: Table 1. Reading is extremely challenging, especially with regard to the main conclusions and limitations. I recommend writing in a more direct manner, such as using bullet points. In addition, I recommend creating a separate table or figure for the STROBE checklist.*

Thank you for your review. We summarized Table 1. according to your comment and we hope it is now more readable in this present form.

68. *Table 2. Qualitative bias and quality assessment were done using the RoB 2 tool, which should be used only to evaluate randomized controlled trials. The correct tool, however, would be ROBINS-I, which is designed for non-randomized studies such as observational ones. I recommend that you address this.*

Thank you for pointing out the inappropriateness of using the RoB 2 tool for our study's qualitative bias and quality assessment. Upon your recommendation, we have re-evaluated the studies using the Newcastle-Ottawa Scale, which is also more suitable for non-randomized studies such as the observational ones included in our review. We have subsequently modified Table 2 to reflect this change.