Peer-Review comments and author responses

Reviewer 1

General Comment:

1. Congratulations on your review. The topic is relevant considering the widespread exposure to air pollution across the globe and the increase in the incidence of CNS tumors in childhood. In general, the study design, methodology, results and discussion are proper and adequate. Check for details in documents attached. **comments are embedded in the text (pass these comments to the response letter also**)

Response: *Thank you for your positive feedback on our review and for highlighting the relevance of our topic. We appreciate your acknowledgment of the design, methodology, results, and discussion as suitable and effective. We carefully reviewed the attached documents and addressed each embedded comment in this response letter. By transferring these comments to the response letter, we aimed to clarify how we incorporated your suggestions and addressed the points raised. Thank you once again for your valuable insights and for helping us improve the quality of our manuscript.*

Reviewer 2

Dear author, I really appreciate your work, because it's really interesting for public health advocacy to investigate the relationship between pollution and cancer. Anyway I will do just some revisions. Minor revisions.

1) Methods:

-**Comment:** Why did you choose the age range 0-19 and not 0-18 for pediatric age?

Response: We selected the age range of 0-19 years according to the World Health Organization's definition, which includes individuals up to 19 years old within the adolescent period (Singh JA et al., 2019). Additionally, several critical studies in our review (Volk et al., 2019; Volk et al., 2020; Hvidtfeldt et al., 2020; Cordier et al., 2004) utilized the same age range, allowing us to incorporate valuable and consistent data relevant to our analysis.

-**Comment:** Did you link the definition of 'no' or 'low exposure' individuals to a geographic localization in the comparison group?

Response: The statement "The comparison group comprised individuals with low or no exposure to air pollution." was modified to: "The comparison group was defined based on air pollutant exposure levels documented within each study (from no to low exposure to air pollution), rather than geographic factors, which were not a primary consideration for determining exposure status."

-**Comment:** Could you specify the difference between 'prenatal' and 'parental' exposure? We suppose that prenatal is a parental exposure, isn't it?

Response: The paragraph was modified from this: "The timing of exposure was evaluated across prenatal (3.84%) (Spycher et al., 2017), parental (11.5%) (Cordier et al., 2004; Huoi et al., 2014; Peters et al., 1981), postnatal periods (34.7%) (DelRiscoKollerud et al., 2014; Feychting et al., 1998; García-Pérez et al., 2016; Hauri et al., 2013, Kaletsch et al., 1999; Kreis et al., 2022; Ortega-García et al., 2017; Ramis et al., 2017; Savitz et al., 1989) and a combination of these timeframes (46.2%) (Danysh et al., 2016; Heck et al., 2013; Hvidtfeldt et al., 2020; Lavigne et al., 2017; McKinney et al., 2003; Park et al., 2017; Raaschou-Nielsen et al., 2001; Raaschou-Nielsen et al., 2018; Reynolds et al., 2004; Volk et al., 2019; Volk et al., 2020, vonEhrenstein et al., 2016)."
To this: "The timing of exposure was evaluated across prenatal (exposure of a developing fetus to certain substances, environmental factors, or conditions during pregnancy) (3.84%) (Spycher et al., 2017), parental (exposures that the parents (mother, father or both) encounter before conception or during pregnancy) (11.5%) (Cordier et al., 2004; Huoi et al., 2014; Peters et al., 1981), postnatal periods (34.7%) (DelRiscoKollerud et al., 2014; Feychting et al., 1998; García-Pérez et al., 2016; Hauri et al., 2013, Kaletsch et al., 1999; Kreis et al., 2022; Ortega-García et al., 2017; Ramis et al., 2017; Savitz et al., 1989) and a combination of these timeframes (46.2%) (Danysh et al., 2016; Heck et al., 2013; Hvidtfeldt et al., 2020; Lavigne et al., 2017; McKinney et al., 2003; Park et al., 2017; Raaschou-Nielsen et al., 2001; Raaschou-Nielsen et al., 2018; Reynolds et al., 2004; Volk et al., 2019; Volk et al., 2020, vonEhrenstein et al., 2016)."

Reviewer 3:

1. **Introduction**

   Comment: The introduction section could be reduced. Avoid using adjectives and concepts, such as "alarmingly" and "prevalent" that could be misinterpreted. Be transparent and objective.

Response: Thank you for the feedback on the introduction section; we have made revisions to enhance its objectivity and clarity. Specifically, we have removed subjective language and adjectives that could be misinterpreted. The revised introduction now focuses on presenting factual information and data to provide a clear and concise overview of the research context.

2. **Methods:**

   Comment: PRISMA guidelines are mentioned as a reference for your work; however, the review registry has not been disclosed. Please consider using initials to identify the authors where needed. For example, two independent reviewers (who?). With more than 20 authors, how do you reach a consensus? Please describe it. Did you use statistical methods to present your data?

Response: We appreciate your comment regarding the review registry. While we followed PRISMA guidelines to ensure transparency and rigor in our methodology, we did not formally register this review; thus, a registration number is unavailable. We will clearly state this in the revised manuscript to avoid any confusion. Thank you for bringing this to our attention.

Regarding the reviewer initials, we modified the text like this: "Two independent reviewers from the team of authors (e.g., M.C.P. and R.D.T.) were responsible for screening the titles and abstracts, excluding irrelevant articles based on predefined criteria. Any discrepancies between the two reviewers were resolved by a third reviewer (e.g., T.S.). The software managed the process entirely, facilitating pairwise independent reviews."

Moreover, finally, related to statistical methods, we added: "No formal statistical methods were used to synthesize the data in this review. The data were summarized qualitatively, focusing on patterns and inconsistencies across the studies. Descriptive summaries of study characteristics, exposure types, and outcomes were used to present the findings."

Thank you for your valuable feedback, which has helped us enhance the transparency and clarity of our methodology

3. Results

-Comment: First, table design requires restructuring to provide the readers with clear and essential data, such as country. Please consider including a succinct Table 1 in the main document, with an overview of the included studies. Which socio-economic variables are considered in the tables? If not, please rename them accordingly. What is the rationale for organizing them? In general, consider the publication date so readers will understand the evolving landscape of this field. Tables 3 and 4 are complex and inconsistent. Add abbreviations meaning, where needed, including risk measurements. Table 5, organize it based on frequency not in alphabetical order. In general, adjust the column's width avoiding alone letters. Consider using, consistently, commas "," for >3 digit numbers, not period "."

Response: Thank you for your valuable feedback on the table formatting and structure. We appreciate your insights and suggestions for improving the clarity and readability of the tables.

1. Table Design and Inclusion of Socioeconomic Variables: We restructured Table 1 to include an overview of the included studies, incorporating essential information such as the country of study. Where socioeconomic variables were not initially considered, we ensured table headers now reflect this, adjusting labels to clarify the organization approach for readers.

2. Tables 3 and 4 Consistency and Complexity: We understood that Tables 3 and 4 needed to be more reader-friendly. To address this, we revised these tables to include complete forms for all abbreviations, particularly for risk measurements and ensured consistency in terminology. We also simplified the tables as much as possible to provide readers with clear, organized information.

3. Table 5 Organization by Frequency: As suggested, we reorganized Table 5 based on the frequency of variables rather than alphabetical order in a pie chart. This change offers a more intuitive understanding of the data patterns.

4. General Formatting Adjustments: We ensured that all tables now consistently use commas for numbers with more than three digits and adjusted column widths to avoid isolated letters, improving readability and maintaining a uniform style throughout the document.

These adjustments have strengthened the presentation of our data and enhanced the overall accessibility of the findings for our readers. Thank you again for your detailed suggestions, and we look forward to your feedback on these revisions.

-Comment: Improve readability by improving table design. Please provide details about population registries.

Response: Thank you for your valuable feedback. We implemented the following changes to enhance the clarity and organization of our manuscript:
-Tables and Population Registries: We appreciate your suggestion to improve table readability. We redesigned the tables and provided more specific details about population registries where applicable to give readers a clearer understanding

4. Discussion:

-Comment: What are your main findings? Describe them in the first paragraph. No significant findings occurred in the field after more than 30 years (1981-2017)?

Response: We began the discussion in the revised manuscript by summarizing our main findings in the opening paragraph. This will give readers a clear and direct understanding of our study's key outcomes.
To address the observation regarding findings from the past 30 years (1981-2017), we explained why some research gaps remain and discuss how our findings contribute to filling these gaps or align with recent evidence. This contextualization highlighted our study's relevance in the field

-Comment: Why do you mention your strengths in the second paragraph instead of how your findings contrast with previous evidence?

Response: We adjusted the placement of the strengths section, following a discussion of our findings in contrast to previous research.

-Comment: What about your limitations?

Response: We provided a dedicated section discussing study limitations, outlining factors that impacted our findings and how these should be considered in interpreting the results.

5. Conclusion

    -Comment: Use "in conclusion" in your conclusion, not before. Avoid using "future research is needed" in your conclusion because it is clear that there are still open questions in the field. What are the implications of your findings and how they impact from a public health perspective? You mentioned this in your title. Improve overall organization.

Response: We revised the conclusion to specify the implications of our findings for public health, as highlighted in the title, and discuss their potential impact on policy and preventive strategies.

Reviewer 4:

1. Introduction

    -Comment: The introduction provides a good rationale; however, it is too extensive. I suggest making it more concise, maybe by focusing the 1st paragraph in "air pollution impact", 2nd paragraph in "adverse effects in pediatrics", 3rd paragraph in CNS tumors importance, incidence and concerns and last paragraph what is not known, ending with will be the objective of the SR, which you mentioned already. In the manuscript I added some comments on which parts you can combine and others that seem repetitive.

Response: Thank you for your insightful feedback on the introduction. We understand the importance of presenting our study's focused and concise rationale. We have restructured the introduction based on your suggestions to improve clarity and coherence. The revised version begins with a concise overview of the impact of air pollution, followed by a discussion of its adverse effects, specifically in pediatric populations. We then address the importance, incidence, and concerns surrounding CNS tumors in children, highlighting the significance of this topic in the context of air pollution exposure. Finally, the introduction concludes with a summary of the knowledge gaps and the primary objective of our systematic review. Additionally, we have revised certain sections based on your embedded comments to reduce redundancy and enhance readability. Thank you for helping us refine this critical section.

    -Comment: Paragraph 2 and 3 –" What is known? The whole paragraph is about the adverse effects of pollution in pediatrics, I suggest combining paragraph 2 and 3."

Response: Thank you for your helpful suggestion regarding the structure of the introduction. We have combined paragraphs 2 and 3 to provide a more cohesive overview of the adverse effects of pollution in pediatrics. This revised structure enhances readability and ensures the information flows logically, giving readers a clear, focused context on known impacts in pediatric health before moving into the study's objectives.

    -Comment: Again, try to converge paragraph 4 and 5 into one. These show interesting data, but remember you have to try to make it a funnel until you point out what is not know?

Response: *We have merged these sections to streamline the introduction and create a more concise progression. This approach aligns with the "funnel" structure you recommended, guiding readers smoothly toward the study's objectives.*

> **-Comment**: Its repetitive: "The potential connection between environmental pollution exposure and the development of CNS tumors in children has emerged as a critical public health concern."

Response: Thank you for highlighting this repetition. We have revised the sentence to eliminate redundancy while maintaining its significance in context. The updated phrasing better integrates with the overall flow, enhancing clarity without repeating previously mentioned points.

> **-Comment**: Add references regarding air pollutants and impact in health

Response: References regarding air pollutants and their impact in health were added.

> **-Comment**: Improve Grammar: for example: "According to the World Health Organization, 99% of the world's population was living in places were air quality levels were not met (WHO guidelines: 2019, 2022).This is detrimental to vulnerable populations, as the pediatric one, that may have exacerbation of underlying pathologies such as asthma and acute respiratory diseases (add references)".

Response: Thank you for the suggestion. We have revised the introduction to incorporate additional references that provide context on the health impacts of various air pollutants. Specifically, we included studies highlighting the effects of pollutants such as nitrogen dioxide, sulfur dioxide, and particulate matter on respiratory and cardiovascular health, along with the broader public health implications of exposure to air pollution (Pénard-Morand & Annesi-Maesano, 2004; Chen et al., 2007). Additionally, recent WHO reports emphasized the widespread nature of pollution exposure and its contribution to premature mortality (WHO, 2022; WHO, 2023; Naureen et al., 2022).
These updates aim to strengthen the rationale for our study by providing a comprehensive overview of the established health risks associated with air pollutants. We hope this enhances the clarity and relevance of the introduction, aligning it more closely with current public health literature.

> **-Comment**: Sentence referring to non-communicable diseases is related to adult population instead of children. I suggest being deleted: "Over the past few decades the evidence associating air pollution with noncommunicable diseases such as ischaemic heart disease, stroke, chronic obstructive pulmonary disease, asthma and cancer, has certainly increased (WHO, 2021

Response: Thank you for pointing this out. Focusing on non-communicable diseases in adults could detract from the relevance of pediatric health concerns. We have removed this sentence to maintain a more targeted emphasis on the effects of air pollution specific to the pediatric population, such as respiratory diseases, neurodevelopmental disorders, and pediatric cancers. This adjustment ensures that the introduction aligns more closely with the study's focus on

children's health outcomes associated with air pollution exposure. We appreciate this constructive suggestion to enhance the clarity and specificity of the introduction.

2. Methods:

-Comment: Provide an order to the lecturer. First is the search strategy, then the study selection.."

Response: We have reorganized this section to guide the reader through the process clearly and logically, starting with the search strategy and study selection, followed by other methodological details. This order enhances clarity and provides a structured overview of our approach.

-Comment: Repetitive, PRISMA adheres to PECOS intrinsically: "This systematic review adhered to predefined eligibility criteria based on the PECOS (Population, Exposure, Comparison, Outcome, Study design) framework."

-Response: Thank you for this observation. We have revised and removed the sentence, as PRISMA inherently follows the PECOS framework. The updated sentence now states adherence to PRISMA guidelines for eligibility criteria, ensuring conciseness without unnecessary repetition.

Comment: Population and Eligibility criteria: exclude population. repetitive, PRISMA adheres to PECOS intrinsically: "This systematic review adhered to predefined eligibility criteria based on the PECOS (Population, Exposure, Comparison, Outcome, Study design) framework."

-Response: Thank you for the constructive feedback. We have revised this section to improve clarity and avoid redundancy. The updated text now states:
"This systematic review adhered to detailed inclusion and exclusion criteria based on PRISMA guidelines, which were applied consistently from the abstract screening stage through to full-text review." This revision removes the repetitive mention of PECOS and clearly references the rigorous eligibility criteria used throughout the review process.

Comment: I believe this criteria was the same as the one used to screen abstracts. Therefore, it would be good to mention it just once: "detailed inclusion and exclusion criteria"

-Response: Thank you for your suggestion. We have revised the text for clarity and to avoid repetition. It now reads:
"The review adhered to detailed inclusion and exclusion criteria, applied consistently from the abstract screening stage to the full-text review."
This update provides an apparent reference to the criteria used throughout the screening process.

-Comment: if you did not applied any restrictions or filters is not necessary to put "on language or publication year" because there are many other filters, you don't have to mention them all: " To ensure a thorough and inclusive review, the search encompassed

literature from the inception of each database through May 4, 2024, without imposing restrictions on language or publication year."

Response: We have reorganized this section and altered the sentence to: "To ensure a thorough and inclusive review, the search encompassed literature from inception of each database until May 4, 2024, without restrictions."

-Comment*: There is inconsistency in the flowchart, please review and correct the number of articles screened. It is indicated 1158 studies screened, but 1158 minus 1006 should be 152, not 150. After that, eligibility is missing 2 articles, as well as studies included, unless they are lost somewhere else above.*

Response: Thank you for catching these inconsistencies in the flowchart. We have carefully reviewed and corrected the numbers to ensure accuracy. The total articles screened now consistently reflects 1216, with the subtraction from 1158 yielding the correct number of 152. Additionally, we accounted for the missing two articles in the eligibility and inclusion stages, ensuring all numbers are now accurately represented. We appreciate your attention to detail, which has helped improve the clarity and accuracy of our flowchart.

-Comment: In the flowchart: What do you mean by retrieval? Is it 2nd check, revaluation or full-text review? What was the criteria for retrieval? I suggest including that in the methodology in case it was different from the ones mentioned before.

Response: Thank you for your observation. In response, we clarified that "retrieval" referred specifically to the full-text review stage. We adjusted the terminology in the flowchart to avoid any ambiguity. Additionally, we provided a clear description of the full-text review criteria in the methodology section to ensure consistency with the earlier screening criteria.

-Comment: I suggest adding in the methodology a list and definition of the variables.

Response: We appreciate the reviewer's suggestion to provide a more detailed list and definitions of the variables in the methodology. To address this, we have expanded the variable list and provided clearer definitions in the Methodology section "2.3 Data Extraction" as follows:

"-Study particulars: Key details including title, authorship, publication year, and study location.

-Study design: Type of study (e.g., cohort, case-control) and methodology used.

-Number of participants: Total sample size for each study, providing context for the robustness of findings.

-Age: Age range or mean age of participants, specified to understand the demographics studied.

-Type of air pollutant: Specific pollutants investigated, such as PM2.5, NO2, benzene, and polycyclic aromatic hydrocarbons (PAHs).

-Exposure definition: Method of measuring or defining exposure levels, such as proximity to pollution sources or direct pollutant measurement.

-Timing of exposure: Specific period (e.g., prenatal, postnatal) during which participants were exposed to air pollution.

-Control definition: Criteria for selecting the control group, used to establish baseline comparisons.

-Type of CNS cancer: Specific CNS tumor types (e.g., astrocytoma, medulloblastoma).

-Reported effect estimates: Statistical outcomes (e.g., odds ratios, hazard ratios) that assess the association between air pollution exposure and CNS tumor risk."

-Comment: Figure 1: "Tried Search terms in PubMed and got 741 articles (until may 2024) instead of 735. . Searched Google scholar: got 364 instead of 350. Searched Cochrane: retrieved 1 trial as stated in flow chart. Pending check Scopus and Embase"

Response: We appreciate your zealous observation of Figure 1 regarding the slight discrepancy in the number of articles retrieved from the PubMed and Google Scholar searches. These inconsistencies can arise due to the dynamic nature of these databases. Newly published articles may have indexing delays, and existing articles might undergo metadata updates or algorithmic changes, which can influence search results, even within a short timeframe. Additionally, the custom range filter in Google Scholar only allows the selection of the year of publication, rather than specific months or days. At the end, we checked all the information shown in the flowchart to be clear and precise about our data.

3. Results

-Comment: Tables 3 and 4 "Correlation between characteristics of case-control and cohort studies, types of CNS tumor and Effect estimate" involve too much information, particularly in effect size. I recommend finding a more self-explanatory way to expose it.

Response: We understood that Tables 3 and 4 needed to be more reader-friendly and revised them to include complete forms for all abbreviations, ensuring consistency in terminology. We simplified them as much as possible to provide readers with more clear and organized information.

-Comment: In the tables, the oldest article is from 1981 and the most recent from 2022 (a retrospective one). Please review with what is mentioned in the Results "line 262".

Response: Thank you for pointing this out. We appreciate your attention to detail. In our Results section (line 262), we initially stated that the included studies spanned from 1981 to 2022. However, the range may have appeared slightly different in the tables because the criteria for the study design (cohort or case-control studies) were separate.

-Comment: Please review the order and coherence of the results synthetized.

Response: *Thank you for your valuable feedback. We reviewed the order and coherence of the results section to ensure a clear and logical flow. Our revisions aimed to present the findings in a structured manner that aligned with the study objectives and provided readers with an intuitive understanding of the data synthesis. We also checked for consistency in terminology and ensured that related findings were grouped to improve readability and coherence*

-Comment: Table 3. The column effect size show too many OR according to exposure making difficult to understand the results.

Response: *Thank you for your suggestion. To enhance clarity and organization, we have revised and simplified Table 3, especially in the "Effect Size" column. The table now presents grouped effect estimates for similar exposures, offering readers a more streamlined and accessible overview of the findings.*

4. **Discussion:**

-Comment: I suggest summarizing the discussion a bit more. You correctly mention some main findings including the strength of evidence and limitations. However, as for the introduction, less is more.

Response: *Thank you for your suggestion. We agree that a more concise discussion can enhance readability and focus. We streamlined the discussion to emphasize the primary findings, strengths, and limitations, removing redundant points.*

5. **References**

-Comment: Cannot find the article with the info McKinney 2003. Please add full references of all studied articles."

Response: *Thank you for pointing this out. We apologize for any confusion regarding the citation for McKinney 2003. We have now ensured that the complete references for this article and all other studies included in our review are listed in the references section.*
"McKinney, P. A., Fear, N. T., Stockton, D., & UK Childhood Cancer Study Investigators (2003). Parental occupation at periconception: findings from the United Kingdom Childhood Cancer Study. Occupational and environmental medicine, 60(12), 901–909. *https://doi.org/10.1136/oem.60.12.901"*