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Air Pollution and Pediatric Central Nervous Tumors: A Systematic Review of Evidence and Public Health Implications

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Abstract

Background: *Exposure to environmental pollution, particularly air pollutants, and its relationship with childhood central nervous system (CNS) tumors is a growing public health concern. Understanding these associations is crucial for the implementation of protective measures for children and the development of strategic public policies.*

Aim: *This systematic review examines the association between air pollution exposure and the risk of CNS tumors in the pediatric population aged 0-19 years.*

Methods: *Following PRISMA guidelines, we used PubMed, SCOPUS, EMBASE, Google Scholar, and CENTRAL baselines up to May 2024. We included only observational studies centering on children exposed to air pollutants, excluding tobacco-related exposures. Data on study design, population characteristics, exposure assessment, and types of CNS tumors were extracted and analyzed.*

Results: *We included 24 studies (case-control and cohort) conducted across North America, Europe, Australia, and Asia. The studies assessed pollutants such as benzene, nitrogen dioxide (NO_2), particulate matter (PM2.5), and polycyclic aromatic hydrocarbons (PAHs). Some studies reported positive associations between specific pollutants and increased CNS tumor risk, while others found no significant links. Variability in exposure assessment methods contributed to inconsistent findings.*

Conclusion: *The evidence associating air pollution with childhood CNS tumors remains inconclusive. Further research, with standardized exposure assessments and consideration of critical exposure windows, is needed to clarify these associations and inform public health policies to reduce environmental risks in children.*

Introduction

Air pollution has been widely documented as a significant threat to public health, affecting a broad spectrum of health outcomes. Studies have demonstrated that exposure to pollutants like nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and respirable particulate matter (PM2.5 and PM10) can have severe implications for respiratory, cardiovascular, and overall health (Chen et al., 2007; Manisalidis et al., 2020; Pénard-Morand & Annesi-Maesano, 2004). The World Health Organization (WHO) recently reported that 99% of the world's population lives in areas where air quality guideline levels are not met, leaving millions vulnerable to the adverse effects of these pollutants (WHO, 2022). Such exposure is estimated to contribute to 6.7 million premature deaths annually, emphasizing the urgent need for effective pollution control measures (Naureen et al., 2022; WHO, 2023).

Pediatric populations are particularly susceptible to the harmful effects of air pollution due to their developing organs and immune systems. Adverse health outcomes in children exposed to air pollution include exacerbated respiratory diseases, increased asthma incidence, preterm birth, low birth weight, neurodevelopmental disorders, and even pediatric cancers (Brumberg, 2021). Understanding these impacts is critical as childhood cancer has become a significant contributor to pediatric morbidity and mortality globally, ranking as the ninth leading cause of childhood disease (Ortiz et al., 2023).

Among pediatric cancers, central nervous system (CNS) tumors are notably prevalent, ranking as the second most common childhood cancer after leukemia. CNS tumors, which include tumors of the brain and spinal cord, account for more than 20% of pediatric cancer cases, with incidence rates exceptionally high in developed regions like Europe, North America, and Australia (Johnston et al., 2014; Johnston et al., 2021). Astrocytic tumors are the most frequently diagnosed, followed by medulloblastomas and other embryonal tumors, though these distributions can vary significantly across regions (Leece et al., 2017).

The marked geographical disparities in CNS tumor incidence rates suggest a possible association with industrialization and related environmental factors (Pagano et al., 2023). According to the International Agency for Research on Cancer, higher exposure to vehicular and industrial emissions containing multiple Group 1 carcinogens is a significant concern in more industrialized areas (Danysh et al., 2015; Shetty et al., 2023). Such pollutants, including polycyclic aromatic hydrocarbons (PAHs), can enter the bloodstream, cross the blood-brain barrier, and potentially induce genetic mutations that lead to tumor formation (Danysh et al., 2015; Pagano et al., 2023). This exposure risk highlights the need to assess the long-term effects of air pollution on pediatric cancer risk, particularly in terms of CNS tumor development.

Despite the increasing interest in the relationship between environmental pollutants and pediatric cancer, particularly CNS tumors, substantial gaps remain in understanding this link in populations under 19 years of age (Navarrete-Meneses et al., 2024). This systematic review examines the association between prenatal and early-life exposure to air pollution and the risk of primary CNS tumors in the pediatric population. By synthesizing existing research, this review aims to provide a clearer understanding of the potential link between air pollution and childhood CNS tumors, offering insights that could shape future research directions and inform public health policies.

Materials and Methods

Search Strategy and Selection of Studies

The review methodology adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines, ensuring a rigorous and transparent approach (Page et al., 2020). A comprehensive literature search was conducted across multiple electronic databases, including PubMed, SCOPUS, EMBASE, Google Scholar, and the Cochrane Central Register of Controlled Trials (CENTRAL). The search strategy employed specific terms to capture relevant literature on "air pollution", "child", and "CNS tumors" (see Appendix A). To ensure a thorough and inclusive review, the search encompassed literature from inception of each database until May 4, 2024, without restrictions.

Eligibility Criteria

The criteria enclosed in the studies center on the pediatric population (0-19 years) as the target demographic. The exposure of interest included all air pollutants, excluding tobacco smoke, and considered prenatal, postnatal, and parental exposure. The comparison group was defined based on air pollutant exposure levels documented within each study, rather than geographic factors (from no to low exposure to air pollution), which

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were not a primary consideration for determining exposure status. The primary outcome of interest was the risk of childhood central nervous system (CNS) tumors. The review included observational studies, specifically cohort and case-control designs. Exclusion criteria were applied to ensure the highest quality of evidence, excluding animal, and in vitro studies, case reports, case series, ecological studies, cross-sectional studies, editorials, expert opinions, review articles, and meta-analyses.

Data Extraction

Covidence software (Covidence, 2024) was employed to streamline and standardize the systematic review process. Following the database searches, all identified articles were imported into Covidence. The software automatically identified and removed duplicate entries, with additional manual checks performed to ensure thoroughness. Covidence also automatically assigned articles to pairs of independent reviewers for assessment. 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. Articles that passed the initial screening underwent a full-text review based on the following list:

1. Study particulars: Key details including the title, authorship, publication year, and study location.
2. Study design: Type of study (e.g., cohort, case-control) and methodology used.
3. Number of participants: Total sample size for each study, providing context for the robustness of findings;
4. Age: Age range or mean age of participants, specified to understand the demographics studied.
5. Type of air pollutant: Specific pollutants investigated, such as PM2.5, NO2, benzene, and polycyclic aromatic hydrocarbons (PAHs).
6. Exposure definition: Method of measuring or defining exposure levels, such as proximity to pollution sources or direct pollutant measurement.
7. Timing of exposure: Specific period (e.g., prenatal, postnatal) during which participants were exposed to air pollution.
8. Control definition: Criteria for selecting the control group, used to establish baseline comparisons.
9. Type of CNS cancer: Specific CNS tumor types (e.g., astrocytoma, medulloblastoma).
10. Reported effect estimates: Statistical outcomes (e.g., odds ratios, hazard ratios) that assess the association between air pollution exposure and CNS tumor risk.

Customized forms within the Covidence platform were used to systematically extract key information such as study design, participant numbers, and ages, types of air pollutants studied, exposure and control group definitions, CNS cancer types, and reported effect estimates. Data on confounding variables, matching factors (in case-control studies), and adjusting factors were also extracted for the studies. 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.

Data Synthesis

Exposures were classified into two primary categories: (I) air pollution exposure subtypes (e.g., proximity to pollution sources) and (II) individual pollutant exposures (e.g., PM2.5, NO2, benzene). Three independent reviewers manually conducted the initial data synthesis, examining the extracted data, identifying common themes and patterns, and noting inconsistencies across studies. Subsequently, the reviewers engaged in comprehensive discussions to reach a consensus on the interpretation of findings, the relative importance of different exposure types, and the overall strength of evidence for each exposure-outcome relationship.

Risk of Bias Assessment

The risk of bias in individual studies was evaluated using the Newcastle-Ottawa Scale (NOS) (Wells et al., 2000). This tool assesses bias across three domains: Selection, Comparability, and Exposure, specifically for case-control and cohort study designs. Two reviewers independently conducted the bias assessment, with any discrepancies resolved by a third reviewer to ensure consensus in final decision-making. The NOS assigns a maximum total score of 9 points. Quality interpretations were aligned with established thresholds for converting NOS scores to Agency for Healthcare Research and Quality (AHRQ) standards, categorizing studies as good, fair, or poor quality (Wells et al., 2000). This approach provided a standardized and comprehensive evaluation of study quality across the included literature.

Results

The review included 24 studies: 18 case-control studies and 6 retrospective cohort studies, covering data from 1981 to 2022 (see Figure 1). Geographically, the studies were predominantly conducted in Europe (15 studies) and North America (8 studies), with one study spanning both regions (see Appendix B: Table 1 and Table 2). Key contributing countries included the United States, the United Kingdom, Spain, Germany, France, and Denmark. Most studies included participants under 15 years of age, including both male and female cohorts.

Exposure

A range of exposures was assessed, including proximity to pollution sources, traffic density near major roads, direct pollutant measurements, air pollution modeling, and occupational exposures. The pollutants studied included particulates (PM2.5, PM10), gasses (NO_2, SO_2, CO, O_3), and volatile organic compounds (e.g., benzene, 1,3-butadiene). Occupational exposures assessed included polycyclic aromatic hydrocarbons (PAHs), asbestos, silica, benzene, and dichloromethane (Appendix B: Table 3 and Table 4).

The timing of exposure was evaluated across prenatal (exposure of a developing fetus to certain substances, environmental factors, or conditions during pregnancy), parental [exposures that the parents (mother, father or both) encounter before conception or during pregnancy] (16.7%) (Cordier et al., 2004; Huoi et al., 2014; Peters et al., 1981; Spycher et al., 2017), postnatal periods (33.3%) (Del Risco Kollerud 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; Savitz & Feingold, 1989) and a combination of these timeframes (50.0%) (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, von Ehrenstein et al., 2016).

Controls

Control groups were selected based on age, sex, geographic location, and absence of disease or exposure. Some studies used parents without exposure to specific pollutants as controls (Peters et al., 1981; Cordier et al., 2004; Huoi et al., 2014). Geographic and temporal matching was standard, with controls selected from the same administrative regions (McKinney et al., 2003). Environmental metrics like road and traffic density were used in some studies (Reynolds et al., 2004; Savitz & Feingold, 1989). Random sampling from population registries was common (Volk et al., 2020; Raaschou-Nielsen et al., 2001; Heck et al., 2013). Others employed set sampling (Kreis et al., 2022; García-Pérez et al., 2016). Four studies lacked clear descriptions of control selection (Hauri et al., 2013, Spycher et al., 2017, Volk et al., 2019 and Ortega-García et al., 2017).

Case-Control Studies

The 18 case-control studies included 14,575 cases and 210,188 controls. Positive associations between exposure and outcome were found in two studies (Kaletsch et al., 1999; Peters et al., 1981). Peters et al. (1981) reported that mothers of children with brain tumors inhaled chemicals, fumes, and dust as an occupational exposure more often than mothers of controls, with an RR of 3.19 (1.30, 7.87 95% CI). Kaletsch et al. (1999) found that children aged less than 15 years with CNS tumors had increased odds of being exposed to higher levels of radon in comparison with controls [OR 3.85 (1.26, 11.81 95% CI)].

In six studies, there were conflicting findings (Cordier et al., 2004, Danysh et al., 2016, von Ehrenstein et al., 2016, García-Pérez et al., 2016, Volk et al., 2019 and Volk et al., 2020). Cordier et al. (2004) reported an OR 1.7 (1.3 - 2.3 95% CI) of fathers exposed to occupational polycyclic aromatic hydrocarbons (PAH) in children having a diagnosis of an astroglial tumor. However, the same study observed no similar effect for maternal occupational prenatal exposure to PAH. In another article, Volk et al. (2020) reported that subjects aged 0-19 with unspecified CNS tumors presented increased odds of having mothers working in industries with postnatal exposure to paper dust (OR 2.28 (1.22- 4.26 95% CI). However, occupational exposure of mothers to other types of organic dust (wood, textile) did not show similar effects.

The remaining ten studies within this category did not find statistically significant associations between the exposure and outcomes (Savitz & Feingold, 1989, Feychting et al., 1998, Raaschou-Nielsen et al., 2001, McKinney et al., 2003, Heck et al., 2013, Reynolds et al., 2004, Huoi et al., 2014, Park et al., 2017, Raaschou-Nielsen et al.; 2018 and Hvidtfeldt et al., 2020).

Retrospective Cohort Studies

The six cohort studies included in this analysis collectively included a substantial sample size, comprising 2,274 cases and a total of 10,233,042 participants. Only the study of Lavigne et al. (2017) showed positive associations between exposure

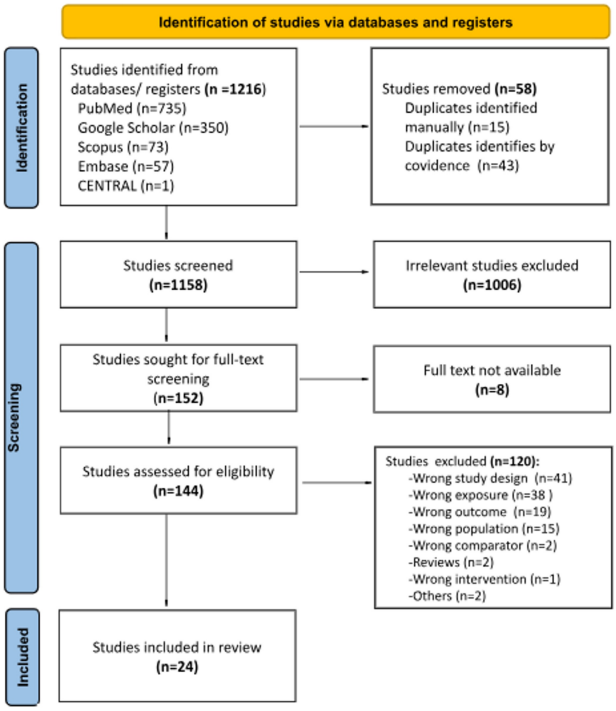

Figure 1: *PRISMA 2020 flow diagram for new systematic reviews, which included searches of databases and registers only.*

and outcome, with an increased risk of childhood astrocytoma when mothers were exposed to higher levels of NO_2 during the third trimester of pregnancy [HR 1.55 (1.02–2.37 95% CI)], or higher levels of PM2.5 during the first trimester of pregnancy [HR 1.40 (1.05–1.86 95% CI)]. In the remaining five cohort studies (Del Risco Kollerud et al., 2014; Hauri et al., 2013; Kreis et al., 2022; Ortega-García et al., 2017 and Spycher et al., 2017), investigators did not find statistically significant associations between exposure and outcomes.

Outcomes, Confounders, and Risk of Bias Assessment

The outcomes show a significant variety of central nervous system tumor types, ranging from more specific tumors such as medulloblastoma and astrocytoma to broader categories like unspecified CNS tumors (Figure 2). Similarly to the exposure analysis, the confounders had a notable variability among studies.

In the case-control studies, authors controlled for demographic characteristics, socioeconomic status, other environmental exposures that could have acted as confounders, and behavioral factors. Cohort studies adjusted for key demographic factors, such as age, sex, race/ethnicity, birth order, socioeconomic status (income, education, parental education), environmental confounders (background radiation, proximity to highways), and health factors (paternal smoking and birth weight). In the case-control studies, authors controlled for demographic characteristics, socioeconomic status, other environmental exposures that could have acted as confounders, and behavioral factors.

The Risk of Bias (ROB) assessment using the Newcastle-Ottawa Scale (NOS) indicated that the majority of included studies were of "Good" quality, with scores ranging from 7 to 9, reflecting robust methodologies across most case-control and cohort studies. Selection criteria and comparability generally met high standards, with nearly all studies demonstrating appropriate control group selection and adjustment for key confounders. Both cohort and case-control studies had consistent outcomes and exposure assessment practices, contributing to reliable data quality. One study by Ortega-García et al. (2017) was rated as "Fair" with a score of 5 due to limited comparability and selection criteria, indicating some limitations in study design (Appendix B: Table 5).

Discussion

This systematic review examined the relationship between air pollution and childhood CNS tumors, concentrating on diverse studies with varied methodologies, exposure types, and geographical locations. Despite early studies like Peters et al. (1981), which hinted at environmental factors as possible contrib-

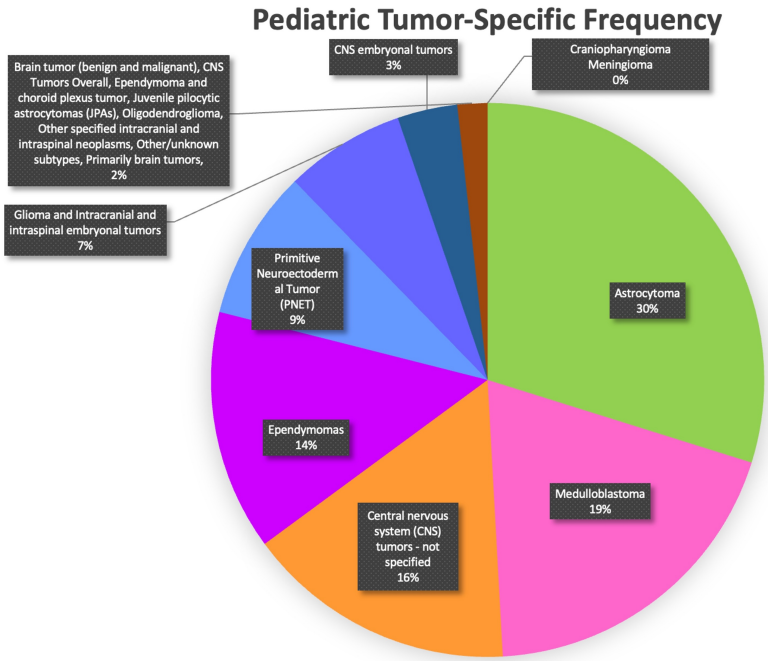

Figure 2: *Pediatric tumor-specific frequency.*

utors to CNS tumors, and later research by Lavigne et al. (2017) suggesting a link between prenatal exposure to PM2.5 and astrocytoma risk, findings remain mixed. Although some studies identified associations with pollutants such as NO_2, SO_2, PM2.5, and radon, most others reported no association or conflicting results. For example, Onyije et al. (2024) and Navarrete-Meneses et al. (2024) found regional variations in pollution-linked CNS tumor incidences, yet overall evidence remained inconsistent across studies.

A systematic review and meta-analysis by Onyije et al. (2024) analyzed 181 observational studies on risk factors for childhood brain tumors. The research highlighted regional differences in cancer incidence rates, suggesting that areas with higher pollution levels had higher rates of childhood cancers. Particularly, NO_2 and SO_2 were linked to higher incidences of CNS tumors Onyije et al. (2024). In a recent scoping review by Navarrete-Meneses et al. (2024) addressing the association between environmental pollution and childhood cancer, the majority of studies indicated a significant association between exposure to air pollutants (e.g., PM2.5, PM10, NO_2, benzene) and an increased risk of childhood leukemia and CNS tumors. While Onyije et al. (2024) provided a comprehensive quantitative synthesis of the evidence about broad risk factors for childhood brain tumors and Navarrete-Meneses et al. (2024) aimed to map the existing literature on the topic, our review specifically concentrated on the narrower theme of the risks of air pollutants for the development of CNS tumors in the pediatric population.

A key strength of this review is its broad inclusion of studies from various regions worldwide, capturing a range of sociodemographic factors. Sample sizes varied significantly, from smaller studies like Feychting et al. (1998) to larger ones like McKinney et al. (2003), which added robustness to our findings. This diversity allowed for a global perspective on air pollution as a potential risk factor for childhood CNS tumors, considering various pollutants, CNS tumor types, and timing of exposure (prenatal and postnatal periods). By including cohort and case-control studies, our review provides a more comprehensive understanding of this issue than prior systematic reviews directing attention to specific pollutant types.

Earlier studies often lacked robust methodologies, contributing to inconclusive results, while newer studies with advanced exposure models have shown limited associations. These discrepancies underscore the impact of study design, exposure assessment techniques, and sample size on findings. Most studies in this review were high-quality, with rigorous methods for selecting cases and controls, assessing exposures and outcomes, and adjusting for confounders. The consistent inclusion of air pollutants and all CNS tumor types strengthens our review's relevance for clinical and policy contexts.

That said, this review has limitations, including the potential for subjective interpretation in synthesizing findings due to manual methods. Despite

this, the inability to quantitatively compare results was carefully documented to maintain transparency. Additionally, differences in study design, pollutant types, geographical diversity, and tumor types posed challenges in establishing clear associations. The inconsistency in findings reflects the complex etiology of childhood CNS tumors, likely involving both genetic and environmental factors. The most substantial evidence remains limited to a few pollutants, such as PM2.5 and PAHs, reinforcing the need for high-quality environmental data in pediatric clinical care (Oliveira et al., 2019).

Subsequent research efforts should standardize exposure assessment techniques, use environmental monitoring, and employ dispersion models to improve exposure accuracy. High-risk cohort studies highlighting the long-term effects of early childhood exposure to pollutants could yield more conclusive evidence. Finally, while evidence suggests possible links between certain air pollutants and childhood CNS tumors, the relationship remains inconclusive. Prioritizing research on exposure timing, gene-environment interactions, and more precise measurement methods could clarify this association and guide public health policy effectively.

Conclusion

In conclusion, data assessing the impact of air pollution on the development and course of CNS tumors in the chosen childhood age group remain limited and inconclusive. This could be related to the variable clinical phenotypes and lack of standardization in pollution exposure in this highly vulnerable group, complicating scientific evaluation. Furthermore, there are suggestions of possible associations between air pollution exposure and childhood CNS tumors, but there is no evidence of the cause-effect relationship between these factors. These findings emphasize a critical need for robust public health strategies to reduce air pollution exposure, especially in areas with heightened pollution levels. Addressing environmental risks associated with childhood health outcomes could substantially mitigate long-term health impacts, supporting both preventive efforts and policy initiatives.

Supplementary Materials

Appendix A: Search Strategy
Appendix B: Tables 1-5

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Conflicts of Interest

The authors declare no conflict of interest.

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