



Does Exposure To Environmental Pollution Increase The Incidence Of CNS Tumors In Children?

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Abstract

Purpose: The postulated risk factor of CNS tumors might be air pollution. In Poland, especially in the Silesian voivodship, air quality is inferior compared to other European countries. The study aimed to evaluate the effect of selected air pollution parameters on the incidence of central nervous system tumors in children.

Material and methods: A group of 460 children (251 boys, 209 girls) aged 0-18 (0.17-18.75) years, diagnosed with CNS cancer were included. The age Standardized Incidence Ratios (SIR) for CNS malignancies in children were calculated. Based on the data concerning air quality, the number and location of air quality monitoring stations for 2003-2016 published by the Regional Inspectorate for Environmental Protection in Katowice, the mean concentrations of benzene (C₆H₆), Nitrogen dioxide (NO₂), benzo(a)pyrene (BaP) and particulates matter with a diameter of 2.5 micrometers (PM 2.5) and 10 micrometers (PM10) were calculated.

Results: The highest PM₁₀ (50.62 μ g/m³), PM_{2.5} (36.14 μ g/m³), BaP (10.9ng/m³) and C₆H₆ (3.67 μ g/m³) concentrations were recorded in the Rybnik area. The highest age-standardized CNS tumor incidence ratio (n/100,000) was also demonstrated in the Rybnik area (3.24). The analysis showed a significant positive correlation between the SIR and the concentration of PM_{2.5} (r=0.89, p=0.039) and PM₁₀ (r=0.93, p=0.007). There was no significant correlation between SIR and NO₂ (r=0.41, p=0.41), BaP (r=0.56, p=0.24), C₆H₆ (r=0.79, p=0.2).

Conclusion: Exposure to high concentrations of particulate matter may increase the risk of developing CNS cancers in children. Further research is needed, especially in the pediatric population.

Keywords

Air Pollution; Central Nervous System Tumors; Children

Introduction

Pediatric malignancies are rare, constituting approximately 1% of all-cause morbidity. Despite this, they remain the second most frequent cause of death in this age group. Central Nervous System (CNS) tumors are the most common solid tumors in children [1]. Many studies identified established and postulated etiological factors for CNS tumors in children. The established aetiological factors include race (ethnicity), male sex, parental age, ionizing radiation and such conditions as neurofibromatosis type 1, neurofibromatosis type 2, tuberous sclerosis (Bourneville-Pringle disease) and familial adenomatous polyposis. The postulated risk factors include: air pollution, high birth weight, congenital disabilities, congenital defects, maternal genetic disorders, pesticides, somatic mutations and epigenetic abnormalities [2,3].

In recent years, many papers discussing the impact of air pollution on children's health and quality of life have been published [4-9].

Air pollution is a mixture of solid particles, gases and organic compounds in the air [25]. Among the gaseous and particulate matter pollutants of the atmospheric air, NO₂, BaP, C₆H₆, PM_{2.5} and PM₁₀ are the most frequently mentioned in the context of impact on human health. The term particulate matter is used by international agencies dealing with air pollution, such as the US EPA (American Environmental Protection Agency), EEA (European Environment Agency) and WHO (World Health Organisation). Particulate matter is divided into PM₁₀ fraction, which means particles smaller than 10 μ m and PM_{2.5} fraction, i.e., particles with a diameter less than 2.5 μ m [2,5]. The diameter of PM is many times smaller than the diameter of human hair, comparable to the diameter of an erythrocyte, which is crucial for its distribution in the human body. When inhaled into the lungs, PM penetrates the bloodstream, causing respiratory and cardiovascular diseases [10]. Dust particles penetrating the brain contribute to the development of neurodegenerative diseases [11-14].

Recent data from the World Health Organization (WHO) have shown that 90% of the world's population breathes highly polluted air. WHO estimated that every year, about 4,2 million people die from exposure to particulate matter, which are components of air pollution [15]. A special report on air pollution exposure and its health effects from the First WHO Global Conference on Air Pollution and Health held in Geneva in 2018 states that air pollution with particulate matter is the world's most significant environmental risk factor and responsible for a much higher number of deaths than other well-known behavioral risk factors such as alcohol, physical inactivity or excessive sodium intake [16]. According to the recommendations of the World Health Organisation (WHO), the annual average concentration limits are ten $\mu\text{g}/\text{m}^3$ for PM 2.5 and 20 $\mu\text{g}/\text{m}^3$ for PM10 [17].

In Poland, air quality is inferior in comparison to other European countries. According to the WHO report on air pollution in 2016, 36 out of 50 most polluted cities in Europe are located in Poland. According to this report, the Silesian Voivodship is Poland's most polluted administrative region and Rybnik is the fourth most polluted city in Europe [50]. WHO recommends that the average daily concentrations for PM 2.5 should not exceed 25 $\mu\text{g}/\text{m}^3$ and for PM 10 -50 $\mu\text{g}/\text{m}^3$. In Poland, the information level for daily concentrations of PM 10 is 200 $\mu\text{g}/\text{m}^3$ and the alert level is 300 $\mu\text{g}/\text{m}^3$ [18,19].

Therefore, the study aimed to evaluate the effect of selected air pollution parameters on the incidence of central nervous system tumors in children in Silesia.

Material and Methods

Participants

A group of 460 children (252 boys, 208 girls) aged 0-18 (0.17-18.75) years, diagnosed with CNS cancer, living in the Silesian voivodship (a sizeable administrative region in Poland) were included in a retrospective analysis. All participants were treated in the Department of Pediatric Oncology, Haematology and Chemotherapy (183 children) or the Department of Neurosurgery (277 children) of the Upper Silesian Children's Health Centre in Katowice between 2000 and 2018. The mean age was 9.07 years. Among the participants, there were 107 children at the age of 0-4 years, 123 of them were at the age of 5-9 years, 120 of them were at the age of 10-14 years and 110 of them were at the age of 15-19 years. Patients were analyzed and grouped according to the latest WHO 2016 classification [Table 1].

Feature	Characteristics of Group
Sex	F=208, M=252
- high-grade CNS tumors	F=77, M=84
- low-grade CNS tumors	F=131, M= 168
Age at the time of diagnosis (years)	7,42 (0,17-18,75)

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[median (min-max)]	
- high-grade CNS tumors	7,5 (0,5-18,5)
- low-grade CNS tumors	5,5 (1-11,5)
CNS tumors localization	
- supratentorial	223 (48%)
- infratentorial	199 (43%)
- spinal cord	27 (6%)
- multifocal	11(2%)
Histopathological diagnosis	Numbers
ASTROCYTIC TUMORS	226
pilocytic astrocytoma	136
anaplastic astrocytoma	9
oligoastrocytoma	11
anaplastic oligoastrocytoma	7
oligodendroglioma	5
glioblastoma	18
xanastrocytoma	5
diffuse astrocytoma	1
optic nerve astrocytoma	10
others astrocytoma	23
EPENDYMAL TUMORS	37
ependymoma	16
myxopapillaryependymoma	2
anaplastic ependymoma	19
CHOROID PLEXUS TUMORS	21
choroid plexus carcinoma	8
choroid plexus papilloma	8
atypical choroid plexus papilloma	5
NEURONAL TUMORS	28
ganglioglioma	19
others neuronal tumors	6
gangliocytoma	3
TUMORS OF THE PINEAL REGION	10
pineocytoma	4
pineoblastoma	5
other tumors of the pineal region	1
EMBRYONAL TUMORS	52
medulloblastoma	46
other embryonal tumors	6
TUMORS OF THE NERVES	7
schwannoma	2

neurofibroma	2
MPNST	1
perineuroma	1
other tumors of the nerves	1
MENINGIOMAS	10
meningioma	6
anaplastic meningioma	1
other meningiomas tumors	3
GERM CELL TUMORS	17
germinoma	11
embryonal carcinoma	1
yolk sac tumor	1
teratoma	4
MESENCHYMAL	8
PNET	8
TUMORS OF THE SELLAR REGIONS	20
craniopharyngioma	16
other tumors of the sellar regions	4
BRAIN STEM TUMORS	24
MPNST - Malignant Peripheral Nerve Sheath Tumor, PNET - Primitive Neuroectodermal Tumor	

Table 1: Clinical characteristics of patients.

Age Standardized Incidence Ratio (SIR) Calculation for CNS Malignancies

The data on the number of children in individual poviats (i.e., smaller administrative regions in Poland) of the Silesian voivodship in 2000-2015 was obtained from the Katowice Branch of the Central Statistical Office. To calculate the incidence ratio, the mean number of children in different age groups was calculated. According to the European standard, the SIR for CNS malignancies in children in particular areas and the entire region was calculated per 100,000 children [Fig. 1].

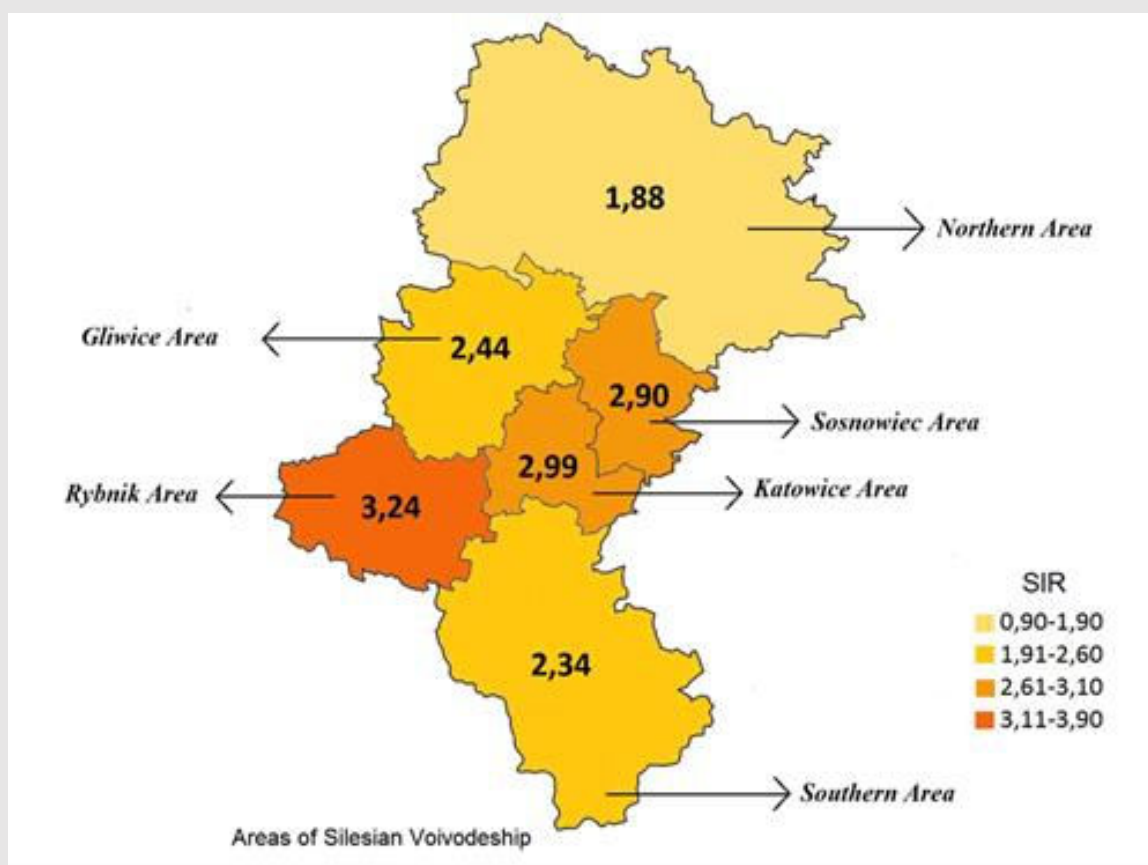


Figure 1: Age Standardized Incidence Ratios (SIR) for CNS malignancies in children in areas of Silesian Voivodship.

Evaluation of selected pollutant concentrations in the Silesian region

Based on the data concerning air quality, the number and location of air quality monitoring stations for 2003-2016 published by the Regional Inspectorate for Environmental Protection in Katowice, the mean concentrations of benzene, PM_{2.5}, PM₁₀, NO₂ and BaP particulate matter were calculated for six individual areas within the region, the data obtained are average concentrations calculated based on average annual concentrations for each area in the period 2003-2016.

The division into those particular areas, as shown in Fig. 1, was based on the location of air quality monitoring stations. The current information about the location of air quality monitoring stations and the values of air pollution parameters can be found at <http://powietrze.katowice.wios.gov.pl/>

Statistical Analysis

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Statistical analysis was performed using Statistica 13.0 PL. The correlation between variables was determined with the Pearson linear correlation coefficient, taking appropriate requirements. P value below .05 was considered statistically significant.

Results

The highest age-standardized CNS tumor incidence ratio (n/100,000) was recorded in the Rybnik area (3.24), where 84 cases were noted, while the lowest was in the northern area (1.88,) with 51 cases. The mean CNS tumor incidence ratio for the entire Silesian region was 2.62 [Fig. 1].

The highest PM10 ($50.62\mu\text{g}/\text{m}^3$), PM2.5 ($36.14\mu\text{g}/\text{m}^3$), BaP ($10.9\text{ng}/\text{m}^3$) and C6H6 ($3.67\mu\text{g}/\text{m}^3$) concentrations were recorded in the Rybnik area. The highest NO₂ concentration ($35.4\mu\text{g}/\text{m}^3$) was recorded in the Katowice area. The lowest mean concentrations of PM10 ($38.1\mu\text{g}/\text{m}^3$), PM2.5 ($26.8\mu\text{g}/\text{m}^3$), BaP ($5.4\mu\text{g}/\text{m}^3$), C6H6 ($1.4\mu\text{g}/\text{m}^3$) were recorded in the Northern area [Fig 2].

For the above data, a statistical analysis was performed to determine the correlation between air pollution parameters and the incidence of CNS tumors in children in the Silesian region. The analysis demonstrated a significant positive correlation between the age Standardised Incidence Ratio (SIR) and the concentration of PM2.5 ($r=0.89$, $p=0.039$) and PM10 ($r=0.93$, $p=0.007$). There was no significant correlation between SIR and NO₂ ($r=0.41$, $p=0.41$), BaP ($r=0.56$, $p=0.24$), C6H6 ($r=0.79$, $p=0.2$).

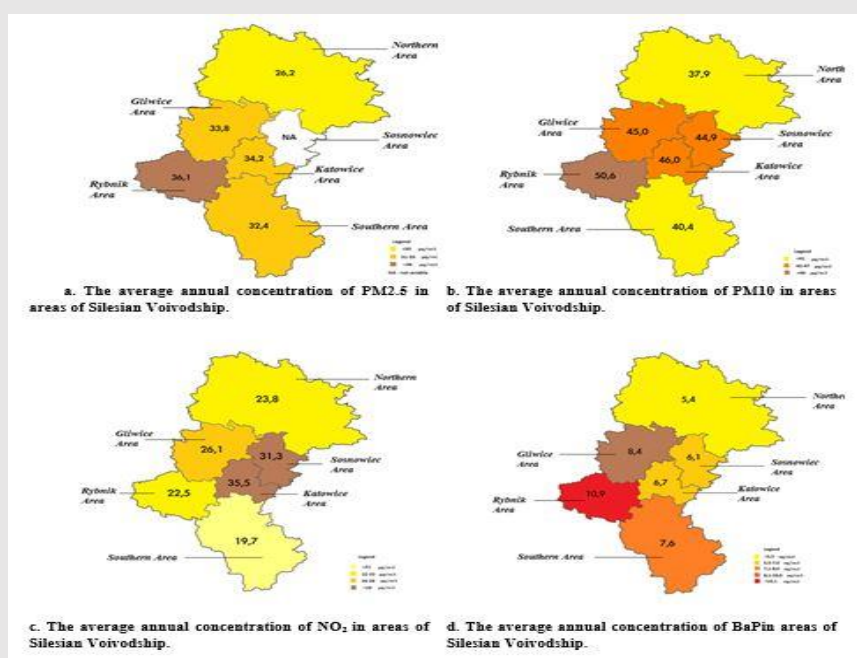


Figure 2: Average annual concentration.

Discussion

Air pollutants include nitrogen oxides, benzene, BaP and PM, a mixture of solid and liquid particles suspended in the air. PM consists of soot, smoke and ash particles, containing dioxins, furans, heavy metals and aromatic hydrocarbons [20]. According to current knowledge, it constitutes one of the greatest threats to human health of all pollutants. Reports from the EAA indicate that Poland is among the leading European countries in particulate matter concentrations [21].

PM_{2.5} fraction is transboundary dust that persists in the air for many weeks and can be transported even over a distance of 2500 km. PM_{2.5} particles enter the lungs and reach the alveoli and the bloodstream [22]. When inhaled, tiny dust particles are believed to reach the brain with blood. They cause oxidative stress, inflammatory response and direct genotoxic effect, leading to nerve cell damage and significantly impacting tumorigenesis. On the other hand, dust particles larger than PM_{2.5} do not pass through the epithelial barrier and thus cannot enter the bloodstream. However, they release soluble substances and metals, which may enter the gastrointestinal tract and lymphoid tissue in the respiratory tract secretion. Soluble toxins are believed to activate inflammatory pathways, whereas released cytokines and macrophages may impair the blood-brain barrier [23].

High concentrations of PM₁₀ and PM_{2.5}, which often exceed permissible limits during the Silesian region's heating period, mainly result from improper combustion (low emission) in household furnaces, which causes smog to form [24]. Detached houses in the Rybnik agglomeration are typically heated with poor-quality fuels.

Poland has as many as 19 of the 20 European cities with the highest BaP pollution. Whereas the World Health Organisation emphasizes that the mean annual BaP concentration should not exceed one ng/m³, the mean annual BaP concentration in the Rybnik area is 10.9 ng/m³ [25]. The International Agency for Research on Cancer (IARC) has designated BaP as one of the most dangerous carcinogenic compounds [26-28].

Road transport is the source of NO₂ emissions. The highest mean annual NO₂ concentration was recorded in the Katowice area, where the road infrastructure is the most developed in the entire region. There was no correlation between SIR and NO₂ concentration in our study.

The effect of air pollution on the development of cardiovascular and respiratory diseases has been well established. However, an increasing number of publications address the impact of environmental pollution on the human nervous system. In adults, the effect of air pollution on neurological disorders, such as Alzheimer's disease and Parkinson's disease, was demonstrated [29]. In children, air pollution was shown to be associated with an increased incidence of attention deficit and hyperactivity disorder, poorer emotional regulation and lower social skill level, as well as an increased incidence of autism spectrum disorder [30-32]. Furthermore, PM was shown to impair cognitive function, memory and verbal and performance IQ scores in children [33].

Based on unequivocal evidence to support the cause-and-effect relationship between exposure to particulate matter in polluted air and the increased risk of lung cancer, PM was classified by IARC in 2013 as a group I compound, which is known carcinogenic to humans [34]. The literature indicates that most research on the relationship between air pollution and cancers focused on lung cancer. On the other hand, the number of studies to determine associations between air pollution and other cancers is slightly lower. The most common study designs are experimental and cohort studies and meta-analyses. There are also reports to indicate the associations between air pollution and breast, prostate or hematopoietic malignancies [35,36].

Several studies describe air pollution-induced de novo brain tumor development of both benign and malignant tumors in adult population [37-39]. We demonstrated a correlation between the concentration of PM_{2.5} and PM₁₀ and the incidence of brain tumors in the studied geographical area. Previously, studies were carried out to determine the link between traffic intensity and cancer development, including CNS tumors, in children. Several studies have suggested an association between an increased incidence of brain tumors and public transport development [15,40]. To date, studies assessing the effect of air pollutants on CNS carcinogenesis were mainly carried out in the adult population. Our results, seem to be partially confirmed by the studies in both adult and animal experiments.

The underlying mechanisms of PM toxicity have been extensively studied recently. The generation of Reactive Oxygen Species (ROS) is an essential mechanism of nanotoxicity. ROS overproduction may induce oxidative stress. As a result, the cells fail to retain their physiological redox-regulated functions. This leads to DNA damage, changes to cell mobility, dysregulated cellular signaling, cytotoxicity, apoptosis and malignant transformation [17]. Apolipoprotein E, a human lipoprotein, is produced by the liver, leukocytes and astrocytes in the brain. Recent studies suggest that the interaction of PM_{2.5} and apolipoprotein E may cause brain aging and accelerate the development of Alzheimer's disease [33].

In their experimental animal study, Ljubimova, et al., [29] demonstrated the effect of PM_{2.5}-10 on the expression of inflammatory pathway genes (IL13-R α 1 and IL16), the early growth response gene-2 (EGR-2) and the Ras-related C3 botulinum toxin substrate-1 gene (RAC-1). Following exposure to PM_{2.5}, Ding, et al., confirmed the overexpression of other genes such as CRCP (calcitonin gene-related peptide receptor component protein), BMP-2 (Bone Morphogenetic Protein-2), F2R (Coagulation Factor II Thrombin Receptor), IL10RB, MECOM (MDS-1 and EVI-1 complex locus), XCR-1 (X-C Motif Chemokine Receptor-1) and NCF-1 (Neutrophil Cytosolic Factor-1) with simultaneous decreased expression of MGLL (Monoglyceride Lipase) and MIF (Macrophage Migration Inhibitory Factor) [41]. The research has confirmed the association between IL-16 immunoreactivity and the incidence of astrocytoma [42]. In comparison, IL-13 plays a role in the development of glioblastoma multiforme [43]. Zhang, et al., demonstrated overexpression of BMP-2 in gliomas, especially in higher-grade tumors. Cai, et al., showed that IL10RB expression had prognostic significance in patients with glioblastoma. The above studies confirm the hypothesis that air pollution leads to the activation of inflammatory pathways, which may accelerate oncogenesis [44].

Particulate matter may also contain metals such as chromium, arsenic and nickel, all of which have an established carcinogenic effect. Chromium may cause lung, prostate, kidney, liver, gastric and pancreatic cancer [45]. The literature shows that chromium triggers overexpression of certain protooncogenes, such as c-Myc and Mdm2, with decreased expression of the p53 and p27 suppressor genes [14]. Arsenic similarly affects the expression of p53 [41]. We suspect that the metals present in PM may also increase the incidence of brain tumors in children. For example, MYC gene amplification was demonstrated in medulloblastoma (a common pediatric CNS malignancy), which correlated with a worse prognosis [46]. Furthermore, the TP53 tumor suppressor gene has recently been recognized as a prognostic marker in patients with medulloblastoma [47].

The European Study of Cohorts for Air Pollution Effects (ESCAPE), a large epidemiological study in 282,000 people with 12 cohorts from six European countries, showed a positive yet non-significant correlation between long-term exposure to PM_{2.5} and the incidence of malignant brain tumors in the adult population [2].

A child's brain, during neurodevelopment, is more susceptible to various carcinogenic factors. Hence CNS tumors are the second most common pediatric malignancy. It is believed that maternal exposure to airborne toxins may have a significant impact on the development of CNS tumors in children. Heck, et al., demonstrated a weak correlation between ependymoma and early exposure to air pollutants in the development of prenatal and early childhood (below one year of age) [18]. On the other hand, Jędrychowski, et al., showed that children of mothers, who were exposed to polluted air during pregnancy, had lower anthropometric parameters at birth as compared to controls and, most importantly, scored lower on the measures of IQ and neurodevelopmental tests at the age of 10 [22]. This confirms that PM permeates through the placenta and, consequently, antenatal exposure to environmental pollution may be associated with neurological disorders in the postnatal period.

In a study conducted from 2001-2009 in Texas (USA) in 1900 children with brain tumors showed an increased risk of astrocytoma in children exposed to hazardous air pollutants and PM compared to children exposed to low concentrations of these substances. There was a positive yet non-significant association between exposure to those harmful substances and medulloblastoma [11].

Jorgensen, et al., confirmed the effect of PM_{2.5} on the development of brain tumors in adults, particularly benign tumors and meningiomas, with no such effect of PM₁₀ [24]. On the other hand, our results show the strong impact of both PM_{2.5} and PM₁₀ on the increased incidence of CNS tumors in the pediatric population. The discrepant results may be due to different chemical compositions of particulate matter in other geographical areas. The PM from Central Europe has the highest content of carbon compounds and the PM North-Western Europe contains the most nitrates and sulfates; in Southern Europe, the PM has the highest mineral dust content [12].

The impact of air pollution on the pathogenesis of CNS tumors is debatable. Valberg, et al., showed no correlation between the incidence of brain cancer and its associated mortality in the

adult population and 30 air pollution parameters [46]. Similarly, McKean-Cowdin, et al., did not show an association between brain cancer mortality and airborne exposure to toxins [32]. A Danish cohort study demonstrated a correlation between the incidence of brain tumors in adults, exposure to higher concentrations of nitric oxide and living in high-traffic zones. Our results did not support the effect of nitric oxide and BaP on the increased incidence of CNS tumors in children [47-52]. Studies on individual toxins and pollutants often do not confirm their impact on CNS tumor development. On the other hand, research into the effects of particulate matter is more promising since particulate matter consists of multiple carcinogens, which are likely to act synergistically to activate molecular signaling pathways. Finally, it should be noted that in many cited works, the mean annual concentrations of PM and PAHs are much lower than in Poland.

Study Limitations

The study is a cross-sectional analysis. Our sample size was limited. There is a need to replicate the study in a larger sample. It may be difficult to compare our results with those of other researchers due to a different study design, research instrument, or sample selection. Assessing individual exposure based on monitoring data is associated with a high risk of estimation errors. Conclusion based on mean annual concentrations may not be sufficient to identify factors affecting the study participants' health unequivocally. However, in the case of long-term studies, a continuous measurement would be too expensive and labor-intensive. Therefore, the longer-term research in large cohorts typically uses the same method we utilized in our study. Furthermore, reports confirm that this method's measurements are accurate and represent personal exposure [19].

Conclusion

To sum up, our study of 460 children with CNS cancers from the Silesian region demonstrated that exposure to high concentrations of particulate matter might increase the risk of developing CNS cancers in children. Although experimental studies have shown the effect of air pollution on CNS cancer, data from clinical studies are contradictory. Therefore, further research is needed to verify these reports, especially in the pediatric population.

Author Contributions

Conceptualization: Katarzyna Musioł; Methodology: Katarzyna Kalata, Magdalena Mierzwa, Magdalena Pogodzińska, Monika Grelich, Weronika-Bulska-Będkowska; Formal analysis and investigation: Katarzyna Musioł, Katarzyna Kalata, Magdalena Mierzwa, Magdalena Pogodzińska, Monika Grelich, Weronika-Bulska-Będkowska; Writing - original draft preparation: Katarzyna Kalata, Magdalena Pogodzińska, Monika Grelich, Weronika-Bulska-

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Conflict of Interest

The authors declare that they have no conflict of interests.

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