Review Article

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Toxic Tides: Exploring the Link Between Environmental Pollution and Epilepsy

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ABSTRACT

Environmental pollution is a highly challenging global problem, and its impact on neurological disorders, including epilepsy, poses a significant threat to the worldwide healthcare system and economies. The most frequent pollutants which contaminate the air, water and soil are particulate matter ($PM_{2.5}$, PM_{10}), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), carbon monoxide (CO), ground-level ozone (O_3), heavy metals, pesticides, and industrial chemicals. Environmental pollution causes 6.7 million premature deaths annually, and 89% of fatalities occur in low-middle-income countries. About 68% of outdoor air pollution-related premature deaths were due to ischemic heart disease and strokes. Neurological disorders are increasingly recognized as significant causes of death and disability worldwide. Epilepsy is a chronic neurological disorder that affects 50 million people worldwide. However, its exact causal relationship with environmental pollution is still poorly understood. Therefore, this review examined the association between environmental pollutants and the incidence, prevalence, and progression of epilepsy and the pathophysiological mechanisms involved between air pollution and epilepsy. This review explores evidence from epidemiological and experimental studies, identifying the significant pollutants implicated in epilepsy and elucidating their neurotoxicity pathways.

Keywords: Environmental pollution, neurological diseases, Epilepsy.

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Introduction

Epilepsy is a chronic, noncommunicable, neurological disease that affects people of all ages. Worldwide, about 50 million people have epilepsy, and 80% are from the low-middle-income states. The premature death risk among people with epilepsy is three times higher than the general population.[1] The most recent literature highlights that the prevalence of epilepsy exceeds 60 million.[2]

Neurological diseases are the leading cause of the global burden of diseases and economies. Study published in Lancet Neurology reveals that since 1990, there has been a significant rise in the number of people with or dying from neurological diseases. In 2021, around 3.40 billion individuals had illnesses affecting the nervous system, equivalent to 43% of the global population. These conditions contributed to 443 million disability-adjusted life years (DALYs), making them a leading cause of disease burden worldwide.[3]

Neurological conditions disproportionately impact low-income and middle-income countries (LMICs). This difference is partly due to the higher prevalence of conditions affecting newborns and children under the age of 5 in LMICs. Generally, males are at a higher risk of neurological conditions than females. However, differences between conditions exist.[3]

Neurological diseases represent a significant burden, affecting millions worldwide and causing profound social and economic impacts. While genetic and lifestyle factors are well-recognized contributors, in recent decades, environmental exposures have gained recognition for their role in the onset and progression of these disorders. Ecological pollutants include "particulate matter ($PM_{2.5}$, PM_{10}), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), carbon monoxide (CO), and ground-level ozone (O_3)", heavy metals, pesticides, and industrial chemicals, have been implicated in neurotoxicity through oxidative stress, neuroinflammation, and blood-brain barrier (BBB)

disruption. This review systematically examines evidence linking environmental pollution with neurological diseases.[4]

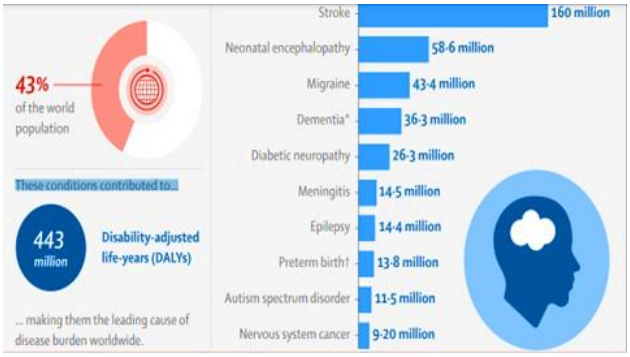

Figure 1. Global burden of conditions affecting the nervous system [The ten neurological conditions accounted for the greatest DALYs in 2021]. Adopted after permission from the GBD Collaborators study.[3]

Global Evidence: Air Pollution and Epilepsy

Epilepsy is a chronic neurological syndrome characterized by recurrent seizures; over 50 million people have epilepsy worldwide.[1] While genetic, metabolic, and traumatic factors are well-established contributors, emerging evidence suggests that environmental elements, including pollution, may play a significant role in the etiology and exacerbation of epilepsy. This review aims to synthesize current knowledge regarding ecological pollution and epilepsy, focusing on air, water, and soil contaminants.

The most frequently occurring air pollutants in the environment are "particulate matter ($PM_{2.5}$, PM_{10}), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), carbon monoxide (CO), and ground-level ozone (O_3)".[5] Global evidence has demonstrated the adverse effects of air pollution on the nervous system.[6,7] However, limited literature assessed the associations between air pollution and epilepsy.[8] The literature highlights that an increase in "air pollutants such as carbon monoxide (CO) and nitrogen dioxide (NO_2) was correlated with an increased admission of 2.0% and 1.1% for epilepsy, respectively".[9] The increased air pollutant levels of $PM_{2.5}$, PM_{10}, CO, NO_2, SO_2, and O_3 are risk factors for hospitalized patients with epilepsy.[10]

A significant association between air pollutants, carbon monoxide (CO) and epileptic seizure risks was observed, with an increased seizure risk of 4% of CO concentrations. The toxic impact was more significant among females, who had an increased risk of seizures when exposed to elevated CO and NO_2 levels. Exposure to high CO concentrations was linked with an increased risk of epileptic seizures.[11] The literature also demonstrated that air pollution was interrelated with neuroinflammation, which may be linked to neurodegenerative conditions[12] and epilepsy.[13,14]

Sharma et al.[15] found that $PM_{2.5}$, PM_{10}, NO_2, SO_2, CO, O_3, and daily mean ambient temperature were associated with seizure incidence and acute episodes of epilepsy. Similarly, Xu C et al reported that a 10 µg/m3 upsurge of "NO_2, SO_2, and O_3" linked to 3.17%; 4.93%, 3.55%, 5.18%, and -0.84% increases in outpatient-visits for epilepsy on the parallel days.[16] The impact of NO2 and SO_2 is more potent when adjusted for $PM_{2.5}$. The authors established a relationship between acute exposure to air pollution and epilepsy and found that NO_2 and SO_2 were associated with outpatient visits of patients with epilepsy.

Yang et al found that "$PM_{2.5}$, PM_{10}, and SO_2" are the leading air pollutants affecting many children.[17] These air pollutants cause convulsions in children. Moreover, an increase in the level of $PM_{2.5}$ in the air per month could increase the occurrence of convulsions in children. Similarly, Cheng et al reported a significant relationship between air pollutants and the rising risk of hospitalizations of children with epilepsy.[18] Each 10 µg/m^3 rise in "$PM_{2.5}$, $PM_{10\text{-}2.5}$, PM_{10}, SO_2, and NO_2" levels was allied with an increase of 1.1%, 1.7 %, 0.8 %, 8.5%, and 4.3% in epilepsy hospitalizations respectively. It was also concluded that short-term exposure to PM particles and gaseous was linked with an increased risk of epilepsy in children.

Antaya et al. reported that exposure to air pollution may increase the risk of seizures and new-onset epilepsy.[19] Specifically, ground-level ozone (O_3), nitrogen dioxide (NO_2), and carbon monoxide (CO) were associated with an elevated risk of seizures. The authors noted that short-term exposure to NO_2, CO, and O_3 may affect the risk of seizures; however, the impact estimates for O_3 and NO_2 were minimal. Epilepsy may also be linked to water and soil pollutants, including pesticides, through mechanisms such as increased oxidative stress and inflammation. However, there is limited literature available that clearly outlines the role of pesticides in the development of epilepsy.

Pesticides and Epilepsy

Pesticides are frequently used in modern agricultural systems, enabling the mass production of food by protecting crops from pests and diseases. However, their

extensive use has raised concerns about potential health risks, particularly neurological conditions. The association between pesticide exposure and epilepsy has gained attention in recent years. Requena et al. conducted a study and reported an increased risk of epilepsy among individuals living in areas with both high and low pesticide use. Their findings suggest that environmental exposure to pesticides may elevate the risk of developing epilepsy.[20] Similarly, Alarcón et al. found a significantly higher risk of epilepsy among farmers engaged in intensive agriculture (i.e., high-yield greenhouse crops) compared to those involved in extensive agriculture (i.e., open-air crops).[21] The risk was especially pronounced among farmers living in rural areas with high pesticide usage and among those who did not use protective measures such as gloves and face masks. Among pesticide sprayers, the highest risk of epilepsy was observed in individuals who did not wear face masks and lived in areas with intensive pesticide use.

Pathophysiology: How air pollution can cause epilepsy

The numerous types of air pollutants can enter the bloodstream and brain through the lungs and gastrointestinal system, altering the permeability of the blood-brain barrier.[8, 22, 23,24] Moreover, air pollutants can enter the brain through the olfactory nerve from the nose and circulate and deposit in various body organs.[8] Deposing air pollutants in the brain causes inflammation and oxidative stress, the primary mechanisms for the damage to the central nervous system induced by air pollution.[22] Brain inflammatory reactions can enhance neuronal excitability, impair cell survival, and alter the innate immune response.[24] These findings have indicated that brain inflammation can contribute to the occurrence of seizures.[25]

Moreover, air pollutants can cause "chronic mitochondrial oxidative stress, which results in dysfunction and have been implicated as contributing factors that render the brain more susceptible to epileptic seizures.[26] Inflammation and oxidative stress have also been identified as the main factors associated with epileptogenesis.[8,26] The complex nature of air pollution and the neurological effects of air pollutants result from the synergistic interaction of multiple pathways.[22] More research is required to establish the link between air pollutant exposures and the risk of epileptic seizures, which is critical for understanding and preventing epilepsy.

Table I: Mechanisms linking pollutants to epilepsy.[22-26]

- **Oxidative Stress:** The imbalance between reactive oxygen species and antioxidants damages the neurons.
- **Systemic inflammation:** Air, water and soil pollutants enter the body and are deposited in the various body organs, including the brain and can cause inflammation
- **Neurotoxicity:** Air, water, and soil pollutants can damage the neurons due to their toxicity.
- **Neuroinflammation:** Pollutants can cause neuroinflammation.
- **Endocrine Disruption:** Pollutants affect neural development and function and hormone regulation.
- **Hypoxia:** Exposure to carbon monoxide and NO2 can cause O2 deprivation and can cause seizures.

Conclusion

Exposure to air pollutants is associated with an increased risk of epileptic seizures; the findings indicate that air pollutant exposure could be a potential risk factor for epilepsy. The information gained from this review could have valuable clinical and public health implications. Environmental pollutants, such as $PM_{2.5}$, PM_{10}, NO_2, SO_2, CO, O_3, heavy metals, pesticides, and industrial chemicals, have been implicated in neurotoxicity and epilepsy. Environmental pollutants may trigger oxidative stress, systemic inflammation, disruption of the blood-brain barrier (BBB), and neuronal degradation. This study's findings could drive new potential approaches to reduce seizure risks by managing behaviour when pollutant levels are high or using air pollution-reducing policies to minimize the prevalence of epilepsy at regional and global levels.

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