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Brain Medicine

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EMERGING TOPIC

Air pollution: an emerging risk factor for autism spectrum disorder

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The global surge in air pollution poses an increasingly concerning environmental risk factor for neurodevelopmental disorders, particularly autism spectrum disorder (ASD). Recent epidemiological studies have revealed compelling associations between exposure to specific air pollutants, including fine particulate matter (PM), nitrogen oxides (NO, NO_2), sulfur dioxide (SO_2) and ozone (O_3), and increased ASD risk. While the rising global ASD prevalence, now affecting 1%–1.5% of the population, partially reflects expanded diagnostic criteria and enhanced screening, mounting evidence points to the critical role of gene–environment interactions in ASD etiology. Air pollutants can trigger multiple pathogenic mechanisms, including neuroinflammation, oxidative/nitrosative stress, epigenetic modifications, and glutamatergic/GABAergic neurotransmitter system disruption. The timing of exposure appears crucial, with heightened vulnerability during prenatal development and early childhood when critical neurodevelopmental processes, such as neuronal migration, synaptogenesis, and myelination occur. Research priorities should focus on how air pollutants affect brain development in genetically susceptible individuals, especially during pregnancy and early childhood. Better ways are needed to identify individuals at the highest risk and develop practical protective measures. Given the rising global pollution levels, this knowledge will help shape meaningful public health policies to protect future generations from environmental factors that may contribute to ASD.

Brain Medicine (2024), 1–4; doi: https://doi.org/10.61373/bm024e.0115; Published online: 12 November 2024.

Keywords: Air pollution, autism spectrum disorder, nitric oxide, neuroinflammation, oxidative stress

Air Pollutants Associated with Autism Spectrum Disorder

Air pollution comprises particulate matter (PM), carbon monoxide (CO), sulfur dioxide (SO_2), nitric oxide (NO), nitrogen dioxide (NO_2), ozone (O_3), and volatile compounds. A study in the United States, Israel, and Taiwan has shown that PM2.5 (airborne particles smaller than 2.5 μm in diameter), NO, and NO_2 are positively associated with the cause of autism (1). The study has also shown that the effect of pollutants depends on the exposure time for pregnant women or children of an early age.

One well-studied air pollutant is PM, including PM10 and PM2.5, the latter of which is particularly hazardous. These particles can enter the respiratory system and the bloodstream. They can also cross the placenta and affect the normal development of the fetal brain. Studies with PM10 have shown its high toxicity and ability to cause autism spectrum disorder (ASD) in pregnant women. Meanwhile, PM2.5 showed even deeper penetration and a more harmful effect during the preconception period, and it also posed an increased risk of ASD in newborns (2).

"NO" is a common air pollutant produced mainly by vehicle emissions and the combustion of fossil and industrial fuels. Exposure to NO and its derivative NO_2 during pregnancy and early childhood can disrupt normal brain development (1, 2). Recent breakthrough research has established the first direct link between nitric oxide and ASD pathogenesis (3, 4). The timing of its exposure is crucial. Exposure to these pollutants during pregnancy and early postnatal development poses a significant risk of ASD since these periods are essential for brain development, including neuronal migration and myelinization (5). Another hazardous factor is ozone. O_3 is a highly reactive oxygen gas. Ground-level O_3 is produced by a photochemical reaction between two significant classes of air pollutants: volatile organic compounds and nitrogen oxides. The study by McGuinn *et al.* has shown an association between O_3, PM2.5, and ASD (6). It has been found that O_3 and PM2.5 exposure during pregnancy and two first postnatal years has a strong association with the disorder (6).

Accumulated evidence has also revealed that SO_2 is a significant air pollutant produced by vehicles, the combustion of fossil fuels in power plants, and other sources. Studies have shown that exposure to SO_2 during a maternal period and the first 4 years of age increases the risk of ASD (7). Benzene is a volatile organic compound commonly found in vehicle emissions, industrial processes, and tobacco smoke. Maternal exposure to NO_2 and benzene during pregnancy can also increase the risk of ASD (8). Another study has shown that co-exposure to a few air pollutants like PM2.5 and SO_2 exert synergistic effects leading to neurodegeneration at low doses, including neuronal apoptosis, reduction of synaptic structural protein postsynaptic density (PSD-95) and synaptic functional protein *N*-methyl-D-aspartate (NMDA) receptor subunits (NR2B) (9). Figure 1 depicts the potential links between air pollution and ASD.

Potential Mechanisms by Which Air Pollutants can Cause ASD

Neuroinflammation and Oxidative/Nitrosative Stress

Neuroinflammation is widely recognized as a key risk factor in neurological disorders. During pregnancy, inhaled air pollutants like PM can induce a systemic inflammatory response in the fetus and cause neuroinflammation in the developing brain. With the blood–brain barrier immature, PM can directly enter the fetal brain, triggering inflammation in astrocytes and microglia. This would release proinflammatory cytokines and activate key inflammatory pathways, such as JNK and nuclear factor-kappa B (NF-κB) (10). Pollutants like NO_2 and PM2.5 can stimulate toll-like receptors (TLRs), particularly TLR4, directly (11) or through oxidative stress (12), inducing an immune response. This activation leads to downstream signaling involving NF-κB, a critical transcription factor modulating numerous inflammatory genes' expression. Chronic activation of NF-κB results in sustained inflammation and has been linked to neurodevelopmental disruptions by altering the balance of pro- and anti-inflammatory mediators in the brain (11). The mitogen-activated protein kinase (MAPK) signaling pathway is also highly responsive to environmental stressors like air pollutants. Exposure to PM2.5 can lead to the phosphorylation of extracellular signal-regulated kinase, part of the MAPK pathway, which is a crucial mediator of inflammation (13).

In the central nervous system, MAPK activation in microglia and astrocytes results in the secretion of proinflammatory cytokines like TNF-α

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Received: 12 October 2024. Revised: 1 November 2024 and 2 November 2024 and 4 November 2024. Accepted: 5 November 2024.

Figure 1. Illustration of the link between air pollution and ASD.

and IL-6, contributing to neuroinflammation and likely altering synaptic plasticity in regions implicated in ASD, such as the prefrontal cortex. These stresses can also imbalance the excitatory (glutamate) and inhibitory (gamma-aminobutyric acid [GABA]) neurotransmitter systems, a common occurrence in ASD (4). Studies have shown that air pollution-mediated oxidative stress has been linked to changes in neurotransmitter levels. The levels of the key neurotransmitters of the reward processing and motor function, dopamine and serotonin, can be diminished by air pollutants in the striatum (14) causing impairments of these functions, characteristic of ASD. Additionally, air pollution exposure has been tied to reductions in norepinephrine and dopamine in the prefrontal cortex, which may impair executive function and decision-making abilities (14).

Prolonged neuroinflammation triggered by NO exposure has been shown to influence the activity of brain regions involved in social and cognitive functions, which are commonly impaired in ASD (4). Exogenous NO and NO_2 can increase the brain's NO level, affecting the NO signaling pathways. Individuals with a genetic predisposition to ASD may be more vulnerable to the harmful effects of NO exposure. Thus, it has been found that mutations of genes involved in the detoxification of oxidative stress or regulating NO signaling may exacerbate the impact of environmental factors like air pollution, contributing to the development of ASD in genetically susceptible individuals (1).

Air pollution exposure during pregnancy can activate the mother's immune system, leading to inflammation and altered fetal brain development. Elevated concentrations of inflammation-related cytokines in maternal serum *in utero* and children during their early life are associated with worse neurodevelopmental outcomes (15). Maternal immune activation can lead to the release of different cytokines (e.g., IL-1b, IL-6, IL-10, and TNF-α), altering brain connectivity and resulting in ASD-like behavior in offspring (15, 16).

Epigenetic Modifications

Air pollution can cause epigenetic changes, such as DNA methylation and histone modification, that alter gene expression. These modifications can affect genes related to brain development and immune function, increasing the risk of ASD (17).

Glutamatergic and GABAergic Systems

Air pollution has been shown to affect neurotransmitter systems, including glutamate and GABA, which are crucial for neural signaling and synaptic plasticity (18). Studies have shown increased total frontal cortex glutamate, glutamine, and GABA levels in both sexes after postnatal exposure to air pollutants. They impact brain glutamate levels and affect developing and adult microglia with glutamate receptors, which can lead to glutamate release upon microglial activation (18). This release, in turn, activates microglia, creating a cycle that potentially drives chronic inflammation (18). Imbalances in the glutamatergic and GABAergic systems are commonly observed in individuals with ASD (4, 19). Air pollutants have been shown to disrupt the normal formation and pruning of synapses during early brain development, leading to altered brain circuits that are associated with ASD symptoms (18).

Endocrine Disruption

Some air pollutants, like PM2.5 and PM10, act as endocrine disruptors, affecting hormone levels critical for brain development (20). Disruptions in hormones such as estrogen and thyroid hormones during critical periods of brain development can lead to neurodevelopmental abnormalities, including ASD (20).

The Dysregulated Metabolic Pathways

Epidemiological studies have shown that air pollution exposure can cause dysregulated metabolic pathways and increase the risk of ASD (21). Metabolic disruptions in fatty acids, amino acids, neurotransmitters, and microbiome processes have been associated with both short- and long-term air pollution exposure, increasing the risk of ASD. Studying these metabolic dysfunctions offers insights into ASD etiology related to air pollution, particularly during the perinatal period when neurodevelopment is highly vulnerable to oxidative stress and inflammation (21).

Biomarkers of Air Pollution with High Risk to ASD

Biomarkers could have held promise for early ASD prevention by identifying individuals at high risk during prenatal or presymptomatic stages. This would enable early intervention to address neurodevelopmental abnormalities or avoid environmental triggers like exposure to air pollutants. To date, no studies have focused on biomarkers that specifically reflect the impact of the air pollutants that pose a risk of ASD (22). NO is both an endogenous signaling neurotransmitter and a pollution-related molecule. Dysregulation in NO signaling pathways has the potential to offer early biomarkers for ASD risk related to air pollution exposure. One such biomarker could be 3-nitrotyrosine, whose levels are increased in the blood plasma of ASD children as a result of nitrosative stress (23, 24). Changes in the blood balance of GABA and glutamate (19) and increased levels of IL-6 (22), as discussed above, can also indicate an early response to air pollution. Elevated expression of C-reactive protein during pregnancy appears to be significantly associated with neuroinflammation and an increased ASD risk in the offspring (25). Another possible marker is micronuclei. They indicate the presence of initial (and reversible) alterations in the chromosomal structure and oxidative damage to DNA caused by air pollution (26). Identifying a specific biomarker or a group of biomarkers may offer early indicators of ASD risk due to pollution exposure. The pathogenic mechanisms linking air pollutants to autism spectrum disorder risk factors are summarized in Figure 2.

Future Perspectives

Numerous studies clearly show that air pollution plays a significant role in ASD and should be considered among the emerging risk factors for this disorder. Yet, the mechanisms underlying the involvement of these factors in ASD pathogenesis are not fully understood (27–29). From this viewpoint, the relationships between air pollutants and ASD warrant further investigation. Since air pollution is a mixture of toxins, they have different biological effects on ASD development. Studying various air pollutants' cumulative/synergistic effects would be particularly interesting. The impact of air pollutants on neurogenesis and neuron development at different time windows is also essential. In the early prenatal stage (first and second trimester), neural stem cells proliferate to form neurons and glial cells. The mid-prenatal stage (second trimester) involves neuronal migration, where neurons drift to their designated place and form structures. Synaptogenesis occurs in late prenatal and early postnatal neuron differentiation (30). Air pollutants can affect neuron development, migration, differentiation, and synapse formation during these

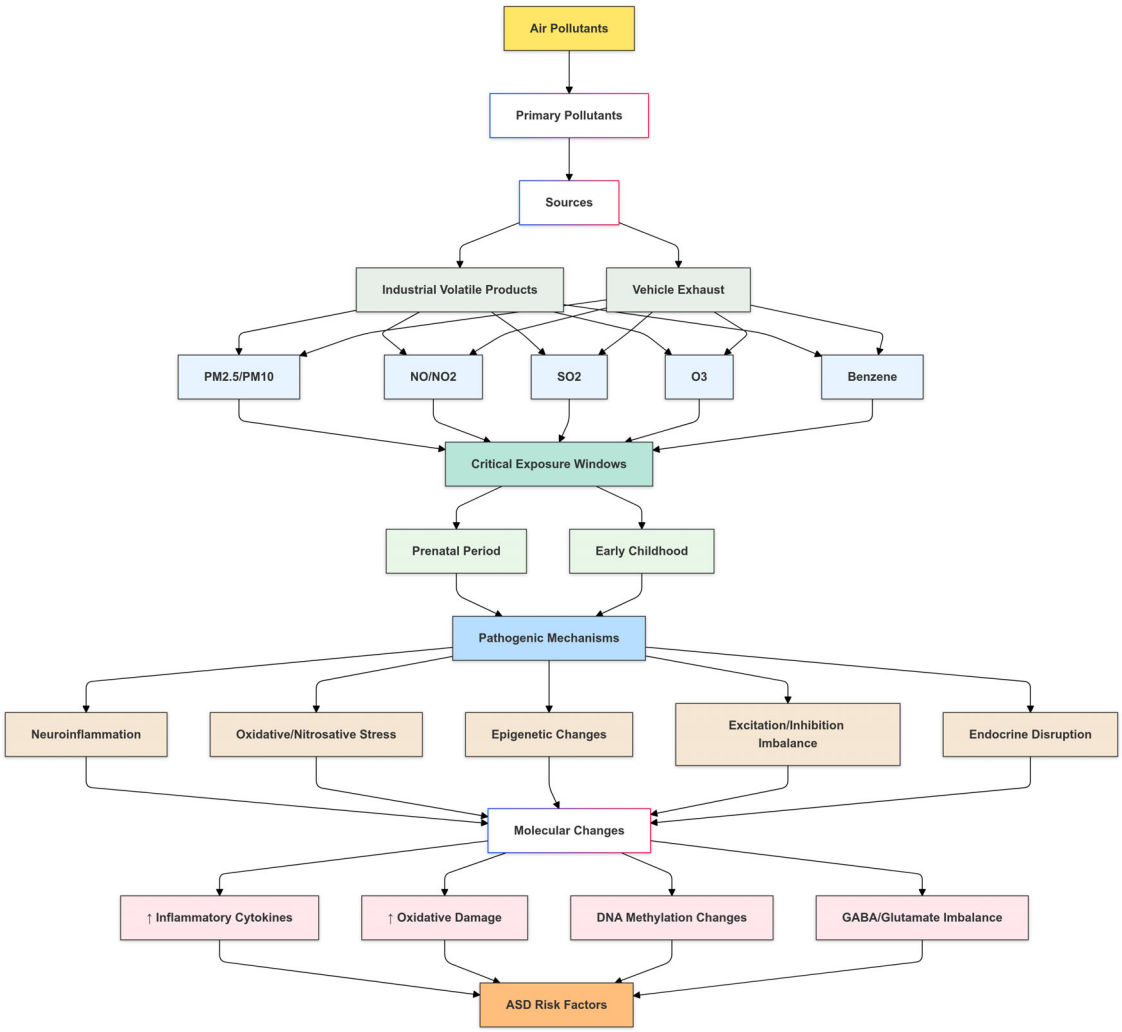

Figure 2. Molecular and cellular pathways linking air pollutants to ASD development. The diagram illustrates the complex cascade of biological events connecting environmental air pollutants to ASD risk factors. Beginning with primary pollutants from industrial and vehicular sources (shown in very light sage), the pathway traces how specific compounds including PM2.5/PM10, nitrogen oxides, sulfur dioxide, ozone, and benzene (highlighted in very light blue) influence neurodevelopment during critical exposure windows. The windows, emphasized in sage green, encompass both prenatal development and early childhood periods (very light green), during which the developing brain is particularly vulnerable. The diagram then reveals the intricate pathogenic mechanisms (medium light blue) triggered by these exposures, including neuroinflammation, oxidative/nitrosative stress, epigenetic modifications, excitation/inhibition imbalance, and endocrine disruption (shown in light ochre). These mechanisms converge to induce molecular changes that manifest as increased inflammatory cytokines, enhanced oxidative damage, DNA methylation alterations, and GABA/glutamate imbalance (depicted in soft pink). The bright yellow header emphasizes the primary air pollutants, while the soft orange endpoint highlights the culmination in ASD risk factors, creating a visual progression from environmental exposure to neurobiological impact. The color-coded framework helps track the progression from external environmental factors through biological mechanisms to clinical outcomes, emphasizing the multifaceted nature of pollution-induced neurodevelopmental disruption.

time windows. Air pollutants in postnatal or childhood periods can also affect synaptic pruning, impair glial function, and cause neuroinflammation (10, 18).

Different confounding factors should be considered while studying the link between air pollutants and ASD. These factors may include microbiome, nutrition, financial state, education level, social aspects, and workplaces. Lifestyle factors, such as active and passive smoking in pregnancy, also need to be taken into account. They could be potent factors for ASD pathogenesis. It is also essential to consider the place of residence and socioeconomic position, as poorer neighborhoods are likely to experience more pollution, higher vulnerability to these factors, and a higher risk of ASD (26). Avoiding exposure to the above-mentioned environmental risk factors could prevent a considerable number of ASD cases. Ultimately, mitigating harmful environmental exposures, especially during pregnancy, could play a crucial role in preventing nongenetic cases of ASD and improving public health outcomes.

Acknowledgments

We thank Dr. Igor Khaliulin and Ms. Maryam Kartawy for contributing to the discussion of this study, as well as the Satell Family Foundation and the Neubauer Family Foundation for their support.

Authors Contributions

SKO wrote a draft and contributed to the discussion. HA was responsible for ideation, project execution, and supervision.

Funding Sources

This work was funded by a U.S. Department of Defense (DoD) grant, a DFG—German Research Foundation Grant, an Israeli Science Foundation (ISF) grant, an Eagles Autism Foundation grant, a California Institute for Regenerative Medicine grant, a National Institute of Psychobiology in Israel (NIPI) grant, an Israeli Council for Higher Education Maof Grant, and a Berettler Centre for Research in Molecular Pharmacology and Therapeutics Grant.

Author Disclosures

HA is a CSO of Point6 Bio and Neuro-NOS. No funds from either of those two companies were received for this study. SKO does not hold any competing interests.

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