ISSN- 0301-1216
Indian J. Prev. Soc. Med. Vol. 53, No.2, 2022

EDITORIAL

Ambient Air Pollution Exposure & Attention-deficit/ hyperactivity disorder (ADHD) in Children

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Air Pollution – An Overview

Air pollution regarded as **"one of the great killers of our time"**, has responsible for **6.4 million deaths** worldwide in 2015, 2.8 million of which were caused by household air pollution and 4.2 million by ambient air pollution. In India, air pollution caused **1.67 million fatalities** (95 percent CI 1.42–1.92) in 2019, accounting for **17%** (15.8–19.5) of all deaths. In the same year, air pollution was responsible for **11.5%** of total DALYs in India, with ambient particulate matter pollution accounting for the majority (6.7% [5.3–8.0])[1].

Although we measure the levels of only six pollutants to assess ambient air quality, there are ample of other pollutants too. Some gaps do exist in measurement of pollutant levels. For example, PM is typically classified by its aerodynamic diameter: PM_{10} is made up of particles 10 microns (μ) in diameter, while $PM_{2.5}$ is made up of particles 2.5 μ in diameter. PM with a diameter of 2.5 to 10 μ is considered "coarse," while PM with a diameter of less than 2.5 μ is considered "fine." Ultrafine PM (UFPM or $PM_{0.1}$, with a diameter of less than 100 nm) is extremely important, especially in terms of neurotoxicity. It is vital to note that PM_{10} refers to all particles with a diameter of less than 10 μ and so includes coarse, fine, and ultrafine PM fractions. Only $PM_{2.5}$ and PM_{10} are monitored, meanwhile, $PM_{0.1}$ is not. It's worth noting that the existing limits are "**mass-based**," which means that UFPM's contribution to total PM could be insignificant. Given the increasing body of data regarding UFPM neurotoxicity, including neurodevelopmental and neurological problems[2], future $PM_{0.1}$ regulation should investigate alternatives to mass-based techniques, such as one based on particle number[3].

Air Pollution & Neurotoxicity

A New Research Dawn?: Recent evidence suggests that, in addition to causing respiratory and cardiovascular diseases, air pollution may also have a negative impact on the brain and make a significant contribution to neurodevelopmental and neurodegenerative disorders[4]. In this regard, $PM_{2.5}$ and Ultrafine particulate matter (UFPM) are of particular concern because they can enter the circulation and distribute to various organs, including the brain, in addition to gaining direct access to the brain via the nasal olfactory mucosa[3].

Basic Mechanisms underlying air pollution neurotoxicity: Microglia activation, oxidative stress, and neuroinflammation caused by air pollutants in the CNS are thought to be causally associated with air pollution-induced neurotoxicity[4–6]. Oxidative and inflammatory responses in the CNS have been observed in vivo in animals[7–9], in vitro systems[9–12], and to a lesser extent in humans[5,6,13] after exposure to air pollution. Children with neurodevelopmental disorders have higher levels of neuroinflammation and systemic inflammation, both of which are associated with traffic-related air pollution[5].

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Submission	10.04.2022	Revision	12.05.2022	Accepted	16.06.2022	Printing	29.06.2022

***Prior Publication*: Nil*; Source of Funding:* Nil; *Conflicts of Interest*: None**

Why children are more vulnerable?

Children may be more vulnerable to neurologic injury from air pollution because their brains are still developing[14] and they have fewer established natural barriers in the lungs to protect against inhaled particles. The proper development of natural barriers such as the blood-brain barrier, nasal, gut, and lung epitheliums is critical for a child's healthy development. These barriers have been shown to be compromised in young urbanites exposed to air pollution, reducing the brain's ability to protect itself from potentially harmful toxicants/particles. Furthermore, children have a higher breathing rate-to-body size ratio and spend more time outside than adults. These factors, in particular, raise a child's risk of exposure to air pollution, especially taking into account that not only are a child's organs developing but so are their sanitary behaviours in relation to their environment. A child may be unaware of a potentially dangerous environment, and increased hand-face-mouth contact may increase the likelihood of ingesting/inhaling environmental toxins[15].

Neurodevelopmental disorders & Air Pollution – Focus on Attention deficit/hyperactivity disorder (ADHD) : Epidemiology has helped us understand the relationship between environmental risk factors and ADHD. Indeed, numerous epidemiological studies have focused on the role that exposure to environmental pollution plays in the development of ADHD. For example, prenatal or postnatal lead exposure in children, as well as polycyclic aromatic hydrocarbons and second-hand smoke exposure, have been linked to ADHD symptoms[16].

ADHD is a neurodevelopmental psychiatric condition that affects approximately 5% of children and adolescents and 2.5 percent of adults worldwide[17]. ADHD is frequently persistent and significantly disabling, increasing the likelihood of negative consequences such as injuries, traffic accidents, higher health-care utilization, substance abuse, criminality, unemployment, divorce, suicide; AIDS risk behaviours, and premature mortality. Genetic and environmental risk factors that influence the structure and functional capacity of brain networks involved in behaviour and cognition have been implicated in the genesis of ADHD in epidemiologic and clinical investigations[18].

Although many studies have addressed the relation between air pollution & attention disorders, their number is not huge. In the same time those studies do have contradictory findings. To start with the list, a study by Perera et al 2012 found out that high prenatal PAH exposure, as measured by personal air monitoring or maternal and cord white blood cell DNA adducts, was linked to symptoms of Anxiety/Depression and Attention Problems (DSM-IV) (p 0.05)[19].

Perera et al (2018) evaluated the combined effects of prenatal PAH exposure and prenatal/childhood material hardship (socioeconomic disadvantage) on ADHD behaviour problems. The association between prenatal PAH exposure & material hardship were not significant. When comparing children with high prenatal PAH exposure and either persistent hardship or any hardship to the others, they found significant differences in the number of ADHD symptoms. These differences were more pronounced when high PAH and persistent hardship were combined [ADHD Index (p=0.008), DSM-IV Inattentive (p=0.006), DSM-IV Hyperactive Impulsive problems (p=0.033), and DSM-IV Index Total (p=0.009)]. These findings warrant multifaceted interventions to safeguard mother & children[20].

While both the above-mentioned studies exposed the association between prenatal PAH exposure & attention disorder, Abid et al concluded that there were no consistent specific pattern of associations found between urinary PAH metabolites & neurodevelopmental disorders[21]. There are many tests & checklists to assess the attention issues of children. Chiu et al utilised Conner's Continuous Performance Test (CPT) which measures omission and commission errors as well as hit reaction time (HRT), with higher scores indicating more errors or a slower reaction time. Same study stated that there were associations between traffic related black carbon (BC) exposure and higher commission errors and slower reaction time. These associations were overall more apparent in boys than girls[22].

Thygesen et al stated that early childhood exposure to NO_2 and $PM_{2.5}$ was associated with a significantly increased risk of ADHD [IRR of 1.38 (Cl: 1.35 to 1.42)] per 10 g/m^3 increase in NO_2 and [IRR of 1.51 (Cl: 1.40 to 1.62)] per 5 g/m^3 increase in $PM_{2.5}$. In two-pollutant model, the association between NO_2 and ADHD remained unchanged, while the association with $PM_{2.5}$ was significantly reduced [(IRR 1.07; 95 percent CI: 0.98 to 1.16)]. But again, greater association with $PM_{2.5}$ was found at lower levels of NO_2. These findings of a strong relationship between $PM_{2.5}$ and ADHD only when NO_2 levels were low supports the hypothesis that different types or sources of $PM_{2.5}$ may have different biological effects[23].

In a cohort study conducted by Newman et al found out that after adjustment, exposure to the highest tertile of elemental carbon attributed to traffic (ECAT) [a surrogate for traffic related air pollution] during the child's first year of life was significantly associated with Hyperactivity T-scores in the "at risk" range at 7 years of age [aOR = 1.7; 95 percent CI: 1.0, 2.7], which was restricted to children whose mothers had more than a high school education. A point to be noted is the Hyperactivity, Attention Problems, Aggression, Conduct Problems, and Atypicality subscales were used to assess ADHD symptoms[24].

Mortamais et al stated explored the relationship between PAH exposure & ADHD in primary school children. Exposure to PAH, especially to benzo[a]pyrene (BPA) even at levels lower than the legislative limit was related with subclinical changes in caudate nucleus. ADHD symptoms and inattentiveness were more common in children who had been exposed to more BPA, but these associations were not statistically significant[25].

A cross-sectional study was conducted by Siddique et al involving two groups of childhood population actually calculated the prevalence of ADHD and its risk factors in both the groups. ADHD was diagnosed in 11.0 % of urban children versus 2.7 % of the control group (p 0.001). Male gender, lower socioeconomic status, 12–14 year age group, and PM_{10} level in breathing air were major risk factors. ADHD was more common in boys in both urban and rural areas. It was found in 18.0 % of the boys and 4.0 % of the girls enrolled in Delhi, for a male/female ratio of 4.5:1. The inattentive type of ADHD was the most common, followed by the hyperactive–impulsive type and the combined type of ADHD. Controlling for potential confounders, ambient PM_{10} level was associated with ADHD (OR = 2.07; 95% CI, 1.08–3.99). According to the above findings, there may be a link between air pollution and behavioural problems in children. Though gender, socioeconomic status, and age all play a role in ADHD prevalence, the link between particulate pollution and ADHD prevalence is the strongest[26].

Min and Min et al, in a cohort study stated that ADHD was diagnosed in 314 people over the research period (3.5 percent). The hazard ratios (HRs) [after adjusting for gender, metropolitan area, income, and history of disease] of childhood ADHD increased by 1 g/m^3 of air pollutants and were 1.18 (95 percent CI: 1.15–1.21) in the case of PM_{10} and 1.03 (95 percent CI: 1.02–1.04) in the case of NO_2. Those with the greatest tertile of PM_{10} (HR = 3.88; 95 percent CI: 2.87–5.23) or NO_2 (HR = 2.10; 95 percent CI: 1.54–2.85) exposure had a 2-to-3-fold greater risk of ADHD compared to those with the lowest tertile of PM_{10} or NO_2 exposure[27].

Conclusion

As air pollution is emerging public health problem of international concern, it becomes mandatory to explore and reveal all it's dimensions through extensive research filling all the knowledge gaps. Respiratory & Cardiovascular effects of air pollution is well established as mentioned in this editorial before, now it becomes necessary to interpret other uncovered effects such as neurotoxicity (both neuro-developmental & neurodegenerative disorders) etc of pollutants. Although in this editorial we have reviewed some major studies exploring the relation between air pollution & ADHD, all those studies do not provide homogenous results. These contradictory findings warrant more extensive research to exclude all possible confounders and biases. Causal association between air pollution and neuro-developmental disorders

including ADHD are still yet to be proved. Aim of this short review was to implicit the necessity of further research in the above mentioned domain. It reflects the uncertainty & gaps in the existing literatures, which might lay a foundation for further research.

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Citation: Kumar P, Ahmad S, KG Naveen. Ambient Air Pollution Exposure and Attention-deficit/ hyperactivity disorder (ADHD) in Children. Indian J Prev Soc Med, 2022; **53 (2): 73-77**.