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Opinion

Air Pollution Cause Mental Retardation in Children: Epigenetic Modification, DNA Methylation and MicroRNAs

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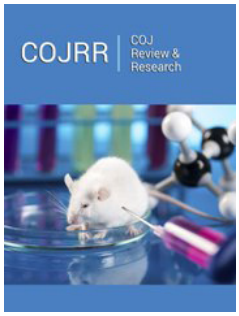

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Opinion

Air pollution is an emerging burden of environmental health issues across the world. To date, several lines of study highlighted the impact of air pollution with human health and diseases: Cardiovascular diseases, liver damage, kidney damage, and respiratory diseases. Air pollution is the presence of substances or chemicals released into the atmosphere that can harm and deter human health and other living things [1, 2]. There are many different types of air pollutants such as particulates, gases, and biological molecules. It is known that air pollution is directly linked to cardiovascular and respiratory health problems and diseases Siddique [3]. However, there is still debating the premise that air pollution can also harm the Central Nervous System (CNS) and cause impairments to the function and structure of the brain. Health intervention like Poor air quality can cause issues short -term and long-term health effects in elderly citizens and children. The World Health Organization (WHO) estimates that 9 out of 10 people across the world are exposed to high levels of air pollution outside which are emitted during emission of fossil fuels in cars, power plants and many industrial processes [4]. There is plenty of research in mental health and air pollution in adults, however, research conducted during the early development of childhood and adolescence is rare. Interestingly, it was reported that adolescents and young children are affected the most by air pollution [5]. Aspects of organ sensitivity following exposure of air pollution in children, it was postulated that the heart, immune system, lungs and developing brain are vulnerable. At birth, the growth rate of the brain is highest and continues to develop throughout childhood which plays an important role in the child's attention span, behavior, and memory [6]. This may result in risk of neurodegenerative diseases later in life. Increasing concern indicates air pollution affects health interaction between maternal and fetus during pregnancy which is influenced by unexpected delivery outcomes.

The global burden of disease attributed 4.2 million deaths and 103 million disability-adjusted life-years to PM_{10} and $PM_{2.5}$. Ischemic heart disease, lower respiratory infections, chronic obstructive pulmonary disease, lung cancer, and cerebrovascular disease are the main diseases attributed to PM with evidence of associations between air pollutants and reproductive, metabolic, respiratory, and neurological/mental health disorders suggesting that the societal impact of air pollutants may be higher than estimated [7-9].

Recent investigations indicate that coincidences of non-accidental deaths attributable to exposure to PM are higher than identified before. In addition, it is suggested that the spatial variation in health impacts could be attributed to the differences in composition. Potential drivers for health effects of particulate matter are the characteristics such as

surface area, presence of transition metals, oxidative potential, and mass concentration. Moreover, the potential translocation of the nanoparticles to the systemic circulation and brain, and the pathological effects produced in the brain following chronic exposure to particles result in important findings that support the dangers of nanoparticles on brain health. The PM can translocate from the lungs to the systemic circulation, and directly interact with extra-pulmonary cells and tissues including the brain depending on their size and chemical composition. As a result, some studies have identified the alterations in the brain following acute and repeated exposure to such effects. The PM can affect the brain through indirect processes, such as peripheral oxidative stress and inflammation, or pulmonary neuronal afferents that explain cardiovascular impacts. The repeated exposure to air pollutants including PM raises the oxidative stress and cytokine production in the brain with impacts on neurotransmitters, neuronal morphology, markers of neurodegenerative disease, altered cognition like mood disorder and psychiatry illness, and depressive-like behaviors including respiratory interventions. As indicated previously, adverse outcomes of particulate matter include impaired cognitive performance, dementia, anxiety, depression, and suicide [4,6,10-12].

Mental illness is defined as the changes in pattern of a person's feeling, thinking, and behavior that can disrupt a person's ability to function [13]. Mental health among adolescents and children is serious because it affects the way children learn and behave. It can be difficult to understand and recognize mental health symptoms in children because they sometimes cannot explain the way they feel. Common mental disorders that affect children include Tourette Syndrome, Conduct Disorder, Attention- Deficit/ Hyperactivity Disorder (ADHD), anxiety, autism, and Post Traumatic Stress Disorder (PTSD) which can affect their ability to function at school and home. Warning signs that may suggest the children have mental health disorder include difficulty sleeping, difficulty concentrating, outbursts of extreme irritability and withdrawing from social interactions [14]. Mental illnesses such as schizophrenia and bipolar disorder are caused by genetic risk factors. Genetics can affect the majority of the phenotypic variation in mental disorders; however, it cannot take full account. There have also been few studies that explored the links between mental illnesses and the physical environment, despite the rising concern about the adverse health effects due to air pollution. This raises a possibility that air quality may have a role in mental health and illnesses [8,15].

Emerging evidence support relationship of health risk between prenatal exposure to outdoor air pollution with childhood cardiovascular and respiratory diseases. Epigenomics suggests that there is an association with air pollution and mental health outcomes. For example, a study revealed that a type of epigenetic mark called DNA methylation has been observed in adults' blood levels when exposed to indoor fuel exposure [15]. Translational studies showed that air pollutant, ultra-fine particulate matter $PM_{2.5}$, increases the risk of diseases in both adults and infants. One study demonstrated they conducted pregnant rats who were exposed to high levels of $PM_{2.5}$ for a set period after collecting biological samples and then it was observed that the exposure increased immune cells in the mother rats while free radicals were accumulated in the amniotic fluid and affected the fetuses indirectly. As a consequence, they found the exposure of $PM_{2.5}$ cause gene alteration with microRNAs expression: exposure of $PM_{2.5}$ increased miRNAs likely miR-3560 (MIMAT0017829), let 7b-5p (MIMAT0006152), which regulate gene expression of Oxct1(3-oxoacid CoA-transferase 1; Chromosome 5, NC_000005.10 human), a homodimer mitochondria matrix enzyme, and Lin 28b (lin-28 homolog B; Chromosome 6, NC_000006.12 human) in which they are responsible cellular function like neurogenesis, glycosylation, neuronal cell differentiation and cellular transformation in hippocampal tissue, respectively. Also, it decreased the expression of microRNA (miR) species such as let-7e-5p (Accession number MIMAT0006155, miRbase) and miR-338-5p (Accession number MIMAT0006277 miRbase) which are related to mental development. Furthermore, MiR-92b-5p (Accession number MIMAT0026810, miRbase) and miR-99a-5p (Accession number MIMAT0002410, miRbase) those which regulate gene expression such as kbtbd8 (kelch repeat and BTB domain containing 8; Chromosome 3, NC_000003.12 human), Adam 11 (a disintegrin and metallopeptidase domain 11;Chromosome 11, NC_000077.7 human) by decreasing which was responsible in the cell mitosis, migration, differentiation, and affected the motor coordination and learning abilities of the fetus [16]. In line with these findings, several human studies explored the effects of prenatal exposure to air pollutants including $PM_{2.5}$, PM_{10} including black carbons, sulfates or PAH, which may contain nitrogen dioxide (NO_2) interact epigenetic level (i.e., generation of microRNAs, histone modification, and DNA methylation) and the genome expressed altered by decreased methylation at the protein coding of L1TD1 (LINE1 type transposase domain containing 1; Chromosome 1, NC_000001.11 human) repetitive elements [17]. In previous studies, they conducted using the genome wide DNA methylation data to explore the associations between cord blood and placenta DNA methylation with air pollutant exposures to NO2 and O3 and further assess epigenetic alteration across the observed tissues. It suggests that gene alteration like epigenomics aspects may one potential link to impact of air pollution to adverse health conditions associated regulatory effect of DNA methylation in prenatal and fetal [18,19]. It is supposed that air pollutants might affect our brains and central nervous system through the neuroinflammatory pathways.

Recently, scientists are willing to challenge the development of a method of detection to easily screen pregnant women for harmful air pollutants linked to childhood development disorders and illnesses using take advantage of omics molecular tools. They explore potential biomarkers that were used to predict, monitor, and surveillance systematic interpretation referring to risk and public action in chronic illness through environmental pollutants. Pollutants are vital contributors to serious and chronic pathologies with significant societal and economic costs. Usually, measuring the environmental component assumes uncertain assessments than measuring the genome. Recently, the exposome concept has

developed into a workable approach for epidemiological research that includes accurate and reliable measurement of many exposures in the external environment, the measurement of a wide range of biological responses in the internal environment, and addressing the dynamic, life-course nature of the exposome. To address such challenges, new tools and technologies such as exposure biomarker, mapping remote sensing, smart phone applications, high-throughput molecular 'omics' techniques and frameworks are used. These tools provide improvement and integration of the scattered and uncertain data on the environmental component in disease etiology, for better understanding of risk factor role to better implement primary prevention strategies [20].

To unveil genomics interaction, Genome-scale DNA measurements were collected for specimens including 175 cord blood samples and 133 placenta samples by using the Infinium Human Methylation 450k platform. Outcome indicated that Air pollutants NO_2 and O_3 exposure levels were based on the residence location of the pregnant women involved in the study. Similarly, to identify the methylated regions that are associated with the prenatal pollutant exposures mentioned above, another group created a technique called bump hunting that was used to identify the difference of sensitivity following pollutants exposures in each tissue and gender difference Ladd-Acosta [13]. Based on the consequence, it was found that there were locus specific changes in DNA methylation in association with the prenatal exposure to NOX and O_3 in tissues that were developmentally relevant. Infants with increased prenatal O_3 exposure had lower levels of DNA methylation Ladd-Acosta [13]. It was identified that there were 6 differentially methylated regions associated with prenatal NO_2 exposure. Differentially methylated regions that were detected in cord blood samples had a consistency in the exposure changes with respect to DNA methylation in the placenta. However, the differentially methylated region that was detected at first in the placenta did not show DNA methylation differences in the cord blood. It indicated that they appear to be tissue specific or tissue tropism. In addition, through the study and its outcome adopted by new approaches like Stratified bump hunting analyses, they determined successfully whether gender plays a role in the epigenetic responses to prenatal air pollutant exposure. In female infants, increasing levels of NO_2 exposure in the mother showed decreased DNA methylation levels in cord blood at the CYP2E1 locus [13]. In contrast, other groups reported the results were the opposite in males subject Tao [12].

Children who were exposed to high levels of air pollutants exposure experienced greater mental disorders at the transition to adulthood. In addition, emerging proof-of -evidence suggests that poor air quality including particular matters can affect an individual's central nervous system and mental health. Pregnant women who lived in disadvantageous neighborhood conditions due to health injustice were associated with higher pollution exposure and a greater risk of developing mental health illness for their children. The locus specific changes in DNA methylation were identified and showed to be related to air pollution and prenatal exposure. The study also demonstrated whether the effects on DNA methylation differed by sex. In females, the differences in cord blood methylation took place at the CYP2E1 locus for NO_2 only. The development of biomarkers to assess severity of air pollution to mental health, such as DNA methylation could help monitor and implement surveillance in both pregnant women and children's health who are at high risk of mental health disorders and prevent it at early detection. It was reported earlier that exposure to the CNS is the most vulnerable feasibility represented as the effects of air pollution [3,15]. There is a suspected relationship between long-term exposure to ambient air pollution and mental health. Relevant disorders are subjective stress, depressive disorders, health-related quality of life (QoL), and suicide. The mental disorders risk using multiple logistic regression analysis depends on the quartiles of air pollutants such as PM_{10}. High concentrations of PM10 are associated with the prevalence of high stress, poor QoL, depressiveness, and suicidal ideation. Men appear to be affected by the increased risk of stress, poor QoL, and depressiveness from air pollution exposure more than are women. Long-term exposure to ambient air pollution may be an independent risk factor for mental health disorders ranging from subjective stress to suicidal ideation Shin et al. [21]. There is no linear correlation between the mental health disorders risk and the concentration of air pollutants. This is because of the threshold effect at low levels of air pollutants. if the concentration increases above the cut-off value, it may affect significantly. There is a strong relationship between air pollution above the cut-off value and other mental health status parameters. The Findings show the ratios at the confidence level of 95% of a mental health disorder according to the air pollutant quartile [21].

In the future, it is worth to reach the value of preventive strategy in terms of risk management in both animal model and clinical data combined with retrospective studies using clinical samples including cross-sectional in molecular oriented epidemiological study using molecular connectivity could be beneficial to ensure biomarker relevance to fine chemical exposure have been conducted among adults which makes it harder to determine the effects of pollution on the central nervous system during the adolescent stage. This is important for implemental surveillance in preventive action because the neurodevelopment process is unclear to exposure of pollutants and when it begins molecular alteration with pathological changes in the brain during the prenatal period and continues into adulthood. Increasing evidence direct scientists were able to measure DNA methylation for the genome scale, however, it does not measure the methylation at every present site and demanded to determine polymorphism of target gene moiety in chromosomal level. Future studies may focus deeper and extensively into the epigenetic modification like methylation and gene regulatory pathway using microRNA pathway for the whole genome is needed to fully show the effects and methylation changes and regulatory network that is linked to prenatal air pollution exposure.

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