Air pollution and neurological development in children

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ABBREVIATIONS

ADHD	Attention-deficit/hyperactivity disorder
ASD	Autism spectrum disorder
PAH	Polyaromatic hydrocarbon
$PM_{2.5}$	Particulate matter with aerodynamic diameter less than 2.5μm
PM_{10}	Particulate matter with aerodynamic diameter less than 10μm
WHO	World Health Organization

Pregnancy and early childhood are periods with high plasticity in neurological development. Environmental perturbations during these sensitive windows can have lifelong developmental consequences. This review summarizes key findings relevant to the effects of air pollution on neurological development. Mounting evidence suggests that exposure to air pollution, both during pregnancy and childhood, is associated with childhood developmental outcomes ranging from changes in brain structures to subclinical deficits in developmental test scores, and, ultimately, developmental disorders such as attention-deficit/hyperactivity disorders or autism spectrum disorders. Although the biological mechanisms of effects remain to be elucidated, multiple pathways are probably involved and include oxidative stress, inflammation, and/or endocrine disruption. Given the alarming global increase in developmental disorders in recent years, and increased human exposures to pollution, it is critical to reduce personal and community-level exposures through tight collaboration of interdisciplinary and multi-level bodies including community partners, physicians, industry partners, policy makers, public health practitioners, and researchers.

Clean air is critical for health and well-being for people of all ages. The World Health Organization (WHO) estimates that more than 90% of the world's population lives in areas where air pollution levels exceed ambient air quality recommendations.[1] There is unequivocal evidence showing that air pollution affects nearly all vital body organs and is associated with multiple health complications across the lifespan, ranging from relatively minor acute symptoms such as headache and respiratory irritation to serious conditions such as chronic respiratory diseases, cardiovascular events such as stroke and myocardial infarction, cancer, and even premature death.[2] Air pollution is currently the fifth largest contributor to the global disease burden and is responsible for 4.2 million premature deaths and more than 103 million disability-adjusted life-years lost each year.[3]

Pediatric populations are particularly vulnerable to air pollution because of their underdeveloped natural defense mechanisms (e.g. blood–brain barrier, immune system), higher ratio of breathing rate to body size, and less awareness of the conditions of their surrounding environment. As the global prevalence of neurological developmental disorders has been increasing at an alarming rate in recent years, it is timely and important to evaluate whether air pollution contributes to developmental risks.[4] Typical brain development is a complex process that involves controlled cell proliferation, neuronal migration, myelination, and the establishment of specific neuronal connections. These complicated and tightly regulated events are sensitive to environmental conditions, especially during periods of rapid brain growth and high neuroplasticity such as pregnancy and early childhood. However, as most existing studies on the health effects of air pollution focus on cardiovascular and respiratory health, the role of air pollution on in utero and early-life neurological development – which probably has lifelong effects – is under-recognized.[5]

Limited recognition about the developmental impacts of air pollution has contributed to the lack of consistent global public health efforts that target reduction in air pollution to protect pediatric populations. On the contrary, mounting evidence suggests that air pollution adversely affects neurological development in children, and that concerted efforts to address air pollution are a critical component of local and global public health initiatives that aim to improve pediatric health. Given the heterogeneity between relevant studies, it is difficult to efficiently evaluate or compare findings and make meaningful decisions or recommendations. This review summarizes key findings pertaining to developmentally relevant ambient air pollutants, related biological mechanisms of neurotoxicity, and epidemiological evidence linking air pollution to developmental disorders. To further add to the literature, the review focuses on exposures both in utero and in early childhood as these windows are critical for neurological

development, and offers multidisciplinary recommendations based on existing evidence.

AIR POLLUTION

Air pollution refers to a multifaceted environmental toxicant comprising a diverse mixture of particulate matter, metals, organic compounds, gases, and other chemicals (e.g. organic volatile compounds) found in the air. Sources of air pollution vary geographically but major contributors include emission from mobile sources (e.g. transportation), residential fuel combustion, power plants, trash burning/incineration, wildfires, refineries, and agricultural and industrial processes. Indoor sources include tobacco smoking, emission from cook stoves, mold, faulty appliances, and household products (e.g. building materials, solvents, cleaning products, flame retardants, pesticides, etc.).

WHO makes air quality recommendations based on pollutants with significant health implications, including particulate matter with diameter less than 10μm (PM_{10}) and less than 2.5μm ($PM_{2.5}$), ground-level ozone, nitrogen dioxide (NO_2), carbon monoxide, sulfur dioxide, and lead. However, regulated pollutants and calculation/interpretation methods for air quality indices may vary by country and region. WHO also has guidelines for selected indoor air pollutants including $PM_{2.5}$, carbon monoxide, polyaromatic hydrocarbons (PAHs), benzene, formaldehyde, naphthalene, NO_2, radon, trichloroethylene, and tetrachloroethylene.[6,7] Within the context of neurological development, NO_2 and $PM_{2.5}$ and its constituents, including PAHs and black carbon, have been identified as important pollutants.[8] Heavy metals such as lead, arsenic, and mercury have also been implicated but their exposures are often assessed by blood concentrations, which also reflect exposures from sources other than air.[9] Some common synthetic chemicals including bisphenol A, polychlorinated biphenyls, phthalates, perfluorinated compounds, and pesticides can also be found in the air and have been identified as having developmental impacts.[10,11] In general, smaller particles, also known as ultrafine or nanoparticles, are especially concerning owing to their greater abundance, larger combined surface area, stronger oxidant capacity, greater inflammatory potential, and higher pulmonary deposition efficiency.

A WHO global air pollution assessment of nearly 3000 cities (2008–2015) shows that approximately 98% of cities in low- and middle-income countries and over 54% of high-income countries do not meet WHO's PM_{10} safety guidelines.[12] Meanwhile, approximately 2 billion children are exposed to potentially unhealthy levels of air pollution, and 300 million live in areas with extremely toxic levels.[13] In the USA and Europe, where air pollution is relatively low, the health effects of air pollution are already equivalent to that of smoking 0.4 to 1.6 cigarettes per day.[14] As about 70% of the world's population is forecasted to be in living urban areas by 2050, air pollution is expected to be an increasingly complex and pressing public health problem.

What this paper adds

- Exposure to air pollution is associated with a range of childhood developmental complications.
- Biological mechanisms may include oxidative stress, inflammation, and endocrine disruption.

In recent decades, while there have been large-scale improvements in air quality in some parts of the world, less developed countries still suffer from poor outdoor and indoor air quality. Profound disparities also exist on the basis of individual- and population-level indicators of socioeconomic status, with those from lower positions exposed to a disproportionately higher burden.[15] Furthermore, individuals and populations with lower socioeconomic status may also experience other risk factors such as stress and lack of resources, which can act synergistically with air pollution to influence risk of developmental complications.[16]

Studies of animals and humans suggest that sustained exposures to significant levels of pollution, both in utero and in early childhood, can adversely affect the developing central nervous system through multiple pathways (Fig. 1). Although the exact underlying mechanisms remain to be elucidated, these studies provide insights that have guided research to date.

DEVELOPMENTAL EFFECTS OF IN UTERO EXPOSURES

Biological mechanisms linking in utero exposures and neurological development

Pollutants, especially fine and ultrafine particles, can invade a pregnant female's respiratory barrier, pass into the maternal bloodstream, and cross the placental barrier by direct transport.[17,18] A recent landmark study found the presence of black carbon particles on both the fetal and maternal sides of human placentae, and the amount of black carbon was positively correlated with the mother's residential exposures.[19] These findings suggest that pollutants inhaled by pregnant females can directly reach the placenta and developing fetus. Once in the placenta, pollutants can trigger multiple omics-scale changes (i.e. genomics, epigenetics, transcriptomics, metabolomics, and proteomics), many of which are capable of altering transplacental oxygenation and nutrient transport, or trigger other mechanisms (e.g. preterm birth, restricted growth) that can adversely affect the developing fetal brain.[20,21]

In addition to placental impairment mechanisms, pollutants can potentially pass the fetal blood–brain barrier, although this has yet to be observed in human studies. In pregnant mice, injected fine particles can be detected in the fetal brain.[22] Once in the brain, pollutants can trigger permanent fetal neurological impairments such as neuroinflammation, microglia activation, and neuronal cell death/damage through oxidative stress and inflammatory mechanisms.[22]

Meanwhile, respiratory uptake by pregnant females can also increase production of systemic oxidative stress and

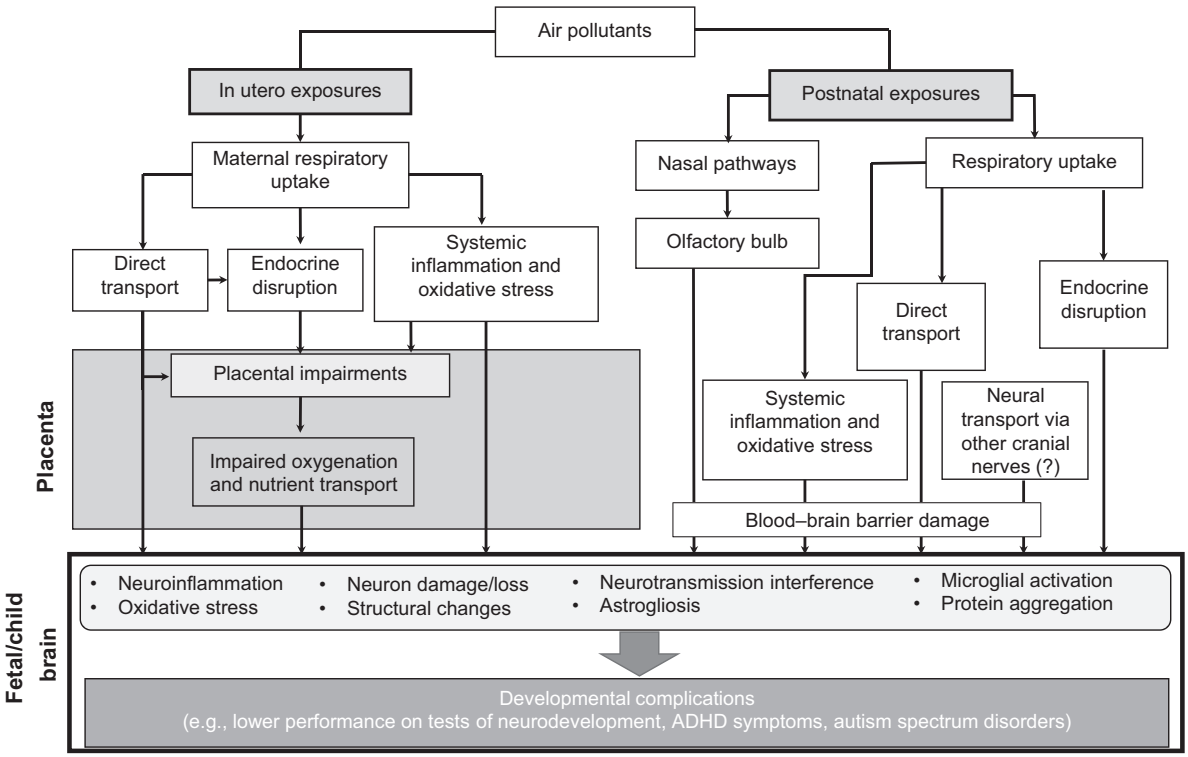

Figure 1: Biological mechanisms linking air pollution exposures to neurological developmental complications. ADHD, attention-deficit/hyperactivity disorder.

inflammatory markers, which can further exacerbate placental impairments, or cause direct developmental damages by directly crossing the blood–brain barrier[22,23] (Fig. 1). Lastly, emerging evidence also shows that some synthetic pollutants resulting from industrial, agricultural, and household applications (i.e. polychlorinated biphenyl, bisphenol A, phthalates, etc.) can also act as endocrine disruptors by disrupting normal homeostasis by either mimicking or blocking hormones.[24]

Epidemiological findings linking prenatal exposure and neurological development

On the basis of the Developmental Origins or Health and Diseases framework (also known as the Barker hypothesis),[25] both in utero and early-life exposures to air pollution have lifelong developmental consequences as the central nervous system is actively forming and growing during these vulnerable periods. Consistent with the biological mechanisms described above, a growing body of human studies suggests that prenatal exposures to combustion-related pollutants including PAHs, $PM_{2.5}$, and NO_2 are associated with developmental complications in early childhood. These complications range from changes in brain structures to subclinical deficits in developmental test scores, and, ultimately, readily identifiable symptoms of developmental disorders such as attention-deficit/hyperactivity disorder (ADHD) or autism spectrum disorders (ASDs).[26] For example, in utero exposure to PAH, a component of $PM_{2.5}$, is associated with a reduction in the surface of white matter (largely on the left side of the brain), slower processing speed, ADHD symptoms, lower global IQ scores, and externalizing problems in young children after adjusting for potential confounders.[27,28] Higher $PM_{2.5}$ is also correlated with reduced cortical thickness, thinner gray matter, reduction in the volume of the corpus callosum, and smaller cerebral cortex, all of which have major implications for information processing, learning, memory, and impulse control.[29,30] In addition, exposure to NO_2 is associated with impaired psychomotor development after birth.[31] Pregnant females who lived closer to major roadways and are exposed to higher traffic-related pollutants have a higher risk of having a child with autism, decreased cognitive functions, and deficits in communication, memory, and attention functions.[8,22,32] A new cohort study also suggests pre- and postnatal exposures to pollution are associated with white matter microstructural changes (lower fractional anisotropy and higher mean diffusivity) in pre-adolescent years.[33] ADHD and ASD have also been linked to higher prenatal exposure to air pollutants including $PM_{2.5}$ and NO_2.[34,35] In recent extensive reviews, endocrine-disrupting chemicals such as PAHs, polychlorinated biphenyls, and phthalates have been linked with developmental complications such as altered brain functions, ASD, ADHD, global developmental delay,

intellectual disability, communication disorders, and unspecified developmental disorders.[10,11] In addition, studies in different parts of the world also report that indoor pollutants from woodstoves (e.g. carbon monoxide) and gas stoves (e.g. sulfur dioxide) during the third trimester also affect neurological development in young children.[36,37]

A few studies also suggest that exposure to air pollution may have sex-specific effects. For example, prenatal exposure to fine particles is related to lower memory and attention scores; and at the same level of exposure, males are more affected than females.[38] This pattern of finding is consistent with the higher prevalence of developmental complications among males and warrants further investigation. A critical timing of exposure is currently unclear given the limited number of studies that aim to address this question. Nevertheless, a few studies have suggested that exposures during later pregnancy (e.g. second and third trimester) have the strongest neurological effects.[39,40]

DEVELOPMENTAL EFFECTS OF POSTNATAL EXPOSURES

Biological mechanisms linking postnatal exposures to neurological development

Owing to their higher ratio of breathing rate to body size, less developed natural barriers and immune system, and less awareness of the conditions of their surrounding environment, children have increased vulnerability to air pollution. Although pollutants reaching a developing fetus must pass through the maternal defense system, children are directly exposed. Thus, healthy natural barriers such as the blood–brain barrier and nasal and lung epithelium are critical components to protect children (and people in general) against air pollutants. Studies have shown that these barriers are more compromised in young children exposed to higher levels of air pollution than those living in less polluted areas.[41] Human pathological studies suggest that, when exposed, pollutants such as fine/ultrafine particles can be directly translocated to the brain through the nasal pathway involving the olfactory bulb, and potentially other cranial nerve pathways (Fig. 1).[22,41] Once in the brain, pollutants can induce neurological impairments including structural changes, neuroinflammation, neuron damage/loss, DNA damage, oxidative stress, astrogliosis, microglial activation, and accumulation of proteins critical in the development of neurological diseases such as tau protein and Aβ42,[41,42] all of which are known to be major contributors to common developmental disorders.

Pollutants can also enter the bloodstream through the respiratory system, pass the blood–brain barrier, and reach the brain, where they can induce neural impairments. Particles smaller than 100nm have been found in the frontal lobe and trigeminal ganglia capillaries in the brain.[43] Alternatively, these pollutants can cause endocrine disruption and/or induce systemic production of inflammatory and oxidative stress markers (e.g. interleukin [IL]-1β, IL-6, tumor necrosis factor [TNF]-α) that can compromise the tight junctions and pass the blood–brain barrier (Fig. 1).[21,41,42]

Epidemiological evidence about postnatal exposures and child neurological development

Epidemiological reports across the world generally support positive associations between developmental complications and postnatal exposures to air pollution, particularly PAH, $PM_{2.5}$, nitrogen oxides, and a few heavy metals such as lead, arsenic, and mercury.[28] These complications range from alteration in the subclinical brain structure to overt signs and symptoms or diagnosis of neuropsychological disorders such as ADHD and ASD. Neuroimaging studies show that childhood exposures to traffic-related air pollutants such as $PM_{2.5}$ can induce changes in the brain's cerebral white matter, cortical gray matter, and the basal ganglia, all of which may have implications for cognition.[29,44,45] A literature review of 31 studies on the effects of air pollution and developmental health across the lifespan suggest that higher pollution exposure in childhood is inversely associated with academic achievement and cognitive performance in children.[46] Early-life exposure is also associated with a reduction in fundamental cognitive abilities, including working memory, conflict attentional network, and, more recently, atypical excitatory neurotransmission and glial inflammatory responses that may have important implications on anxiety disorders.[47,48]

Although studies are still limited, systematic reviews suggest detrimental effects of elemental carbon, black carbon, particulate matter, and NO_2 on ADHD[49] as well as risk of ASD.[50] A study of almost 4500 children also found that ambient lead, mercury, and arsenic concentrations, as measured by the US EPA National-Scale Air Toxics Assessment, were positively associated with higher ASD prevalence at the census tract level.[51] Removal of lead from fuel and paint in the USA led to significant decreases in ambient air lead concentrations and levels of blood lead in children, which are known to be strong predictors of developmental complications.[52] Direct effects of these policies on neurological development are beneficial but difficult to quantify given there are other sources and routes of exposures. Many US children are still exposed to elevated levels of blood lead based on the US Centers for Disease Control and Prevention reference value of 5μg/dL.[53] Natural experiments related to closures of coal-power plants, which are known to be major sources of air pollution, have been shown to have positive effects on longitudinally measured developmental outcomes among children within the proximity.[54] Lastly, like prenatal exposures, postnatal exposures to endocrine-disrupting chemicals such as PAHs, polychlorinated biphenyls, phthalates, and heavy metals have also been associated with a range of developmental outcomes including ASD and ADHD.[10,11]

In terms of potentially susceptible subgroups, a few studies have also suggested that males, those from lower socioeconomic status, and children carrying the ε4 allele of apolipoprotein E (*APOE*) gene, a known major genetic risk

factor of Alzheimer disease, are more susceptible to developmental problems when exposed to air pollution.[55–58] A critical window of exposure has not been clearly identified for postnatal exposures but there is some evidence suggesting that exposures after birth have stronger and more consistent effects than prenatal exposures.[59]

Despite the mounting evidence suggesting that air pollution has deleterious effects on neurological development, it is important also to acknowledge that not all studies confirmed this association.[26,31,50,60] For example, in a recent systematic review/meta-analysis that examined the effects of fine particulate exposures on ADHD, three of the 12 studies that met inclusion criteria did not find any association.[60] The discrepancies in findings across some studies are probably a result of heterogeneity in various aspects of study design. It is also important to note that while most associations identified between air pollution and developmental outcomes are weak (but statistically significant), the public health significance is still high given the high prevalence of exposures across the world.

IMPLICATIONS AND FUTURE DIRECTIONS

The growing recognition and evidence supporting air pollution as a risk factor for developmental health suggests that it may be a contributor to the global increase in developmental disorders. While a full understanding of how air pollution affects development is still emerging, on the basis of the Precautionary Principle adopted by the United Nations in 1992, a precautionary approach should be widely applied. In places where threats of serious or irreversible damage posed by air pollution are present, lack of full scientific certainty should not be a reason for postponing cost-effective measures. Despite challenges, exposure to air pollution is a modifiable public health problem and can be addressed by using multi-level strategies ranging from individual awareness to clinical practice, research efforts, and public policy.

Public health policy

Given that air pollution has no natural geographic boundaries, effective mitigation strategies require concerted multidisciplinary efforts at the local, regional, and global levels. Although the composition of air pollution varies by region depending on the sources, combustion-related pollutants consistently appear to have important developmental implications (and many other health outcomes beyond this review) and merit attention. Thus, emission reduction strategies for existing sources, judicious permission and careful review of new sources (especially those in proximity to vulnerable populations), and promotion and expansion of fuel efficiency and clean energy should be public policy priorities aiming to improve public/pediatric health. Reducing combustion-related emissions also has other benefits, including reduction of greenhouse gases and prevention of many other health complications across the lifespan such as preterm birth and low birthweight, both of which also contribute to risk of developmental complications. Meanwhile, air pollution regulatory standards should give more consideration to the growing evidence on the deleterious effects of air pollution on neurological development. All children and pregnant females should be considered vulnerable populations as opposed to the traditional belief that air pollution mainly affects those with respiratory complications.

Clinical practice

Air pollution is generally not a traditional risk factor that physicians discuss with their patients. Studies show that few physicians discuss the effects of air pollution with their patients, and many are not prepared for such discussion.[61,62] In the US study of 1751 health professionals, the proportion that reported talking with patients about limiting air pollution exposures was 56% in pediatrics and 0% in obstetrics and gynecology.[61] Thus, there is a clear need for more discussion between physicians and patients, especially to vulnerable populations such as pregnant females and young children, as well as tools and resources to help healthcare providers communicate the deleterious effects of air pollution. Strategies to minimize exposures and resources are available to help physicians in their discussion,[61,63] but formal environmental health training in medical schools and continuing education requirements have also been suggested as valuable.[64] In addition, well-designed and accessible public resources that provide critical information on risk mitigation behaviors and health impacts are recommended. In areas where indoor cookstoves are prevalent, alternative cleaner options should be considered.

Research

Several important research gaps need to be addressed. First, research to further understand the biological mechanisms linking air pollution and neurological development is critical. This understanding will also inform efforts to find effective strategies to mitigate community and individual exposures and/or target negative physiological/pathological effects of air pollution are warranted. For example, given systemic oxidative stress and inflammation are major mechanisms mediating the adverse effects of air pollution, antioxidants and anti-inflammatory nutrients may play an important role and can be further studied. One study of more than 1000 births showed that while prenatal PM_{10} exposure was associated with lower IQ, this relation was not present among children of mothers with high levels of serum folate.[65] Other studies suggest that dietary supplementations (e.g. antioxidants, folate) may mitigate some negative effects of air pollution, although the direct effects on developmental outcomes are unclear and should be investigated.[65–67] Such understanding may shed light on novel cost-effective interventions that can help mitigate the negative effects of air pollution.

Second, research on the effects of air pollution on neurological development, particularly in vulnerable populations such as pregnant females and young children, are

mostly limited by indirect exposure measurements, some of which are based on outdoor monitors close to residential addresses and/or mathematical models. Indirect measures of air pollution often cannot account for small spatial variations of pollution nor account for daily activities patterns (e.g. times spent indoors, time away from residence, residential relocations, temporary migration), leading to exposure misclassification. The recent emergence of wearable devices and more sophisticated modelling approaches offer novel opportunities to better estimate personal exposures for longitudinal health investigation beyond the early childhood years. These approaches have been implemented in more recent studies and should be utilized in future research. Third, given the increasingly diverse population and complexity of environmental threats, future studies should identify specific constituents of air pollution that are responsible for developmental effects, explore the interactions between pollutants, identify critical windows of exposures and sensitive subgroups, and investigate the developmental effects of cumulative exposures over the life course. Ideally, there should also be consensus on how to design and report findings from such studies to ensure consistency and reproducibility, and facilitate clinical and policy decisions. Currently, there is a high degree of heterogeneity in terms of approaches to air pollution assessment, neurological development complication assessment, and reporting of results, which hinders efforts to make comparisons and summarize current knowledge. Nevertheless, existing evidence, especially that from more robust study designs (e.g. large prospective cohorts), is compelling in showing that children living in more polluted areas experience higher risks of developmental complications.

In addition, provision of timely, accurate, and accessible surveillance data on air pollution, social determinants of health, as well as pregnancy and developmental outcomes is also critical, especially in developing countries and areas where there are vulnerable populations. Ideally, these data can be linked longitudinally across the lifespan to allow the study of short- and long-term effects of air pollution.

CONCLUSION

Air pollution is considered a 'silent public health emergency' and 'the new tobacco' by WHO. Fetuses and children are particularly vulnerable, especially during periods with high developmental plasticity. There is mounting evidence that exposure to air pollution, both during pregnancy and after birth, may be a contributor to developmental complications and the increasing trend in developmental disabilities around the world. Although the biological mechanisms of effects are still unclear, multiple pathways are involved and may include oxidative stress, systemic inflammation, and/or endocrine disruption. Owing to the difficulty in eliminating anthropogenic environmental pollution, a successful solution could be to reduce exposures through collaboration of interdisciplinary and multi-level bodies including community advocates, physicians, industry partners, policy makers, public health practitioners, and researchers.

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REFERENCES

1. World Health Organization. Ambient (outdoor) air pollution [Internet]. Geneva: World Health Organization, 2018 Available at: https://www.who.int/news-room/fact-sheets/detail/ambient-(outdoor)-air-quality-and-health (accessed 17 August 2020)..
2. World Health Organization. Review of evidence on health aspects of air pollution – REVIHAAP Project. Copenhagen, Denmark: World Health Organization, Regional Office for Europe, 2013.
3. Cohen AJ, Brauer M, Burnett R, et al. Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015. *Lancet* 2017; **389**: 1907–18.
4. Global Research on Developmental Disabilities C. Developmental disabilities among children younger than 5 years in 195 countries and territories, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Glob Health* 2018; **6**: e1100–21.
5. Schraufnagel DE, Balmes JR, Cowl CT, et al. Air pollution and noncommunicable diseases: a review by the Forum of International Respiratory Societies' Environmental Committee, part 2: air pollution and organ systems. *Chest* 2019; **155**: 417–26.
6. World Health Organization. WHO Guidelines for indoor air quality: selected pollutants. Denmark: World Health Organization, 2010.
7. World Health Organization. WHO Guidelines for indoor air quality - household fuel combustion. Geneva: World Health Organization, 2014.
8. Payne-Sturges DC, Marty MA, Perera F, et al. Healthy air, healthy brains: advancing air pollution policy to protect children's health. *Am J Public Health* 2019; **109**: 550–4.
9. Gorini F, Muratori F, Morales MA. The role of heavy metal pollution in neurobehavioral disorders: a focus on autism. *Rev. J Autism Dev Disord* 2014; **1**: 354–72.
10. Rivollier F, Krebs MO, Kebir O. Perinatal exposure to environmental endocrine disruptors in the emergence of neurodevelopmental psychiatric diseases: a systematic review. *Int J Environ Res Public Health* 2019; **16**: 1318.
11. Schug TT, Blawas AM, Gray K, Heindel JJ, Lawler CP. Elucidating the links between endocrine disruptors and neurodevelopment. *Endocrinology* 2015; **156**: 1941–51.
12. World Health Organization. Concentration of particulate matter with an aerodynamic diameter of 10 μm or less (PM10) in nearly 3000 urban areas, 2008–2015 [Internet]. Geneva: World Health Organization, 2016. Available at: http://gamapserver.who.int/mapLibrary/Files/Maps/Global_pm10_cities_2008_2015.png (accessed 20 August 2020).
13. Rees N. Clear the air for children. The impact of air pollution on children. New York, NY: Division of Data, Research and Policy, UNICEF, 2016.
14. Muller R, Muller E. Air pollution and cigarette equivalence. Berkeley, CA, USA: Berkeley Earth, 2020. Available at: http://berkeleyearth.org/archive/air-pollution-and-cigarette-equivalence/ (accessed 4 September 2020).
15. Hajat A, Hsia C, O'Neill MS. Socioeconomic disparities and air pollution exposure: a global review. *Curr Environ Health Rep* 2015; **2**: 440–50.

16. Landrigan PJ, Rauh VA, Galvez MP. Environmental justice and the health of children. *Mt Sinai J Med* 2010; **77**: 178–87.
17. Muoth C, Aengenheister L, Kucki M, Wick P, Buerki-Thurnherr T. Nanoparticle transport across the placental barrier: pushing the field forward!. *Nanomedicine* 2016; **11**: 941–57.
18. Wick P, Malek A, Manser P, Meili D, et al. Barrier capacity of human placenta for nanosized materials. *Environ Health Perspect* 2010; **118**: 432–6.
19. Bove H, Bongaerts E, Slenders E, et al. Ambient black carbon particles reach the fetal side of human placenta. *Nat Commun* 2019; **10**: 3866.
20. Luyten LJ, Saenen ND, Janssen BG, et al. Air pollution and the fetal origin of disease: a systematic review of the molecular signatures of air pollution exposure in human placenta. *Environ Res* 2018; **166**: 310–23.
21. Sunyer J, Dadvand P. Pre-natal brain development as a target for urban air pollution. *Basic Clin Pharmacol Toxicol* 2019; **125**(Suppl 3): 81–8.
22. Genc S, Zadeoglulari Z, Fuss SH, Genc K. The adverse effects of air pollution on the nervous system. *J Toxicol* 2012; **2012**: 782462.
23. Dimasuay KG, Boeuf P, Powell TL, Jansson T. Placental responses to changes in the maternal environment determine fetal growth. *Front Physiol* 2016; **7**: 12.
24. Street ME, Angelini S, Bernasconi S, et al. Current knowledge on endocrine disrupting chemicals (EDCs) from animal biology to humans, from pregnancy to adulthood: highlights from a national Italian meeting. *Int J Mol Sci* 2018; **19**: 1647.
25. Heindel JJ, Skalla LA, Joubert BR, Dilworth CH, Gray KA. Review of developmental origins of health and disease publications in environmental epidemiology. *Reprod Toxicol* 2017; **68**: 34–48.
26. Xu X, Ha SU, Basnet R. A review of epidemiological research on adverse neurological effects of exposure to ambient air pollution. *Front Public Health* 2016; **4**: 157.
27. Peterson BS, Rauh VA, Bansal R, et al. Effects of prenatal exposure to air pollutants (polycyclic aromatic hydrocarbons) on the development of brain white matter, cognition, and behavior in later childhood. *JAMA Psychiatry* 2015; **72**: 531–40.
28. Suades-Gonzalez E, Gascon M, Guxens M, Sunyer J. Air pollution and neuropsychological development: a review of the latest evidence. *Endocrinology* 2015; **156**: 3473–82.
29. de Prado Bert P, Mercader EMH, Pujol J, Sunyer J, Mortamais M. The effects of air pollution on the brain: a review of studies interfacing environmental epidemiology and neuroimaging. *Curr Environ Health Rep* 2018; **5**: 351–64.
30. Herting MM, Younan D, Campbell CE, Chen JC. Outdoor air pollution and brain structure and function from across childhood to young adulthood: a methodological review of brain MRI studies. *Front Public Health* 2019; **7**: 332.
31. Shang L, Yang L, Yang W, et al. Effects of prenatal exposure to NO_2 on children's neurodevelopment: a systematic review and meta-analysis. *Environ Sci Pollut Res Int* 2020; **27**(20): 24786–24798.
32. Ha S, Yeung E, Bell E, et al. Prenatal and early life exposures to ambient air pollution and development. *Environ Res* 2019; **174**: 170–5.
33. Lubczynska MJ, Muetzel RL, El Marroun H, et al. Exposure to air pollution during pregnancy and childhood, and white matter microstructure in preadolescents. *Environ Health Perspect* 2020; **128**: 27005.
34. Chun H, Leung C, Wen SW, McDonald J, Shin HH. Maternal exposure to air pollution and risk of autism in children: a systematic review and meta-analysis. *Environ Pollut* 2020; **256**: 113307.
35. Myhre O, Lag M, Villanger GD, et al. Early life exposure to air pollution particulate matter (PM) as risk factor for attention deficit/hyperactivity disorder (ADHD): need for novel strategies for mechanisms and causalities. *Toxicol Appl Pharmacol* 2018; **354**: 196–214.
36. Dix-Cooper L, Eskenazi B, Romero C, Balmes J, Smith KR. Neurodevelopmental performance among school age children in rural Guatemala is associated with prenatal and postnatal exposure to carbon monoxide, a marker for exposure to woodsmoke. *Neurotoxicology* 2012; **33**: 246–54.
37. Vrijheid M, Martinez D, Aguilera I, et al. Indoor air pollution from gas cooking and infant neurodevelopment. *Epidemiology* 2012; **23**: 23–32.
38. Allen JL, Oberdorster G, Morris-Schaffer K, et al. Developmental neurotoxicity of inhaled ambient ultrafine particle air pollution: parallels with neuropathological and behavioral features of autism and other neurodevelopmental disorders. *Neurotoxicology* 2017; **59**: 140–54.
39. Mortamais M, Pujol J, Martinez-Vilavella G, et al. Effects of prenatal exposure to particulate matter air pollution on corpus callosum and behavioral problems in children. *Environ Res* 2019; **178**: 108734.
40. Chiu YH, Hsu HH, Coull BA, et al. Prenatal particulate air pollution and neurodevelopment in urban children: examining sensitive windows and sex-specific associations. *Environ Int* 2016; **87**: 56–65.
41. Block ML, Calderon-Garciduenas L. Air pollution: mechanisms of neuroinflammation and CNS disease. *Trends Neurosci* 2009; **32**: 506–16.
42. Brockmeyer S, D'Angiulli A. How air pollution alters brain development: the role of neuroinflammation. *Transl Neurosci* 2016; **7**: 24–30.
43. Calderon-Garciduenas L, Solt AC, Henriquez-Roldan C, et al. Long-term air pollution exposure is associated with neuroinflammation, an altered innate immune response, disruption of the blood-brain barrier, ultrafine particulate deposition, and accumulation of amyloid beta-42 and alpha-synuclein in children and young adults. *Toxicol Pathol* 2008; **36**: 289–310.
44. Beckwith T, Cecil K, Altaye M, et al. Reduced gray matter volume and cortical thickness associated with traffic-related air pollution in a longitudinally studied pediatric cohort. *PLoS ONE* 2020; **15**: e0228092.
45. Cserbik D, Chen JC, McConnell R, et al. Fine particulate matter exposure during childhood relates to hemispheric-specific differences in brain structure. *Environ Int* 2020; **143**: 105933.
46. Clifford A, Lang L, Chen R, Anstey KJ, Seaton A. Exposure to air pollution and cognitive functioning across the life course—a systematic literature review. *Environ Res* 2016; **147**: 383–98.
47. Rivas I, Basagana X, Cirach M, et al. Association between early life exposure to air pollution and working memory and attention. *Environ Health Perspect* 2019; **127**: 57002.
48. Brunst KJ, Ryan PH, Altaye M, et al. Myo-inositol mediates the effects of traffic-related air pollution on generalized anxiety symptoms at age 12years. *Environ Res* 2019; **175**: 71–8.
49. Aghaei M, Janjani H, Yousefian F, Jamal A, Yunesian M. Association between ambient gaseous and particulate air pollutants and attention deficit hyperactivity disorder (ADHD) in children; a systematic review. *Environ Res* 2019; **173**: 135–56.
50. Flores-Pajot MC, Ofner M, Do MT, Lavigne E, Villeneuve PJ. Childhood autism spectrum disorders and exposure to nitrogen dioxide, and particulate matter air pollution: a review and meta-analysis. *Environ Res* 2016; **151**: 763–76.
51. Dickerson AS, Rahbar MH, Bakian AV, et al. Autism spectrum disorder prevalence and associations with air concentrations of lead, mercury, and arsenic. *Environ Monit Assess* 2016; **188**: 407.
52. EPA. Policy Assessment for the review of the lead national ambient air quality. Standards Research Triangle Park, NC: US Environmental Protection Agency, 2014.
53. Dignam T, Kaufmann RB, LeStourgeon L, Brown MJ. Control of lead sources in the united states, 1970–2017: public health progress and current challenges to eliminating lead exposure. *J Public Health Manag Pract* 2019; **25**(Suppl 1): S13–22.
54. Amster E, Lew Levy C. Impact of coal-fired power plant emissions on children's health: a systematic review of the epidemiological literature. *Int J Environ Res Public Health* 2019; **16**: 2008.
55. Wang P, Tuvblad C, Younan D, et al. Socioeconomic disparities and sexual dimorphism in neurotoxic effects of ambient fine particles on youth IQ: a longitudinal analysis. *PLoS ONE* 2017; **12**: e0188731.
56. Kern JK, Geier DA, Homme KG, et al. Developmental neurotoxicants and the vulnerable male brain: a systematic review of suspected neurotoxicants that disproportionally affect males. *Acta Neurobiol Exp* 2017; **77**: 269–96.
57. Alemany S, Vilor-Tejedor N, Garcia-Esteban R, et al. Traffic-related air pollution, apoeepsilon4 status, and neurodevelopmental outcomes among school children enrolled in the BREATHE Project (Catalonia, Spain). *Environ Health Perspect* 2018; **126**: 087001.
58. Calderon-Garciduenas L, Kavanaugh M, Block M, et al. Neuroinflammation, hyperphosphorylated tau, diffuse amyloid plaques, and down-regulation of the cellular prion protein in air pollution exposed children and young adults. *J Alzheimers Dis* 2012; **28**: 93–107.
59. Kerin T, Volk H, Li W, et al. Association between air pollution exposure, cognitive and adaptive function, and ASD severity among children with autism spectrum disorder. *J Autism Dev Disord* 2018; **48**: 137–50.
60. Donzelli G, Llopis-Gonzalez A, Llopis-Morales A, Cioni L, Morales-Suarez-Varela M. Particulate

matter exposure and attention-deficit/hyperactivity disorder in children: a systematic review of epidemiological studies. *Int J Environ Res Public Health* 2019; **17**: 67.

61. Mirabelli MCD, Damon SA, Beavers SF, Sircar KD. Patient-provider discussions about strategies to limit air pollution exposures. *Am J Prev Med* 2018; **55**: e49–52.
62. Zielonka T, Zycinska K. Are physicians specialists on the impact of air pollution on health? *Eur Resp J* 2016; **48**(Suppl 60): PA4288.
63. Carlsten C, Salvi S, Wong GWK, Chung KF. Personal strategies to minimise effects of air pollution on respiratory health: advice for providers, patients and the public. *Eur Respir J* 2020; **55**: 1902056.
64. Tinney VA, Paulson JA, Bathgate SL, Larsen JW. Medical education for obstetricians and gynecologists should incorporate environmental health. *Am J Obstet Gynecol* 2015; **212**: 163–6e1.
65. Loftus CT, Hazlehurst MF, Szpiro AA, et al. Prenatal air pollution and childhood IQ: preliminary evidence of effect modification by folate. *Environ Res* 2019; **176**: 108505.
66. Barthelemy J, Sanchez K, Miller MR, Khreis H. New opportunities to mitigate the burden of disease caused by traffic related air pollution: antioxidant-rich diets and supplements. *Int J Environ Res Public Health* 2020; **17**: 630.
67. Peter S, Holguin F, Wood LG, et al. Nutritional solutions to reduce risks of negative health impacts of air pollution. *Nutrients* 2015; **7**: 10398–416.