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Review Article

Gestational and Early Life Exposure to Ambient Air Pollution: Evidence of the Negative Effects on Neurodevelopment

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Abstract

Background: Air pollution is a recognized risk for human health. Globally, since air pollution was responsible for 7 million deaths in 2012, reinforcing the control of human exposure to pollutants is quite necessary. Gestational exposure is of great concerns by intrauterine environmental observations.

Methodology: In this overview, we have explored the current evidence on the impact of air pollution (particulate matter (ultrafine; 2,5 and 10) metal, polycyclic aromatic hydrocarbon, black carbon-nitrogen dioxide, ozone, monoxide carbon, sulphur dioxide) on maternal, fetal and child health in the context of neurodevelopment, its pathophysiological mechanisms and policy implications. There is plausible evidence for the association between prenatal and/or early-life exposure to air pollution, and negative neurobehavioral outcomes during childhood.

Conclusion: Our findings suggest that prenatal and/or early-life exposure to air pollution is associated with negative neurobehavioral outcomes during childhood, adding arguments to the urgent need to control air pollution.

Keywords: *Air Pollution; Gestational Exposure; Fetal Development; Developmental Biology; Toxicology; Neurodevelopment*

Abbreviations

WHO: World Health Organization; DOHaD: Developmental Origins of Health and Disease; PAH: Polycyclic Aromatic Hydrocarbons; PM: Particulate Matter; NOx: Nitrogen Oxide; SOx: Sulfur Oxide; O_3: Ozone; VOC: Volatile Organic Compound; ASDl: Autism-Spectrum Disorders; ADHD: Attention-Deficit Hyperactivity Disorder; MDI: Mental Developmental Index; PDI: Psychomotor Developmental Index; CCCEH: Columbia Center for Children's Environmental Health; NAAQS: National Ambient Air Quality Standards; LUR: Land Use Regression; CCAAPS: Cincinnati Childhood Allergy and Air Pollution Study; DEP: Prenatal Diesel Exhaust; GD: Gestational Day; IL: Interleukin; 5-HIAA: 5-Hydroxy-Indole-Acetic Acid; GABA: Gamma-Amino Butyric Acid; TNF: Tumor Necrosis Factor

Introduction

Air pollution is recognizable risk for human mortality and morbidity due to respiratory and cardiovascular events [1,2] as well as lung cancer [3]. In 2012, air pollution was responsible for 7 million deaths globally [4], reinforcing the urgent need to control human exposure to pollutants. The air pollution exposure affects especially vulnerable groups such as children, pregnant women and the elderly.

Current scientific evidence shows that air pollution is also related to many other health impacts [5] and even prenatal exposures may affect health [6]. Recently, epidemiological studies are pointing out that prenatal exposure to air pollution can damage brain development, adding strength to this evidence [7]. If that is true, reducing this exposure will protect the health of both the current and future generation.

To face outdoor exposure, the World Health Organization (WHO) has set air quality targets for common pollutants [8]. For indoor exposure, WHO focuses on household fuel combustion. Nevertheless, pesticides, solvents, and other industrial chemicals, which are already in widespread use, also play a role [9].

Influence of environmental factors on illness, disability, and death among children has been increasingly recognized. However, establishing a causal relationship between these factors and deleterious effects on health such as asthma, cancer, low birth weight, birth defects and neurodevelopmental deficits in humans is difficult due to limited exposure assessment, inadequate control of potential confounders.

Exposures of expectant mothers are of great concern since the intrauterine environment is determinant for fetal development and any perturbation that occurs during this critical period of life can determine individuals to later life diseases (e.g. diabetes, hypertension), compromising the health of the next generation [10]. The theory of developmental origins of health and disease (DOHaD) shows that the intrauterine and external environment in which the fetus and young child grow influences the risk of later diseases [11]. That is supported by several studies showing early life conditions might have long-term effects on the risks of non-communicable diseases [12,13].

The widespread contamination of the ambient air with noxious substances is well known for its potential to impair fetal and child development. In this sense, if we consider the DOHaD approach, in which negative influences on the initial stages of life (embryo/fetus) increase the risk of later life diseases, such as diabetes, metabolic syndromes, and cardiovascular diseases, unavoidable exposures to air pollution during pregnancy would have a profound impact in public health strategies to prevent most common health issues.

Here, we explored the current evidence on the impact of environmental exposures to air pollution derived from fossil fuel combustion on maternal, fetal and child health, particularly in the context of neurodevelopment and its pathophysiological mechanisms. Special attention was given to public health implication of these findings due to the fact that the type of exposure explored here is mostly unavoidable in urban areas and some of the effects are long-lasting and, in some cases, critical for learning and behavioral trajectories.

Materials and Methods

In order to get a general overview of the neurodevelopment effects that can be attributed to exposure to air contaminants in specific life periods, this overview was undertaken based upon a search of medical and biological scientific published papers. The search was conducted on the online public database (Pubmed, Web of Science, Scielo) using the following keywords or a combination of them: air pollution, pregnancy, maternal health, exposure, gestation, neurodevelopment, behavior, and brain. Articles were systematically reviewed and classified into four categories:

(a) Studies of the possible effects of pollutants derived from traffic (PM_{10}, $PM_{2.5}$, NOx, SOx, O_3, PAH, BC);

(b) Studies of the possible effects of heavy metals;

(c) Studies of biomarkers of the toxic effects on the nervous system;

(d) Mechanistic studies of the effects of air pollution on fetal and child neurodevelopment.

Publications were identified and scanned based on the following inclusion criteria: (1) the study needed to focus on environmental exposure to air pollutants or to some of its constituents; (2) the observed effects should be related to gestational, childhood and/or adolescence exposure (until 15 years) (3) the study was required to be in English; Papers describing experimental studies were used to support information for epidemiological investigations and pathophysiological mechanisms. The exclusion criteria were: a) Adulthood exposure; b) Maternal drug use (nicotine, cannabis, etc); c) non original studies.

Results and Discussion

Outdoor and indoor air pollution

Outdoor air pollution, largely derived from combustion processes of fossil fuels (vehicle emissions, coal combustion) in urban areas, is a mixture containing many toxic components that include CO, NO_2, SO_2, O_3, particulate matter (PM) and polycyclic aromatic hydrocarbons (PAH), which is a pollutant produced by incomplete combustion of fossil fuels. Particulate matter is a complex mixture of small particles and liquid droplets composed by sulfates, nitrates, organic substances (e.g. VOC, PAH), metals (e.g. Cd, Pb), and dust particles [8].

According to data from IARC [14], exposure to outdoor air pollutants occurs continuously across microenvironments, including indoors. In this particular case, exposure is higher among women and children who spend the most time at home [15]. It is also estimated that around 3 billion people still use solid fuels (i.e. wood, charcoal, coal, dung, crop wastes) to cook and heat their home. As a result, more than 50% of premature deaths due to pneumonia among children under 5 are caused by the PM inhaled from household air pollution [15].

The use of fossil fuel can deteriorate the quality of ambient air, however other anthropogenic sources such as industrial activities, mining, crops burning, agriculture and livestock farming agriculture and pesticides contributes significantly to emissions of greenhouse gases.

Air pollution exposure and health effects

There is a growing consensus that the exposures to the above-mentioned pollutants are associated with an increased incidence of reproductive and developmental disorders, including disorders of neurobehavioral development and impairment in brain function. Grandjean and Landrigan [16] conducted a systematic review of the published clinical and epidemiological studies into the neurotoxicity of different industrial chemicals, and they found that there are nearly 200 neurotoxicants present in our environment that are reported to harm adults. However, this number might increase since there are chemicals that have never been tested for neurodevelopmental toxicity. Every year, new data on the neurotoxicity of environmental contaminants is emerging with special emphasis on pollutants derived from fossil fuel combustion.

Maternal, fetal and early development effects of air pollution

Negative impacts of urban air pollution on pregnancy and fetal development were recently recognized. Increased risks for low birth weight, prematurity, neonatal and post-neonatal mortality, and congenital defects are consistently associated with environmental exposures. Moreover, accumulated exposures during gestation may also be related to gestational diabetes, hypertension, and preeclampsia; however, the evidence is fewer consistent [17,18].

Exposures during sensitive periods of fetal development may lead to developmental abnormalities, congenital defects and changes in anthropometric measurements, such as a reduction in head circumference and femur length, which were inversely associated with and PM_{10} and NO_2 levels in several studies [19,20]. Vrijheid., *et al.* [21] systematically reviewed epidemiologic studies on ambient air pollution and congenital anomalies and found out an increased risk for different cardiac anomaly (e.g. coarctation of the aorta, tetralogy of Fallot).

Fetal developmental disruptions may occur indirectly (maternally mediated), or as a result of direct effects on the fetus or it can be a combination of both. In most cases, embryo/fetal toxicity occurs via maternal exposure to toxic agents; nevertheless, male exposure to contaminants may be teratogenic or impair gestation if the chromosomes in spermatozoa are damaged [22].

Developing organisms are more vulnerable to environmental contaminants because they differ significantly from adults with respect to physiology, metabolism, and behavior [23]. The immune and detoxification system is not fully developed until 10 to 14 years of age [24]. External interferences during critical windows of development can lead transitory to permanent functional and/or structural abnormalities impairing their potential developmental. Further, the adverse health outcomes are aggravated by cumulative exposures in lifelong as well as modulated by social factors such as poverty, poor water quality and sanitation, violence, maternal depression, stress, health care access, and parental education level [25].

Effects of air pollution on neurodevelopment

The developing brain is especially vulnerable to toxic injury because of the immaturity of the defense mechanisms; the blood-brain barrier is not completely developed until about 6 months of age. However, even after fully developed it only protects the brain partially from lipid-soluble environmental toxicants, such as lead, methylmercury, and PAHs [26].

Neurodevelopmental alterations also have been reported to be associated with gestational exposure to urban air pollution and these alterations are suggested to underlie a variety of behavioral and neuropsychiatric disorders during childhood and later in life. Mechanisms involved in these associations are starting to be elucidated and are described elsewhere in this overview.

In the following topics, epidemiological and experimental findings will be presented in order to demonstrate neurotoxicity effects induced by air pollution derived from fossil fuel and indoor biomass burning in gestational, childhood and adolescence periods of exposure. Epidemiological data on the relation between air pollutants and negative neurobehavioral outcomes in children are compiled in table 1.

Author	Country	Cases	Type of study	Pollutant	Exposure Concentration	Objective	Effects
Perera., *et al*. 2006	New York, USA	183 children (3 years old)	Prospective cohort	PAH, ETS, pesticide (chlorpyrifos)	PAH: 3.49 ng/m^3	To evaluate the role of prenatal exposure to urban pollutants, including PAHs, environmental tobacco smoke (ETS) and pesticides, in the pathogenesis of neurobehavioral disorders.	Prenatal exposure to PAHs was not associated with psychomotor development index or behavioral problems. High prenatal exposure to PAHs was associated with lower mental development index at age 3. There are significant age × PAH effect on mental development
Windham., *et al*. 2006	San Francisco, USA	284 cases 657 controls	Case-control	Metals and PAH	PAH and metals (Environmental levels)	To explore possible associations between ASD and environmental exposures to air pollutants	Potential association between autism and estimated metal concentrations, and possibly solvents, in ambient air around the birth residence
Suglia., *et al*. 2008	Boston, USA	202 children (mean age 9.7 years)	Prospective birth cohort	BC	BC (annual level): 0.56 µg/m^3	To examine the relation between BC and cognition among children	Higher levels of BC predicts decreased cognitive function (verbal and nonverbal intelligence and memory)
Perera., *et al*. 2009	New York, USA	249 mother-child pairs (children assessed at 5 years old)	Prospective cohort	PAH	PAH (median): 2.26 ng/m^3	To evaluate the relationship between prenatal exposure to airborne PAHs and child intelligence	Environmental PAHs levels can affect children's IQ adversely
Wang., *et al*. 2009	Quanzhou, China	861 children in clear area school (mean age = 9.09 years) 430 children in polluted area school (mean age 9.09 years)	Case–control	NO_2, PM_{10}	School A NO_2: 7 µg/m^3 PM_{10}: 68 µg/m^3 School B NO_2: 22 µg/m^3 PM_{10}: 80 µg/m^3	To explore the association between traffic-related air pollution exposure and its effects on neurobehavioral function in children	A significant relationship between chronic low-level traffic-related air pollution exposure and neurobehavioral function in exposed children
Freire., *et al*. 2010	Spain	210 children living in urban and rural areas (5 years old)	Birth cohort	NO_2	NO_2(µg/m^3): urban area: 29.71 rural area: 9.17	To investigate the association between exposure to NO_2 and cognitive development in children	Results were not statistically significant. Suggestion of an association between exposure to NO_2 early in life and cognitive functions, even at low exposure levels

Siddique *et al*, 2011	Delhi, India	969 children of Delhi (mean age = 14 years) 850 children from rural areas (mean age 14 years)	Cross-sectional	PM_{10}, SOx, NOx	PM_{10} (μg/m^3): Dehli: 161.3 ± 4.9 Control: 74.6 ± 3.3 SOx (μg/m^3): Dehli: 9.6 ± 1.0 Control: 5.6 ± 2.2 NOx (μg/m^3): Dehli: 50.1 ± 7.1 Control: 30.3 ± 5.2	To explore whether sustained exposure to vehicular air pollution affects the behavior and activities of children	Association between air pollution and behavioral problems in children, and the prevalence of ADHD
Volk., *et al*. 2011	California, USA	304 cases 259 controls	Case-control	Measures for residential distance to freeways as a surrogate for exposures	Distance classes: - <309m; - 309-647 m; - 647-1419m; - >1419 m	To evaluate the association between autism and proximity of residence to freeways and major roadways during pregnancy and near the time of delivery	Adjusting for sociodemographic factors and maternal smoking, autism was associated with residential proximity (<309 m) to a freeway during the third trimester
van Kempen., *et al*. 2012	Spain	553 children (mean age 10.5 years)	Cross-sectional	NO_2, PM_{10}	PM_{10}(μg/m^3): Home: 26.2 ± 1.5 School A: 25.9 ± 0.9 School B: 26.0 ± 1.0 NO_2(μg/m^3): Home: 30.8 ± 5.5 School A: 31.0 ± 5.1 School B: 31.7 ± 6.0 Road traffic noise ($_{LAeq,\ 7–23h}$ in dB(A)): Home: 50.2 ± 7.3 School A: 48.7 ± 8.6 School B: 49.6 ± 8.6 Aircraft noise ($_{LAeq,\ 7–23h}$ in dB(A)): Home: 48.1 ± 7.1 School A: 48.6 ± 7.1 School B: 49.6 ± 8.6	To investigate the relationship between air pollution and transportation noise on the cognitive performance of primary schoolchildren	Exposure to NO_2 at school was associated with a decrease in the memory span length, and combined exposure of air pollution and road traffic noise had a significant effect on cognitive functioning of children
Jung., *et al*. 2013	Taiwan	49,073 children (baseline mean age 1.01 years)	Prospective cohort	O_3, CO, NO_2, SO_2, PM_{10}	*Seasonal variation of the pollutants was measured during the study period.	To investigate the associations between long-term exposure to air pollution and newly diagnostic ASD	Children exposure to O_3, CO, NO_2 and SO_2 in the preceding 1 year to 4 years may increase the risk of ASD diagnosis
Perera., *et al*. 2013	Krakow, Poland	248 children (assessed at 9 years old)	Longitudinal birth cohort	PAH	PAH during pregnancy: 20.7 ng/m^3	To evaluate potential interactions between prenatal exposure to airborne PAHs and maternal psychological distress during pregnancy on subsequent behavioral problems in children	The combination of high prenatal exposure to environmental PAH and maternal demoralization adversely affects child behavior. Maternal demoralization has a greater effect among children with high prenatal PAH exposure for a majority of behavioral symptoms

Volk., *et al*. 2014	California, USA	279 cases 245 controls	Case-control	NO_2, $PM_{10,}$ $PM_{2.5}$	The regional pollutants were measured based on average concentrations for the time period of interest.	To examine the relationship between traffic-related air pollution, air quality, and autism	Exposure to traffic-related air pollution, NO_2, $PM_{2.5}$ and PM_{10} during pregnancy and during the first year of life was associated with autism
Newman., *et al*. 2013	Cincinnati, USA	576 children (assessed at 7 years old)	Birth cohort	Elemental carbon attributed to traffic (ECAT)	ECAT: 0.4 ± 0.1μg/m^3	To explore the association between early-life exposure to traffic-related air pollution using a surrogate, elemental carbon attributed to traffic, and attention-deficit/hyperactivity disorder symptoms at 7 years of age	Exposure during infancy to elemental carbon derived from traffic was associated with higher hyperactivity scores in children; the effect was modified by maternal educational level
Guxens., *et al*. 2014	The Netherlands, Germany, France, Italy, Greece, Spain	9,482 children	6 European population-based birth cohorts	NO_2, NOx, $PM_{2.5}$, PM_{10}, PM coarse	NO_2(μg/m^3, median range): 11.5– 43.9 $PM_{2.5}$(μg/m^3, median range): 13.4– 22	To assess whether air pollution exposure during pregnancy affects cognitive and psychomotor development in childhood	Air pollution exposure during pregnancy, particularly $NO_{2,}$ was associated with delayed psychomotor development during childhood. No associations were found between any air pollutant exposure and cognitive development
Kalkbrenner., *et al*. 2015	California and North Carolina, USA	North Carolina 645 cases 12,434 controls California 334 cases 2,232 controls (children born between 1994 to 2000)	Case-cohort	PM_{10}	PM_{10} (μg/m^3) in third trimester North Carolina: 1994: 24.5± 3.2 1996: 24.0± 4.1 1998: 25.0± 5.7 2000: 23.0 ± 2.6 California: 1996: 22.9 ± 3.1	To investigate whether higher exposures to PM_{10} would be associated with increased prevalence of autism and that exposures during certain prenatal and postnatal periods would be more strongly associated than others	Early-life PM exposure, especially during the third trimester of pregnancy, was associated with increased risk of autism.
Lin., *et al*. 2014	Taiwan	533 mother-child pairs (assessed at different ages until 18 months)	Prospective birth cohort	PM_{10}, CO, O_3, SO_2, NO_2, total hydrocarbons (THCs), non methane hydrocarbons (NMHCs)	Pollutants concentrations means were measured at different periods (trimesters and months)	To investigate the relationship between exposure to ambient air pollutants during the prenatal and postnatal periods and with early childhood neurodevelopment	Ambient air pollution, even low-level SO_2 exposure, during pregnancy and up to 12 months of age is associated with poor subclinical neurodevelopment in early childhood

Kim., *et al*. 2014	South Korea	520 mother-child pairs (children assessed at different ages until 24 months)	Prospective birth cohort	NO_2, PM_{10}	PM_{10}: 53.19 μg/m^3 NO_2: 26.30 ppb	To investigate the association between prenatal exposure to PM_{10}, NO_2, and neurodevelopment in children during the first 24 months of life	Negative associations between maternal exposure to PM_{10} and NO_2 mental and psychomotor developmental indexes at 6 months, but no significant association was found at 12 and 24 months of age
Jedrychowski., *et al*. 2015	Krakow, Poland	170 mother-child pairs (children mean age 7 years)	Longitudinal pre-birth cohort	PAH	PAH Prenatal: 43.00 ± 55.34 Postnatal: 47.01± 64.19	To assess the association between depressed verbal IQ score and prenatal PAH exposure measured by cord blood PAH–DNA adducts	Only the level of cord blood PAH–DNA adducts (ln-transformed) and postnatal indoor PAH level had a significant negative impact on the cognitive dysfunction of children
Harris., *et al*. 2015	Massachusetts, USA	1,109 mother-child pairs (children assessed between birth to 6 years)	Longitudinal pre-birth cohort	BC, $PM_{2.5}$	BC (μg/m3) Third trimester: 0.69 ± 0.23 Birth–6 years: 0.56 ± 0.16 Year before cognitive testing: 0.47 ± 0.1 PM2.5 (μg/m3) Third trimester: 12.3 ± 2.6 Birth–6 years: 11.3 ± 1.7 Year before cognitive testing: 9.4 ± 1.9	To examined associations of gestational and childhood exposure to traffic-related pollution with childhood cognition	Prenatal and childhood near-residence traffic density, BC, and $PM_{2.5}$ did not display consistent patterns of association with child cognition. However, third-trimester and childhood BC exposures were associated with lower verbal IQ in minimally adjusted models; but after adjustment for socioeconomic covariates, associations were attenuated or reversed
Sunyer., *et al*. 2015	Barcelona, Spain	2,715children (mean age 8.5 years)	Prospective cohort	NO_2, elemental carbon, ultrafine particle number (UFP 10-700nm)	Elemental carbon outdoor:1.32 (1.03-1.73) indoor: 1.26 (0.86-1.78) NO_2 outdoor: 48.5 (35.1-57.4) indoor: 29.8 (20.5-38.6) UFP outdoor: 22,157 (16,27-28,257) indoor: 14,407 (11,096-19,968)	To assess the relationship between long-term exposure to traffic-related air pollutants at school and cognitive development measurements in primary school children	Children attending schools with higher traffic-related air pollution had a smaller improvement in cognitive development over time, suggesting that traffic-related air pollution in schools negatively affects cognitive development

Lertxundi., *et al*. 2015	Spain	438 mother-child pairs (children assessed at 15 months (range 13-18))	Birth cohort	$PM_{2.5}$, NO_2, benzene	$PM_{2.5}$(μg/m^3): 16.98 ± 2.51 NO_2(μg/m^3): 20.33± 6.57 Benzene (μg/m^3): 0.86 ± 0.22	To assess whether prenatal exposure to $PM_{2.5}$, NO_2, and benzene was associated with impaired development in infants during their second year of life	Prenatal residential exposure to $PM_{2.5}$ and NO_2 adversely affects infant motor and cognitive developments, respectively
Harris., *et al*. 2016	Massachusetts, USA	1,212 mother-child pairs (children assessed between birth to 6 years)	Longitudinal prebirth cohort	BC, $PM_{2.5}$	BC (μg/m^3) - third trimester: 0.69 ± 0.23 - birth to age 3: 0.61 ± 0.17 Birth to age 6: 0.56 ± 0.16 $PM_{2.5}$ (μg/m^3) - third trimester: 0.69 ± 0.23 - birth–age 3:0.61 ± 0.17 - birth–age 6: 0.56 ± 0.16	To examine associations of gestational and childhood exposure to traffic-related pollution with executive function and behavior problems in children	Children with higher mid-childhood exposure to BC and greater near-residence traffic density in mid-childhood had greater problems with behavioral regulation as assessed by classroom teachers, but not as assessed by parents. Third trimester BC was associated with lower scores (representing fewer problems) on measures of metacognition and behavioral problems
Guxens *et al* 2016	Sweden, The Netherlands, Italy, Spain	8,079 children (4-10 years old)	European population-based birth/child cohort studies (three prospective cohorts, one longitudinal)	NO_2, NOx, $PM_{2.5}$, PM_{10}, PM coarse		To assess whether prenatal air pollution exposure is associated with childhood autistic traits in the general population	Prenatal exposure to NO_2 and PM was not associated with autistic traits in children from 4 to 10 years of age
Basagaña *et al* 2016	Barcelona, Spain	2,618 schoolchildren (mean age 8.5 years)	Cohort	$PM_{2.5}$	$PM_{2.5}$ (μg/m^3) Outdoor: 28.1 (22.6-35.8) Indoor: 35.6 (29.2-41.5)	To explore the role of all the different sources of $PM_{2.5}$ in school air on cognitive development	Traffic was the only source of fine particles associated with a reduction in cognitive development

Saenen., *et al*. 2016	Flanders, Belgium	310 children (mean age 10.2 years)	Cohort	$PM_{2.5}$, PM_{10}, BC	Inside Classroom (median (IQR)): $PM_{2,5}$ (μg/m^3): 5.14 (8.85) PM_{10} (μg/m^3): 33.5 (55.2) Chronic at residential address (median (IQR)): $PM_{2.5}$(μg/m^3): 15.7 (1.16) PM_{10} (μg/m^3): 21.3 (1.61 BC (μg/m^3): 1.54 (0.20) Recent at resident: median concentration was calculated from lag 0 to lag 2 (see article)	To investigate with repeated measures whether the neurobehavioral performance was differently associated with recent versus chronic air pollution exposure in a panel of primary schoolchildren	Neither recent nor chronic PM exposure did affect short-term memory. However, it was found a negative association of selective attention with both recent classroom and chronic ambient residential PM exposure. Decreased sustained attention was associated only with chronic ambient PM exposure at residence. Visual information processing speed seemed to decrease only in conditions of recent PM exposure, either in the classroom or at residence
Sunyer., *et al*. 2017	Barcelona, Spain	2,687 children (7–10 years old)	Follow-up	NO_2, elemental carbon	Indoor pollution (μg/m^3) NO_2 = 30.09 ± 9.51 EC = 1.27 ± 0.42 Ambient air pollution (μg/m^3) NO_2 = 37.75 ± 18.41 EC = 1.34 ± 0.84	To examine the daily association of traffic air pollution on attention among school children and the extent to which these associations are independent of its chronic relationship	Short-term association of traffic-related air pollutants with attention fluctuations adds to the evidence that air pollution affects the cognitive performance of school children while at the school and may have potentially harmful effects on neurodevelopment
Mortamais., *et al*. 2017	Barcelona, Spain	242 children (8–12 years old)	Cross-sectional	PAHs, benzo[a] pyrene (BPA)	Outdoor: -Total PAHs: 1458 ± 704pg/m^3 - BAP: 99 ± 62 pg/m^3 Indoor: - Total PAHs: 1710 ± 1107pg/m^3 - BAP: 105 ± 72 pg/m^3	To investigate the effects of PAHs exposure in indoor and outdoor school environments on white matter, gray matter and BG (putamen, caudate nucleus and globus pallidus) in children from the general population	Chronic exposure to PAHs during the pre-adolescent school-age years is associated with subclinical changes on the caudate nucleus, even for below levels established in the European Union

Table 1: *Associations between gestational and childhood exposure to air pollution and negative neurobehavioral outcomes in children. *The seasonal variation of five main air pollutants during the study period was measured: CO (ppm), NO_2 , SO_2 and O_3 (ppb), PM_{10} (μg/m^3). The authors examined the results of Spearman correlation for the average concentration of preceding 1 year before newly diagnostic ASD.*

Epidemiological studies

Gestational exposure to air pollution is considered a risk factor for cognitive impairments, autism-spectrum disorders (ASD), anxiety-spectrum disorders, depression, schizophrenia, and attention-deficit hyperactivity disorder (ADHD). However, studies have recognized that there are many uncertainties on this association between impairments on neurobehavioral development, mental health, and air pollution exposures.

Mental development

Studies conducted in different countries have found that *in utero* and early childhood exposures to common urban air pollutants are associated with mental development impairments. Literature has shown that exposure during the gestational period is determinant to such outcome and, among the pollutants, PM and NO_2 are the most associated with negative effects.

The association between prenatal exposure to PM_{10} and NO_2, and neurodevelopment in children during the first months of their lives has been assessed all around the world. In Korea, evaluations were conducted using the Mental Developmental Index (MDI) and Psychomotor Developmental Index (PDI) from the K-BSID-II. These tests measure a child's level of development in three domains: cognitive, motor, and behavioral. Data have revealed negative associations between maternal exposure to PM_{10} and the index MDI ($\beta = -2.83$; $p = 0.003$) and PDI ($\beta = -3.00$; $p = 0.002$) throughout the first 24 months of child life. Maternal exposure to NO_2 was correlated to impairment of psychomotor development ($\beta = -1.30$; $p = 0.05$) and prenatal exposure was found to have significant effects on MDI and PDI at 6 months of age – even, though these effects tend to disappear in a long-term [27]. Also, another study from Southern Spain examined the effects of NO_2 in a birth cohort. The evaluation of cognitive development at the age of 4 years showed that children living in urban areas exposed to higher NO_2 (> 24.75 $\mu g/m^3$) presented a decrease in the general cognitive score and also a decrease in working memory and in gross motor areas. However, differences were not statistically significant [28].

Other pollutants as non-methane hydrocarbon and SO_2 were negatively associated with damage in neurodevelopment performance (gross motor, fine motor, language/communication, and social/self-care abilities) in different periods of development. Lin., *et al.* [29] have found different association between gestational and postnatal air pollution exposure and children neurodevelopment. At six months of age, children had an effect on gross motor scores associated to non-methane hydrocarbon exposure; while at eighteen months, they presented a decrease in fine motor development performance scores associated with SO_2 exposure No other pollutants assessed (PM_{10}, CO, O_3, NO_2, and total hydrocarbons) had a significant effect on neurobehavioral development performance at 6 months and 18 months of age.

In a prospective study from 39 schools in Barcelona, Spain, children aged 7 and 10 years exposed to higher levels of elemental carbon (EC), NO_2 and ultrafine particles, both indoors and outdoors, have experienced substantially smaller improvement in all the cognitive measurements of Working Memory, Superior Working Memory and Inattentiveness when compared with children from lowly polluted schools [30]. At school, children are usually exposed to many sources of PM such as mineral, organic/textile/chalk, traffic, secondary sulfate and organics, secondary nitrate, road dust, metallurgy, sea spray, and heavy oil combustion. Among them, only traffic was the source of fine particles associated with a reduction in cognitive development in this children sample [31].

In a case-control study in China, Wang., *et al.* [32] have verified that there is also an association between traffic-related air pollution exposure and decreased neurobehavioral function in children. They have evaluated primary school children from two school settings, one located in a clean air area and the other one in a polluted area. Air pollution was assessed by the levels of NO_2 and PM_{10} as indicators for traffic-related air pollution for 2 consecutive days. Mean concentrations of NO_2 in the clean and polluted school was 7 $\mu g/m^3$ and 36 $\mu g/m^3$, and results from the neurobehavioral testing revealed that children from the polluted area presented low performance for six out of nine tests (66.7%): Visual Simple Reaction Time with preferred hand and with non-preferred hand, Continuous Performance, Digit Symbol, Pursuit Aiming, and Sign Register.

An interestingly study evaluated the difference in the neurobehavioral performance of recent versus chronic air pollution exposure in primary schoolchildren from Belgium. Neither recent nor chronic PM exposure affect short-term memory. However, it was found

a negative association of selective attention with both recent classroom and chronic ambient residential PM exposure and decreased sustained attention was associated only with chronic ambient PM exposure at residence. The visual information processing speed seemed to decrease only in conditions of recent PM exposure, either in the classroom or at the residence [33].

In the USA, researchers also have investigated the associations of gestational and childhood exposure to traffic-related pollution with executive function and behavior problems in children. Pre and postnatal exposure to traffic-related pollution (PM and BC) impact newborns weights and lengths, as well as executive function, behavior problems, and cognition in children. A prospective birth cohort study conducted by Suglia., *et al.* [7] in Boston (USA) have evaluated the association between pre and postnatal BC exposure and verbal and nonverbal intelligence in children, as well as child's ability to actively learn and memorize different information. Evidence has indicated a relationship between exposure to BC and reduced neurocognitive functioning in urban 8 - 11-year-old children.

Recently, parents and classroom teachers were requested to perform a Behavior Rating Inventory of Executive Function (BRIEF) and the Strengths and Difficulties Questionnaire (SDQ) to examine associations of gestational and childhood exposure to traffic-related pollution with executive function and behavior problems in children in Massachusetts, USA. It was observed that higher childhood BC exposure and mid-childhood residential traffic density were associated with higher teacher-rated BRIEF Behavioral Regulation Index (BRI) scores. From birth to age 3, BC was not associated with BRIEF or SDQ scores. Children who were exposed during the third trimester of pregnancy to BC were not found to be associated with teacher-rated BRI scores. $PM_{2.5}$ exposure was associated with teacher-rated BRIEF and SDQ scores in minimally adjusted models, but associations attenuated with covariate adjustment. None of the parent-rated outcomes suggested adverse effects of greater pollution exposure at any time point [34]. The same research group evidenced an association between major roadway proximity and cognition impairment in children exposed during the prenatal period. The main results have shown that children with birth addresses within 50m of a major roadway had lower mid-childhood nonverbal IQ scores, verbal IQ scores, and visual motor scores than participants who lived ≥ 200m from a major roadway. However, prenatal and childhood exposure to traffic density and $PM_{2.5}$ did not appear to be associated with lower cognitive performance. On the other hand, third-trimester and childhood BC exposures were found to be associated with lower verbal IQ in minimally adjusted models, but after adjustment for socioeconomic covariates, associations were attenuated or reversed [35].

In a study of population-based birth cohorts conducted by Guxens., *et al.* [36], it was demonstrated no associations between air pollution (nitrogen oxides (NO_2, NOx), $PM_{2.5}$, PM_{10} and PM coarse) and cognitive development. Even though, it was observed a decrease of 0.7 points on a psychomotor development scale for each 10 $\mu g/m^3$ increase in pregnancy average NO_2 levels in children assessed between 1 and 6 years of age [36].

Recently, a study has also investigated the exposure to benzene in association with $PM_{2.5}$ and NO_2. Although there was a decrease in the motor score and a decrease in mental score related respectively to $PM_{2.5}$ and NO_2 exposure during pregnancy, benzene did not show any significant association with development [37].

Calderón-Garcidueñas., *et al.* [38] have evaluated the neuropsychological functioning and structural brain alterations of clinically healthy children (around 9 - 10 years of age) with a lifetime residency in two significantly different urban environments, one with high concentrations of air pollutants in Mexico City and the other one with levels within the current USA National Ambient Air Quality Standards (NAAQS) located in Polotitlán, Mexico State. Children were assessed using the Wechsler Intelligence Scale for Children-Revised WISC-R [39] and significant cognitive deficits in areas of fluid cognition, memory, and executive functions when compared to socioeconomically matched children residing in a low polluted environment. The MRI of children's brains has shown that exposure was also associated with structural alterations revealed by prefrontal white matter hyperintense lesions.

Others air pollution components have been associated with mental development damages. In the CCCEH (Columbia Center for Children's Environmental Health) New York cohort, prenatal exposure to PAH has been associated with multiple adverse effects including developmental delay at 3 years of age [40] and reduced IQ at 5 years of age [41].

In Poland, studies have shown the combination of high prenatal exposure to environmental PAH and maternal demoralization adversely affects child behavior [42] and higher prevalence of depressed verbal IQ index (DepVIQ) in children at the age of 7 [43]. The postnatal PAH exposure also increased the risk of DepVIQ and long-term exclusive breastfeeding (at least 6 months) has presented a protective effect.

A prospective birth cohort study has investigated the role of prenatal exposure to urban air pollutants in the pathogenesis of neurobehavioral disorders. In these investigated regions, the outdoor and indoor air pollution is mostly derived from a coal-burning power plant, home heating, traffic emissions, and by indirect means. Briefly, they have evaluated the health benefits on the neurodevelopment of children living near a coal-burning power plant during the non-operating season and found out that reduced exposure during neurodevelopment diminishes the frequencies of developmental delay in all developmental quotient's areas, except for language [44].

In Guatemala, Dix-Cooper., *et al.* [45] investigated the effects of indoor biomass burning (wood smoke) on children's neurodevelopment and behavioral performance. Their study shows that CO exposure in the third trimester can affect children's neuropsychological performance, more significantly than infant-CO exposure in the first 9 months of life. Average personal 48-h CO exposure levels were 3.8 - 3 ppm for mothers during the third trimester, 3.0 - 2.5 for mothers in the second trimester and 2.2 - 2 ppm for infants (9 months of age). However, they have not controlled other environmental exposures, e.g.: lead, pesticides, and maternal intelligence, which could influence the association.

Besides this, the relationship between air pollution and transportation noise on the cognitive performance of primary school children has been investigated. NO_2 exposure was significantly associated with a decrease in the memory span length, after adjusting for a range of socioeconomic and lifestyle factors in children aged between 9 - 11 years and combined exposure of air pollution and road traffic noise had a significant effect on the reaction time [46].

Autism spectrum disorder (ASD)

Autism Spectrum Disorder (ASD) is a complex neurodevelopment disorder that presents communication impairment and deficit in social communication and interaction. ASD may also present a deficit in non-verbal communications behavior, abnormalities in eye contact, hyper or hyporeactivity to sensory input, language impairment, among other characteristics related to social communication and interaction [47]. In the USA, data from 14 Developmental Disabilities Monitoring (ADDM) sites, estimated ASD prevalence among children aged 8 years, in 2008, was 23.6 per 1,000 (one in 42) in boys and 5.3 per 1,000 (one in 189) in girls [48].

Windham., *et al.* [49] were one of the first to evidence a possible association between ASD and exposures to urban air pollution. They found that solvents concentration, diesel exhaust particles, metals (mercury, cadmium, and nickel), as well as chlorinated solvents in ambient air around the birth residence were associated with ASD incidence.

Volk., *et al.* [50] have verified the association between proximity of residences to freeways and major roadways during pregnancy and autism in California (USA). In summary, they have found that children living within 309 m of a freeway around the time of birth have an increased risk of autism, possibly due to high levels of pollutants. In a second study, authors reported associations of autism with estimates of exposure to the mixture of traffic-related air pollution and with regional measures of NO_2, $PM_{2.5}$ and PM_{10}. Children residing in homes with the highest levels of modeled traffic-related air pollution were 3 times more likely to have autism than children residing in homes with the lowest levels of exposure [51].

Regarding to air pollution exposure during pregnancy, higher maternal exposure to $PM_{2.5}$ and PM_{10}, particularly in the third trimester, was associated with a greater likelihood of a child having ASD [52]. Approximately 59% of risk increase was observed in China per every 10 ppb increase in O_3 level, 37% risk increase per 10 ppb in CO, 340% risk increase per 10 ppb increase in NO_2 level, and 17% risk increase per 1 ppb in SO_2 level in ASD diagnostic in children from 3 to 9 years of age [53].

Different from studies in US, European studies have related no associations between air pollution exposure and ASD risk. A population cohort study has shown that related prenatal exposure to NO_2 and PM was not associated with autistic traits in children from 4 to 10 years of age even after adjusting for several socioeconomic status variables and urbanicity [54]. Besides this, air pollution exposure during the prenatal period was not associated with ASD overall (OR = 1.00; 95% CI: 0.86, 1.15 per 10-μg/m^3 increase in PM_{10} and OR = 1.02; 95% CI: 0.94, 1.10 per 20-μg/m^3 increase in NOx during mother's pregnancy) [54].

Nevertheless, Nevison [55] have found that vehicular emissions of several components (e.g. PAH, CO, VOCs, and particulate organic carbon) have a decreasing temporal trend that is anti-correlated to trends in autism in the USA. According to this study, these trends can be explained by the decreased highway emissions of pollutants that contribute to $PM_{2.5}$ and ozone formation since the 1980s.

Schizophrenia

Although a family history of schizophrenia is the most important risk factor for the disease, recent studies point out that factors such as living in urban areas, repeated exposure to toxic substances, infections and diet could also be associated with increased risk [56]. To test whether air pollution in urban areas could be associated with increased risk for schizophrenia Pedersen [57] used data from a birth cohort from the Danish cancer society evaluating whether air pollution from traffic causes cancer in childhood. In this study, the level of traffic (RR 4.40, 95% CI: 1.25 - 15.50), CO and benzene on the residence at birth explained some of the differences in schizophrenia risk in rural and urban population. The level of NOx and NO_2 had no impact on the risk of schizophrenia [57]. Furthermore, a recently published review shown other constituents of environmental pollution as the potential triggering of the pathophysiology of schizophrenia [58].

Behavior and emotional disorders

Air pollutants have been associated with behavioral and emotional disorders, such as attention-deficit hyperactivity disorder (ADHD) and anxiety. In this context, a study in India found that the prevalence of ADHD is 4 times higher among children (9 - 17 years of age) residing in Delhi compared to children residing in less polluting rural areas of the country. Major risk factors were observed in male gender, lower socioeconomic status, 12 - 14 year age group, and $PM_{2.5}$ level in breathing air (OR = 2.07; 95% CI, 1.08 - 3.99) [59].

Recently, a study verified daily ambient levels of NO_2 and EC from traffic-related were negatively associated with all attention processes assessed by child Attention Network Test (ANT) from 265 classrooms in 39 schools in Barcelona [60]. Perera., *et al.* [61] followed children from *in utero* to 6 - 7 years in New York City, and also found that gestational exposure to environmental levels of PAH was positively associated with symptoms of anxious/depressed and attention problems in children of nonsmoking mothers.

Newman., *et al*. [62] collected data on exposure to EC attributed to traffic during infancy and behavioral scores at 7 years from Cincinnati Childhood Allergy and Air Pollution Study (CCAAPS) birth cohort. Exposure during the first year of life was estimated and parents answered the Behavioral Assessment System for Children (BASC) when they were 7 years of age. They found that children exposed to traffic-related air early in life are more likely to present attention to ADHD symptoms at 7 years of age.

Furthermore, a study has investigated the effects of PAHs on basal ganglia volumes and ADHD symptoms in school children aged 8 - 12 years. They found ADHD symptoms and inattentiveness increased in children with higher exposure to benzo[a]pyrene (BPA), one of most common PAH, but these associations were not statistically significant while total PAHs and BPA were associated to decreased caudate nucleus volume [63].

Mechanism

The neurodevelopment is a complex process and it can be influenced by environmental conditions, and disturbances in this critical period can cause permanent abnormalities. As described before, epidemiological studies demonstrated that exposure to air pollution (gestational and early childhood) can impair cognitive function and behavior later in life, but the mechanisms involved in this association are beginning to be elucidated. Experimental studies of controlled exposure to real-world air pollutants or to some of its components during neurodevelopment give plausibility and support for the epidemiological findings.

The role of the placenta

In the past, there was a conception that the placenta was a barrier that protects the fetus against any harmful substance present in the mother's organism. Nowadays, more evidence shows that this conception is mistaken and that the placenta does not protect the fetus against several chemical compounds, including environmental chemicals.

In animal studies, we have shown that urban air pollution affects placental functional morphology. Gestational exposure to real-world levels of $PM_{2.5}$ in São Paulo city, Brazil, was associated with reduced volumes, calibers, and surface areas of maternal blood spaces and with greater fetal capillary surfaces and diffusive conductance [64]. In humans, there are evidences that impairments of placental function can compromise fetal growth and are involved in the deleterious outcomes [19,65].

Exogenous substances are capable of crossing the placenta barrier mainly by passive diffusion. Other possible mechanisms are facilitated diffusion, active transport, pinocytosis, and filtration. However, some chemicals can bind to transporter proteins and trigger of corresponding proteins through biological membranes might have some effect on it. The velocity of transplacental transfer and substance accumulation depends on its physicochemical characteristics (e.g. polar compounds cross the placenta slowly and accumulate in amniotic fluid and in the fetal gut lumen; while lipophilic substances cross the placenta rapidly and the distribution depends on relative maternal and fetal affinity) [66].

All tissues express some drug-metabolizing enzymes, and so that placental metabolism should not be neglected. During pregnancy, the placenta expresses several forms of cytochrome P450 enzymes. It is well known that several substances are not toxic, but metabolites can cause harmful effects to the health [67].

Pathophysiology

The pathophysiological mechanisms by which air pollutants could cause adverse health effects are characterized by their ability to directly act as pro-oxidants of lipids and proteins or as free radical generators, promoting oxidative stress, inflammatory responses and damage to mitochondrial function [68,69]. The first system that is affected by air pollution is the respiratory tract; however, mechanistic studies have shown that the particulate matter can translocate into secondary target organs, including the brain [70,71].

The scientific literature is still scarce; however, experimental studies based on controlled exposures to different air pollutants, e.g. concentrated ambient particles, diesel exhaust and ozone, are helping researchers to elucidate the mechanism involved in the association between air pollution and neurodevelopmental disorders and providing new translational information. In this context, Bolton., *et al*. [72] demonstrated that prenatal exposure to diesel exhaust particles increase the cytokine levels of IL-1, IL-6 and IL-10 and the chemokines CCL2/MCP-1 and CX3CL1 on the fetal brain.

Yokota., *et al.* [73] showed that prenatal administration of DEP can reduce the locomotor activity and dopamine turnover in the striatum and nucleus accumbens. In addition, another experimental study showed that levels of dopamine, noradrenaline, and its metabolites were increased in the prefrontal cortex and the dopamine and noradrenaline turnover were decreased in several brain regions after DEP administration on the prenatal period [74]. These data suggest that DEP exposure induced dopamine and noradrenaline impairments, in addition to neuroinflammation in the fetus resulting in behavioral and predisposition to clinical conditions later in life.

Ozone is widely distributed in environments with high levels of air pollution. Experimental evidence show that prenatal exposure to ozone can cause morphological changes (e.g. necrotic signs, unusual Purkinje cells nuclei) and permanent cerebellar damage in rats [75], also decreased levels of dopamine, norepinephrine, dihydroxyphenilacetic acid and homovanillic acid in the cerebellum of 5-day-old rats, increased levels of 5-hydroxy-indole-acetic acid (5-HIAA) in the cerebellum of 10-day-old rats [76] and reduced levels of nerve growth factor in the hippocampus and increased levels of brain-derived neurotrophic factor in the striatum [77].

The first infancy is also an important period for the neurodevelopment, and just as the gestational period, it is vulnerable to environmental factors. Exposure to the particulate matter on this period can produce persistent changes in the central nervous system such as microglial activation in the corpus callosum and cortex, marked glutamate-dopamine imbalance particularly in the frontal cortex, decreased levels of corticosterone indicating hypothalamic-pituitary-adrenal axis dysfunction and increased frontal cortex GABA. These findings are also displayed by other neurological conditions, like Alzheimer's and Parkinson's disease [78].

In humans, a case-control study conducted in Mexico showed, besides the systemic inflammation evidenced by high serum concentrations of MCP-1 and TNF-α, children exposed to higher levels of air pollution presented poor cognitive performance and significant differences in white matter volumes assessed by MRI when compared to children living in low levels of air pollution city [38]. Others studies verified the association between decreased caudate nucleus volume and total PAHs and BPA exposure [63].

In addition, an experimental study demonstrated that dogs exposed to high concentrations of urban air pollution displayed tissue damage and accumulated metals (e.g. nickel and vanadium) at target brain regions in a gradient manner (e.g. olfactory mucosa > olfactory bulb > frontal cortex), which suggest the nasal pathway as a key portal of entry [79].

Policy implications

Despite the scientific evidence of the dangers of air pollution on children's health and development, very few specific efforts have been made to ensure that children will grow up in a safe environment and reach their full developmental potential. In addition, the incidence of neurodevelopmental disabilities, including autism, ADHD and other cognitive impairments seem to be increasing in frequency worldwide and recent evidence points out that exposure to environmental toxicants, such as air pollution, during pregnancy and early- life period, could be involved.

The third WHO International Conference on Children's Health and the Environment, held in the Republic of Korea in 2009 [80], was a landmark in discussing critical issues to children's health and their environment. The Conference highlighted that for a future healthy environment it will be necessary simultaneous work at international, national and local levels to assess children's environmental health risks, develop policies addressing their unique vulnerabilities and programs to mitigate such exposures worldwide.

Reducing or eliminating children's exposures to contaminated air can prevent many of the damages and diseases as these presented in this overview. There are many open questions concerning the mechanisms involved in neurodevelopmental toxicity of air pollution: which of the components are more toxic? Are the neurobehavioral disorders secondary to brain structural damage or a functional alteration? Does accumulated exposure increase the size of the effects? Is prenatal exposure more critical than childhood and early adolescence exposure? Are there safe levels of exposure for these neurobehavioral effects? What are the risks associated with maternal and gestational exposure to air pollution and child health mental disorders?

Communication of science to the general public can help to promote actions on these avoidable outcomes due to air pollution exposure. Air pollution derived from fossil fuels is a consequence of human activity; therefore, it can be prevented or modified. Not just public policies, but individual actions from physicians and scientists are also useful, because of their special knowledge, abilities, and training [80].

Conclusion

This overview shows a line of associative evidence between early- life air pollution exposure and its adverse effects on neurodevelopment. The traffic is an important source of pollutants in big cities, and inhalation is the main route of exposure to these contaminants in humans. The adverse effects on health vary mainly according to the pollutant and period of exposure.

Pollution exposures are different between countries, and it might vary according to the economic profile and the development and environmental protection laws. It is important that policies are taken mainly in developing countries aiming to decrease the emissions of pollutants. The current options of fossil fuels which are related to the main neurodevelopment damages are also the main energy source used in the world. Thus, sound policies aiming at protecting children's health from air pollution, as well as researches focusing on global improvements of air quality should give strong consideration by international agencies and competent authorities.

In the end, still remains important elucidate the key features associated with brain impairment due to environmental exposures to air pollution. Further, mechanistic studies using real-world air pollution exposure scenarios are needed to explain how gestational and early-life exposures affect the development and function of the brain, as well as to investigate which specifics components of environmental pollution are linked to risk for mental, neurodevelopmental, and neurodegenerative diseases. However, while mechanisms are not completely understood the policies decision must be based on research data and available evidence.

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Conflict of Interest

The authors declare no conflict of interest.

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