Laura Ros Medina

Final Master Project

Master in Nutrition and Metabolism

EFFECTS OF PRENATAL EXPOSURE TO AIR AND ENVIRONMENTAL POLLUTION ON THE OFFSPRING'S NEUROCOGNITIVE OUTCOMES: A SYSTEMATIC REVIEW

NUTRITION AND MENTAL HEALTH RESEARCH GROUP

Universitat Rovira i Virgili

Directed by:

Dr. Victoria Arija and PhD Lucía Iglesias

UNIVERSITAT ROVIRA i VIRGILI

AGRADECIMIENTOS

Este año ha sido complicado para todos, ya que, debido a la situación pandémica, se han minado mucho los ánimos y se han creado una serie de complicaciones inesperadas. Aun así, se ha podido resurgir y todo ha salido según lo acordado. Quería empezar agradeciendo a la Dra. Victoria Arija, que me permitió adentrarme en el estudio ECLIPSES, así como realizar mi Trabajo de Final de Máster en su grupo de investigación, gracias al que he aprendido muchas más cosas de las que hubiera imaginado.

Quería agradecer de todo corazón a Lucía Iglesias. Una persona de una calidad óptima no solo como trabajadora e investigadora, sino también como persona. Es realmente fascinante la cantidad de trabajo que puede abordar sin dejar nada atrás, de forma sublime y añadiendo una pizca de cariño en todo lo que hace. Ha sido muy bonito y muy fácil aprender de ella. Realmente ha sido la pieza clave en este trabajo.

Quería agradecer también a la Dra. Begoña Muguerza, que me instó a embarcarme en el mundo de la nutrición y la clínica e hizo en gran parte que escogiera este Máster, y a la Dra. Francisca Isabel Bravo que fue de gran ayuda en cuanto a mi elección.

Finalmente, agradecer siempre la ayuda que me presta toda mi familia, aquellos que están presentes en las buenas, en las malas y en todo lo que se ponga por delante.

SUMMARY

ABSTRACT

Environmental pollution is known to widely affect human health, leading to the appearance of alterations in many mechanisms, including neurocognitive pathways. Prenatal exposure to these toxicants can lead to impairments in fetal neurodevelopment, generating delays in cognition and motor skills during childhood, although its association has been poorly investigated. This systematic review evaluated the association between prenatal exposure to air and environmental pollutants, and neurocognitive outcomes during childhood. Articles were selected according to inclusion criteria (studies conducted in pregnant woman, prenatal exposure to pollution, children's neurocognitive development as main outcome). No restriction in language or date of publication was applied. After filtering and exclusion of articles not following inclusion criteria, 26 articles were reviewed and divided whether prenatal exposure to pollutants was assessed by air monitoring (assessing air pollution) or in biological samples (assessing environmental pollution). The vast majority of studies showed associations between both air and environmental pollution exposure and lower neurocognitive outcomes measured by psychological tests, although a small number of studies did not obtain significant results. Neurocognitive impairments were showed until ten years of age, suggesting that pollution during fetal development may have long-lasting effects in neurocognitive outcomes. Many studies investigated whether gestational period of exposure played a role in exposure to air and environmental toxicants. An association was found between exposure to air pollution at third trimester and lower cognitive outcomes, which indicates that this time of exposure may be an important window of susceptibility. Regarding sex-differences, boys showed lower cognitive scores than girls when prenatally exposed to pollutants. This systematic review concluded that both air and environmental pollutants alter neurocognitive outcomes during childhood, and that both gestational trimester of exposure and baby's sex may be powerful covariates. However, more studies are needed to ultimately conclude associations between environmental pollution and neurocognitive outcomes during childhood.

INTRODUCTION

1- AIR POLLUTION

Air pollution is a mixture of different ambient air toxicants, including particulate matter, sulfur oxides, nitrogen oxides, ozone, carbon monoxide, methane and other volatile compounds (such as benzene) and metals (lead, arsenic, manganese, cadmium) (1,2). These toxicants, widespread among environmental sources, are known to have negative effects in human health. These pollutants are derived from different sources, including traffic, industry processing, natural biologic processes, combustion and others (1). Due to their ubiquity, they are found in atmosphere, ambient air, indoor air, food and water, and thus easily affecting human everyday environments (3,4). Regarding the timing or space where these pollutants are found, air chemical composition varies highly, and thus its capacity of exposure and toxicity to human health (1). Mostly, humans are exposed to environmental pollutants via inhalation. According to World Health Organization (WHO), air pollution in developing countries is above the healthy limits imposed, leading to a major source of negative health outcomes in human populations (5). For that reason, air pollution is becoming an important health issue to consider.

Air pollutants are known to be neurotoxic, carcinogens and mutagens. Thus, ambient air pollution is related to many medical conditions, such as cancer, cardiovascular and respiratory diseases. Many components of ambient air pollution can enter the human body via inhalation and settle in alveolar regions of the lungs, contributing to the appearance of oxidative stress and inflammation and, consequently, cardiorespiratory illnesses. These toxicants can also introduce circulatory tracts and thus expand through peripheral regions of the body (6). Moreover, already from the past decade, air pollutants are also known to reach the central nervous system (CNS), leading to microglia inflammation, white matter abnormalities, oxidative stress and neurodegenerative diseases (Parkinson or Alzheimer) (1,7). As air pollution is found in everyday environments, continuous exposure to these toxicants lead to chronical neurotoxicity, leading to neuronal inflammation and damage.

As it will be further explained in next sections, environmental toxicants are also known to affect children's neurocognitive and behavioral development, leading to a lower intelligence quotient (IQ), worse behavioral performances, and a higher risk of autism spectrum disorder (1).

Traffic-related pollutants

One of the most studied groups of toxicants is traffic-related pollutants, which include air toxicants mainly produced by burning of diesel and gasoline powered vehicles (8,9). These pollutants are mostly found in environment, atmosphere, water and food and the main exposure via to them is inhalation (1,3,10). This group includes polycyclic aromatic hydrocarbons (PAH), particulate matter (PM), carbon dioxide (CO_2), carbon monoxide (CO), ozone (O_3), sulfur dioxide (SO_2), nitrogen dioxide (NO_2) and black carbon (BC), among others (1). The exposure to all of these air toxicants are associated with negative health outcomes (8,11).

PM is an ultrafine compound of air pollution, defined for its diameter: PM_{10} (Ø<10µm), $PM_{2,5}$ (Ø<2,5µm) and ultrafine (UF) or $PM_{0,1}$ (Ø<0,1µm). These particles are easily inhaled and deposited in alveolar and lung tracts, thus producing negative respiratory outcomes. PM is known to worsen asthma and respiratory illnesses (1,7). PM is also known to affect development of the brain and microglia, leading to decreased neuronal development, difficulties in learning and worse neurocognitive performances in children (1)

PAHs, CO and BC are produced mainly due to the incomplete burning of carbon, diesel and gasoline, and traffic-diesel exhaust is the main source of these pollutants (1,9). PAHs are known to be trans-placental carcinogens (12). They are also present in tobacco smoke and grilled or boiled foods. They are related to cardiovascular and respiratory problem (8). CO is known to interfere with oxygen transport, and thus decreasing normal circulation of oxygen among tissues and systems, such as the central nervous system (CNS). This leads to impairing of neurocognitive functions (11). BC is related with cardiovascular problems, along with PM and PAHs. It is also related with negative effects in disruption of neurobehavioral matters, such as cognitive, emotional and behavioral, leading in some cases to neuropathology characteristics (9).

Metals

Ambient air pollution also include volatile metals present in house dust, tobacco smoke and vapors released in high temperature processes (2). Gasoline combustion, coal incinerators and battery factories are also sources of metals in environment (13). These metals include: lead (Pb), cadmium (Cd), mercury (Hg), arsenic (As) and zinc (Zn), among others. Humans are exposed due to inhalation, and its toxicity arises due to its persistence in the body.

Briefly, the prolonged exposure to these metals has been found related with detrimental health effects. Lead, mainly found in dust, is related to adverse neurocognitive outcomes and also to an increase of artery thickness and stiffness, leading to hypertension and cardiovascular abnormalities (14). Cadmium is known to produce lung damage and also induce toxicity to bone tissue and kidney, leading to renal disease and osteoporosis (2). Another metal, mercury, is known to generate negative alterations in cardiovascular, renal and immune systems (14). Arsenic is known to be neurotoxic, as its first target is the CNS. Exposure to arsenic is associated to lower cognitive outcomes (15). Zinc can enter the body via inhalation and reach the brain through the olfactory system. Its exposure is related to neurocognitive delays (1).

2- PREGNANCY

Despite exposure to air pollution directly and indirectly affects human health throughout life, pregnancy is a particularly sensitive and fragile stage in regards to this concern. The high amount of developmental changes produced in the fetus at relatively short time of gestation become this moment a window of time really important to consider. For that reason, the prenatal exposure to air pollution can affect both the mother and the developing fetus, leading to congenital abnormalities, developmental delays or premature deaths (16,17).

For many years, these complications were associated with sociodemographic factors, such as maternal age, lifestyle including diet, body mass index, and socioeconomic status. Lately, it has been proven that exposure to environmental pollutants, both outdoor and indoor also plays a role in such pregnancy difficulties (16,17). Indeed, environmental air pollution caused 3,7 million premature deaths in 2012, and household air pollution was associated to

3,8 premature deaths around the globe in the same year, according to WHO (17).

Specifically, pregnancy health difficulties that have been associated with prenatal exposure to air pollution include gestational diabetes mellitus and hypertension, pregnancy loss and preeclampsia (16,17). Preeclampsia is a multisystem disorder that presents a pathologic outline including hypertension and proteinuria (16). On the other hand, pregnancy loss is classified in two different concepts: spontaneous abortion, defined as loss of the fetus before gestational week (GW) 20 , and stillbirth, defined as loss of the fetus after that time (17,18). Many studies have concluded that air pollutants, both indoor and environmental, are a major cause of the gestational complications mentioned above. Cooking smoke, for example, is highly associated with stillbirth and sulfur dioxide and ozone are strongly related with spontaneous abortion (16). Moreover, traffic-related pollution exposure is known to increase the risk of suffering from hypertension and gestational diabetes mellitus during pregnancy. All these findings show that exposure to air pollutants can be defined as one of the main causes of pregnancy loss and alterations, and thus be considered a major health issue (16,17).

Complications and appearance of pathologies during pregnancy affect directly or indirectly fetal outcomes and development, leading to intrauterine growth restriction and congenital anomalies, among others (18). Environmental exposures *in utero* and during early life may permanently modify body's structure, physiology and metabolism of offspring (19). Pregnant women exposed to outdoor air pollution, such as PM and NO_2 have a higher risk of generating negative outcomes in the offspring, such as decreased body length and low birth weight, thus associated with a larger number of newborn mortality and morbidity (16,17). In addition, pregnant women exposed to lead are related to newborns with lower birthweight (17). Many of these newborn alterations are known to persist throughout early childhood or in some cases, for life, leading to developmental growth and neurocognitive delays among years, causing a diminishment of the quality of life (1).

Other important anthropometrical outcome, apart from weight and height in newborns, is head circumference. This value is related to worse neurocognitive

and behavioral performances and lower intelligence quotient (IQ) during first years of life (20). In this regards, smaller head circumference has been observed in children whose mothers were prenatally exposed to air pollution, especially to PAHs and arsenic (21,22), thus leading to learning difficulties in scholar years.

All of these abnormalities are mainly caused due to the fact that pollutants can travel across de trans-placental barrier, reaching placenta and inducing changes and alterations in the fetus (20). As mentioned in the last paragraph, air pollution can not only affect anthropometric values, but also produce alterations in neurocognitive and behavioral outcomes.

3- NEUROCOGNITIVE OUTCOMES

The vast majority of morphological traits of the CNS are formed during the first eight weeks of gestation, and they continue to develop during pregnancy and after birth (18). For that reason, these first stages of pregnancy are crucial and of high importance for the correct formation of synaptic connections and brain structures. Prenatal developmental stages are of essential importance, due to the high brain plasticity –which decreases throughout years–, leading to a higher susceptibility to environmental alterations (4). Thus, maternal exposure to any environmental toxicity can lead to abnormalities in CNS formation, leading to developmental delays and cognitive disorders in the newborns (4,18).

The prenatal neuroanatomic development of the CNS follows four stages (23):

1- Neurogenesis: formation of neuron cells in the brain.
2- Neuronal migration: process where neurons travel from their origin to their final position in the brain.
3- Synaptogenesis: formation of synaptic connections between neurons.
4- Myelination: formation of the fatty envelops covering neuronal processes and fibers that enable and facilitate electrical transmission.

Following the stages mentioned above, studies have classified brain development into the three gestational trimesters, according to the distinct features that occur during each moment.

First trimester (From GW0 to GW13)

- Neurogenesis and neuronal migration start.
- Between the second and third weeks, the neural tube is formed.
- At GW5-6, starts the first synaptic connections, leading to a primarily cortex circuit.
- During the eight week, early fetal cortex is created.

During the first trimester, also sensory and motor systems are beginning to develop in the following sequence: first, the somatosensory system; secondly, the chemosensory system (taste and smell); in the third place, auditory system; and the latest one, visual system.

This first stage of gestation is considered an essential window of susceptibility due to the many developmental features that occur. Any alteration during this period can, therefore, lead to failing in the formation of neural tube or abnormal neurogenesis.

Second trimester (from GW13 to GW26)

- The subplate, an early structure that will end up forming the cerebral cortex, is being formed and becomes visible. This represents an essential point during development. is.
- Between GW20 and GW28, starts the maturation of myelin.
- Starts the synaptic refinement, which will end between 8-12 months after delivery.
- The chemosensory and somatosensory pathways are completed during this trimester.

Third trimester (from 26GW to GW40)

- The CNS maturation is almost completed.
- Around 26 and 29GW, myelination is completed
- The neuronal migration ends, leading to a mostly completed circuit of synaptic connections.
- At GW32, the developing cortex reaches its maturity
- At GW34, signaling between the two hemispheres is reached.

- Motor skills are also obtained
- At GW32, face mobility, as swallowing or lips movements, can be observed, being an essential key point to asses fetus health (23).

Because of the accuracy and fragility of all of the processes mentioned above, minimal changes in the maternal environment can lead to abnormalities in fetal development. Many maternal inputs are known to affect brain development, as smoking, alcohol and drugs consumption, diet, lifestyle, composition of microbiota, genetics and environmental features (24). Environmental toxicants can enter the maternal organism throughout many ways, mostly inhalation, cross the blood-placenta and the blood-brain barriers, thus reaching fetal brain and being present at the first years of CNS development (4,10).

Many environmental pollutants are known to affect early childhood neurocognitive and behavioral outcomes. Air pollution is related to behavioral and neurocognitive difficulties, leading to autism spectrum disorder, attention deficit hyperactivity disorder, impaired social behaviors, worst motor skills and language difficulties (10). These findings show that environmental prenatal exposure is of a high importance regarding postnatal neurocognitive and behavioral outcomes.

Although a wide scientific evidence supports the detrimental effects of long-term maternal exposure to environmental pollutants on anthropometric health outcomes in the offspring (12,20,25,26), only few studies have considered neurocognitive, language and motor skills as a main outcome to assess. After acknowledging all of this information, the objective of this systematic review was to gather the available studies on this issue in order to offer a comprehensive view about the association of *in utero* exposure to both environmental and air pollution with neurocognitive outcomes during childhood.

METHODS

Search strategy

PubMed was used as essential database for searching up the articles. The search was done until 3rd March of 2021 for papers that assessed the relation between prenatal exposure to air pollution and neurocognitive outcomes in the

offspring. The search strategy used combinations of various terms, including MeSH terms, British and American English spelling to amplify the search. The entire combination of words used was the following: (((“Air Pollution”[Mesh] OR “Air Quality” OR “Environmental Toxicants” OR “Environmental Pollutants” OR “Air Pollutants” OR "Particulate Matter"[Mesh] OR “Traffic-related pollution” OR “Nitrogen Dioxide” OR “Pollution Exposure” OR Contaminants) AND (pregnancy OR Pregnant OR gesta* OR Prenatal OR Fetal OR Foetal OR Maternal OR Fetus OR Foetus) AND (Behaviour OR Behavior OR Neurobehavioural OR Neurobehavioral OR Neurodevelopment OR Cognitive OR Cognition OR “cognitive disorders” OR Psychomotor OR "Psychomotor Performance"[Mesh] OR “Psychomotor Development Index” OR PDI OR Mental OR “Mental Development Index” OR MDI OR “Intellectual functioning” OR “Intellectual Quotient” OR IQ OR Intelligence OR Child OR children OR infant OR Offspring OR "Language/abnormalities"[Mesh] OR "Language/pathology"[Mesh])) NOT (weight OR birthweight OR length OR height OR “head circumference” OR anthropometry OR “physical development” OR growth))

To proceed with the selection of articles that would be included in the systematic review, titles and abstracts were assessed and those papers with possible relation and potential interest for the review were selected. To continue with the filtering, full texts were read carefully to determine whether they were relevant for the research objective. Those studies that followed the inclusion criteria were selected for the review.

Inclusion and exclusion criteria

The articles included in the systemic review met the following inclusion criteria: studies conducted in pregnant woman, which assessed the effects of prenatal exposure to air pollution on children’s neurocognitive development.

There were no exclusion criteria regarding the age when child’s cognitive development was assessed. Otherwise, reviews, meta-analysis, reports, commentaries and protocols were excluded, as well as *in* vitro studies and studies conducted in animal species. Studies that assessed exposure to endocrine disruptors, maternal smoking, radiation or contamination via water or diet were also excluded, along with those that determined maternal exposure

measuring presence of toxicants in early childhood and in breastmilk, as it was categorized as postnatal exposure. Those studies assessing neurological structural development, using magnetic resonance neurography or other anthropometric techniques were excluded, as well as those that did not assess neurodevelopment in psychological tests or scales. Finally, behavior outcomes or social problems as autism or attention deficit hyperactive disorder were not included in the review. There were no restrictions in terms of language, type of study or year of publication.

Data extraction

The articles reviewed were separated and discussed in two different groups, based on whether the exposure to air/environmental pollution was analyzed directly by air monitoring and geolocation or indirectly by biological samples (urine, hair, maternal blood, cord blood). The information extracted from the included studies was the following: author's name, year of publication, country where the study was conducted, sample size, exposure assessment, trimester of pregnancy when the exposure to environmental pollution was assessed, neurocognitive tests and scales used to assess cognitive development of children, punctuation or scores obtained by children in the mentioned tests, children's age when the neurocognitive assessment was performed and main findings of each study. An article in Chinese was included but as its abstract provided enough information for the systematic review, full article was not needed.

RESULTS

A total of 9.937 articles were identified from the search in PUBMED electronic database. From these, 8.967 were excluded by reading the titles due to the exclusion criteria specified in **Figure 1,** and screening of possible relevant abstract was made in 403 articles. After excluding 377 more articles, 26 original studies were finally included in the systematic review: 12 based on directly-measured air pollution exposure (4,8,9,11,18,19,27–32) and 15 based on indirect measurements of the exposure to environmental toxicants (2,3,8,13,15,21,22,33–40). One article assessed the exposure to environmental pollution in both ways (8), so it is included in both sections.

The articles include dates from 2006 to 2020, and are variate in size, location, type of pollutant and outcome assessment, although all of the articles are associated with neurodevelopmental features afterbirth. As it was observed that the articles found differ on the methodology used to assess the exposure, they were classified according if they used air monitoring (**Table 1**) or biological samples (urine, hair samples, maternal blood and cord blood) (**Table 2**). The first ones will be referred as “air pollution” and the latter as “environmental pollution”.

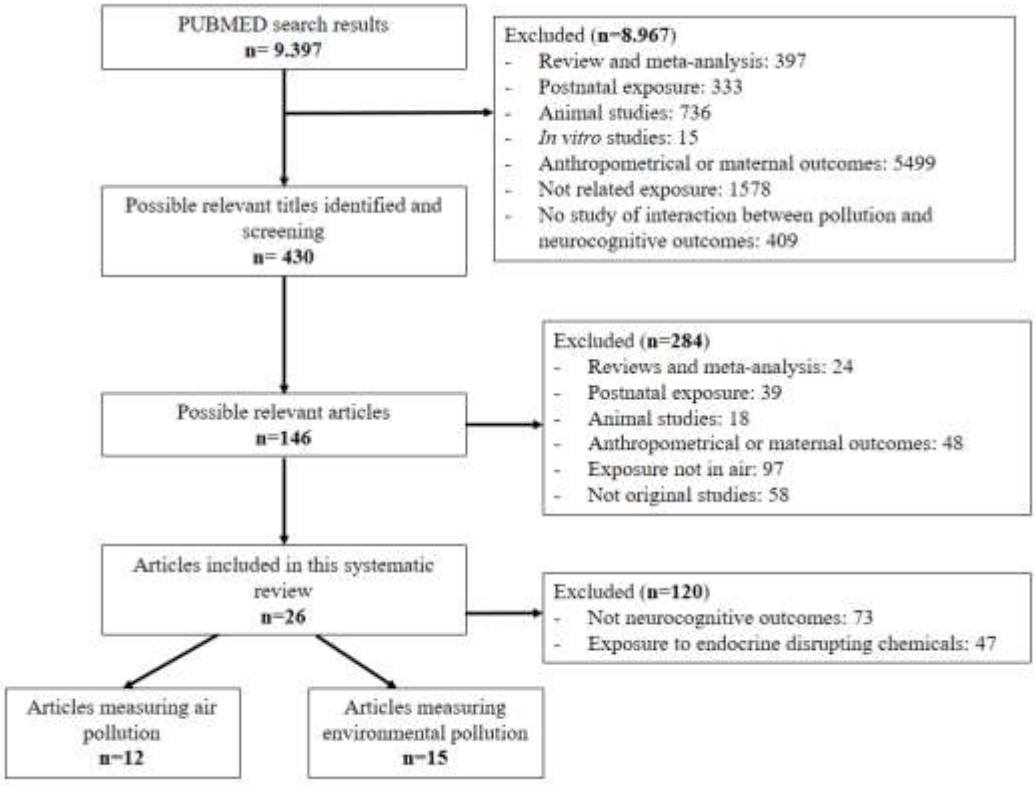

Figure 1. Workflow of the included articles of this review.

Air pollution

After the filtering, 12 articles were included in the systematic review. **Table 1** shows the characteristics of the studies assessing the effects of prenatal exposure to air pollution and child’s neurodevelopment. Most of them were conducted in developed countries: five in Spain (4,19,29,31,32), five in United States (9,18,27,28,30), and one in Poland (8). Just one study was performed in a developing country, Taiwan (11).

All the studies determined the exposure to traffic-related pollutants, measured during the whole pregnancy in most of them (4,8,9,11,18,19,28,29,31,32) and only at the third trimester of pregnancy in two cases (27,30). Air pollution was monitored using either aerosol samplers or air pollution monitors located near the areas where the study was conducted (4,11,31), land-use regression models using monitoring databases information and geolocation of mothers' addresses during pregnancy (9,18,19,29,30,32) or 48-h personal air monitoring (8,27). In one article, exposure was assessed through questionnaires addressed to mothers and the use of pesticides and environmental-containing products was determined (28).

Regarding the timing when neurocognitive assessment was evaluated, five studies conducted the tests between 6 and 25 months of age (4,11,28,31,32) and six other in scholar ages (between 4 and 10 years old) (8,9,19,27,29,30). Only one study evaluated neurocognitive outcomes throughout the time, between one and 36 months of age (18). Neurocognitive outcomes were determined using psychomotor and skills tests and scales, all of them adapted to the language of the country where it was held. Bayley's Scale of Infant Development (BSID) was the most used test for toddlers and preschoolers (4,28,31,32). This test includes a wide range of items assessing mental development by examination of language skills, motor scores and cognitive performances.

Other tests used were The Birth Cohort Study Scale (TBCS scale) (11), Wide Range Assessment of Memory and Learning or Visual Motor Abilities (WRAML/VMA) (9,30), Wechsler Preschool and Primary Scale of Intelligence (WPPSI) (27), Attention Network Test (ATN) (19) and McCarthy Scales of Children's Abilities (29), Raven Coloured Progressive Matrices (RCPM) (8), and Ages and Stages Questionnaires (ASQ) (18).

Table 1. Characteristics of included studies assessing air pollution.

AUTHORS	YEAR	COUNTRY	N	POLLUTANT	SAMPLE	TIME OF EXPOSURE	OUTCOME	TEST	CHILD'S AGE
Jiang, H (28)	2020	USA	190	Air toxicants	Questionnaire to mothers	Whole pregnancy	Children's Language Development	Bayley Scales of Infant Development - III	14-23 and 20-25m
Ha, S (18)	2019	USA	5825	PM O_3	Land-use regression models	Whole pregnancy	Fine motor Gross motor Communication skills	Ages and Stages Questionnaires	1,12,18,24, 30 and 36 m
Tozzi, V (32)	2019	Spain	391	PM	Land-use regression models	Whole pregnancy	Developmental scores	Bayley Scales of Infant Development	15 m
Lertxundi, A (29)	2019	Spain	1119	PM NO_2	Land-use regression models	Whole pregnancy	General Cognitive Index Motor skills	McCarthy Scales of Children's Abilities	4-6 y
Rivas, I (19)	2019	Spain	2221	PM	Land-use regression models	Whole pregnancy	Working memory and attentiveness	Attention Network Test	7-10 y
Harris, MH (30)	2015	USA	1109	BC PM	Land-use regression models	Third trimester	Verbal skills Nonverbal skills Motor skills	Visual Memory Index of the Wide Range Assessment of Memory and Learning	6-10 y
Cowell, WJ (9)	2015	USA	258	BC	Land-use regression models	Whole pregnancy	General Memory Index	Wide Range Assessment of Memory and Learning abilities	6 y
Lertxundi, A (31)	2015	Spain	438	PM NO_2 C_6H_6	Air pollution monitor	Whole pregnancy	Mental scale score	Bayley Scales of Infant Development	15 m
Lin, CC (11)	2014	Taiwan	533	PM CO CO_2 O_3 SO_2 NO_2	Air quality monitoring stations	Whole pregnancy	Gross motor Fine motor Language skills Social-self-care abilities	The Birth Cohort Study Scale	6 and 18 m
Guxens, M (4)	2012	Spain	1889	NO_2 C_6H_6	Air samplers	Whole pregnancy	Mental Development	Bayley Scales of Infant Development	14 m
Edwards, SC (8)	2010	Poland	214	PAH	48-h air monitoring Cord blood	At delivery	Intelligence Quotient	Raven Coloured Progressive Matrices	5 y
Perera, FP (27)	2009	USA	249	PAH	Personal air monitoring	Third trimester	Intelligence Quotient	Wechsler Preschool and Primary Scale of Intelligence	5 y

PM: Particulate Matter; NO_2: Nitrogen Dioxide; CO: Carbon Monoxide; CO_2: Carbon Dioxide; O_3: Ozone; SO_2: Sulfur Dioxide; BC: Black Carbon; C_6H_6: Benzene; PAH: polycyclic aromatic hydrocarbons.

Environmental pollution

Fifteen articles assessed prenatal exposure to environmental pollution in biological samples. Information about the articles is specified in **Table 2**. Most of them were conducted in Asian areas: seven in China (2,3,21,22,36,37,39), one in Taiwan (13), one in Nepal (34), and one in Bangladesh (15). The rest were conducted in American and European countries, including the United States (35), Mexico (40) and Poland (8,33,38).

The pollutants assessed include both traffic-related pollutants and metals. The exposure to metals mixtures (including lead, arsenic, manganese or zinc) were assessed in three studies (15,22,34), to lead in three studies (13,38,40) and cadmium in other one (2). PAHs were measured in six articles (3,8,35–37,39). In addition, two studies assessed the exposure to both PAHs and metal mixtures (21,33).

Outcome assessment was determined mainly in cord blood (8,15,21,22,34–36) although some studies additionally collected maternal blood (2,13,38–40). Urine samples were collected in two studies (3,37), while other collected maternal hair and urine together with cord blood (33). Although some studies assessed the exposure throughout pregnancy (33,38,40) or at third trimester (13), most of them collected the biological samples at delivery (2,3,8,15,21,22,34–37,39).

As for the assessment of developmental outcomes, the vast majority of studies conducted psychomotor tests between one and two years old (2,3,15,21,33,38,40) and three studies did so between neonatal stage and 6 months (22,34,37). Two studies conducted the neurocognitive test during scholar years (35,36) and two other throughout the years until 5 and 9 years of age, respectively (13,39). Regarding the tests used for neurocognitive scores, BSID was again the mostly employed, being used in five studies (15,33,34,38,40). In addition, Gessel Development Scale (GDS) was used in many studies (2,3,21,39), RCPM in one case (8), Wechsler Intelligence Scale for Children (WISC) in two studies (35,36) and Neonatal Behavioral Neurological Assessment (NBNA) (22,37). One study handled both BSID and WISC to estimate children's capabilities (13).

Table 2. Characteristics of included studies assessing environmental pollution.

AUTHORS	YEAR	COUNTRY	N	POLLUTANT	SAMPLE	TIME OF EXPOSURE	OUTCOME	TEST	CHILD'S AGE
Cao, X (3)	2020	China	158	PAH	Urine Cord blood	At delivery	Developmental Quotient	GDS	2 y
Polanska, K (38)	2018	Poland	402	Pb	Maternal blood Cord blood	Whole pregnancy	Cognitive performance Language development	BSID	12 and 24 m
Lee, J (39)	2017	China	217	PAH	Maternal blood Cord blood	At delivery	Developmental Quotient Intelligence Quotient	GDS WISC	2 y/ 5 y
Valeri, L (15)	2017	Bangladesh	825	As Mn Pb	Cord blood	At delivery	Cognitive development score Llanguage development score	BSID-III	20-40 m
Vishnevetsky, J (35)	2015	USA	276	PAH	Cord blood	At delivery	Intelligence Quotient	WISC-IV	7 y
Wang, Y (2)	2015	China	149	Cd	Maternal blood Cord blood	At delivery	Developmental Quotient	GDS	1 y
Polanska, K (33)	2013	Poland	198	Pb Cd Hg PAH	Cord blood Hair samples Urine	Whole pregnancy	Cognitive skills Motor skills Language skills Adaptative behavior	BSID-III	12 and 24 m
Parajuli, RP (34)	2013	Nepal	94	Pb As Zn	Cord blood	At delivery	Mental Developmetal Index Psychomotor Developmental Index	BSIDII	6 m
Li, XH (37)	2012	China	297	PAH	Urine	At delivery	General assessment scores	NBNA	Neonatal
Perera, F (36)	2012	China	122	PAH	Cord blood	At delivery	Intelligence Quotient	WPPSI	5 y
Huang, PC (13)	2012	Taiwan	66	Pb	Venous blood Cord blood	Third trimester	Mental Developmental Index Psychomotor Developmental Index Intelligence Quotient	BSID-II WISCIII	2-3, 5-6, 8-9 y
Yu, XD (41)	2011	China	1652	Pb Hg As Cd	Cord blood	At delivery	General assessment scores	NBNA	3 days
Edwards, SC (8)	2010	Poland	214	PAH	48-h air monitoring Cord blood	At delivery	Intelligence Quotient	RCPM	5 y
Tang, D (21)	2008	China	110	PAH	Cord blood	At delivery	Developmental Quotient	GDS	2 y
Hu, H (40)	2006	Mexico	146	Pb	Maternal blood Cord blood	Whole pregnancy	Mental Developmental Index	BSID-II	2 y

PAH: Polycyclic Aromatic Hydrocarbons; Pb: Lead; As: Arsenic; Mn: Manganese; Cd: Cadmium; Hg: Mercury; Zn: Zinc; GDS: Gessel Development Scale; BSID: Bayley's Scale of Infant and Toddler Development; WISC: Wechsler Intelligence Scale for Children; NBNA: Neonatal Behavioral Neurological Assessment; WPPSI: Wechsler Preschool and Primary Scale of Intelligence; RCPM: Raven Coloured Progressive Matrices

DISCUSSION

Almost all the studies reviewed showed significant associations between air and environmental pollutants and neurocognitive outcomes in both preschool and school years, leading to impairments until age ten years, concluding a long-lasting effect in development. Air pollution exposure showed significant differences including time of exposure and sex-differences.

Air pollution

Many studies found significant results between prenatal exposure to traffic-related pollutants and worst neurocognitive performances, although, in some cases, conclusions were not consistent.

In this regards, Lertxundi et al. (29) found slightly lower motor skills outcomes in scholar-age children whose mothers were prenatally exposed to air pollutants compared with their counterparts, although no significant results were found.

Harris et al. (30) demonstrated that a higher prenatal exposure to BC was associated with significantly lower verbal IQ in children at 6 to 10 years of age. Similarly, Perera et al. (27) found a significant association between prenatal PAHs exposure and worse scores in full-scale and non-verbal IQ at six years of age. These results are related to Edwards et al. (8), that shows lower IQ scores correlated with higher prenatal exposure to PAHs.

Rivas et al. (19) also found that PM prenatal exposure is associated with lower scores in working memory between 7-10 years of age, suggesting that air pollutant exposures during prenatal life may generate disparities and affect long-term neurocognitive outcomes.

Concerning preschooler years, Lertxundi et al. (31) found significant results between maternal exposure to PM and NO2 during pregnancy and lower psychomotor and cognitive performances at two years of age. Ha et al. (18) found that PM exposure during whole pregnancy was related to lower fine motor development from 8 months onward. This could be because at newborn ages is difficult to evaluate cognitive performances due to an early age. Prenatal exposure to PM was related to lower motor development at children at 15

months of age (32), and Jiang et al. (28) also showed that household toxicant exposure during pregnancy was associated with lower language skills and cognitive performances at 1 and 2 years of age. Guxens et al. (4) found that prenatal exposures to NO_2 and benzene were inversely correlated with mental development, despite the results did not reach statistically significance.

Although is it still not known how air pollutants interact with neurodevelopmental pathways, it is hypothesized that oxidative stress in brain regions and activation of immune responses may be triggered by traffic-related pollutants (1). Air toxicants can enter the organism via inhalation and then reach the placental barrier, thus going through the fetal cavity and reaching the fetal brain through the blood-brain barrier. Traffic-related pollutants are known to activate maternal immune responses, leading to an increased number of pro-inflammatory cytokines (42). These are known to generate oxidative stress in the brain and neuroinflammation, known to disrupt myelination and synaptogenesis during fetal neurodevelopment. Pro-inflammatory cytokines are also known to alter brain cell organization and neurogenesis, and disrupt the production of brain derived neurotrophic factor, needed for memory synaptic-plasticity in the hippocampus (42). Neuroinflammation is also related to microglia activation; which is needed for developing normal brain functions, although its excessive and chronic activation leads to neurotoxicity, and neural damage. In fact, microglial excessive activation is seen at neurodegenerative diseases, such as Alzheimer or Parkinson disease (1,3). Based on previous knowledge, PM exposure generates neurotoxic responses of the microglia and activation of pro-inflammatory pathways that can lead to impairments in developmental fetal life (42). Similarly, exposure to PAHs is associated with lower white matter surface during scholar years, which involves abnormal language skills (43).

When distributing by pregnancy trimester exposure, Lin et al. (11) found lower gross motor scores at 6 months when exposure was higher only at second and third trimesters. Moreover, SO_2 exposure during the whole pregnancy was negatively associated with fine motor scores at 12 and 18 months. Harris et al. (30) also found associations between third trimester exposures and lower IQ, although in this case, neurocognitive outcomes where assessed at scholar ages. Ha et al. (18) also demonstrate significant results in third trimester PM exposure

and lower neurocognitive performances and PM in second trimester and fine motor development at 2 years of age. These results show that maybe third trimester of exposure is a highly susceptible due to the fact that many myelination and maturation processes occur in the last trimester of gestation (1).

In all studies that estimated sex differences, boys showed more susceptibility than girls to air pollution. Cowell et al. (9) showed lower Attention Concentration Index in exposed boys than girls, although this study also estimated exposure to maternal stress during pregnancy, and thus individual associations may not be individually correlated only to air pollution. Rivas et al. (19) also showed worst working memory performances in boys than girls prenatally exposed to air pollutants. Lertxundi et al. (29) also found worse outcomes in boys in memory and verbal development exposure when exposed at PM. These results suggest differences in fetal development by sex and different windows of susceptibility to air pollutants, having a wider impact in males. Sex differences among neural development had been studied in previous studies. Wheelock et al. found differences in functional brain connectivity using fetal Magnetic Resonance Imaging (MRI) images during 25-38 weeks of gestation. In this study, males showed greater cerebellum volume and higher volume in other brain regions, leading to a higher susceptibility to prenatal exposure to air pollution (44). These results show different windows of susceptibility during fetal development.
As conclusion of this part, prenatal exposure to air pollutants induces impairments in neurocognitive aspects, being the third trimester of gestation the most susceptible period. According to the literature, both gestational timing of exposure and sex of the baby may play a role in the effect of prenatal exposure to air pollution on cognitive development of the offspring.

METAL POLLUTION

One of the most studied metals with neurotoxic potential is lead, which is known to affect the CNS development, inducing alterations in processes such as myelination, neuron differentiation and synaptogenesis (40,45). Despite it is mainly introduced in the body via inhalation, lead can trespasses the blood-placental and blood-brain barriers reaching the fetal brain (40). These mechanisms occur in different moments during gestation and current knowledge is not conclusive at which gestational age lead exposure causes

more damage. However, what is clear according to the studies gathered in this systematic review is that lead generates impairments in cognitive development even at low levels of exposure.

In this regards, Polanska et al. (38) showed that prenatal lead exposure affects neurocognitive outcomes even at low concentrations, measured in cord blood,. Specifically, the exposure during second and third trimesters of pregnancy was associated with significant results although only in boys. On the other hand, Hu et al. (40) found significant correlations between lead exposures during first trimester of gestation and lower neurodevelopmental scores at 24 months of age.

Other studies showed slight negative correlation between levels of different lead in maternal samples and neurocognitive development although results did not reach statistically significance (13,34,41). In one case, lack of significance may be attributed to an early time of outcome assessment, as neurocognitive test where held when the baby was three days old, maybe an extremely early stage for neurodevelopmental impairments to appear (44). Otherwise, the small sample size could be the reason in the case of Huang et al. (13) or Parajuli et al. (34).

In addition to lead, many studies assessed the association between prenatal exposure to other toxic metals and the offspring neurodevelopment. Again, although many studies did not find significant results, others showed strong associations. Thus, Yu et al. (41) found high concentrations of mercury, thallium, arsenic and cadmium in cord blood to be correlated with a lower child's cognitive development. Specifically, already a medium concentration of arsenic, which is known to be harmless in adults, was showed to be dangerous during fetal life, suggesting the high sensitivity of fetal stage for neurodevelopment.

As for mercury, despite being a widely known neurotoxic metal, previous findings show that environmental exposure may not be one of the riskier ways to impair fetal development. Nonetheless, mercury intake via diet or contaminated water may be the most harmful pathway to widely affect gestational development, possibly due to its high concentrations in the organism when entering that way. Tang et al. (21) showed that higher mercury

concentrations correlated with lower developmental quotients. Valeri et al. (15) showed that joint effects of lead, arsenic and manganese correlated with lower developmental scores at 20 and 40 months of age, being manganese the most neurotoxic. Polanska et al. (33) found associations between exposure to lead and cognitive function only in older ages, but not in the group of 12-months old, which could be due to the fact that the test applied was not sensitive to such earlier ages. Wang et al. (2) showed that high cadmium levels were related to lower social development quotients, although no associations were found in language, gross motor, fine motor and adaptive quotients. As found in the previous study, maybe the test applied may not be too precisely for these four outcomes assessment in the first year of life. However, this article studied how high maternal levels of cadmium affect brain-derived neurotrophic factor (BDNF), essential for hippocampal prenatal processes involving learning and memory (42). In this regard, the authors found that high cadmium levels prenatally led to a decrease in BDNF, which triggers to possible cognitive alterations emerging in early childhood, maybe mediated by inflammatory processes.

Heavy metals enter the body by inhalation, and reach systemic circulation. They mimic essential elements for the organism, trespassing membranes by ionic transporters and accumulating in the brain. Its potential risk is mainly generated by their long-lasting effects on the brain (45,46). Metal mixtures are known to alter brain functions due to activation of oxidative stress, neural apoptosis and impairments in neurotransmitters. Its way of action is still not concluded but it is hypothesized that metal mixture can induce changes of polarization in the ion channels, generating alterations in neural responses. As these processes are altered, Reactive Oxygen Species (ROS) are excessively produced, leading to cellular stress and then to cognitive dysfunction.

ENVIRONMENTAL TOXICANTS

All studies included in this section estimated PAHs as environmental toxicant assessment. These measurements were evaluated in maternal urine, cord blood and maternal plasma samples, as it was concluded that toxicant measures in these samples correlated with fetal exposures. No study showed sex-differences or time-of-exposure differences.

PAHs enter the body and they can be modified due to monohydroxylations, leading to PAHs metabolites that are excreted via urinary tract. These hydroxylated metabolites are used as biomarkers to assess PAH exposure. Cao et al. (3), who measured PAH-OH in urine and cord blood samples, found significant differences between higher concentrations of these metabolites with lower motor scores at two years of age. These results are related to the ones found by Li et al. (37), which showed that higher PAH-OH urine concentrations were related with lower NBNA scores at neonatal age.

Edwards et al. (8) found significant differences between higher concentrations of PAH metabolites in cord blood and lower non-verbal intelligence quotients at 5-years of age, suggesting the long-lasting neurocognitive effects of prenatal exposure to PAHs. Both Tang et. al (36) and Vishnevetsky et. al (35) assessed exposure measuring DNA-PAH adducts in cord blood.

PAHs are known to affect fetal development in many ways, including epigenetic. They can generate covalent bonds with DNA and thus form adducts, used as PAH exposure biomarkers (39). These metabolites provide inter-individual information of susceptibility and exposure to these toxicants. Tang et. al (36) found inverse correlation between levels of DNA-PAH and developmental quotient scores in language skills, motor skills and in general quotient. These results are cofirmed by subsequent studies, as Vishnevetsky et al. (35) findings showed that higher adducts in cord blood were related to lower IQ scores and processing speed.

PAH are known to generate cancerigenous, neurotoxic and detrimental health effects in human health (39). The fetus is ten times more susceptible than mother to epigenetic mutations lead by exposure to PAHs (47). Many mechanisms of action have been hypothesized, although no final conclusion has been reached. These mechanisms include DNA damage induced by activation of apoptosis, oxidative neural stress generated by disrupted regulation of antioxidant brain mediators, epigenetic alterations and endocrine disruption (35). Intrauterine growth retardation is observed in fetus highly exposed to PAHs, due to binding of these toxicants to growht placental factors. This leads to alterations in placental growht and thus to developmental delays in many areas (25). As for epigenetic pathways, PAHs can bind the DNA creating

adducts and thus changing the expression of relevant genes involved in neurogenesis and neural cell differentiation (35).

Nonetheless, two of the articles reviewed showed no significant differences between PAH concentrations in maternal samples and lower neurocognitive scores. Perera et al. (36) showed slight reductions in full-scale IQ at 5 years of age when higher prenatal exposure to PAHs, although results were not significant. However, when studying exposure of PAHs along with environmnetal tabacco smoke, results showed significance. Polanska et al. (33) did not find associations between PAH concentrations and psychomotor outcomes at preschool years. This lack of relevant results may appear due to limited sample size in both studies, or outcome assessment at a too earlier age in the latter.

CONCLUSIONS

Prenatal exposure to both air and environmental pollution affects the neurocognitive development of children during childhood. Furthermore, long-lasting effects of prenatal exposure to air pollutants, metal mixtures and environmental toxicants have been observed, with a window of susceptibility at third trimester of gestation; these toxicants can interact with neurodevelopmental pathways and alter their correct functioning, thus leading to cognitive impairements even until 10 years of age. However, sex-differences were found in this regards, with boys being at greater risk than girls from prenatal air pollution. This suggests, therefore, that both gestational trimester of exposure and baby's sex may act as powerful factors modulating the effect of air pollution on child's cognitive development. Although most studies show significant results, some of them do not show statistical differences, for what the conclusions are slightly controversial. Also, the wide variability of psycholgical tests and ages of outcome assessment prevented us to generalize the results. For these reasons, further studies investigating the effect of prenatal exposure to air pollutants, as well as metals and environmental toxicants, on neurocognitive outcomes in early childhood are guarenteed. Based on our findings, this studies should include the time-of-exposure and baby's sex as covariates in order to explore their role in the observed associations.

REFERENCES

1. Block ML, Elder A, Auten RL, Bilbo SD, Chen H, Chen C, et al. the Outdoor Air Pollution. 2013;33(5):972–84.

2. Wang Y, Chen L, Gao Y, Zhang Y, Wang C, Zhou Y, et al. Effects of prenatal exposure to cadmium on neurodevelopment of infants in Shandong, China. Environ Pollut. 2016;211:67–73.

3. Cao X, Li J, Cheng L, Deng Y, Li Y, Yan Z, et al. The associations between prenatal exposure to polycyclic aromatic hydrocarbon metabolites, umbilical cord blood mitochondrial DNA copy number, and children's neurobehavioral development. Environ Pollut [Internet]. 2020;265:114594. Available from: https://doi.org/10.1016/j.envpol.2020.114594

4. Guxens M, Aguilera I, Ferran B, Estarlich M, Fernández- Somoano A, Lertxundi A, et al. Research | Children ' s Health Prenatal Exposure to Residential Air Pollution and Infant Mental Development : Modulation by Antioxidants and Detoxification Factors. 2012;144(1):144–9.

5. Shang L, Yang L, Yang W, Huang L, Qi C, Yang Z, et al. Effects of prenatal exposure to NO2 on children's neurodevelopment: a systematic review and meta-analysis. Environ Sci Pollut Res. 2020;27(20):24786–98.

6. Sentís A, Sunyer J, Dalmau-Bueno A, Andiarena A, Ballester F, Cirach M, et al. Prenatal and postnatal exposure to NO2 and child attentional function at 4–5 years of age. Environ Int [Internet]. 2017;106(2):170–7. Available from: http://dx.doi.org/10.1016/j.envint.2017.05.021

7. Calderón-Garcidueñas L, Solt AC, Henríquez-Roldán C, Torres-Jardón R, Nuse B, Herritt L, 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 β-42 and α-synuclein in children and young adult. Toxicol Pathol. 2008;36(2):289–310.

8. Edwards SC, Jedrychowski W, Butscher M, Camann D, Kieltyka A, Mroz

E, et al. Prenatal exposure to airborne polycyclic aromatic hydrocarbons and children's intelligence at 5 years of age in a prospective cohort study in Poland. Environ Health Perspect. 2010;118(9):1326–31.

9. Cowell WJ, Bellinger DC, Coull BA, Gennings C, Wright RO, Wright RJ. Associations between prenatal exposure to black carbon and memory domains in urban children: Modification by sex and prenatal stress. PLoS One. 2015;10(11):1–14.

10. Gonzalez-Casanova I, Stein AD, Barraza-Villarreal A, Feregrino RG, DiGirolamo A, Hernandez-Cadena L, et al. Prenatal exposure to environmental pollutants and child development trajectories through 7 years. Int J Hyg Environ Health [Internet]. 2018;221(4):616–22. Available from: https://doi.org/10.1016/j.ijheh.2018.04.004

11. Lin CC, Yang SK, Lin KC, Ho WC, Hsieh WS, Shu BC, et al. Multilevel analysis of air pollution and early childhood neurobehavioral development. Int J Environ Res Public Health. 2014;11(7):6827–41.

12. Choi H, Jedrychowski W, Spengler J, Camann DE, Whyatt RM, Rauh V, et al. International studies of prenatal exposure to polycyclic aromatic hydrocarbons and fetal growth. Environ Health Perspect. 2006;114(11):1744–50.

13. Huang PC, Su PH, Chen HY, Huang H Bin, Tsai JL, Huang HI, et al. Childhood blood lead levels and intellectual development after ban of leaded gasoline in Taiwan: A 9-year prospective study. Environ Int [Internet]. 2012;40(1):88–96. Available from: http://dx.doi.org/10.1016/j.envint.2011.10.011

14. Hill DT, Petroni M, Larsen DA, Bendinskas K, Heffernan K, Atallah-Yunes N, et al. Linking metal (Pb, Hg, Cd) industrial air pollution risk to blood metal levels and cardiovascular functioning and structure among children in Syracuse, NY. Environ Res [Internet]. 2021;193(October 2020):110557. Available from: https://doi.org/10.1016/j.envres.2020.110557

15. Valeri L, Mazumdar MM, Bobb JF, Henn BC, Rodrigues E, Sharif OIA, et al. The joint effect of prenatal exposure to metal mixtures on

neurodevelopmental outcomes at 20–40 months of age: Evidence from rural Bangladesh. Environ Health Perspect. 2017;125(6):1–11.

16. Bai W, Li Y, Niu Y, Ding Y, Yu X, Zhu B, et al. Association between ambient air pollution and pregnancy complications: A systematic review and meta-analysis of cohort studies. Environ Res [Internet]. 2020;185(January):109471. Available from: https://doi.org/10.1016/j.envres.2020.109471

17. Grippo A, Myneni AA, Mu L. Abortion and Stillbirth. Jubb, Kennedy Palmer's Pathol Domest Anim. 2007;33(3):480–537.

18. Ha S, Yeung E, Bell E, Insaf T, Ghassabian A, Bell G, et al. Original Investigation Prenatal and Early Life Exposure to Ambient Air Pollution and Development. Physiol Behav. 2019;176(5):139–48.

19. Rivas I, Basagaña X, Cirach M, López-Vicente M, Suades-González E, Garcia-Esteban R, et al. Association between early life exposure to air pollution and working memory and attention. Environ Health Perspect. 2019;127(5):1–11.

20. Perera FP, Rauh V, Tsai WY, Kinney P, Camann D, Barr D, et al. Effects of transplacental exposure to environmental pollutants on birth outcomes in a multiethnic population. Environ Health Perspect. 2003;111(2):201–5.

21. Tang D, Li TY, Liu JJ, Zhou ZJ, Yuan T, Chan YH, et al. Effects of prenatal exposure to coal-burning pollutants on children's development in China. Environ Health Perspect. 2008;116(5):674–9.

22. Yu XD, Yan CH, Shen XM, Tian Y, Cao LL, Yu XG, et al. Prenatal exposure to multiple toxic heavy metals and neonatal neurobehavioral development in Shanghai, China. Neurotoxicol Teratol [Internet]. 2011;33(4):437–43. Available from: http://dx.doi.org/10.1016/j.ntt.2011.05.010

23. Borsani E, Della Vedova AM, Rezzani R, Rodella LF, Cristini C. Correlation between human nervous system development and acquisition of fetal skills: An overview. Brain Dev [Internet]. 2019;41(3):225–33. Available from: https://doi.org/10.1016/j.braindev.2018.10.009

24. Kolb B, Mychasiuk R, Gibb R, Stevens M, Frobisher C, Hawkins M, et al. The British Childhood Cancer Survivor Study: Objectives, methods, population structure, response rates and initial descriptive information. Pediatr Blood Cancer. 2008;50(5):1018–25.

25. Dejmek J, Solansky I, Benes I, Lenicek J, Sram RJ. The Impact of Polycyclic Aromatic Hydrocarbons and Fine Particles on Pregnancy Outcome. Environ Health Perspect. 2000;108(12):1159.

26. Hehua Z, Qing C, Shanyan G, Qijun W, Yuhong Z. The impact of prenatal exposure to air pollution on childhood wheezing and asthma: A systematic review. Environ Res [Internet]. 2017;159(36):519–30. Available from: http://dx.doi.org/10.1016/j.envres.2017.08.038

27. Perera FP, Zhiang L, Whyatt R, Hoepner L, Wang S, Camann D, et al. Prenatal Airbone Polycyclic Aromatic Hydrocarbon Exposure and Child IQ at Age 5 Years. Pediatrics. 2009;23(1):1–7.

28. Jiang H, Justice LM, Purtell KM, Bates R. Exposure to Environmental Toxicants and Early Language Development for Children Reared in Low-Income Households. Clin Pediatr (Phila). 2020;59(6):557–65.

29. Lertxundi A, Andiarena A, Martínez MD, Ayerdi M, Murcia M, Estarlich M, et al. Prenatal exposure to PM2.5 and NO2 and sex-dependent infant cognitive and motor development. Environ Res [Internet]. 2019;174(2):114–21. Available from: https://doi.org/10.1016/j.envres.2019.04.001

30. Harris MH, Gold DR, Rifas-Shiman SL, Melly SJ, Zanobetti A, Coull BA, et al. Prenatal and childhood traffic-related pollution exposure and childhood cognition in the project viva cohort (Massachusetts, USA). Environ Health Perspect. 2015;123(10):1072–8.

31. Lertxundi A, Baccini M, Lertxundi N, Fano E, Aranbarri A, Martínez MD, et al. Exposure to fine particle matter, nitrogen dioxide and benzene during pregnancy and cognitive and psychomotor developments in children at 15months of age. Environ Int [Internet]. 2015;80:33–40. Available from: http://dx.doi.org/10.1016/j.envint.2015.03.007

32. Tozzi V, Lertxundi A, Ibarluzea J, Baccini M. Causal Effects of Prenatal Exposure to PM 2 . 5 on Child Development and the Role of Unobserved Confounding. (2).

33. Polanska K, Hanke W, Sobala W, Trzcinka-Ochocka M, Ligocka D, Brzeznicki S, et al. Developmental effects of exposures to environmental factors: The polish mother and child cohort study. Biomed Res Int. 2013;2013.

34. Parajuli RP, Fujiwara T, Umezaki M, Furusawa H, Watanabe C. Home environment and prenatal exposure to lead, arsenic and zinc on the neurodevelopment of six-month-old infants living in Chitwan Valley, Nepal. Neurotoxicol Teratol [Internet]. 2014;41:89–95. Available from: http://dx.doi.org/10.1016/j.ntt.2013.12.006

35. Vishnevetsky J, Tang D, Chang H-W, Roen E, Wang Y, Rauh V, et al. Combined Effects of Prenatal Polycyclic Aromatic Hydrocarbons and Material Hardship on Child IQ. Neurotoxicol Teratol. 2015;176(1):139–48.

36. Perera F, Li TY, Lin C, Tang D. Effects of prenatal polycyclic aromatic hydrocarbon exposure and environmental tobacco smoke on child IQ in a Chinese cohort. Environ Res. 2012;114:40–6.

37. Li XH, Liu GZ, He QY, Zhang B Bin, Wei W, Yang SR, et al. [Study of the correlation between polycyclic aromatic hydrocarbons exposure during pregnancy and neonatal neurobehavioral development in Taiyuan and Changzhi cities]. Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi. 2012;

38. Polanska K, Hanke W, Pawlas N, Wesolowska E, Jankowska A, Jagodic M, et al. Sex-dependent impact of low-level lead exposure during prenatal period on child psychomotor functions. Int J Environ Res Public Health. 2018;15(10):1–11.

39. Lee J, Kalia V, Perera F, Herbstman J, Li T, Jisheng N, et al. Prenatal airborne polycyclic aromatic hydrocarbon exposure, LINE1 methylation and child development in a Chinese cohort. Physiol Behav. 2017;176(1):139–48.

40. Hu H, Téllez-Rojo MM, Bellinger D, Smith D, Ettinger AS, Lamadrid-Figueroa H, et al. Fetal lead exposure at each stage of pregnancy as a predictor of infant mental development. Environ Health Perspect. 2006;114(11):1730–5.

41. Yu XD, Yan CH, Shen XM, Tian Y, Cao LL, Yu XG, et al. Prenatal exposure to multiple toxic heavy metals and neonatal neurobehavioral development in Shanghai, China. Neurotoxicol Teratol. 2011;

42. Green HF, Nolan YM. Inflammation and the developing brain: Consequences for hippocampal neurogenesis and behavior. Neurosci Biobehav Rev [Internet]. 2014;40:20–34. Available from: http://dx.doi.org/10.1016/j.neubiorev.2014.01.004

43. Peterson BS, Rauh VA, Sc D, Bansal R, Ph D, Hao X, et al. HHS Public Access. 2015;72(6):531–40.

44. Wheelock MD, Hect JL, Hernandez-Andrade E, Hassan SS, Romero R, Eggebrecht AT, et al. Sex differences in functional connectivity during fetal brain development. Dev Cogn Neurosci [Internet]. 2019;36(March):100632. Available from: https://doi.org/10.1016/j.dcn.2019.100632

45. Karri V, Schuhmacher M, Kumar V. Heavy metals (Pb, Cd, As and MeHg) as risk factors for cognitive dysfunction: A general review of metal mixture mechanism in brain. Environ Toxicol Pharmacol [Internet]. 2016;48:203–13. Available from: http://dx.doi.org/10.1016/j.etap.2016.09.016

46. Liu J, Lewis G. Environmental Toxicity and Poor Cognitive Outcomes in Children and Adults. Colourage. 2015;61(10):82–6.

47. Herbstman JB, Tang D, Zhu D, Qu L, Sjödin A, Li Z, et al. Prenatal exposure to polycyclic aromatic hydrocarbons, benzo[a]pyrene-DNA adducts, and genomic DNA methylation in cord blood. Environ Health Perspect. 2012;120(5):733–8.