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Air pollution and neurodevelopmental skills in preschool- and school-aged children : A systematic review

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Corresponding Author:	Rosario Montirosso Scientific Institute, IRCCS Eugenio Medea Bosisio Parini, LC Italy
First Author:	Annalisa Castagna
Order of Authors:	Annalisa Castagna
	Eleonora Mascheroni
	Silvia Fustinoni
	Rosario Montirosso
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Suggested Reviewers:	Christina Demski demskicc@cardiff.ac.uk
	Ruth Ann Etzel retzel@gwu.edu

Dr Rosario Montirosso
Scientific Institute, IRCCS E. Medea
0-3 Center for the at-Risk Infant
23846 Bosisio Parini, Lecco, Italy
Rosario.montirosso@lanostrafamiglia.it

To:
Giovanni Laviola
Editors-in-Chief: *Neuroscience & Biobehavioral Reviews*

Dear Editors,

We are pleased to submit the manuscript entitled “Air pollution and neurodevelopmental skills in preschool- and school-aged children: A systematic review” co-authored by Annalisa Castagna, Eleonora Mascheroni, Silvia Fustinoni and Rosario Montirosso for consideration as a Systematic Review by *Neuroscience & Biobehavioral Reviews*.
The current work deals with a timely issue that may have important implications in the field of neurodevelopmental science. In particular, in the present manuscript we try to shed some lights on the effect of early life exposure to air pollution and specific neurodevelopmental skills in typically developing pre-school and children, paying particular attention to the possible effects of prenatal or postnatal air pollution exposure. Results reported in the review may serve as a urgent claim not only in increasing research in this field, but also in underling the need for a global action to reduce environmental pollutants exposure with a particular attention to sensitive at risk populations such as pregnant women and young children. In the light of the aims of *Neuroscience & Biobehavioral Reviews*, we believe that this manuscript might adequately meet the interests of both clinicians and researchers who work in the fields of developmental psychology and behavioral sciences who are readers of the Journal. The corresponding author confirms that all the authors have read the manuscript and agreed to submit it for publication. Each author had complete access to the study data that support the publication. All individuals listed as authors meet the appropriate authorship criteria. Nobody who qualifies for authorship has been omitted from the list, contributors, and their funding sources have been properly acknowledged. All authors and contributors have approved the acknowledgment of their contributions and the manuscript as submitted. There is no conflict of interest.

Please address all correspondence concerning this manuscript to me at:
rosario.montirosso@lanostrafamiglia.it

Thank you for your consideration of this manuscript.

Sincerely,

Rosario Montirosso
On behalf of co-authors

Highlights

- Exposure to pollutants may be a risky for brain maturation and neurodevelopment
- Air pollution may have detrimental effect on different neurodevelopmental skills
- Air pollution mainly affect global intellective functioning and attentive skills
- The greatest risk for neurodevelopment seems to occur through prenatal exposure

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Air pollution and neurodevelopmental skills in preschool- and school-aged children: A systematic review

Annalisa Castagna[1*], Eleonora Mascheroni[1*],

Silvia Fustinoni[2,3], Rosario Montirosso[1#]

[1] *0-3 Center for the at-Risk Infant*, Scientific Institute IRCCS “Eugenio Medea”, Bosisio Parini, Lecco, Italy

[2] *EPIGET - Epidemiology, Epigenetics, and Toxicology Lab, Department of Clinical Sciences and Com-munity Health, Università degli Studi di Milano, Milano, Italy*

[3] *Environmental and Industrial Toxicology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy*

*These authors contributed equally to this work.

Corresponding author at:

[#]Rosario Montirosso, *0-3 Center for the at-Risk Infant*, Scientific Institute IRCCS “Eugenio Medea”, Bosisio Parini, Lecco, Italy. Phone: +39 031 877464; email: rosario.montirosso@lanostrafamiglia.it

Conflict of interest

None for any authors.

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Contributions

Concept and design: RM; Study concept and design: EM, AC, SF ; Acquisition of data: EM, AC, SF; Analysis and interpretation of data: EM, AC, SF, RM; Drafting and Critical revision of the manuscript for important intellectual content: RM, EM, AC, SF

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1. Introduction

1.1 General framework

Air pollution can be defined as the presence of toxic chemicals or compounds (including those of biological origin) in the air, at levels that pose a health risk. Recent data from the World Health Organization (WHO, 2018) revealed that 9 out of 10 people breathe air that is above WHO guideline limit values (WHO, 2021), with the highest levels of exposure in low- and middle-income countries. With a specific focus on pediatric age, the WHO (2018) reported that 1.8 billion children around the world breathe polluted air, which, in turn, has been associated with seriously detrimental effects on their health and physical development, such as respiratory and cardiovascular disease. Importantly, a growing number of studies have shown that exposure to air pollution either during fetal life or during the early developmental stages might have negative effect also on neurodevelopmental skills (Lopuszanska and Samardakiewicz, 2020; Shang et al., 2020), with long last impact through the entire life-span (Brockmeyer and D'Angiulli, 2016). Neurodevelopment is a term referring to the brain maturation of neurological pathways underlying perceptual, motor and cognitive performance or functioning, such as motor and sensorimotor functions, intellectual functioning, language, executive function, memory and learning and attention (from here on: neurodevelopmental skills). It is well known that changes in brain architecture depend on the dynamic interplay between biological, experiential and environmental factors (Fox et al., 2010). Therefore, exposure to environmental chemical insults, such as air pollution, presumably interferes with brain maturation processes, which, in turn, could contribute to a variety of neurodevelopmental difficulties (Boda, Rigamonti, & Bollati, 2020; Woodward, Finch, & Morgan, 2015). Indeed, Magnetic Resonance Imaging (MRI) studies observed that high concentrations of air pollutants were related to changes in the brain's white matter or lower functional integration and segregation in children's brain networks (Lopuszanska and Samardakiewicz, 2020). Given the growing concern of the impact that air pollutants may have on child neurodevelopment (Boda et al., 2020; Lopuszanska and Samardakiewicz, 2020), the aim of the current work is to systematically review the relationship between air pollution exposure and neurodevelopmental skills in preschool- and school-aged children.

1.2 Air pollutant and neurodevelopmental skills

A relevant source of air pollution is motorized traffic that produces pollutants such as NO_2, PM of variable size, elemental and black carbon (EC and BC), polycyclic aromatic hydrocarbons (PAHs) and volatile organic compounds, from the combustion of fossil fuels. These pollutants are also known as traffic related air pollution (TRAP).

NO_2 is a major traffic air pollutant. In general, high temperature combustion processes primary produce nitrogen oxides (NOX) by oxidation of atmospheric nitrogen; NO_2 is mostly formed as secondary pollutant, mainly by oxidation of NO.

Atmospheric particulate matter (PM) is a set of particles with a great variety of physical, chemical, geometric and morphological characteristics, dispersed in the atmosphere for sufficiently long times to undergo diffusion and transport phenomena. The sources can be natural (such as soil erosion, marine spray, pollen dispersion, etc.) or anthropogenic (e.g. combustion processes in general and vehicular traffic in particular). It is not a specific chemical entity; major components of PM are sulfates and nitrates, ammonia, sodium chloride, carbon, mineral dust. To a lower amount, PM contains also metals and polycyclic aromatic hydrocarbons (PAHs). Regarding the size, PM10 and PM2.5 are the fraction of particles collected with a selection system having an efficiency established by the standard and equal to 50% for those particles of aerodynamic diameter of 10 µm and 2.5 µm, respectively. PM10 and PM2.5 are, sometimes, called coarse or fine PM. Ultrafine particles (UFPs) are particulate matters of nanoscale size (less than 0.1 µm or 100 nm in diameter).

Elemental carbon (EC) and black carbon (BC) are both carbonaceous fraction of PM; they are carbon particles with microstructure similar to that of graphite and aggregated in small spheres with a diameter between 10 and 50 nm. There is no full agreement in their definition and often this is based on the different methods used for their measurement. Elemental carbon (EC) can be defined as a substance containing only carbon, not bound to other elements, and its various allotropic forms;

operationally, it is the carbonaceous fraction that is thermally stable up to 3,500 °C, in an inert atmosphere. Black carbon (BC) is defined as the set of carbonaceous particles capable of absorbing light with a characteristic wavelength in the visible spectrum (380 ÷ 760 nm). These very small particles can reach the deepest part of the respiratory tract and act as carrier of toxic chemicals.

The analysis of PM2.5 revealed the presence of several organic and inorganic components from different anthropogenic sources; among them, there are ions of metallic elements, including cupper (Cu). Among organic components, there are high molecular weight polycyclic aromatic hydrocarbons (PAHs), that are a class of hydrocarbons consisting of multiple condensed aromatic rings formed during incomplete combustion of fossil fuels.

Notably, these pollutants were considered in most studies that have investigated neurodevelopmental toxicity of air pollution. While several works (for a literature review, see: Cory-Slechta, Sobolewski, & Oberdörster, 2020) reported an association between air pollution and neurodevelopmental disorders such as Autism Spectrum Disorders (ASD) and Attention Deficit Hyperactivity Disorders (ADHD) (Grandjean and Landrigan, 2006, 2014; Suades-Gonzalez et al., 2015; Costa et al., 2017; Costa et al., 2020; Ritz et al., 2018; Shih et al., 2020), some recent studies are now focusing on main neurodevelopmental skills, such as intellectual functioning (e.g., Loftus et al, 2019), memory and learning (e.g., Alemany et al., 2018), attention (e.g., Guxen et al., 2018), motor functions (e.g., Lertxundi et al., 2019), behavior problems (Ren et al., 2019), even in typically developing children (Grandjean and Landrigan, 2014).

1.3 Neuroplasticity and periods of exposure to pollutants

Human brain development is a protracted process which extends through late adolescence (Raznahan et al., 2012). However, there is evidence suggesting that early exposure to pollutants is critical for brain maturation with effects on neuroplasticity (Salvi and Salim, 2019). Neuroplasticity refers to functional brain adjustments based on neural processes such as neurogenesis, synaptogenesis (i.e., synaptic proliferation), pruning (i.e., reduction in the number of synapses and number of axons) and myelination (Kolb & Gibb, 2011). By the end of the embryonic period, there is rapid growth and elaboration of both cortical and subcortical structures, including the rudiments of the major fiber pathways (Kostovic and Jovanov-Milosevic, 2006; Stiles and Jernigan, 2010). These biological processes depend on the molecular events of gene expression, but they are also influenced by a continuous series of dynamic interactions between genetic influences and environmental conditions which can interfere with these maturational processes (LaFreniere & MacDonald, 2013). As a consequence, early exposure to pollutants during prenatal and postnatal period, including childhood can potentially lead to lasting brain alterations with more serious consequences for the developing brain than in subsequent phases of development (Lee et al., 2017).

1.4 The current review

In the light of these considerations, the current systematic review was addressed to examine the impact of traffic related air pollution on specific neurodevelopmental skills (i.e., intellective functioning, memory and learning, attention and executive functions, verbal language, numeric ability and motor and/or sensorimotor functions) in typically developing children. We focused on preschool- and school-age including children between 3 and 12 years of age. We decided not to include studies focused on infancy (which enrolled children aged 0-3 years) due to the fact that major neurodevelopmental skills are generally consolidated starting in preschool, whereas in infancy generally only some precursors of these skills can be assessed (Ellis et al., 2020). Although a recent systematic review has examined the relationship between early exposure to air pollution and cognitive and motor development in children (Lopuszanska and Samardakiewicz, 2020), authors did not discuss in details the specific impact that period of exposure to pollutants (i.e., prenatal and postnatal exposure) might have on a broader number of specific neurodevelopmental skills. Indeed, while several studies examined the impact of air pollutants during the gestational period, generally from the third trimester to infant's birth (i.e., prenatal exposure) (Jedrychowski et al., 2015; Chiu et al., 2016; Shang et al., 2020), a number of research focused on later developmental period, during infancy and childhood (i.e., postnatal exposure), and only a few studies have investigated the impact of the double exposure (prenatal plus postnatal) (Pujol et al., 2016; Wang et al., 2017; Alemany et al., 2017). Thus, an understanding on differential impact that prenatal, postnatal or double exposure might have on neurodevelopmental skills during preschool- and school-age could provide new insights about the specific relevance of periods during which fetus/child is exposed to air pollutants on brain development. Accordingly, we analyzed the effect of prenatal, postnatal and double exposure (prenatal plus postnatal) to air pollution, separately. The main aims were: (a) to provide a comprehensive state-of-the-art account of research regarding the association between air pollution exposure (prenatal and postnatal) and specific neurodevelopmental skills in preschool- and school-age children; (b) to highlight future directions of research in this field.

2. Methods

2.1 Search strategy

The systematic review was carried according to the Referred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines (Liberati et al., 2009; Moher et al., 2015). Records were searched on four databases (i.e., Embase, Pubmed, Scopus and Web of Science) until September 2021. All database searches were conducted using the following terms: “air pollution” OR “particulate matter” OR “environmental pollution” OR “environmental pollutants” OR “urban pollution” AND “cognition” OR “cognitive function” OR “intelligence” OR “brain” OR “developmental quotient” OR “intelligence quotient” OR “neurodevelopment” AND “child” OR “infant”.

2.2 Selection

We selected articles according to some inclusion and exclusion criteria in order to identify the articles that met our goals. Inclusion criteria were: (1) articles written in English; (2) studies that examined only exposure to air pollution and not other types of environmental pollutants; (3) prenatal and/or postnatal exposure to air pollutions; (4) assessment of neurodevelopmental skills (i.e., intellective functioning, memory and learning, attention and executive functions, verbal language, numeric ability and motor and/or sensorimotor functions); (5) studies that used valid and standardized tools to assess neurodevelopmental skills; (6) studies that considered sample of preschool and school-age children (i.e., between 3 and 12 years). Furthermore, we did not include in the review: (1) meta-analyses and reviews; (2) studies that considered environmental pollutants such as fertilizers or household pollutants such as nicotine (3) studies that evaluated the relation between air pollution and neurodevelopmental disorders (i.e., ADHD, ASD); (4) studies that evaluated the relation between air pollution and behavioral problems.

First, eligible articles were screened by reading titles and abstracts by one author expert in child development (AC). Second, selected paper were further reviewed by one author with environmental pollution expertise (SF) and by two authors expert in child development (EM and RM). Disagreement was solved in conference.

The search strategy yielded a total of 1169 studies (Embase *n* = 141; Pubmed *n* = 297; Scopus n = 24; Web of Science *n* = 707). After checking for duplicates and a prior screening on the titles and abstracts we identified 56 potential articles. On the basis of the inclusion and exclusion criteria, a total of 30 studies were included in the review. The study selection process is reported in Figure 1.

INSERT FIGURE 1

2.3 Quality appraisal

The methodological quality of the included papers was evaluated using the Quality Assessment Tool for Quantitative Studies (Jackson et al., 2005). Especially, it was considered sections A–F (A, selection bias; B, study design; C, confounders; D, blinding; E, data collection methods; F, withdrawal and dropouts) and they were coded by two independent authors (AC and EM) as 3 (*weak*), 2 (*moderate*), or 1 (*strong*) according to the component rating scale criteria. 96% agreement was reached for the A–F components, and disagreement was generally due to different interpretations of studies. Disagreement was solved in conference through the supervision of a third author (RM). In order to evaluate the quality of air pollution analyses, an additional ad-hoc factor (G) was added to the methodological assessment. The author with a broad expertise in air pollutant analyses (SF) gave the evaluation based on following the score: 3 (*weak*), 2 (*moderate*), or 1 (*strong*) (table 2). A final 1–3 score is assigned to each paper according to the presence of 2 or more weak scores (3, *weak*), only 1 weak score (2, *moderate*), no weak scores (1, *strong*).

For most studies (*n* = 21) the selected individuals are at least somewhat likely or very likely to be representative of the target population even if 9 studies considered population that restrict generalizability. Given the complexity of the studies, 50% of them had enough evidence of withdrawals to obtain low (*weak*) scores on the quality appraisal. All studies, except 2 (Calderón-Garcidueñas et al., 2011; Talaeizadeh et al., 2018), adjusted for a series of relevant confounders (e.g. demographic and socioeconomic variables); moreover, all works used valid data collections tools to evaluate neurodevelopmental outcome. Finally, as regard exposure assessment, 23 studies applied sophisticated methodologies based on a combination of measurements and models, taking into consideration specific time frames, and were evaluated as strong, 5 were evaluated as moderate, as based on less accurate evaluation of exposure and 2 studies merely compared heavily polluted vs. less polluted areas and were evaluated as weak. Overall, *n* = 24 studies (80%) were strong (*n* = 11, 37%) or strong to moderate (*n* = 13, 43%) (see Table 1); only 6 studies were classified as weak.

INSERT TABLE 1

2.4 Data synthesis and analysis

After identifying the papers, classification have been created to synthesize the included studies according to two main parameters. First, articles were categorized in six cluster according to the neurodevelopmental skills considered (i.e., intellective functioning; memory and learning; attention and executive functions; verbal language; numeric ability; motor and sensorimotor functions). Second, in each of the 6 categories studies were further grouped according to air pollution exposure period (i.e., prenatal exposure; postnatal exposure; both prenatal and postnatal exposure). The analyses of the study also consisted of the synthesis of: (a) geographical area of exposure to air pollutants; (b) exposure context (i.e., urban/metropolitan/polluted area, clean air/green area); (c) methodological aspect of the studies (i.e., study design; sample size and sample characteristics); (d) considered air pollutant/s (i.e., PM2.5, PM10, ultrafine particles, nitrogen dioxide, elemental carbon, black carbon, polycyclic aromatic hydrocarbons, airborne copper, traffic related air pollution); (e) analysis carried out to evaluate exposure; (f) test used to evaluate neurodevelopmental skills; (g) considered confounding variables, and h) main findings.

3. Results

3.1 General methodological aspects

Included studies considered sample of different sizes ranged from 30 (Calderón-Garcidueñas et al. 2011) to 8198 (Midouhas et al. 2018) participants. Most of the studies were carried out in Europe (*n* = 23), 9 studies were conducted in USA, one study in Mexico (Mexico City) and one study in Tehran (Iran). Eight studies considered preschool-aged children, while 23 studies considered school aged children.

The most represented European country was Spain with 12 studies (54% of the studies conducted in Europe). The other European studies were conducted in the Netherlands (n = 3), in Italy (in Rome, *n* = 2), in Poland (in Krakow, *n* = 2), in Germany (*n* = 1), Belgium (*n* = 1) and UK (*n* = 1). Notably, only one of the considered work analyzed data from four different European population-based birth cohorts (Netherlands, Germany, Italy and Spain).

Notably most of the included studies (n = 24) were part of brooder projects: 8 of them were part of the BRain dEvelopment and Air polluTion ultrafine particles in scHool children (BREATHE) project (Spain), 3 were part of the INMA – INfancia y Medio Ambiente (INMA) project (Spain), 2 were part of the project Viva, 2 of Asthma Coalition on Community, Environment and Social Stress (ACCESS) project. One study were part of Generation R Study, 1 of Gene and Environment Prospective Study on Infancy in Italy (GASPII) project, 1 of Conditions Affecting Neurocognitive Development and Learning in Early Childhood (CANDLE) study, 1 of Maternal-Infant Smoking Study of East Boston, 1 of European Study of Cohorts for Air Pollution Effects (ESCAPE) project, 1 of COGNition and Air pollution in Children (COGNAC) study, 1 of Millennium Cohort Study (MCS), 1 of Risk Factors for Antisocial Behavior (RFAB) twin study and 1 of Road traffic and Aircraft Noise exposure and children's Cognition and Health (RANCH) project.

3.2 Air pollution exposure

Traffic related air pollution (TRAP) included in this review encompass the following air pollutants: NO_2 (12 studies), PM of different sizes (13 studies), and components of PM such as: black carbon (BC, 5 studies), elemental carbon (EC, 4 studies), polycyclic aromatic hydrocarbons (PAHs, 6 studies) and cupper (2 studies). Fifteen articles consider a single pollutant; eight include two pollutants, five studies consider 3 pollutants and two studies include TRAP in general.

Most studies considered a polluted geographical area, evaluating the effect of TRAP on neurodevelopment. Ten studies investigated prenatal exposure to air pollution, 14 studies postnatal exposure and 6 studies both prenatal and postnatal exposure. Prenatal exposure to pollutants was estimated at the maternal residence using dispersion models or by personal monitoring (exposure to PAHs) or by biological monitoring using blood from the umbilical cord (exposure to PAHs). As for postnatal exposure, studies estimated exposure to pollutants at the child's residence and/or in the neighborhood of the school, considering, in some cases, both outdoor and indoor (in classroom) exposure. Both land use regression models or other models and measurement of air pollutants were used. Two studies considering both prenatal and postnatal exposure merely compared heavy polluted vs. less polluted areas, based on historical data from air quality networks.

3.3 Neurodevelopmental skills

3.3.1 Intellective functioning

Fourteen studies investigated full-scale intelligent quotient (IQ) considering both global score, verbal IQ (VIQ, an index of skills regarding verbal knowledge, comprehension, and verbal mathematical reasoning) and performance IQ (PIQ, which provides a measure of visuospatial abilities, spatial processing, attentiveness to details, and visual-motor integration). Studies included in this section are synthetized in Table 2.

INSERT TABLE 2

Prenatal exposure. Two studies (Chiu et al., 2016; Lubczynska et al., 2017) estimated prenatal exposure to PM2.5 reporting conflicting results. Chiu and colleagues (2016) highlighted that increased PM2.5 exposure in late pregnancy was associated to lower IQ scores, at 6 years of age but only in boys. On the other hand, no significant association emerged in Lubczynska et al.'s study (2017). Another study conducted on a large sample of children aged between 4 and 6 years reported a negative association between increase in PM10, but not in NO_2, and lower IQ, VIQ and PIQ scores (Loftus et al., 2019). Lertxundi et al. (2019) evaluated the global cognitive functions in relation to exposure to PM2.5 and NO_2 in children aged 4 to 6 years but unlike the Loftus and Freire's studies global cognitive function was negatively associated with NO_2 only in boys. Further, three studies, two on preschoolers and on school-age children, found significant associations between PAH exposure and IQ/PIQ scores (Edwards et al., 2010), IQ/VIQ scores (Perera et al., 2009), and VIQ score (Jedrychowski et al., 2015).

Postnatal exposure. One study reported that a longer black carbon (BC) exposure at children's residence was associated with lower IQ/VIQ/PIQ scores (Suglia et al., 2018). Wang and colleagues (2017) revealed a significant adverse PM2.5 effects on PIQ, but not on full-scale IQ and VIQ. In another study (Freire et al., 2010) the general cognitive function of preschoolers was measured in relation to NO_2 exposure but it did not reveal a significant association. Two works investigated the effect of air pollution comparing groups from critical polluted area and from healthy air area. In particular, Calderón-Garcidueñas et al. (2011) considered a small sample of children aged between 7 and 8 years lived either in a high concentrations of air pollutants (Mexico City) or in clean air environment (Polotitlán, Mexico State) (i.e. control group). Authors found that volumetric brain alterations (i.e., white matter hyperintensities) detected by MRI was associated with for air pollution exposure. Children who lived in Mexico City were further classified according to presence or absence of MRI prefrontal white matter hyperintensities. Analyses revealed that children with white matter hyperintensities obtained lower score in the VIQ; moreover, children without white matter hyperintensities but that lived in Mexico City obtained lower score in PIQ. In the study by Talaeizadeh et al. (2018) 90 female students at age of 8-10 living in two areas, one was critical polluted and one with a healthy air, were considered. Results showed significantly lower VIQ scores in girls who lived in the polluted area.

Prenatal/Postnatal exposure. Only two studies investigated the association between air pollution and intellective functioning considering both prenatal and postnatal exposure, reporting conflicting results.. In particular, in both studies air pollutant exposure was estimated at three time windows: during pregnancy, between birth and the time of the neurodevelopment assessment, at the year before the assessment visit. In the study of Porta and colleagues (2016) exposure to higher level of NO_2 in the three time windows was associated with IQ and VIQ assessed when children were 7 years old. In contrast, in a larger sample of primary school children, aged between 6 and 10 years old, prenatal and postnatal exposure to BC and to PM2.5 did not result to be associated with lower VIQ and PIQ scores (Harris et al., 2015).

3.3.2 Learning and memory

Sixteen studies investigated learning and memory considering different aspects of memory such working memory and short-term span memory. Studies included in this section are synthetized in Table 3.

INSERT TABLE 3

Prenatal exposure. Three studies investigated the association between prenatal exposure to air pollution and memory function. While one study conducted on a sample of 783 children aged between 6 and 10 years old revealed no significant association between exposure to air pollutants (NO_2, PM10, PM2.5, elemental carbon, coarse particle) and short-term and working memory function (Guxens et al., 2018), the two other papers found significant sex-dependent association. More specifically, a significant link emerged between PM2.5 and NO_2 exposure and memory only for preschool-age boys (Lertxundi et al., 2019). Also, an association between higher PM2.5 levels in early-to-mid pregnancy and impaired memory performances (Visual Memory Index (VIM) and General Memory Index (GM)) emerged only for 6-year-old girls (Chiu et al., 2016).

Postnatal exposure. Ten studies have considered postnatal exposure. Using the Wide Range Assessment of Memory and Learning (WRAML) test, one study conducted on children aged between 8 and 11 years found that BC level at children’s residence predicted decrease on several memory and learning scales score (i.e., verbal learning scale, visual learning scale, global learning scale, and the general index scale) (Suglia et al., 2008). Moreover, higher level of indoor (classroom of schools) PM2.5 exposure was associated with a significant reduction in working memory in 8.5-years-old children (Basagaña et al., 2016). A significant negative link between several pollutants (EC)/NO_2/PM2.5 and ultrafine particles (UFP), estimated both indoor and outdoor school building, and children memory difficulties was observed (Forns et al. 2017). Alemany and colleagues (2018) evaluated the association between traffic air pollution exposure and working memory considering the moderating role of Apolipoprotein E (APOE) genotype (e4 allele carriers), a well-known risk factor that increase vulnerability to air pollution through neuroinflammatory and oxidative stress processes. In particular, it was observed an association with high level of school outdoor exposure to PAHs/NO_2 and working memory in the APOE e4 allele carriers. Furthermore, working memory impairments in children aged between 7 and 11 years was also associated with long-term exposure to school indoor NO_2 and EC (Sunyer et al., 2017). In contrast, no significant association emerged between working memory and higher NO_2 exposure both in preschooler (Freire et al., 2010) and school-age children (Pujol et al., 2016). Similarly, short-term memory was not significantly associated with air pollutants exposure, neither in case of recent exposure (at school and at home) to PM2.5, PM10 and BC (Saenen et al., 2016), nor in case of chronic exposures to NO_2 (Van Kempfen et al., 2012) and to PM2.5, PM10 and BC (Saenen et al., 2016) at home in children aged between 9 and 11 years. However, Van Kempfen and colleagues (2012) found that exposure to NO_2 at school was significantly associated with a decrease of the memory span length. Furthermore, to children who lived in a high concentrations of air pollutants (Mexico City) compared children from healthy air area showed consistent and progressive deficits in short term memory (Calderón-Garcidueñas et al., 2011).

<u>Prenatal/Postnatal exposure</u>. Findings from Harris et al. (2015) did not show a significant association between prenatal/postnatal exposure to BC and PM2.5 and memory functions in primary school children. In contrast, a more recent work conducted on a large sample of children aged between 7 and 10 years old reported stable negative associations between increase of PM2.5 and working memory evaluated in the two assessment times with an interval of three months between the two assessment time points, with stronger associations at the most recent assessment of air pollution, with boys showing much higher vulnerability (Rivas et al., 2019).

3.3.3 Attention and executive functions

Fifteen studies have investigated several aspects attention and executive functions such as omission errors (i.e., missing responses), inhibition errors (i.e., do not ignore irrelevant distracting stimuli), reaction time (i.e., time between introducing a stimulus and response to it), reaction speed (i.e., speed used to respond to a stimulus) and switching attention (i.e., ability to shift attention from one stimulus to another one). Studies included in this section are synthetized in Table 4.

INSERT TABLE 4

Prenatal exposure. Four studies examined the association between air pollution exposure during fetal life and different attention/executive function. For instance, higher PM2.5 levels at 20–26 weeks of gestation were significantly associated with more omission errors and higher PM2.5 exposure at 32–36 weeks of gestation were significantly associated with slower hit reaction time in 6-year-old boys (Chiu et al., 2016). Similarly, prenatal exposure to fine particulate (PM2.5) was correlated to a higher number of inhibition errors in a sample of 783 children aged between 6 and 10 years old (Guxens et al., 2018). In another study, PAHs exposure was related with slower information processing speed during intelligence testing in children between 7 and 9 years old, although the association was mediated by reduced left hemisphere white matter (Peterson et al., 2015). Finally, the Attention Concentration Index score (e.g., a subtest of the Wide Range Assessment of Memory and Learning which assesses the individual’s ability focus and maintain attention and concentration on a task) was lower for 6-year-old boys with high prenatal BC exposure (Cowell et al., 2015).

Postnatal exposure. Higher inattentiveness was correlated with higher level PM2.5 both indoor and outdoor the school building (Basagaña et al., 2016) and airborne copper outdoor exposure (Alemany et al., 2017). Furthermore, inattentiveness impairments in children aged between 7 and 11 years was associated with higher level of school outdoor exposures to PAHs in the APOE e4 allele carriers (Alemany et al., 2018). Also Sunyer et al. (2017) found a significant association between impaired attention performance (i.e., increased hit reaction time, omissions, and commissions errors) and daily environmental levels of NO_2/EC and long-term NO_2 exposure at school in children aged between 7 and 10 years old. Moreover, in 10-years old children longer reaction times in selective attention task were significantly related to recent inside classroom PM2.5 and PM10 exposures and reaction times in both selective and sustained attention tasks were associated to chronic exposure at residence to PM2.5 and PM10 (Saenen et al., 2016). However, four studies (Van Kempen et al., 2012; Pujol et al., 2016; Mortamais, et al., 2017; Freire et al., 2010) did not found significant associations between air pollutants and attentive functions. Three of them failed to found a significant association between NO_2 exposure and attentive function in preschool-age (Freire et al., 2010) and in school age children (Van Kempen et al., 2012; Pujol et al., 2016). Moreover, the non-significant association were also found considering other type of air pollutant, in particular PM10 (Van Kempen et al., 2012), elemental carbon (Pujol et al., 2016;) and PHAs (Mortamais, et al., 2017).

Prenatal/Postnatal exposure. One study reported a significant association between higher exposure to prenatal levels of NO_2 and difficulties in executive function (i.e., an increase in the standard error of the hit reaction time and an increase in the number of omission errors) in a large sample of preschoolers (Sentís et al., 2017). When considering pre- and postnatal NO_2 a similar but weaker significant association were found with the number of omission errors. Stratifying the analysis by sex, this association persisted only in girls. Another work detected exposure to PM2.5 levels during the prenatal period and from the fourth postnatal year in a sample of 2221 school-age children (aged between 7 and 10 years old). Higher exposure was associated with a worse performance in a specific higher-level forms of attention implicated in the resolution of conflict among stimulus elements (e.g., resolve conflict in tasks like color-word Stroop effect). The same study fails to found a significant association when considering attentiveness (Rivas et al., 2019). Finally, the work by Harris et al. (2016) investigated the association between BC residential exposure from birth through 6 years of child age and in the year before the neuropsychological assessment in school aged children. Results indicate that higher average BC postnatal residential exposure predicted greater problems with behavioral regulation, a component of executive function involving inhibitory control of emotion and impulses.

3.3.4 Verbal language

Five studies assessed verbal language abilities. Verbal language skills refer to the ability to comprehend verbal information, the vocabulary competences, the maturity of verbal concepts, and the ability to express oneself through language. Studies included in this section are synthetized in Table 5.

INSERT TABLE 5

Prenatal exposure. Only one study investigated the possible impact of NO_2 and PM2.5 prenatal exposure on child's ability to comprehend verbal information and to express oneself through language in a sample of 1119 preschool children, finding a significant negative association between air pollution exposure and verbal language skills only for boys (Lertxundi et al., 2019).

Postnatal exposure. Four studies assessed the possible impact of postnatal exposure to air pollutants and verbal language abilities. Children exposure to high levels of NO_2 both at 9 months and 3 years of age was related to lower verbal ability (i.e., vocabulary competences end expressive language) at 3 years of age (Midouhas et al., 2018). Also postnatal residential exposure to BC was associated with decreases in the vocabulary competences in children aged between 8 and 10 years (Suglia et al., 2008).

Other two works assessed air pollution exposure comparing groups of children from critical polluted area and from healthy air area (Calderón-Garcidueñas et al., 2011; Talaeizadeh et al., 2018). In particular, Calderón-Garcidueñas and colleagues (2011) found that children who lived in a high concentrations of air pollutants (Mexico City) showed poorer vocabulary competences compared to children that lived in a clean air environment (Polotitlán, Mexico State) both at 7 and at 8 years old. Similarly, Talaeizadeh et al. (2018) found school-aged girls that lived in a critical polluted area exhibited significant poorer abilities in vocabulary competences and in verbal information comprehension compared to girls that lived in a healthy air area.

__Prenatal/Postnatal exposure.__ No studies that investigated verbal language abilities tested air pollution exposure both in prenatal and in postnatal period.

3.3.5 Numeric ability

Three studies evaluated numeric ability such as arithmetic skills (i.e., the ability to associate quantities to verbal numerical labels) and reasoning with numbers. Studies included in this section are synthetized in Table 6.

INSERT TABLE 6

Prenatal exposure. Only one study investigated the possible impact of NO_2 and PM2.5 prenatal exposure on child's numeric ability in children aged between 4 and 6 years showing a significant negative association between exposure to NO_2 and numeric ability, association becoming more negative for boys after stratifying by gender (Lertxundi et al., 2019).

Postnatal exposure. Only one study evaluates postnatal air pollution exposure, comparing groups of children from critical polluted area and from healthy air area found that children who lived in a high concentrations of air pollutants (Mexico City) outperformed in arithmetic measures children that lived in a clean air environment (Calderón-Garcidueñas et al., 2011).

__Prenatal/Postnatal exposure.__ Porta and colleagues (2016) considered prenatal and postnatal (between birth and the time of the cognitive test and the last year before the test) exposure to NO_2, PM coarse, PM2.5, PM2.5. In 7-years-old children, the exposure to higher level of NO_2 in the three time windows was associated with poorer arithmetic reasoning abilities.

3.3.6 Motor and sensorimotor skills

While motor functions involve gross-motor skills (e.g., independent sitting, crawling, walking, or running), fine-motor skills, sensorimotor functions include competences such as motor or visual speed and precision (i.e., visual motor skills), perceptual coding, and spatial ability. Studies included in this section are synthetized in Table 7.

INSERT TABLE 7

Prenatal exposure. Two studies considered prenatal exposure to air pollution. Lubczynska et al. (2017) analyzed data from 4 European population-based birth cohorts in the Netherlands, Germany, Italy and Spain. Motor skills (fine and gross) were assessed between 1 and 9 years of age. Results observed that PM2.5 exposure was not associated to both abilities. However, increase in the levels of airborne iron, one of the main elements of traffic-related air pollution, was negatively associated with fine-motor skills. More recently, Lertxundi et al. (2019) reported a negative association between NO_2 exposure and fine-motor skills in children at 4–6 years of age, but only for boys.

Postnatal exposure. Three studies investigated the association between air pollution exposure and motor and/or sensorimotor functions. One study investigated the association between postnatal exposure to NO_2 and neurodevelopment in 4-year-old children. In particular, a significant negative association between emerged between high home outdoor NO_2 levels and gross motor skills (Freire et al., 2010). Saenen et al. (2016) investigated whether neurobehavioral performance was associated with recent and chronic air pollution postnatal exposure in a sample of primary school children. Findings suggest visual information processing speed was related to recent inside classroom PM2.5 or PM10 exposure. Additionally, authors reported that visual information processing speed was negatively associated with recent residential PM2.5, PM10 and BC exposure. Finally, in their study Calderón-Garcidueñas and collaborators (2011) reported a significant difference in terms of spatial abilities between children without white matter hyperintensities and children with white matter hyperintensities, indicating that living in a polluted area could be a risk factor also for sensorimotor functions. In contrast, in Van Kempen et al. (2012) study did not emerge any significant correlations between exposure to NO_2 and PM10 at school and at home and both hand–eye coordination and perceptual coding in children aged between 9 and 11 years.

***Prenatal/Postnatal exposure*.** One study estimated BC and PM2.5 exposure in prenatal (late pregnancy) and postnatal (mid-childhood) periods (Harris et al., 2015). Authors found that prenatal residential proximity to a polluted area (< 50 m) was associated with poorer visual motor abilities in mid-childhood. However, contrary to expectation, PM2.5 postnatal exposure from birth to 6 years was associated with a small increase in visual motor skills in mid-childhood.

4. Discussion

Findings from the current systematic review of 30 studies highlight significant trend effects of some air pollutants on some cognitive functions and sensorimotor abilities with detrimental effects on children's neurodevelopmental skills. Main results are synthetized and discussed below, considering prenatal exposure and postnatal exposure or both.

Prenatal exposure to PAHs was negatively associated with the global intellective quotient (Edwards et al., 2010; Jedrychowski et al., 2015; Perera, 2009) of 5-year-olds (Edwards et al., 2010; Perera, 2009) and of 7-years-olds (Jedrychowski et al., 2015), suggesting that PAHs prenatal exposure was associated with an estimated decrease in mean scores of approximately 3-4 IQ points (Suades-González, Gascon, Guxens, and Sunyer, 2015). Two postnatal exposure studies found that school-aged children who lived in areas with high air pollution obtained significant lower score than those who lived in the healthy air area in global intellective function and verbal intellective quotient (Calderón-Garcidueñas et al., 2011; Talaeizadeh et al., 2018). However, both studies did not score particularly good on quality appraisal and did not consider possible confounding variables. Thus, even if these results support a possible role for exposure to air pollution in postnatal period and lower intellectual functioning, results from these studies must be considered with caution. Thus, in sum results seems to indicate that while prenatal exposure to PHAs increase possible negative consequences on intellectual functioning during childhood, findings from postnatal exposure studies provide only a partial relationship between air pollution and intellective function.

A robust result emerged for attention and executive functions. Most of the studies included in this cognitive domain (12/16) revealed that several air pollutants (e.g., PM2.5, PM10, NO_2, black carbon, PAHs) were associated with inattentiveness of children aged between 6 and 11 years olds (Peterson et al., 2015; Chiu et al, 2016; Cowell et al., 2015; Guxens et al., 2018). Specifically, all four prenatal exposure studies found an association between exposure to TRAP, NO_2, PM10, PM2.5, PHAs, and elemental carbon and poorer attention abilities and inhibitory control (i.e., an executive function skill) in school-aged children aged 6 to 10 years (Peterson et al., 2015; Chiu et al, 2016; Cowell et al., 2015; Guxens et al., 2018). In two cases, the association was moderated by gender, in particular males were at higher risk of developing difficulties with attention and executive functions (Chiu et al, 2016; Cowell et al., 2015). Double exposure studies (i.e., during pregnancy and within the birth-age 4) revealed that NO_2 and PM2.5 could be a risk factor for attention/executive functions assessed at ages 6-11 years (Harris et al., 2016; Sentís et al., 2017), especially in female children (Rivas et al., 2019). Finally, postnatal exposure research (i.e., middle childhood) found conflicting results. Indeed, only 5 out of 9 included studies found a relationship between air pollutants and attention/executive functions during childhood (Alemany et al., 2017; Alemany et al., 2018; Basagaña, 2016; Saenen, 2016; Sunyer, 2017), with a robust association for studies with a larger sample size. While the controversial results may be explained by methodological differences (i.e., method to determine the concentration of air pollution, the use of different cognitive measures and several developmental periods), overall these findings seem to suggest that exposure to air pollutants especially in the prenatal period associates with an increased risk of attention impairments during childhood.

Significant associations emerged for learning and memory, as well. Four prenatal exposure studies documented that PAHs, NO_2, BC and PM2.5 was associated with decreases across memory and learning function (Chiu et al, 2016; Cowell et al., 2015; Guxens et al., 2018; Lertxundi et al., 2019). Prenatal exposure predictive a higher risk of developing learning difficulties in boys (Lertxundi et al., 2019), but a more risk for visual memory impairments in girls (Chiu et al., 2016), suggesting that the above mentioned association was moderated by sex. Postnatal and double exposure studies only partially corroborate the relationship between air pollution and memory/learning difficulties. Specifically, 7 out of 12 included studies found a significant association with global deficit (Almanay et al., 2018; Basagaña et al., 2016; Calderón-Garcidueñas et al., 2011; Forns et al., 2017; Van Kempen et al., 2012; Suglia et al., 2008; Sunyer et al., 2017), with four studies reporting a specific working memory impairment (Almanay et al., 2018; Basagaña et al., 2016; Forns et al., 2017; Sunyer et al., 2017).

A further observation is about initial evidence of links between pollutants exposure (i.e., PM2.5, PM10, NO_2, BC) and both verbal language and numeric abilities impairments (Midouhas et al., 2018; Suglia et al., 2008), regardless from timing of exposure. Five studies investigated language development (Calderón-Garcidueñas et al., 2011; Lertxundi et al., 2019; Midouhas et al., 2018; Suglia et al., 2008; Talaeizadeh et al., 2018) and three numeric abilities (Calderón-Garcidueñas et al., 2011; Lertxundi et al., 2019; Porta et al., 2016). Most of these studies (Lertxundi et al., 2019; Midouhas et al., 2018; Porta et al., 2016), both those considering verbal language (n = 3) and numeric abilities (n = 2), found that both domains were negatively associated with NO_2 exposure.

Finally, as for motor and sensorimotor skills, 1 out of 2 prenatal exposure studies found that NO_2 and PM2.5 were associated with lower fine-motor abilities (Lertxundi et al., 2019). 4 out of the 5 postnatal exposure studies documented that air pollution was negatively associated gross motor skills (Freire, 2010), spatial abilities (Calderón-Garcidueñas et al., 2011), visual information processing speed (Saenen et al., 2016) and visual-motor ability (Harris et al., 2015). Although additional research is needed, these findings seem to indicate that both prenatal and postnatal exposure can be associated with delayed sensorimotor development during childhood.

Taken together, results seem to suggest that exposure to air pollutants may be a risk factor for neurodevelopmental skills in preschool- and school-aged children. Although verbal language, numerical skills and sensorimotor abilities are affected by air pollution, the most adverse outcomes concern global intellective functioning, executive functions and attention. This latter finding is consistent with previous data on neuropsychiatric disorders which suggest that early-life exposure to air pollutants associate with an increased risk of ADHD, which core symptom is the attention deficit (Aghaei et al., 2019). Moreover, many studies highlight that moderating role of gender, with higher risk of developing difficulties with attention and executive functions (Chiu et al, 2016; Cowell et al.,

2015) and learning difficulties in boys (Lertxundi et al., 2019), and with higher risk for visual memory impairments in girls (Chiu et al., 2016).

As reported in Figure 2 our findings also support a potential role of specific air pollutants in explaining potential impaired neurodevelopmental outcomes (i.e., PM2.5, NO_2, and PAHs). PM2.5 and NO_2 are the most investigated pollutants in the included studies. They appear to be particularly risky when the child is exposed to in prenatal periods but there are also some evidence about exposure during postnatal phase. PAHs is considered in fewer studies but it still emerges as a potential risk for children's neurodevelopment especially as regard prenatal exposure. All these results are strengthened by the fact that studies that have considered these air pollutants have controlled for many confounding variables such as demographic and socioeconomic variables. BC is also measured by a large number of studies, however results are very heterogeneous. More studies are needed to better understand the risk level of this air pollutant. TRAP seems to have greater effects in the postnatal phase, however, studies that have considered these mixture of air pollution generally have controlled for few confounding variables (e.g. socio-economic variables) and therefore further investigation is needed. Finally, regarding other air pollutants there is too little evidence to draw conclusions and more research is needed.

INSERT FIGURE 2

Overall, findings indicate that air pollution exposures during pregnancy, especially exposure to PAHs, PM2.5 and NO_2, appeared strongly associated with difficulties in later neurodevelopmental skills, suggesting that early exposure to these pollutants can have adverse long-term outcomes especially regarding intellective function, attention, learning and memory skills. It is not surprising given that there is concern regarding the potential impact of pollutants on gestation, and during the very first period of extrauterine life (Bosetti et al., 2010; Stieb et al., 2012), which represent a sensitive developmental period for neuroplasticity. In this time infant brain is particularly vulnerable or receptive to the quality of environment, thus that air pollution can have a profound effect on the immature brain as it is organizing itself. Regarding postnatal exposure during early and middle childhood (between 3 and 11 years old), the relationship between air pollution and specific neurodevelopmental skills in preschool- and school-age children remains less clear and requires further research.

4.1 Limitations

There are some limits that call for caution in the interpretation and generalization of findings from the current review. First, although all reviewed studies contained standardized instruments for assessing neurodevelopmental skills, there is a variability in the tools used for measuring the same function or ability that prevent stronger comparisons. This methodological issue could explain some inconstancies we found even for the same neurodevelopmental skill, when it was examined by different studies. This has also limited the possibility to carry out a meta-analysis. Second, all studies estimated air pollution focusing on specific geographical areas in certain countries. This limits the generalizability of the results especially on a larger scale such as continental level. Moreover, in some studies was not considered the intensity of pollutants in the air, thus in some cases the inconsistency of findings might be due to relatively low levels of a specific pollutant compared to studies reporting associations. Finally, reliability of studies on the potential impact of pollutants on the brain has recently been questioned (de Prado et al., 2018). One critical point is that infants exhibit large individual variability, so that caution is needed in interpreting results from this filed research.

4.2 Recommendation for future directions

Further work is needed to strengthen the methodological accuracy and the extent of research in this field. Specifically, it will be critical to examine a number of factors in more in depth. As suggested by different authors (Loftus et al., 2019; Porta et al., 2016) the consistency of studies' findings could be improved by considering the intensity of air pollution (low, medium, high air pollution). For example, the lack of findings in Loftus et al. (2019) could be due to relatively low NO_2 levels compared to studies reporting associations (Porta et al., 2016). Therefore, in order to find a stronger and significant association between air pollution exposure and neurodevelopmental skills it would be important to determine the intensity of air pollution. Measuring not only pollutants type but also their quantitative level in the air would strengths studies' results and would provide more reliable evidence for the neurotoxicity of air pollution. Furthermore, given that the number of associations between air pollution and different neurodevelopmental skills assessment, it would be important to use homogenous neurodevelopmental measurement methods in order to obtain more comparable results.

5 Conclusion

Intrauterine epoch and early postnatal life are critical time periods for brain plasticity in the human infant developing brain. Throughout these life phases, the human fetus and the infant are highly susceptible to environmental variations, including atmosphere pollution. This review suggests that greater early life exposure to air pollutants, especially to PM2.5, NO_2 and PAHs, is associated with neurodevelopmental negative outcomes in children. Even if their performances do not fall into clinical range and further research is needed to support robust recommendations, air pollution may increase risk of some difficulties in cognitive domains such as attention and intellective functioning. This evidence underscores the importance of this issue and its impact on public health, which, as of today, can not longer be left on the back burner (Philipsborn et al., 2021). The cautious principle should be applied to protect the general population, and especially pregnant women and infants, given their vulnerability and the potential long-term effects of accumulated toxic exposure at various stages of life beginning in utero (Dadvand et al., 2013). Thus, regardless of a strong causal evidence, lowering of these pollutants could potentially have important preventive impacts on the risk of adverse neurodevelopmental outcomes in typically developing children (Lopuszanska & Samardakiewicz, 2020). Results reported in this review corroborate the need for a global action to be taken to reduce exposure to environmental pollutants and to implement public health policies worldwide, especially during pregnancy and infant developmental ages.

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Figure 1.

PRISMA flow diagram.

Figure2.

Risk level of each pollutant considering prenatal and/or postnatal exposure and the different neurodevelopmental functions considered.

Note: PM2.5 = particles of aerodynamic diameter of 2.5 µm; PM10 = particles of aerodynamic diameter of 10 µm; PMcoarse = PM2.5 and PM10; UFPs = ultrafine particles; NO_2 = nitrogen dioxide, EC = elemental carbon; BC = black carbon; PAHs = polycyclic aromatic hydrocarbons; Cu = copper

**TRAP (traffic related air pollution), considered by two studies (Calderón-Garcidueñas et al., 2011; Talaeizadeh et al., 2018), is not a singular pollutant as other but it is a mixture of pollutants. Therefore it will be not consider in this figure*

Table 1

Quality appraisal of the included studies.

Study	A	B	C	D	E	F	G	Final
Guxens, 2018	2	2	1	2	1	1	1	1
Alemany, 2018	3	2	1	2	1	3	1	3
Loftus, 2019	2	2	1	2	1	1	1	1
Porta, 2016	3	2	1	2	1	2	1	2
Sentís, 2017	3	2	1	2	1	3	1	3
Lertxundi, 2019	1	2	1	2	1	3	1	2
Rivas, 2019	3	2	1	2	1	2	1	2
Basagaña, 2016	3	2	1	2	1	1	1	2
Calderón-Garcidueñas, 2011	3	2	3	2	1	3	3	3
Jedrychowski, 2015	2	2	1	2	1	3	2	2
Pujol, 2016	3	2	1	2	1	3	1	3
Suglia, 2008	1	2	1	2	1	3	1	2
Harris, 2016	2	2	1	2	1	3	1	2
Edwards, 2010	2	2	1	2	1	2	2	1
Alemany, 2017	2	2	2	2	1	2	1	1
Cowell, 2015	2	2	1	2	1	3	1	2
Perera, 2009	1	2	1	2	1	2	2	1
Talaeizadeh, 2018	2	2	2	2	1	3	3	3
Lubczynska, 2017	2	2	1	2	1	2	1	1
Forns, 2017	2	2	1	2	1	3	1	2
Saenen, 2016	2	2	1	2	1	1	1	1
Midouhas, 2018	2	2	1	2	1	3	2	2

Wang, 2017	2	2	1	2	1	1	1	1
Mortamais, 2017	3	2	1	2	1	3	1	3
Sunyer, 2017	3	2	1	2	1	1	1	2
Chiu, 2016	2	2	1	2	1	3	1	2
Harris, 2015	2	2	1	2	1	3	1	2
Peterson, 2015	2	2	1	2	1	1	2	1
Van Kempen, 2012	1	2	1	2	1	1	1	1
Freire, 2010	1	2	1	2	1	1	1	1

Labels: A, selection bias; B, study design; C, confounders; D, blinding; E, data collection methods; F, withdrawals and dropout; G, quality of air pollution exposure assessment. Quality codes: 1, strong; 2, moderate; 3 weak.

Table 2.

Synthesis of studies that considered intellective functioning.

First author, year	**Country**	**Exposure context**	**Study design**	**Sample (N)**	**Age of the children**	**Air pollutants**	**Exposure assessment**	**IQ Specific function**	**Standardized test**	**Controlled confounding variables**	**Main findings**
Prenatal exposure											
Perera, 2009	Washington Heights, Harlem, South Bronx in New York (USA)	metropolitan area	prospective cohort	249 children	5 years of age	PAHs	Measurements. Prenatal exposure to PAHs by 48 h personal monitoring of pregnant woman (mean 3.48±3.68 ng/m^3)	Total (full-scale) IQ, verbal IQ and performance IQ	Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R)	maternal intelligence, quality of the home caretaking environment, environmental tobacco smoke exposure, and other potentially confounding factors	<u>Significant association:</u> > PAHs → < Full-scale IQ > PAHs → < Verbal IQ <u>Non-significant association:</u> PAHs and Performance IQ
Edwards, 2010	Krakow (Poland)	urban area	prospective cohort	214 children	5 years of age	PAHs	Measurements. Prenatal exposure to PAHs by 48 h personal monitoring of pregnant woman (mean 39.5 ± 48.1 ng/m^3, median 17.96 ng/m^3)	Non verbal intelligence	Raven Coloured Progressive Matrices (RCPM)	maternal report of ETS exposure in the household during pregnancy, sex of the child, maternal education, maternal intelligence	<u>Significant association:</u> > PAHs → < Full-scale IQ > PAHs → < Performance IQ

Jedrychowski, 2015	Krakow (Poland)	urban area	longitudinal study	170 children	7 years of age	PAHs	Measurements. Prenatal exposure to PAHs assessed by DNA-PAH adducts in the cord blood	Verbal IQ and performance IQ	Wechsler Intelligence Scale for Children-Revised (WISC-R)	child's gender, parity, gestational age maternal education, breastfeeding practice, environmental tobacco smoke (ETS) and postnatal PAH exposure	Significant association: > PAHs → < Verbal IQ Non-significant association: PAHs and Performance IQ
Chiu, 2016	ACCESS study. Boston (USA)	urban area	pregnancy cohort	267 children	approximately 6 years of age	PM2.5	Estimates with a satellite-based spatio-temporally resolved model. Median prenatal exposure to PM2.5 at residence: 11.3 µg/m^3	Total IQ (full-scale IQ)	Wechsler Intelligence Scale for Children (WISC-IV)	maternal age, education, race, and smoking; child's sex, date of birth, parity, gestational age at birth, and birth weight, duration of breast feeding and children's blood lead levels	Significant association: > PM2.5 → < IQ, but only in males
Lubczynska, 2017	ESCAPE study. Netherlands, Germany, Italyand Spain: 40 sites in the Netherlands/Belgium and Catalunya, and 20 sites in Ruhr area and Rome	two countries from the northern part of Europe and two from the southern part, with varying levels and sources of air pollution	4 European population-based birth cohorts	7246 children	1-9 years of age	PM2.5 and elemental composition of PM2.5, considering: Cu, Fe, K, Ni, S, Si, V, Zn	Model estimates with LUR. Prenatal exposure to PM2.5 in the range 10 35 µg/m^3	Cognitive function (general, verbal and non-verbal)	McCarthy Scales of Children's Abilities (MSCA)	Maternal information (age at delivery, pre-pregnancy body mass index, smoking during pregnancy, alcohol consumption during pregnancy, marital status, parity, height, pre-pregnancy weight); Parental information (educational level and country of birth)	Non-significant association: PM2.5 and intellective functioning (general, verbal, and non-verbal)

Lertxundi, 2019	INMA study. Gipuzkoa, Sabadell and Valencia provinces (Spain)	Atlantic coast (Gipuzkoa) and Mediterranean coast (Valencia and Sabadell)	population-based birth cohort	1119 mother-child pairs	4-6 years of age	PM2.5, NO_2	Model estimates with LUR (1 region) and measurements at air monitoring stations. (2 regions). Mean prenatal exposure NO_2: 18.4 - 41.8 µg/m^3; PM2.5: 15.1-21.7 µg/m^3	Global cognition	McCarthy scales of Children's Abilities (MSCA)	maternal educational level, social class, country of birth, smoking during pregnancy, pre-pregnancy body mass index, and age at delivery; child's sex and gestational age and anthropometric measures	Significant association: > NO2 → < global cognition only in boys Non-significant association: PM2.5 and global cognition
Loftus, 2019	CANDLE study. Shelby County in Memphis region, TN (USA)	area with plants, the largest cargo airport in the world and the third-largest US rail center	prospective pregnancy cohort study	1005 mothers and their children	4-6 years of age	NO_2 and PM10	Model estimates with LUR. Median prenatal exposure to PM10 and NO_2: 20.79 µg/m^3(IQR=2.76) µg/m^3 and 11.96 µg/m^3 (IQR=3.81) µg/m^3, respectively	General IQ, verbal and nonverbal IQ	Stanford Binet Intelligence Scales, edition 5 (SB-5)	child age at assessment, child sex, maternal demographic, maternal race, socioeconomic status, prenatal smoking and depression, child birth order, reported nutrition, maternal plasma folate in second trimester	Significant association: > PM10 → < Full-scale IQ > PM10 → < Verbal IQ > PM10 → < Non-verbal IQ Non-significant association: NO2 and Full-scale IQ
Postnatal exposure											
Suglia, 2008	Maternal-infant smoking study. Boston, Massachusetts (USA)	urban area in the Greater Boston area	prospective birth cohort	202 children	8-11 years of age	Black carbon	Model estimates with LUR. Annual black carbon exposure at residence (mean 0.56 ± 0.13 µg/m^3)	Verbal IQ, nonverbal IQ and composite IQ	Kaufman Brief Intelligence Test (K-BIT)	sociodemographic factors, birth weight, blood lead level, or tobacco smoke exposure	Significant association: > BC at children's residence → < Full-scale IQ > BC at children's residence → < Verbal IQ > BC at children's residence → < Non-verbal IQ

Freire, 2010	INMA study. Granada Province (Spain)	urban area and non-urban area	population-based birth cohort	210 children	4 years of age	NO_2	Model estimates with LUR. Mean annual NO_2 at residence: 20.88 $\mu g/m^3$.	Global cognition	McCarthy Scales of Children's Abilities (MSCA)	Sociodemographic covariates (place of residence, maternal and paternal education, maternal occupational status, parity, duration of breastfeeding, type of delivery, marital status, smoking during pregnancy and age of mothers and children), birth weight and length and gestational age and Parents' mental health scale scores and parent-to infant attachment scale scores	<u>Non-significant association:</u> NO2 and global cognition
Calderón-Garcidueñas, 2011	Mexico City and Polotitlán	Mexico City: urban area with over 40,000 industries and urban traffic pollutants	prospective protocol	20 children from Southwest Mexico City (SWMC) and 10 children from Polotitlán	7-8 years of age	Heavy air pollution (including PM2.5 and O_3)	Geographical partitioning between Mexico city (pollutants above air quality standards) and Polotitlán (pollutants below the standards)	Verbal IQ and Performance IQ	Wechsler Intelligence Scale for Children-Revised, WISC-R) (spanish version)	na	<u>Significant association:</u> Children who lived in Mexico city: WMH^+ → < Verbal IQ WMH^- → < Performance IQ
Wang, 2017	RFAB study. Southern California (communities in Los Angeles and surrounding counties)	urban area	prospective longitudinal study	1360 children	9-11 and 18-20 years of age	PM2.5	Spatiotemporal model to estimate exposure at residence 1-, 2- and 3-years preceding the IQ testing. PM 2.5 1-year preceding the testing: 2.14 – 25.36 $\mu g/m^3$	Verbal IQ (VIQ), performance IQ (PIQ) and general IQ (full scale IQ)	Wechsler Abbreviated Scale of Intelligence ((WASI)	demographic characteristics, family socioeconomic status (SES), parents' cognitive abilities, neighborhood characteristics, and other spatial confounders	<u>Significant association:</u> > PM2.5 at children's residence → < Performance IQ <u>Non-significant association:</u> > PM2.5 → < Full-scale IQ > PM2.5 → < Verbal IQ

Talaeizadeh, 2018	Tehran, districts 20 (high pollution) and 22 (low pollution) (Iran)	Tehran	cross-sectional	190 girls	8-10 years of age	Heavy air pollution (including SO_2, NO_2, PM2.5, PM10, O_3, CO)	Geographical partitioning between different areas of Tehran. Air monitoring stations used to identify area of the city with high and low pollution	Verbal IQ (VIQ), performance IQ (PIQ) and general IQ (full scale IQ)	Revised Wechsler Intelligence Scale for Children (WISC-R)	family economic status, height, weight, and nutrition situation	Significant association: polluted area < Verbal IQ but only in girls
Prenatal and postnatal exposure											
Harris, 2015	VIVA study. eastern Massachusetts (USA)	urban and suburban area	prospective birth cohort	1109 mother–child pairs	6-10 years of age	BC and PM2.5	Model estimates with LUR. Exposure during the third trimester of pregnancy, the first 6 y of life, the year before testing. BC third trimester 0.69 ± 0.23 µg/m^3, BC birth–6 years 0.56 ± 0.16 µg/m^3 and BC the year before testing 0.47 ± 0.15 µg/m^3. PM2.5 : third trimester 12.3 ± 2.6 µg/m^3, PM2.5 birth–6 years 11.3 ± 1.7 µg/m^3 and PM2.5 the year before testing 9.4 ± 1.9 µg/m^3	Verbal and non verbal IQ	Kaufman Brief Intelligence Test (KBIT-2)	characteristics of the child (sex, age at cognitive testing, breastfeeding duration, blood lead in early childhood), of the mother (IQ, parity, age at enrollment, marital/cohabitation status, education, race/ethnicity, smoking status, exposure to secondhand smoke during pregnancy, blood lead in pregnancy, alcohol consumption during pregnancy) of the father (education, household, annual income at time of cognitive assessment) and of the neighborhood (median annual income for census tract of residence at cognitive testing)	Non-significant association: BC and PM2.5 and Verbal/Non-verbal IQ

Porta, 2016	GASPII study. Rome (Italy)	city with urban traffic	prospective birth cohort	474 children	7 years of age	NO$_2$, PM coarse, PM2.5, PM2.5 absorbance	Model estimates with LUR. Exposure at birth (proxy of prenatal exposure); exposure during life and before testing; exposure the year before testing: Median exposure at birth: NO$_2$ 43,3 (from 22,5 to 85,1) µg/m^3; PM 2.5: 18.7 (17.0-27.4) µg/m^3; PM coarse: 15,7 (10.8-31.5) µg/m^3; PM 2.5 absorbance: 2.52 (2.16-4.77) 10^{-5} m^{-1}	Verbal IQ (VIQ), performance IQ (PIQ) and general IQ (full scale IQ)	Wechsler Intelligence Scale for Children-III (WISC-III)	gender, child age at cognitive test, birth weight, maternal age at delivery, parental educational level, siblings, socio-economic status, maternal smoking and alcohol consumption during pregnancy, psychologist administering the cognitive test, maternal body mass index before pregnancy	Significant association: > NO2 both pre and postnatnal → < Full-scale IQ > NO2 both pre and postnatal → < Verbal IQ Non-significant association: NO2 and Performance IQ; PMcoarse/PM2.5/PM2.5 absorbance and Full-scale/Verbal/Performance IQ

Table 3.

Synthesis of studies that considered memory and learning.

First author, year	Country	Exposure context	Study design	Sample (N)	Age of the children	Air pollutants	Exposure assessment	Memory specific function	Standardized test	Controlled confounding variables	Main findings
Prenatal exposure											
Chiu, 2016	ACCESS study. Boston (USA)	urban area	pregnancy cohort	267 children	approximately 6 years of age	PM2.5	Estimates with a satellite-based spatio-temporally resolved model. Median prenatal exposure to PM2.5 at residence: 11.3 µg/m^3	Memory	Wide Range Assessment of Memory & Learning, 2nd Edition (WRAML-2)	maternal age, education, race, and smoking; child's sex, date of birth, parity, gestational age at birth, and birth weight, duration of breast feeding and children's blood lead levels	Significant association: > PM2.5 → < Visual Memory Index (VIM) > PM2.5 → < General Memory Index (GM)
Guxens, 2018	Generation R study. Rotterdam (The Netherlands)	urban areas	population-based birth cohort	783 children	6-10 years of age	NO_2, PM2.5, PM coarse, PM absorbance	Model estimates with LUR. Median prenatal residential exposure NO_2: 39.3 (25.3–73.3) µg/m^3; PM2.5: 20.2 (16.8–28.1) µg/m^3; PM coarse: 11.8 (9.2–17.8) µg/m^3; PM absorbance: 1.9 (1.2-3.6) 10^{-5} m^{-1}	Short-term and working memory	Developmental Neuropsychological Assessment (NEPSY-II) (Dutch version);	socioeconomic and lifestyle characteristics	Non-significant association: NO_2/ PM2.5/ PM coarse/ PM absorbance and memory
Lertxundi, 2019	INMA study. Gipuzkoa, Sabadell and Valencia provinces (Spain)	Atlantic coast (Gipuzkoa) and Mediterranean coast (Valencia and Sabadell)	population-based birth cohort	1119 mother-child pairs	4-6 years of age	PM2.5, NO_2	Model estimates with LUR (1 region) and measurements at air monitoring stations. (2 regions). Mean prenatal exposure NO_2: 18.4 - 41.8 µg/m^3; PM2.5: 15.1-21.7 µg/m^3	Memory	McCarthy scales of Children's Abilities (MSCA)	maternal educational level, social class, country of birth, smoking during pregnancy, pre-pregnancy body mass index, and age at delivery; child's sex and gestational age and anthropometric measures	Significant association: > PM2.5 → < memory > NO2 → < memory but only for boys
Postnatal exposure											

Suglia, 2008	Maternal-infant smoking study. Boston, Massachusetts (USA)	urban area in the Greater Boston area	prospective birth cohort	202 children	8-11 years of age	Black carbon	Model estimates with LUR. Annual black carbon exposure at residence (mean 0.56 ± 0.13 µg/m^3)	Child's ability to actively learn and memorize a variety of information	Wide Range Assessment of Memory and Learning (WRAML)	sociodemographic factors, birth weight, blood lead level, or tobacco smoke exposure	Significant association: > BC at children's residence → < memory and learning
Freire, 2010	INMA study. Granada Province (Spain)	urban area and non-urban area	population-based birth cohort	210 children	4 years of age	NO$_2$	Model estimates with LUR. Mean annual NO$_2$ at residence: 20.88 µg/m^3.	Working memory, memory span or short-term memory	McCarthy Scales of Children's Abilities (MSCA)	Sociodemographic covariates (place of residence, maternal and paternal education, maternal occupational status, parity, duration of breastfeeding, type of delivery, marital status, smoking during pregnancy and age of mothers and children), birth weight and length and gestational age and Parents' mental health scale scores and parent-to infant attachment scale scores	Non-significant association: NO2 and working memory
Calderón-Garcidueñas, 2011	Mexico City and Polotitlán	Mexico City: urban area with over 40,000 industries and urban traffic pollutants	prospective protocol	20 children from Southwest Mexico City (SWMC) and 10 children from Polotitlán	7-8 years of age	Heavy air pollution (including PM2.5 and O$_3$)	Geographical partitioning between Mexico city (pollutants above air quality standards) and Polotitlán (pollutants below the standards)	Short term memory	Wechsler Intelligence Scale for Children-Revised, WISC-R) (spanish version)	age and socioeconomic status	Significant association: Children who lived in Mexico city < short term memory
Van Kempen, 2012	RANCH study. Amsterdam (The Netherland); 24 primary schools around	urban area near airport with road traffic	cross-sectional based on school children	485 children	9-11 years of age	NO$_2$ and PM10	Model estimates with LUR. Annual median exposure to PM10: 25.8 µg/m^3 at home, 25.8 µg/m^3 at school; NO$_2$: 31.2 µg/m^3 home, 30.4 µg/m3 at school.	Memory: ability to memorise as long as possible sequences	Neurobehavioral Evaluation System (NES): Digit Memory Span Test (DMST)	socio-economic and life-style factors	Significant association: > NO2 at school → < memory span length (the effect of PM10 was not further investigated) Non-significant

	Schiphol-Amsterdam Airport									association: Chronic exposure at school to NO2 and memory
Basagaña, 2016	BREATHE study. Barcelona	metropolitan area with high urban traffic	population based cohort of primary schoolchildren	2618 children	8.5 years of age	PM2.5	Measurements at school. Median yearly school outdoor and indoor exposure to PM2.5: 28.1 µg/m^3 and 35.6 µg/m^3	Working memory and superior working memory	Computerized n-back task	Sociodemographic factors: parental education, marital status, environmental tobacco smoke at home, and a neighborhood socioeconomical status vulnerability index	Significant association: > PM2.5 at school (indoor) → < working memory
Pujol, 2016	BREATHE study. Barcelona	metropolitan area with high urban traffic	population based cohort of primary schoolchildren	263 children	8-12 years of age	Traffic Related Air Pollution (TRAP) in school as indoor and outdoor EC and NO$_2$	Measurements at school. Mean yearly school outdoor and indoor exposure to elemental carbon (EC): 1.4 ± 0.6 and 1.2 ± 0.5 µg/m^3. Mean outdoor and indoor exposure to NO$_2$: 46.8 ± 12.0 and 29.4 ± 11.7 µg/m^3.	Working memory	Computerized version of the N-Back task	Socio-demographic factors: neighborhood socioeconomic status vulnerability index, parental education, height and weight	Non-significant association: NO2/EC and working memory
Saenen, 2016	COGNAC study, Flanders (Belgium)	three primary schools in urban areas	longitudinal (panel study)	310 children	approximately 10 years of age (3rd to 6th grade)	PM2.5, PM10 and BC	Measurements of recent exposure at school; estimates with spatial temporal interpolation method for recent and chronic exposure at residence. Median recent exposure at school to PM2.5, PM10: 5.14 and 33.5 µg/m^3; recent exposure at residence to PM2.5, PM10, BC: 15-16, 19-21, 1.4-1.5 µg/m^3; chronic exposure at residence to PM2.5, PM10, BC: 15.7, 21.3, 1.54 µg/m^3	Short term memory	Digit Span Forward and Backward Tests	sex, age, education of the mother, highest rank of occupation of either parents, passive smoking, out-of-school sport activities, traffic noise, hours of computer screen time per week, and day of the week	Non-significant association: PM2.5/PM10/BC and short term memory
Forns, 2017	BREATHE study. Barcelona	metropolitan area with high urban traffic	population based cohort of primary schoolchildren	1439 children	7-9 years of age at baseline	Traffic Related Air Pollution (TRAP) in school as	Measurements at school. Outdoor median yearly exposure to EC: 1.5	Working memory	N-back test	child's date of birth and sex, maternal education, environmental	Significant association: > EC/NO2/PM2.5/UFP

						indoor and outdoor EC, NO_2, PM2.5, ultrafine particles (UFP)	µg/m³; NO_2: 48 µg/m³; PM2.5: 5.2 µg/m³; UFP: 22000.			tobacco smoke at home, Urban Vulnerability Index at home address	at school (outdoor and indoor) → < working memory
Sunyer, 2017	BREATHE study. Barcelona	metropolitan area with high urban traffic	population based cohort of primary schoolchildren	2687 children	7-10 years of age	Traffic Related Air Pollution (TRAP), expecially EC, and NO_2 at air monitoring stations and in schools	Measurements at schools and at a fixed air quality station. Indoor and ambient air median yearly exposure to EC: 1.24 and 1.13 µg/m³; indoor and ambient air median yearly exposure to NO_2: 29.4 and 33.5 µg/m³.	Working memory	N-back task	neighborhood socioeconomic vulnerability index, Parental educational level, Symptoms of ADHD and other characteristics of individuals and contextual variables	Significant association: > long term exposure at school to NO2 → < working memory > long term exposure at school to EC → < working memory Non-significant association: short term exposure at school to NO2/EC and working memory
Alemany, 2018	BREATHE study. Barcelona	metropolitan area with high urban traffic	population based cohort of primary schoolchildren	1667 children	7-11 years of age	PAHs, EC, and NO_2	Measurements at school. Mean yearly school exposure to PAHs: 1546 ± 775 pg/m³; EC: 1.46 ± 0.68 µg/m³; NO_2 47.74 ± 12.95 µg/m³	Working memory	Computerized nback task	Sociodemographic data: including child age and sex, maternal educational level, maternal smoking during pregnancy, and exposure to environmental tobacco smoke at home; residential neighborhood socioeconomic status (SES) vulnerability index	Significant association: > PAHs at school (outdoor) → < working memory > NO2 at school (outdoor) → < working memory Non-significant association: EC and working memory
						Prenatal and postnatal exposure					

Harris, 2015	VIVA study. eastern Massachusetts (USA)	urban and suburban area	prospective birth cohort	1109 mother–child pairs	6-10 years of age	BC and PM2.5	Model estimates with LUR. Exposure during the third trimester of pregnancy, the first 6 y of life, the year before testing. BC third trimester 0.69 ± 0.23 µg/m³, BC birth–6 years 0.56 ± 0.16 µg/m³ and BC the year before testing 0.47 ± 0.15 µg/m³. PM2.5 : third trimester 12.3 ± 2.6 µg/m³, PM2.5 birth–6 years 11.3 ± 1.7 µg/m³ and PM2.5 the year before testing 9.4 ± 1.9 µg/m³	Visual memory	Wide Range Assessment of Memory and Learning (WRAML2)	characteristics of the child (sex, age at cognitive testing, breastfeeding duration, blood lead in early childhood), of the mother (IQ, parity, age at enrollment, marital/cohabitation status, education, race/ethnicity, smoking status, exposure to secondhand smoke during pregnancy, blood lead in pregnancy, alcohol consumption during pregnancy) of the father (education, household, annual income at time of cognitive assessment) and of the neighborhood (median annual income for census tract of residence at cognitive testing)	Non-significant association: BC/PM2.5 and memory
Rivas, 2019	BREATHE study. Barcelona	metropolitan area with high urban traffic	population based cohort of primary schoolchildren	2221 children	7-10 years of age	PM2.5	Model estimates with LUR. Mean residential prenatal and postnatal (first 7 years) PM2.5: 16.5 ± 3.0 and 16.8± 2.9 µg/m^3	Working memory	computerized n-back test	sociodemographic factors including participants' age and sex, parental education and occupation, marital status, family origin, and residence history	Significant association: > PM2.5 (both pre and postnatal) → < working memory

Table 4.

Synthesis of studies that considered attention and executive functions.

First author, year	Country	Exposure context	Study design	Sample (N)	Age of the children	Air pollutants	Exposure assessment	Attention and FE specific function	Standardized test	controlled confounding variables	Main findings
Prenatal exposure											
Cowell, 2015	ACCESS study. Boston, Massachusetts (USA)	urban area	prospective pregnancy cohort	258 mother-child dyads	6 years of age	traffic-related black carbon (BC)	Model estimates with LUR. Median prenatal BC exposure at residence: 0.4 (0.11-1.10) µg/m^3	Memory and learning	Wide Range Assessment of Memory and Learning (WRAML2)	child sex, parental stress, maternal age, race/ethnicity, education, smoking status, birth weight, gestational age	<u>Significant association:</u> > PAHs → < Attention Concentration Index only for boys
Peterson, 2015	Washington Heights, Harlem, South Bronx in New York (USA)	metropolitan area	prospective cohort	625 mother-child pairs	7-9 years of age	PAHs	Measurements. Prenatal exposure to PAHs by 48 h personal monitoring of pregnant woman (mean 3.21 ± 6.30 ng/m^3)	Processing speed	Wechsler Intelligence Scale for Children IV (WISC-IV)	child sex, income, maternal education, maternal ethnicity, gestational age, birth weight, prenatal cotinine levels, postnatal PAH exposure	<u>Significant association:</u> > PAHs → < information processing speed

Chiu, 2016	ACCESS study. Boston (USA)	urban area	pregnancy cohort	267 children	approximately 6 years of age	PM2.5	Estimates with a satellite-based spatio-temporally resolved model. Median prenatal exposure to PM2.5 at residence: 11.3 μg/m^3	Attention and Response Inhibition	Conners' Continuous Performance Test-II (CPT-II)	maternal age, education, race, and smoking; child's sex, date of birth, parity, gestational age at birth, and birth weight, duration of breast feeding and children's blood lead levels	<u>Significant association:</u> > PM2.5 → < omission errors in boys > PM2.5 → > inhibition errors in boys
Guxens, 2018	Generation R study. Rotterdam (Netherlands)	urban areas	population-based birth cohort	783 children	6-10 years of age	NO_2, PM2.5, PM coarse, PM absorbance	Model estimates with LUR. Median prenatal residential exposure NO_2: 39.3 (25.3–73.3) μg/m^3; PM2.5: 20.2 (16.8–28.1) μg/m^3; PM coarse: 11.8 (9.2–17.8) μg/m^3; PM absorbance: 1.9 (1.2-3.6) 10^{-5} m^{-1}	Attention	Developmental Neuropsychological Assessment (NEPSY-II) (Dutch version)	socioeconomic and lifestyle characteristics	<u>Significant association:</u> > PM2.5 → < inhibition errors <u>Non-significant association:</u> NO_2, PM coarse, PM absorbance and attention
Postnatal exposure											
Freire, 2010	INMA study. Granada region (Spain)	urban area and non-urban area	population-based birth cohort	210 children	4 years of age	NO_2	Model estimates with LUR. Mean annual NO_2 at residence: 20.88 μg/m^3.	Executive functions	McCarthy Scales of Children's Abilities (MSCA)	Sociodemographic covariates (place of residence, maternal and paternal education, maternal occupational status, parity, duration of breastfeeding, type of delivery, marital status,	<u>Non-significant association:</u> NO2 and attention

										smoking during pregnancy and age of mothers and children), birth weight and length and gestational age and Parents' mental health scale scores and parent-to infant attachment scale scores	
Van Kempen, 2012	RANCH study. Amsterdam (The Netherland); 24 primary schools around Schiphol-Amsterdam Airport	urban area near airport with road traffic	cross-sectional based on school children	485 children	9-11 years of age	NO_2 and PM10	Model estimates with LUR. Annual median exposure to PM10: 25.8 $\mu g/m^3$ at home, 25.8 $\mu g/m^3$ at school; NO_2: 31.2 $\mu g/m^3$ home, 30.4 µg/m3 at school.	Attention: individual reaction speed	Neurobehavioral Evaluation System (NES): Simple Reaction Time Test (SRTT)	socio-economic and life-style factors	Non-significant association: NO2/PM10 and attention
								Switching attention: ability to switch rapidly between responses	Neurobehavioral Evaluation System (NES): Switching Attention Test (SAT)		
								Attention	Neurobehavioral Evaluation System (NES): Symbol Digit Substitution Test (SDST)		

Basagaña, 2016	BREATHE study. Barcellona	metropolitan area with high urban traffic	population based cohort of primary school children	2618 children	8.5 years of age	PM2.5	Measurements at school. Median yearly school outdoor and indoor exposure to PM2.5: 28.1 µg/m^3 and 35.6 µg/m^3	Inattentiveness	attentional network task (ANT)	Sociodemographic factors: parental education, marital status, environmental tobacco smoke at home, and a neighborhood socioeconomical status vulnerability index	Significant association: > PM2.5 at school (outdoor and indoor) → > inattentiveness
Pujol, 2016	BREATHE study. Barcellona	metropolitan area with high urban traffic	population based cohort of primary school children	263 children	8-12 years of age	Traffic Related Air Pollution (TRAP) in school as indoor and outdoor EC and NO_2	Measurements at school. Mean yearly school outdoor and indoor exposure to elemental carbon (EC): 1.4 ± 0.6 and 1.2 ± 0.5 µg/m^3. Year mean outdoor and indoor exposure to NO_2: 46.8 ± 12.0 and 29.4 ± 11.7 µg/m^3.	Motor response speed and attention	computerized Attentional Network Test, child version (Child ANT)	Socio-demographic factors: neighborhood socioeconomic status vulnerability index, parental education, height and weight	Non-significant association: EC/NO2 and attention
Saenen, 2016	COGNAC study, Flanders (Belgium)	three primary schools in urban areas	longitudinal (panel study)	310 children	approximately 10 years of age (3rd to 6th grade)	PM2.5, PM10 and BC	Measurements of recent exposure at school; estimates with spatial temporal interpolation method for recent and chronic exposure at	Selective attention	Stroop Test	sex, age, education of themother, highest rank of occupation of either parents, passive smoking, out-of-school sport activities,	Significant association: > recent exposure at school (indoor) to PM2.5/PM10 → > reaction times in Stroop Test

							residence. Median recent exposure at school to PM2.5, PM10: 5.14 and 33.5 µg/m³; recent exposure at residence to PM2.5, PM10, BC: 15-16, 19-21, 1.4-1.5 µg/m³; chronic exposure at residence to PM2.5, PM10, BC: 15.7, 21.3, 1.54 µg/m³	Sustained attention	Continuous Performance Test	traffic noise, hours of computer screen time per week, and day of the week	> chronic exposure at residence to PM2.5/PM10 → > reaction times in both tests <u>Non-significant association:</u> Recent exposure at school to PM2.5/PM10 and sustained attention; recent exposure at home to PM2.5/PM10/BC and attention; chronic exposure at residence to BC and attention
Alemany, 2017	BREATHE study. Barcellona	metropolitan area with high urban traffic	population based cohort of primary school children	1645 children	7-11 years of age	Copper in PM2.5	Measurements at school. Mean yearly school outdoor and indoor copper: 7.79 ±2.74 and 7.78 ± 2.03 µg/m³	Inattentiveness	computerized Attentional Network Test (ANT)	age, sex, maternal education, and seasonality	<u>Significant association:</u> > copper in PM2.5 at school (outdoor) → > inattentiveness

Mortamais, 2017	BREATHE study. Barcellona	metropolitan area with high urban traffic	population based cohort of primary schoolchildren	242 children	8-12 years of age	PAHs benzo[a]pyrene	Measurements at school. Mean yearly school outdoor and indoor PAHs: 1458 ±704 and 1710± 1107 pg/m³; mean yearly school outdoor and indoor benzo[a]pyrene: 99 ±62 and 105± 72 pg/m³	Inattentiveness	child attention network test (ANT)	intracranial volume, age, sex, maternal education and home socioeconomic vulnerability index	Non-significant association: PAHs and inattentiveness
Sunyer, 2017	BREATHE study. Barcellona	metropolitan area with high urban traffic	population based cohort of primary schoolchildren	2687 children	7-10 years of age	Traffic Related Air Pollution (TRAP), expecially EC, and NO_2 at air monitoring stations and in schools	Indoor and ambient air median yearly exposure to NO_2: 29.4 and 33.5 µg/m³. Indoor and ambient air median yearly exposure to EC: 1.24 and 1.13 µg/m³	Inattentiveness	child Attention Network test (ANT)	neighborhood socioeconomic vulnerability index, Parental educational level, Symptoms of ADHD and other characteristics of individuals and contextual variables	Significant association: > short term exposure to NO2 → > inattentiveness > short term exposure to EC → > inattentiveness > long term exposure at school to NO2 → > inattentiveness Non-significant association: long term exposure to EC and inattentiveness
Alemany, 2018	BREATHE study. Barcellona	metropolitan area with high urban traffic	population based cohort of primary schoolchildren	1667 children	7-11 years of age	PAHs, EC, and NO2	Measurements at school. Mean yearly school exposure to PAHs: 1546 ± 775	Inattentiveness	Attentional Network Test (ANT)	Sociodemograpich data: including child age and sex, maternal	Significant association: > PAHs at school

							pg/m^3; EC: 1.46 ± 0.68 μg/m^3; NO_2 47.74 ± 12.95 μg/m^3			education level, maternal smoking during pregancy and exposure to environmental tabacco smoke at home, residential neighborhood socioeconomic status (SES) vulnerability index	(outdoor) → > inattentiveness Non-significant association: EC/NO2 and inattentiveness
Prenatal and postnatal exposure											
Harris, 2016	VIVA study. eastern Massachusetts (USA)	urban and suburban area	prospective birth cohort	1212 children	6-11 years of age	BC and PM2.5	Spatiotemporal LUR models. Mean exposure at residence during the third trimester of pregnancy, from birth to 3, from birth to 6, the year before testing. For BC: 0.69 ± 0.23, 0.61 ± 0.17, 0.56 ± 0.16 and 0.47 ± 0.14 μg/m^3. For PM2.5: 12.3 ± 2.5, 12.0 ± 1.8, 11.3 ± 1.7 and 9.4 ± 1.9 μg/m^3.	Executive function	Behavior Rating Inventory of Executive Function (BRIEF)	Child characteristics (Sex, Gestational age, Birth weight, Duration of breastfeeding, Early childhood blood lead); Maternal characteristics (Age at enrollment, IQ, Parity, Education, Race/ethnicity, Alcohol consumption during pregnancy, Smoking status, Exposure to secondhand smoke during pregnancy, Marital/cohabitation status, Blood lead in pregnancy);	Significant association: > BC (postnatal) → > behavioral regulation Non-significant association: PM2.5 and behavioral regulation

										Paternal characteristics (Education); Household/neighborhood characteristics (Household income at mid-childhood, HOME-SF score)	
Sentís, 2017	INMA study. Valencia, Sabadell, Asturias, and Gipuzkoa regions (Spain)	Valencia and Sabadell have a greater congestion of urban traffic than Gipuzkoa and Asturias	population-based birth cohort	1298 children	4-5 years of age	NO_2	Model estimates with LUR. Prenatal and postnatal mean exposure to NO_2: 31.1 (from 18.4 to 37.9) µg/m³ and 25.7 (from 19.5 to 35.2 µg/m³)	Inattention, impulsivity, sustained attention, and vigilance	Kiddie-Conners Continuous Performance Test - Second Edition (K-CPT2)	parental education level, maternal and paternal age, parents' social class, maternal and paternal countries of birth, maternal height and pre pregnancy weight, paternal body mass index, maternal smoking and exposure to second hand smoke; maternal alcohol use, maternal consumption of fish, fruit, vegetables, vitamin D, and folic acid; maternal noise annoyance; and household gas appliances	Significant association: > NO2 (pre and postnatal) → > omission errors only in girls

Rivas, 2019	BREATHE study. Barcellona	metropolitan area with high urban traffic	population based cohort of primary schoolchildren	2221 children	7-10 years of age	PM2.5	Model estimates with LUR. Mean residential prenatal and postnatal (first 7 years) PM2.5: 16.5 ± 3.0 and 16.8± 2.9 $\mu g/m^3$	Attentiveness	Attentional Network Test	sociodemographic factors including participants' age and sex, parental education and occupation, marital status, family origin, and residence history	Significant association: > PM2.5 (pre and postnatal) → > attention

Table 5.

Synthesis of studies that considered verbal language.

First author, year	Country	Exposure context	Study design	Sample (N)	Age of the children	Air pollutants	Exposure assessment	Verbal language specific function	Standardized test	Controlled confounding variables	Main findings
							Prenatal exposure				
Lertxundi, 2019	INMA study. Gipuzkoa, Sabadell and Valencia (Spain)	Atlantic coast (Gipuzkoa) and Mediterranean coast (Valencia and Sabadell)	population-based birth cohort	1119 mother-child pairs	4-6 years of age	PM2.5, NO_2	Model estimates with LUR (1 region) and measurements at air monitoring stations. (2 regions). Mean prenatal exposure NO_2: 18.4 - 41.8 $\mu g/m^3$; PM2.5: 15.1-21.7 $\mu g/m^3$	Verbal function	McCarthy scales of Children's Abilities (MSCA)	maternal educational level, social class, country of birth, smoking during pregnancy, pre-pregnancy body mass index, and age at delivery; child's sex and gestational age and anthropometric measures	<u>Significant association:</u> > PM2.5 → < verbal language skill only in boys > NO2 → < verbal language skill only in boys
							Postnatal exposure				
Suglia, 2008	Maternal-infant smoking study. Boston, Massachusetts (USA)	urban area in the Greater Boston area	prospective birth cohort	202 children	8-11 years of age	Black carbon	Model estimates with LUR. Annual black carbon exposure at residence (mean 0.56 ± 0.13 $\mu g/m^3$)	Language (vocabulary scale)	Kaufman Brief Intelligence Test (K-BIT)	sociodemographic factors, birth weight, blood lead level, or tobacco smoke exposure	<u>Significant association:</u> > BC at residence → < vocabulary competences
Calderón-Garcidueñas, 2011	Mexico City and Polotitlán	Mexico City: urban area with over 40,000 industries and urban traffic pollutants	prospective protocol	20 children from Southwest Mexico City (SWMC) and 10 children from Polotitlán	7-8 years of age	Heavy air pollution (including PM2.5 and O_3)	Geographical partitioning between Mexico city (pollutants above air quality standards) and Polotitlán (pollutants below the standards)	Language (vocabulary subtest)	Wechsler Intelligence Scale for Children-Revised, WISC-R) (spanish version)	age and socioeconomic status	<u>Significant association:</u> Children who lived in Mexico city → < vocabulary competences

Midouhas, 2018	MILLENIUM cohort (United Kingdom)	England and Wales (air pollution of NO_2 regularly exceeding the legal levels)	longitudinal survey	8198 children	3 years of age	NO_2	Annual mean exposure to NO_2 at residence, based on data of the National Atmospheric Emissions Inventory. NO_2 deciles: from 9.26 to 33.89 µg/m^3	Spoken vocabulary: expressive language ability, vocabulary knowledge of nouns, general knowledge and language development and stimulation	British Ability Scales II Naming Vocabulary test	child-level covariates: gender, age, and low birth weight); family-level covariates: maternal education, maternal psychological distress, residential stability and maternal involvement)	Significant association: > BC (prenatal and postnatal) → verbal ability
Talaeizadeh, 2018	Tehran (Iran)	districts 20 (high pollution) and 22 (low pollution)	cross-sectional	190 girls	8-10 years of age	Heavy air pollution (including SO_2, NO_2, PM2.5, PM10, O_3, CO)	Geographical partitioning between different areas of Tehran. Air monitoring stations used to identify area of the city with high and low pollution	Language (vocabulary and comprehension tests)	Revised Wechsler Intelligence Scale for Children (WISC-R)	family economic status, height, weight, and nutrition situation	Significant association: polluted area < vocabulary competences and information comprehension but only in girls

Table 6.

Synthesis of studies that considered numeric abilities.

First author, year	Country	Exposure context	Study design	Sample (N)	Age of the children	Air pollutants	Exposure assessment	Numeric specific function	Standardized test	Controlled confounding variables	Main findings
Prenatal exposure											
Lertxundi, 2019	INMA study. Gipuzkoa, Sabadell and Valencia (Spain)	Atlantic coast (Gipuzkoa) and Mediterranean coast (Valencia and Sabadell)	population-based birth cohort	1119 mother-child pairs	4-6 years of age	PM2.5, NO_2	Model estimates with LUR (1 region) and measurements at air monitoring stations. (2 regions). Mean prenatal exposure NO_2: 18.4 - 41.8 μg/m^3; PM2.5: 15.1-21.7 μg/m^3	numeric ability (numeric scale)	McCarthy scales of Children's Abilities (MSCA)	maternal educational level, social class, country of birth, smoking during pregnancy, pre-pregnancy body mass index, and age at delivery; child's sex and gestational age and anthropometric measures	Significant association: > NO2 → < numeric ability Non-significant association: PM2.5 and numeric ability
Postnatal exposure											
Calderón-Garcidueñas, 2011	Mexico City and Polotitlán	Mexico City: urban area with over 40,000 industries and urban traffic pollutants	prospective protocol	20 children from Southwest Mexico City (SWMC) and 10 children from Polotitlán	7-8 years of age	Heavy air pollution (including PM2.5 and O_3)	Geographical partitioning between Mexico city (pollutants above air quality standards) and Polotitlán (pollutants below the standards)	arithmetic ability (arithmetic subtest)	Wechsler Intelligence Scale for Children-Revised, WISC-R) (spanish version)	age and socioeconomic status	Significant association: Children who lived in Mexico city → < arithmetic competences
Prenatal and postnatal exposure											

Porta, 2016	GASPII study. Rome (Italy)	city with urban traffic	prospective birth cohort	474 children	7 years of age	NO$_2$, PM coarse, PM2.5, PM2.5 absorbance	Model estimates with LUR. Exposure at birth (proxy of prenatal exposure); exposure during life and before testing; exposure the year before testing: Median exposure at birth: NO$_2$ 43,3 (from 22,5 to 85,1) µg/m^3; PM 2.5: 18.7 (17.0-27.4) µg/m^3; PM coarse: 15,7 (10.8-31.5) µg/m^3; PM 2.5 absorbance: 2.52 (2.16-4.77) 10^{-5} m^{-1}	arithmetic reasoning (arithmetic reasoning subtest)	Wechsler Intelligence Scale for Children-III (WISC-III)	gender, child age at cognitive test, birth weight, maternal age at delivery, parental educational level, siblings, socio-economic status, maternal smoking and alcohol consumption during pregnancy, psychologist administering the cognitive test, maternal body mass index before pregnancy	Significant association: > NO2 → < arithmetic reasoning abilities Non-significant association: PMcoarse/PM2.5/PM2.5 absorbance and reasoning abilities

Table 7.

Synthesis of studies that considered motor and sensorimotor skills.

First author, year	Country	Exposure context	Study design	Sample (N)	Age of the children	Air pollutants	Exposure assessment	Motor and/or sensorimotor specific function	Standardized test	Controlled confounding variables	Main findings
Prenatal exposure											
Lubzynska, 2017	ESCAPE study. Netherlands, Germany, Italyand Spain: 40 sites in the Netherlands/Belgium and Catalunya, and 20 sites in Ruhr area and Rome	two countries from the northern part of Europe and two from the southern part, with varying levels and sources of air pollution	4 European population-based birth cohorts	7246 children	1-9 years of age	PM2.5 and elemental composition of PM2.5, considering: Cu, Fe, K, Ni, S, Si, V, Zn	Model estimates with LUR. Prenatal exposure to PM2.5 in the range 10 35 μg/m^3	Psychomotor functions (fine and gross motor functions)	McCarthy Scales of Children's Abilities (MSCA)	Maternal information (age at delivery, pre-pregnancy body mass index, smoking during pregnancy, alcohol consumption during pregnancy, marital status, parity, height, pre-pregnancy weight); Parental information (educational level and country of birth)	Significant association: > airborne iron → < fine motor skills Non-significant association: PM2.5 and motor skills
Lertxundi, 2019	INMA study. Gipuzkoa, Sabadell and Valencia provinces (Spain)	Atlantic coast (Gipuzkoa) and Mediterranean coast (Valencia and Sabadell)	population-based birth cohort	1119 mother-child pairs	4-6 years of age	PM2.5, NO_2	Model estimates with LUR (1 region) and measurements at air monitoring stations. (2 regions). Mean prenatal exposure NO_2: 18.4 - 41.8 μg/m^3; PM2.5: 15.1-21.7 μg/m^3	Perceptive-Manipulative function and motor (gross and fine) functions	McCarthy scales of Children's Abilities (MSCA)	maternal educational level, social class, country of birth, smoking during pregnancy, pre-pregnancy body mass index, and age at delivery; child's sex and gestational age and anthropometric measures	Significant association: > NO2 → < fine motor skills only in boys Non-significant association: NO2 and gross motor skills; PM2.5 and motor skills

Postnatal exposure										
Freire, 2010	INMA study. Granada Province (Spain)	urban area and non-urban area	population-based birth cohort	210 children	4 years of age	NO$_2$	Model estimates with LUR. Mean annual NO$_2$ at residence: 20.88 µg/m^3.	Gross and fine motor functions	McCarthy Scales of Children's Abilities (MSCA)	Sociodemographic covariates (place of residence, maternal and paternal education, maternal occupational status, parity, duration of breastfeeding, type of delivery, marital status, smoking during pregnancy and age of mothers and children), birth weight and length and gestational age and Parents' mental health scale scores and parent-to infant attachment scale scores	Significant association: > NO2 at home → < gross motor skills Non-significant association: NO2 and fine motor skills
Calderón-Garcidueñas, 2011	Mexico City and Polotitlán	Mexico City: urban area with over 40,000 industries and urban traffic pollutants	prospective protocol	20 children from Southwest Mexico City (SWMC) and 10 children from Polotitlán	7-8 years of age	Heavy air pollution (including PM2.5 and O$_3$)	Geographical partitioning between Mexico city (pollutants above air quality standards) and Polotitlán (pollutants below the standards)	Spatial ability (Picture Completion subtest)	Wechsler Intelligence Scale for Children-Revised, WISC-R) (spanish version)	age and socioeconomic status	Significant association: Children who lived in Mexico city: WMH$^+$ > spatial abilities than WMH$^-$

Van Kempen, 2012	RANCH study. Amsterdam (The Netherland); 24 primary schools around Schiphol-Amsterdam Airport	urban area near airport with road traffic	cross-sectional based on school children	485 children	9-11 years of age	NO_2 and PM10	Model estimates with LUR. Annual median exposure to PM10: 25.8 µg/m^3 at home, 25.8 µg/m^3 at school; NO_2: 31.2 µg/m^3 home, 30.4 µg/m3 at school.	Locomotion: coordination	Neurobehavioral Evaluation System (NES): Hand–Eye Coordination Test (HECT)	socio-economic and life-style factors	Non-significant association: NO2 and coordination and perceptual coding (the effect of PM10 was not further investigated)
								Perceptual coding	Neurobehavioral Evaluation System (NES): Symbol Digit Substitution Test (SDST)		
Saenen, 2016	COGNAC study, Flanders (Belgium)	three primary schools in urban areas	longitudinal (panel study)	310 children	approximately 10 years of age (3rd to 6th grade)	PM2.5, PM10 and BC	Measurements of recent exposure at school; estimates with spatial temporal interpolation method for recent and chronic exposure at residence. Median recent exposure at school to PM2.5, PM10: 5.14 and 33.5 µg/m3; recent exposure at residence to PM2.5, PM10, BC: 15-16, 19-21, 1.4-1.5 µg/m^3; chronic exposure at residence to PM2.5, PM10, BC: 15.7, 21.3, 1.54 µg/m^3	Visual information processing speed domain	Digit-Symbol Test	sex, age, education of themother, highest rank of occupation of either parents, passive smoking, out-of-school sport activities, traffic noise, hours of computer screen time per week, and day of the week	Significant association: > recent exposure at school (indoor) to PM2.5/PM10 → < visual information processing speed > recent exposure at residence to PM2.5/PM10/BC → visual information processing Non-significant association: chronic exposure at residence to PM2.5/PM10/BC and visual information processing
								Visual information processing speed domain	Pattern Comparison Tests		
Prenatal and postnatal exposure											

Harris, 2015	VIVA study. eastern Massachusetts (USA)	urban and suburban area	prospective birth cohort	1109 mother–child pairs	6-10 years of age	BC and PM2.5	Model estimates with LUR. Exposure during the third trimester of pregnancy, the first 6 y of life, the year before testing. BC third trimester 0.69 ± 0.23 µg/m³, BC birth–6 years 0.56 ± 0.16 µg/m³ and BC the year before testing 0.47 ± 0.15 µg/m³. PM2.5 : third trimester 12.3 ± 2.6 µg/m³, PM2.5 birth–6 years 11.3 ± 1.7 µg/m³ and PM2.5 the year before testing 9.4 ± 1.9 µg/m³	Visual motor performance	Wide Range Assessment of Visual Motor Abilities (WRAVMA) (Visual-Motor subtest)	characteristics of the child (sex, age at cognitive testing, breastfeeding duration, blood lead in early childhood), of the mother (IQ, parity, age at enrollment, marital/cohabitation status, education, race/ethnicity, smoking status, exposure to secondhand smoke during pregnancy, blood lead in pregnancy, alcohol consumption during pregnancy) of the father (education, household, annual income at time of cognitive assessment) and of the neighborhood (median annual income for census tract of residence at cognitive testing)	<u>Significant association:</u> Prenatal residential proximity to a polluted area → < visual motor skills > PM2.5 (postnatal) > visual motor skills <u>Non-significant association:</u> PM2.5 (prenatal)/BC and visual motor skills

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Table S1.

Classification of neurodevelopmental skills measured in the 30 studies and their short description.

Neurodevelopmental skills	Description
Intellective functioning	A general cognitive index defined by intellective quotient (IQ) which is obtained by the administration of tests and it is the ratio of chronological age to mental age. Usually the total IQ is composed by verbal IQ and non-verbal (performance) IQ
Attention and executive functions	Set of cognitive processes that allow to direct and focus the mental resources on some information rather than others. The attention is also involved in the use of the executive functions that can be defined as the ability to program and control cognition and behavior. The attention function includes selective attention and sustained attention
Memory and learning	Cognitive process of coding, storage, consolidation and recovery of information and experiences derived from the environment and from the activity of thought. It includes short term memory and working memory
Verbal language	A cognitive function aimed at the transmission of information through the use of a symbolic system. Ii includes different aspect like espressive language, vocabulary competences, receptive language, comprehension tests
Numeric abilities	Ability to recognize, manipulate, understand and reason with numbers and quantity. It includes basic (preverbal) mathematical skills like subitizing, stima and numerical acuity and verbal mathematical skills (arithmetic) like counting ability and mathematical reasoning
Motor and/or sensorimotor skills	Motor skills: a set of assumptions, of organic, co-ordinative and perceptive physical nature, through which motor actions can be carried out. They concer motor learning and motor response, i.e. the ability to

	interpret and rework the motor gestures that must be performed. Motor skills are divided into gross motor skills and fine motor skills Sensorimotor functions: connect the sensory and motor system and they can be motor or visual speed and precision (visual motor skills), perceptual coding, spazial ability

Table S2:

Description of standardized tools used in the included to assess specific neurodevelopmental skills.

AUTHORS	**TEST**	**DESCRIPTION**	**NEURODEVELOPMENTAL SKILLS**
Guxen, 2018	Developmental Neuropsychological Assessment (NEPSY-II) (Dutch version)	NEPSY II (Second edition of NEPSY), consisting of a battery of multiple tests, provides a neuropsychological assessment of the cognitive abilities of subjects from 3 to 16 years of age, in relation to specific cognitive domains: attention and executive functions, language, memory and learning, sensorimotor functions, social perception and visual processing	attention and executive functions, memory, verbal language, sensorimotor functions
Alemany, 2018; Rivas, 2019; Basagaña, 2016; Alemany, 2017	Attentional Network Task (ANT)	The ANT is a task designed to test three attentional networks in children and adults: alerting, orienting, and executive control	attention
Pujol, 2016; Mortamais, 2017; Sunyer, 2017	Child Attentional Network Task (ANT)	Child ANT measure the functioning of and interactions between the alerting, exogenous and endogenous visual spatial orienting, and executive control systems in young school children	attention and sensorimotor function
Alemany, 2018; Rivas, 2019; Basagaña, 2016; Pujol, 2016; Talaeizadeh, 2018; Forns, 2017; Sunyer, 2017	N-back task	The N-back is a paradigm used to assess working memory function. In the N-Back task, participants are presented a sequence of stimuli one-by-one; for each stimulus, they need to decide if the current stimulus is the	memory

		same as the one presented N trials ago	
Loftus, 2019	Stanford Binet Intelligence Scales, edition 5 (SB-5)	SB-5 is a test to measure the cognitive abilities (knowledge, quantitative, visual-spatial, and working memory) and intellingence (verbal IQ, nonverbal IQ, brief IQ, full Scale IQ) of children, adolescents, and adults	Intelligence quotient
Calderón-Garcidueñas, 2011; Jedrychowski, 2015; Talaeizadeh, 2018	Wechsler Intelligence Scale for Children-Revised (WISC-R)	WISC-R is a revised and updated version of the WISC, which was first published in 1949 and it's a clinical and diagnostic tool that evaluate the intellectual abilities of children from 6 to 16 years and 11 months. The score provides a Verbal IQ (VIQ), a Performance IQ (PIQ) and a Total IQ (TIQ)	memory, language, sensorimotor functions, numeric ability, intelligence quotient
Perera, 2009	Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R)	WIPPSI-R is a revised and updated version of the WIPPSI, which is the version of the Wechsler scales for preschoolers, from 4 to 6 years and a half. The score provides a Verbal IQ (VIQ), a Performance IQ (PIQ) and a Total IQ (TIQ)	intelligence quotient

Porta, 2016; Lubczynska, 2017	Wechsler Intelligence Scale for Children-III (WISC-III)	WISC-III is the development of WISC-R added an optional sub-test (search for symbols) and a fourth factor (processing speed). The score provides a Verbal IQ (VIQ), a Performance IQ (PIQ) and a Total IQ (TIQ) and four optional Factor Deviation Quotients (FDQ): Verbal Comprehension (CV), Perceptual Organization (PO), Freedom from Distraction (FD), Processing Speed (PS)	memory, language, sensorimotor functions, numeric ability, intelligence quotient
Chiu, 2016; Peterson, 2015	Wechsler Intelligence Scale for Children (WISC-IV)	WISC-IV is an updated version of WISC-III and it provides 5 composite scores: a Total Intellectual Quotient (IQQ) to represent the complex cognitive abilities, and 4 additional scores: the Verbal Comprehension Index (ICV), the Perceptive Reasoning Index (PRI), the Working Memory Index (WMI), the Processing Rate Index (PRI)	memory, intelligence quotient
Wang, 2017	Wechsler Abbreviated Scale of Intelligence ((WASI)	WASI is linked to both the Wechsler Intelligence Scale for Children (WISC-III) and the Wechsler Adult Intelligence Scale (WAIS-III) and it evaluates intellectual ability by measuring the verbal, nonverbal, and general cognition of individuals from 6 to 89 years of age	intelligence quotient

Talaeizadeh, 2018	Wechsler Memory Scale (WMS)	WMS is a neuropsychological test designed to measure different memory functions in a person ages 16 to 90	memory
Sentís, 2017	Conners Kiddie Continuous Performance Test - Second Edition (K-CPT2)	K-CPT2 (Second edition of K-CPT) is a computerized software program assessment tool used to identify attention problems and measure treatment effectiveness in very young children (ages 4 – 7 years)	attention
Chiu, 2016	Conners' Continuous Performance Test-II (CPT-II)	CPT-II (Second Edition of CPT) provides a task-based computerized assessment of attention problems and neurological functioning for subjects aged 6 years and over	attention
Lertxundi, 2019; Lubczynska, 2017; Freire, 2010	McCarthy scales of Children's Abilities (MSCA)	MSCA is a psychological instrument for young children aged from 2 years 6 months to 8 years 6 months that measures cognitive ability in six domain areas: verbal, perceptual-performance, quantitative, general cognitive, memory, and motor	general cognition, executive functions, memory, language, psychomotor and sensorimotor functions, numeric ability
Suglia, 2008	Wide Range Assessment of Memory and Learning (WRAML)	WRAML is a clinical assessment instrument designed to evaluate memory and learning in children between 5-17 years. The battery includes nine subtests on verbal memory, visual memory, and learning. Combined, the subtest form a General	memory

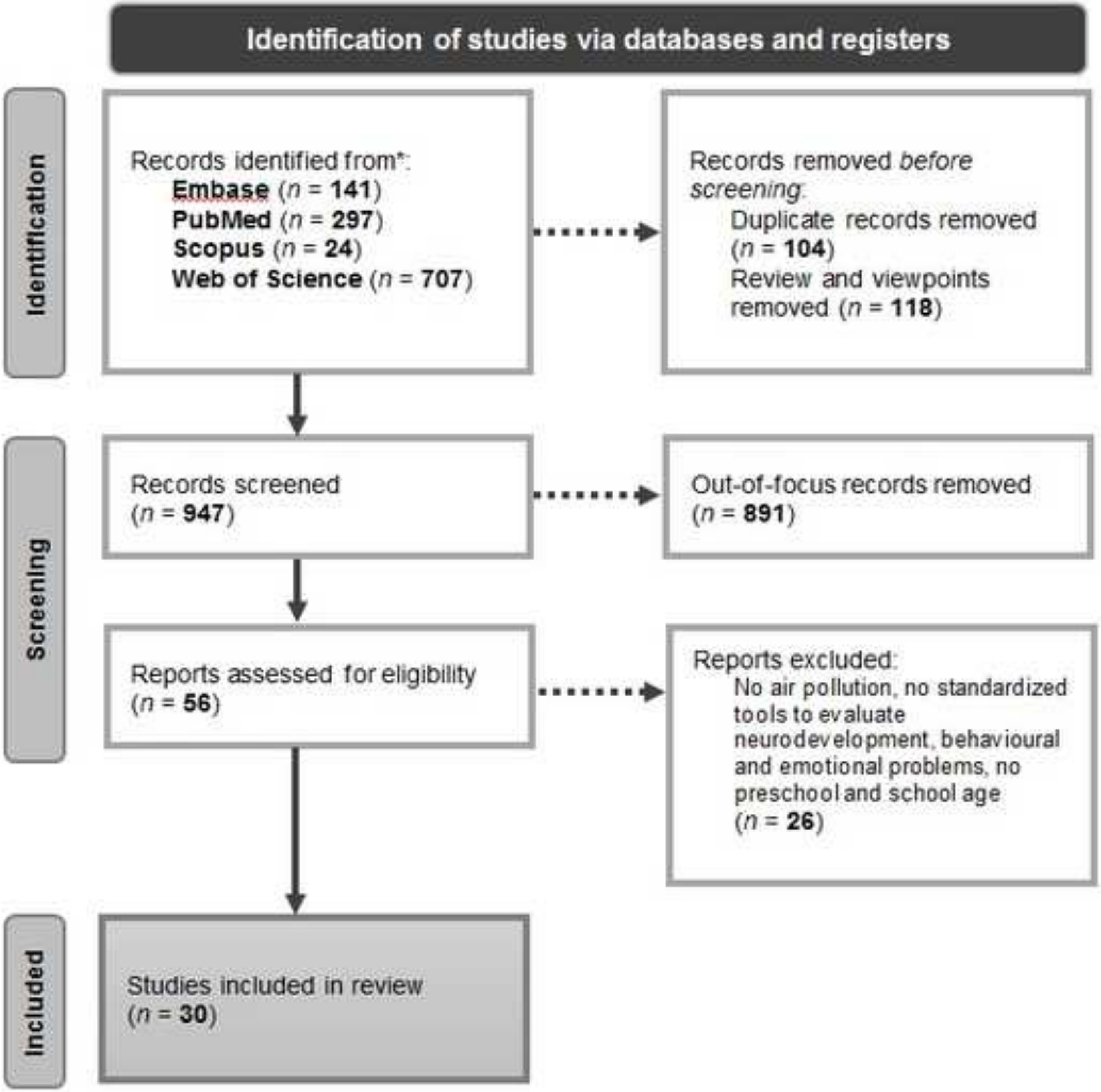
		Memory Index	
Cowell, 2015; Chiu, 2016; Harris, 2015	Wide Range Assessment of Memory and Learning - Second Edition (WRAML2)	WRAML2 is an updated version of WRAML and it extended assessment age of the WRAML from 5–17 to 5–90 years; several subtests from the original WRAML are now optional or limited to a specific age group. The WRAML-2 Core Battery consists of Verbal, Visual and Attention/Concentration subtests. Three Index Scores are derived from these six subtests: a Verbal Memory Index, a Visual Memory Index, and an Attention/Concentration Index; the three indexes together form a General Memory Index	memory
Harris, 2015	Wide Range Assessment of Visual Motor Abilities (WRAVMA)	The WRAVMA is a tool that provides a reliable, accurate evaluation of visual-motor skills of children and adolescents ages 3-17 years (it assesses three areas using three tests)	sensorimotor functions
Suglia, 2008	Kaufman Brief Intelligence Test (K-BIT)	The K-BIT is a short measure of verbal and non-verbal intelligence for children, adolescents and adults aged 4 to 90. Two subscales, vocabulary and	intelligence quotient

		matrices, comprise the test, as well as a composite intelligence quotient score	
Harris, 2015	Kaufman Brief Intelligence Test (KBIT-2)	KBIT-2 is an updated version of K-BIT with changes in sub-tests: added subtest riddles for verbal IQ	intelligence quotient
Harris, 2016	Behavior Rating Inventory of Executive Function (BRIEF)	BRIEF is a questionnaire for parents and teachers to assess executive functions at home and at school of children and adolescents aged 5 to 18 years	executive functions
Edwards, 2010	Raven Coloured Progressive Matrices (RCPM)	RCPM is a version of Raven Progressive Matrices and it is nonverbal test of reasoning ability and intelligence based on figural materials or patterns for children from 4 to 9/10 years and persons with disabilities. (This test has only the matrices A and B present in the standard test with an additional test (AB) of 12 elements)	intelligence quotient
Lubczynska, 2017	De Snijders-Oomen Niet-verbale Intelligentie test-Revisie (SON-R)	SON-R (revision of SON) is a non-verbal intelligence test suitable for children (2.5-7 years) and adults (6-40 years)	Intelligence quotient
Lubczynska, 2017	Hamburg Wechsler Intelligenz test für Kinder (HAWK-IV)	HAWK-IV (Fourth edition of HAWK) is a intelligence test for children and adolescents aged 6 to 16 years and it is the German adaptation of Wechsler	Intelligence quotient

		Scales	
Saenen, 2016	Stroop Test	Stroop test is a measuring instrument for selective attention, in particular for inhibitory processes of irrelevant information (the task is to touch as fast as possible the button that has the same color as the name, ignoring the color of the printed name)	attention
Saenen, 2016	Continuous Performance Test	CPT is a visual sustained attention assessment test (the task is to immediately respond to the cat's silhouette in this case by pressing the spacebar, but not the silhouette of another animal)	attention
Saenen, 2016	Digit Span Forward and Backward Tests	Digit Span Test is a verbal memory span measurement test (digit memory) (in the first part, the task is to reproduce a series of digits after an auditory presentation in the order of the presentation; in the second part of the test, the task is to reproduce the digits in the reverse order of the presentation)	memory
Saenen, 2016	Digit-Symbol Test	Digit-Symbol Test is an assessment tool for evaluation of psychomotor performance (when a digit is shown,	sensorimotor functions

		the task is to indicate as fast as possible the symbol which is paired with this digit in the row of symbols at the bottom of the screen)	
Saenen, 2016	Pattern Comparison Test	Pattern Comparison Test is an assessment tool to evaluate processing speed (the task is to compare three matrices consisting of 10 × 10 blocks and to indicate which pattern is different from other two pattern)	sensorimotor functions
Midouhas, 2018	British Ability Scales II (Naming Vocabulary test)	British Ability Scale II is a battery of individually administered tests of cognitive abilities and educational achievement for children and adolescents aged from 2 years, 6 months to 17 years, 11 months. The Naming Volcabulay test assesses the spoken vocabulary of children and is selected from the Early Years Battery for children age 3 to 5	language
Van Kempen, 2012	Neurobehavioral Evaluation System (NES)	NES is a battery of tests and it consists of over 15 computerized neurobehavioral tests and questionnaires that tap the broad functional domains of psychomotor speed and control, perceptual speed, learning and memory, attention and affect	attention and executive functions, memory, sensorimotor functions

Figure 1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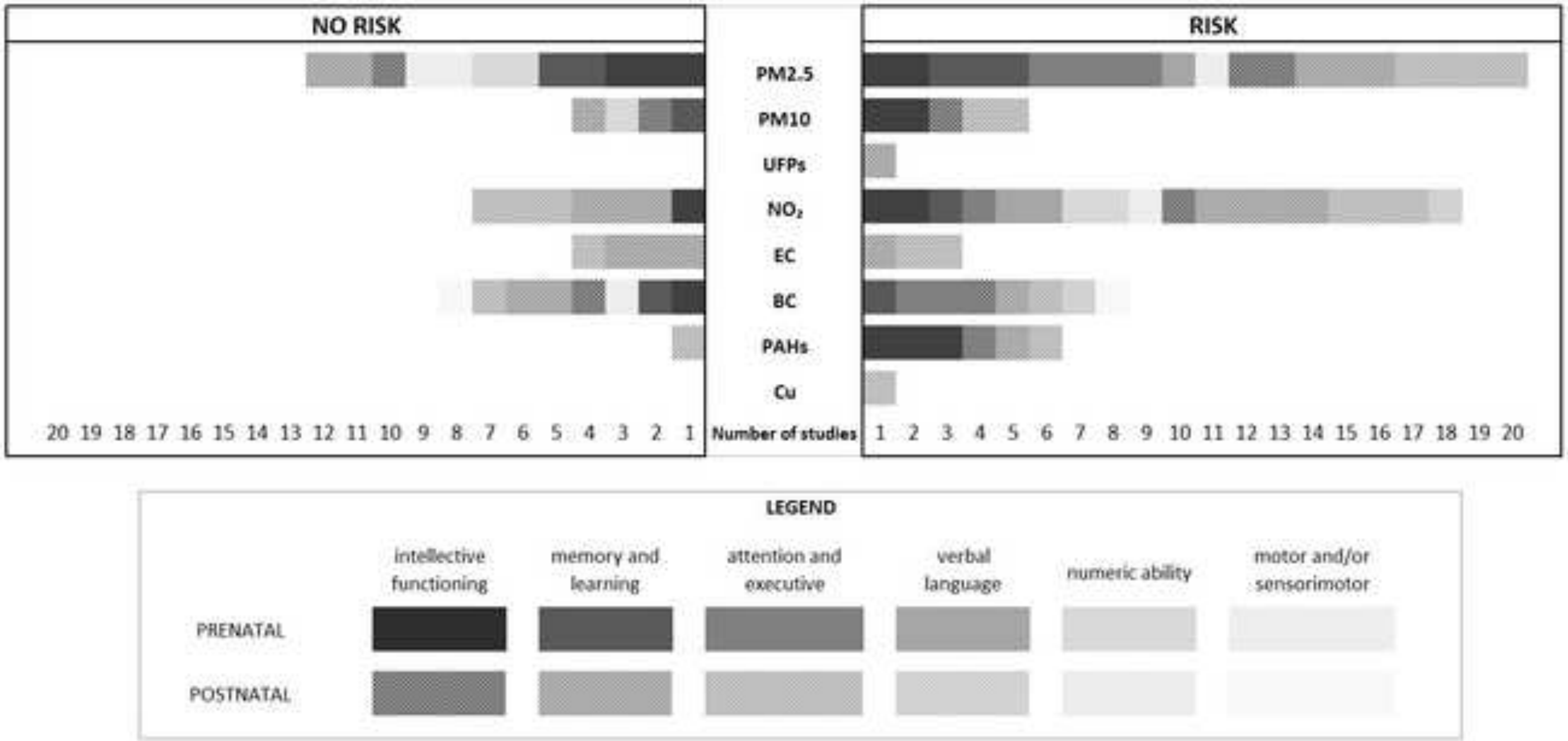
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PRENATAL
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