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Breathing in the Future: Unraveling the Link Between Prenatal Outdoor Air Pollution and Neurodevelopment in Offspring: A Systematic Review

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Abstract

Introduction: *Air pollution exposure has been associated with general negative effects on the nervous system and, consequently, on children's neurodevelopment. This review aims to assess the main damages of prenatal air pollution exposure on the offspring's neurodevelopment.*

Methods: *A systematic review was conducted using PubMed/Medline, Cochrane, Ovid, and Scopus. The studies from the last ten years were assessed in compliance with PRISMA 2020 Guidelines and evaluated regarding quality.*

Results: *From an initial 675 references, 24 observational studies encompassing 115,228 children aged 0 to 10 years were deemed eligible. On average, the women in the studies were around 30 years old at delivery. Various exposure assessment methods, pollutants, and neurodevelopmental outcome scales were utilized. All the studies included found an association between air pollutant exposure and neurodevelopment in different magnitudes. All 24 studies included in our review were observational and, therefore, assessed using the Newcastle-Ottawa Scale (NOS). Of them, 19 were considered good quality, 1 was fair quality, and 4 were poor quality.*

Conclusion: *This comprehensive review presents evidence suggesting that prenatal exposure to air pollution has a harmful impact on cognitive and neurological development in offspring. However, future studies are needed to corroborate these results.*

Introduction

Air pollution is one of the most crucial worldwide health hazards associated with up to 6.7 million deaths globally and can affect almost all organs of the human body (Schraufnagel et al., 2019; World Health Organization, 2022). Several studies have shown the negative effect of air pollution on the nervous system, including decreased cognitive function, auditory deficits, and neurodevelopmental and psychological consequences (Costa et al., 2014, 2017; Lee et al., 2019; Russ et al., 2019; Sram et al., 2017).

Neurodevelopmental delay (NDD) is a broad term that describes delays in the developmental skills of infants and young children. There are a lot of definitions of NDD in the literature. However, all refer to a significant delay in one or more developmental domains than expected for a typical development (Villagomez et al., 2019). Several factors can lead to NDD, including genetic, biochemical, psychosocial, and environmental factors, like air pollution, is one of the significant elements (Blazkova et al., 2022; Harris et al., 2015; Hurtado-Díaz et al., 2021; Khan & Leventhal, 2023). Some air pollutants, such as delicate particulate matter with a diameter of 2.5 µm (PM2.5), nitrogen dioxide (NO2), and polycyclic aromatic hydrocarbons (PAHs), can cross the placental barrier and potentially affect the fetal development Field (Chiarello et al..(Chiarello et al., 2023; Johnson et al., 2021).

Despite some studies recognizing the impact of prenatal exposure to air pollution on brain architecture and development, there is no consensus on the neurodevelopmental outcomes (Johnson et al., 2021; Veras et al., 2022). While some studies found impairments in neurodevelopment in general (Li et al., 2021; P. Wang et al., 2021), others found only some affected domains (Guxens et al., 2014; Su et al., 2022). This review aims to assess the main damages of prenatal air pollution exposure on the offspring's neurodevelopment.

Materials and Methods

Search Strategy

A systematic search was conducted between July 15th and July 28th, 2023, to investigate the effects of prenatal outdoor air pollution exposure on the neurological development of the offspring. We used the following databases: PubMed/Medline, Cochrane, Ovid, and Scopus, following the PRISMA 2020 guidelines. Through a background search, 112 possible keywords were found. After deleting duplicates and organizing them using our search topic, population, exposure, and outcome definitions, 43 keywords were initially eligible to build a search strategy in Pubmed. The search terms used in the title, abstract, and MeSH terms fields for this initial Medline-Pubmed search, keywords, and combinations are available in the Appendix (Appendix 1, Keywords). The search strategy was manually translated and adapted for Ovid, Cochrane, and Scopus databases. The reference lists of selected and recent systematic review reports were manually examined during August 2023 to identify potentially relevant studies that met the inclusion criteria and were not achieved within the search strategy.

We included references from the last ten years in the English language without excluding study design to conduct a comprehensive search, as there was uncertainty about the amount of evidence available in the field.

Eligibility Criteria

Titles and abstracts were reviewed according to the following inclusion criteria: Studies with a population of pregnant women (any trimester) and their children, with no age limit for the outcome assessment during childhood, exposure to any outdoor air pollutant during pregnancy and early childhood, outcomes related to overall neurodevelopment or its psychomotor, cognitive, language, or behavioral domains.

In addition, studies were excluded if they assessed occupational exposure, other air pollutants (e.g., organophosphates, pesticides, or tobacco), indoor isolated pollutants, or solely physical abnormalities or birth defects. Related diagnoses like attention-hyperactivity disorder (AHD) or autism spectrum disorder (ASD) were excluded from the analysis.

Data Extraction and Quality Assessment

Utilizing Rayyan app® (Ouzzani et al., 2016) in a rigorously blinded manner, a pair of independent reviewers (E.B, S.M) initiated the preliminary records screening, with a third impartial reviewer (Y.A) resolving conflicts arising from the initial blinded review of titles and abstracts.

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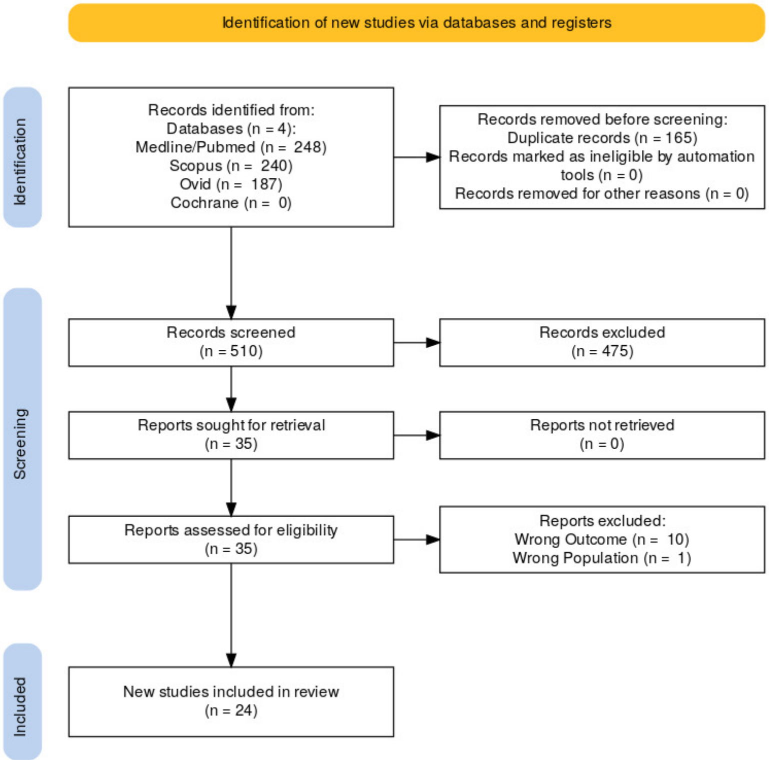

Figure 1: *PRISMA flow diagram.*

The retrieved full-text articles were reviewed by independent researchers (M.O, P.D, I.M) to confirm inclusion and exclusion criteria and to assess quality using the Newcastle-Ottawa Scale (NOS) for observational studies (Wells et al., 2000), its adapted version for cross-sectional studies NOA and Cochrane collaboration risk of bias tool (CCRBT) for RCT's (Chung et al., 2012). The included articles were analyzed for data extraction and synthesis. At the end of the analysis, the studies are classified as good, fair, or poor quality.

Results

A comprehensive examination of 675 references sourced from databases effectively eliminated 165 duplicate entries. Subsequently, out of the remaining 510 entries, 475 were excluded based on the title and abstract following the pre-defined inclusion and exclusion criteria. A total of 35 reports were sought for retrieval and then assessed in full text for eligibility. After a full-text review, 24 articles were included in the main analysis, as shown in Figure 1 (Appendix 2, PRISMA Flow Chart.)

All 24 studies included in our review were observational (Appendix 3, Table 1) and, therefore, were assessed using the NOS (Wells et al., 2000). Of them, 19 were considered good quality, 1 was fair quality, and 4 were poor quality (Appendix 4, Table 2).

Study Characteristics

Of the 24 observational studies deemed eligible, 23 were cohort studies, and one was cross-sectional, and together, they encompass 115,228 children aged 0 to 10 years. On average, the study's mothers were around 30 years old at delivery. Our review found that air pollution exposure during pregnancy was associated with neurodevelopment in offspring. The pollutants measured across studies included black carbon (BC), NH4+, sulfate (SO42-), dust, carbon oxide (CO), SO2, total hydrocarbons (THCS), non-methane hydrocarbons (NMHCS), ozone (O3), nitrogen oxides (NOx), nitrogen dioxide (NO2), particulate matter with a diameter of 10 micrometers or less (PM10) and particulate matter with a diameter of 2.5 micrometers or less (PM2.5), with the latter being measured most frequently.

Six studies were undertaken in Europe, five in the United States, one in Mexico, and twelve in Asia. Several methods were used to assess air pollution exposure and ND outcomes. Exposure periods and outcome assessment age vary across studies, with details shown in Table 1 (Appendix 3, Table 1), and the main findings are summarized as follows:

Pollutant Measure Methods

Id	Author/Year	Country	Study Design	Sample	Age Range y/mo	Aim of Study
1	Loftus et al.,2020	Shelby, USA	Prospective Cohort	1,503 mother-child pair (MCP)	Mothers: 16–40 years (y). Children 1.5–5 years	Association between prenatal and childhood exposure to NO2 and PM10 and childhood behavioral disorders.
2	Harris et al., 2015	Massachusetts, USA.	Longitudinal cohort (Project Viva Study)	1,109 MCP	Mothers: 32.1 +- 5.4 y. Children: 8.0 +- 0.8 y.	Associations of gestational and childhood exposure to traffic-related pollution with childhood cognition.
3	Hurtado-Diaz et al., 2021	Mexico City, Mexico.	Longitudinal birth cohort	740 MCP	Mothers: 27.1 ± 5.5 y. Children: 24 months (m).	Long-term effects of prenatal exposure to PM2.5 on neurodevelopment in children.
4	Morgan et al., 2023	Southern California.	Longitudinal cohort	161 MCP	Mother: >18 y. Age 29.02 +/- 6.21. Children: 24 m.	Prenatal exposure to NO2, PM2.5 and PM10 and association with neurodevelopmental outcomes.
5	Girardi et al.,2021	Italy	Cross-sectional	1157 MCP	Mothers: not mentioned. Children: 5 to 8 y.	Link between prenatal exposure to PM10 and the development of school-age children (5 to 8 years) in multiple domains.
6	Lei et al., 2022	China	Prospective Cohort	2435 MCP	Mother: 29.0 ± 3.4. Children: 12 m.	Associations of prenatal PM2.5 and its composition exposure with infant cognitive and motor function.
7	Blazkova et al., 2022	Karvina/ Ceske Budejovice, Czech Republic.	2 Prospective Cohorts	168 MCP	Mother: 31.9±4.5. Children 5 y.	Impact of oxidative damage associated with PM2.5 during prenatal period on the cognitive development at 5 years.
8	Lin et al. ,2014	Taiwan	Prospective Cohort	533 MCP	Mother: not mentioned. Children: 6 and 18 m.	Association between exposure to ambient air pollutants during the prenatal/ postnatal periods with early childhood ND.
9	Su et al., 2021	Foshan, China.	Birth Cohort. Birth registry.	15,778 MCP	Mother: mean 29.7 y. Children: mean 11.5m.	Associations between prenatal air pollution exposure (pm 2.5, pm 1, pm10, No2 and So2) and ND delay.
10	Wang et al., 2021	China	Prospective Cohort	4009 MCP	Mother: 28.81 ± 4.09. Children: 2, 6, 12, and 24 m.	Association between prenatal PM2.5 exposure and childhood ND till 2 y. and identify the potential critical windows of PM2.5 exposure during pregnancy.

Table 1: *Summary of characteristics among included studies.*

11	Xu et al., 2022	China	Cohort	1531 infants	Mother: 30.99 ± 3.82. Children: 11–12.5 m.	Associations between prenatal exposure to PM2.5 and neurodevelopment in offspring at 1 year old, and assess whether individual PM2.5 constituents exert distinct effects.
12	Ha et al.,2019	New York, USA.	Prospective Cohort	5825 infants	Mother: mean 30.6 y. Children: 8, 12, 18, 24, 30 and 36 m.	Association of residential proximity to major roadways or exposures to PM2.5 and ozone during pregnancy and early developmental screening failure during the first 3 y.
13	Porta et al., 2016	Rome, Italy	Prospective Cohort	719 infants	Mother: 18–30 :118 (25%); 31–35: 207 (45%); >35: 140 (30%). Children: 6, 15 m. and 4, 7, and 8 y.	Potential link between early life exposure to air pollution, particularly traffic-related pollutants, and cognitive impairment in children.
14	Kim et al., 2014	South Korea	Prospective Cohort	520 MCP	Mother: 30.4y +/- 3.4y. Children: 24 m.	Association between prenatal exposure to PM10 and NO2, and ND in children during the first 24 m.
15	Guilbert et al., 2023	France	Cohort	1271 MCP	Mother: 29 y. (IQR: 26.7, 32.6). Children 0-5-6 y.	Impact of prenatal and early postnatal exposure to PM10, PM2.5, and NO2 on child cognition.
16	Guxens et al.,2018	Rotterdam, Netherlands.	Retrospective Cohort	783 MCP	Mother: 30.7 +- 4.9. Children: 6-10 y.	Prenatal air pollution exposure and brain morphology, mediation effect between air pollution exposure and cognitive function in school-age children.
17	Wang et al., 2022	Shanghai, China	Prospective Cohort	267 MCP	Mother: 29.75 ± 4.29. Children 0; 6; 12 and 24 m.	Effects of prenatal exposure to PM2.5 and its components on child ND, analyze the change of sEVs-derived miRNAs in response to this exposure and the associations between the PM2.5-associated miRNAs and child ND. Identify the key miRNAs that may serve as potential biomarkers.

Table 1: *Summary of characteristics among included studies.*

18	Wang et al., 2022	Wuhan city, China.	Prospective Cohort	1331 MCP	Mother: 28.6 ± 3.4. Children: 2 y.	Associations of prenatal and early postnatal exposure to PM with offspring neurodevelopment at 2 y. and identify sensitive periods to its effects on ND.
19	Shih et al., 2022	Taiwan	Prospective Cohort	17683 MCP	Mother: <25 y. (3507), 25-35 y. (11 986), >35 y. (2122). Children: 0 to 18 m.	Association between ambient PM2.5 during prenatal and postnatal periods and infant ND.
20	Ni et al., 2022	Memphis, San Francisco, Minneapolis, Rochester, Seattle TIDES, Seattle GAPPS and Yakima, USA.	Prospective Multi-Cohort Study	1967 MCP	Mother: mean 28.5 y. Children: mean 5.2 y.	Associations between air pollution exposures and child behavioral functioning and cognitive performance.
21	Yorifuji et al., 2016	Japan	Retrospective Cohort	46039 infants	Mother: Mean 30±4.5 y. Children: 2.5 and 5.5 y.	Associations between prenatal exposure to traffic-related air pollution and child behavioral development delays
22	Yu et al., 2022	Shanghai, China.	Prospective Cohort	225 MCP	Mother: 29.01 ± 3.09 y. Children: 24 to 36 m.	Explore prenatal exposure to ambient SO2 and NO2 on toddler neurodevelopment and the effect-modification by ambient temperature.
23	Sun et al., 2023	Shanghai China	Prospective Cohort	512 MCP	Mother: Not mentioned. Children: 0-6 y.	Associations between prenatal PM2.5 and its six constituents and the IQ levels of 6-year-old children
24	Guxens et al., 2014	Netherlands, Germany, France, Italy, Greece and Spain.	Population-based birth multi-cohorts.	9482 infants	Mother: mean 30-33 y. Children: 1 and 6 y.	Assess whether air pollution exposure during pregnancy affects cognitive and psychomotor development in childhood.

MCP= Mother-child pairs; **ND**= Neurodevelopment; **Al**= Aluminum; **aOR** = Adjusted odds ratio; **aRR** = Absolute risk reduction; **ASQ** = Ages & Stages Questionnaire; **ASQ3** = Ages & Stages Questionnaire, Third Edition; **BC** = Black carbon; **BG** = Bender Visual Motor Gestalt Test; **BSID I** = Bayley Scales of Infant and Toddler Development, First Edition; **BSID-II** = Bayley Scales of Infant and Toddler Development, Second Edition; **BSID-III** = Bayley Scales of Infant and Toddler Development, Third Edition; **CBCL**= Child Behavior Checklist; **CI** = Confidence Interval; **CO** = Carbon monoxide; **DDST II** = Denver Developmental Screening Test, Second Edition; **DP-3** = Developmental Profile, Third Edition; **GDS** = Gesell Development Schedules; **GEE** = Generalized estimating equation; **IQ** = Intelligence quotient; **IQR** = Interquartile range; **KBIT-2** = Kaufman Brief Intelligence Test; **K-BSID-II** = Korean Bayley Scale of Infant Development II; **MCD I** = Mild Cognitive Dysfunction; **MDI** = Mental developmental index; **miRNAs** = microRNA; **MRI** = Magnetic resonance imaging; **MSCA** = McCarthy Scales of Children's Abilities; **NESCC** = Neuropsychological Examination Scale for Chinese Children; **NEPSY-II** = NEuroPSYchological Assessment, Second Version; **NH4+** = Ammonium; **NMHCs** = Nonmethane hydrocarbons; **NO2** = Nitrogen dioxide; **NO3** = Nitrate; **O3** = Ozone; **OC** = Organic carbon; **ORs** = Odds ratios; **PA** = Physical activity; **Pb** = Lead; **PDI** = Psychomotor developmental index; **PM** = Particulate matters; **PM2.5** = Fine particulate matter with a diameter of 2.5 micrometers or less; **PM10** = Particulate matter smaller than 10 micrometers; **RCPM** = Raven Colored Progressive Matrices test; **RR** = Relative risk; **sEVs** = Small extracellular vesicles; **SD** = Standard deviation; **SDD** = Suspected developmental delay; **SO2** = Sulfur dioxide; **SO42-** = Sulfate; **TBCS** = The Birth Cohort Study; **THCs** = Total hydrocarbons; **Ti** = Titanium; **V** = Vanadium; **WHO** = World Health Organization; **WISC-IV** = Wechsler Intelligence Scale for Children, Fourth Edition; **WPPSI-III** = Wechsler Preschool and Primary Scale of Intelligence Third Version; **WRAML-2** = Wide Range Assessment of Memory and Learning, Second Edition; **WRAVMA** =Wide Range Assessment of Visual Motor Abilities.

Table 1: *Summary of characteristics among included studies.*

Article	Study type	NEWCASTLE-OTTAWA SCALE (NOS)*			
		Selection	Comparability	Outcome/ Exposure	Overall Study quality
Loftus et al.,2020	Cohort	★★★★	★★	★★★	GOOD
Harris et al., 2015	Cohort	★★★★	★★	★★★	GOOD
Hurtado-Diaz et al., 2021	Cohort	★★★★	★★	★★★	GOOD
Morgan et al., 2023	Cohort	★★★★	★★	★★★	GOOD
Girardi et al.,2021	Cross-sectional	★★	★★	★★	FAIR
Lei et al., 2022	Cohort	★★★★	★★	★	POOR
Blazkova et al., 2022	Cohort	★★★★	★★	★★	GOOD
Lin et al. ,2014	Cohort	★★★★	★★	★★	GOOD
Su et al., 2021	Cohort	★★★★	★★	★★	GOOD
Wang et al., 2021	Cohort	★★★★	★★	★★	GOOD
Xu et al., 2022	Cohort	★★★★	★★	★★	GOOD
Ha et al.,2019	Cohort	★★★★	★★	★★★	GOOD
Porta et al., 2016	Cohort	★★★★	★★	★★	GOOD
Kim et al., 2014	Cohort	★★★★	★★	★★	GOOD
Guilbert et al., 2023	Cohort	★★★★	★★	★★★	GOOD
Guxens et al.,2018	Cohort	★★★★	★★	★★★	GOOD
Wang et al., 2022	Cohort	★★★★	★★	★★★	GOOD
Wang et al., 2022	Cohort	★★★★	★★	★★★	GOOD
Shih et al., 2022	Cohort	★★★★	★★	★	POOR
Ni et al., 2022	Cohort	★★★★	★★	★★	GOOD
Yorifuji et al., 2016	Cohort	★★★★	★★	★	POOR
Yu et al., 2022	Cohort	★★★★	★★	★★	GOOD
Sun et al., 2023	Cohort	★★★★	★★	★★	GOOD
Guxens et al., 2014	Cohort	★★★★	★★	★	POOR

* Newcastle-Ottawa Scale (NOS) and Cross-sectional adaptation from Wells et al., 2000

Table 2: *Newcastle-Ottowa Scale (NOS) assessment.*

Air pollutant exposure levels during pregnancy were assessed through a range of methods. These methods included utilizing air quality monitoring data from stations situated in cities, states, or countries. Additionally, statistical prediction models relying on regression analyses were employed. Furthermore, geolocation data was used to determine proximity to major roadways. Spatiotemporal techniques combined air quality data from monitoring stations with supplementary measurements, such as aerosol optical depth (AOD) data collected from satellites. The data obtained from environmental databases or networks played a significant role in the assessment process.

Sometimes, entire air pollution estimations were based on comprehensive air quality databases and specialized air pollution platforms. These extensive datasets were instrumental in estimating pollutant concentrations at specific locations and time intervals. The frequency of data collection varied across studies, with measurements obtained hourly, daily, monthly, or yearly. This variation allowed researchers to capture different temporal patterns and trends in air pollutant exposure. Notably, two studies utilized air sampling methods. Blaskova et al. (2022) conducted air monitoring at two distinct locations to measure PM2.5 concentrations directly, providing precise data on particulate matter levels. In Wang et al. (2022), pregnant women participated in personal air sampling using SKC INC (Seoul, South Korea) equipment, which calculated their exposure to PM2.5. (Appendix 5, Table 3)

Air Pollution Exposure Period

All analyzed studies assessed the effect of air pollutants during pregnancy and ND on the offspring. Air pollution exposure was measured during the prenatal period in all the included studies and the postnatal period in seven. (Appendix 5, Table 3)

Neurodevelopmental Measurement and Scales Used

The 24 observational studies measured ND and categorized it into cognitive, motor, or behavioral domains. Depending on the scale or questionnaire used, studies focused on different developmental characteristics. The cognitive development dimension included verbal and nonverbal intelligence, problem-solving abilities, visual motor performance, and visual memory. Language was included in some studies and measured both receptive and expressive communication. Behavioral development included socio-emotional adaptive behavior and social response, among others. Motor performance was assessed through fine and gross domains.

A diversity of scales/questionnaires was used to measure ND. They included the Child Behavior Checklist (CBCL), Kaufman Brief Intelligence Test Second Edition (KBIT-2), Bayley Scales of Infant Development (BSID-I to III), Developmental Profile Three (DP3), Ages and Stages Questionnaires (ASQ), Bender-Gestalt Test (BGT), Raven Colored Progressive Matrices Test (RCMPT), Neuropsychological Examination Scale for Chinese Children (NESCC), Wechsler Intelligence Scale for Children III-IV (WISC III-IV), Comprehensive Neuropsychological Battery for Children Ages 3-12 (NEPSY-II) and Gesell Developmental Schedules (GDS). One study assessed the association of pollution with structural changes in Magnetic resonance imaging (MRI) scans along with the NEPSY-II test for cognitive function (Guxens et al., 2018).

The BSID-III scale was the most used because it has been tested internationally with adaptations showing high validity and reliability (Cronbach's alpha coefficient was above 0.77 for all subscales), making adjustments for different cultures. Another advantage of this scale is that it is less susceptible to recall and response bias compared to other questionnaires, as two parts rely on the responses, while the other three rely on the neurological evaluation (Hurtado-Díaz et al., 2021; McLester-Davis et al., 2021; Pitchik et al., 2023; Torras-Mañá et al., 2016). Regarding time for assessment, the age range was between two months and ten years (Guxens et al., 2018; Shih et al., 2023; P. Wang et al., 2021; Yu et al., 2022). (Appendix 5, Table 3)

Leading Associations Found Regarding Air Pollution and ND

There is a consensus among the students regarding the negative impact of prenatal air pollution exposure on the offspring's neurodevelopment. However, they differ regarding the affected neurodevelopment domain and the magnitude of the effect. Additionally, while some studies address air pollutants in general, others focus on specific pollutant components. Proximity to major roadways and exposure to particular pollutants (PM2.5 and ozone) during pregnancy was associated with significant developmental delays in children (Ha et al., 2019). Additionally, Harris et al. (2015) found that living close to a major roadway was the most harmful factor linked with low performance in both verbal and nonverbal IQ and visual motor abilities. Both prenatal and early postnatal exposure to PM2.5 and PM10 were associated with decreased offspring general neurodevelopment (H. Wang et al., 2022). Average SO2 exposure during pregnancy and up to 12 months of age was associated with subclinical neurodevelopmental issues in early childhood (Lin et al., 2014). A positive association between prenatal exposure to various air pollutants and risk of neurodevelopmental delay was found, with stronger associations during the first trimester (Su et al., 2022). In the cognitive domain, maternal exposure to PM10 and PM2.5 was negatively associated with cognitive scores in infants during the first 24 months of life and early school age (Guilbert et al., 2023; Kim et al., 2014). Physical activity and prolonged breastfeeding may mitigate these effects (Sun et al., 2023). Also, higher NO2 exposure during pregnancy was associated with lower verbal IQ scores, suggesting cognitive effects (Porta et al., 2016), and air pollution was associated with a thinner cerebral cortex, inhibition errors, and reduced cognitive abilities in a neuroimaging study (Guxens et al., 2018). A possible mediation by oxidative stress in the mother's blood at delivery relative to PM2.5 exposure in cognitive function was also addressed (Blazkova et al., 2022). Behavior was studied by three authors, where higher prenatal and postnatal NO2 levels appear to be associated with increased behavior problems (Loftus et al., 2020; Ni et al., 2022) and an increased risk of behavioral development delays for each air pollutant exposure (Yorifuji et al., 2016). A decrease in language function in children was associated with exposure to PM2.5 during the third trimester of pregnancy (Hurtado-Díaz et al., 2021). In the motor domain, PM2.5, PM10, and SO42- were associated with an increased risk of non-optimal gross motor development in infants and decreased offspring motor development or motor skills (Lei et al., 2022; H. Wang et al., 2022; Xu et al., 2022). (Appendix 5, Table 3)

Discussion

Most of the studies included in our review have demonstrated that both prenatal and postnatal exposure to air pollution, particularly PM2.5, PM10, and NO2, is associated with a variety of neurodevelopment impairments in children (Guxens et al., 2018; Kim et al., 2014; Lei et al., 2022; Lin et al., 2014; Porta et al., 2016; H. Wang et al., 2022; Xu et al., 2022). These delays include lower IQ and visual motor abilities (Ha et al., 2019), decreased cognitive function (Guilbert et al., 2023), increased behavior problems (Loftus et al., 2020; Ni et al., 2022), decreased language function (Hurtado-Díaz et al., 2021), and impaired motor development (Lei et al., 2022; H. Wang et al., 2022; Xu et al., 2022).

Previous reviews reported similar findings that found an association between exposure to PM10 and NO2 and negative gross motor development in children (Parasin et al., 2023). Another systematic review and meta-analysis by (Shang et al., 2020) found that prenatal exposure to NO2 is associated with impaired neural development in children. Moreover, a liter-

Exposure				Outcome		
Pollutant	**Study**	**Method**	**Period**	**Domain**	**Assessment**	**Association**
NO2	Loftus et al.,2020	Air quality monitoring data + Geocoding (AQMD+G)	Prenatal	Behavior	Child Behavior Checklist	2 ppb higher NO2 associated with a 6% increase (95% CI: 1, 11%) in externalizing behavior problems.
			Postnatal			Stronger association: 8% increase (95% CI: 0, 16%) per 2 ppb NO2. Increased odds of clinically significant internalizing and externalizing behaviors.
	Su et al., 2021	AQMD+G - China High Air Pollutants (CHAP)	Prenatal	General ND	NESCC	Score decrease 1.06 (95% CI: 0.94, 1.19) per 10 µg/m3 NO2 elevation during the entire pregnancy.
	Porta et al., 2016	AQMD+G- land use regression models (ESCAPE)	Prenatal	Cognition	Wechsler Intelligence Scale for Children-III	A 10 µg/m3 higher NO2 exposure associated with a decrease of 1.4 points in verbal IQ and a decrease of 1.4 points in verbal comprehension IQ. Other pollutants also showed negative associations, but with larger confidence intervals. Associations were found for traffic intensity in a 100 m buffer around the home.
	Kim et al., 2014	AQMD+G - Inverse Distance Weighting (IDW) modeling.	Prenatal	General ND	K-BSID-II	Negatively associated with PDI (β = −1.30; p = 0.05), but not with MDI (β = −0.84; p = 0.20). This means that for every 10 ppb increase in NO2 exposure, there was a 1.30-point decrease in PDI.
	Guxens et al.,2018	AQMD+G- land use regression models.	Postnatal	Cognition	MRI scans, NEPSY-II test	Thinner Cerebral Cortex associated with exposure and increased Inhibition Errors in cognitive assessment Notable association between cortex thickness and inhibition of task performance.
	Ni et al., 2022	AQMD+G	Prenatal	General ND	Full-Scale IQ and child behavior checklist 4-6 years	Higher NO2 exposures, especially in the I and II trimesters, had an increased likelihood of behavioral problems..
	Yorifuji et al., 2016	AQMD + municipality-level traffic-related air pollution.	Prenatal	General ND	Survey	Each air pollutant was associated with an increased risk of behavioral development delays. 1.24 (95% CI: 1.07, 1.43) for the inability to compose a two-phrase sentence. 1.14 (95% CI: 1.04, 1.25) for the inability to say their own name. 1.24 (95% CI: 1.00, 1.54) for the inability to use a spoon to eat.
	Yu et al., 2022	AQMD + G	Prenatal	General ND	Gesell Development Schedules (GDS) (Chinese version)	Exposure during 3rd trimester have a negative impact on toddler neurodevelopment.
	Guxens et al., 2014	AQMD+G- land use regression models.	Prenatal	General ND	MCD I,BSID II, BSID I, BSID III,DDST II, MSCA	For each 10 µg/m3 increase in NO2, global psychomotor development scores were reduced by 0.68 points
	Loftus et al.,2020	AQMD + G	Prenatal/Postnatal	Behavior	Child Behavior Checklist	PM10 and road proximity did not show associations with the outcomes
	Morgan et al., 2023	AQMD + G	Prenatal	General ND	BSID-III	Negative association with composite cognitive scores, with β values of -2.01 [-3.89, -0.13]. Higher average exposure demonstrated negative associations with composite motor scores (β=-2.35 [-3.95, -0.74]), composite language scores (β=-1.87 [-3.52, -0.22]), scaled motor scores (β=-0.77 [-1.30, -0.24]), gross motor scores (β=-0.37 [-0.70, -0.04]), fine motor scores (β=-0.40 [-0.71, -0.09]), scaled language scores (β=-0.61 [-1.18, -0.05]), and expressive communication scaled scores (β=-0.36 [-0.66, -0.05]).

Table 3: *Exposure measurement, outcome assessment and association.*

PM10	Girardi et al.,2021	AQMD + G + Satellite based	Prenatal	General ND	Developmental Profile 3 (DP-3)	Decrease in cognitive score during the second trimester (+13.2 μg/m3 PM10 increase: −0.30 points; 95%CI: −0.12–−0.48) and third trimester (−0.31 points; 95%CI: −0.11–−0.50). In the second trimester negatively influenced the communicative domain.
	Su et al., 2021	AQMD+G - China High Air Pollutants (CHAP)	Prenatal	General ND	NESCC	PM10: 1.12 (95% CI: 1.02, 1.24) per 10 μg/m3 elevation during the entire pregnancy.
	Kim et al., 2014	AQMD+G - Inverse Distance Weighting (IDW) modeling.	Prenatal	General ND	K-BSID-II	Negatively associated with MDI (β = −2.83; p = 0.003) and PDI (β = −3.00; p = 0.002) at 24 m. For every 10 μg/m3 increase in PM10, there was a 2.83-point decrease in MDI and a 3.00-point decrease in PDI.
	Guilbert et al., 2023	AQMD+G - Satellite based.	Prenatal	Cognition	WPPSI-III + NEPSY-II at 5 y. WISC-IV + NEPSY-II at 6 y.	Exposure during II-III Trimester was associated with lower scores in general cognitive abilities and non-verbal abilities.
	Wang et al., 2022	Personal exposure-SKC air sampling equipment.	Prenatal	General ND	BSID	Associated with decreased offspring MDI and PDI scores.
			Posnatal			Stronger association with decreased offspring MDI and PDI scores.
	Harris et al., 2015	AQMD+G - Satellite based.	Prenatal	Cognition	KBIT-2, Visual-Motor subtest of the WRAVMA, Visual Memory Index of the WRAML-2.	Exposure to traffic density and PM2.5 did not show associations with poorer cognitive performance.
			Postnatal			Third-trimester exposure to black carbon (BC) showed no association with verbal IQ after adjusting socioeconomic covariates. Living within 50 meters of a major roadway at birth had lower nonverbal IQ scores (-7.5 points; 95% CI: -13.1, -1.9), lower verbal IQ scores (-3.8 points; 95% CI: -8.2, 0.6) and visual motor abilities (-5.3 points; 95% CI: -11.0, 0.4) compared to those living at least 200 meters away. Childhood exposure to black carbon (BC) showed no association with verbal IQ after adjusting socioeconomic covariates.
	Hurtado-Diaz et al., 2021	Satellite based	Prenatal	General ND	BSID-III	1μg/m3 increase in PM2.5 air pollution was associated with a decrease in language function by approximately -0.38 points (95% CI: -0.77 to -0.01). PM2.5 during the third trimester of pregnancy had the greatest impact on this observed association.
	Morgan et al., 2023	AQMD + G	Prenatal	General ND	BSID-III	Negative association with composite cognitive scores, with β values of -1.97 [-3.83, -0.10]. Air pollution in mid and late pregnancy was linked to lower motor, cognitive, and language skills in children.
	Lei et al., 2022	AQMD + G + Satellite based	Prenatal	General ND	ASQ 3	Associated with lower scores in the gross motor, problem-solving, and personal-social domains. All compositions except organic matter were correlated with lower problem-solving scores. Primary/secondary particles related to lower gross motor scores and inversely associated with communication, fine motor, and personal-social scores. Boys and infants breastfed for less than 6 months appeared to be more susceptible to the effects of PM2.5.

Table 3: *Exposure measurement, outcome assessment and association.*

	Blazkova et al., 2022	High Volume (HiVol) 3000 Air Sampler (model ECO-HVS3000, Ecotech, Australia) on Pallflex membrane filters (EMFAB, TX40HI20 WW)	Prenatal	Cognition	BG test and RCPM test.	Did not observe any significant effect of PM2.5 concentrations in the third trimester on the RCPM test. Level of 15-F2t-IsoP (biomarker of oxidative stress) in mother's plasma at delivery was significantly associated with results of BG test and RCPM test in five-year-old children. Indirect negative effect of PM2.5 by oxidative stress. Worse cognitive performance of girls exposed by the BG test
	Su et al., 2021	AQMD+G - China High Air Pollutants (CHAP)	Prenatal	General ND	NESCC	PM1: 1.12 (95% CI: 1.01, 1.25) per 10 μg/m3 elevation during the entire pregnancy. PM2.5: 1.15 (95% CI: 1.03, 1.29) per 10 μg/m3 elevation during the entire pregnancy. Associations more robust for trimester 1 and trimester 2, particularly trimester 1.
	Wang et al., 2021	Satellite based + G	Prenatal	General ND	ASQ 3	Poorer ASQ-T scores at 2, 6, and 24 months old. Dose-dependent relationship between PM2.5 exposure and poorer ASQ-T scores. Effects most significant during mid- to late pregnancy (weeks 18 to 34). Higher risk of Specific Developmental Disorder (SDD), particularly in the domain of problem-solving.
PM2.5 (BC, NH4+, SO42-, NO3, OC, Soil and BC)	Xu et al., 2022	Satellite based + G	Prenatal	General ND	BSID-III	PM2.5 Associated with an increased risk of non-optimal gross motor development (aRR: 1.31; 95 % CI: 1.04, 1.64). SO42− Associated with an increased risk of non-optimal gross motor development (aRR: 1.40; 95 % CI: 1.08, 1.81).
	Ha et al.,2019	AQMD + G	Prenatal	General ND	ASQ	Proximity to major roadway had twice the risk of failing the communication domain. Prenatal exposures to PM2.5 during pregnancy associated with failing any developmental domain.
			Postnatal			PM2.5 exposures were mixed and did not show consistent associations.
	Guilbert et al., 2023	AQMD+G - Satellite based.	Prenatal	Cognition	WPPSI-III + NEPSY-II at 5 y. WISC-IV + NEPSY-II at 6 y.	Exposure during II-III Trimester was associated with lower scores in general cognitive abilities and non-verbal abilities.
			Postnatal			Higher exposure between 3-4 years was associated with lower scores in general, verbal, and non-verbal cognitive abilities.
	Guxens et al.,2018	AQMD+G- land use regression models.	Postnatal	Cognition	MRI scans, NEPSY-II test	Thinner Cerebral Cortex associated with exposure and increased Inhibition Errors in cognitive assessment Notable association between cortex thickness and inhibition of task performance.
	Wang et al., 2022	Personal exposure-SKC air sampling equipment.	Prenatal	Cognition	ASQ 3 (Chinese)	Exposure to PM2.5, in the 2nd and 3rd trimesters, were associated with decreased ASQ scores in communication, problem-solving, and personal-social domains in children aged 2 or 6 months.
	Wang et al., 2022	AQMD + G	Prenatal	General ND	BSID (Chinese)	Associated with decreased offspring MDI and PDI scores.
			Posnatal			Stronger association with decreased offspring MDI and PDI scores.
						2nd trimester exposure associated with increased risks of delays in gross motor neurodevelopmental milestones (OR 1.09 per 10 μg/m³ increase).

Table 3: *Exposure measurement, outcome assessment and association.*

	Shih et al., 2022	AQMD + G	Prenatal	General ND	Home interview at 6 and 18 months of age.	2nd trimester exposure associated with increased risks of delays in gross motor neurodevelopmental milestones (OR 1.09 per 10 μg/m³ increase). Delayed fine motor development was related to PM2.5 exposure in the II and III trimesters (OR 1.06). Personal-social skill development associated with exposure in the II trimester (OR 1.11) and III trimester (OR 1.06).
			Postnatal			Neurodevelopmental parameters were unrelated to postnatal PM2.5 exposure.
	Ni et al., 2022	AQMD+G	Postnatal	General ND	Full-Scale IQ and child behavior checklist 4-6 years	Higher exposures to PM2.5 at childhood 2-4 years old associated with poorer child behavioral functioning and cognitive performance.
	Yorifuji et al., 2016	AQMD + municipality-level traffic-related air pollution.	Prenatal	General ND	Survey	1.10 (95% CI: 1.04, 1.17) for the inability to listen without fidgeting. 1.06 (95% CI: 1.00, 1.13) for the inability to focus on one task. 1.10 (95% CI: 1.05, 1.16) for the inability to express emotions. 1.08 (95% CI: 1.02, 1.14) for the inability to keep promises.
	Sun et al., 2023	Satellite based + G	Prenatal	Intelligence	WISC-IV, Chinese version.	Associated with lower IQ scores in 6-year-old children. More pronounced in boys. Physical activity (PA) and longer breastfeeding duration may help mitigate the detrimental effects.
	Guxens et al., 2014	AQMD+G- land use regression models.	Prenatal	General ND	MCD I,BSID II, BSID I, BSID III,DDST II, MSCA	For each 5 μg/m3 increase in PM2.5, scores were reduced by 1.64 points. Air pollution during pregnancy was linked to lower global psychomotor development scores in children.
	Lin et al. ,2014	AQMD + G	Prenatal/Postnatal	General ND	TBCS scale	Exposure during pregnancy and up to 12 months is associated with poor subclinical neurodevelopment in early childhood.
SO2	Su et al., 2021	AQMD+G - China High Air Pollutants (CHAP)	Prenatal	General ND	NESCC	SO2: 1.58 (95% CI: 1.11, 2.23) per 10 μg/m3 elevation during the entire pregnancy.
	Yu et al., 2022	AQMD + G	Prenatal	General ND	Gesell Development Schedules (GDS) (Chinese version)	Exposure during 1st and 3rd trimesters have a negative impact on toddler neurodevelopment. Low temperature may exacerbate the neurotoxic effects of prenatal SO2 exposure
O3	Ha et al.,2019	AQMD + G	Prenatal	General ND	ASQ	Prenatal exposures to O3 during pregnancy and failing any developmental domain.
			Postnatal			Average daily postnatal ozone positively associated with failing the screening at different time points: eight months (3.3%), twelve months (17%), and thirty months (7%).
Others	Lin et al. ,2014	AQMD + G	Prenatal/Postnatal	General ND	TBCS scale	Maternal NMHC exposure during the 2nd and 3rd trimesters of pregnancy is associated with poor gross motor development at 6 months of age.

Al= Aluminum; **aOR** = Adjusted odds ratio; **aRR** = Absolute risk reduction; **ASQ** = Ages & Stages Questionnaire; **ASQ3** = Ages & Stages Questionnaire, Third Edition; **BC** = Black carbon; **BG** = Bender Visual Motor Gestalt Test; **BSID I** = Bayley Scales of Infant and Toddler Development, First Edition; **BSID-II** = Bayley Scales of Infant and Toddler Development, Second Edition; **BSID-III** = Bayley Scales of Infant and Toddler Development, Third Edition; **CBCL**= Child Behavior Checklist; **CI** = Confidence Interval; **CO** = Carbon monoxide; **DDST II** = Denver Developmental Screening Test, Second Edition; **DP-3** = Developmental Profile, Third Edition; **GDS** = Gesell Development Schedules; **GEE** = Generalized estimating equation; **IQ** = Intelligence quotient; **IQR** = Interquartile range; **KBIT-2** = Kaufman Brief Intelligence Test; **K-BSID-II** = Korean Bayley Scale of Infant Development II; **MCD I** = Mild Cognitive Dysfunction; **MDI** = Mental developmental index; **miRNAs** = microRNA; **MRI** = Magnetic resonance imaging; **MSCA** = McCarthy Scales of Children's Abilities; **NESCC** = Neuropsychological Examination Scale for Chinese Children; **NEPSY-II** = NEuroPSYchological Assessment, Second Version; **NH4+** = Ammonium; **NMHCs** = Nonmethane hydrocarbons; **NO2** = Nitrogen dioxide; **NO3** = Nitrate; **O3** = Ozone; **OC** = Organic carbon; **ORs** = Odds ratios; **PA** = Physical activity; **Pb** = Lead; **PDI** = Psychomotor developmental index; **PM** = Particulate matters; **PM2.5** = Fine particulate matter with a diameter of 2.5 micrometers or less; **PM10** = Particulate matter smaller than 10 micrometers; **RCPM** = Raven Colored Progressive Matrices test; **RR** = Relative risk; **sEVs** = Small extracellular vesicles; **SD** = Standard deviation; **SDD** = Suspected developmental delay; **SO2** = Sulfur dioxide; **SO42-** = Sulfate; **TBCS** = The Birth Cohort Study; **THCs** = Total hydrocarbons; **Ti** = Titanium; **V** = Vanadium; **WHO** = World Health Organization; **WISC-IV** = Wechsler Intelligence Scale for Children, Fourth Edition; **WPPSI-III** = Wechsler Preschool and Primary Scale of Intelligence Third Version; **WRAML-2** = Wide Range Assessment of Memory and Learning, Second Edition; **WRAVMA** =Wide Range Assessment of Visual Motor Abilities. **ESCAPE**= European Study of cohorts for air Pollution effects. **AQMD + G** = Air Quality Monitoring Data + Geolocation.

Table 3: *Exposure measurement, outcome assessment and association.*

ature review by Johnson et al. (2021) also found that maternal exposure to PM particles, especially fine (PM2.5) and ultrafine (PM0.1) particles, can lead to various adverse health effects in children, including adverse birth outcomes, respiratory problems, reduced lung function, impaired immune function, brain development, and cardiometabolic problems. Furthermore, (Volk et al., 2021) conducted a literature review on the relationship between prenatal air pollution exposure and neurodevelopmental outcomes, which also found evidence supporting the impact of prenatal air pollution with several limitations regarding spatial and temporal variation in exposure across existing studies. While variations in study designs, populations, and exposure assessment methods contribute to heterogeneity, the consistent efforts to mitigate potential bias enhance the confidence in the observed associations. The authors addressed potential bias and confounding by making rigorous adjustments and conducting sensitivity analyses. Thus strengthening the credibility of their findings. It has been discovered that socioeconomic status plays a significant role in the connection between prenatal air pollution exposure and developmental outcomes. Researchers have used various approaches to address potential biases and confounding factors in studies, such as adjusting for birth-related factors and maternal characteristics, including health behaviors during pregnancy. Despite the observational complexities, these strategies have enhanced the credibility of the studies. However, other studies in this systematic review have limitations regarding confounder considerations and inaccurate exposure assessment. Confounders such as maternal education, smoking and alcohol consumption during pregnancy, pregnant nutrition status, and other environmental exposures were not always assessed. The variability of air pollution levels and the reliance on self-reported measures also affected the accuracy of the measured air pollution exposure. These limitations made establishing a true association between independent and dependent variables difficult. (Please refer to Appendix 3, Table 1 for studies 1-15, 17-24.)

Detecting significant associations could be problematic in studies with small sample sizes. However, 20 of the included studies had more than 500 participants. Many included articles with large sample sizes were population-based cohorts in different countries, which could favor generalizability. Additionally, less frequently discussed limitations encompassed concerns about missing data during follow-up, which was more relevant in longer periods and was only sometimes addressed.

One of the main strengths of our study is the broad eligibility criteria regarding the type of pollutant and outcome. While other systematic reviews focused on specific pollutants such as PM (Parasin et al., 2023) and/or distinct disorders such as ADHD (Donzelli et al., 2019), our approach allowed us to examine a great variety of these variables. In turn, these variables presented different exposure and outcome assessments, allowing us to evaluate the current state of research on this topic thoroughly. However, the possibility of publication bias remains as we included only articles published in peer-reviewed journals without registers, gray literature, or other sources of information. In addition, the interpretation of results should consider the high heterogeneity of the included studies.

Conclusion

Observational studies published in the last ten years support the hypothesis that prenatal outdoor air pollution exposure is associated with neurodevelopmental delay in children. The major air pollutants involved included PM2.5, PM10, ozone, SO2, and NO2. The differences in neurodevelopmental outcomes occurred regardless of the scales used to perform this evaluation. However, the BSID-III was utilized in the vast majority of analyzed studies.

This review is significant because it highlights the increasing amount of information on the impact of air pollution exposure during pregnancy on child neurodevelopment. Pregnant women should reduce their exposure to air pollution when air quality levels are poor, as our review results show that prenatal air pollution exposure is linked to neurodevelopmental delays in offspring. This evidence substantiates the need for policymakers and public health authorities to focus on developing long-lasting strategies to mitigate these consequences. However, caution is advised in interpreting the results presented due to the limitations of the studies included in this review.

Future research is needed to improve the scope of this review. Additionally, studies should standardize exposure assessment using objective methods, carefully controlling for potential confounding factors, and relying on validated neurodevelopment scales. By addressing the knowledge gaps in this area through the lens of different research areas, a better understanding of the association between prenatal air pollution exposure and neurodevelopmental delay will allow us to take concrete steps toward protecting the optimal development of newborns.

Supplementary materials

Appendix 1, 2, 3, 4, 5.

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Conflicts of Interest

The authors declare no conflict of interest.

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