ARTICLE REVIEW

Prenatal PM2.5 Exposure and Its Association with Neurodevelopmental Impairment in Children: A Narrative Review

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ABSTRACT

Introduction Air pollutants, including $PM_{2.5,}$ are an increasing threat to public health. Studies have reported the adverse effect of $PM_{2.5}$ exposures during pregnancy on neurodevelopment in children. We performed a narrative review using the PubMed, Web of Science, and Scopus databases from 2017 to 2022 using keywords such as prenatal, particulate matter, neurodevelopment, and children. This review aims to identify symptoms of impaired neurodevelopment in children associated with prenatal $PM_{2.5}$ exposure, the association between the timing of prenatal exposure $PM_{2.5}$ and symptoms of impaired neurodevelopment in children as well as other factors that may influence the association of prenatal $PM_{2.5}$ exposure and symptoms of impaired neurodevelopment in children.

Methods A total of 25 articles were included in this review.

Results Symptoms of neurodevelopmental impairment associated with prenatal exposure to $PM_{2.5}$ include language, speech, and communication symptoms; motor skills; behaviour and social skills; memory as well as learning/cognitive symptoms. Neurodevelopmental impairments were associated with exposure to $PM_{2.5}$ across all three trimesters with impairment in communication and behavioural domains predominating in those exposed during the first trimester.

Conclusions Generally, males were more susceptible to having neurodevelopmental impairment symptoms compared to females. More information regarding the effect of prenatal $PM_{2.5}$ exposure on neurodevelopmental domains of children will support public health policies that reduce air pollution and improve children's health.

Keywords Prenatal Exposure- $PM_{2.5}$-Neurodevelopmental Impairments-Children.

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INTRODUCTION

The early life of offspring, including prenatal and early postnatal periods, is a critical window of neurodevelopmental vulnerability due to the complexity of neurodevelopmental processes occurring during the initial months of gestation. Developmental exposure to neurotoxicants such as particulate matter (PM) from polluted air can lead to developmental neurotoxicity.[1] Rising evidence from research suggests that maternal exposure to $PM_{2.5}$ during pregnancy can lead to oxidative stress (producing reactive oxygen species) and inflammatory response (through inflammatory mediators) in the placenta[2] and that it has the potency to cross the blood-placental barrier into the foetal circuit.[3] As a result, prenatal $PM_{2.5}$ exposures may increase the risk of unfavourable birth outcomes such as preterm birth, low birth weight, congenital anomalies, and even increase the risk of infant mortality.[4] Furthermore, recent evidence suggests a link between prenatal $PM_{2.5}$ exposure and offspring neurodevelopment. Subtle disruptions of neurodevelopment during this critical window may elevate susceptibility to a range of neurological disorders later in life. Previous population-based studies have linked exposure to $PM_{2.5}$ during pregnancy to adverse children's neurodevelopment including cognitive and motor problems such as memory difficulties, inattention, executive functioning deficits, language deficits, and behavioural deficits.[5-7]

Air pollution continues to be a serious global threat to the environment. According to the World Health Organization (WHO), more than 90% of the global population breathes air that exceeds WHO guidelines,[8] particularly those in low- and middle-income countries. Particulate matter (PM) is one of the primary components of air pollutants that affect the population worldwide. PM is classified into two types based on their aerodynamic equivalent diameter: coarse particulate matter (PM_{10}) with an aerodynamic diameter of less than 10 μm and fine particulate matter ($PM_{2.5}$) with an aerodynamic diameter of 2.5 μm or less.[9] Fine particulate matter ($PM_{2.5}$) poses an increasing threat to environmental security and public health and can be produced directly by industrial processes or combustion, as well as indirectly by the condensation of aerosol precursor gases.[10, 11]

Particulate air pollution has become a globally recognized threat to human health in recent years and is associated with an increased risk of several adverse health outcomes including mortality, cardiovascular disease, and asthma.[12, 13] Pregnant women and children are generally more vulnerable to the effects of environmental toxins, including air pollutants. According to the World Health Organization (WHO), more than 90% of children under the age of 15 were exposed to $PM_{2.5}$ levels that exceeded WHO air quality guidelines in 2016, and children accounted for 9% of total deaths caused by ambient air pollution.[14] However inconsistent results have been recorded. In a study of 1109 mother-child couples in the United States, prenatal exposure to $PM_{2.5}$ did not appear to be associated with cognitive impairment.[15] The inconsistency in results may be attributable to the heterogeneity between studies in terms of exposure (e.g., $PM_{2.5}$ evaluation methods, $PM_{2.5}$ exposure levels, or different constituents of $PM_{2.5}$), outcome (e.g., tools for neurodevelopmental assessment, the definition of cases, age of neurodevelopmental assessment) and varied confounders (e.g., gestational age and infant feeding were considered as confounders in some but not all studies).

The aim of this study was to review the current relevant literature on prenatal $PM_{2.5}$ exposures on child neurodevelopment effect focusing on articles published between January 2017 till December 2022. The unique contribution of our findings will summarize descriptively the finding from updated literature that specifically addressed the symptoms of impaired neurodevelopment in children associated with prenatal $PM_{2.5}$ exposure, the association between the timing of prenatal exposure (trimester related) to $PM_{2.5}$ and symptoms of impaired neurodevelopment in children and other factors that may influence the association of exposure and symptoms of impaired neurodevelopment in children.

METHODS

Three databases used in the literature searching process: PubMed, Web of Science and Scopus. Keywords include prenatal or gestational, $PM_{2.5}$ or particulate matter, exposure or contact, neurodevelopment or behaviour or memory or motor skills, and children or offspring were used. The databases were selected based on their coverage of the topic of interest. Duplication was removed by analysing the title, abstract and content. The selection criteria included all types of study (randomized control trial, cohort, case-control, cross-sectional and case report studies). The articles selected were published in English language. The date of publication was between January 2017 till December 2022. Data were extracted from the 25 included articles using a standardised data extraction form and organised using Microsoft Excel. The information collected in the form included: (1) author/publication year, (2) country, (4) study design, (5) statistical analysis, and (6) results/findings. All results with signifant p-value were included and the findings were synthesised using a narrative synthesis. Study quality was not appraised due to the nature of the narrative review.

RESULTS

Overall, twenty-five original research articles on Prenatal $PM_{2.5}$ Exposure and Impaired Neurodevelopment in Children were included in this review. Results from the above search could be discussed under the following headings:

- The symptoms of impaired neurodevelopment in children associated with prenatal $PM_{2.5}$ exposures.
- The association between the timing of prenatal exposure (trimester related) to $PM_{2.5}$ and symptoms of impaired neurodevelopment in children.
- Other factors that may influence the association of exposure and symptoms of impaired neurodevelopment in children.

The Symptoms of Impaired Neurodevelopment in Children Associated with Prenatal $PM_{2.5}$ Exposure.

Based on the review, all twenty-five articles answered the first research question and showed multiple symptoms of impaired neurodevelopment in children that associated with prenatal $PM_{2.5}$ exposures. The symptoms are divided into language and speech, motor skills, behaviour, memory, and learning. The findings were summarized in table 1.

Table 1 The symptoms of impaired neurodevelopment in children associated with prenatal $PM_{2.5}$ exposures.

Symptoms	Findings
Language, speech, and communication	• Lower language scores.[16] • Lower functional communication.[17] • Deficits in communication.[17, 18] • Lower functioning on the expressive language subscale among developmental delay cases.[19] • Negative association between prenatal $PM_{2.5}$ exposures with verbal domain among males.[20]
Motor skills	• Significant decrease in motor scales.[6, 21] • Negatively associated with: - fine motor.[18, 22] - gross motor in infant.[22-24] - offspring psychomotor development index (PDI).[25, 26]
Behaviour/social skills	- Positively associated with risk of child hyperactivity.[27, 28] - Increase in conflict attentional network, indicating poorer performance.[30] - Poor neurobehavior performance.[31] - Significantly associated with early infant negative affectivity.[33] - Positively associated with behaviour symptoms (interrupting others, failure to pay attention when crossing a street, lying, causing public disturbance).[32] - First trimester exposure: - Significantly associated with risk of ADHD.[29] - Negatively associated with personal social scores in infants.[22, 23] - Lower adaptive skills composites score.[17] - Lower adaptive subscales which is adaptability and social skills.[17] - Increase in behavioural subscales including attention problems and withdrawal subscales.[17] - Second trimester exposure: - Negatively associated with behaviour score.[31] - Negatively associated with active tone score.[31]
Memory	• Adverse memory performance among girls.[5] • Negative association with memory and verbal domain among boys.[20] • Reduction in working memory score.[30] • Increase in the conflict attentional network.[30]
Learning/cognitive	• Lower MSEL scores.[19] • Predicted lower cognitive score.[16] • Increase risk of suspected development delay.[35] • Exposure in the second and third trimesters correlated with increased odds of low performance.[36] • Slightly positive association with problem solving domains.[18]

- Inversely associated with offspring MDI scores.[25, 26]
- Negatively associated with
  - offspring neurodevelopment.[26, 34]
  - problem solving in infants aged 12 months.[23]
  - general cognitive index.[20]
- Decrease scores for all neurodevelopment domains of children aged 2, 6 and 24 months.

Language, speech, and communication symptoms

Out of twenty-five articles, five articles discussed on language and speech symptoms. Increased $PM_{2.5}$ exposure predicted lower language scores. During the 6 months' assessment, language score significantly decreases with adjusted language score reduction of −0.95.[16] Higher concentrations of $PM_{2.5}$ exposures during the first trimester were associated with lower Adaptive Skills composites scores, as well as lower scores of adaptive subscales which is Functional Communication.[17] Prenatal $PM_{2.5}$ exposures was associated with deficits in communication[17, 18] and was associated with lower functioning on the expressive language subscale among developmental delay cases.[19] Lertxundi et al found a significant negative association between prenatal $PM_{2.5}$ exposures with verbal domain among males.[20]

Motor skills symptoms

Seven articles discussed on motor skills symptoms. Increase in prenatal $PM_{2.5}$ exposures was found associated with a significant decrease in motor scale[6, 21] and was negatively associated with fine motor[18, 22] and gross motor in infant.[22-24] Prenatal $PM_{2.5}$ exposures was also negatively associated with offspring psychomotor development index (PDI).[25, 26] All air pollutants except $PM_{2.5}$ absorbance, were associated with lower motor function in children aged 40 days.[21]

Behaviour/social skills symptoms

Eleven articles discussed on behaviour symptoms. The risk of child hyperactivity was positively associated with $PM_{2.5}$ exposure.[27, 28] The exposure to $PM_{2.5}$ during the first trimester was significantly associated with the risk of attention deficit hyperactivity disorder (ADHD),[29] and negatively associated with personal social scores in infants.[22, 23] Higher concentrations of $PM_{2.5}$ exposures during the first trimester were associated with lower adaptive skills composites scores, as well as lower scores of the adaptive subscales which is adaptability and social skills.[17] There were also associations between first trimester $PM_{2.5}$ exposure and increases in a few of the behavioural subscales, including attention problems and withdrawal subscales.[17] Increase in $PM_{2.5}$ resulted in increase in the conflict attentional network of 11.31 (95% CI: 6.05, 16.57) milliseconds, indicating a poorer performance.[30]

Prenatal exposure to $PM_{2.5}$ was linked to poor neurobehavioral performance of newborns[31]. $PM_{2.5}$ exposures in second trimester was negatively associated with behaviour score -0.003 (95% CI: -0.006, -0.001) and the inverse relation was more pronounced in male infants. In addition, $PM_{2.5}$ level in the second trimester was negatively related to active tone score -0.012 (95% CI: -0.021, -0.002) in a dose-dependent manner for both genders.[31] Odds ratios following a one- interquartile-range increase in suspended particulate matter (SPM) were 1.06 (95% CI: 1.01, 1.11) for interrupting others, 1.09 (95% CI: 1.03, 1.15) for failure to pay attention when crossing a street, 1.06 (95% CI: 1.01, 1.11) for lying, and 1.07 (95% CI: 1.02, 1.13) for causing public disturbance[32]. Prenatal $PM_{2.5}$ exposures also significantly associated with early infant negative affectivity (Sadness, Distress to Limitations, Fear, Falling Reactivity).[33]

Memory symptoms

Three articles discussed on memory symptoms. Chiu et al found that there was a significant association between higher $PM_{2.5}$ levels in early-to-mid pregnancy and adverse memory performances among girls[5]. Meanwhile, Lertxundi et al show association between the average concentration $PM_{2.5}$ prenatal exposures with memory and verbal domain among the boys and the associations is statistically significant.[20] Increase in $PM_{2.5}$ resulted in a reduction in the working memory score of −19:50 (95% CI: −31:44, −7:57) points and an increase in the conflict attentional network of 11.31 (95% CI: 6.05, 16.57) milliseconds, indicating a poorer performance.[30]

Learning/cognitive symptoms

Eleven articles discussed on learning/ cognitive symptoms. Prenatal $PM_{2.5}$ exposures was associated with lower Mullen Scales of Early Learning (MSEL) scores19 and was inversely associated with offspring Mental Development Index (MDI) scores.[25, 26] There is a slightly positive association between prenatal $PM_{2.5}$ exposure and problem-solving domains.[18] Prenatal $PM_{2.5}$ exposures was negatively associated with offspring neurodevelopment[26, 34] and was significantly associated with decreased scores for all neurodevelopmental domains of children at ages 2, 6, and 24 months.[35] Increased prenatal $PM_{2.5}$ exposure was significantly associated with increased

risk of suspected development delay 1.52 (95% CI: 1.19, 2.03), specifically, in problem-solving domain for girls 2.23 (95% CI: 1.22, 4.35).[35] Prenatal $PM_{2.5}$ exposures was negatively associated with both problem-solving in infants aged 12 months old,[23] and general cognitive index.[20] Prenatal $PM_{2.5}$ exposures in the second and third trimesters correlated with increased odds of low-performance 1.59 (95% CI: 1.16, 2.17), p=0.004.[36] Increased $PM_{2.5}$ exposures also predicted lower cognitive score.[16] During the 6 months' assessment, cognitive scores significantly decrease with adjusted cognitive score reduction of −0.93.[16]

The Association Between the Timing of Prenatal Exposure (Trimester Related) to $PM_{2.5}$ And Symptoms of Impaired Neurodevelopment in Children.

From the eligible articles, eighteen articles showed association between the timing of prenatal exposure to $PM_{2.5}$ and symptoms of impaired neurodevelopment in children. The timing of prenatal exposure was divided into first, second and third trimester. The findings were summarized in table 2.

Table 2 The association between the timing of prenatal exposure (trimester related) to PM2.5 and symptoms of impaired neurodevelopment in children.

Trimester	Findings
First trimester (First 13 weeks of pregnancy)	• Significantly associated with risk of ADHD.[29] • Lower VABS communication and daily living skills scores among ASD cases.[19] • Lower Adaptive Skills composites scores and scores of the three adaptive subscales namely adaptability, social skills, and functional communication.[17] • Deficits in social skills and communication.[17] • Increases in a few of the behavioural subscales, including attention problems and withdrawal subscales.[17] • Lower scores on the MSEL visual reception scale among Developmental Delay cases.[19] • Increased risk of failing the overall developmental screening.[18] • Lower scores on the visual reception scale among ASD cases.[19] • Inversely associated with offspring MDI as well as PDI scores.[25]
Second trimester (14 weeks to 26 weeks of pregnancy)	• Increased risks of delays in gross motor neurodevelopmental milestones.[22] • Increased risk of non-optimal gross motor development.[24] • Slightly inverse association with fine motor development.[18] • The most sensitive time window for the developments of behaviour and active tone.[31] • Negatively associated with behaviour score and the inverse relation was more pronounced in male infants.[31] • Negatively related to active tone score in a dose-dependent manner for both genders.[31] • Significantly associated with omission errors.[5] • Increased global negative affectivity scores as well as higher sadness and fear scores.[33] • Predicted poorer Go/No-Go performance.[36] • Delayed fine motor development.[36] • Significantly associated with ASQ scores and suspected development delay (SDD).[35] • Delay in personal and social neurodevelopmental.[22] • Significantly associated with an increased global negative affectivity (NA) factor.[33] • Increased variability in response time across the test (HRT-SE) among boys.[5]
Third trimester (27 weeks to 40 weeks of pregnancy)	• Positively associated with the risk of child hyperactivity at the age of 3.[27] • Lower VABS composite scores, daily living skills and socialization scores.[19] • Contributed most to the effect on cognitive,[16, 23] languages,[16] and motor functions.[23] • Lower scores in gross motor, problem-solving and personal-social domains.[23]

- Lower IQ.[5]
- Slower hit response time (HRT), and increase HRT standard Error (HRT-SE) among boys.[5]
- Lower scores on the MSEL visual reception scale among Developmental Delay cases.[19]
- Increased risk of failing the overall developmental screening.[18]

First trimester (first 13 weeks of pregnancy)

Higher concentrations of $PM_{2.5}$ during the first trimester were significantly associated with the risk of ADHD,[29] and lower Vineland Adaptive Behaviour Scales (VABS) communication and daily living skills scores, among autistic spectrum disorder (ASD) cases,[19] lower Adaptive Skills composites scores, as well as lower scores of the three adaptive subscales namely Adaptability, Social Skills, and Functional Communication[17]. $PM_{2.5}$ concentrations during the first trimester was associated with an increased odd of being in the at-risk/ clinical range for Adaptive Skills and Functional Communication subscales and was also associated with deficits in social skills and communication.[17] There were also associations between first trimester $PM_{2.5}$ exposure and increases in a few of the behavioural subscales, including Attention Problems and Withdrawal subscales.[17] $PM_{2.5}$ exposure during the first trimester was also associated with lower scores on the MSEL visual reception scale among Developmental Delay cases.[19] A 10 μg/m3 increase in $PM_{2.5}$ exposure during first trimester was associated with a 1.6% increased risk of failing the overall developmental screening.[18] Cognitive wise, $PM_{2.5}$ exposures during the first trimester was associated with lower scores on the visual reception scale among ASD cases[19] and was inversely associated with offspring MDI as well as PDI scores.[25]

Second trimester (14weeks to 26 weeks of pregnancy)

$PM_{2.5}$ exposures during the second trimester was associated with increased risks of delays in gross motor neurodevelopmental milestones with adjusted odds ratio 1.09 per 10 μg/m3 increase in exposure to $PM_{2.5}$,[22] and was significantly associated with an increased risk of non-optimal gross motor development with aRR of 1.14 (95 % CI: 1.04, 1.25) per 10 μg/m3 increase.[24] A slightly inverse association was observed for second trimester $PM_{2.5}$ exposure and fine motor development (-0.2%).[18]

The second trimester was the most sensitive time window for the developments of behaviour and active tone. $PM_{2.5}$ exposures in second trimester was negatively associated with behaviour score -0.003 (95% CI: -0.006, -0.001) and the inverse relation was more pronounced in male infants. In addition, $PM_{2.5}$ level in the second trimester was negatively related to active tone score -0.012 (95% CI: -0.021, -0.002) in a dose-dependent manner for both genders.[31] There was also a significant association between higher $PM_{2.5}$ levels in mid-pregnancy (20–26 weeks of gestation) with omission errors[5]. Increased exposure to $PM_{2.5}$ in mid-pregnancy was also associated with increased global negative affectivity scores as well as higher sadness and fear scores.[33]

Prenatal $PM_{2.5}$ exposures in second and third trimester predicted poorer Go/No-Go performance,[36] and delayed fine motor development (aOR 1.06).[22] Prenatal $PM_{2.5}$ exposures in weeks 18 to 34 was significantly associated with both Ages and Stages Questionnaire (ASQ) scores and suspected development delay (SDD).[35] Delay in personal and social neurodevelopmental milestones were associated with $PM_{2.5}$ exposure in the second (aOR 1.110,) and third trimester (aOR 1.062).[22] Increased daily $PM_{2.5}$ exposure from 14 to 20 weeks gestation and towards the end of gestation were significantly associated with an increased global negative affectivity (NA) factor.[33] Higher $PM_{2.5}$ exposure in mid-to-late pregnancy (22–40 weeks of gestation) were also associated with increased variability in response time across the test (HRT-SE) among boys.[5]

Third trimester (27weeks to 40 weeks of pregnancy)

The risk of child hyperactivity at the age of 3 years was positively associated with $PM_{2.5}$ exposures during the seventh month of pregnancy to the fourth month after birth, and the strongest association was observed during the ninth month of pregnancy with OR of 1.062 (95% CI: 1.024–1.102) per 10 g/m3 increase.[27] Third trimester $PM_{2.5}$ exposures was associated with lower VABS composite scores, daily living skills and socialization scores.[19]

$PM_{2.5}$ exposures at third trimester of pregnancy contributed most to the effect on cognitive,[16, 23] languages,[16] and motor functions.[23] Each 10μg/m3 increase in $PM_{2.5}$ exposures during third trimester and the entire pregnancy was associated with lower scores in gross motor, problem-solving and personal-social domains.[23] Higher PM2.5 levels at 31-38 weeks were associated with lower IQ,[5] and slower hit response time (HRT), and increase HRT standard Error (HRT-SE) among boys.[5] $PM_{2.5}$ exposures during the third trimesters was also associated with lower scores on the MSEL visual reception scale among Developmental Delay cases.[19] A 10 μg/m3 increase in $PM_{2.5}$ exposures during third trimester was associated with 2.7%

increased risk of failing the overall developmental screening.[18]

Other Factors That May Influence the Association of Exposure and Symptoms of Impaired Neurodevelopment in Children

A total of ten articles discussed regarding other factors that may influence the association between the exposure and symptoms of impaired neurodevelopment in children.

Seven articles discussed on gender factor. Male subject was more vulnerable as compared to females.[31] Positive associations between air pollution exposure during first trimester and neurodevelopmental delay were stronger in males than in females for $PM_{2.5}$, PM_{10} and SO2.[34] Among males, increased daily $PM_{2.5}$ exposures in early pregnancy (1–4 weeks gestation) was significantly associated with decreased fear scores, while increased daily $PM_{2.5}$ exposure in late pregnancy (35–40 weeks gestation) was significantly associated with elevated Fear scores.[33] $PM_{2.5}$ exposures in second trimester was negatively associated with behaviour score -0.003 (95% CI: -0.006, -0.001) and the inverse relation was more pronounced in male infants.[31] Higher $PM_{2.5}$ exposures in mid-to-late pregnancy (22–40 weeks of gestation) showed increased variability in Hit Reaction Time-Standard Error (HRT-SE) test among males.[5] Male subject also showed significant association between increased $PM_{2.5}$ exposure in late pregnancy (31–38 weeks of gestation) and lower IQ scores.[5] There was a significant association between the average concentration $PM_{2.5}$ prenatal exposure with memory and verbal domain among male subject[20]. In contrast, Chiu et al. in their study found that female subject showed significant associations between higher $PM_{2.5}$ levels in early-to-mid pregnancy and adverse memory performances.[5] Increased daily $PM_{2.5}$ exposures among females in mid-pregnancy (20–24 weeks gestation) was significantly associated with elevated Fear scores.[33] The associations between $PM_{2.5}$ and Total Behaviour Problems score were generally stronger in females.[37] $PM_{2.5}$ exposures might increase the risk of suspected developmental delay for boys and girls, specifically in the problem-solving domain for females.[35]

Mode of conception also showed a significant interaction. A significant association between $PM_{2.5}$ and non-optimal cognition development was observed among infants who conceived spontaneously.[24] In term of mode of delivery, children born vaginally had stronger associations than their counterparts born by Caesarean section, only for $PM_{2.5}$, PM_{10} and NO2 exposure over first trimester.[34] Boys and infants who were breastfed for less than 6 months appeared to be more susceptible to $PM_{2.5}$ and its compositions.[23] In one study, infants of women living closer which is less than 100 meters to metal processing activities were found to have decreased motor score by -3.20 and decreased mental score by -2.7.[6]

Table 3 Other factors that may influence the association of exposure and symptoms of impaired neurodevelopment in children.

Factor	Finding
Gender	• Positive associations between air pollution exposure during first trimester and neurodevelopmental delay were stronger in males than in females.[34] • Increased daily $PM_{2.5}$ exposures in early pregnancy (1–4 weeks gestation) was significantly associated with decreased fear scores among boys.[33] • Increased daily $PM_{2.5}$ exposures in late pregnancy (35–40 weeks gestation) was significantly associated with elevated Fear scores among boys.[33] • $PM_{2.5}$ exposures in second trimester was negatively associated with behaviour score and was more pronounced in male infants.[31] • Higher $PM_{2.5}$ exposures in mid-to-late pregnancy (22–40 weeks of gestation) showed increased variability in Hit Reaction Time-Standard Error (HRT-SE) test among males.[5] • Significant association between increased $PM_{2.5}$ exposures in late pregnancy (31–38 weeks of gestation) and lower IQ scores in boys.[5] • Significant association between the average concentration $PM_{2.5}$ prenatal exposures with memory and verbal domain in males.[20] • Significant associations between higher $PM_{2.5}$ levels in early-to-mid pregnancy and adverse memory performances among girls.[5] • Increased daily $PM_{2.5}$ exposures among females in mid-pregnancy (20–24 weeks gestation) was significantly associated with elevated Fear scores.[33] • The associations between $PM_{2.5}$ and Total Behaviour Problems score were generally stronger in females.[37]

	• $PM_{2.5}$ exposures might increase the risk of suspected developmental delay for boys and girls, specifically in the problem-solving domain for females.[35]
Mode of conception	• A significant association between $PM_{2.5}$ and non-optimal cognition development was observed among infants who conceived spontaneously.[24]
	• Children born vaginally had stronger associations than born by Caesarean section, for $PM_{2.5}$ exposures over first trimester.[34]
Breastfeeding history	• Boys and infants who were breastfed for less than 6 months appeared to be more susceptible to $PM_{2.5}$ and its compositions.[23]
Housing area	• Infants of women living less than 100 meters to metal processing activities were found to have decreased motor score by -3.20 and decreased mental score by -2.7.[6]

DISCUSSION

$PM_{2.5}$, or particles with an aerodynamic diameter of less than 2.5 μm, is defined as fine particles containing carbon and have an ability to absorb various chemical compounds such as metals, organic compounds and salts and biological groups such as pollen and toxins which have potential to cause severe impacts on human health.[38, 39] The particle's large surface area and small diameter enable it to contain a variety of toxic elements.[40] The unique properties of this particle have resulted in its association with greater mortality rate than larger particles such as PM_{10}.[41] Chronic exposure to ambient $PM_{2.5}$ is the largest environmental risk factor for human health, with an estimated 4.1 million attributable deaths worldwide in 2019.[42] $PM_{2.5}$ can carry various potentially harmful molecules and penetrate the lung tissue, and subsequently affect the respiratory, cardiovascular, and circulatory system of a person.[43] Sources of $PM_{2.5}$ in the environment include direct emissions from forest fires and agricultural waste burning, windblown mineral dust from arid regions, and inefficient fuel combustion.[44] In addition, $PM_{2.5}$ is also a result of secondary emissions from atmospheric chemical reactions between primary gas-phase pollutant precursors. Certain processes such as residential energy use, on- and off-road vehicles, energy generation, solvent use, industrial processes, and agricultural fertilizer application may emit these precursors.

An increasing number of studies suggest that air pollution exposure in early life, especially prenatal $PM_{2.5}$ exposures, has adverse effects on the normal development of the mammalian nervous system and it has become a major global environmental and public health threat.[35] Exposure to PM2.5 may occur through dermal, ingestion and inhalation route, however, PM2.5 is primarily absorbed through the respiratory system, where it can infiltrate the lung alveoli and reach the bloodstream.[45, 46] This review has found a range of impaired neurodevelopmental symptoms associated with prenatal exposure to $PM_{2.5}$, such as language, speech, and communication symptoms; motor skills symptoms; behaviour and social skills symptoms; memory symptoms as well as learning/cognitive symptoms among the study populations. In humans, a critical period of development of the nervous system begins in the embryo and extends into early infancy[1] with the developing nervous system is vulnerable while the blood-brain barrier is not fully developed until the middle of the first year of life.[47] In addition, the developmental vulnerability of the human brain to neurotoxicants such as $PM_{2.5}$ usually occurs in utero, during infancy, and can persist up to early childhood.[48] Studies conducted in rodent models showed exposure to particulate matter during gestation and early life have caused neuroinflammation, neurotransmitter imbalance, and oxidative stress, and particulate matter crossing the placenta was also suggested.[49, 50] Furthermore, a study conducted in Mexico reported a possible role of the apolipoprotein E genotype E4 (APOE-€4) in the response to PMs exposure in the developing brain.[51]

This review also found varied findings on the neurodevelopmental domains in different studies conducted. The different patterns of exposure and magnitudes of the effect estimates observed for the different cognitive outcomes assessed. This might be attributed to the different proportions of the $PM_{2.5}$ components which vary substantially across locations, and some components may be more harmful to health than others.[52] However, how $PM_{2.5}$ affected different neurodevelopmental domains are not well understood. For example, for language domains, it has been proposed that early language development may be affected through cell loss that inhibits processing of available linguistic information.[53,54] Clinically, structural alterations of the corpus callosum are frequently observed in many cognitive and behavioral abnormalities, including ASD and ADHD. Animal studies have shown that gestational $PM_{2.5}$ exposures could result in lower corpus callosum volume and this has been attributed to the neuroinflammatory changes.[55] Exposure to $PM_{2.5}$ exposures during the third trimester was associated with reduced corpus callosum volume,

resulting in an increase in behavioral problems, both in animal and human studies.[28, 56]

The association between the timing of prenatal exposure to $PM_{2.5}$ and symptoms of impaired neurodevelopment in children is also examined. The determination on the critical gestational window of $PM_{2.5}$ exposures which will have the most impact on children's neurodevelopmental domains is important for further understanding of the mechanism as well as for further intervention strategies. Generally, the neurodevelopmental impairments were associated with exposure to $PM_{2.5}$ across all three trimesters. The impairment in communication and behavioral domains predominate in those with positive associations between gestational first trimester $PM_{2.5}$ exposure and neurodevelopmental impairment. Those who were exposed to $PM_{2.5}$ during the second and third trimester have widespread neurodevelopmental impairment across all the domains. For this review, we also found that the gestational exposure to $PM_{2.5}$ affects the probability of failing the overall developmental screening, regardless of the timing of exposure.[18, 35] Fetal neurodevelopment starts about 25 days after conception, when the neural tube begins to form and by the end of the embryonic period (gestational week 10), the basics of the neural system are established.[57] All the structures continue to develop throughout the fetal period and early childhood. There are relatively few studies that examined critical windows of prenatal $PM_{2.5}$ exposures in terms of neurodevelopment in early life stages. Furthermore, most epidemiologic studies assessed a critical window that was based on artificially divided or clinically defined trimesters,[58, 59] and these divisions may not necessarily correspond to vulnerable periods of neurodevelopment.[61]

One of the factors that may influence the association between the exposure and symptoms of impaired neurodevelopment in children discussed in these articles was gender. This review found that, overall, male was more susceptible to have unfavourable neurodevelopmental impairment symptoms compared to females. Male children were more likely to have stronger association between prenatal $PM_{2.5}$ exposure and neurodevelopmental delay including behaviour domain.[31, 34] Male also found to have lower IQ, memory and verbal scores after prenatal $PM_{2.5}$ exposure compared to females.[5, 20] The findings on prenatal $PM_{2.5}$ exposure and impairment in memory domain among males is consistent with another study done in the United States of America, though the opposite finding was reported in which female subjects showed significant associations between higher $PM_{2.5}$ levels in early-to-mid pregnancy and adverse memory performances.[5] There are several theories that may be able to explain the sex-differential susceptibility towards prenatal $PM_{2.5}$ exposure. Animal study found a sex-specific alteration of the dopamine function[61] or the influence of sex hormones. Female sex hormones, such as estrogen, showed an anti-inflammatory effect by regulating cytokine expression.[62] Consequently, the hormones could help to counteract the inflammatory response to $PM_{2.5}$ exposures in girls. Air pollution has also been found to have genotoxic effects.[63] Genes linked to intelligence are overrepresented in the X chromosome[64] with 500 out of 800 genes coding for protein in the X chromosome are expressed in the brain.[65] Thus, any genotoxicity effect on the genes on the X chromosome is more likely to affect males because they are depending on only one X chromosome.

With abundant findings of neurodevelopmental effect on the children from the prenatal exposure of $PM_{2.5}$, several suggestions have been proposed to reduce the effect. As oxidative stress pathway has been suggested as one of the mechanisms, some studies look at the role of antioxidants and detoxification factors to modulate this association. A study conducted in Spain reported that though prenatal exposure to residential air pollutants may adversely affect infant mental development, these effects may be limited to infants whose mother reports low antioxidant intakes, such as from fruits and vegetables.[66] However, the findings from another study failed to support this mitigation measure.[6] The use of mechanical ventilation systems could mitigate the intrusion of outdoor $PM_{2.5}$ during standard work hours, while filters with ratings of MERV 13-14 or MERV 15+ were associated with a 30.9%- 39.4% reduction of indoor $PM_{2.5}$..[67] However, no study was conducted to specifically look at the effect of ventilation and filtration methods on the neurodevelopmental impairment among children.

A few limitations encountered throughout the course of the narrative review. Results obtained from this review could have been skewed given the frequency of certain countries reported in the studies. Nineteen out of twenty-five studies were conducted in three countries (China, United States of America and Spain). Furthermore, the inclusion of articles available in the English language for the past 5 years only will further limit the number of potential studies. All the studies reviewed are ecological in nature, hence limitations associated with ecological studies need to be acknowledged. Further analyses will help to overcome these limitations and to establish more complete interpretations.

CONCLUSION

This narrative review provides an improved understanding regarding the effect of prenatal PM2.5 exposures towards neurodevelopmental

domains of the children. The findings on association between prenatal exposure of PM2.5 and these adverse effects served as evidence that will support public health policies that reduce air pollution, especially particulate matters. These policies development is important particularly for this sensitive population and disproportionately exposed groups. Apart from regular air quality monitoring with systematic dissemination of air quality level to the population, self-protective measures such as wearing appropriate masks, reducing outdoor activities, keeping doors and windows closed as well as installing air purifier should be encouraged, especially among the pregnant women. Further research on health effects of particulate matters, specific effects based on possible sources, as well as the effectiveness of mitigation strategies will help in protecting the children by reducing the health effects in them.

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