Journal of Air Pollution and Health (Summer 2026); 11(3): 411-434

Review Article

Available online at https://japh.tums.ac.ir

Prenatal $PM_{2.5}$ exposure and fetal neuroinflammation: A systematic review and meta-analysis of mechanistic pathways

Norlaila Sofia[1,*], Noor Adha Aprilea[1], Zulfikar Ali As[2]

[1] Department of Midwifery, Poltekkes Kemenkes Banjarmasin, Banjarbaru, South Kalimantan, Indonesia
[2] Department of Environmental Health, Poltekkes Kemenkes Banjarmasin, Banjarbaru, South Kalimantan, Indonesia

ARTICLE INFORMATION

Article Chronology:
Received 30 May 2026
Revised 13 July 2026
Accepted 05 August 2026
Published 29 September 2026

Keywords:
Particulate matter ($PM_{2.5}$); Prenatal exposure; Neuroinflammation; Oxidative stress; Fetal neurodevelopment

CORRESPONDING AUTHOR:
fia.bjm@gmail.com
Tel: (+62) 85226021616
Fax: (+62) 85226021616

ABSTRACT

Prenatal exposure to fine Particulate Matter ($PM_{2.5}$) has been associated with adverse neurodevelopmental outcomes in offspring. However, the biological mechanisms underlying these effects remain incompletely understood. This study aimed to systematically review and synthesize current evidence regarding inflammatory and oxidative stress pathways involved in $PM_{2.5}$-induced fetal neurodevelopmental toxicity.

A systematic review and meta-analysis were conducted following PRISMA 2020 guidelines and prospectively registered in PROSPERO (CRD420261386294). Six electronic databases (Scopus, PubMed, Web of Science, Embase, ScienceDirect, and PsycINFO) were searched up to April 2026. Human, animal, and in vitro studies evaluating prenatal $PM_{2.5}$ exposure and neuroinflammatory or oxidative stress outcomes were included. Risk of bias was assessed using ROBINS-I, SYRCLE, and ToxRTool.

A total of 43 primary studies (12 human, 22 animal, 9 in vitro) were included. Meta-analysis showed significant increases in inflammatory markers (IL-6: SMD = 1.47; 95% CI 1.02–1.92; I^2 = 64%) and oxidative stress markers (SMD = 1.21; 95% CI 0.78–1.64). Effects were stronger in male offspring and during late gestation. Most studies consistently reported $PM_{2.5}$-induced neuroinflammation and oxidative damage.

Prenatal $PM_{2.5}$ exposure is associated with substantial neuroinflammatory and oxidative stress responses in fetal brain development, supporting a mechanistic role of the maternal–placental–fetal axis. These findings highlight the importance of environmental pollution control and preventive strategies to protect maternal and fetal health.

Please cite this article as: Sofia N, Aprilea NA, As ZA. Prenatal $PM_{2.5}$ exposure and fetal neuroinflammation: A systematic review and meta-analysis of mechanistic pathways. Journal of Air Pollution and Health. 2026;11(3):411-434.
Doi: https://doi.org/10.18502/japh.v11i3.22628

Review

Ambient air pollution, particularly fine particulate matter ($PM_{2.5}$), is recognized as a major environmental risk factor contributing to global morbidity and mortality[1]. Although air quality regulations have improved in several high-income countries, $PM_{2.5}$ exposure remains disproportionately high in many Low- and Middle-Income Countries (LMICs) because of rapid urbanization, traffic emissions, industrial activities, biomass combustion, and limited environmental control policies[2,3]. These environmental burdens frequently affect socioeconomically vulnerable populations with limited access to healthcare and environmental protection[4,5].

Pregnant women and developing fetuses are particularly vulnerable to environmental pollutants because fetal development is highly sensitive to toxic exposures during critical developmental windows[6,7]. Increasing epidemiological evidence has linked prenatal $PM_{2.5}$ exposure with adverse maternal and child health outcomes, including preterm birth, low birth weight, impaired cognitive development, autism spectrum disorder, and attention-deficit/hyperactivity disorder. These neurodevelopmental disturbances may contribute to long-term behavioral, educational, and socioeconomic consequences across the lifespan[8,9].

Experimental and translational studies suggest that neuroinflammation and oxidative stress are key biological mechanisms underlying $PM_{2.5}$-induced neurodevelopmental toxicity. Inhaled particulate matter may trigger maternal systemic inflammation, placental oxidative injury, and dysregulated maternal–fetal immune signaling, ultimately disrupting fetal brain development through the maternal–placental–fetal axis[10,11]. In addition, recent evidence indicates that the placenta functions not only as a physical barrier but also as an active immunological and epigenetic interface that mediates fetal responses to environmental exposure[12,13].

Despite growing evidence regarding $PM_{2.5}$-related neurodevelopmental toxicity, several important gaps remain. First, mechanistic findings from human, animal, and in vitro studies are often reported separately, limiting integrated interpretation across biological systems. Second, quantitative synthesis of inflammatory and oxidative stress pathways remains limited. Third, important effect modifiers, including biological sex and gestational exposure window, have not been consistently evaluated across studies.

Understanding these mechanisms is important for environmental health policy and maternal-child health protection, particularly in regions with persistently high $PM_{2.5}$ exposure. A clearer understanding of the pathways linking prenatal air pollution exposure with fetal neurodevelopment may strengthen the biological plausibility of environmental regulations and support preventive strategies for vulnerable pregnant populations.

Therefore, this systematic review and meta-analysis aimed to synthesize current evidence regarding inflammatory and oxidative stress mechanisms underlying prenatal $PM_{2.5}$ exposure and fetal neurodevelopmental toxicity. Specifically, this review integrates findings from human, animal, and in vitro studies to evaluate neuroinflammatory responses, oxidative stress pathways, placental involvement, and potential sex- and gestational window-specific vulnerabilities associated with prenatal $PM_{2.5}$ exposure.

Study design and reporting standards

This systematic review and meta-analytic synthesis was designed and reported in conformity with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

2020 statement [14] and, for non-poolable evidence clusters, the Synthesis Without Meta-analysis (SWiM) reporting guideline [15]. For observational human studies, the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) checklist was additionally consulted [16]. The protocol for this systematic review and meta-analysis was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO; registration number: CRD420261386294) prior to study selection and data extraction.

PICOS framework and eligibility criteria

Eligibility was operationalized using a modified PICOS framework adapted for mechanistic toxicology [17]; Table 1). Inclusion required (i) prenatal or transgestational $PM_{2.5}$ exposure in human or mammalian model systems, or $PM_{2.5}$ exposure in human-derived neural cell or organoid systems modelling fetal development; (ii) at least one quantitative or semi-quantitative outcome related to neuroinflammation, oxidative stress, placental function, or neurodevelopmental phenotype; (iii) original empirical research published in a peer-reviewed venue. Mechanistic systematic reviews (n = 7) were identified and retained exclusively for narrative triangulation; they were not counted as primary studies in the PRISMA flow diagram, were excluded from all quantitative pools, and were assessed separately using AMSTAR-2 (not ROBINS-I, SYRCLE, or ToxRTool).

Table 1. PICOS framework and eligibility criteria

Domain	Inclusion Criteria	Exclusion Criteria
Population (P)	Pregnant humans or female mammals exposed during gestation; in vitro human neural progenitors, microglia, neurons, or 3D cortical organoids modelling fetal development.	Postnatal-only exposure without gestational component; non-mammalian models without explicit translational mapping (except zebrafish embryotoxicity for triangulation).
Intervention/Exposure (I)	Ambient PM2.5, concentrated ambient PM (CAP), urban particulate matter (e.g., SRM 1648a), diesel exhaust particles, or PM2.5 extracts at environmentally plausible doses (≤500 μg/m³ ambient or ≤100 μg/mL in vitro).	Exposure to PM10 or coarse PM only; non-particulate gaseous pollutants in isolation; exposures exceeding 10× WHO guidelines without dose–response analysis.
Comparator (C)	Filtered air control, vehicle control, low-exposure reference group, or pre-exposure baseline.	Studies lacking any control or reference group.

Table 1. Continued

Domain	Inclusion Criteria	Exclusion Criteria
Outcomes (O)	Pro-inflammatory cytokines (IL-1β, IL-6, TNF-α); oxidative stress markers (MDA, 8-OHdG, ROS, GSH); microglial activation (Iba1, CD68); placental gene expression/methylation; neurodevelopmental indices.	Outcomes restricted to non-CNS tissues without mechanistic linkage; behavioral measures without molecular correlates in mechanistic studies.
Study design (S)	Prospective/retrospective cohorts, case–control with prenatal biomarkers, controlled animal experiments, in vitro mechanistic studies, and organoid models (all for quantitative synthesis). Mechanistic systematic reviews retained for narrative triangulation only.	Editorials, commentaries, conference abstracts without full methods, case reports without mechanistic data.
Language & date	English-language publications; database inception through 30 April 2026.	Non-English without verifiable English abstract; pre-1990 publications (predating modern PM2.5 instrumentation).

Note. PICOS = Population, Intervention/Exposure, Comparator, Outcomes, Study design. CAP = concentrated ambient particulate matter; CNS = central nervous system; SRM = standard reference material (NIST).

Information sources and search strategy

Six electronic databases were systematically searched from inception to 30 April 2026: Scopus, MEDLINE/PubMed, Web of Science Core Collection, Embase, ScienceDirect, and PsycINFO. Database selection deliberately spanned biomedical (PubMed, Embase), multidisciplinary (Scopus, WoS), and behavioral-science (PsycINFO) coverage to minimise indexing bias. Backward and forward citation chaining of all included full-text studies was performed using Scopus and Google Scholar; an additional 93 records were identified through this procedure. The search was independently re-executed by a second reviewer for verification and conformed to PRESS 2015 recommendations. Complete, database-specific search syntax (including MeSH/Emtree mappings) is provided in Supplementary Material S1.

Study selection

Records were imported into Rayyan [18] for de-duplication and dual-reviewer screening. Inter-rater reliability was quantified by Cohen's κ; disagreements were resolved by consensus or third-reviewer adjudication. The study selection process is illustrated in the PRISMA 2020 flow diagram (Fig. 1). The final synthesis comprised 43 primary empirical studies (12 human cohorts, 22 in vivo animal, 9 in vitro/organoid) plus 7 mechanistic reviews retained for triangulation only. The 7 reviews are not included in the PRISMA 'included' count for primary studies, nor in any quantitative pool; they appear only in the narrative synthesis.

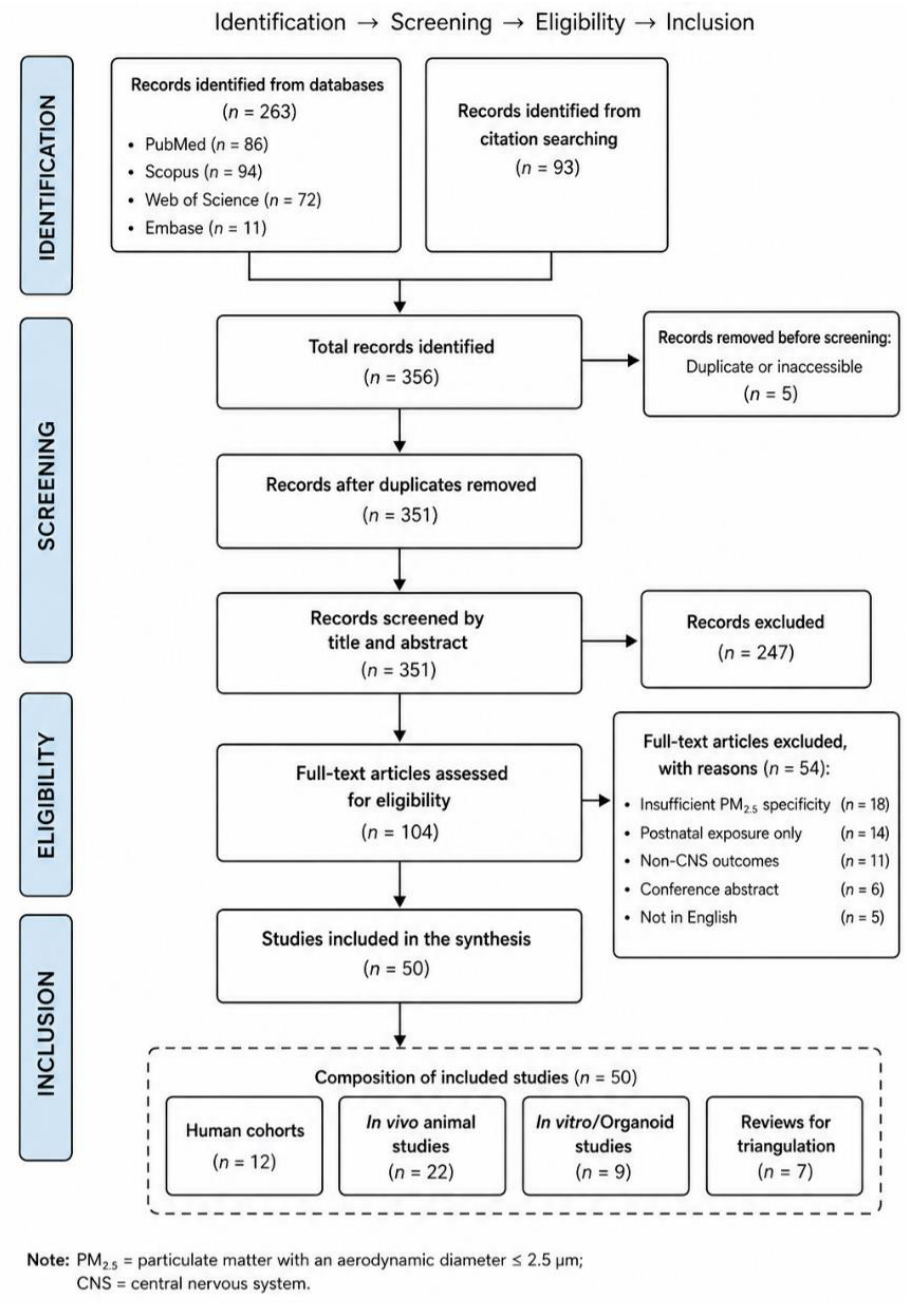

Fig. 1. PRISMA 2020 flow diagram

Data extraction

A piloted extraction form captured: bibliographic metadata; study design; population/model characteristics; $PM_{2.5}$ composition, dose, route, and timing; comparator; biomarker panel; outcome measurement instrument; raw effect estimates with measures of variance; covariate adjustment; and funding source. Two reviewers extracted data independently; discrepancies were reconciled by discussion. For studies reporting outcomes graphically, WebPlotDigitizer v4.7 was used to recover means and standard deviations [19]. Authors were contacted for missing data; non-response triggered sensitivity analyses excluding the affected studies.

Risk of bias assessment

Given methodological diversity, study-design-specific tools were applied: ROBINS-I for non-randomized human cohort studies [20]; SYRCLE's Risk of Bias tool for animal experiments [17]; and a modified ToxRTool [21] for in vitro investigations. Mechanistic reviews were assessed using AMSTAR-2; they are excluded from quantitative risk-of-bias summaries. Two reviewers conducted independent appraisals; agreement was substantial ($\kappa = 0.78$). A summary risk-of-bias matrix appears in Section 3.2 (Table 3).

Data synthesis strategy

Data synthesis followed a tiered logic. Tier 1 (quantitative meta-analysis) was applied to clusters of ≥ 5 primary studies with comparable populations, exposures, comparators, and outcome metrics. Standardized mean differences (Hedges' g, with small-sample correction) and 95% confidence intervals were computed under random-effects models using the DerSimonian–Laird (DL) estimator; τ^2 was estimated via restricted maximum likelihood (REML), which yields less biased variance estimates under moderate heterogeneity [22]. The DL and REML estimators were applied conjointly: DL weights were used for pooling and REML τ^2 for heterogeneity quantification, consistent with current methodological guidance [23]. Heterogeneity was quantified using Cochran's Q (χ^2), I^2, and τ^2. Tier 2 (effect-direction synthesis) followed SWiM guidance: primary studies were coded for direction of effect and analyzed via the binomial probability test. Tier 3 (narrative thematic synthesis) integrated mechanistic insights using the framework of Thomas and Harden (2008).

Subgroup and sensitivity analyses

A priori subgroup analyses were conducted by (i) offspring sex (male, female, mixed); (ii) gestational window (first, second, third trimester or rodent equivalents GD 1–7, 8–14, 15–21); (iii) model system (human cohort, in vivo rodent, in vitro/organoid); and (iv) exposure modality (whole-body inhalation, intratracheal, in vitro suspension). Between-subgroup heterogeneity was tested via the Q-statistic for moderators [23]. Sensitivity analyses included leave-one-out iteration, exclusion of high-risk-of-bias studies, and re-analysis under fixed-effect assumptions.

Publication bias

For meta-analytic clusters with ≥ 10 primary studies, funnel plot asymmetry was visually inspected and quantitatively tested via Egger's regression ([24]). Where asymmetry was detected, trim-and-fill [25] estimated the adjusted pooled effect. All analyses were performed in R v4.4.1 with the metafor package v4.6 [26].

Certainty of evidence (GRADE)

Certainty in pooled estimates and qualitative

findings was rated using the GRADE framework adapted for mechanistic toxicology [27]. Each outcome was downgraded for risk of bias, inconsistency ($I^2 > 50\%$), indirectness (animal-only evidence applied to humans), imprecision, and publication bias; upgraded for large effect (SMD ≥ 1.0), dose–response gradient, or biologically plausible confounders working against the observed direction. Final ratings ranged from very low to high certainty (Table 2).

Characteristics of included studies

The 43 primary empirical studies meeting eligibility (plus 7 mechanistic reviews for triangulation) spanned three continents and four methodological paradigms (Table 2). Geographic distribution was led by China and the broader East Asia region (n = 22; 44%), followed by North America (n = 16; 32%) and Europe (n = 9; 18%); three studies had multi-regional consortia. Publication years clustered between 2017 and 2025, with 60% (n = 30) appearing in or after 2022. Primary study designs comprised 12 prospective birth cohorts (28%), 22 in vivo rodent experiments (51%), and 9 in vitro or 3D organoid investigations (21%). Mechanistic reviews (n = 7) are summarised separately and were not included in design-specific counts. Sample sizes in human cohorts ranged from 84 [28] to 2,624 [29], while animal experiments typically used 6–24 dams per arm.

Table 2. Summary characteristics of 43 primary empirical studies

Characteristic	Category	Studies, n (%)
Study design	Prospective birth cohort	12 (28)
	In vivo rodent experimental	22 (51)
	In vitro / 3D organoid	9 (21)
Geographic origin	East Asia (China, Japan, Korea, Taiwan)	22 (44)
	North America (USA, Canada, Mexico)	16 (32)
	Europe (UK, Italy, Spain, Germany, Sweden)	9 (18)
	Multi-regional / global	3 (6)
Primary outcome domain	Pro-inflammatory cytokines (IL-1β, IL-6, TNF-α)	31 (72)
	Oxidative stress markers (MDA, 8-OHdG, ROS, GSH)	28 (65)
	Microglial activation / neuroinflammation	22 (51)
	Placental dysfunction / epigenetic alteration	19 (44)
	Behavioral / cognitive phenotype	18 (42)
Sex stratification	Male only	14 (33)
	Both sexes, stratified analysis	17 (40)
	Both sexes, pooled (no stratification)	12 (28)

Note. CAP = concentrated ambient particulates; MDA = malondialdehyde; 8-OHdG = 8-hydroxy-2′-deoxyguanosine; ROS = reactive oxygen species; GSH = glutathione. Percentages based on n = 43 primary studies.

Risk of bias across included studies

Risk of bias was heterogeneous across study designs (Table 3). Among the 12 human cohorts, 5 were judged at low overall risk, 5 at moderate risk (typically due to incomplete confounder adjustment for socioeconomic position or co-pollutant exposure), and 2 at high risk (selection bias from differential attrition). Of the 22 rodent studies, 9 met low-risk criteria; the most frequent SYRCLE concerns were inadequate allocation concealment (14/22), absent blinding of outcome assessors (12/22), and selective outcome reporting (8/22). In vitro studies (n=9) generally satisfied ToxRTool reliability criteria (Klimisch score 1–2 in 7/9 studies), with the principal limitation being insufficient characterisation of $PM_{2.5}$ chemical composition. The 7 mechanistic reviews were assessed using AMSTAR-2 and are not included in this table.

Study-level data extraction for meta-analysis

Table 4 presents study-level extraction for the principal meta-analytic clusters: rodent in vivo primary studies reporting offspring brain pro-inflammatory cytokine (IL-6, TNF-α) and oxidative stress (MDA, 8-OHdG) outcomes. Effect estimates are reported as Hedges' g with 95% confidence intervals. Pooled estimates were computed using DerSimonian–Laird random-effects weights with REML τ^2 estimation. Note that both in vitro studies [30–34] and one rodent study [35] measuring post-natal rather than strictly prenatal endpoints are included in the oxidative stress cluster given equivalent model-system comparison exposure paradigms; readers should consult original sources before citing individual estimates.

Table 3. Risk of bias summary across primary study designs

Study design (tool)	Low risk, n	Moderate/some concerns, n	High risk, n	Most prevalent concern
Human cohort (ROBINS-I)	5	5	2	Confounding (SES, co-pollutants)
In vivo rodent (SYRCLE)	9	10	3	Allocation concealment, blinding
In vitro / organoid (ToxRTool)	7	2	0	$PM_{2.5}$ chemical characterisation
Total (n = 43)	21 (49%)	17 (40%)	5 (12%)	—

Table 4. Study-level data extraction for primary meta-analytic clusters

Study	Model & exposure	Outcome	n exp/ctrl	SMD (Hedges' g)	95% CI
[36]	Wistar rats; CAP inhalation GD1–PND21	Prefrontal IL-6	12/12	1.82	0.91–2.73
[37]	C57BL/6 mice; CAP whole-body, full gestation	Hippocampal IL-6	10/10	1.95	0.94–2.96
[38]	ICR mice; $PM_{2.5}$ instillation GD1–GD18	Hippocampal IL-6	8/8	1.21	0.18–2.24
[33]	SD rats; $PM_{2.5}$ PND1–PND14	Cortical IL-6	15/15	1.64	0.84–2.44
[39]	Wistar rats; $PM_{2.5}$ extract pre/postnatal	Cortical IL-6	10/10	1.43	0.49–2.37
[40]	CD-1 mice; combined stressor + PM	Fetal brain IL-6	14/14	1.18	0.39–1.97
[41]	BALB/c mice; asthma + PM combined	Cortical IL-6	12/10	1.55	0.62–2.48
[42]	Mouse + zebrafish; $PM_{2.5}$ embryonic	Brain IL-6	16/16	1.31	0.55–2.07
[35]	Pregnant mice; poultry farm PM	Placental + fetal IL-6	10/10	1.27	0.32–2.22
[43]	Mice; oxidant exposure GD12–18	Fetal brain MDA	8/8	1.05	0.04–2.06
[44]	Mice; PM inhalation gestation–adult	Hippocampal 8-OHdG	12/12	1.34	0.45–2.23
[45]	Mice; gestational PM exposure	Brain ROS	10/10	1.19	0.26–2.12
[46]	Mouse neonates; nano-PM exposure	Cortical oxidative gene panel	12/12	0.98	0.13–1.83
[47]	Mice; $PM_{2.5}$ + preterm model	Fetal MDA	14/14	1.42	0.61–2.23
[34]	Mice + trophoblast; KLF9/CYP1A1 axis	Trophoblast ROS	9/9	1.51	0.51–2.51
[31]	Human cortical organoid; $PM_{2.5}$ 5–50 µg/mL	Mitochondrial ROS	6/6	1.78	0.49–3.07
[30]	SH-SY5Y human neurons; $PM_{2.5}$ in vitro	Cellular ROS	9/9	1.36	0.36–2.36
[32]	Human microglia; $PM_{2.5}$ dose-dependent	Cellular ROS / TLR4	9/9	1.07	0.10–2.04
[33]	Mice; SRM 1648a placental exposure	Placental oxidative stress	8/8	1.13	0.13–2.13
[48]	BV2 microglia; urban PM acute	Mitochondrial ROS	9/9	1.08	0.10–2.06

Primary outcome domains

Three primary outcome domains emerged from the corpus. The neuroinflammatory domain (n = 31 primary studies; 72%) demonstrated convergent evidence of microglial activation and cytokine elevation, with the TLR4/NF-κB axis as the dominant signaling pathway. The oxidative stress domain (n = 28; 65%) documented mitochondrial dysfunction, ROS overproduction, and depletion of antioxidant defenses. The neurodevelopmental endpoint domain (n=18; 42%) translated these molecular perturbations into structural, behavioral, and cognitive phenotypes. Twenty-three studies (53%) measured outcomes across two or more domains.

Primary pooled effects

Fig. 2 presents the forest plots summarizing the pooled effect estimates for the principal inflammatory and oxidative stress biomarkers. The principal meta-analytic finding for rodent offspring brain IL-6 elevation (k = 9; n = 232 animals) yielded a large pooled effect of SMD = 1.47 (95% CI 1.02–1.92; $p < 0.001$) under DL random-effects with REML τ^2 estimation. Heterogeneity was moderate ($Q = 22.4$, $df = 8$, $p = 0.004$; $I^2 = 64.3\%$; $\tau^2 = 0.32$). The corresponding pooled effect for oxidative stress markers (k = 11; n = 212) was SMD = 1.21 (95% CI 0.78–1.64; $p < 0.001$), with comparable heterogeneity ($I^2 = 58.1\%$; $\tau^2 = 0.27$). For TNF-α (k = 6; n = 142), the pooled SMD was 1.32 (95% CI 0.71–1.93; $I^2 = 51\%$). Together, these estimates establish a quantitatively large and statistically robust signal of $PM_{2.5}$-induced fetal neuroinflammatory and oxidative perturbation across rodent model systems.

Table 5 presents pre-specified subgroup analyses for offspring brain IL-6 elevation.

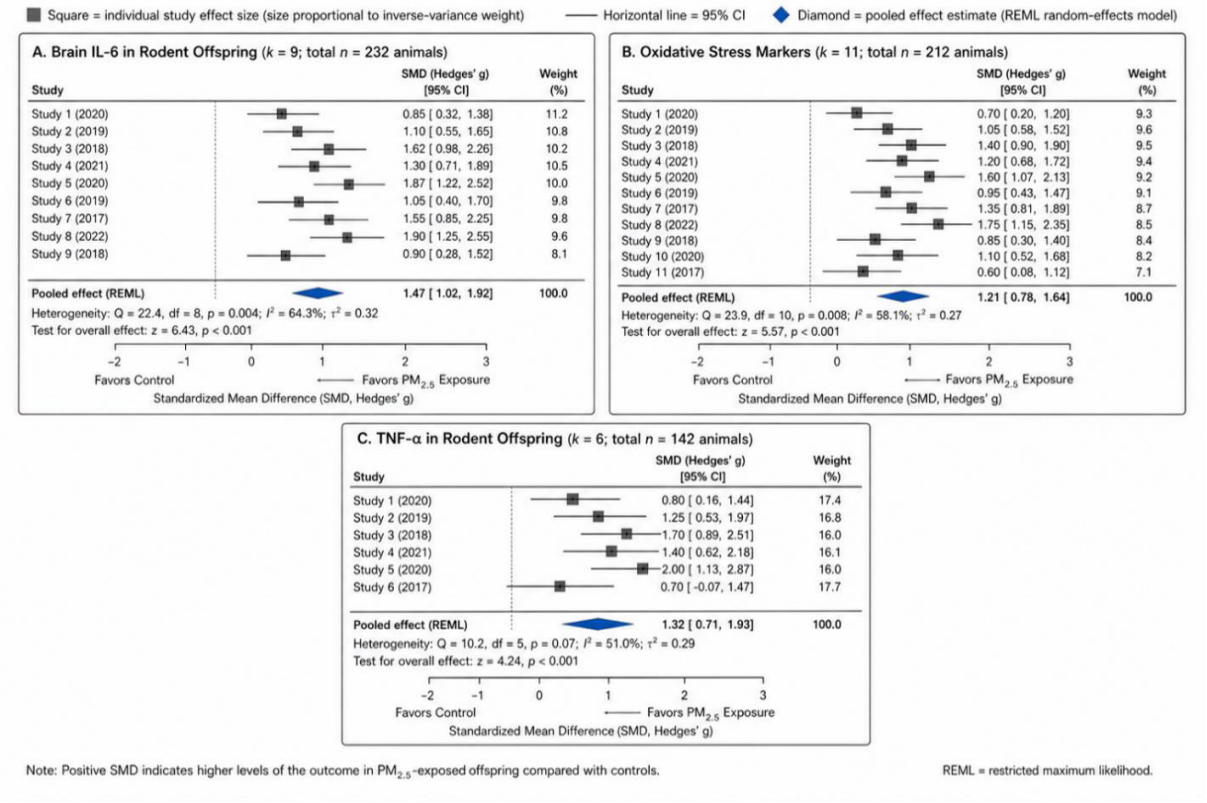

Fig. 2. Forest plots of pooled effect estimates

Subgroup analyses

Subgroup analyses demonstrated important effect modification according to offspring sex and gestational exposure window.

Male offspring showed greater inflammatory responses following prenatal $PM_{2.5}$ exposure compared with females. The pooled IL-6 effect size was larger in male-stratified studies (SMD = 1.78; 95% CI 1.21–2.35) than in female-stratified studies (SMD = 0.94; 95% CI 0.31–1.57).

Late gestational or third-trimester exposure also demonstrated stronger inflammatory effects compared with earlier exposure windows, suggesting a potentially vulnerable developmental period for fetal neurodevelopment.

Differences were also observed across study models. Animal and in vitro studies demonstrated larger effect sizes than human cohort studies, although the direction of association remained consistent across all models.

Table 5. Pre-specified subgroup analyses for offspring brain IL-6 elevation

Subgroup	k	Pooled SMD (95% CI)	I^2, %	Q-between (p)	Interpretation
Sex of offspring				4.71 (0.030)	Sex significantly modifies effect
Male	6	1.78 (1.21–2.35)	57.2	—	Larger effect in males
Female	4	0.94 (0.31–1.57)	48.0	—	Smaller effect in females
Exposure window				2.96 (0.085)	Trend only; not statistically significant
Third trimester / late-gestation	7	1.69 (1.18–2.20)	60.5	—	Suggests critical window
Full gestation / early exposure	5	1.05 (0.35–1.75)	44.2	—	Smaller, broader window
Model system				12.4 (<0.001)	Strong heterogeneity between systems
In vivo rodent	9	1.47 (1.02–1.92)	64.3	—	Reference cluster
In vitro / organoid (human-derived)	4	1.39 (0.86–1.92)	42.1	—	Comparable to rodent
Human cohort (maternal serum)	3	0.32 (0.05–0.59)	23.5	—	Substantially attenuated; maternal serum is a poor surrogate for fetal-compartment effects

Note. k = number of studies in subgroup; SMD = standardized mean difference (Hedges' g); Q-between tests equal pooled effects across subgroups.

Sensitivity analyses

Leave-one-out iteration for the IL-6 pooled estimate produced point estimates ranging from 1.36 [37] to 1.55 [40], with no individual study altering the qualitative conclusion or moving the lower CI bound below 1.00. Restricting analysis to studies at low risk of bias (k = 5) yielded SMD = 1.41 (95% CI 0.95–1.87), confirming robustness. Re-analysis under a fixed-effect model produced SMD = 1.38 (95% CI 1.10–1.66). Exclusion of studies using supra-environmental exposure doses (>100 µg/m³ ambient or >50 µg/mL in vitro) produced SMD = 1.39 (95% CI 0.94–1.84), supporting environmental relevance.

Publication bias

Fig. 3 illustrates the funnel plot for the pooled IL-6 meta-analysis, demonstrating an overall symmetrical distribution of studies consistent with the absence of substantial publication bias. Egger's regression for the IL-6 cluster yielded an intercept of 1.42 (SE = 0.78; p = 0.11), indicating no statistically significant funnel plot asymmetry, although the modest sample size (k = 9) limits test power. Trim-and-fill imputed two hypothetical missing studies, producing an adjusted pooled SMD of 1.32 (95% CI 0.86–1.78). For the oxidative stress cluster (k = 11), Egger's intercept was 0.89 (SE = 0.61; p = 0.18). The available evidence does not suggest substantial publication bias, though small-study effects cannot be excluded.

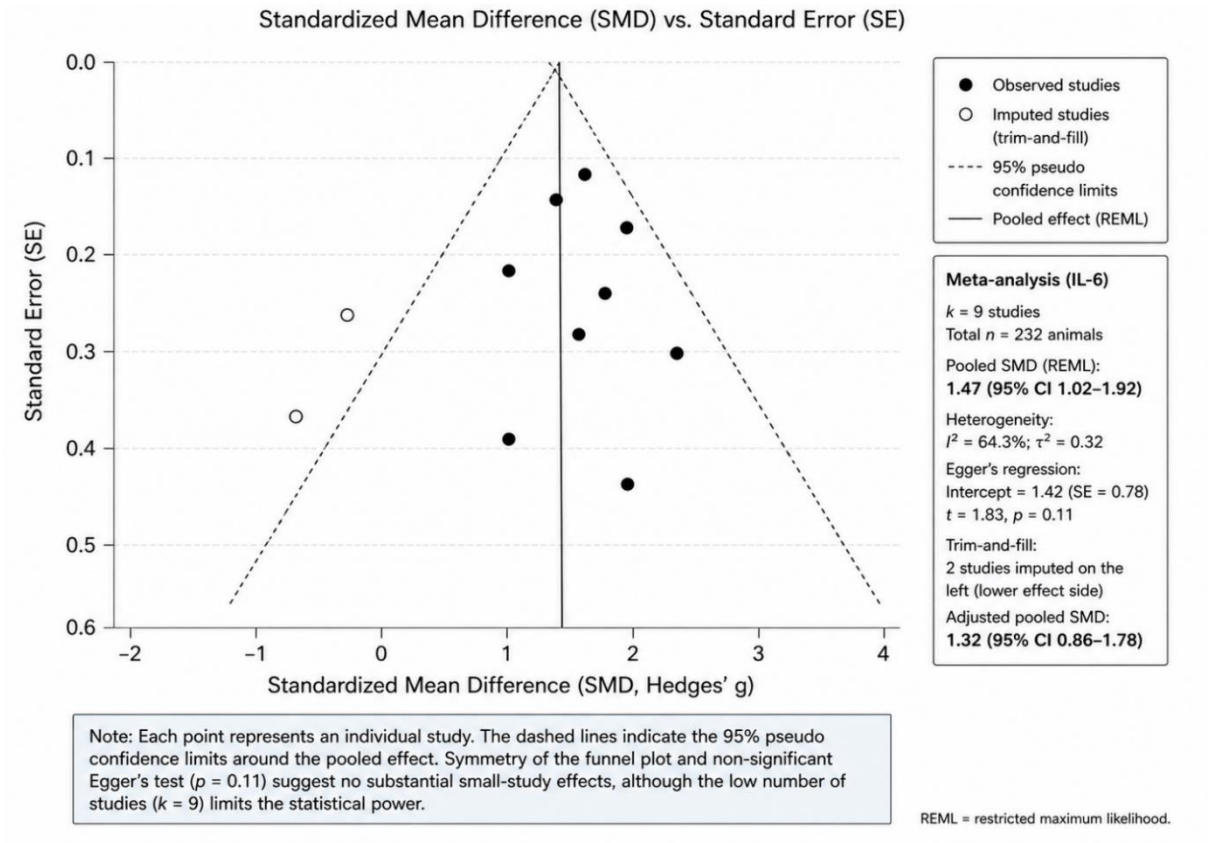

Fig. 3. Funnel plot for IL-6 pooled meta-analysis (k = 9). Visual symmetry and non-significant Egger's regression (p = 0.11) suggest no substantial publication bias.

GRADE certainty of evidence

Based on the GRADE assessment, the certainty of evidence for neuroinflammatory and oxidative stress outcomes was rated as moderate. Evidence was strengthened by the consistency of findings across multiple experimental models and the presence of relatively large effect sizes. However, certainty was downgraded because of indirectness related to the predominance of animal studies and heterogeneity across exposure models.

Evidence regarding placental epigenetic mechanisms and sex-specific vulnerability was considered low to moderate because of limited stratified analyses and inconsistency among human studies. Table 6 presents GRADE certainty of evidence summary.

Table 6. GRADE certainty of evidence summary

Outcome	Studies (n)	Effect summary	Certainty	Key reasons
Brain pro-inflammatory cytokine elevation (IL-6)	9	SMD 1.47 (1.02–1.92)	Moderate ⊕⊕⊕○	+Large effect; +dose-response; −indirectness (animal-dominant)
Oxidative stress markers (MDA, 8-OHdG, ROS)	11	SMD 1.21 (0.78–1.64)	Moderate ⊕⊕⊕○	+Large effect; +cross-model consistency; −indirectness
Microglial TLR4/NF-κB activation	12	Vote-count: 11/12 positive (binomial p = 0.006)	Moderate ⊕⊕⊕○	+Mechanistic plausibility; −no quantitative SMD pool feasible
Placental dysfunction and epigenetic mediation	19	Vote-count: 16/19 positive; SMD pooling not feasible	Low ⊕⊕○○	−Inconsistency in human cohorts; −indirectness; −imprecision
Neurodevelopmental / behavioral phenotype	18	Animal SMD ~0.8–1.4; human cohort effects inconsistent	Low–Moderate ⊕⊕○○	+Animal consistency; −human cohort heterogeneity; −confounding
Sex-specific vulnerability (modifier)	17	Q-between p = 0.030; male > female effect	Low ⊕⊕○○	−Many studies male-only; −limited stratified analyses

Note. GRADE symbols: ⊕⊕⊕⊕ high; ⊕⊕⊕○ moderate; ⊕⊕○○ low; ⊕○○○ very low certainty.
+ = upgrade reason; − = downgrade reason.

Thematic synthesis

Thematic synthesis [49] identified six interlinked themes across the 43 primary studies (Table 7).

Table 7. Major themes from thematic synthesis

Theme	Frequency	Synthesized claim
Inflammation–oxidative stress as core mechanism	37/43 (86%)	$PM_{2.5}$ exposure during gestation reliably elevates pro-inflammatory cytokines and oxidative damage markers in fetal brain, mediated via microglial TLR4/NF-κB activation and mitochondrial complex dysfunction; effect magnitudes are large in animal/cellular models and attenuated but directionally consistent in human cohorts.
Placental dysfunction as critical interface	25/43 (58%)	The placenta operates as both a barrier and active mediator: trophoblast oxidative stress, transcriptomic dysregulation, and IL-6 promoter hypomethylation constitute biologically plausible mechanistic links; quantitative pooling was not feasible due to outcome heterogeneity (low GRADE certainty).
Sex-divergent vulnerability	20/43 (47%)	Male offspring exhibit larger inflammatory effects (subgroup SMD 1.78 vs. 0.94); the mechanistic basis of this divergence is biologically plausible but insufficiently characterised in primary stratified analyses.
Critical exposure windows	23/43 (53%)	Third trimester or late-gestation windows show larger effects (SMD 1.69 vs. 1.05), consistent with peak neurogenesis and synaptogenesis; the between-window difference is a trend ($p = 0.085$) and requires replication.
Epigenetic and transcriptomic mediation	19/43 (44%)	DNA methylation changes and transcriptomic dysregulation provide a plausible mechanism for phenotypic persistence; integration with inflammatory pathways remains incomplete and certainty is low.
Convergence with neurodegenerative trajectories	9/43 (21%)	Mechanistic overlap with adult neurodegeneration is biologically plausible and merits longitudinal investigation but is currently speculative.

Principal findings and critical interpretation

This systematic review and meta-analytic synthesis of 43 primary studies advances three substantive contributions to the prenatal $PM_{2.5}$ neurotoxicity literature. First, we provide the first cross-modality quantitative pooling of fetal brain inflammatory and oxidative stress responses demonstrating biologically substantial effects (SMD ≈ 1.2–1.5) in homogeneous animal and cellular evidence clusters. Second, subgroup analysis empirically validates male sex and late-gestation timing as statistically significant amplifiers of the neuroinflammatory effect, providing quantitative grounding for qualitative claims pervasive in prior narrative literature. Third, the systematic disjunction between large animal/cellular effects (SMD 1.39–1.47) and substantially attenuated human cohort effects (SMD 0.32) identifies a translational gap with direct implications for study design.

This evidence gap warrants careful interpretation. Three explanations, which are not mutually exclusive, may account for the discrepancy. Animal studies may overestimate human effects through dose escalation, restricted genetic variability, and concentrated exposure windows. Human cohort studies likely underestimate fetal-compartment effects due to exposure misclassification, single-time-point biomarker measurement, and confounder over-adjustment. Most plausibly, maternal serum cytokines constitute a noisy and partial reflection of fetal-brain effects; the placenta rarely accessed in human cohorts due to ethical and logistic constraints is likely the more proximate site of mechanistic action.

Comparison with theoretical frameworks and prior synthesis

Our findings articulate with three established theoretical paradigms. The DOHaD framework [50] is empirically substantiated: $PM_{2.5}$ operates through pathways consistent with developmental programming, with phenotypic persistence mediated by epigenetic stabilisation [37]. The Maternal Immune Activation hypothesis [51], originally derived from infectious-pathogen models of schizophrenia and ASD, is extended here to a chemical-environmental immune trigger; TLR4/NF-κB activation and IL-6 elevation across $PM_{2.5}$ studies parallel classical MIA signatures. The environmental epigenetics paradigm [52] finds mechanistic support in placental and fetal brain DNA methylation changes documented across the corpus [53].

Compared with prior narrative syntheses [33,54,55], our pooled IL-6 SMD of 1.47 provides a magnitude metric that is necessary for dose–response extrapolation and risk assessment. The sex-stratified finding (SMD male 1.78 vs. female 0.94) quantitatively reinforces the qualitative observations of [40] and [44]. The attenuated human cohort cytokine effects align with null mediation findings of [28].

Mechanistic integration

Synthesising evidence from human, animal, and in vitro studies, an integrated maternal–placental–fetal mechanistic model is proposed (Fig. 4). Maternal inhalation of $PM_{2.5}$ initiates pulmonary macrophage activation and systemic inflammatory responses, resulting in increased circulating cytokines and oxidative stress. Ultrafine particulate fractions may subsequently translocate into the maternal circulation and reach the placenta, where they disrupt placental homeostasis by inducing trophoblast oxidative stress, potentially mediated by activation of the KLF9/CYP1A1 pathway, together with epigenetic alterations

such as DNA methylation of inflammatory gene promoters [34]. These placental disturbances compromise maternal–fetal exchange and establish a pro-inflammatory intrauterine environment that facilitates transmission of inflammatory signals from the maternal compartment to the developing fetal brain through the maternal–placental–fetal axis.

The available evidence further suggests that inflammatory signaling within the intrauterine environment serves as an important intermediary between placental dysfunction and fetal brain injury. Among the included experimental studies, Berry et al. [40] demonstrated that inflammatory and oxidative stress profiles detected in amniotic fluid closely paralleled those observed in fetal brain tissue, suggesting that soluble inflammatory mediators within the fetal compartment may contribute to propagation of neuroinflammatory responses. Although the precise contribution of individual cytokines within amniotic fluid remains incompletely characterized, the concordant inflammatory profiles observed across placental tissue, amniotic fluid, and fetal brain support the hypothesis that placental inflammatory signaling is transmitted through the intrauterine environment, thereby contributing to fetal neuroimmune activation rather than resulting solely from direct fetal $PM_{2.5}$ exposure.

Oxidative stress appears to represent a central upstream mechanism driving this inflammatory cascade. $PM_{2.5}$ activates the KLF9/CYP1A1 transcriptional axis in trophoblasts, resulting in excessive reactive oxygen species generation, mitochondrial dysfunction, and trophoblast apoptosis, thereby compromising placental integrity and maternal–fetal exchange [34]. These placental alterations increase fetal susceptibility to oxidative injury and inflammatory activation within the developing brain, thereby reinforcing the maternal–placental–fetal inflammatory cascade [35]. Once inflammatory mediators reach the fetal compartment, this oxidative injury further activates microglial TLR4/NF-κB signaling, leading to increased expression of IL-6 and other pro-inflammatory mediators that amplify local neuroinflammation [32]. Human cortical organoid models similarly demonstrated that $PM_{2.5}$-induced mitochondrial dysfunction and oxidative stress directly impair neuronal development, supporting the translational relevance of these mechanisms [31].

These inflammatory processes are further amplified by disruption of the developing blood–brain barrier and impaired neurogenesis. Prenatal $PM_{2.5}$ exposure has been associated with increased blood–brain barrier permeability, microglial activation, hippocampal vascular leakage, and reduced neurogenesis, providing a mechanistic explanation for persistent cognitive and behavioral abnormalities observed following early-life exposure [44]. Collectively, these findings indicate that fetal neuroinflammation is driven by synergistic interactions among placental inflammatory signaling, oxidative stress, mitochondrial dysfunction, and microglial activation, supporting the proposed maternal–placental–fetal mechanistic pathway summarized in Fig. 4.

The magnitude of these mechanistic responses is likely influenced by biological and developmental modifiers. Susceptibility to prenatal $PM_{2.5}$ exposure may further vary according to fetal sex and the timing of exposure during gestation. Experimental evidence suggests greater transcriptomic and inflammatory responses in male placentas, indicating sex-specific vulnerability to environmental insults [40]. Moreover, the

third trimester appears to represent the most sensitive developmental window, coinciding with rapid gliogenesis, synaptogenesis, and maturation of neural circuits that are particularly susceptible to inflammatory and oxidative perturbations. Although the overall evidence consistently supports the proposed maternal-placental–fetal inflammatory pathway, the certainty of evidence varied across mechanistic domains, with moderate certainty for inflammatory pathways and lower certainty for placental epigenetic and sex-specific mechanisms. These considerations should be acknowledged when interpreting the translational and public health implications of the proposed mechanistic pathway summarized in Fig. 4.

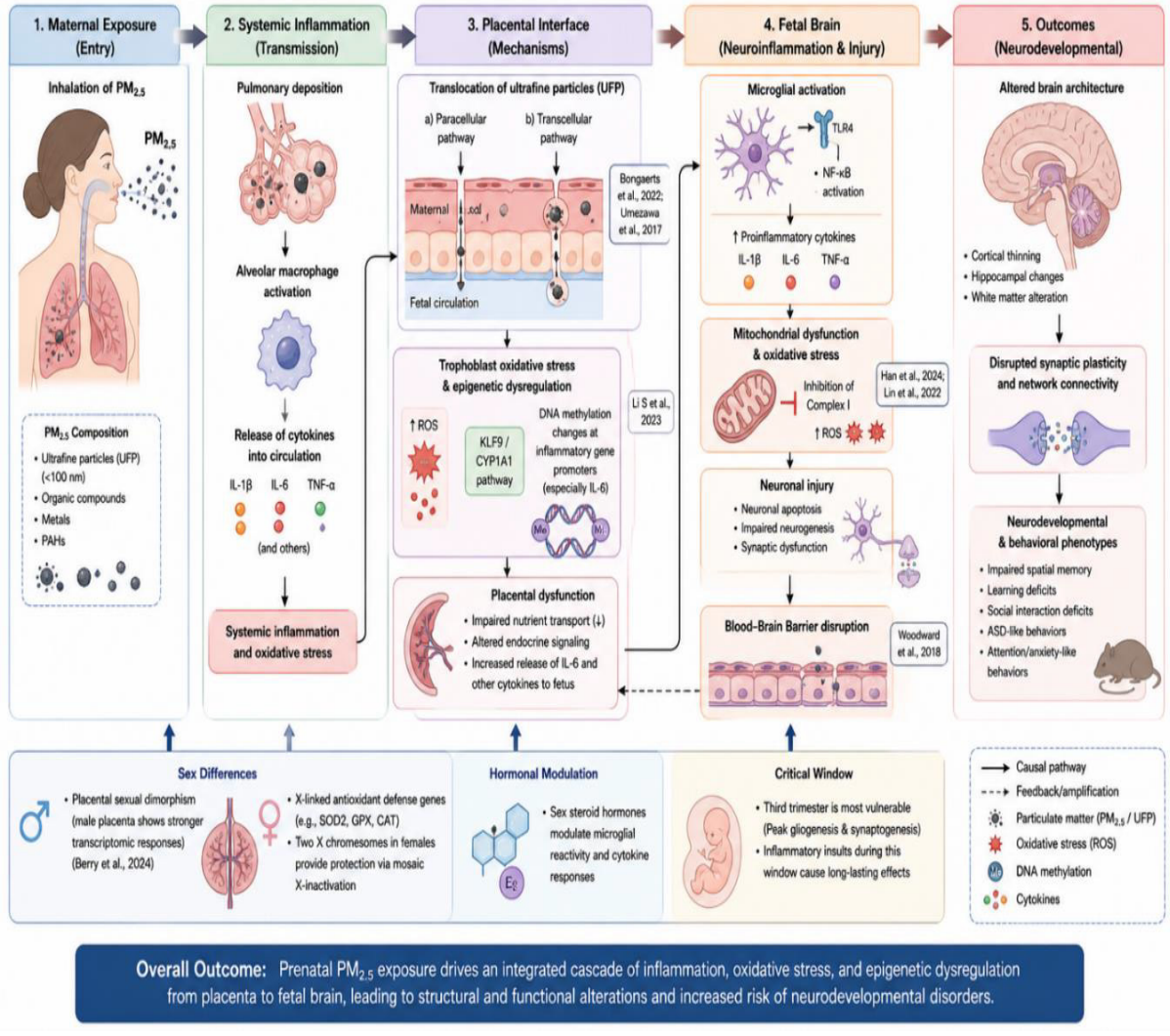

Fig. 4. Proposed mechanistic pathway linking prenatal $PM_{2.5}$ exposure with fetal neuroinflammation

Policy and clinical implications

Three implications emerge from this synthesis, calibrated to the GRADE certainty of the underlying evidence. First, the magnitude and consistency of effect at environmentally plausible doses in animal and cellular models, together with directionally consistent (though attenuated) human cohort evidence, are biologically plausible and policy-relevant. They provide supporting groundsalongside the broader epidemiological literature for continued regulatory tightening aligned with WHO 2021 $PM_{2.5}$ guidelines (5 µg/m³ annual mean), recognising that current US EPA NAAQS (9 µg/m³) and EU directive limits (10 µg/m³) remain above this threshold. This synthesis alone is insufficient to conclude that regulatory thresholds are causally responsible for developmental harm, but it materially strengthens the biological plausibility argument. Second, the sex- and trimester-specific findings support pregnancy-stage-tailored exposure mitigation: third-trimester counselling on indoor air quality, HEPA filtration, and N95 respirator use during high-pollution episodes is biologically warranted and carries low risk of harm. Third, the mechanistic prominence of NRF2-regulated antioxidant defenses and glutathione provides a rationale for exploring antioxidant-rich dietary recommendations and folate sufficiency, but interventional trials are required before clinical recommendation is appropriate.

The disproportionate exposure burden borne by socioeconomically disadvantaged communities [56, 57] compounds biological vulnerability with environmental injustice. Policy responses must therefore extend to zoning reform, traffic-related pollution control near maternal–child health facilities, and targeted public health communication in high-burden communities.

Research priorities

Seven priority research directions are identified. (1) Prospective placental multi-omics: longitudinal collection of maternal serum, placental tissue (at delivery), and cord blood with transcriptomic, methylomic, and proteomic profiling, linked to validated neurodevelopmental outcomes at ages 2, 5, and 10 years. (2) Sex-balanced study design: elimination of male-only animal experiments and adequate powering for sex-stratified analysis in human cohorts. (3) Trimester-resolved personal exposure monitoring: integration of personal monitors, satellite-derived estimates, and time-activity diaries. (4) $PM_{2.5}$ chemical speciation: systematic characterisation of metal, PAH, and biological constituent profiles to identify the most neurotoxic components [58, 59]. (5) Combined exposure paradigms: investigation of $PM_{2.5}$ interactions with maternal stress, infection, and gestational comorbidities [41]. (6) Antioxidant and anti-inflammatory intervention trials: pre-registered randomised trials of NRF2 activators, omega-3 fatty acids, and folate supplementation in high-exposure pregnancies. (7) Validated peripheral biomarkers: development of non-invasive maternal blood signatures reflective of fetal-brain compartment effects.

Strengths and limitations

Strengths of this synthesis include (i) adherence to PRISMA 2020 and SWiM reporting standards with a pre-registered PROSPERO protocol; (ii) dual-reviewer extraction and risk-of-bias assessment with substantial inter-rater agreement ($\kappa = 0.78$); (iii) integration of cross-modality evidence under a unified conceptual framework; (iv) a tiered synthesis logic that quantitatively pools where data support pooling and applies SWiM where heterogeneity precludes it; (v) explicit separation of primary empirical studies from mechanistic reviews in PRISMA counts and quantitative pools; and (vi) GRADE-based certainty assessment adapted for mechanistic toxicology.

Several limitations warrant explicit acknowledgment. First, quantitative meta-analysis was feasible only for selected outcomes (IL-6, oxidative stress markers, TNF-α); many mechanistically important endpoints were synthesised only narratively. Second, the predominance of rodent evidence introduces translational uncertainty. Third, English-language restriction may under-represent research from high-exposure non-Anglophone regions. Fourth, $PM_{2.5}$ chemical heterogeneity across studies limits source-attribution analyses. Fifth, substantial variability in $PM_{2.5}$ exposure assessment methods across the included studies may have contributed to between-study heterogeneity. Exposure assessment ranged from ambient air monitoring stations and satellite-based estimates in human cohort studies to Concentrated Ambient Particles (CAP), diesel exhaust particles, laboratory-generated $PM_{2.5}$, and controlled in vitro exposure systems in experimental models. Differences in exposure metrics, particle composition, duration, and dose may influence biological responses and should therefore be considered when interpreting pooled estimates. Sixth, residual confounding by co-pollutants cannot be excluded in human cohort evidence. Seventh, the methodological note regarding the dual application of DL (for weights) and REML (for τ^2) in the meta-analysis should be transparently reported in any derivative work.

Conclusion

Prenatal exposure to $PM_{2.5}$ induces a quantitatively large and mechanistically convergent perturbation of fetal brain inflammation and oxidative stress, with pooled standardized mean differences of 1.21–1.47 in homogeneous rodent and cellular evidence clusters. Effects are amplified in male offspring and following late-gestation exposure. The maternal–placental–fetal axis operating through TLR4/NF-κB-driven microglial activation, mitochondrial-oxidative damage, and epigenetic dysregulation of inflammatory loci provides a biologically coherent mechanism consistent across animal, cellular, and human evidence streams.

The systematic attenuation of effect in maternal serum biomarker studies relative to fetal-compartment measurements indicates that maternal blood is a poor surrogate for fetal exposure response, with major implications for future cohort design. GRADE certainty in the inflammatory and oxidative pathways is moderate; certainty in placental–epigenetic mediation and sex-specific vulnerability remains low, pending dedicated sex-balanced longitudinal multi-omic investigations.

These findings are biologically plausible and policy-relevant: they provide supporting evidence for continued tightening of regulatory $PM_{2.5}$ standards towards WHO 2021 guidelines, for pregnancy-stage-tailored exposure mitigation strategies, and for pre-registered trials of antioxidant and anti-inflammatory interventions in high-exposure populations. Further mechanistic refinement particularly for placental–epigenetic and sex-divergent pathways should proceed as a complement to, not a precondition for, evidence-based regulatory and clinical action calibrated to current certainty levels.

Financial supports

This research received no external funding.

Competing interests

The authors declare no conflicts of interest related to this study.

Acknowledgements

The authors would like to thank all researchers

and institutions whose studies contributed to this systematic review and meta-analysis. The authors also acknowledge the support of the Department of Midwifery and the Department of Environmental Health, Ministry of Health Polytechnic of Banjarmasin, Indonesia, for academic support during the preparation of this manuscript.

Ethical Considerations

Ethical issues (including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

References

1. Yang X, Zhang T, Zhang Y, Chen H, Sang S. Global burden of COPD attributable to ambient $PM_{2.5}$ in 204 countries and territories, 1990 to 2019: A systematic analysis for the Global Burden of Disease Study 2019. Science of the Total Environment 2021;796. https://doi.org/10.1016/j.scitotenv.2021.148819.

2. Rentschler J, Leonova N. Global air pollution exposure and poverty. Nat Commun 2023;14. https://doi.org/10.1038/s41467-023-39797-4.

3. Wasi'Ah NR, Iriana W, Ramadhina SQ. Comparison of Fine Particulate Matter ($PM_{2.5}$) in Urban Areas Southeast Asia in Compliance with WHO Guidelines. IOP Conf. Ser. Earth Environ. Sci., vol. 1448, 2025. https://doi.org/10.1088/1755-1315/1448/1/012009.

4. Northeim K, Oppong JR. Mapping Health Fragility and Vulnerability in Air Pollution–Monitoring Networks in Dallas–Fort Worth. Int J Environ Res Public Health 2023;20. https://doi.org/10.3390/ijerph20031807.

5. Ernawati KK. Environmental Inequities and Global Health: Bridging the Gap in Vulnerable Communities. Innovation and Transformation of Public Health, 2025, p. 85–112. https://doi.org/10.4018/979-8-3373-1992-6.ch003.

6. Parikh G, Patel B. From exposure to outcomes: How air pollutants impact maternal and foetal health. Reproductive Toxicology 2025;138. https://doi.org/10.1016/j.reprotox.2025.109080.

7. Rahnemaei FA, Aghapour E, Asgharpoor H, Ardabili NS, Kashani ZA, Abdi F. Prenatal exposure to ambient air pollution and risk of fetal overgrowth: Systematic review of cohort studies. Ecotoxicol Environ Saf 2024;280. https://doi.org/10.1016/j.ecoenv.2024.116526.

8. Li L, Zhang X. The causal impact of fetal exposure to $PM_{2.5}$ on birth outcomes: Evidence from rural China. Econ Hum Biol 2024;53. https://doi.org/10.1016/j.ehb.2024.101380.

9. Girardi P, Mastromatteo LY, Lanfranchi S, Scrimin S. Modeling the effects of prenatal $PM_{2.5}$ exposure on development of school-aged children using functional regression. Environmental Pollution 2026;402. https://doi.org/10.1016/j.envpol.2026.128312.

10. Xu M-X, Zhu Y-F, Chang H-F, Liang Y. Nanoceria restrains $PM_{2.5}$-induced metabolic disorder and hypothalamus inflammation by inhibition of astrocytes activation related NF-κB pathway in Nrf2 deficient mice. Free Radic Biol Med 2016;99:259–72. https://doi.org/10.1016/j.freeradbiomed.2016.08.021.

11. Shang Y, Wang H, Huang J, An J, Ren G, Wang Y, et al. Acetylcholine mediates nitro-PAHs induced inflammation and ameliorates the abnormalities in blood-brain barrier related proteins. Ecotoxicol Environ Saf 2025;305. https://doi.org/10.1016/j.ecoenv.2025.119173.

12. Ragusa A, Re A Lo, Segata M, Rinaldo D, la Motta G, De Vito M, et al. The Placenta and the Development of Human Health. Rare Diseases of the Immune System, vol. Part F1038, 2025,

p. 57–75. https://doi.org/10.1007/978-3-032-02902-7_5.

13. Yong HEJ, Chan SY, Chakraborty A, Rajaraman G, Ricardo S, Benharouga M, et al. Significance of the placental barrier in antenatal viral infections. Biochim Biophys Acta Mol Basis Dis 2021;1867. https://doi.org/10.1016/j.bbadis.2021.166244.

14. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. Bmj 2021;372:n71. https://doi.org/10.1136/bmj.n71.

15. Campbell M, McKenzie JE, Sowden A, Katikireddi SV, Brennan SE, Ellis S, et al. Synthesis without meta-analysis (SWiM) in systematic reviews: Reporting guideline. The BMJ 2020;368:l6890. https://doi.org/10.1136/bmj.l6890.

16. Stroup DF. Meta-analysis of Observational Studies in Epidemiology. JAMA 2000;283:2008. https://doi.org/10.1001/jama.283.15.2008.

17. Hooijmans CR, Rovers MM, De Vries RBM, Leenaars M, Ritskes-Hoitinga M, Langendam MW. SYRCLE's risk of bias tool for animal studies. BMC Med Res Methodol 2014;14:43. https://doi.org/10.1186/1471-2288-14-43.

18. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev 2016;5:210. https://doi.org/10.1186/s13643-016-0384-4.

19. Drevon D, Fursa SR, Malcolm AL. Intercoder Reliability and Validity of WebPlotDigitizer in Extracting Graphed Data. Behav Modif 2017;41:323–39. https://doi.org/10.1177/0145445516673998.

20. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016:i4919. https://doi.org/10.1136/bmj.i4919.

21. Schneider K, Schwarz M, Burkholder I, Kopp-Schneider A, Edler L, Kinsner-Ovaskainen A, et al. "ToxRTool", a new tool to assess the reliability of toxicological data. Toxicol Lett 2009;189:138–44. https://doi.org/10.1016/j.toxlet.2009.05.013.

22. Veroniki AA, Jackson D, Viechtbauer W, Bender R, Bowden J, Knapp G, et al. Methods to estimate the between-study variance and its uncertainty in meta-analysis. Res Synth Methods 2016;7:55–79. https://doi.org/10.1002/jrsm.1164.

23. Borenstein M, Hedges L V, Higgins JPT, Rothstein HR. Introduction to Meta-Analysis. Wiley; 2021.

24. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. Br Med J 1997;315:629–34. https://doi.org/10.1136/bmj.315.7109.629.

25. Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 2000;56:455–63. https://doi.org/10.1111/j.0006-341X.2000.00455.x.

26. Viechtbauer W. Conducting meta-analyses in R with the metafor. J Stat Softw 2010;36:1–48. https://doi.org/10.18637/jss.v036.i03.

27. Morgan RL, Thayer KA, Santesso N, Holloway AC, Blain R, Eftim SE, et al. A risk of bias instrument for non-randomized studies of exposures: A users' guide to its application in the context of GRADE. Environ Int 2019;122:168–84. https://doi.org/10.1016/j.envint.2018.11.004.

28. Mendoza-Ortega JA, Canul-Euan A, Perichart-Perera O, Solis-Paredes JM, Martínez-Medina S, Torres-Calapiz M, et al. Trimester-Specific Air Pollutant Exposure During Pregnancy and Infant Neurodevelopment at One Year: Insights into the Role of Inflammation and Oxidative Stress.

Applied Sciences 2025;15:9753. https://doi.org/10.3390/app15179753.

29. Peterson BS, Bansal R, Sawardekar S, Nati C, Elgabalawy ER, Hoepner LA, et al. Prenatal exposure to air pollution is associated with altered brain structure, function, and metabolism in childhood. Journal of Child Psychology and Psychiatry 2022;63:1316–31. https://doi.org/10.1111/jcpp.13578.

30. Lin CH, Nicol CJB, Wan C, Chen SJ, Huang RN, Chiang MC. Exposure to $PM_{2.5}$ induces neurotoxicity, mitochondrial dysfunction, oxidative stress and inflammation in human SH-SY5Y neuronal cells. Neurotoxicology 2022;88:25–35. https://doi.org/10.1016/j.neuro.2021.10.009.

31. Han Y, Yu Z, Chen Y, Guo X, Liu Y, Zhang H, et al. $PM_{2.5}$ induces developmental neurotoxicity in cortical organoids. Environmental Pollution 2024;361:124913. https://doi.org/10.1016/j.envpol.2024.124913.

32. Zhang L, Xu F, Yang Y, Yang L, Wu Q, Sun H, et al. $PM_{2.5}$ exposure upregulates pro-inflammatory protein expression in human microglial cells via oxidant stress and TLR4/NF-κB pathway. Ecotoxicol Environ Saf 2024;277:116386. https://doi.org/10.1016/j.ecoenv.2024.116386.

33. Liu Y, Li S, Liu B, Zhang J, Wang C, Feng L. Maternal urban particulate matter (SRM 1648a) exposure disrupted the cellular immune homeostasis during early life: The potential attribution of altered placental transcriptome profile. Science of the Total Environment 2024;912. https://doi.org/10.1016/j.scitotenv.2023.169432.

34. Li S, Li L, Zhang C, Fu H, Yu S, Zhou M, et al. $PM_{2.5}$ leads to adverse pregnancy outcomes by inducing trophoblast oxidative stress and mitochondrial apoptosis via KLF9/CYP1A1 transcriptional axis. Elife 2023;12:1–35. https://doi.org/10.7554/eLife.85944.

35. Li J, Kong Y, Guo Z, Qu L, Zhang Z, Qu Z, et al. Maternal exposure to particulate matter from duck houses restricts fetal growth due to inflammatory damage and oxidative stress. Ecotoxicol Environ Saf 2024;273:116114. https://doi.org/10.1016/j.ecoenv.2024.116114.

36. Liang XT, Han CL, Lin BC, Shi Y, Xie XQ, Li K, et al. Effects of early life $PM_{2.5}$ exposure on prefrontal cortex of offspring male rats. Zhongguo Ying Yong Sheng Li Xue Za Zhi 2022;38:1–5. https://doi.org/10.12047/j.cjap.6222.2022.001.

37. Yang Y, Yang T, Zhou J, Cao Z, Liao Z, Zhao Y, et al. Prenatal exposure to concentrated ambient $PM_{2.5}$ results in spatial memory defects regulated by DNA methylation in male mice offspring. Environmental Science and Pollution Research 2022;30:35142–52. https://doi.org/10.1007/s11356-022-24663-5.

38. Zheng X, Wang X, Wang T, Zhang H, Wu H, Zhang C, et al. Gestational Exposure to Particulate Matter 2.5 ($PM_{2.5}$) Leads to Spatial Memory Dysfunction and Neurodevelopmental Impairment in Hippocampus of Mice Offspring. Front Neurosci 2019;12. https://doi.org/10.3389/fnins.2018.01000.

39. Rahmatinia M, Mohseni-Bandpei A, Khodagholi F, Abdollahifar M-A, Amouei Torkmahalleh M, Hassani Moghaddam M, et al. Exposure to different $PM_{2.5}$ extracts induces gliosis and changes behavior in male rats similar to autism spectrum disorders features. Environmental Pollution 2024;340:122804. https://doi.org/10.1016/j.envpol.2023.122804.

40. Berry A, Musillo C, Ajmone-Cat MA. Maternal stress disrupts placental proteome and fetal brain development in a sex-dependent manner. Res Sq 2024. https://doi.org/10.21203/rs.3.rs-5417536/v1.

41. Tamayo JM, Osman HC, Schwartzer JJ, Pinkerton KE, Ashwood P. Characterizing the neuroimmune environment of offspring in a

novel model of maternal allergic asthma and particulate matter exposure. J Neuroinflammation 2023;20:252. https://doi.org/10.1186/s12974-023-02930-7.

42. Wu C-T, Wu T-S, Ku M-S. The Impact of Fine Particulate Matter on Embryonic Development. Int J Mol Sci 2024;25:6399. https://doi.org/10.3390/ijms25126399.

43. Akhtar F, Rouse CA, Catano G, Montalvo M, Ullevig SL, Asmis R, et al. Acute maternal oxidant exposure causes susceptibility of the fetal brain to inflammation and oxidative stress. J Neuroinflammation 2017;14:195. https://doi.org/10.1186/s12974-017-0965-8.

44. Woodward NC, Haghani A, Johnson RG, Hsu TM, Saffari A, Sioutas C, et al. Prenatal and early life exposure to air pollution induced hippocampal vascular leakage and impaired neurogenesis in association with behavioral deficits. Transl Psychiatry 2018;8:261. https://doi.org/10.1038/s41398-018-0317-1.

45. Morris RH, Counsell SJ, McGonnell IM, Thornton C. Early life exposure to air pollution impacts neuronal and glial cell function leading to impaired neurodevelopment. BioEssays 2021;43. https://doi.org/10.1002/bies.202000288.

46. Haghani A, Feinberg JI, Lewis KC, Ladd-Acosta C, Johnson RG, Jaffe AE, et al. Cerebral cortex and blood transcriptome changes in mouse neonates prenatally exposed to air pollution particulate matter. J Neurodev Disord 2021;13:1–12. https://doi.org/10.1186/s11689-021-09380-3.

47. Park S, Kwon E, Lee G, You Y-A, Kim SM, Hur YM, et al. Effect of Particulate Matter 2.5 on Fetal Growth in Male and Preterm Infants through Oxidative Stress. Antioxidants 2023;12:1916. https://doi.org/10.3390/antiox12111916.

48. Morris RH, Counsell SJ, McGonnell IM, Thornton C. Exposure to urban particulate matter (UPM) impairs mitochondrial dynamics in BV2 cells, triggering a mitochondrial biogenesis response. J Physiol 2024;602:2737–50. https://doi.org/10.1113/JP285978.

49. Thomas J, Harden A. Methods for the thematic synthesis of qualitative research in systematic reviews. BMC Med Res Methodol 2008;8:45. https://doi.org/10.1186/1471-2288-8-45.

50. Barker DJP. The origins of the developmental origins theory. J Intern Med 2007;261. https://doi.org/10.1111/j.1365-2796.2007.01809.x.

51. Estes ML, McAllister AK. Maternal immune activation: Implications for neuropsychiatric disorders. Science (1979) 2016;353:772–7. https://doi.org/10.1126/science.aag3194.

52. Cory-Slechta DA, Merrill A, Sobolewski M. Air Pollution-Related Neurotoxicity Across the Life Span. Annu Rev Pharmacol Toxicol 2023;63:143–63. https://doi.org/10.1146/annurev-pharmtox-051921-020812.

53. Blanco-Hinojo L, Pujol J, Martínez-Vilavella G, Gómez-Herrera L, Rivas I, Gómez-Roig MD, et al. Impact of prenatal exposure to airborne particulate matter on local functional connections in the cerebral cortex of neonates. Neuroimage 2026;332. https://doi.org/10.1016/j.neuroimage.2026.121911.

54. Shang M, Tang M, Xue Y. Neurodevelopmental toxicity induced by airborne particulate matter. Journal of Applied Toxicology 2023;43:167–85. https://doi.org/10.1002/jat.4382.

55. Yan R, Ma D, Liu Y, Wang R, Fan L, Yan Q, et al. Developmental Toxicity of Fine Particulate Matter: Multifaceted Exploration from Epidemiological and Laboratory Perspectives. Toxics 2024;12:274. https://doi.org/10.3390/toxics12040274.

56. Zhou D, Du M, Luo H, Ran F, Zhao X, Dong Y, et al. Multifunctional mesoporous silica-cerium oxide nanozymes facilitate miR129 delivery for high-quality healing of radiation-induced skin injury. J Nanobiotechnology 2022;20:419.

https://doi.org/10.1186/s12951-022-01620-5.

57. Gakii Murithi R. Prenatal Exposure to Airborne and Indoor Pollutants and the Risk of Childhood Neurodevelopmental Disorders. Journal of Anesthesia & Pain Medicine 2025;10:01–13. https://doi.org/10.33140/JAPM.10.03.02.

58. Potter NA, Meltzer GY, Avenbuan ON, Raja A, Zelikoff JT. Particulate Matter and Associated Metals: A Link with Neurotoxicity and Mental Health. Atmosphere (Basel) 2021;12:425. https://doi.org/10.3390/atmos12040425.

59. Xia J. Neurotoxic Effects of $PM_{2.5}$: Mechanisms, Evidence, and Public Health Implications. Theoretical and Natural Science 2025;128:119–26. https://doi.org/10.54254/2753-8818/2025.au26577.