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Small extracellular vesicles: connecting early life exposure outcomes to air pollution during pregnancy to early childhood health

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Abstract
Exposure to air pollution poses a serious threat to maternal and child health, particularly during critical developmental periods. Extracellular vesicles (EVs), as key mediators of intercellular communication, have emerged as a novel mechanism through which environmental exposures, including air pollutants, exert systemic effects. This review synthesizes current evidence on the role of small EVs (sEVs) in mediating the biological impacts of prenatal air pollution exposure, with a focus on their molecular profile, including the presence of signaling molecules like miRNAs and proteins, and their implications for childhood health outcomes. In this review, we explore mechanisms involving sEVs in transplacental exposure, signaling and epigenetic modifications, linking exposure to adverse developmental and health effects in early life. Furthermore, we highlight the potential of sEVs as biomarkers for exposure assessment and predictors of adverse health outcomes. Relevant studies were identified through a comprehensive literature search and systematic review of experimental and epidemiological evidence. By integrating insights from toxicology, epidemiology, and molecular biology, we identify specific needs for further research into sEVs, both as mechanistic mediators and diagnostic tools for air pollution-related health risks.

Keywords Exosomes, Particulate Matter, Oxidative Stress, Inflammation, Neurodevelopment, Cardiovascular Dysfunction

Introduction

Air pollution, consisting of particles, toxic gases, and vapors from both anthropogenic and natural sources, represents a significant health risk, with evidence suggesting that even low-level exposures can have adverse effects [1, 2]. Ambient air pollution is the leading environmental driver of disease and mortality [3]. Indoor air pollution (IAP) is second. IAP often comes from burning solid biomass fuels, including agricultural byproducts, animal waste, charcoal, and coal [3]. In high-income countries, IAP from residential gas use has measurable health impacts: one attributable-fraction study estimates that 12.7% of U.S. childhood asthma is linked to kitchen NO_2 from gas stoves [4]. A randomized crossover trial replacing gas with induction cooktops lowered

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24-h mean indoor NO_2 by 56% and $PM_{2.5}$ by 35% [5]; and laboratory and in-home measurements show benzene emissions during gas cooking at levels that can double children's lifetime leukaemia risk in poorly ventilated dwellings [6].

Air pollution exposure is linked to many harms. These include respiratory diseases and systemic conditions such as cardiovascular disease and diabetes. Specifically, short-term exposure is strongly linked to acute respiratory complications, while long-term exposure contributes to the development of chronic diseases, including diabetes, cardiovascular disorders, and increased mortality [7, 8]. The World Health Organization (WHO) identifies particulate matter (PM), Black Carbon (BC), tropospheric ozone (O_3), carbon monoxide (CO), sulfur dioxide (SO_2), nitrogen oxides (NO_x), as major atmospheric contaminants contributing to health risks [9]. Particulate matter (PM) is categorized by aerodynamic diameter, from $PM_{0.1}$ to PM_{10}, which $PM_{0.1}$ and $PM_{2.5}$ can penetrate deep into the lungs and enter the bloodstream. Because of this, they can affect multiple organ systems [10, 11]. Early-life exposure to air pollutants during critical developmental periods (i.e. during gestation that will impact the mother and getus) can have lasting and profound effects on health in childhood and adulthood. Such exposures have been linked to adverse birth outcomes, as well as increased risks of developing chronic diseases and neurodevelopmental issues later in life [12, 13].

Emerging evidence suggests that extracellular vesicles (EVs), membrane-bound nanoparticles secreted by nearly all cell types, play an important role in mediating biological responses to air pollution during pregnancy [14]. Among these, small extracellular vesicles (sEVs) (< 200 nm) are particularly relevant because of their roles in inflammation, immune modulation, and tissue remodeling [15, 16], and their ability to cross biological barriers such as the placental barrier and the blood–brain barrier [17, 18]. SEVs carry proteins, nucleic acids, lipids, metabolites, and small molecules that can influence cellular function at both local and distant sites [19, 20]. SEV surface molecules (membrane-bound/external) and cargo (intraluminal) both determine biological effects. The surface controls tropism and uptake. The cargo drives downstream signaling [21–23]. SEV characteristics reflect the physiological or pathological state of their cell of origin and can be altered by environmental stressors, including air pollution [24].

Terminology considerations. The nomenclature for EVs remains a source of confusion. According to the MISEV 2023 guidelines [23], EVs are broadly classified by size into small EVs (< 200 nm) and medium/large EVs (> 200 nm). Within the sEV category, exosomes are a specific subtype generated via the endosomal pathway, whereas small ectosomes bud directly from the plasma membrane. In practice, however, most primary studies included in this review identify their vesicles based on size, density, and marker expression, criteria sufficient for classification as sEVs but insufficient to confirm exosomal origin. Many cited studies call their vesicles "exosomes." In this review, we use the broader, MISEV-aligned term "sEV." We keep the original wording only in direct quotes. This approach preserves terminological precision and still acknowledges the source literature. sEVs are secreted via complex biogenesis pathways involving the endosomal sorting complexes required for transport (ESCRT) machinery, lipid-mediated processes, and calcium-dependent membrane fusion events [25–27]. Other EV subtypes include microvesicles (measuring 100–1000 nm, generated by outward budding of the plasma membrane) [28] and apoptotic bodies (500–5000 nm which are released during cell death and containing nuclear and organelle components) [29]. After release, sEVs bind receptors, fuse directly with membranes, or enter via endocytosis. Endocytic routes include clathrin-mediated endocytosis and macropinocytosis [30, 31].

This review evaluates how sEVs mediate the effects of maternal air-pollution exposure during pregnancy. We focus on fetal development and long-term health outcomes.. We explore mechanisms by which sEVs may transport pollutants and their molecular signatures across biological barriers, modulate placental and fetal tissue responses, and influence developmental trajectories. Drawing on current evidence regarding sEV miRNA and protein cargo, we highlight their dual role as mechanistic mediators and promising non-invasive biomarkers of pollution-related effects. Despite increasing evidence that maternal exposure to air pollution alters sEV biogenesis, their cargo and signaling functions, the precise pathways linking these changes to adverse pregnancy and child health outcomes remain poorly defined. This gap limits our ability to identify early biomarkers for at-risk pregnancies. Given that sEVs circulate in accessible biofluids and carry molecular signatures of their tissue of origin, in depth studies on sEV from liquid biopsis represents a promising avenue for early detection and monitoring of adverse outcomes. Moreover, it is expected to provide mechanistic links between environmental exposures and neurodevelopmental health risks, thus supporting the design of both preventive and therapeutic strategies.

Methods

Search strategy and study selection

We conducted a comprehensive literature search across PubMed, Scopus, and Web of Science to identify relevant studies. The search strategy combined keywords and Boolean operators to capture the topic's scope, as follows: ("air pollution" OR "ambient air pollution" OR

"traffic-related air pollution" OR TRAP OR smog OR "particulate matter" OR PM2.5 OR PM10 OR "fine particle*" OR "ultrafine particle*" OR UFP OR UFPs OR "diesel exhaust" OR "black carbon" OR BC OR soot) AND ("extracellular vesicle*" OR "small extracellular vesicle*" OR exosome* OR EV OR EVs OR sEV OR sEVs) AND (pregnancy OR pregnant OR prenatal OR antenatal OR perinatal OR gestation OR gestational OR "in utero" OR maternal OR "maternal exposure" OR mother* OR fetus OR fetal OR "fetal development" OR "fetal growth" OR intrauterine OR placent* OR trophoblast* OR "cord blood" OR neonate* OR newborn* OR infant* OR infancy OR "early life" OR "early childhood" OR child*). No date restrictions were applied and all publication years up to the search date were eligible, and results were limited to English-language publications. The database search initially retrieved 523 records. After removing duplicates and screening titles and abstracts, 31 studies met the inclusion criteria and were retained for qualitative synthesis. The included studies are clearly indicated in the supplementary table. We also performed manual snowballing by examining the reference lists of key papers, but no additional eligible studies were identified.

Inclusion and exclusion criteria

Inclusion criteria

We included peer-reviewed original studies that investigated the role of sEVs (including exosomes) in mediating the effects of air pollution exposure, including PMs and gaseous pollutants (O_3, NO_2, SO_2, CO) under the umbrella term 'ambient air pollution,' during pregnancy and measurable effects on fetal or early childhood health outcomes. Eligible study designs included in vitro cell-based experiments, in vivo animal models, and human (clinical or epidemiological) research, provided they examined how maternal or early-life exposure to ambient pollutants influenced sEV characteristics or functions relevant to development or health. We focused on studies that offered mechanistic insight into sEV-mediated pathways (e.g. changes in sEV cargo, signaling, or release) linking maternal exposure to air pollutants to outcomes in the placenta, fetus, or early childhood.

Exclusion criteria

Studies were excluded if they did not report original data or did not specifically assess EVs in the context of air pollution exposure. We excluded publications that lacked any mechanistic EV data (e.g., studies on air pollution and pregnancy outcomes without assessing EVs or their cargo were not included given this review's mechanistic focus). Similarly, studies focusing on exposures outside the scope of air pollution (e.g., unrelated environmental toxicants) or on vesicle types unrelated to sEVs, such as larger apoptotic bodies or microvesicles not categorized as small EVs, were omitted. Non-English articles, conference abstracts, and other non-peer-reviewed reports were not considered. In cases where relevance was unclear, the authors reached consensus to determine eligibility, ensuring that all included studies directly pertained to sEVs as mediators of pollution-related effects on prenatal or early childhood health.

Data extraction and organization

All information from the included articles was extracted and organized using Mendeley (reference management software). The final set of included studies was imported into Mendeley to facilitate data management, and duplicate references were removed during the initial selection process. For each included study, we catalogued key details such as the study design (in vitro, animal, or human), characteristics of the exposure (type of air pollutant and exposure conditions), the source and type of EVs examined (e.g., placental exosomes, maternal plasma sEVs, cord blood sEVs, cell culture-derived vesicles), and the main findings relevant to the review.

To aid in analysis, the studies were categorized on multiple axes. First, we grouped studies by their experimental approach: separating in vitro mechanistic studies, in vivo (animal) studies, and human observational studies. Within these categories, we further sorted studies by the type of pollutant exposure investigated, for example, particulate matter (PM2.5, PM10, ultrafine particles), traffic-related or household air pollution, specific chemical constituents like heavy metals (e.g. cadmium) or Polycyclic Aromatic Hydrocarbons (PAHs), and mixed pollutant exposure scenarios. We also noted the primary outcomes or endpoints reported: for instance, alterations in sEV cargo composition (such as changes in miRNA or protein content), differences in sEV release or concentration, and any observed links to biological or health outcomes in the offspring such as (i) perinatal biomarkers, birth weight, gestational age, and epigenetic marks in placental or cord-blood tissues; and (ii) early-childhood health measures, including anthropometry and growth trajectories, physician-diagnosed wheeze/asthma, lung-function z-scores, blood pressure, systemic inflammatory or immune markers, and neuro-cognitive or motor developmental indices such as Bayley or Ages & Stages scores. Storing these categories as custom tags in Mendeley allowed systematic comparison of findings and rapid recognition of recurring patterns. This multi-dimensional categorization in Mendeley allowed us to efficiently compare findings across studies and extract recurring patterns.

The extracted data were qualitatively synthesized. We compared findings across experimental, clinical, and epidemiological designs to evaluate whether, and to what extent, the evidence converges or diverges on a role for

sEVs in mediating the effects of early-life air-pollution exposure. By organizing the literature in this manner, we highlight both the mechanisms repeatedly observed across study types and the areas where results remain inconsistent or scarce.

Results

Air pollution and early life exposure

Emerging evidence suggests that air pollutants may further disrupt fetal development by altering the biogenesis and cargo of sEVs, which are critical for intercellular communication [32, 33]. Exposure to environmental pollutants, including PM and its constituents such as heavy metals (e.g., cadmium) and organic compounds (e.g., PAHs), can induce alterations in the composition of sEVs [34, 35] These changes may disrupt the transfer of essential biomolecules, proteins, lipids, and nucleic acids, thereby interfering with critical immune, neurological, and metabolic signaling pathways during fetal development. [33, 36, 37]. Such perturbations can increase the risk of both immediate developmental complications and long-term health issues. Recent cohort and meta-analytic evidence demonstrates that prenatal and early-life exposure to ambient air pollution is associated with lasting child health outcomes. For respiratory health, higher early-life $PM_{2.5}$ and NO_2 concentrations were associated with increased incidence of physician-diagnosed asthma through childhood in the U.S. ECHO-CREW consortium, and greater prenatal $PM_{2.5}$ exposure was linked to lower school-age lung function in the Swiss LUIS study, consistent with impaired lung growth from in-utero exposure [38, 39]. A meta-analysis links prenatal PM exposure to higher childhood blood pressure, and trajectory studies show that greater prenatal urban exposures, including air pollution, predict faster rises in diastolic BP from childhood to early adulthood [40, 41]. Neurodevelopment and growth outcomes show similar patterns. A 2024 systematic review and meta-analysis quantified an exposure–response relationship between $PM_{2.5}$ and child cognition, with the strongest decrements in performance IQ, and a large prospective cohort (~47,600 mother–child pairs) linked prenatal $PM_{2.5}$ to altered BMI growth trajectories up to age six, suggesting lasting impacts on somatic growth [42, 43]. Additionally, studies have shown that exposure to cadmium during pregnancy is associated with adverse birth outcomes, including reduced birth weight and impaired placental function [44]. Similarly, exposure to PAHs has been linked to increased production of sEVs and potential developmental toxicity [35]. Therefore, it is crucial to investigate the mechanistic roles of sEVs in mediating these pollutant-induced effects during fetal organ development.

Air pollution toxicity and sEVs

Exposure to environmental air pollutants triggers a multifaceted cascade of cellular responses that markedly affect the formation, secretion, and molecular composition of sEVs [33]. Air pollutants can inflict a range of cellular injuries by inducing the endoplasmic reticulum (ER) stress, promoting the accumulation of misfolded proteins [45] and causing DNA damage that can initiate repair mechanisms, enforce cell cycle arrest, or trigger apoptosis [46, 47]. Additional effects include the onset of cellular senescence [48, 49] and impairment of the immune system by disrupting signaling pathways, thereby increasing the risk of infections and autoimmune disorders, as well as provoking the release of inflammatory mediators by immune cells [50]. Some pollutants compromise the BBB, allowing toxic substances to enter the brain and potentially leading to neuronal damage, cell death, and neurodegeneration [51, 52]. Exposure to PM can also weaken the nasal epithelial barrier by reducing the expression of tight junction proteins and elevating pro-inflammatory cytokine levels [53].

Beyond these known effects, pollutant-induced cellular stress also profoundly influences sEV dynamics, enhancing their release and modifying their molecular cargo. These vesicles may carry stress-response proteins, cytokines, and regulatory RNAs, thereby transmitting toxic signals systemically. Such sEVs can reach distant organs, including the placenta, altering tissue function and contributing to adverse maternal and fetal outcomes [54, 55].

Air pollution and placenta

Placental cells include a diverse set of specialized cells such as trophoblasts (cytotrophoblasts and syncytiotrophoblasts (STBs)), endothelial cells, and mesenchymal stromal cells that work in concert to form the placenta, an organ essential for nutrient, gas, and waste exchange, and hormone production that modulates fetal growth and maternal adaptation during pregnancy [56]. A study using the HTR-8 trophoblast cell line examined the effects of $PM_{2.5}$ on placental cells [57]. It was found that $PM_{2.5}$ was internalized by the cells, accumulating in mitochondria and causing damage. Key disruptions included cytotoxicity, compromised membrane integrity, elevated protease activity, and hormonal imbalances with decreased human chorionic gonadotropin (hCG) and increased progesterone, which are believed to be affected by PAHs. Additionally, exposure may trigger an inflammatory response (reflected by Interleukin-6 (IL-6) secretion), oxidative stress, mitochondrial structural damage, and morphological changes. These findings suggest that $PM_{2.5}$ impairs cellular functions, hormone regulation, mitochondrial health, and cell viability, contributing to placental dysfunction and potential

pregnancy complications such as preeclampsia and intrauterine growth restriction (Fig. 1) [57, 58].

Throughout pregnancy, the syncytiotrophoblast serves as the primary source of placental sEVs, thereby facilitating maternal–fetal communication and adjusting maternal physiology to support the developing fetus [59]. These sEVs are central mediators of maternal–fetal communication. They deliver a specialized cargo not only to modulate maternal immune tolerance and promote angiogenesis and vascular remodeling but also to regulate trophoblast invasion, nutrient transport, and metabolic homeostasis [36]. Furthermore, emerging evidence indicates that these sEVs can influence fetal neurodevelopment and epigenetic programming [60, 61]. Placental sEV content, biogenesis, and release are tightly regulated by the placental microenvironment [62, 63]. For instance, studies have shown that trophoblast cells increase sEV production in response to hypoxic conditions or elevated glucose levels [64]. Similarly, maternal exposure to pollutants can perturb sEV generation and cargo loading through multiple mechanisms. Recent studies also indicate that maternal exposure to pollutants such as $PM_{2.5}$ can alter the quantity and content of these sEVs by activating oxidative and inflammatory pathways within placental cells [32]. For example, exposure to diesel exhaust particles has been shown to increase the expression of inflammatory cytokines and activate the NF-κB pathway, which influences sEV cargo loading [32, 65]. Such exposure also affects the expression of placental miRNAs involved in fetal growth and neurodevelopment, which are packaged into sEVs and transferred to both maternal and fetal compartments [66, 67].

These altered vesicles may carry damage-associated molecular patterns (DAMPs), apoptotic signals, or stress-responsive miRNAs such as miR-21 and miR-146a, which modulate immune and developmental pathways in the fetus [68]. The resulting changes may compromise placental vascular remodeling, nutrient delivery, and trophoblast invasion, potentially leading to complications like fetal growth restriction. [67–70] Syncytin-1–positive vesicles (a hallmark of syncytiotrophoblast origin) can package miRNAs with anti-inflammatory signatures.

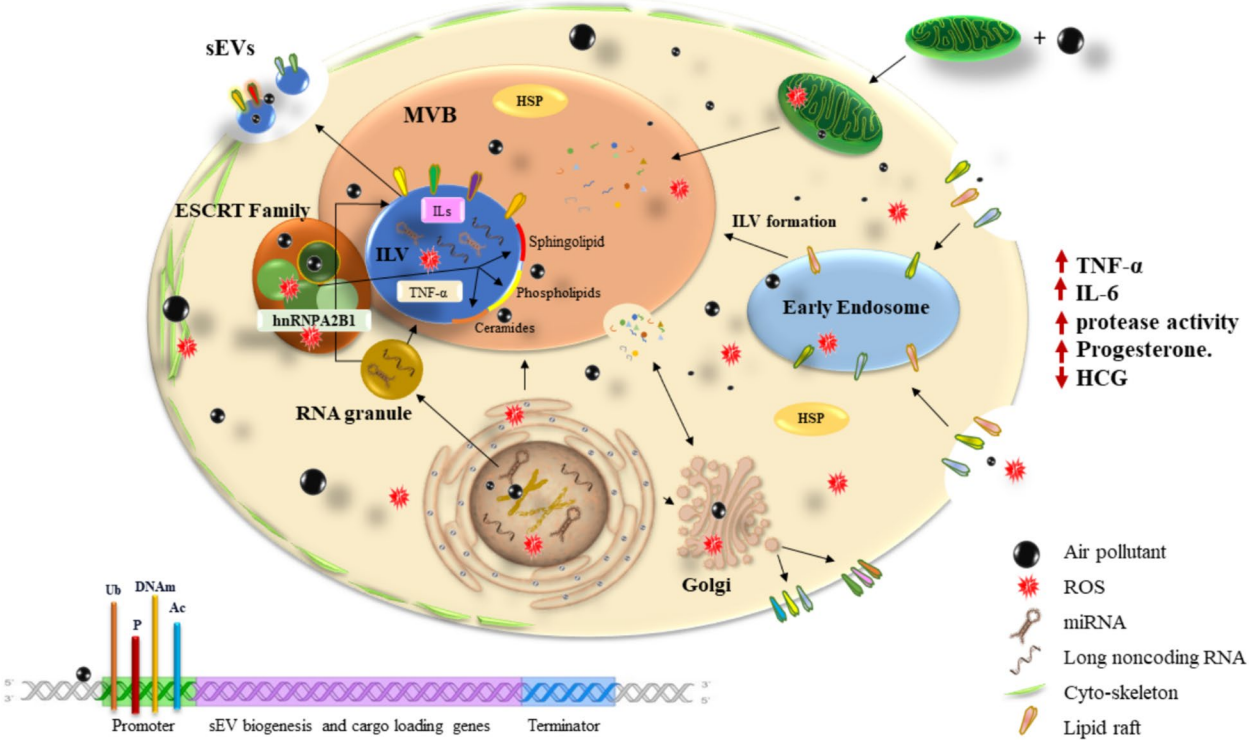

Fig. 1 Trophoblast cells exposure to air pollutants ($PM_{2.5}$) and effects on sEVs biogenesis. Small extracellular vesicle (sEV) formation begins with the inward budding of early endosomes, generating intraluminal vesicles (ILVs) within multivesicular bodies (MVBs). $PM_{2.5}$ accumulates in trophoblast cells and induces histone modifications, such as ubiquitination, phosphorylation, methylation, and acetylation, which alter gene expression and amplify cellular stress through cytokines like TNF-α, IL-6, and heat shock proteins (HSPs). Lipophilic air pollutants can modify sEV stability by directly attaching to the sEV surface, thereby changing the lipid profile of the sEV membrane and altering the redox balance of sEV cargo. Direct interactions with pollutants can also affect proteins like hnRNPA2B1, which influences selective miRNA loading and promotes cytoskeletal aggregation. Additionally, $PM_{2.5}$ causes mitochondrial damage, oxidative stress, and inflammation. Air pollutants can also cause deformation and swelling of mitochondria, further disrupting cellular function. Pollutants, including heavy metals and organic compounds, also impact hormonal balance and immune responses by altering levels of hCG, progesterone, and IL-6

During uncomplicated pregnancy, these Syncytin-1$^+$ vesicles have been reported to attenuate pro-inflammatory signaling, suggesting a physiological buffering mechanism that may partially counteract air-pollution–related inflammatory stress [71]. This duality of stress-amplifying versus compensatory sEV signals, supports a model in which net placental responses reflect the balance between exposure intensity, placental state, and vesicle subpopulation dynamics. Thus, placental sEVs act not only as biomarkers of environmental exposure but also as active players in transmitting air pollution-induced stress signals to the developing fetus, affecting multiple developmental pathways.

Air pollution and sEV biogenesis, release, and loading

Fine PM provokes reactive oxygen–driven and inflammatory signaling (e.g., NF-κB/p38 pathways) that upregulates sEV biogenesis and secretion and remodels vesicular composition, thereby amplifying distal inflammatory signaling [72, 73]. Mechanistically, pollution-induced stress engages ESCRT-independent, ceramide-dependent budding via neutral sphingomyelinase-2 (nSMase2) and related sphingolipid pathways, while P2X7 → NF-κB activation in phagocytes further augments EV output [72, 74, 75]. In parallel, selective cargo sorting is skewed under oxidative and inflammatory conditions through RNA-binding proteins such as hnRNPA2B1 that recognize EXOmotifs, yielding exposure-specific miRNA signatures (Fig. 1) [76].

Human and experimental exposure studies corroborate these mechanisms. A randomized crossover trial of traffic-related air pollution showed genome-wide shifts in plasma sEV-derived miRNAs within hours of exposureAdditionally, short-term PM exposure increased EV-packaged miRNAs associated with coagulation, indicating rapid systemic signaling potential [77, 78]. Source-specific toxicants act similarly: PAHs increase EV production (in vitro and in vivo) with the aryl hydrocarbon receptor (AhR) -dependent involvement and alter sEV-derived cargo composition, while PM-exposed nasal epithelium releases sEV enriched for miR-19a/miR-614 that drive M1 macrophage polarization in recipient cells [79, 80]. Finally, functional causality is supported by rodent studies showing that inhibiting pulmonary sEV generation with GW4869 blunts the systemic effects of inhaled particulate exposure, consistent with an EV-mediated conduit between the respiratory tract and distant organs [81].

Direct interactions with sEVs components

Lipophilic pollutants can insert into the sEV lipid bilayer, modifying its physical properties and influencing vesicle stability, release, and uptake by recipient cells via mechanisms such as endocytosis and direct fusion [82, 83]. Moreover, pollutants such as heavy metals or organic compounds may bind directly to sEV proteins that are crucial for cargo sorting or membrane fusion, potentially altering protein conformation and function [84]. Additionally, interference with the cargo-sorting machinery such as the ESCRT complex can further modify sEV composition [85–87]. Alterations in sEV surface characteristics by pollutants can also reduce vesicle stability and affect receptor-mediated uptake by target cells [83, 88], while oxidative stress may change the oxidation state of sEV components (Fig. 1) [73].

Epigenetic modifications influencing sEV biogenesis

Beyond direct physical interactions, air pollutants modulate sEV biology through epigenetic mechanisms. Pollutants can alter DNA methylation patterns, particularly within promoter regions of genes associated with sEV biogenesis and cargo loading, thereby modifying gene expression without changing the underlying DNA sequence [89]. In addition, changes in histone modifications (including ubiquitination, phosphorylation, methylation, and acetylation) impact chromatin structure and the accessibility of genes, ultimately influencing sEV release and composition [90]. In macrophages, PM2.5 enhances sEV release via P2X7 receptor activation, thereby triggering NF-κB signaling and inflammatory cytokine production [72]. These modifications can have lasting and even transgenerational effects on intercellular communication [91].

Impact on sEVs' cargo composition

Exposure to environmental pollutants modifies the protein content of sEVs, often reflecting a cellular response to stress or inflammation [92]. Pollutants, especially those with pro-inflammatory properties, can stimulate the release of sEVs enriched in cytokines (e.g., interleukins, TNF-α) and chemokines, thereby amplifying inflammatory responses [92]. Additionally, stress-induced changes include alterations in acute-phase proteins and the packaging of heat shock proteins (HSPs) that are critical for cellular repair and protection [27, 93].

Environmental stressors induce significant changes in the lipid composition of sEVs, which are essential for membrane stability and cellular signaling [81]. Modifications in bioactive lipids, including sphingolipids, phospholipids, and ceramides can alter the biophysical properties of sEVs and influence signaling pathways related to proliferation, apoptosis, and inflammation [87, 94–97]. These changes in lipid profiles not only affect sEV biogenesis but may also reflect broader shifts in cellular lipid metabolism. For instance, PAHs have been shown to modify sEV release and cholesterol content via the AhR receptor activation, leading to increased secretion and apoptosis [98], while PM exposure is linked to altered

sEV lipid profiles and systemic inflammatory responses in rodent models [81].

miRNA loading into sEVs is a selective event during ILV formation within MVBs, coordinated by two cooperating mechanisms. (i) Sequence-directed selection: RNA-binding proteins (notably hnRNPA2B1) recognize miRNA EXOmotifs to recruit specific transcripts into nascent ILVs [99–101]. (ii) Membrane-driven sorting: cholesterol/sphingolipid-rich microdomains and nSMase2-generated ceramide promote ESCRT-independent inward budding and enhance miRNA incorporation [75, 102–107]. Chemical/structural RNA modifications can further modulate RBP-membrane affinity and sorting efficiency [76, 107–110]. Quantitatively, sEVs carry very low miRNA copy numbers (≈1 molecule per ~ 10 vesicles), reflecting the stringency of this process [107, 111].

Exposure to air pollution markedly disrupts these finely tuned miRNA loading mechanisms. Oxidative stress and inflammatory signaling induced by pollutants alter cellular miRNA expression, which is then reflected in the sEV cargo [80, 112]. Epigenetic alterations extend to RNA molecules such as miRNAs and long noncoding RNAs, affecting their selective packaging into sEVs [113–115]. As a consequence, sEVs released from pollutant-exposed cells often carry miRNAs associated with stress responses and inflammatory signaling, thereby contributing to processes such as altered cytokine production, proliferation, and apoptosis [80, 112, 116, 117]. For instance, a randomized crossover trial involving 35 healthy college students in Shanghai found that traffic-related air pollution (TRAP) significantly altered the plasma-derived sEV miRNA profile, with 212 miRNAs upregulated and 59 downregulated, including miR-3612, miR-21-5p, and miR-195-5p which are implicated in cardiovascular regulation, cytokine signaling, and immune responses [78]. In another example, exposure to PM increased the levels of miR-19a and miR-614 in human nasal epithelial cells; these miRNAs were packaged into sEVs and transferred to macrophages, where they downregulated the anti-inflammatory gene RORα and promoted polarization toward a pro-inflammatory M1 phenotype [80]. Such pollutant-induced alterations in sEV-associated miRNA profiles not only play a role in disease development (e.g., cancer and neurodegenerative disorders) but also offer significant potential as noninvasive biomarkers for monitoring environmental exposure and its associated health risks, as the stability of these miRNAs in biological fluids like blood, urine, and cerebrospinal fluid facilitates early diagnosis and risk assessment (Fig. 1) [73, 118, 119]. Taken together, these findings implicate sEVs as vehicles through which maternal pollutant exposures can influence fetal development.

Linking air pollution to sEV modulated maternal and fetal health

sEVs in the maternal respiratory system and fetal development

When inhaled, air pollutants first encounter the airway epithelium, a physical barrier that actively contributes to pulmonary defense. Upon exposure, epithelial cells generate reactive oxygen species (ROS) and secrete pro-inflammatory cytokines (e.g., IL-6 and IL-8), impairing mucociliary clearance and potentially leading to long-term airway remodeling [120, 121]. In addition to these responses, lung cell types including epithelial cells, alveolar macrophages, neutrophils, and endothelial cells, release sEVs. These vesicles mediate intercellular communication, thereby contributing to local inflammatory responses and maintaining pulmonary homeostasis by transporting essential components such as membrane mucins, antimicrobial peptides, and antioxidants, as shown in Fig. 2 [120–122].

Chronic air pollution exposure disrupts the normal sEV profile. Altered sEV-associated miRNA signatures in bronchial epithelial cells can modulate gene expression related to inflammation, cellular proliferation, and fibrosis [123]. Pollutant-exposed cell-derived sEVs activate NF-κB, TGF-β, and MAPK pathways. These activations enhance inflammatory responses, fibroblast activation, and tissue remodeling [124–127].

The maternal lung releases sEVs locally when exposed to air pollution. Upon activation, it also emits sEVs into systemic circulation [20, 77, 128, 129]. Systemically, sEVs released from lung-resident cells (including epithelial cells, alveolar macrophages, and endothelial cells) carry pro-inflammatory signals that recruit immune cells, which in turn may release additional sEVs with pro- or anti-inflammatory effects [130, 131]. For instance, endothelial cell–derived sEVs help maintain vascular and alveolar integrity during respiratory stress [124, 130], while short-term exposures (e.g., 24-h exposure to PM_{10} and $PM_{2.5}$) have been shown to alter sEV composition and function, affecting immune cell migration and protein cargo in individuals with chronic airway inflammation [125, 130–132]. Repeated exposures further amplify systemic inflammatory signals, a phenomenon especially observed in overweight individuals [133, 134].

Exposure to cigarette smoke extract and PM also increases the release of circulating sEVs from endothelial and immune cells, contributing to systemic pro-inflammatory and oxidative stress responses [54]. Altered sEV-miRNAs such as miR-19a and miR-614 can remotely change gene expression in cardiovascular tissues. These changes may promote cardiovascular dysfunction and drive M1 macrophage polarization [80, 135–137].

In pregnancy, some maternal lung-derived sEVs cross the placenta. They can influence fetal lung development

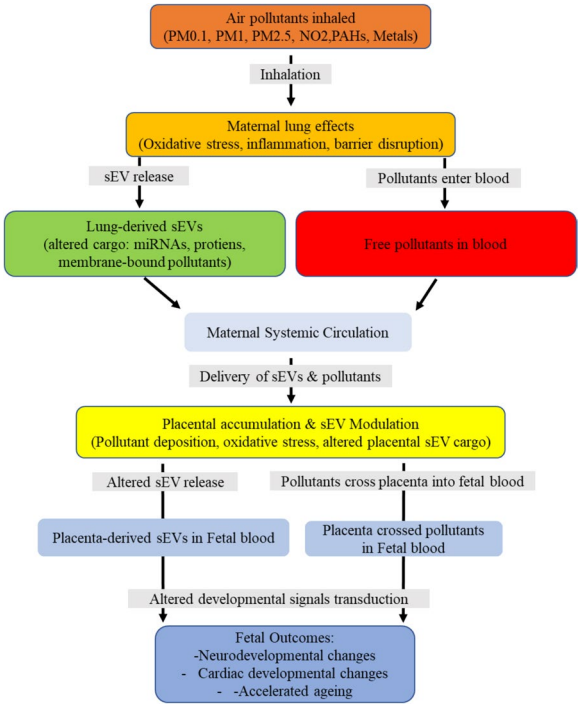

Fig. 2 Pathway linking maternal air-pollution exposure to sEV-mediated placental and fetal effects. Maternal inhalation of ambient pollutants ($PM_{0.1}$/PM_1/$PM_{2.5}$, black carbon/soot, NO_2, PAHs, and metals) initiates lung effects characterized by oxidative stress, inflammation, and epithelial barrier disruption. From the lung, two parallel streams enter the maternal circulation: (i) lung-derived sEVs whose cargo (miRNAs, proteins, membrane-associated pollutants) is altered by exposure, and (ii) free pollutants themselves. Both streams reach the placenta, where pollutants can accumulate and/or cross the placental barrier into the fetal circulation. Together with maternal sEV signals, inflammatory mediators, and locally induced placental responses, these exposures trigger placental oxidative/inflammatory stress and modulate placental sEV biogenesis and cargo. Placenta-derived sEVs carrying altered developmental signals then enter the fetal circulation. Consequently, the fetus is exposed via both direct pollutant transfer and indirect signaling pathways, contributing to adverse outcomes including neurodevelopmental alterations, cardiac developmental changes, and features of accelerated biological ageing. Gray callouts on the diagram label key processes (e.g., inhalation, sEV release, pollutant entry to blood, delivery to placenta, transplacental pollutant transfer, altered placental sEV release, signal transfer). Arrows indicate direction of information/particle flow

and immune maturation. They have also been implicated in adverse developmental outcomes [138, 139]. Beyond its role in nutrient transport and environmental sensing, the placenta actively contributes to fetal brain development by releasing sEVs into both maternal and fetal circulations. These placental vesicles serve as biomarkers for developmental abnormalities and mediate adaptive responses to intrauterine conditions [65, 66, 140]. Therefore, it is crucial to examine how air pollution may alter these placenta-derived sEVs and compromise their functions.

In summary, lung-derived sEVs released under PM exposure carry inflammatory and immune-modulatory signals into the circulation and can reach the placenta/fetus. This respiratory–systemic–placental axis offers a plausible route by which maternal inhalation exposures program fetal tissues, and it supports cross-compartment sEV profiling (airway, plasma, placenta).

The effect of the air pollution on sEVs derived from the placenta

Placenta-derived sEVs are detectable in maternal blood as early as six weeks post-conception, with concentrations increasing steadily throughout gestation. Alterations in their molecular profiles have been closely linked to pregnancy complications, particularly under maternal exposure to environmental stressors such as air pollution [36, 141]. These vesicles transport molecular cargo from placental and fetal tissues to maternal systems, regulating essential processes including trophoblast migration, placental implantation, and the vascular remodeling necessary for proper placentation [67]. Circulating placental sEVs are being investigated as early biomarkers for preeclampsia [59], underscoring their potential to foreshadow pregnancy complications.

Air pollutants such as $PM_{2.5}$ and NO_2 induce oxidative stress in placental cells by elevating ROS, which in turn activate inflammatory signaling cascades, notably the NF-κB and MAPK/p38 pathways [32, 69]. These pathways drive the secretion of pro-inflammatory cytokines and stress-related proteins into sEVs, contributing to a systemic inflammatory milieu that can affect both maternal and fetal tissues. p38 MAPK activation is frequently observed in sEVs from pollutant-exposed placentas, serving as a central mediator of cellular stress responses, [142] while NF-κB activation is reflected in altered protein cargo [69, 70]. Stress proteins such as HMGB1—associated with necrosis or sterile inflammation—are enriched in sEVs under pollutant exposure [68], alongside apoptotic markers such as caspase-4 [68].

Pollutant exposure dysregulates placental sEV-associated ncRNAs. Upregulation of miR-21 and miR-146a are promoting inflammatory and immune signaling, whereas changes in the miR-29 family affect apoptosis and cell survival. Together, these shifts create a pro-inflammatory placental environment that can disrupt embryonic implantation and placental function. [67, 69, 143] Together, these molecular changes contribute to a pro-inflammatory placental environment that can disrupt implantation and placental function [141].

In addition to transcriptomic and proteomic alterations, $PM_{2.5}$ exposure can induce epigenetic changes such as altered DNA methylation patterns. These modifications may influence sEV biogenesis and molecular composition, thereby altering their functional role and enhancing their potential as biomarkers of placental stress [68]. Such biomarker potential is supported by

consistent links between altered sEV profiles and adverse pregnancy outcomes [67, 143].

Placenta-derived sEVs also play a role in modulating maternal immune and vascular systems. Under pollutant exposure, sEVs can carry altered cargo that promotes systemic inflammation and oxidative stress, thereby increasing the risk for gestational complications [68]. Syncytiotrophoblast (STB)-derived sEVs may express ligands such as MIC-A/B and UL16-binding proteins for inhibitory receptors on natural killer (NK) cells, a mechanism exacerbated by pollutant exposure and linked to preeclampsia and gestational hypertension [65, 67, 143]. Furthermore, pollutant-altered placental sEVs can transfer molecular changes directly to maternal vascular cells, potentially impairing vascular health and contributing to hypertensive disorders during pregnancy [144].

Placental sEV molecular profiles are increasingly being linked to child health outcomes. Prenatal $PM_{2.5}$ exposure has been associated with altered placental sEV miRNAs that correlate with neurodevelopmental delay in children. Maternal plasma sEV miRNA signatures have also been shown to reflect ambient air pollution exposure, supporting their dual role as early biomarkers and plausible mediators of long-term offspring effects [66, 112].

In the placenta, pollutant-driven ROS activates NF-κB and p38 MAPK, which boosts sEV release and loads vesicles with stress-related cargo such as HMGB1, p38 MAPK, miR-21, miR-146a, and the miR-29 family. These vesicles can shape maternal immune and vascular responses, contribute to conditions such as preeclampsia and gestational hypertension, and track with offspring neurodevelopmental outcomes. Collectively, these findings highlight placenta-derived sEVs as both mechanistic mediators and early biomarkers of air-pollution-related pregnancy complications.

Early life air pollution exposure and sEVs role in fetus cardiac diseases

Prenatal exposure to air pollutants, particularly fine $PM_{2.5}$, has been linked to altered neonatal blood pressure and changes in cardio-metabolic biomarkers (e.g., hemoglobin A1c, insulin, adiponectin, and leptin), which are predictive of an increased risk for cardiovascular disorders in early childhood [145–148]. Inflammatory markers such as C-Reactive Protein (CRP), Interleukin-8 (IL-8), Monocyte Chemotactic Protein-1 (MCP-1), and Tumor Necrosis Factor-α (TNF-α) measured in cord blood further underscore the link between prenatal air pollution exposure and subsequent cardio-metabolic dysfunction [148].

Recent studies have highlighted the critical role of sEVs as mediators of these adverse cardiovascular effects. Exposure to air pollutants actively increases the participation of these vesicles in the pathogenesis of cardiovascular diseases by promoting endothelial dysfunction, vascular inflammation, and pro-coagulant activity [149]. sEVs are thought to serve as messengers during fetal programming, with their altered molecular cargo contributing to the early development of cardiovascular disorders [150]. For example, in one study, platelet-derived sEVs (P-sEVs) from $PM_{2.5}$-exposed platelets were shown to transfer pro-inflammatory signals to human umbilical vein endothelial cells (HUVECs). The treatment of HUVECs with these P-sEVs resulted in increased expression of inflammatory factors such as IL-6, intercellular adhesion molecule-1 (ICAM-1), and TNF-α, as well as elevated ROS. Additionally, these sEVs modulated apoptotic pathways by upregulating Bax, cytochrome C, and cleaved caspase-3 while downregulating the anti-apoptotic protein Bcl-2, indicating the activation of the mitochondrial apoptotic pathway [151]. Changes in the levels of sEV-associated miRNAs in HUVECs further suggest that miRNAs transferred via sEVs can alter cellular function and promote endothelial damage.

Moreover, a study demonstrated that respiratory-derived sEVs carrying miR-421 contribute to cardiac dysfunction following $PM_{2.5}$ exposure. This study showed that miR-421, when delivered to cardiac tissue, targets and downregulates angiotensin-converting enzyme 2 (ACE2) and induces myocardial cell apoptosis and cardiac dysfunction. In experimental models, inhibiting. miR-421 or modulating sEV release with the GW4869 inhibitor was found to restore normal cardiac function, thereby directly implicating sEV-mediated miRNA transfer in pollutant-induced cardiac pathology [152].

Complementing these findings, it has been reported that P-sEVs from $PM_{2.5}$-exposed platelets significantly enhance vascular endothelial injury [151]. This study further supports the notion that sEVs serve as a conduit between environmental exposures and fetal cardiovascular programming.

Together, these studies reinforce the concept that prenatal air pollution exposure triggers the release of sEVs with altered cargo including specific miRNAs such as miR-421, which in turn can disrupt cardiovascular development by promoting endothelial dysfunction, inflammation, and apoptosis. The emerging evidence suggests that sEV-associated miRNAs not only serve as biomarkers of early life exposure but may also actively mediate the developmental origins of fetal cardiac diseases.

In summary, evidence from cell, animal, and cohort studies suggests that pollutant-altered sEVs (e.g., platelet- or respiratory-derived; miR-laden vesicles targeting ACE2 and endothelial pathways) promote endothelial dysfunction, inflammation, and apoptosis. These signals align with observed childhood blood-pressure

alterations, supporting an sEV-mediated cardiovascular programming hypothesis.

Early life air pollution exposure and sEVs role in fetus neurodevelopment

Likewise, the developing fetal brain is susceptible to pollution driven sEV alterations. Early exposure to air pollutants, particularly $PM_{2.5}$ and $PM_{2.5-0.1}$, can detrimentally affect fetal neurodevelopment through both direct and indirect mechanisms. Studies in adult brain shows that these particles may enter the central nervous system (CNS) via the olfactory nerve pathway, bypassing the lungs to directly induce neuroinflammation, oxidative stress, and even neurodegenerative changes [153, 154]. Animal studies further demonstrate that such exposures disrupt embryonic brain growth by impairing myelination and synaptogenesis, processes critical for proper cognitive and behavioral outcomes [155].

Systemically, inhaled pollutants trigger widespread inflammation and oxidative stress that compromise the BBB, thereby allowing toxic substances to reach the developing brain. In parallel, air pollution-induced oxidative damage and DNA damages in the placenta can disrupt nutrient and oxygen delivery, further impairing fetal brain development [68, 156]. Toxic metals contained in $PM_{2.5}$ such as lead (Pb), aluminum (Al), vanadium (V), and titanium (Ti) can cross the placental barrier. These metals have been linked to the downregulation of neurodevelopmentally important miRNAs (e.g., miR-101-3p and miR-520d-5p), induction of mitochondrial dysfunction, and alteration of key signaling pathways such as PI3K-Akt, neurotrophin, and FoxO, thereby contributing to neurotoxicity [66, 156, 157].

sEVs serve as crucial mediators between polluted environments and the developing brain by transporting molecular signals, including proteins, lipids, and miRNAs. sEVs released from pulmonary cells following PM exposure carry a distinct miRNA signature (e.g., miR-146a, miR-222, and miR-9) that modulates glial reactivity, neural stem cell function, and neuroinflammatory responses [77, 137, 156, 158, 159]. Similarly, placental sEVs reflect exposure-related alterations; for example, changes in miR-320a-3p, miR-520d-5p, and miR-101-3p levels in these vesicles have been directly associated with $PM_{2.5}$ exposure and subsequent neurodevelopmental delays [66]. Moreover, recent work highlights that sEV lipid composition may also influence inflammatory signaling. One study suggests that alterations in sEV lipids can modulate neuroinflammatory responses, adding another layer to the mechanistic impact of air pollutants [160].

In addition to miRNA-mediated signaling, epigenetic modifications play an important role in how sEVs influence neurogenesis. For instance, increased levels of DNA methyltransferase 1 (DNMT1) in the brains of animals exposed to diesel exhaust particles, together with altered placental DNA methylation patterns, correlate with adverse neurodevelopmental outcomes [155, 156, 161]. A complementary study, which assessed placental epigenetic alterations-specifically promoter DNA methylation in key DNA repair and tumor suppressor genes (e.g., APEX1, OGG1, ERCC4, and p53) in response to air pollution, reinforces the hypothesis that pollutant-induced epigenetic changes may influence fetal brain development through disruption of essential cellular processes during early development [162].

Furthermore, recent evidence suggests a dynamic interplay between autophagy and sEV release. Autophagy can regulate sEV secretion, and its inhibition may enhance sEV release, thereby facilitating the extracellular clearance of neurotoxic proteins such as amyloid-β and phosphorylated tau. This mechanism is potentially relevant to the early stages of Alzheimer's disease. A recent study assessed the interplay between sEVs and autophagy [163], which provides insights into how disruptions in these pathways may exacerbate neurodegeneration [164–168].

Collectively, these findings indicate that sEVs not only serve as biomarkers reflecting environmental exposure but also actively mediate cellular pathways that contribute to neuroinflammation and impaired brain development in the fetus. Beyond organ-specific effects, evidence suggests that prenatal sEV alterations could also contribute to accelerated aging phenotypes. This understanding opens avenues for early diagnostics and potential therapeutic interventions targeting sEV-mediated signaling in the context of air pollution exposure.

In summary, pollution-responsive sEVs, originating from the maternal lung and placenta, carry miRNAs and lipids that modulate glial reactivity, neuronal development, and neuroinflammation, while placental sEV profiles correlate with early-life neurodevelopmental performance. This convergence supports sEVs as mechanistic links and candidate biomarkers for exposure-related neurodevelopmental risk.

Air pollution exposure and sEVs role in cellular ageing of the fetus

Aging is a multifaceted process characterized by a gradual deterioration in physiological integrity. It manifests through genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication [169, 170]. Both intrinsic factors and external environmental exposures, collectively referred to as the "exposome," contribute to this cumulative cellular damage, ultimately driving long-term health risks as posited

by the Developmental Origins of Health and Disease (DOHaD) hypothesis. [171, 172].

Cellular senescence is associated with an increased release of sEVs, as part of the senescence-associated secretory phenotype (SASP), partly mediated by p53-dependent mechanisms [173, 174], which transmit senescence-associated signals to both neighboring and distant cells. Studies in aged human fibroblasts indicate that these senescent cell–derived sEVs are enriched with miRNAs possessing pro-survival properties [175, 176]. Moreover, senolytic treatments that selectively eliminate senescent cells have been shown to alter the miRNA profile of sEVs, resulting in a more youthful cellular phenotype and enhanced tissue regeneration [177]. Similarly, sEV transfer from young donors to aged recipients has demonstrated rejuvenating effects and extended lifespan in animal models [178]. Consequently, the exposome significantly impacts both the quantity and content of sEVs, underscoring their importance in mediating environmental influences on aging.

Alterations in sEV cargo following exposure to environmental stressors, such as air pollution, may induce immediate changes in organ development and trigger long-lasting disruptions in tissue homeostasis. In the context of fetal development, these changes may "program" accelerated aging, thereby predisposing individuals to chronic conditions such as atherosclerosis, dementia, and osteoporosis later in life [179].

Air pollution, particularly $PM_{2.5}$, accelerates cellular aging by eliciting oxidative stress and inflammation. The deposition of PM along the airway epithelium induces a pro-inflammatory response that promotes both local and systemic "inflamm-aging" [180, 181]. In elderly subjects, increased levels of sEV-associated miRNAs linked to oxidative stress and immune dysregulation have been observed following long-term $PM_{2.5}$ exposure, correlating with heightened risks of cardiovascular events [182, 183]. Moreover, at the respiratory level, ultrafine particles stimulate the release of macrophage-derived sEVs that further propagate local inflammation and may contribute to accelerated lung aging [184].

Emerging studies also suggest that sEVs may influence telomere dynamics, a crucial determinant of cellular aging. Recent work indicates that pollutant-induced oxidative stress can alter the molecular cargo of sEVs in ways that modulate telomerase activity and telomere maintenance. For instance, research has demonstrated that oxidative stress from environmental pollutants modifies sEV-associated miRNAs and proteins that regulate telomerase expression and telomere length [185]. Similarly, increased oxidative-stress-induced senescence in amnion epithelial cells, simulated by a 48-h exposure to cigarette smoke extract, leads to the translocation of nuclear components, specifically the alarmin HMGB1 and cell-free fetal telomere fragments (cffTF), into the cytoplasm. These molecules are subsequently co-packaged into sEVs. The study proposed that sEV-mediated delivery of HMGB1 and cffTF functions as a fetal signal, triggering inflammatory changes in adjacent uterine tissues that promote parturition [186]. Although these studies were not conducted exclusively in the prenatal setting, they raise the possibility that similar sEV-mediated mechanisms may contribute to accelerated fetal aging following maternal air pollution exposure.

Notably, sEVs originating from the respiratory tract can enter systemic circulation and cross biological barriers such as the placenta, thereby delivering pollutant-altered cargo, including inflammatory mediators and telomere-regulatory factors, to fetal tissues [128, 129]. This transplacental transfer may initiate epigenetic modifications and disrupt telomere maintenance during critical developmental windows, ultimately predisposing offspring to premature aging and age-related diseases later in life.

In summary, air pollution exposure has been demonstrate to alter sEV release and its cargo composition in such a way that it accelerates cellular aging in the fetus. Addressing the mechanistic details of these processes, establishing quantitative exposure–response relationships qhile considering critical windows of exposure are essential steps toward developing effective preventive interventions to safeguard long-term maternal and child health.

Discussion

A growing body of evidence demonstrates that sEVs may function as critical mediators of early-life exposure to air pollution, offering a mechanistic link between prenatal/postnatal environmental insults and developmental outcomes. They cross biological barriers, such as the placenta, transporting molecular cargo (e.g., miRNAs, proteins) that can modulate inflammation, immune function, and cellular homeostasis in both maternal and fetal tissues. This complex intercellular communication may help explain how air pollutants contribute to adverse pregnancy outcomes, including preterm birth and low birth weight, and longer-term risks such as cardiovascular disease, respiratory disorders, and neurodevelopmental impairments [33, 122, 133].

Substantial in vitro and in vivo data demonstrate that PM disrupts sEV biogenesis and composition via oxidative stress and inflammation [55, 85, 156]. Pollutant-induced ROS can activate signaling pathways (e.g., NF-κB, MAPK) that stimulate the release of sEVs enriched in proinflammatory mediators or epigenetically active miRNAs [33, 54]. These vesicles can then act systemically, reaching distant sites such as the fetal compartment, where they may alter placental function or fetal organ development [128]. This chain of events

underscores how seemingly localized respiratory exposures propagate biologic responses in multiple organ systems.

In particular, miRNAs within sEVs have drawn attention for their role in regulating gene expression in recipient cells, impacting developmental and immune-related pathways. Studies have shown that exposure to air pollution significantly alters the miRNA profile in maternal, placental, and fetal sEVs. For instance, miR-21, miR-146a, and miR-29 family members are frequently upregulated in response to pollutant exposure and have been implicated in inflammation, immune dysregulation, and placental dysfunction [66, 67, 69]. Additionally, altered levels of miRNAs such as miR-101-3p, miR-520d-5p, and miR-320a-3p in placental sEVs have been linked to neurodevelopmental delays and epigenetic modifications in placental tissues [66, 156, 162]. These findings not only support the functional role of miRNAs in mediating pollutant effects but also emphasize their utility as minimally invasive biomarkers in maternal or cord blood [66, 78, 112].

Researchers now view sEV profiles as integrated footprints of environmental exposures [187]. For example, sEV-miRNAs in human breast milk collected one month postpartum correlate with maternal air pollution exposure [188], reinforcing their value as exposure biomarkers. Several ongoing cohort studies (e.g., ENVIRONAGE) [189] are beginning to collect serial biosamples from pregnant mothers and newborns to investigate whether sEV signatures reliably predict adverse outcomes such as gestational hypertension, low birth weight, or neurodevelopmental delays [128, 190]. If reproducible sEV-based biomarkers are identified, this could pave the way for early risk stratification and targeted interventions. For instance, maternal blood sEV assays might be used prenatally to identify fetuses at elevated risk of growth restriction or neurocognitive impairment, thus enabling closer clinical monitoring and preventive measures [187, 191–193].

Mitigating air pollution at a population level remains the most effective strategy for reducing pollution-related health burdens [3, 180]. However, at the individual level, certain measures, such as improved indoor air purification systems, the use of lower-emission cookstoves in low-income settings, and reduced vehicular traffic near residential areas, may decrease exposure to fine and ultrafine PM [171, 194–196]. It is conceivable that lowering exposure might alter the sEV cargo profile in pregnant women, thereby ameliorating inflammation and associated risks. Future longitudinal studies should explore how specific policy interventions or personal exposure reduction strategies affect sEV-mediated pathways and subsequent child health outcomes [128, 189].

Despite a growing body of evidence, critical gaps in knowledge persist. First, the mechanistic details of how particular pollutants (e.g., $PM_{2.5}$ vs. ozone) selectively alter sEV biogenesis and cargo sorting remain incompletely understood [33]. Second, most insights stem from short-term in vitro experiments or animal studies, necessitating human-based longitudinal research to confirm the temporal relationship between exposure, sEV alterations, and clinical outcomes [164]. Third, while sEV-associated miRNAs and proteins are well-studied, there is a need for broader omics analyses (e.g., lipidomics) to capture the full spectrum of sEV cargo. Comprehensive "omics" profiling may reveal new biomarkers or pathways amenable to intervention.

Finally, investigating the interplay among sEVs, autophagy [197], and senescence [198] may offer novel perspectives on how prenatal and early-life exposures accelerate aging processes and predispose individuals to age-related diseases [173, 199]. This is particularly relevant given the concept of DOHaD, which posits that in utero and early childhood conditions can shape life-long susceptibility to chronic disorders [146, 171].

In summary, sEVs serve a dual role as both messengers and potential sentinels of air pollution's biological impacts. These nanosized vesicles encapsulate and deliver pollutant-altered cargo to maternal and fetal tissues, facilitating epigenetic shifts and fueling systemic inflammation. Consequently, adverse pregnancy outcomes and childhood health issues, ranging from respiratory pathologies to neurodevelopmental disorders, may be partially driven by sEV-mediated communication. The identification of sEV-associated biomarkers holds promise for enhancing exposure monitoring and enabling earlier interventions. Elucidating the mechanisms underlying sEV modulation by air pollution and validating sEV-based diagnostics in clinical settings remain pivotal next steps in safeguarding maternal and child health in the face of escalating environmental pollution.

This review was conducted through a comprehensive literature search across PubMed, Scopus, and Web of Science, and systematically evaluated experimental and epidemiological studies on sEVs in the context of air pollution exposure during pregnancy. While this approach strengthens the robustness of the synthesis, the number of available studies remains limited, with substantial heterogeneity in study design, exposure types, and outcome measures. These gaps highlight the need for further well-designed research to elucidate the precise mechanisms by which pollutant-altered sEVs contribute to fetal development and childhood health.

Abbreviations

ACE2	Angiotensin-converting enzyme 2
Al	Aluminum
BBB	Blood–brain barrier

BC	Black Carbon
cffTF	Cell-free fetal telomere fragments
CNS	Central nervous system
CO	Carbon monoxide
CRP	C-Reactive Protein
DAMPs	Damage-associated molecular patterns
DNMT1	DNA methyltransferase 1
DOHaD	Developmental Origins of Health and Disease
ER	Endoplasmic reticulum
ESCRT	Endosomal sorting complexes required for transport
EVs	Extracellular vesicles
FAK	Focal adhesion kinase
hCG	Human chorionic gonadotropin
IAP	Indoor air pollution
HMGB1	High Mobility Group Box 1
HSPs	Heat shock proteins
HUVECs	Human umbilical vein endothelial cells
ICAM-1	Intercellular adhesion molecule-1
IL-8	Interleukin-8
ILVs	Intraluminal vesicles
ISEV	International Society for Extracellular Vesicles
MAPK	Mitogen-activated protein kinase
MCP-1	Monocyte Chemotactic Protein-1
MPs	Microparticles
MVBs	Multivesicular bodies
MVs	Microvesicles
NF-κB	Nuclear factor-κB
NK	Natural killer
NO_x	Nitrogen oxides
nSMase2	Neutral sphingomyelinase 2
O_3	Tropospheric ozone
P-sEVs	Platelet-derived small extracellular vesicles
PAHs	Polycyclic aromatic hydrocarbons
Pb	Lead
PM	Particulate matter
RBPs	RNA-binding proteins
ROS	Reactive oxygen species
SASP	Senescence-associated secretory phenotype
sEVs	Small extracellular vesicles
SO_2	Sulfur dioxide
Ti	Titanium
TNF-α	Tumor Necrosis Factor-α
TRAP	Traffic-related air pollution
V	Vanadium
WHO	World Health Organization

Supplementary Information

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Supplementary Material 1.

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Data availability
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Declarations

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