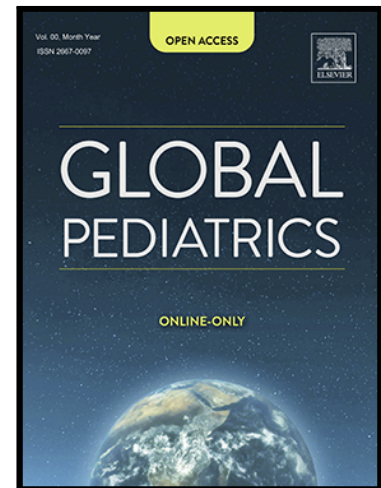


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Early life in the Plasticene: short and long-term effects of perinatal exposure to microplastics and plastic-associated chemicals – PART I

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Abstract

Over the last decades, the rapid expansion of plastic production, combined with poor circularity, inadequate waste management, and the long-term persistence of synthetic polymers, has led to widespread environmental contamination. Plastics are now so pervasive that they have been proposed as a defining feature of the so-called *Plasticene*. The perinatal period represents a critical window of susceptibility, during which environmental exposures can shape developmental processes and influence long-term health trajectories. The aim of this two-part narrative review is to explore the sources and health implications of plastic exposure during the prenatal (Part I) and early neonatal (Part II) periods, with a focus on microplastics and plastic-associated chemicals as complex and cumulative components of the early-life exposome.

Current evidence indicates that exposure to microplastics and plastic-associated chemicals can begin before birth, with maternal exposure occurring through multiple routes. Microplastics have been found in the placenta, amniotic fluid and cord blood, supporting biological access to the fetoplacental unit and the possibility of transplacental passage. Available human studies have explored potential associations between prenatal microplastic exposure and adverse pregnancy and fetal outcomes, including impaired growth and altered cord-blood endocrine profiles, but the evidence is preliminary and limited by predominantly cross-sectional designs and substantial heterogeneity in analytical methods, such as differences in particle-size detection thresholds and polymers assessed. Evidence for plastic-associated chemicals, particularly phthalates, is more extensive and suggests associations with preterm birth, endocrinological alterations, and neurodevelopmental outcomes, although residual confounding, exposure misclassification, and co-exposure to complex chemical mixtures remain important limitations. Further prospective studies using repeated measurements, rigorous contamination-control procedures, and long-term follow-up are needed to better characterize these associations and their potential consequences for offspring health.

The ubiquitous nature of plastic exposure, coupled with the growing body of evidence on its potential consequences, warrants urgent action. Effectively tackling the perinatal plastic exposome requires coordinated multidisciplinary efforts within a One Health framework, integrating environmental, clinical, and regulatory strategies to reduce exposure and protect early-life health.

Keywords: microplastics, exposome, phthalates, One Health, SDGs, plastisphere

Abbreviations

AGD, anogenital distance

ASQ, Ages and Stages Questionnaire

BPA, bisphenol A

CCCEH, Columbia Center for Children's Environmental Health birth cohort

DEHP, di-(2-ethylhexyl)phthalate

DiNP, diisononyl phthalate

DOHaD, developmental origins of health and disease

EDCs, endocrine-disrupting chemicals

EFSA, European Food Safety Authority	PA, polyamide
FT4, free thyroxine	PAHs, polycyclic aromatic hydrocarbons
ICC, intraclass correlation coefficient	PBS, polybutylene succinate
IQ, intelligence quotient	PE, polyethylene
IUGR, intrauterine growth restriction	PET, polyethylene terephthalate
MBzP, monobenzyl phthalate	PFAS, per- and polyfluoroalkyl substances
MEP, monoethyl phthalate	PM2.5, particulate matter $\leq 2.5 \mu\text{m}$
MEHP, mono(2-ethylhexyl) phthalate	PP, polypropylene
mIBP, monoisobutyl phthalate	PPROM, preterm prelabour rupture of membranes
MITM, meet-in-the-middle analysis	PS, polystyrene
MnBP, mono-n-butyl phthalate	PVC, polyvinyl chloride
MPs, microplastics	ROS, reactive oxygen species
MRI, magnetic resonance imaging	SDGs, Sustainable Development Goals
NDD, neurodevelopmental delay	TSH, thyroid-stimulating hormone
NNNS, NICU Network Neurobehavioral Scale	T/H, testosterone-to-luteinizing hormone ratio
NIAS, non-intentionally added substances	UK, United Kingdom
NPs, nanoplastics	US, United States

1. Introduction

Global plastic production has increased dramatically over the past decades, rising from approximately 2 million tonnes in 1950 to 475 million tonnes in 2022. If current trends continue, the annual production of plastic is projected to exceed 1200 million tonnes by 2060[1]. At the same time, less than 10% of plastic is recycled, leading to progressive accumulation in terrestrial and aquatic environments[1]. One of the most visible manifestations of this global plastic accumulation is the formation of large marine plastic debris zones, commonly referred to as “garbage patches” (e.g., the Great Pacific Garbage Patch[2]), within subtropical ocean gyres in the Pacific, Atlantic, and Indian Oceans. These areas contain tonnes of plastic and act as long-term, dynamic reservoirs of environmental contamination.

Because of their global distribution and persistence in sediments, plastics have been increasingly regarded as distinctive stratigraphic markers of modern human activity[3]. In this context, the term “Plasticene” has been proposed as an informal stage within the broader Anthropocene, characterized by the ubiquitous presence of synthetic polymers throughout the biosphere[4].

However, plastic pollution should not be viewed merely as an environmental issue. Rather, it constitutes a complex and systemic challenge with far-reaching consequences for ecosystem integrity, animal health, and human well-being, requiring coordinated action within a One Health framework[5]. Moreover, it has been argued that plastic pollution effectively undermines progress towards at least 12 out of 17 United Nations Sustainable Development Goals[6] (SDGs), the framework developed in 2015 within the 2030 Agenda for

Sustainable Development as a global call to action to promote environmental sustainability, human health and social equity.

Over time, plastic materials progressively fragment into microplastics (MPs), defined as plastic particles <5 mm in size[7]. While primary MPs are intentionally manufactured at microscopic dimensions for commercial applications such as cosmetic microbeads or industrial pellets, secondary MPs result from the degradation and fragmentation of larger plastic items. However, plastic exposure is not solely particulate exposure. Indeed, plastic particles can also act as carriers of a wide range of potentially toxic chemicals, including plasticizers (e.g., phthalates), bisphenols, per- and polyfluoroalkyl substances (PFAS), polycyclic aromatic hydrocarbons (PAHs), flame retardants, heavy metals, pigments, and other contaminants that may either be intentionally added to the polymer matrix or adsorb onto plastic surfaces throughout the plastic life cycle. Consequently, humans can be exposed to a dynamic and cumulative mixture of particles and chemicals that continuously interacts with biologic systems across the life course. Within the broader framework of the exposome (i.e., the totality of non-genetic exposures encountered throughout life), this complex and dynamic *ensemble* of plastic-related exposures could be conceptualized as the “plastic exposome”.

Among all stages of life, pregnancy and early neonatal life represent particularly vulnerable windows for exposure to MPs and plastic-associated chemicals. The fetus and newborn have immature metabolic, immune, and barrier systems, which may increase susceptibility and limit the ability to eliminate xenobiotics and respond to toxic insults. Consistent with the Developmental Origins of Health and Disease (DOHaD) paradigm, environmental exposures occurring during these critical developmental windows may influence long-term health trajectories.

The aim of the present narrative review is to provide an overview of current evidence on perinatal exposure to MPs and plastic-associated chemicals, particularly phthalates, and its short- and long-term health effects on offspring health.

2. Methods

To provide a broad overview of a rapidly evolving field, the present narrative review is organized into two complementary parts: Part I focuses on sources and pathways of exposure to MPs and plastic-associated chemicals during pregnancy, as well as their potential effects on the fetoplacental unit, fetal and neonatal development. Part II will examine exposure during the early postnatal period and its potential implications for neonatal and early-life health. Although the term *perinatal* formally refers to the period surrounding birth, from 22 completed weeks' gestation to 7 days post-birth[8], it is used here in a broader sense to encompass pregnancy and the neonatal period, thus reflecting the continuity of prenatal and early postnatal exposure.

A literature search was conducted between March and June 2026 in PubMed, Scopus, Embase, Web of Science, and Google Scholar to identify relevant studies published up to June 2026. Database-specific search strategies were developed using combinations of terms related to MPs, nanoplastics (NPs), plastic-associated chemicals (including phthalates, bisphenols and PFAS), and maternal, fetal and neonatal health. Additional relevant articles were identified by manually screening the reference lists of the included articles.

For the present narrative review, peer-reviewed articles published in English were considered. Preference was given to articles published within the last 5 years, to include the most recent advances in the field. Selected older publications were retained when they represented foundational studies or provided historical and conceptual context. Original research articles were prioritized, whereas narrative and systematic reviews were used mainly to contextualize the available evidence and retrieve additional primary studies. Grey literature, including reports from international organizations and regulatory agencies, was consulted when appropriate. Conference abstracts, preprints, and other non-peer-reviewed publications were excluded. Given the clinical focus of this narrative review, priority was given to evidence derived from human studies.

Findings from *in vitro* or animal studies were nonetheless incorporated into the discussion when relevant, to elucidate biological mechanisms or to complement the limited human evidence available.

Studies were selected by the authors based on their relevance to the predefined scope of the review. The evidence collected was then summarized narratively by the authors and organized into three main thematic areas: biological interactions and mechanisms of toxicity; sources and pathways of exposure; health implications. Consistent with the narrative design of the review, no formal risk-of-bias or certainty-of-evidence assessment was performed.

Although a structured literature search was undertaken to ensure broad coverage of the available evidence, the lack of a predefined systematic review protocol may have introduced selection bias in study identification and inclusion. Moreover, in the absence of prespecified criteria for the critical evaluation of the evidence, the assessment of individual findings and the relative emphasis placed on them by the review authors may have been susceptible to interpretive and confirmation bias.

3. Biological interactions and mechanisms of toxicity of MPs

The toxicological behaviour of MPs depends on multiple characteristics, such as polymer composition, particle size and shape, and the wide range of chemicals, environmental contaminants and microorganisms adsorbed onto their surfaces or embedded within their matrix. This heterogeneity inevitably complicates toxicological evaluations. Furthermore, most of the currently available evidence derives from *in vitro* or experimental models that may not fully reproduce real-world human exposure conditions, including chronic low-dose and mixed exposures.

MPs are most commonly made of polyethylene (PE), polyethylene terephthalate (PET), polypropylene (PP), polystyrene (PS), polyvinyl chloride (PVC) and polyamide (PA). Polymer composition influences physicochemical properties and the profile of associated chemical additives, which may contribute to different biological effects. However, currently available human evidence is insufficient to determine whether specific polymers are intrinsically more harmful than others. Nonetheless, some authors have reported interesting polymer-specific differences, as discussed below. Based on experimental animal studies, it has been hypothesized that certain physicochemical profiles may facilitate epithelial barrier crossing and distal tissue accumulation. Specifically, PE, PS and PET particles have been reported to have higher translocation potential, while PP particles often produce minimal systemic effects[9]. Furthermore, the greater surface area-to-volume ratio of smaller particles may contribute to the adhesion of proteins in biologic fluids and the formation of the protein corona, thereby affecting particle recognition and internalization via multiple passive and active routes[9]. Upon contact with cell membranes, MPs have also been shown to stretch the lipid bilayer, destabilizing it[10]. In experimental cellular models, internalized plastic particles have been observed within endosomal compartments, from which they may escape through membrane destabilization and rupture. Following their release into the cytosol, MPs can interact with intracellular organelles, particularly mitochondria, promoting mitochondrial dysfunction and excessive generation of reactive oxygen species (ROS). The resulting oxidative stress can disrupt essential cellular functions and ultimately trigger regulated cell death pathways[11]. Beyond their cytotoxicity, MPs have been associated with genotoxicity, inducing oxidative DNA damage and DNA strand breaks, and impairing DNA repair processes[12]. Emerging evidence further indicates that MPs may induce epigenetic alterations, such as changes in DNA methylation. Evidence from animal models suggests that the epigenetic effects of MPs could extend beyond the directly exposed individual and potentially affect subsequent generations even in the absence of continued exposure[13,14].

Beyond their intrinsic particle toxicity, MPs may also function as “Trojan horses”, transporting environmental pollutants, metals, microorganisms, and plastic-associated chemicals. The recently developed PlastChem database mapped more than 16000 chemicals associated with plastics, approximately ¼ of which were classified as “of concern” because of persistence, bioaccumulation, mobility, and/or toxicity[15]. Importantly,

several of these compounds are classified as endocrine-disrupting chemicals (EDCs), capable of interfering with hormonal and metabolic functions. Plastic-associated chemicals include plasticizers such as phthalates, bisphenols such as bisphenol A (BPA) and its analogues, PFAS, PAHs, parabens, as well as non-intentionally added substances (NIAS). Many plastic-associated chemicals are not covalently bound to the polymer matrix, allowing them to leach into the surrounding environment. This migration can be enhanced by factors such as heat, humidity, ultraviolet radiation, mechanical stress, and material aging[16], and can occur at any stage of the plastic life-cycle [15].

Finally, plastic debris is frequently colonized by polymicrobial biofilms. These highly diverse plastic-attached microbial communities are collectively referred to as the “Plastisphere”[17]. The plastisphere may harbour microorganisms potentially pathogenic to humans, including *Vibrio spp.*, *Salmonella spp.*, *Escherichia coli* and other opportunistic bacteria[17,18], raising concerns about their dissemination across ecosystems and food webs due to the extremely durable, persistent and mobile nature of MPs. Furthermore, the plastisphere may facilitate the spread of antimicrobial resistance, a major One Health priority[19]. MPs have a high adsorptive capacity and can concentrate antibiotics, heavy metals, and other compounds from the surrounding environment on their surfaces. These substances can also be incorporated into the plastic matrix during manufacturing. The resulting selective pressure on the MP-attached microbial communities can promote the selection of antibiotic resistance genes. The close physical proximity of microorganisms within the biofilm then facilitates horizontal gene transfer between them at rates potentially higher than those of free-living bacteria, thereby contributing to the spread of antimicrobial resistance[19]. Interestingly, biofilm formation on MPs in marine environments has been speculated to modify their organoleptic properties, making them less readily recognized as inedible particles by fish[20] and favouring ingestion by filter-feeders (e.g., oysters)[21]. This may ultimately contribute to human exposure through contaminated seafood and to a wider diffusion of antimicrobial resistance genes. Beyond acting as vectors for microorganisms, MPs have also been shown to alter the composition and diversity of the gut microbiota in experimental models[22–24]. Several mechanisms have been proposed, including physical damage to the gastrointestinal tract, and transport of pathogens and toxic chemicals[23]. Collectively, these effects can disrupt host-microbiome homeostasis, inducing dysbiosis and potentially contributing to chronic disease. Similar observations have also been reported with regard to human milk, where MP contamination has been associated with taxonomic shifts in the human milk microbiota[25].

4. Routes of MP exposure during pregnancy

Pregnancy is characterized by profound physiologic adaptations and behavioural changes, which may also influence exposure pathways and susceptibility to environmental contaminants. Furthermore, since during pregnancy the maternal body becomes the biologic interface between the external environment and the developing fetus, pollutants and toxicants affecting the mother may also affect the fetoplacental unit and the offspring, with potential short- and long-term implications. The main routes of exposure to MPs are ingestion, inhalation, and dermal exposure. Table 1 provides an overview of current human evidence on MP exposure during pregnancy.

4.1 Ingestion

Ingestion is considered a major route of MP exposure for humans. It has been estimated that, globally, humans may ingest on average 0.1-5 g of MPs per week[26]. MPs have been identified in shellfish[27], commercial salt[28,29], sugar and rice products[30], and chewing gum[31], suggesting that dietary exposure may represent a widespread source of MP intake during pregnancy. In a recent Indonesian study[32] on 30 pregnant women (56.7% in their second trimester of pregnancy), MPs were found in all fecal samples collected, ranging from 4 to 21 particles per 25 g of stool. The concentration of MPs in stool samples varied significantly according to seafood consumption levels.

Drinking water represents another relevant source of MPs, which have been detected in both tap[33] and bottled water[34]. A recent UK study[35] estimated an average daily intake among pregnant women of approximately 1 MP/kg body weight from drinking water. Although estimates vary across studies due to differences in analytical methodologies and particle size detection thresholds, Jamison Hart et al.[36] reported significantly higher concentrations of MPs in bottled water than in treated tap water, with NPs (<1 µm in size[7]) accounting for over 50% of the particles detected in both samples. MPs are thought to originate primarily from packaging materials, including bottles and bottle caps, as well as from industrial filtration processes. Conversely, with regard to tap water, an interesting study conducted in the Barcelona Metropolitan Area[37] documented that MPs are already present in upstream freshwater systems. However, their concentrations were found to decrease substantially throughout the drinking water treatment process before distribution to consumers, with an overall removal efficiency of approximately 93%.

MPs can be released from food-contact materials such as plastic packaging and food containers. Interestingly, one study documented that the abundance of MPs in the placenta of mothers who reported consumption of take-away food (which is commonly plastic-packaged) was 4.7 times higher than that found in the placenta of those who ate only home-cooked food[38]. Exposure to high temperatures may increase the release of MPs. A notable example in this regard is tea bags, which, when immersed in boiling water, have been shown to release large quantities of MPs[39]. However, the reported particle counts vary considerably across studies, likely due to differences in tea bag composition, experimental conditions, and analytical methodologies. Accordingly, the European Food Safety Authority (EFSA)[40] recently noted that, although the release of plastic particles from food-contact materials such as tea bags is well established, current evidence suggests that the magnitude of this release is likely lower than initially suggested in earlier studies. Cutting boards may represent another potential domestic source of MP exposure. Plastic cutting boards, most commonly made of PE or PP, may release MPs primarily through mechanical abrasion during routine food preparation, producing plastic fragments that can transfer to food. In their interesting study, Yadav et al. [41] estimated that using a PE cutting board could contribute between 20% and 33% of a person's daily intake of MPs via food. Importantly, MP release was associated with several factors, including cutting-board material, chopping style, and food characteristics, with harder foods (e.g., carrots), requiring greater cutting force, associated with greater particle release.

4.2 Inhalation

Airborne MPs are pervasive in both indoor and outdoor environments and may pose an under-recognized risk due to possible inhalation[42]. Recent studies have reported outdoor MP concentrations in diverse urban settings, such as Graz[43], Kyoto Prefecture[44], Shanghai[45] and Leipzig[46], although comparability between studies in terms of absolute values is hindered by methodological differences. Among the main sources of outdoor airborne plastics in urban contexts are traffic-related plastic particles derived from tyre wear or brake dust [47]. Conversely, indoor airborne MPs consist mainly of synthetic fibres shed from clothes, floor coverings, curtains and furniture, which can remain suspended in the air and continuously recirculate within enclosed spaces, thereby increasing exposure. Indoor concentrations of airborne MPs may exceed outdoor levels, as shown in a recent study conducted in the outskirts of Seoul reporting a 1.8-fold difference in the average abundances of indoor vs. outdoor air MPs (4.11 ± 2.63 vs 2.21 ± 1.28 particles/m³)[48]. The same study identified frequent and prolonged ventilation as an effective measure to reduce indoor MP concentrations [48]. Similarly, an Australian study found an inverse association between indoor MP deposition rates and frequency of vacuum cleaner use, whereas no association was found with nearby road density [49].

4.3 Dermal exposure

Dermal contact may represent an additional pathway of exposure to MPs, including through personal care products (e.g., scrubs, cosmetics, hair products) and synthetic textiles used in clothing and bedding. Evidence

from nanoparticle studies suggests that hydration state of the skin, mechanical stress, and particle size may play a role in skin penetration[50]. Although the stratum corneum normally provides an efficient barrier to absorption, during pregnancy physiological changes may occur that can modify skin structure and barrier function, potentially influencing dermal permeability[51]. However, *in vivo* human evidence on dermal absorption of MPs is still limited.

Personal care products may also represent a source of exposure to plastic-associated chemicals. Evidence from a recent prospective Canadian pregnancy and birth cohort study[52] showed that a more frequent use of hair sprays and gels, nail care products, fragrances and perfumes, makeup, and hair dyes, was associated with higher maternal plasma PFAS concentrations between 6 and 13 weeks' gestation. Additionally, prenatal or postnatal use of several personal care products was associated with higher PFAS concentrations in breast milk between 2 and 10 weeks postpartum. Notably, with the exception of general hygiene products (e.g., toothpaste, shampoo, soap), reported use of many cosmetic and personal care products appears to be less frequent among pregnant than non-pregnant women[53,54] and tends to decline during pregnancy[55].

5. Placental exposure and transplacental passage of MPs

After entering the maternal body through different pathways, MPs may reach the bloodstream and potentially distribute to multiple organs, including the placenta. The landmark study by Ragusa et al.[56] provided the first evidence of MPs within human placental tissue, identifying 12 pigmented fragments measuring 5-10 μm in 4 of 6 placentas, distributed across the maternal side, fetal side, and chorioamniotic membranes. Subsequent studies have expanded upon these observations. In 2023, a Czech study by Halfar et al.[57] reported the detection of MPs and/or additives (e.g., calcium zinc PVC stabilizer, zinc molybdate) in 8 of 10 placentas and in 6 of 10 amniotic fluid samples collected from pregnancies complicated by preterm prelabour rupture of membranes (PPROM). In 7 of the 10 patients, particle counts were lower in the amniotic fluid than in placental tissue, which the authors interpreted as suggesting that the placenta may function as a "partial barrier". Further studies have also identified MPs in venous umbilical cord blood[58], and in meconium[59,60]. Collectively, these findings are compatible with fetal exposure to plastic particles. Experimental *in vitro*, *ex vivo* and animal studies further support the biological plausibility of transplacental transfer, although the underlying transport mechanism is still unclear [61]. However, Sun et al.[58] reported no significant correlation between total MPs in maternal blood and those detected in the placenta, fetal membranes, umbilical cord, umbilical vein blood or amniotic fluid. Halfar et al.[57] did not report a correlation analysis between paired placental and amniotic fluid particle concentrations. Moreover, contamination during sample collection and processing cannot be excluded, particularly in studies conducted in clinical settings. Notably, Braun et al. [60] detected polyurethane both in airborne fallout from the operating room and in placental samples, raising the possibility of sample contamination.

The detection of MPs within tissues documents their presence in biological matrices but does not necessarily establish toxicologically meaningful exposure or direct clinical harm. However, experimental evidence from *in vitro* and animal models supports the biological plausibility of MP-induced placental dysfunction. In Sprague-Dawley rats[62], maternal exposure to 5- μm PS MPs through drinking water induced preeclampsia-like symptoms. Mechanistic analyses implicated activation of the HIF-1 α /TFRC axis, leading to iron overload and ferroptosis in trophoblast cells. Although animal studies may provide important mechanistic insights, their findings cannot be directly extrapolated to humans because of substantial species-specific differences in placental structure and function that may limit cross-species comparability. Additionally, differences between controlled experimental conditions and real-world exposures should be considered. Using the human trophoblast cell line HTR-8/SVneo, Hu et al.[63] reported that 100-nm PS NPs entered both the cytoplasm and nucleus of trophoblasts. Exposure was reported to reduce cell viability, induce cell-cycle arrest, impair cell migration and invasion, and increase levels of intracellular ROS and proinflammatory cytokines in a dose-dependent manner. These findings suggest that NPs may affect placental function through oxidative

stress and inflammatory pathways, mechanisms that have been associated with adverse pregnancy outcomes such as fetal loss, preeclampsia, preterm birth and other pregnancy-related complications. However, the authors acknowledge that the experimental concentrations used in their study may exceed environmental exposure levels and that the use of a single trophoblast cell line limits extrapolation to the human placenta.

Placental MP exposure has also been investigated in relation to telomere length, a well-established marker of biological aging. Specifically, in a Chinese cohort of 1121 pregnant women, Zhang et al.[64] reported a significant inverse association between placental concentrations of PVC and PBS and cord-blood and placental telomere length, and between placental PP and placental telomere length. No statistically significant interaction by infant sex was observed. Mixture analyses further showed that a one-quartile increase in combined MP exposure was associated with shorter telomere length in both cord blood and placenta, although the exposure-response relationship was non-linear. Importantly, the observational design of the study precludes any causal inferences. Similar inverse associations with telomere length have been reported for other environmental pollutants. For example, a 5 $\mu\text{g}/\text{m}^3$ higher PM_{2.5} exposure over the entire pregnancy was associated with 8.8% shorter cord blood leukocyte telomeres and 13.2% shorter placental telomeres [65].

Table 1. Overview of exposure to microplastics (MPs) during pregnancy: current evidence and knowledge gaps.

	Current human evidence	Main methodological limitations	Knowledge gaps	References
Maternal exposure routes	Ingestion and inhalation represent potential routes: MPs have been detected in food, drinking water, indoor and outdoor air, as well as in fecal samples from pregnant women.	Limited pregnancy-specific data on exposure routes; small sample sizes in pregnancy-specific studies; indirect assessment of exposure sources through environmental measurements and/or self-reported dietary and lifestyle questionnaires.	Longitudinal characterization of maternal MP exposure throughout pregnancy; relative contribution of individual exposure pathways to maternal MP burden; dermal exposure has been proposed, but evidence of systemic absorption through this route remains limited.	[32,35,38,58,59]
Placental exposure	MPs have been identified in human placental tissue, including maternal and fetal compartments. Several polymer types have been reported, with substantial variability in particle abundance and composition across studies.	Incomplete characterization of polymers; potential environmental and procedural contamination; placental sampling is generally performed at delivery and may not reflect exposure throughout pregnancy; heterogeneity in tissue sampling, processing, analytical methods and particle-size detection thresholds limits comparability between studies.	Relationship between maternal MP circulating levels and placental MP burden; temporal variation in placental MP burden throughout pregnancy; preferential accumulation of specific particle sizes or polymers; biological significance of placental MP deposition and accumulation.	[38,56–60]

Transplacental passage and fetal exposure	Detection of MPs in amniotic fluid, umbilical cord, umbilical venous blood and meconium supports the possibility of prenatal fetal exposure.	Small samples; limited paired maternal-fetal measurements; heterogeneous analytical methods and detection thresholds; incomplete characterization of particle transfer; potential contamination.	Extent, timing and mechanisms of maternal-to-fetal MP transfer under real-world exposure conditions; relationships between maternal, placental and fetal MP burdens; determinants of particle transfer and retention; actual fetal tissue exposure.	[57–60]
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6. Potential implications for offspring health

6.1 Microplastics

Although the presence of MPs has been widely documented in maternal, fetal and neonatal matrices, evidence on the association between prenatal exposure and adverse offspring outcomes is still limited and subject to substantial methodological limitations. In particular, analytical limitations in the detection of particles below specific size thresholds and the analysis of only selected polymers may result in incomplete characterization of placental MP burden[66–68]. Additionally, variability in tissue sampling and processing, together with the possibility of contamination, may affect particle counts[64,67–69]. Collectively, these limitations may lead to exposure misclassification and should thus be considered when interpreting the reported associations.

6.1.1 Preterm birth and IUGR

Despite the strong biological plausibility suggested by experimental studies, human evidence linking prenatal MP exposure to preterm birth is still limited. While Halfar et al.[57] identified MPs and additives in placental tissue and amniotic fluid samples from pregnancies complicated by PPROM, the study included only 10 women, all affected by PPROM. The lack of a control group, as well as the observational study design, limits the possibility to make causal inferences. Thus, although the study provides evidence of the presence of MPs in the biological matrices investigated, it cannot establish whether MP exposure is associated with PPROM or preterm birth.

Emerging human studies have reported associations between placental MP burden and fetal growth. An Iranian cross-sectional study[38] on 43 dyads reported a significantly higher load of plastic particles in placentas from term pregnancies complicated by intrauterine growth restriction (IUGR) compared with normal-growth pregnancies. Furthermore, the study found inverse associations between placental MP abundance and neonatal birth weight, length, head circumference, and 1-minute Apgar score. However, the study was limited by the cross-sectional design and small sample size, particularly in the IUGR group (n = 13). Additionally, the reported exposure-outcome relationships were based largely on correlation analyses, limiting the ability to account for potential confounding. A substantially larger Chinese cross-sectional study[67] involving 1750 mother-infant pairs found that higher placental MP concentrations were associated with lower birth weight, length, and head circumference, with evidence of polymer- and sex-specific differences. An interquartile-range increase in total placental MPs was associated with 107.7 g lower birth weight, with stronger associations observed among male infants. Mixture analyses supported cumulative inverse associations between placental MPs and fetal growth, although effect estimates varied across modelling approaches. The large sample size, standardized placental sampling and contamination-control

procedures are among the main strengths of the study. Nevertheless, despite the multivariable adjustment for a wide range of maternal, perinatal and socio-economic variables, other potential confounders, such as maternal diet, occupational exposures, or environmental co-pollutants, were not accounted for. Moreover, the observational, cross-sectional design, with both placental MP burden and birth outcomes assessed at delivery, limits the assessment of temporality and precludes causal inference. Finally, the fact that the study was conducted in a single region and included only term pregnancies may limit generalizability to other settings and populations.

6.1.2 Other outcomes

Endocrine disruption represents another biologically plausible pathway through which prenatal MP exposure may affect offspring development. In a Chinese study of 1324 pregnant women, higher placental MP burdens measured at delivery were associated with lower glucocorticoid concentrations and higher androgen levels in cord blood, with polymer-specific associations[66]. The large sample size, adjustment for several maternal and perinatal covariates, and complementary mixture analyses represent important strengths of this study. However, the cross-sectional design precludes causal inference, and residual confounding by unmeasured environmental exposures, diet, maternal health or other endocrine-disrupting contaminants cannot be excluded.

A subsequent study from the same institution involving 1250 mother-infant pairs reported that higher placental concentrations of PVC, PP, and PBS were associated with lower cord blood thyroid-stimulating hormone (TSH) and free T4 (FT4) levels, whereas PP was associated with higher free T3 concentrations[70]. However, several potentially relevant determinants, including maternal iodine intake, thyroid antibodies and parity-specific gestational weight gain, were not assessed. Importantly, cord-blood thyroid hormones may not fully represent fetal thyroid function.

Polymer-specific and mixture associations between placental MPs and higher cord-blood levels of liver enzymes (i.e., alkaline phosphatase, aspartate aminotransferase, and gamma-glutamyl transferase) [69], creatinine and cystatin C[68] were recently reported. Both studies benefited from direct quantification of placental MPs, adjustment for several maternal and perinatal covariates, and mixture-based statistical approaches. However, these biochemical measures cannot be interpreted as evidence of established fetal organ injury. Consequently, the clinical significance and long-term implications of these findings remain uncertain.

Notably, most of the studies reporting associations between placental MP burden and endocrine, hepatic and renal, as well as growth-related outcomes were conducted in the same city in northeastern China, during overlapping recruitment periods, and using similar participant selection criteria and analytical methodologies[66–70]. The extent of participant overlap across these studies is not clearly reported and should be considered when interpreting the apparent consistency of their findings. Regardless, the restriction to a single geographical and environmental context limits the generalizability of their findings. Consequently, although these studies provide interesting and thought-provoking evidence, independent replication in other, more diverse populations is warranted.

6.2 Plastic-associated chemicals

A major challenge in interpreting the available evidence on the health impacts of MPs is disentangling the effects of plastic particles from those of plastic-associated chemicals. In the following paragraphs we focus specifically on phthalates, given their widespread use as plasticizers and the growing evidence concerning their potential developmental toxicity. Nonetheless, prenatal exposure to other compounds, including BPA and PFAS, has also been associated with adverse offspring outcomes, particularly regarding growth, endocrine function, and neurodevelopment[71–74].

6.2.1 Preterm birth

Exposure to phthalates, a class of chemicals widely used as plasticizers to enhance the flexibility and durability of plastics, has been associated with higher odds of preterm birth in epidemiological studies, although the magnitude and consistency of these associations vary across compounds and study populations. According to a recently published global disease-burden modelling study[75], in 2018 approximately 1.97 million preterm births worldwide were estimated to be attributable to exposure to di-(2-ethylhexyl) phthalate (DEHP), representing nearly 9% of all global preterm births. Of these, 1.93 million cases were estimated to be attributable to DEHP used in plastic products. Similar estimates have been reported for diisononyl phthalate (DiNP), an alternative plasticizer. Interestingly, the authors[75] noted that the estimated effects of DEHP and DiNP might not solely reflect their specific toxicological effects, as these compounds could also act as proxies for broader exposure to MPs. However, it is important to emphasize that the reported figures are model-derived estimates, thus they should not be interpreted as directly observed cases of preterm births attributable to phthalate exposure.

Phthalates are more frequently encountered as complex mixtures than as individual compounds, thus mixture effects should be considered. In a pooled analysis of more than 6000 pregnancies from 16 prospective studies in the US, Welch et al.[76] found generally higher odds of preterm birth with increasing maternal urinary phthalate metabolite concentrations. In the mixture analysis, restricted to 5471 participants from 14 studies, an interquartile-range increase in a mixture of 9 maternal urinary phthalate metabolites was associated with a 25% increase in the odds of preterm birth (OR 1.25, 95% CI 0.88-1.77), although the wide 95% confidence interval including the null limits statistical certainty. The authors[76] further estimated that a hypothetical 50% reduction in maternal exposure to the phthalate mixture would correspond to 11.1 fewer preterm births per 1000 live births, highlighting the potential public health impact of reducing prenatal exposure. Major strengths of this study included its large pooled prospective sample, with inclusion of individual-level data from almost all US studies that quantified phthalate metabolites in pregnancy, and greater geographic and sociodemographic diversity than previous single-cohort studies. Sensitivity analyses generally supported the robustness of the findings, with little evidence of between-study heterogeneity and similar estimates after additional adjustment and leave-one-out analyses, although associations for some metabolites were attenuated after exclusion of the LIFECODES cohort. However, exposure assessment differed across cohorts, with some studies relying on a single spot urine sample, despite the known short half-life of phthalates. Additionally, residual confounding, particularly by diet, could not be excluded. Finally, spontaneous and indicated preterm births were not examined separately.

6.2.2 Endocrinological alterations

Many commonly used phthalates are recognized EDCs. In rodent models, prenatal phthalate exposure has been associated with impaired fetal testicular steroidogenesis, and with the so-called “phthalate syndrome”, a phenotype characterized by reduced anogenital distance (AGD), cryptorchidism, and other abnormalities of androgen-dependent reproductive development[77]. Whether a similar syndrome occurs in humans has yet to be demonstrated. Prompted by studies in animals, Swan et al.[78] evaluated the relationship between the concentration of maternal urinary phthalate metabolites and an age-adjusted AGD-to-weight index in 85 boys, reporting inverse associations for several phthalate metabolites. However, exposure was assessed in one urine sample collected at a mean gestational age of 28.3 weeks, potentially failing to capture exposure during the most sensitive developmental window, and children’s AGD was measured only once, between 2 and 36 months of age. Additionally, the validity of the AGD-to-weight index used in the study was subsequently questioned [79]. A more recent prospective study[80] on 506 mother-infant pairs measured maternal urinary phthalate metabolites before 18 weeks’ gestation and, in a subsample of 342 women, again at 18-25 weeks’ gestation. AGD was assessed at a median age of 12.9 months. Among 276 boys, prenatal phthalate concentrations were not associated with AGD, while associations with narrower penile width did

not persist after correction for multiple comparisons. Conversely, prenatal exposure to Σ DEHP and Σ DiNP was associated with longer AGD in female infants.

A Danish study[81] on 479 pregnant women from the Odense Birth Cohort Study evaluated the association between 12 urinary metabolites of six phthalate diesters measured at 28 weeks' gestation and infants' sex hormones at 3 months corrected age. The authors[81] reported a significant decrease in T/LH ratio during minipuberty in boys prenatally exposed to phthalates, which the authors interpreted as potentially indicative of impairment of Leydig cells. No clear association pattern was found in girls. Importantly, infant phthalate exposure was not assessed, precluding distinction between persistent effects of prenatal exposure and the potential contribution of concurrent postnatal exposure. Additionally, variability in the timing of infant assessment may have resulted in hormone measurements being obtained outside the minipuberty window in some participants, despite adjustment for age at examination.

Potential associations between prenatal phthalate exposure and the timing of pubertal onset have also been investigated. In the systematic review and meta-analysis by Uldbjerg et al.[82], the qualitative synthesis indicated an overall trend towards earlier menarche, thelarche, and pubarche in girls, with prenatal exposure to monoethyl phthalate (MEP) showing the most consistent associations. In boys, no clear trend emerged for genital development or pubarche, although some studies suggested earlier testicular enlargement. These trends were not consistently supported by the quantitative synthesis. The relatively small number of studies and the substantial methodological heterogeneity limited the possibility to draw definite conclusions. Additionally, evidence was insufficient to identify windows of increased susceptibility during pregnancy, while possible synergies and mixture effects that might have explained the associations between the EDCs considered and the timing of pubertal onset could not be adequately assessed.

Several studies have suggested that prenatal phthalate exposure may influence maternal[83,84], fetal, and neonatal thyroid hormone homeostasis, although the direction and magnitude of these associations vary across studies, and findings differ by metabolite, age and sampling method. In a prospective US birth cohort study, Romano et al.[84] evaluated prenatal exposure to phthalates by measuring 9 maternal urinary phthalate metabolites at 16 and 26 weeks' gestation and examined their association with thyroid hormone levels in cord serum samples from 276 newborns collected at delivery. The average of the two maternal urinary measurements was used to better characterize exposure across pregnancy. While only one phthalate metabolite (monobenzyl phthalate, MBzP) was significantly associated with reduced TSH levels in cord blood, mixture analyses revealed that combined prenatal exposure to phthalates was associated with lower cord blood TSH and total thyroxine levels. These findings suggest that mixture-based analyses may capture associations not evident when phthalate metabolites are considered individually. However, they should be interpreted with caution, since the study included a relatively small sample size, residual confounding by unmeasured thyroid-disrupting exposures could not be excluded, and numerous statistical tests were performed without correction for multiple comparisons, raising the possibility of chance findings. Moreover, the observed changes in cord-serum thyroid hormone concentrations were generally small and their clinical significance is uncertain. More recently, Xiong et al. [85] investigated prenatal exposure to phthalates and phthalate alternatives in 1202 mother-infant pairs from the prospective Wuhan Healthy Baby Cohort Study. Maternal urinary metabolites were measured in each trimester of pregnancy, while neonatal TSH was measured in heel-prick blood collected 48-72 hours after birth. Averaging concentrations across pregnancy, higher levels of many individual metabolites (including MMP, MEP, MEOHP, MEHHP, and the phthalate-alternative metabolite MECPTP) were associated with higher neonatal TSH, with estimated increases ranging from approximately 8% to 14% per interquartile-range increase in exposure. Trimester-specific analyses identified a larger number of positive associations during the second and third trimesters, particularly among girls, leading the authors to suggest that mid-to-late pregnancy may represent a period of greater susceptibility, although this pattern was not uniform across metabolites or sex. In mixture analyses, higher prenatal phthalate exposure was consistently associated with higher neonatal TSH levels in each trimester of

pregnancy. The repeated exposure assessment across pregnancy and the use of postnatal heel-prick TSH rather than cord-blood TSH are notable strengths of this study. However, thyroid function was assessed only by TSH, without T3 or T4 measurements, and information on maternal diet, other environmental pollutants, and genetic determinants of thyroid function was unavailable. Furthermore, since the analytic sample was a selected subset of the original birth cohort, selection bias cannot be excluded.

Longitudinal evidence further suggests that prenatal exposure to phthalates may be associated with altered thyroid function later in childhood as well. A study conducted within the Columbia Center for Children's Environmental Health (CCCEH) birth cohort[86] found that higher maternal urinary concentrations of mono(2-ethylhexyl) phthalate (MEHP, the primary metabolite of DEHP) in late pregnancy (mean gestational age 33.8 weeks) were unexpectedly associated with higher FT4 concentrations in 3-year-old children, with similar associations in girls and boys, whereas no prenatal phthalate metabolites were associated with TSH. Interpretation of these findings is nevertheless limited by the relatively small sample ($n = 181$) and by reliance on a single urinary measurement in late pregnancy, which may poorly characterize exposure over gestation given the short half-life and temporal variability of phthalates. Furthermore, maternal thyroid function was not measured, thus preventing assessment of whether maternal thyroid status might have contributed to the observed associations. Finally, in a prospective Korean cohort of 492 children, Kim et al. [87] evaluated the association between maternal phthalate exposure in the second trimester of pregnancy and offspring's thyroid function at 6 years, while also considering childhood phthalate exposure at 2, 4, and 6 years of age. Higher maternal urinary mono-n-butyl phthalate (MnBP) concentrations during pregnancy were associated with lower childhood TSH levels. No prenatal phthalate metabolite was associated with FT4 or T3. Interpretation of these findings is nevertheless once again limited by the use of a single maternal spot urine sample collected during the second trimester, which may not adequately represent exposure across pregnancy. Moreover, only a limited panel of metabolites was assessed.

6.2.3 Neurodevelopmental outcomes

A growing number of epidemiological studies have investigated whether prenatal phthalate exposure is associated with offspring neurodevelopment, although findings are often inconsistent across studies. A recent study on mother-newborn pairs enrolled in the Atlanta African American Maternal-Child Cohort[88] reported associations between maternal urinary phthalate metabolite concentrations and neonatal metabolomic features measured in dried blood spots collected within 24-48 h after birth, with several implicated metabolites and pathways related to tyrosine and tryptophan metabolism, which are involved in brain development and maturation. Additionally, in exploratory meet-in-the-middle (MITM) analyses conducted in smaller subsets of participants with data from the two exposure visits ($n = 81$ and $n = 71$), several neonatal metabolomic features were associated with at least one prenatal urinary phthalate metabolite and with attention or arousal scores on the NICU Network Neurobehavioral Scale (NNNS) at 2-4 weeks of age, corrected for gestational age at birth. Based on the results of the MITM analyses, the authors speculated that these metabolic perturbations might represent intermediate biological pathways potentially involved in the association between prenatal phthalate exposure and early neurobehavioural function. However, the MITM analysis was explicitly exploratory and based on a limited sample size, and no associations remained significant after correction for multiple testing.

Associations with neurodevelopmental outcomes assessed later in childhood and adolescence have also been investigated. However, the overall evidence is heterogeneous, with considerable variability across cohorts, neurodevelopmental domains, and metabolites considered. A 2020 systematic review found no clear overall pattern of association across cognitive, motor, behavioural, infant-behaviour and social outcomes, with most phthalate-outcome combinations supported by slight or indeterminate evidence [89]. More recently, a population-based neuroimaging study on 775 mother-child pairs from the Generation R cohort[90] reported that higher maternal urinary concentrations of MEP averaged across pregnancy were associated with smaller

total grey matter volumes in offspring at 10 years of age. Among the 671 participants with IQ data, mediation analysis suggested a possible indirect pathway between prenatal MEP exposure and lower full-scale Intelligence Quotient (IQ) at age 14 through smaller total grey matter volume. However, the estimated indirect effect's 95% confidence interval included the null, while the association between MEP and IQ was not statistically significant. In addition, higher prenatal concentrations of monoisobutyl phthalate (mIBP) were associated with smaller cerebral white matter volumes only in girls, and these structural differences partially mediated the relationship between mIBP and lower IQ among girls. This was reportedly the first study to investigate associations between prenatal phthalate exposure and offspring brain volumes using brain MRI, as well as the potential implications for general cognition. Exposure assessment was strengthened by the use of three spot urine measurements across pregnancy, which were averaged to better characterize gestational exposure. However, the moderate intraclass correlation coefficients between the three phthalate measures (ICCs; 0.37-0.68) indicate within-person variability, raising the possibility of residual exposure misclassification. Finally, the possibility of unmeasured confounding should be considered when interpreting the results of the mediation analysis.

Park et al.[91] extended previous research by evaluating both individual phthalate metabolites and their mixture. The authors investigated the associations between prenatal phthalate exposure and the odds of an Ages and Stages Questionnaire (ASQ-3) result indicating potential neurodevelopmental delay (NDD) in children aged 12-36 months in a large, multi-cohort US population (2378 pregnant parent-child dyads from 10 Environmental influences on Child Health Outcomes - ECHO - Cohorts). While several individual metabolites were associated with higher odds of potential NDD across multiple ASQ-3 domains, the direction and magnitude of associations were inconsistent, with some metabolites showing inverse associations. Mixture analyses were mostly non-significant, except for an inverse association between overall prenatal phthalate exposure and odds of delay in the personal-social domain. Since the authors did not adjust for multiple comparisons, these findings should be interpreted with caution. Furthermore, while, on the one hand, the inclusion of 10 geographically and demographically diverse cohorts provided a large sample with a broad range of exposure levels, on the other hand, this diversity also introduced heterogeneity between cohorts, including differences in population characteristics, timing of urine collection, and exposure assessment. Although the analyses accounted for cohort clustering and the findings were broadly consistent in leave-one-cohort-out analyses, some residual between-cohort variability may still have influenced the results. Exposure assessment was further limited by the availability of only one urine sample for approximately half of the participants and by the low ICCs observed for repeated measurements (0.08-0.29), indicating considerable potential for exposure misclassification. Moreover, children were assessed across a broad age range (12-36 months), characterized by marked developmental changes, potentially introducing additional heterogeneity in developmental profiles. The limited availability of repeated assessments also precluded evaluation of longitudinal developmental patterns.

7. Conclusions

The Plasticene may pose novel threats to early-life health.

During pregnancy, maternal exposure to MPs may occur through multiple routes, primarily ingestion and inhalation. MPs have been detected in placental tissue, amniotic fluid, umbilical cord blood, and meconium, providing evidence of placental and fetal exposure and supporting the possibility of transplacental passage, although its extent and mechanisms are still poorly understood.

Human evidence on prenatal MP exposure and adverse pregnancy and fetal outcomes is still scarce. Available data are currently insufficient to determine whether exposure to MPs contributes to preterm birth, despite biological plausibility. Inverse associations have been reported between placental MP burden and neonatal anthropometric measures. Higher placental MP concentrations have also been associated with altered cord-blood hormone profiles, changes in hepatic and renal biochemical markers, and shorter placental and cord-

blood telomeres. However, the clinical significance of these findings remains uncertain and causal relationships have yet to be ascertained.

The evidence for plastic-associated chemicals is substantially broader, particularly for phthalates. Epidemiological studies have reported associations between prenatal phthalate exposure and preterm birth. Endocrine findings are heterogeneous across compounds, exposure windows, sex, and timing of outcome assessment, and no consistent endocrine phenotype has emerged. Evidence on later neurodevelopmental outcomes is also growing, with longitudinal studies reporting associations between prenatal exposure to phthalates and subsequent neurobehavioural and cognitive outcomes, although findings are inconsistent across compounds and developmental domains.

Interpretation of the available evidence on both MPs and phthalate exposure is affected by several methodological limitations. Many MP studies are cross-sectional and assess placental exposure only at delivery, limiting temporal and causal inference. Additionally, several studies derive from relatively small or geographically restricted cohorts. Differences in particle-size detection thresholds and polymers assessed further limit comparability across studies, while sample contamination is often difficult to exclude, especially in clinical settings. Studies of plastic-associated chemicals are largely susceptible to exposure misclassification, residual confounding and challenges related to the assessment of complex chemical mixtures.

Overall, current evidence supports the occurrence of prenatal exposure to both MPs and plastic-associated chemicals and identifies potentially relevant fetal, neonatal, and longer-term associations. However, definitive causal relationships have not yet been established. Large multicentre prospective cohort studies with repeated exposure assessment throughout pregnancy and rigorous contamination-control protocols are needed to clarify exposure pathways, transplacental transfer and clinically meaningful short- and long-term consequences of prenatal exposure.

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CRedit authorship contribution statement

Alessandra Consales: Conceptualization, Writing - original draft, Writing - review & editing. Pilar Guerrieri: Writing - review & editing. Monica Fumagalli: Writing - review & editing, Supervision. Fabio Mosca: Conceptualization, Writing - Review & editing, Supervision.

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☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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