

Air Pollution Affects Placental DNA Methylation

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The Developmental Origins of Health and Disease (DOHaD) concept postulates that in utero exposures influence fetal programming and health in later life. Throughout pregnancy, the placenta plays a central role in fetal programming; it regulates the in utero environment and acts as a gatekeeper for nutrient and waste exchange between the mother and the fetus. Maternal exposure to air pollution, including heavy metals, can reach the placenta, where they alter DNA methylation patterns, leading to changes in placental function and fetal reprogramming. In this entry, we explore the current knowledge on placental DNA methylation changes associated with prenatal air pollution (including heavy metals) exposure and highlight its effects on fetal development and disease susceptibility.

[DOHaD concept](#)[air pollution](#)[heavy metals](#)[pregnancy](#)[placenta](#)[DNA methylation](#)

1. Introduction

Air pollution is an environmental problem that threatens human health and is a major cause of mortality worldwide. In 2019, air pollution caused an estimated 6.67 million deaths, accounting for 12% of all deaths globally [\[1\]](#). Pregnant women and their developing fetuses are particularly vulnerable to the adverse health effects of air pollution. In pregnant women, the respiratory adaptation to pregnancy leads to an increase in tidal volume and an increase in oxygen consumption [\[2\]\[3\]](#). Air pollution particles, due to their small size, are inhaled into the lungs, and the smallest particles infiltrate into the bloodstream reaching the placenta and fetus [\[4\]\[5\]\[6\]](#). Such in utero exposures can affect fetal development, cause adverse birth outcomes, and increase the risk of developing certain diseases in later life, as postulated by the Developmental Origins of Health and Disease (DOHaD) concept [\[7\]\[8\]\[9\]\[10\]](#).

Substantial evidence has associated prenatal air pollution exposure with a range of adverse health outcomes including gestational diabetes [\[11\]](#), preeclampsia [\[12\]\[13\]](#), spontaneous abortions [\[14\]\[15\]](#), preterm births [\[16\]\[17\]](#), low birth weights [\[18\]](#), macrosomia [\[19\]](#), and stillbirths [\[20\]](#). Furthermore, air pollution exposure during pregnancy was associated with an increased risk of developing cardiovascular diseases [\[21\]](#), neurodevelopmental alterations [\[22\]](#), respiratory problems [\[23\]\[24\]](#), and cancer [\[25\]\[26\]](#). However, due to the complex composition of air pollution and the intricate processes involved in fetal development, the mechanisms by which air pollution causes these adverse health effects are not yet completely understood.

During the entire pregnancy, the placenta serves as a functional interface that connects the mother to the developing fetus [\[27\]](#). It secretes hormones and regulates the in utero environment for optimum fetal growth and

development. Subsequently, the placenta transfers nutrients from the mother to the fetus and regulates gas and waste exchanges [27]. In this way, the placenta plays a central role in fetal programming, and we suggest that altered placental physiology and function, possibly through epigenetic modifications such as DNA methylation, can provide a mechanism linking prenatal air pollution exposure with pregnancy complications, fetal growth abnormalities, altered newborn phenotypes, and an increased risk of developing certain diseases during the lifespan. Here, we explore the current knowledge on placental DNA methylation changes associated with prenatal air pollution (including heavy metals) exposure and highlight its effects on fetal development and disease susceptibility.

2. Prenatal Air Pollution Exposure and Placental DNA Methylation

Numerous studies have shown that prenatal air pollution exposure affects global DNA methylation patterns in the human placenta [28][29][30][31][32][33]. In the ENVIRONAGE birth cohort, exposure to PM_{2.5} during different stages of pregnancy was associated with a lower degree of placental global DNA methylation [30]. In another study, mothers residing near major roadways, an indicator of traffic-related air pollution, showed decreased placental *LINE1* but not *AluYb8* methylation, common markers of global DNA methylation [31]. Furthermore, residing near a major roadway was associated with newborns that had low birth weights; however, the change in placental *LINE1* methylation did not mediate this relationship [31]. In contrast, a Chinese case-control study found that exposure to PM₁₀ in the first trimester was associated with decreased *LINE1* methylation in the placenta of fetal growth-restricted newborns [29].

A nested case-control study in Iran observed a positive correlation between global DNA methylation in the placenta and exposure to PM_{2.5} and PM₁₀ during the first trimester [33]. However, no significant correlation was found between exposures to particulate matter or placental global DNA methylation and birth outcomes such as gestational age, weight, length, and head and chest circumference [33]. The EDEN cohort showed a positive association with PM₁₀ exposure the day before birth and placental *Alu* methylation [28]. Furthermore, the EARLI study found that nitrogen dioxide and ozone also induced changes in placental global DNA methylation levels [32].

Apart from global DNA methylation, prenatal air pollution exposure was found to alter the promoter methylation of placental candidate genes that are involved in key biological processes [28][29][31][32][34][35][36][37][38][39][40]. In the EDEN cohort, exposure to nitrogen dioxide and PM₁₀ altered the methylation patterns of *ADORA2B*, *PXT1*, *KCTD20*, *CAPN10*, *SLC44A5*, *ADCK5*, *TGM6*, *TUBGCP2*, and *KYNU* in placental tissues [28]. These genes function in placental development and were previously associated with hypoxia and preeclampsia [41][42], a pathology that has been linked with air pollution exposure during pregnancy [12][13]. In a separate study, mothers living near major roadways showed differential methylation at seven CpG sites, three of which were located in protein-coding genes (*PTPRN2*, *TMEM125*, and *VPS4A*) [31]. Similarly, in the EARLI cohort, differentially methylated regions were found in five protein-coding genes (*F11R*, *ZNF442*, *SLC25A44*, *STK38*, and *PTPRH*) in the placenta of women exposed to high levels of nitrogen dioxide and ozone during pregnancy [32]. These differentially methylated regions in the placenta did not show DNA methylation changes in cord blood, and hence,

they appeared to be tissue-specific. Additionally, differentially methylated regions of three genes (*RNF39*, *CYP2E1*, and *PM20D1*) in cord blood showed consistent nitrogen dioxide and ozone exposure-related altered DNA methylation in the placenta [32], indicating that placental DNA methylation changes may be passed onto the developing fetus. These genes regulate immune and inflammatory responses, and their altered methylation patterns might play a role in preeclampsia.

In China, exposure to PM_{10} during the first and second trimesters increased *HSD11B2* methylation, a gene involved in fetal growth and glucocorticoid metabolism [29]. Furthermore, the increase in *HSD11B2* methylation was more prominent in the placental tissues of fetal growth-restricted newborns compared to the normal-growth newborns. Previously, *HSD11B2* methylation was negatively associated with placental *HSD11B2* gene expression, fetal growth indices, and adverse neurobehavioral outcomes in infants [43]. The Shanghai Mother-Child Pairs Cohort found that exposure to $PM_{2.5}$ during the second and third trimesters as well as the entire pregnancy was associated with increased methylation of *BID* and decreased methylation of *IGF2*; these genes are essential for fetal growth [40]. Furthermore, for every 1% increase in *BID* methylation, there was a decrease in head circumference and biparietal diameter in the second trimester [40]. In Korea, the COCOA study showed that high $PM_{2.5}$ exposure and low cord blood vitamin D levels during the first trimester were associated with decreased placental methylation of *AHRR*, *DPP10*, and *HLA-DRB1*, and early-onset persistent atopic dermatitis in children [39].

In the ENVIRONAGE birth cohort, $PM_{2.5}$ and black carbon exposure increased placental DNA mutation rates as well as increased the promoter methylation of tumor suppressor (*p53*) and DNA repair (*APEX1*, *OGG1*, and *ERCC4*) genes. This study suggested that prenatal $PM_{2.5}$ and black carbon exposure reduces the DNA repair capacity of the placenta and fetus, which may increase the risk for carcinogenesis in later life [36]. In the same cohort, the analysis of placental tissue from mothers exposed to $PM_{2.5}$ in the first and third trimesters showed altered methylation of the genes (*CLOCK*, *CRY1*, *NPAS2*, and *PER1–3*) involved in circadian rhythm regulation [35]. Previously, dysregulation in placental methylation of these circadian pathway genes was associated with preeclampsia [44]. Another study indicated that second-trimester $PM_{2.5}$ exposure decreased promoter methylation of the *Lep* gene, a hormone involved in intrauterine development, embryo implantation, energy regulation, and fetal growth [37]. Interestingly, the promoter methylation of *Lep* was higher in the placental tissue of male neonates compared to those of female neonates, suggesting that altered DNA methylation in the placenta may be sex-specific [37].

Prenatal air pollution exposure was also associated with altered placental mitochondrial DNA methylation [34][38]. In the ENVIRONAGE cohort, placental mitochondrial DNA methylation was analyzed in the *D-loop* control region and *MT-RNR1* region. First trimester $PM_{2.5}$ exposure was associated with increased mitochondrial DNA methylation at both the *D-loop* and *MT-RNR1* regions [34]. An increase in *D-loop* and *MT-RNR1* methylation was also observed in placental tissue following exposure to $PM_{2.5}$ for the entire pregnancy [34]. These findings were confirmed in a smaller sample population of the ENVIRONAGE cohort, where $PM_{2.5}$ and black carbon exposure throughout pregnancy increased *D-loop* and *LDLR* methylation [38]. In both studies, mitochondrial DNA methylation was negatively associated with mitochondrial DNA content, a measure of damaged mitochondria and mitophagy [34][38].

PM_{2.5} and black carbon exposure for the entire pregnancy also decreased placental promoter methylation of *PINK1*, a gene involved in mitochondrial quality control and mitophagy [38]. Moreover, a 0.42% increase in *D-loop* methylation was associated with decreased newborn birth weight [38].

3. Prenatal Heavy Metal Exposure and Placental DNA Methylation

Heavy metals such as arsenic, cadmium, lead, manganese, mercury, and nickel are common constituents of industry and traffic-related air pollution. Particulate matter, mainly PM_{2.5} and PM₁₀, has a strong potential for adsorbing heavy metals, which then enter the human body through inhalation [45]. There is increasing evidence that heavy metals bound to particulate matter play a crucial role in the adverse health effects caused by particulate matter [46][47][48]. Therefore, we also included studies investigating placental DNA methylation changes and prenatal exposure to heavy metals [49][50][51][52][53][54][55][56].

Most studies on prenatal heavy metal exposure and placental DNA methylation changes were conducted within the RICHHS cohort. In the RICHHS cohort, maternal exposure to high levels of arsenic, cadmium, lead, mercury, and manganese were associated with increased placental *NR3C1* methylation compared to the low exposure groups [49]. Placental *NR3C1* plays a vital role in cognitive and neurodevelopment by regulating the development of the child's hypothalamic-pituitary-adrenal (HPA) axis and cortisol levels. Therefore, altered placental *NR3C1* methylation may provide insight into cognitive and neurodevelopmental abnormalities in children in later life [49]. In a separate study, mothers with high toenail cadmium concentrations were found to have low levels of placental *PCDHAC1* methylation and were at an increased odds of giving birth to an infant that was small for gestational age or with a decreased head circumference [51]. Another study showed that high placental cadmium levels were associated with differential methylation at 17 CpG sites, and DNA methylation at 9 of these 17 CpG sites was associated with increased expression of genes involved in inflammatory signaling and cell growth (*TNFAIP2*, *EXOC3L4*, *GAS7*, *SREBF1*, *ACOT7*, and *RORA*) [52]. Furthermore, high placental expressions of *TNFAIP2* and *ACOT7* were associated with decreased birth weight. High placental expression of *ACOT7* was also associated with decreased birth length and decreased head circumference [52]. Moreover, within the RICHHS cohort, exposure to mercury, measured in infant toenails, was associated with differential methylation at 339 loci; 10 of these differentially methylated loci resided in the *CPLX1*, *TTC23*, and *EMID2* genes and were associated with a high risk for adverse neurobehavioral profiles [55]. Exposure to high levels of manganese, measured in infant toenails, was associated with differential methylation at 5 CpG loci (*EMX2OS*, *ATAD2B*, *FTO/RPGRIP1L*, *EN1*, and *LOC284276*). These CpG loci resided in genes involved in neurodevelopment (*EMX2OS*, *ATAD2B*, and *EN1*) and fetal growth (*FTO/RPGRIP1L*) [54]. The function of *LOC284276* is currently unknown; however, for every 10% increase in placental *LOC284276* methylation, there was a decrease in birth weight [54].

In the New Hampshire Birth Cohort Study, placental arsenic levels were associated with differential methylation at 163 CpG sites. Of these, 13 CpG sites attained genome-wide significance and were located at the *LYRM2* (11 CpG sites), *CAMTA1* (1 CpG site), and *CCDC57* (1 CpG site) genes [53]. A nested cohort in Bangladesh found that maternal exposure to arsenic, via contaminated drinking water, was associated with hypermethylation at several

CpG sites, which were mainly located within open sea regions [50]. Moreover, prenatal arsenic exposure was associated with CpG methylation at the *NR3C1* gene (unadjusted analysis) and the *TRA2B*, *PLCE1*, and *CD36* genes (adjusted analysis) [50].

The omega cohort and pilot case-control placenta microarray study showed that cadmium levels were higher in the placental tissues from female neonates (5 ng/g) compared to male neonates (2 ng/g). High cadmium levels were associated with hypomethylation at three CpG sites (*ARL9*, *SIAH3*, and *HS3ST4*) and one genomic region (region 86974674 to 86975244 on chromosome 7; *CROT* and *TP53TG1*) in the placental tissue of female neonates [56]. In the placental tissue of male neonates, high cadmium levels were associated with hypomethylation at two CpG sites (*MECOM*) and two genomic regions (region 169379554 to 169380078 on chromosome 3 and region 1792758 to 1792758 on chromosome 8; *MECOM* and *ARHGEF10*) as well as hypermethylation at one CpG site (*SALL1*) [56]. These differentially methylated genes are involved in cell damage response (*SIAH3*, *HS3ST4*, and *TP53TG1*) in females and cell differentiation, angiogenesis, and organ development (*MECOM* and *ARHGEF10*) in males. These results suggest that cadmium-associated placental DNA methylation changes may induce fetal growth abnormalities in a sex-dependent manner [56].

4. Conclusion

As a natural barrier that directly connects the mother to the developing fetus, the placenta is continuously in contact with substances to which both the mother and fetus are exposed [27]. Perturbations in the maternal environment can be transferred to the fetus through altered placental functions, a concept known as fetal reprogramming. As a result, the placenta, which is genetically identical to the fetus, contains important information on the in utero fetal life and can be considered as a “mirror” of the future health and development of the newborn [35]. The studies included in this entry provide evidence that prenatal air pollution and heavy metal exposure is associated with altered placental DNA methylation at both the global and candidate gene promoter levels [28][29][30][31][32][33][34][35][36][37][38][39][40][49][50][51][52][53][54][55][56] (summarized in Figure 1); however, whether the changes in gene promoter methylation affected the expression of the gene was not established in the majority of studies.

Aside from the studies on placental mitochondrial DNA methylation [34][38], no genes were investigated in more than one study. This makes it difficult to determine if the alterations in candidate gene promoter methylation are specific to a particular socio-demographic population or to prenatal air pollution exposure in a certain geographical location. Different locations have different sources and chemical compositions of air pollution and individual components are not often encountered in isolation within natural settings.

Two studies also showed that PM_{2.5} and cadmium-induced DNA methylation of genes were different in the placentae from male and female neonates [37][56], suggesting that the adverse health effects of these air pollutants may be sex-specific. Furthermore, prenatal exposure to air pollution induced inconsistent placental global DNA methylation changes, which may result from several other factors such as maternal diet or nutritional status and folate supplementation; folate is an essential micronutrient and methyl donor required during pregnancy to prevent neural tube defects in the fetus. Interestingly, trimester-specific analyses indicated that most of the placental DNA

methylation changes observed at birth followed air pollution exposures during the early stages of pregnancy [28][29][30][33][34][35][39], which is also when fetal epigenetic reprogramming occurs. Although this suggests that air pollution and heavy metal exposure during the early stages of pregnancy may, through altered placental DNA methylation, be responsible for fetal growth abnormalities, there was insufficient evidence linking prenatal air pollution and heavy metal-induced placental DNA methylation changes with specific diseases. Follow-up studies are required to determine if placental DNA methylation changes persist to the fetus and into adulthood and its possible implications on fetal development and disease susceptibility throughout the lifespan. Together, the findings depicted in this entry highlight the need for more effective and stricter environmental and public health policies to reduce air pollution and protect human health.

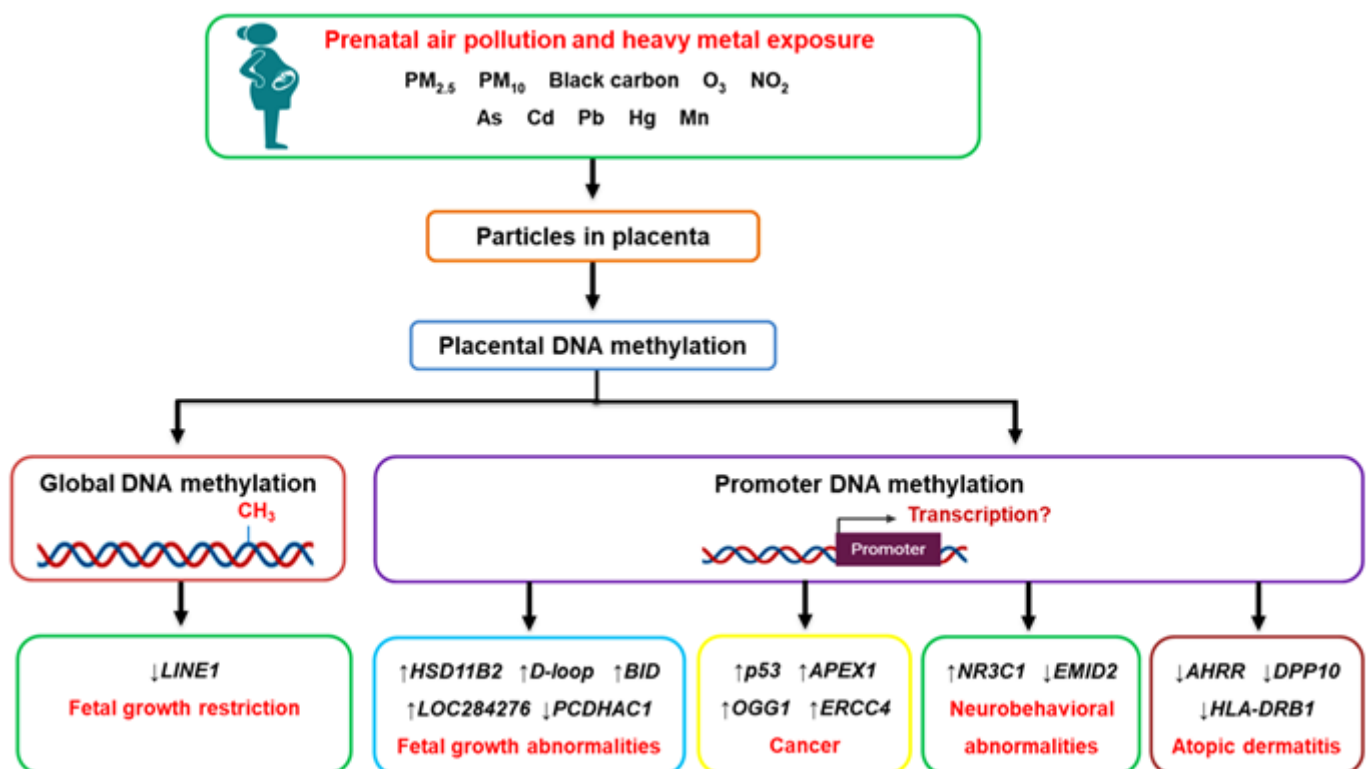


Figure 1. The effects of prenatal air pollution exposure on placental DNA methylation patterns and its implications on fetal development and future disease susceptibility. Maternal exposure to air pollution, including heavy metals, can reach the placenta, where they alter DNA methylation patterns at both the global and gene promoter level. The aberrant methylation of genes affects fetal growth (*HSD11B2*, *BID*, *D-loop*, *PCDHAC1*, *LOC284276*) and increases the risk of developing cancer (*p53*, *APEX1*, *OGG1*, *ERCC4*), neurobehavioral abnormalities (*NR3C1*, *EMID2*), and atopic dermatitis (*AHRR*, *DPP10*, *HLA-DRB1*) in later life.

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