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Placental gene networks at the interface between maternal $PM_{2.5}$ exposure early in gestation and reduced infant birthweight

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Authors' contributions

MAD conceptualized and contributed to the writing of the manuscript. MJR informed the implementation of the DLM analysis. MNE and GAW provided access and informed the processing of the daily $PM_{2.5}$ data. IK and JDS informed the modeling parameters to generate the daily estimates in $PM_{2.5}$ exposure. SP and KH provided access and insight into processing the placental RNAseq data. CJM is the Principal Investigator of the study population and provided access to all relevant datasets. CJM and JC contributed to the design, review of analysis and interpretation of study findings. All authors read and approved the final manuscript.

Ethics Approval and consent to participate

All participants provided informed consent, and the protocols were approved by the Institutional Review Boards at Women and Infants Hospital and Emory University.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Declaration of interests

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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Abstract

Background: A growing body of evidence links maternal exposure to particulate matter < 2.5 μM in diameter ($PM_{2.5}$) and deviations in fetal growth. Several studies suggest that the placenta plays a critical role in conveying the effects of maternal $PM_{2.5}$ exposure to the developing fetus. These include observed associations between air pollutants and candidate placental features, such as mitochondrial DNA content, DNA methylation and telomere length. However, gaps remain in delineating the pathways linking the placenta to air pollution-related health effects, including a comprehensive profiling of placental processes impacted by maternal $PM_{2.5}$ exposure. In this study, we examined alterations in a placental transcriptome-wide network in relation to maternal $PM_{2.5}$ exposure prior to and during pregnancy and infant birthweight.

Methods: We evaluated $PM_{2.5}$ exposure and placental RNA-sequencing data among study participants enrolled in the Rhode Island Child Health Study (RICHS). Daily residential $PM_{2.5}$ levels were estimated using a hybrid model incorporating land-use regression and satellite remote sensing data. Distributed lag models were implemented to assess the impact on infant birthweight due to $PM_{2.5}$ weekly averages ranging from 12 weeks prior to gestation until birth. Correlations were assessed between $PM_{2.5}$ levels averaged across the identified window of susceptibility and a placental transcriptome-wide gene coexpression network previously generated using the WGCNA R package.

Results: We identified a sensitive window spanning 12 weeks prior to and 13 weeks into gestation during which maternal $PM_{2.5}$ exposure is significantly associated with reduced infant birthweight. Two placental coexpression modules enriched for genes involved in amino acid transport and cellular respiration were correlated with infant birthweight as well as maternal $PM_{2.5}$ exposure levels averaged across the identified growth restriction window.

Conclusion: Our findings suggest that maternal $PM_{2.5}$ exposure may alter placental programming of fetal growth, with potential implications for downstream health effects, including susceptibility to cardiometabolic health outcomes and viral infections.

Keywords

birthweight; air pollution; placenta; RNAseq

Background

Studies to date have established that maternal exposure to air pollution can lead to deviations in infant birthweight, an indicator of gestational quality with implications for postnatal health. Spanning high and low income countries, these studies particularly point to reductions in fetal growth due to exposure to fine particulate matter < 2.5 μM in diameter ($PM_{2.5}$)(1–8). Reported findings include temporal associations between maternal $PM_{2.5}$ exposure and infant birthweight, suggesting critical windows of susceptibility during

gestation(9–16). Additional nuances in the overall relationship between maternal $PM_{2.5}$ exposure and birth outcomes include reports of sex-specific effects(17).

The mechanism through which maternal $PM_{2.5}$ exposure derails appropriate fetal development is not well characterized. The placenta, a transient gestational organ that sits at the maternal-fetal interface, is a likely candidate for conveying the effects of maternal $PM_{2.5}$ exposure to the developing fetus. Studies have shown the responsiveness of placental molecular features to $PM_{2.5}$ exposure, including alterations in global methylation(18), mitochondrial methylation(19), gene-specific expression(20) and gene-specific methylation(21). A few studies have further examined whether $PM_{2.5}$-induced changes in birthweight may be mediated through alterations in these placental molecular features, including global methylation(22), candidate gene expression levels(22), and mitochondrial DNA content(23). However, no reports to date include a whole transcriptomic survey that comprehensively captures placental processes in the pathway between maternal $PM_{2.5}$ exposure and aberrant fetal growth. We recently described a placental gene coexpression network(24) and reported associations with deviations in birthweight and trace metal exposure(25). In the current study, we leverage this placental gene network to evaluate coordinated perturbations in placental processes that may impart $PM_{2.5}$-related deviations in fetal growth.

Methods

Study Population.

Women were enrolled at Women and Infants Hospital in Rhode Island between 2009 and 2013 (n=840) as part of the Rhode Island Child Health Study (RICHS). Sex and gestational age matched birthweight percentiles were generated based on the 2013 Fenton growth curve(26). Small for gestational age (SGA, ≤10th birthweight percentile) and large for gestational age (LGA, ≥90th birthweight percentile) infants were oversampled in this population and matched by sex, gestational age and maternal age to appropriate for gestational age infants (AGA, >10th and <90th birthweight percentile). Enrollment was restricted to non-pathologic, singleton, term (≥37 weeks) pregnancies without congenital/chromosomal abnormalities. Obstetric and anthropometric data were abstracted from the medical record and additional lifestyle and family history data were recorded through an interviewer-administered questionnaire.

Air Pollution Exposure.

Daily $PM_{2.5}$ estimates were assigned to maternal residential addresses using hybrid spatiotemporal models as previously described(27–29). Briefly, participant addresses at the time of delivery were geocoded using ArcMap 10.1 (ESRI; Redlands, CA). Daily satellite aerosol optical depth (AOD) measurements were assigned to grid cells at a 1×1km resolution. Predicted $PM_{2.5}$ values for each grid cell were based on daily calibrated models (R^2=0.88), regressing ground-level $PM_{2.5}$ data from monitoring sites on the assigned AOD-based $PM_{2.5}$ values and additional temporal and land use predictors using mixed-effects models. The initial set of daily calibrated $PM_{2.5}$ models were fit on data where both ground monitoring and AOD measurements were available. These models were then updated and

applied to fill in predictions for cells with missing monitoring data as well as days with missing AOD values. Finally, the residuals of the finalized models were regressed against local land use factors at a 200 × 200m scale to map predicted grid-level exposures to residential address-specific estimates. Among participants of the RICHS cohort, $PM_{2.5}$ data was available for infants born prior to 2013 and with a known residential address at the time of delivery. For each participant, we evaluated $PM_{2.5}$ exposure during a window spanning 12 weeks pre-conception until birth. We focus on this exposure window as it captures the timespan most relevant to placental development. In the period immediately prior to conception, air pollution may derail maternal processes necessary to support optimal placentation(30). Following placentation, air pollution may continue to impede placental function throughout gestation as the placenta adapts to accommodate the needs of the developing fetus.

Placenta Specimen Collection.

Placental biopsies were excised exclusively on the fetal side from four quadrants within 2 cm of the cord insertion site, rinsed, and stored in RNALater. Within 72 hours, the biopsies were pooled, snap-frozen in liquid nitrogen, homogenized and stored at −80°C until further analysis.

Nucleic Acid Extraction and RNA-sequencing.

Total RNA was isolated from placental samples using an RNeasy Mini Kit. RNA yield was quantified using a NanoDrop ND-1000, and RNA integrity was assessed using an Agilent Bioanalyzer. Following rRNA depletion using a RiboZero kit, RNA libraries were prepared for sequencing on a HiSeq 2500 platform (Illumina, San Diego, CA). Sequencing runs generated single-end 50bp reads. Raw FASTQ files that passed quality control assessment using the FASTQC software were mapped to the human reference genome (hg19) using the Spliced Transcripts Alignment to a Reference (STAR) aligner. The data was filtered to remove lowly expressed genes, adjusted for GC content, corrected for library size using the trimmed mean of M values (TMM) method, and transformed to log counts per million (CPM) values. The final data-set included 12,135 genes. Placental RNASeq data was generated in a representative subset of RICHS participants (n=200) (24).

Statistical Analysis.

Daily estimated levels of $PM_{2.5}$ exposure for each participant were aggregated into weekly averages, We implemented distributed lag models (DLMs) to evaluate the time-varying association between $PM_{2.5}$ exposure during a given week and size for gestational age at birth (birthweight percentile, SGA vs. AGA, LGA vs. AGA). This method incorporates data from all time points simultaneously and assumes that the association between the outcome and exposure at a given time point, controlling for exposure at all other time points, varies smoothly as a function of time. The shape of the exposure-lag-response relationship is constrained by a set of basis functions (e.g., splines), with the functions defining the exposure-response relationship and the lag-response relationship combined in a bi-dimensional space of cross-basis functions. Estimation is then performed using a standard regression model, including the matrix of cross-basis functions in the model formula(31). In the current study, the exposure-response relationship was assumed to be linear, and the lag-

response relationship was fit using basis spline (B-spline) functions centered at 0, with degrees of freedom selected based on model parsimony and Akaike information criterion (AIC). The continuous birthweight percentile model was fit with 2 degrees of freedom, the SGA model was fit with 2 degrees of freedom, and the LGA model was fit with 4 degrees of freedom; additional smoothing did not significantly improve the model. Sensitive windows to $PM_{2.5}$ exposure were identified in regions where point estimates and 95% confidence bands do not include 0 (continuous models) or 1 (categorical models). Models were also evaluated stratified by infant sex. DLMs were performed using the dlnm R package version 2.3.9.

Weighted gene coexpression network analysis (WGCNA) was performed using placental transcriptome-wide gene expression data as previously described(24). Briefly, a similarity matrix was generated based on absolute values of pairwise Pearson correlations and transformed into an adjacency matrix using a weighted soft threshold (β =6). Genes were grouped into modules based on hierarchical clustering of their topological overlap. Each module was summarized by the first principal component of each module, defined as the module eigengene. To overlay $PM_{2.5}$ exposure with the placental gene coexpression network, $PM_{2.5}$ exposure was averaged across the identified growth restriction exposure window (GREW, 12 weeks prior to conception through 13 weeks gestation). Spearman correlations were calculated between average $PM_{2.5}$ and the module eigengenes.

In addition to accounting for infant sex and gestational age in the Fenton growth curve-based outcome assignment, all regression models were additionally adjusted for maternal age, maternal education, and season of birth. All analyses were conducted using R version 3.6.2. R code for the presented analysis is available at https://github.com/mdeyssen/RICHS_WGCNA_AirPop.

Results

The demographic characteristics of the study population and comparisons to the full RICHS cohort are shown in Table 1. For the current study, we performed two sub-cohort analyses, one leveraging all participants with available $PM_{2.5}$ exposure data (n=471) and one overlapping the $PM_{2.5}$ data with available placental gene network information (n=149). Overall, both sub-cohorts are representative of the full cohort, reflecting a population of primarily of Caucasian descent (> 70%) and average $PM_{2.5}$ levels across gestation of approximately 8 $\mu g/m^3$. Notable differences include a slightly older maternal age, a shift in the season of birth distribution and higher birthweight percentiles among the analyzed sub-cohorts compared to the full RICHS cohort.

We observe a reduction in infant birthweight percentiles due to a 1ug increase in $PM_{2.5}$ sustained across all lags. However, this cumulative effect did not meet statistical significance (−4.62, [95% Confidence Interval (CI): −9.35, 0.09]). Evaluating the time-varying association between maternal $PM_{2.5}$ exposure and infant birthweight percentiles, we observe a significant inverse association during an exposure window spanning 12 weeks prior to conception until 13 weeks gestation (Figure 1a). For the categorical birthweight outcomes (AGA, LGA and SGA), we observe a significant increased risk of SGA status due to a 1 ug

increase in $PM_{2.5}$ sustained across all lags (cumulative Risk Ratio (RR): 1.60, [95% CI: 1.03, 2.47]. In addition, an increased risk of SGA compared to AGA status is specifically observed during an exposure window spanning 2 weeks prior to conception until 14 weeks gestation (Figure 2a). There is no significant effect on LGA status due to a 1 ug increase in $PM_{2.5}$ sustained across all lags (cumulative RR: 0.93, [95% CI: 0.67, 1.29]. However, a time-varying effect on LGA status due to $PM_{2.5}$ is observed during two sensitive exposure windows. A decreased risk of LGA compared to AGA status is observed during an exposure window spanning 3 weeks prior to conception until 8 weeks gestation. Additionally, an increased risk of LGA compared to AGA status is observed during an exposure window spanning 29 until 32 weeks gestation (Figure 3a).

In our sex-stratified analysis, we observe a significant cumulative effect on birthweight percentiles due to a 1 ug increase in $PM_{2.5}$ sustained across all lags among female infants (−7.37, [95% Confidence Interval (CI): −14.68, −0.06]). In addition, a significant inverse association is specifically observed between maternal $PM_{2.5}$ exposure in the 6 weeks prior to conception until 13 weeks gestation and birthweight percentiles (Figure 1b). No significant cumulative effect across all lags (−2.71, [95% Confidence Interval (CI): −9.18, 3.77]) or sensitive window of exposure is observed among male infants (Figure 1c). Modeling birthweight as a categorical outcome, we observe a significant cumulative effect on SGA status due to a 1 ug increase in $PM_{2.5}$ sustained across all lags among female infants (cumulative RR: 2.13, [95% CI: 1.09, 4.16]) but not male infants (cumulative RR: 1.64, [95% CI: 0.83, 3.24)]. We observe a time-varying effect on SGA risk due to maternal $PM_{2.5}$ exposure among both male and female infants, in offset windows of exposure. Among female infants, a sensitive exposure window is detected between 7 and 16 weeks gestation (Figure 2b). Among male infants, a sensitive exposure window is detected between 12 and 7 weeks prior to conception (Figure 2c).

No significant cumulative effect on LGA status due to a 1 ug increase in $PM_{2.5}$ sustained across all lags is observed among female infants (cumulative RR: 0.79, [95% CI: 0.46, 1.34]) or male infants (cumulative RR: 1.06, [95% CI: 0.68, 1.65]). However, two sensitive windows of $PM_{2.5}$ exposure are observed in relation to LGA status is observed among female infants. A significant inverse association is observed in the 5 weeks prior to conception until 6 weeks gestation, and a positive association is observed between 26 weeks and 30 weeks gestation (Figure 3b). No significant sensitive window of exposure was observed in relation to LGA status among male infants (Figure 3c).

To overlay our $PM_{2.5}$-related findings with our previously described placental gene coexpression network(24), we averaged maternal $PM_{2.5}$ exposure from 12 weeks prior to conception and 13 weeks gestation, corresponding to the sensitive window of exposure identified in the birthweight percentile analysis, as this window also includes the growth restriction window identified in the SGA and LGA analyses. We refer to this summary measure as the $PM_{2.5}$ growth-restriction exposure window (GREW) average. Differences in this $PM_{2.5}$ GREW average across the birth weight groups are shown in Figure S1.

Consistent with the full cohort of participants with $PM_{2.5}$ measurements (n=470), in the sub-cohort of participants with both $PM_{2.5}$ and placental gene expression data (n=149),

birthweight decreases as average $PM_{2.5}$ levels increase, although this change did not reach statistical significance (p=0.10).

In a previous study, we identified 17 placenta gene modules in the placenta(24). Spearman correlations between these coexpression modules and the $PM_{2.5}$ GREW average as well as key demographic variables are shown in Figure 4. The Gene Ontology (GO) enrichment analysis terms associated with each module are shown along the y-axis. The $PM_{2.5}$ GREW average is positively correlated with modules enriched in amino acid transport (red), cellular respiration (turquoise) and cell adhesion (tan) processes and inversely correlated with modules enriched in the vasculature development (blue) and organ development (yellow) processes. As shown in the figure, the amino acid transport (red) and cellular respiration (turquoise) modules are additionally inversely correlated with birthweight percentiles. An increase in both amino acid transport and cellular respiration module activity as well as $PM_{2.5}$ GREW average is linked to a decrease in birthweight percentiles. Hence, the positive correlation between the $PM_{2.5}$ GREW average and these two modules is consistent with their respective inverse relationships with fetal growth.

Figures 5 and 6 further demonstrate the opposing direction in the correlations between genes in the cellular respiration and amino acid transport modules and the $PM_{2.5}$ GREW average and birthweight percentiles. Thirty-two genes in the cellular respiration module are correlated ($r > |0.20|$) with both the $PM_{2.5}$ GREW average and birthweight percentile, as indicated on the y-axis of each panel in Figure 5. Thirty genes (*ACBD3*, *C14orf153*, *C1orf212*, *CCDC53*, *CLTB*, *DCTN6*, *DNLZ*, *EIF5A*, *FUNDC2*, *GNG4*, *HSD17B10*, *LLPH*, *NCRNA00116*, *NDUFA1*, *NDUFB10*, *PDE6D*, *PGM2*, *PTMA*, *RAB2A*, *SNRPG*, *SRP54*, *SSU72*, *SYAP1*, *TMUB1*, *TXNDC12*, *UBQLN1*, *UBXN1*, *UTP18*, *ZBTB11*, *ZC3H15*) are positively correlated with the $PM_{2.5}$ GREW average and inversely correlated with birthweight percentiles, and 2 genes (*CDK18*, *LRRC4*) are inversely correlated with the $PM_{2.5}$ GREW average and positively correlated with birthweight percentiles. Additionally, as these are among the genes most highly correlated with the module eigengene value (x-axis of each plot), these genes are considered module hub genes reflective of overall module activity. In the amino acid transport module (Figure 6), only one gene, *SPTY2D1*, is correlated ($r > |0.20|$) with both the $PM_{2.5}$ GREW average and birthweight percentiles. This gene is positively correlated with the $PM_{2.5}$ GREW average and inversely correlated with birthweight percentiles. Given its correlation with the module eigengene value (x-axis), *SPTY2D1* expression is also a module hub gene representative of overall module activity.

Discussion

We observed associations between maternal $PM_{2.5}$ exposure extending from the preconception to the early gestational period and reductions in infant birthweight. The identified window of sensitivity was largely consistent across different parameterizations of birthweight. The window identified in association with reduced birthweight percentiles (12 weeks prior to conception – 13 weeks gestation) is consistent with the $PM_{2.5}$ window in association with increased risk of SGA compared to AGA status (2 weeks prior to conception – 14 weeks gestation) and the $PM_{2.5}$ window in association with decreased risk of LGA compared to AGA status (3 weeks prior to conception – 8 weeks gestation). In the

LGA analysis, a $PM_{2.5}$ exposure window late in gestation (29 weeks – 32 weeks gestation) is additionally associated with increased risk of LGA compared to AGA status. Stratifying by sex, the findings among female infants coincide with the overall findings while the findings among male infants are largely null.

Our findings of a $PM_{2.5}$ exposure window early in gestation in association with reduced birthweight is consistent with a number of studies reported in the literature (9,10,12–14,16,32–35). We also identified an exposure window late in gestation that is associated with LGA status. Prior studies that specifically evaluated fetal overgrowth have reported similar associations (36,37). The apparent differential effect of $PM_{2.5}$ exposure on birthweight in early gestation compared to late gestation could reflect a shift in how the placenta functions as it adapts to accommodate the increasing metabolic demands of the fetus. $PM_{2.5}$ may impact the role of the placenta in appropriate implantation and establishment of maternal blood flow early in gestation. Later in gestation, the placenta plays a more pronounce role in growth hormone and fatty acid regulation, and $PM_{2.5}$ exposure may disrupt these placental processes in support of the rapid fetal growth and changes in fetal tissue composition that occur during this period.

However, there are also studies that did not identify specific temporal windows (2,37–44) while others identified different temporal windows (45–61). It is important to note that our findings are based on weekly averages of $PM_{2.5}$ while these prior reports mainly evaluated trimester-specific effects. Trimesters represent three month averages that can coincide with seasonal trends in $PM_{2.5}$ levels, introducing a potential bias due to induced correlations among the averages. The implementation of a distributed lag model on weekly $PM_{2.5}$ averages as applied in the current study is less susceptible to this type of bias(62). Given that not all developmental processes are neatly encapsulated within trimesters, using a more fine-scale approach of weekly averages also has the additional benefit of greater sensitivity to identify more refined windows of susceptibility that can capture perturbed biological processes that may otherwise be missed using trimester-level averages. While we did not interrogate the biological underpinnings of the preconception and early pregnancy period of susceptibility identified in the current study, this window may reflect an impact due to $PM_{2.5}$ exposure on maternal physiology that compromises the ability to adequately establish and provide placental support to the developing fetus. Indeed, studies have shown that exposure to criteria air pollutants in the preconception and early pregnancy period are associated with maternal comorbid conditions, such as gestational diabetes. (63). Priming of such derailments in maternal physiology may occur as early as the pre-conception period, impeding maternal support of placental development required for adequate fetal growth.

Few studies to date have reported on sex-specific effects of maternal $PM_{2.5}$ exposure on fetal growth(17,64). Contrary to the findings reported in the current study, these studies report a stronger deficit in fetal growth among male infants due to PM2.5 exposure. However, the studies differ in how PM2.5 exposure was parameterized and evaluated, limiting the comparability of the reported findings. For example, one study evaluated personal PM2.5 exposure levels averaged across a 48hr period during the second trimester, and another study evaluated ambient PM2.5 averaged across gestation and stratified by maternal obesity.”

The underpinnings of a differential impact on female infants due to preconception and early gestational $PM_{2.5}$ exposure warrant further exploration.

Overlaying our previously delineated placental gene coexpression network with $PM_{2.5}$ exposure averaged across the identified growth restriction window, we identified 5 coexpressed gene modules that are correlated with maternal $PM_{2.5}$ exposure. Out of these five modules, modules enriched for amino acid transport and cellular respiration processes, based on Gene Ontology (GO) enrichment analysis, are additionally correlated with birthweight percentiles.

Consistent with the Gene Ontology term assigned to the cellular respiration module, ATP-dependent processes predominate among the module hub genes that are correlated with maternal $PM_{2.5}$ exposure and infant birthweight percentile. These include genes that directly interact with mitochondrial processes, including *ACBD3*(65), *C14orf153*(66), *DCTN6*(67), *DNLZ*(68), *FUNDC2*(69), *HSD17B10*(70), *NDUFA1*(71,72), *NDUFB10*(72). The upregulation of mitochondrial processes fuels ATP-dependent cellular processes, with genes involved in cell motility (*PDE6D*)(73), muscle contractility (*SYAP1*, *TMUB1*)(74,75), intracellular vesicle transport (*ACBD3*, *DCTN6*, *CCDC53*) (65,76,77), and autophagy (*TMUB1*, *UBQLN1*)(78,79). Autophagy, in turn, is an important component in host response to viral infections (*ACBD3, TMUB1, C1orf212, DCTN6, UBXN1*) (65,78,80–82). Changes in CpG methylation levels at one of these viral infection susceptibility loci, *C1orf212*, was previously additionally linked with $PM_{2.5}$ exposure(83). For the amino acid transport module, only one hub gene, *SPTY2D1*, was correlated with both maternal $PM_{2.5}$ exposure and infant birthweight percentile. Prior studies most commonly link single nucleotide polymorphisms (SNPs) in this gene with overall(84,85) and sex-specific(86) differences in lipid profiles.

Recently reported human and animal studies also implicate $PM_{2.5}$ exposure with alterations in the placenta, including histopathology changes(87,88), increased oxidative stress(89), increased placental aging(90), altered expression of candidate genes(20,91), mitochondrial DNA content and elevated global methylation(92). Among these studies, those that additionally evaluated placental impacts across temporal windows of exposure also identified early gestation as a critical period of sensitivity(20,92). The findings of the current study build upon these early links through a more comprehensive placental transcriptomic survey that pinpoints specific biologic processes as candidates for being dysregulated through $PM_{2.5}$ exposure during the early gestational period. Taken together, these findings suggest that early maternal exposure to $PM_{2.5}$ impacts fetal growth, particularly among female infants, and may program immune activation in response to viral infections and cardiometabolic outcomes later in life.

There are several limitations in this study that warrant caution in the interpretations of the findings. Complete data on maternal $PM_{2.5}$ exposure, placental gene expression, and infant birthweight was only available on a subset of the cohort (n=149), limiting the power of our study. For example, formal testing of the placental network genes as mediators in the pathway between maternal $PM_{2.5}$ exposure and infant birthweight was not feasible since the main effect between maternal $PM_{2.5}$ exposure and infant birthweight did not reach statistical

significance within the subcohort of participants with both $PM_{2.5}$ and placental gene expression data. In addition, gene expression changes were evaluated in placenta collected at birth while the presented findings suggest early gestation as a sensitive window to maternal $PM_{2.5}$ exposure. While it is possible that early gestational exposure impacts appropriate placentation with persistent effects detectable at term (e.g., insufficient vascularization), we cannot discern whether our identified marks reflect such a direct effect or rather a secondary adaptive placental response. A live birth bias may also impact our findings if we expect air pollution exposure to contribute to early fetal loss(93). Since early fetal loss is often unreported, this critical susceptible subset among the truly exposed is not accounted for in our study, and conditioning our analyses on data stemming from recorded birth information can introduce a selection bias. Finally, our air pollution exposure assessment specifically focused on particulate matter components while data on other criteria air pollutants (e.g., carbon monoxide, nitrogen dioxide and ozone) and indoor air pollutants were not available to be evaluated. Future studies that account for the mixed sources and composition of air pollution may better capture effects reflective of true exposure profiles.

Conclusions

This study adds to the existing body of literature pinpointing the preconception and early gestation periods as critical windows of susceptibility to maternal $PM_{2.5}$ exposure induced effects on fetal growth restriction. Furthermore, this is among the first epidemiologic studies linking a critical window of susceptibility due to maternal $PM_{2.5}$ exposure to potential placental programming impacts on fetal development. Our findings suggest that maternal $PM_{2.5}$ exposure may alter placental programming of fetal growth, with potential implications for downstream health effects, including susceptibility to viral infections and cardiometabolic health outcomes. This adds to the growing policy impetus to reduce global air pollutant levels to protect the unborn child. Until this goal is realized, interim strategies should focus on emphasizing exposure mitigation strategies, particularly among women of childbearing age.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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List of Abbreviations

AIC	Akaike information criterion
AOD	Aerosol optical depth
B-spline	Basis spline
DLM	Distributed Lag Model

GO	Gene Ontology
GREW	Growth restriction exposure window
$PM_{2.5}$	Particulate matter < 2.5 μM in diameter
SGA	Small for gestational age
LGA	Large for gestational age
AGA	Appropriate for gestational age
STAR	Spliced Transcripts Alignment to a Reference
RICHS	Rhode Island Child Health Study
WGCNA	Weighted Gene Coexpression Network

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Highlights

- $PM_{2.5}$ exposure in the periconceptional and early prenatal period is associated with reductions in fetal growth.
- Female infants are particularly vulnerable to $PM_{2.5}$ induced deficits in fetal growth.
- Disruptions in placental processes involved in protein transport and other ATP-driven processes may play an important role in conveying the impact of $PM_{2.5}$ on the developing fetus.

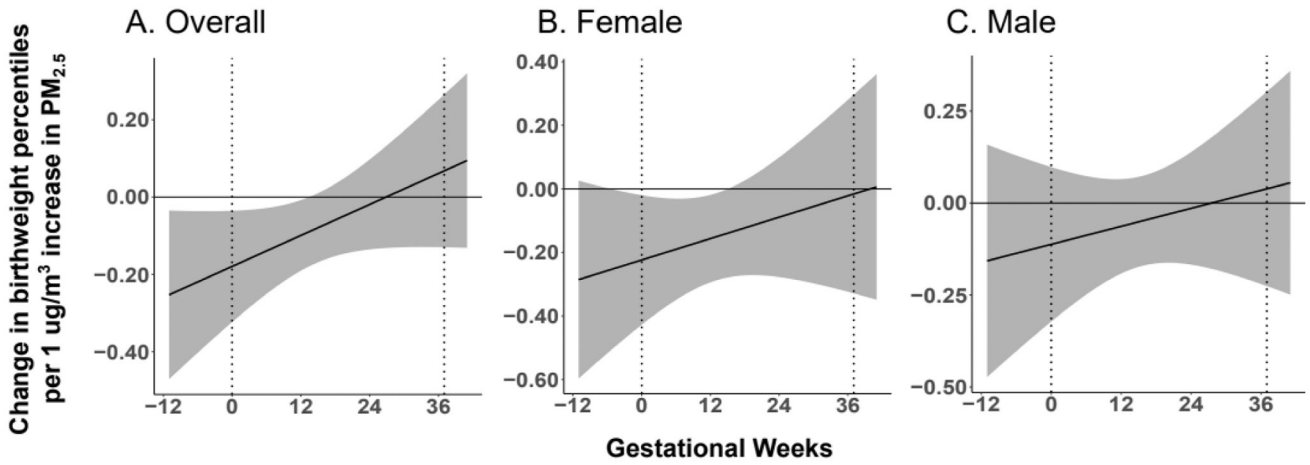

Figure 1. Association between maternal $PM_{2.5}$ exposure and infant birthweight percentiles.

A. Maternal $PM_{2.5}$ exposure from 12 weeks prior to conception until 13 weeks gestation is inversely associated with infant birthweight percentiles. B. Among female infants, maternal $PM_{2.5}$ exposure from 6 weeks prior to conception until 13 weeks gestation is inversely associated with birthweight percentiles. C. Among male infants, no association is observed between maternal $PM_{2.5}$ exposure and birthweight percentiles. Stratifying our analyses by sex, an overall cumulative effect on infant birthweight percentiles due to a 1 ug increase in $PM_{2.5}$ sustained across all lags is observed among female infants (−7.40, [95% CI: −14.78, −0.03]) but not among male infants (−2.72, [95% CI: −9.21, 3.77]).

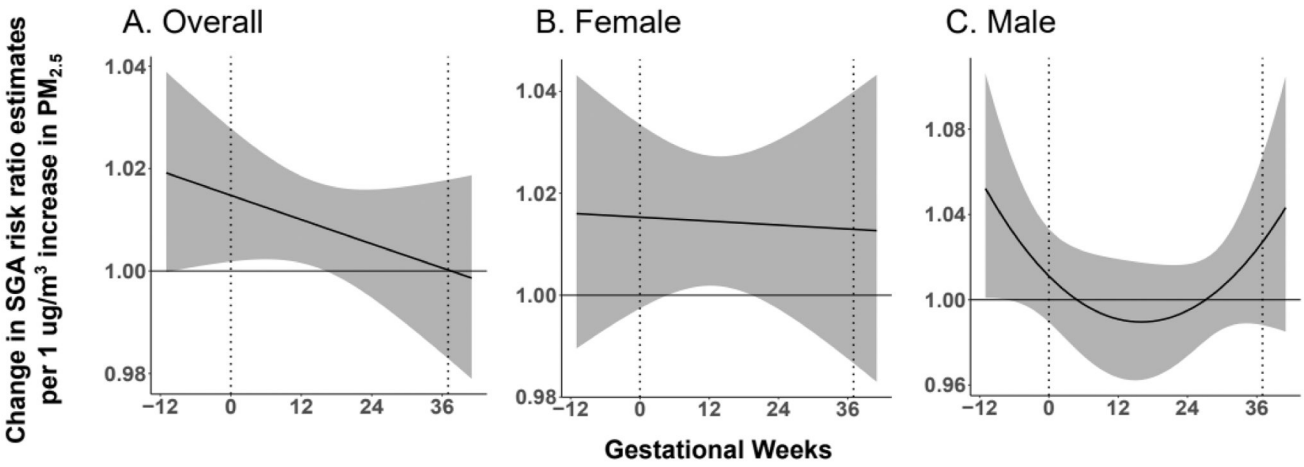

Figure 2. Association between maternal $PM_{2.5}$ exposure and SGA status at birth.

A. Maternal $PM_{2.5}$ exposure from 2 weeks prior to conception until 14 weeks gestation is associated with increased risk of SGA status at birth. B. Among female infants, maternal $PM_{2.5}$ exposure from 7 weeks to 16 weeks gestation is associated with increased risk of SGA status at birth. C. Among male infants, maternal $PM_{2.5}$ exposure between 12 weeks to 7 weeks prior to conception is associated with increased risk of SGA status at birth.

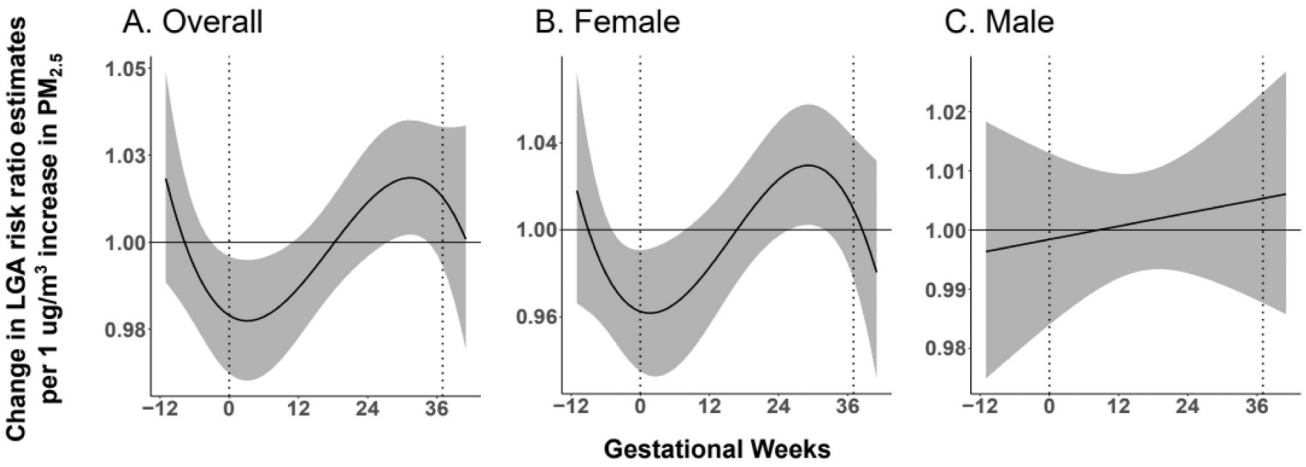

Figure 3. Association between maternal $PM_{2.5}$ exposure and LGA status at birth.

A. Maternal $PM_{2.5}$ exposure from 3 weeks prior to conception until 8 weeks gestation is associated with a decreased risk of LGA status at birth. In addition, $PM_{2.5}$ exposure from 29 weeks gestation until 32 weeks gestation is associated with an increased risk of LGA status at birth. B. Among female infants, $PM_{2.5}$ exposure from 5 weeks prior to conception until 6 weeks gestation is associated with a decreased risk of LGA status at birth. In addition, $PM_{2.5}$ exposure from 26 weeks until 30 weeks gestation is associated with an increased risk of LGA status at birth. Among male infants, no association between $PM_{2.5}$ exposure and LGA status at birth is observed.

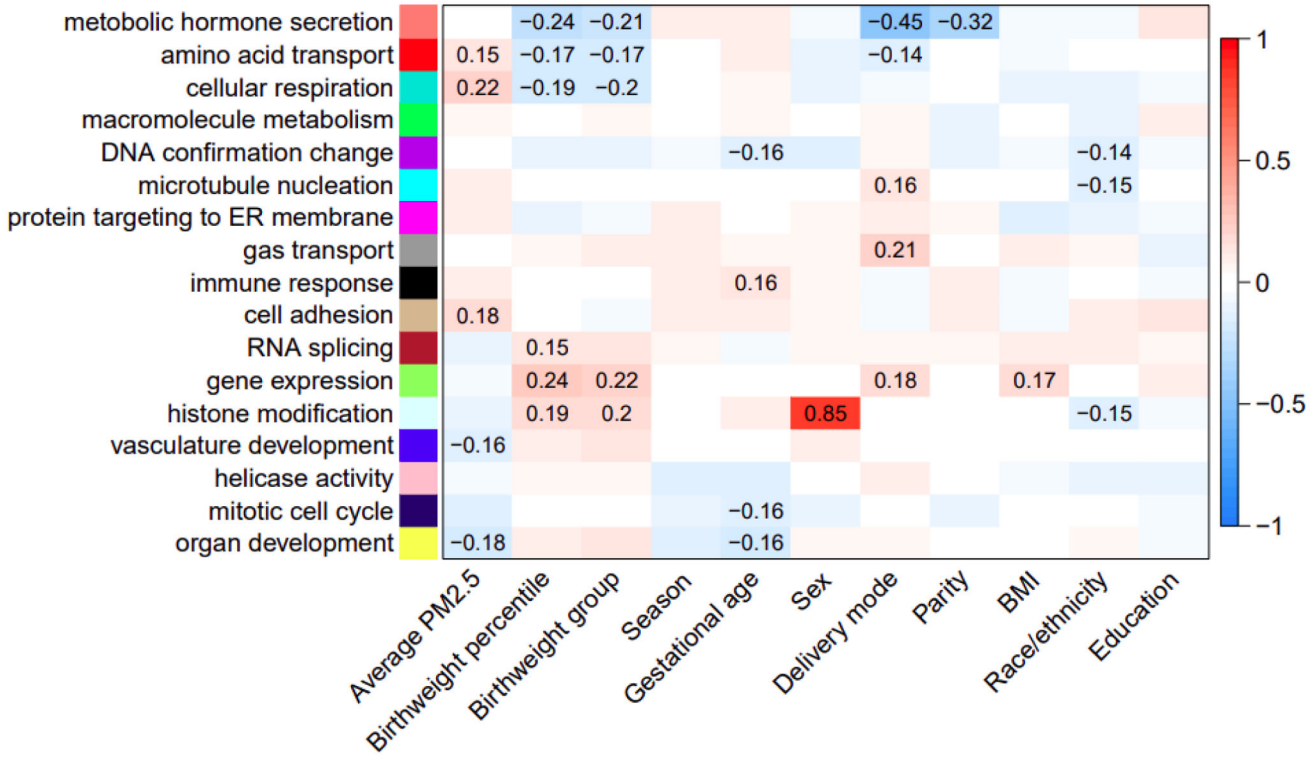

Figure 4. Spearman correlations between placental coexpression modules and RICHS demographic characteristics.

The y-axis indicates the Gene Ontology terms enriched in each module. The color gradient reflects the direction (red = positive, blue = negative) and strength of the correlation between the eigengene values of the modules (y-axis) and RICHS study participant characteristics (x-axis). Significant correlation coefficent values ($p<0.05$) are indicated on the plot.

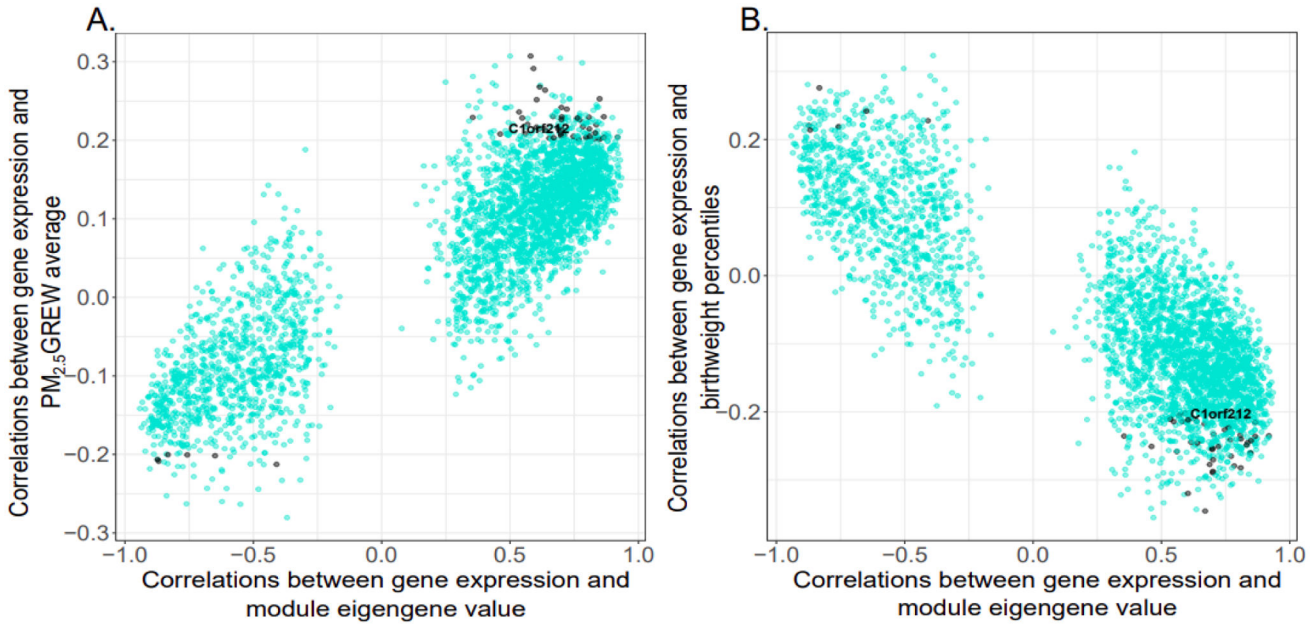

Figure 5. Cellular respiration module gene correlations (n=3073) with maternal $PM_{2.5}$ exposure and infant birthweight percentiles.

The x-axis indicates the correlation between gene expression and the module eigengene value. The y-axis indicates the correlation between genes and (A) maternal $PM_{2.5}$ exposure or (B) infant birthweight percentiles. Genes with correlation coefficients > |0.20| with both maternal $PM_{2.5}$ exposure and infant birthweight percentiles are indicated on the plot with black points, and all other genes are indicated as turquoise points. One locus, C1orf212, is labeled in the plot to illustrate the inverse gene correlations observed with maternal $PM_{2.5}$ exposure and infant birthweight percentile.

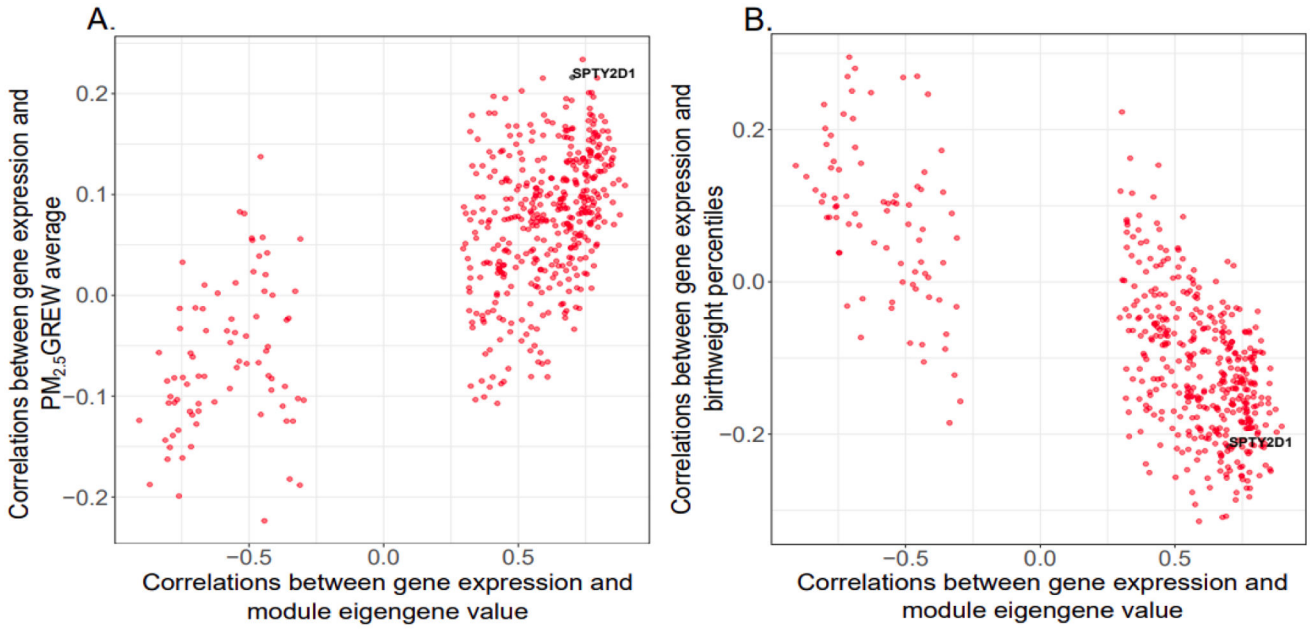

Figure 6. Amino acid transport module gene correlations (n=486) with maternal $PM_{2.5}$ exposure and infant birthweight percentiles.

The x-axis indicates the correlation between gene expression and the module eigengene value. The y-axis indicates the correlation between genes and (A) maternal $PM_{2.5}$ exposure or (B) infant birthweight percentiles. Genes with correlation coefficients > |0.20| are indicated on the plot with black points, and all other genes are indicated as red points. Only one gene, *SPTY2D1*, passed this threshold.

Table 1.

Demographic characteristics of the study population compared to the full RICHS cohort (n=799)

	Full cohort (n=799)	$PM_{2.5}$ subset (n=471)	WGCNA subset (n=149)	p-value
	Mean (SD)	*Mean (SD)*	*Mean (SD)*	
Birthweight percentile	53.48 (34.48)	58.18 (34.07)	56.93 (34.14)	0.05
Gestational age (weeks)	39.00 (0.95)	38.99 (0.92)	38.95 (0.96)	0.87
Maternal age (years)	29.72 (5.47)	30.03 (5.65)	31.23 (4.78)	0.01
Maternal BMI (kg/m^2)	26.60 (7.00)	26.94 (7.10)	26.25 (6.28)	0.53
$PM_{2.5}$ (ug/m^3)	7.97 (0.79)	7.97 (0.79)	7.99 (0.74)	0.94
	N (%)	*N (%)*	*N (%)*	
Birthweight Group				0.12
SGA	157 (19.6)	77 (16.3)	22 (14.8)	
AGA	456 (57.1)	260 (55.2)	82 (55.0)	
LGA	186 (23.3)	134 (28.5)	45 (30.2)	
Sex (Male)	398 (49.8)	244 (51.8)	78 (52.3)	0.73
Delivery Mode (Vaginal)	391 (48.9)	221 (46.9)	82 (55.0)	0.23
Maternal Race/Ethnicity				0.50
White	585 (73.2)	361 (76.6)	120 (80.5)	
Black	60 (7.5)	28 (5.9)	7 (4.7)	
Other	151 (18.9)	81 (17.2)	22 (14.8)	
NA	3 (0.4)	1 (0.2)	0 (0.0)	
Maternal Education				0.19
Less than HS grad	400 (50.1)	249 (52.9)	91 (61.1)	
HS grad	144 (18.0)	76 (16.1)	17 (11.4)	
Some College	60 (7.5)	26 (5.5)	5 (3.4)	
College grad and above	188 (23.5)	115 (24.4)	34 (22.8)	
NA	7 (0.9)	5 (1.1)	2 (1.3)	
Maternal Smoke status				0.38
No	746 (93.4)	441 (93.6)	142 (95.3)	
Yes	42 (5.3)	23 (4.9)	3 (2.0)	
NA	11 (1.4)	7 (1.5)	4 (2.7)	
Season of Birth				0.03
Spring	171 (21.4)	136 (28.9)	42 (28.2)	
Summer	216 (27.0)	111 (23.6)	29 (19.5)	
Fall	261 (32.7)	137 (29.1)	55 (36.9)	
Winter	151 (18.9)	87 (18.5)	23 (15.4)	