



# Maternal residential air pollution and placental imprinted gene expression



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## ABSTRACT

**Background:** Maternal exposure to air pollution is associated with reduced fetal growth, but its relationship with expression of placental imprinted genes (important regulators of fetal growth) has not yet been studied.

**Objectives:** To examine relationships between maternal residential air pollution and expression of placental imprinted genes in the Rhode Island Child Health Study (RICHHS).

**Methods:** Women-infant pairs were enrolled following delivery between 2009 and 2013. We geocoded maternal residential addresses at delivery, estimated daily levels of fine particulate matter (PM<sub>2.5</sub>; n = 355) and black carbon (BC; n = 336) using spatial-temporal models, and estimated residential distance to nearest major roadway (n = 355). Using linear regression models we investigated the associations between each exposure metric and expression of nine candidate genes previously associated with infant birthweight in RICHHS, with secondary analyses of a panel of 108 imprinted genes expressed in the placenta. We also explored effect measure modification by infant sex.

**Results:** PM<sub>2.5</sub> and BC were associated with altered expression for seven and one candidate genes, respectively, previously linked with birthweight in this cohort. Adjusting for multiple comparisons, we found that PM<sub>2.5</sub> and BC were associated with changes in expression of 41 and 12 of 108 placental imprinted genes, respectively. Infant sex modified the association between PM<sub>2.5</sub> and expression of *CHD7* and between proximity to major roadways and expression of *ZDBF2*.

**Conclusions:** We found that maternal exposure to residential PM<sub>2.5</sub> and BC was associated with changes in placental imprinted gene expression, which suggests a plausible line of investigation of how air pollution affects fetal growth and development.

## 1. Introduction

The placenta plays a vital role in fetal development as it regulates the exchange of nutrients, gas, and waste between mother and fetus, and optimizes the maternal-fetal environment for proper development (Sandovici et al., 2012). An important group of genes responsible for these functions, and for that adaptability, are those genes whose expression is controlled through genomic imprinting. Genomic imprinting is a form of epigenetic gene regulation in which one parental allele is expressed and the other is silenced (Jirtle and Skinner, 2007). The

highly controlled pattern of expression of these genes is critical to normal development and plays a particularly important role in the placenta functioning (Fowden et al., 2006; Miozzo and Simoni, 2002; Reik and Walter, 2001). For example, loss of genomic imprinting (LOI) early in development can lead to placental and fetal growth restriction (Lambertini et al., 2012a), and recent studies have shown that even relatively modest differences in imprinted gene expression are associated with fetal growth/birth weight (Kappil et al., 2015a; Lambertini et al., 2012b). Moreover, in both human and animal studies imprinted gene expression has been associated with exposure to a number of

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environmental exposures, including, maternal nutrition, alcohol use, tobacco use, and BPA exposure, and imprinted gene expression has been highlighted as a potentially useful environmental sensor (Kappil et al., 2015b).

Maternal exposure to ambient air pollution during fetal development has been associated with reduced fetal growth, even at exposure levels lower than National Ambient Air Quality Standards (Dadvand et al., 2013; Lamichhane et al., 2015; Sapkota et al., 2010; Stieb et al., 2012; Sun et al., 2016; Zhu et al., 2015). However, the underlying molecular mechanisms remain unknown. Maternal residential proximity to major roadways has been associated with changes in placental DNA methylation and maternal exposure to ambient fine particulate matter (PM<sub>2.5</sub>) has been associated with placental gene expression (Kingsley et al., 2016; Saenen et al., 2015). However, to our knowledge, no study has examined the association between maternal exposure to air pollution and placental imprinted gene expression as a potential mechanism for altering fetal growth.

Accordingly, we examined the relationship between maternal residential levels of PM<sub>2.5</sub>, and placental expression of imprinted genes in a cohort of 410 women-infant pairs from the Rhode Island Child Health Study (RICHS). We hypothesized that mothers exposed to higher levels of PM<sub>2.5</sub> have altered imprinting profiles compared to mothers exposed to lower levels of PM<sub>2.5</sub>. We also examined the associations between placental imprinted gene expression and residential exposure to black carbon (BC) and proximity to nearest major roadway as markers of traffic-related pollution.

## 2. Materials and methods

### 2.1. Study population

The Rhode Island Child Health Study (RICHS) enrolled women-infant pairs from March 2009 to May 2013 following delivery at Women and Infants Hospital of Rhode Island (Marsit et al., 2012). Eligibility criteria included singleton, viable, full term births to mothers 18 years or older without a life-threatening complication for the mother or a congenital or chromosomal abnormality of the infant. Infants born small for gestational age (SGA) and large for gestational age (LGA) were selected and matched to infants born appropriate for gestational age (AGA) based on gender, gestational age ( $\pm 3$  days), and maternal age ( $\pm 2$  years). Exposure histories, residential address, and lifestyle and demographic information were collected from structured medical chart reviews and in person interviewer-administered questionnaires. Information on residential addresses was available for 410 participants. The study protocol was approved by the Institutional Review Boards of Brown University and Women and Infants Hospital of Rhode Island.

### 2.2. Imprinted gene expression in placenta

Placenta samples were taken within 2 h of delivery from four quadrants of the maternal side of the placenta, 2 cm from the umbilical cord-insertion site and free of maternal decidua. The samples were immediately placed in RNALater (Life Technologies, #AM7024) and stored at 4 °C for at least 72 h, then blotted dry, snap-frozen in liquid nitrogen, homogenized and stored at  $-80$  °C until analysis. DNA was extracted using QIAmp DNA mini kit (Qiagen, #51306) and RNA was extracted using RNeasy mini kit (Qiagen, #74106).

We examined expression of 108 established imprinted genes, the selection of which was informed by two databases (Jirtle, 2012; Morison et al., 2001) encompassing empirically determined imprinted genes as well as those computational predicted, and limited to those genes that have been found to be consistently expressed in a majority ( $> 50\%$ ) of the sample, as previously described (Kappil et al., 2015a). The Nanostring nCounter system was used to perform a direct count of the presence of imprinted gene mRNA expressed in the placenta. Briefly, samples of RNA were incubated overnight with reporter and

capture probes. After removal of unbound probes, the samples were aligned and immobilized on imaging cartridges. To obtain code counts, the cartridges were sealed and scanned in an nCounter Digital Analyzer (Kappil et al., 2015a). The nanoString Norm package was used to normalize nCounter data (Waggott, 2014). The raw code count data was normalized against the geometric mean of spike-in positive control probes and against the geometric mean of the housekeeping genes, *GAPDH*, *RPL19*, and *RPLP0*. The limit of detection for each sample was set at two standard deviations above the mean of the included negative control probes.

### 2.3. Exposure assessment

Using ArcMap 10.1 (ESRI; Redlands, CA) we geocoded participant addresses at time of delivery. We estimated daily PM<sub>2.5</sub> levels at each maternal residential address using a hybrid spatial-temporal model that uses land-use regression methodologies and satellite measurements of aerosol optical depth (AOD) at a 1 km resolution, as previously described (Kloog et al., 2014). Briefly, land use regression and satellite-based AOD are used to fit a daily calibration regression using ground-level PM<sub>2.5</sub> measurements with a high prediction accuracy ( $R^2 = 0.88$ ) (Kloog et al., 2014). To estimate exposure on a finer scale (200 m  $\times$  200 m), the differences in AOD and measured PM<sub>2.5</sub> are regressed against local land use features such as distance to source emission points, traffic density, and visibility (Kloog et al., 2014). PM<sub>2.5</sub> estimates were available for the entire study period. We estimated daily BC levels at each maternal residential address using an extended version of a validated spatial-temporal land-use regression model that includes daily average BC estimates from five Rhode Island BC monitors, meteorological data from nearly two dozen local weather stations, state land use data, latitude and longitude, daily meteorological factors and other characteristics (e.g.: day of week, day of season), and interaction terms between land-use measures and daily meteorological factors (Gryparis et al., 2007). The model performed well in both cold (November–April) and warm seasons (May–October) with 10-fold cross validated  $R^2$  of 0.73 and 0.75, respectively. BC estimates were available from the start of the study period to 2011 (excludes 22 participants). BC and PM<sub>2.5</sub> estimates were averaged over the length of pregnancy and used as exposure.

We calculated the Euclidean distance to nearest major roadway and defined major roadways as those with US Census feature class codes A1 (primary highway with limited access), A2 (primary road without limited access), or A3 (secondary and connecting roads). We considered participants living  $\leq 150$  m of an A1 or A2 roadway or  $\leq 50$  m of an A3 roadway as “exposed” and unexposed otherwise (Kingsley et al., 2016).

### 2.4. Covariates

We considered several maternal and infant characteristics collected from in-person interviewer-administered questionnaires as potential confounders. We categorized parity (1, 2,  $\geq 3$ ), maternal race (Caucasian, other), maternal education (less than high school, some college, college or more), annual household income ( $< \$25,000$ ,  $\$25,000$ – $49,999$ ,  $\$50,000$ – $79,999$ ,  $\$80,000$ – $99,999$ ,  $\geq \$100,000$ ), health insurance (none/self-pay, private, public/other), and prenatal care during pregnancy (yes, no). Maternal alcohol, tobacco, and prenatal vitamin use during pregnancy (defined as regularly taking prenatal vitamins) were each dichotomized as yes or no. Marital status was defined as married or not married (single, separated, or divorced). Maternal body mass index (BMI) before pregnancy was calculated from self-reported height and weight. Maternal age was measured in years. Covariate data for the infant included sex and gestational age at birth (weeks).

To address potential confounding by neighborhood socioeconomic status (SES), we calculated z-scores for each of six census tract-level variables (median household income; percent of households with

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