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Association of ischemic placental disease in a Southern California Birth Cohort and PM_{2.5} chemical species and oxidative potential markers

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Abstract

Road traffic is a significant source of particulate matter pollution, whose exposure is a significant risk factor in pregnancy-related health outcomes. The exact mechanisms behind the relationship between traffic-related air pollution (TRAP) exposure and adverse pregnancy outcomes remain unclear. We aim to assess the relationship between exposure to brake and tire wear-associated metals and oxidative potential and ischemic placental disease (IPD). Data were assembled from a final population of 178 women who sought specialized prenatal care at UCLA between 2016 and 2019 in Los Angeles, CA. Modeled first trimester exposures to chemical constituents and oxidative stress potential of PM_{2.5}, black carbon, and PM_{2.5} mass concentration. Speciated measurements included tracers of brake wear (barium), tire wear (zinc), and oxidative potential markers based on metal concentrations (KM-SUB-ELF ROS) or laboratory assays (DTT loss, OH radical formation). Exposures were modeled by integrating data from filter samples, a low-cost PM_{2.5} sensor network, and land-use data. We used logistic regression to estimate the associations between air pollution exposures and IPD, adjusting for covariates assessed through medical records and interviews. Scaled to the interquartile range, odds ratios (95% CI) were as follows: barium OR: 1.7 (1.1, 2.7), zinc OR: 1.4 (.86, 2.4), and oxidative potential markers, both modeled as well as measured through DTT loss and OH formation assays (ORs ranging from 1.1-2.0). Point estimates of effect sizes for PM_{2.5} and black carbon were lower than most measurements (ORs: 1.3-1.4). mass and black carbon. Our findings suggest two key points: (i) metals associated with brake and tire wear, currently unregulated, may play a role in the relationship between TRAP and adverse pregnancy outcomes, and (ii) reducing tailpipe emissions may not be sufficient to protect pregnant women from TRAP.

1. Introduction

Exposure to high levels of traffic-related air pollution (TRAP) is a major risk factor for various adverse health outcomes, contributing substantially to premature mortality alongside a host of other diseases [1, 2]. TRAP itself is a multisource mixture whose PM emissions stem from both tailpipe emissions as well as non-tailpipe sources, including brake and tire wear and road dust resuspension. Southern California studies have found that TRAP contributes to 32% of all ambient PM_{2.5} [3]. In recent decades, government regulation and advancements in technology have substantially reduced tailpipe emissions in California, altering the profile of particulates in TRAP [4]. Current clean air regulation in the US does not regulate non-exhaust emissions, which due to increased fleet efficiency and electrification is expected to contribute a greater share of particulates to TRAP and overall PM emissions [5]. As TRAP composition evolves with changes in vehicle trends, health studies assessing effects of air pollution will require up-to-date, informative exposure assessment [6], such as the use of metals as tracers of brake and tire wear [6–8].

A recent review found a number of adverse pregnancy and birth outcomes associated with exposure to TRAP, including term low birth weight and small for gestational age [2]. One potential pathway through which PM affects pregnancy and birth outcomes is through oxidative stress. Oxidative stress plays an important role in the pathophysiology of the human placenta, where a balance of antioxidants and reactive oxygen species (ROS) helps regulate placental development [9]. The disruption to the balance of antioxidants and ROS has been shown to induce inflammation and subsequent morphological changes [10]. These degenerative changes in the placenta have been found associated with several pregnancy complications, including preeclampsia, fetal growth restriction, placental abruption, and gestational hypertension [9]. These disorders, while symptomatically different, have a common underlying etiology in placental ischemia, and are commonly grouped under a single term, ischemic placental disease (IPD) [11].

Prior studies have implicated oxidative stress as a primary mechanism through which PM exposure impacts human health [12]. Heightened PM exposure increases levels of oxidative stress, which have been found to correspond to inflammation leading to morphological changes in the placenta [10]. This is reflected in prior cohort studies, which have found associations between ambient PM_{2.5} and outcomes including intrauterine inflammation [13], preeclampsia [14], altered lipid metabolic gene expression [15], placental DNA methylation [16], and IPD [17].

Most studies have focused on ambient PM_{2.5} or other proxy variables to assess exposure to air pollution. PM is a non-specific, multisource mixture whose components vary widely based on time of year and geography [18]. One study showed that within a single city and time period, PM_{2.5} samples showed measurable differences in oxidative potential [19]. A review found that chemical species may modify the association between PM_{2.5} exposure and adverse health effects, and that the use of unspicated PM_{2.5} may run the risk of exposure classification [20]. This is especially salient when assessing TRAP, as brake and tire wear are rich in metals and organic compounds that are notably capable of generating oxidative stress [5]. Consequently, there have been increasing concerns that despite reductions in tailpipe emissions, increased exposure to TRAP may continue to disrupt placental function leading to downstream adverse birth outcomes [21–24].

Here, we attempt to bridge the above mentioned knowledge gap concerning possible adverse effects of brake and tire wear-related TRAP exposures and pregnancy. We employ conventional exposure metrics, namely PM_{2.5}, black carbon, and novel set of exposure measures, including tracers of brake and tire wear and markers of oxidative potential. We relied on a well-documented birth cohort [25] with detailed clinical follow-up throughout pregnancy to assess associations of IPD with different measures of ambient TRAP.

2. Methods

2.1. Study population

The study cohort was established as part of the Placental Assessment in Response to Environmental Pollution (PARENTs) study. The PARENTs study enrolled a birth cohort of pregnant women who sought prenatal care and planned to deliver at UCLA hospitals between 2016 and 2019. Details regarding the cohort are summarized elsewhere [25]. Briefly, subjects were screened for eligibility early in the first trimester and subsequently followed prospectively until birth. Patient information was ascertained with both medical records and standardized questionnaires. Interviews were conducted during pregnancy, i.e. during the first trimester, early to mid-second trimester, third trimester, as well as delivery and post-partum to collect information on demographics, medical history, tobacco use, and various maternal behaviors including diet and residential and occupational exposures.

The cohort was approved by the UCLA IRB. Participants provided informed consent after the trained study personnel explained the study. Details are listed by ClinicalTrials.gov (NCT02786420) [26].

2.2. Outcome assessment

We defined the main outcome, IPD, as the noted presence of one or more of the following complications: placental abruption, hypertensive disease of pregnancy (preeclampsia or gestational hypertension), a newborn considered small-for-gestational age, or fetal growth restriction. Fetal growth restriction was defined as fetuses with an estimated fetal weight or abdominal circumference that was less than the 10th percentile for gestational age [25]. These four diseases, while symptomatically different, are all related to a placental ischemia induced by excessive oxidative stress and are grouped under the composite outcome IPD [11].

We defined preeclampsia as blood pressure (BP) of 140/90 mmHg or higher on two occasions at least four hours apart after 20 weeks of gestation with previously normal BP, and proteinuria of >300 mg/24 h [27]. In the absence of proteinuria, preeclampsia was defined as new-onset hypertension with new onset of thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema, cerebral or visual symptoms [27].

Gestational hypertension refers to hypertension developing after 20 weeks of gestation not associated with systemic features of preeclampsia. Chronic hypertension, on the other hand, was defined as BP 140/90 mmHg or higher that either pre-dated pregnancy or developed before 20 weeks of gestation [27].

We assessed information such as birth weight (grams), gestational age (days), and BP from participants' medical records. Small-for-gestational age was defined as a newborn birth weight less than the 10th percentile per Fenton's growth charts with a subclassification below the 3rd percentile. In this study, SGA was defined as a newborn birth weight less than the 10th percentile per Fenton's growth charts [28].

2.3. Exposure assessment

2.3.1. $PM_{2.5}$ mass and elemental concentrations

We generated seven 30 by 30 meter exposure surfaces using three data sources: (i) air monitoring campaigns measurements from two campaigns we conducted in 2019-20, (ii) land-use data from public and private sources, and (iii) the PurpleAir low-cost sensor network. We previously described our data collection and modeling processes in a prior publication [8, 29]. In brief, we obtained $PM_{2.5}$ chemical species and oxidative potential marker data from a fieldwork campaign detailed in Oroumieh *et al* [8]. Samplers measuring $PM_{2.5}$ during September 2019 and February 2020 were placed at government monitoring locations and individual residences, including at 17 PARENTs participants' homes. Oroumieh *et al* describe chemical speciation analyses in detail [8, 30, 31], and Shen *et al* discuss at length the assays used to measure black carbon and oxidative potential in the filter samples [19].

After obtaining speciation and oxidative potential marker data, we modeled the following:

- Ba (representing brake wear) [5]
- Zn (representing tire wear) [5]
- DTT loss (biological reductant surrogate) [32–35]
- OH formation (reactive species formed in lung lining when exposed to aerosol particles) [36]
- KM-SUB-ELF ROS (an estimate of ROS generation based on Cu and Fe concentrations) [37]
- Black carbon (combustion byproduct and diesel tailpipe tracer) [38]
- $PM_{2.5}$ mass concentration

We have detailed our exposure modeling in a prior article [29]. Briefly, for each exposure, we generated a model across the Southern California area employing universal co-kriging with each exposure as the primary variable; a land-use regression model as an external drift; and PurpleAir low-cost sensor network as an auxiliary, more spatially resolved variable, and other adverse birth outcomes [39].

Monthly estimates of co-kriged $PM_{2.5}$, Ba, Zn, and oxidative potential were scaled by modifying the model from Liu *et al* [29]. measurements in the PurpleAir network. For each month, the cross-covariance between the seven exposures and PurpleAir $PM_{2.5}$ were modeled using the gstat package, which was used to predict monthly exposure estimates. This process can be expressed as the following equation:

$$y_{i,m}(s) = x_i^T(s) \beta + w_{i,m}(s) + \epsilon_i(s), \quad i = 1, 2, \dots, q \quad m = 1, 2, \dots, 11, 12 \quad (1)$$

where m refers to the months between January and December. In equation (1), $y_{i,m}(s)$ refers to the estimated monthly concentrations of the chemical species discussed above at location s . The term $w_{i,m}(s)$ refers to the spatial dependence (1) within the chemically speciated data collected across the study area and (2) between the chemically speciated data and the unspicated mean PurpleAir $PM_{2.5}$ concentrations from a given month m .

This study focused on estimating first trimester exposures. Although other periods of pregnancy, such as the third trimester, are associated with some of our outcomes, such as term low birth weight, our outcomes

are suspected to share a common etiology in placental dysfunction, which starts early in pregnancy. We thus restricted our exposure assessment to the first trimester, the period most relevant to placental outcomes.

We generated each subject's first trimester exposure measure by subtracting the gestational age at birth from the birth date, and adding 92 days (13 weeks). Within this date range, exposure estimates were calculated as a weighted average of the monthly exposures that were included in each woman's first trimester. For subjects who moved residences during their first trimester, the weighted average was calculated based on residence time at each address. This process can be expressed as the following equation:

$$E_s = \frac{\sum d_{s,m_i} E_{s,m_i}}{\sum (d_{s,m_i})} \quad (2)$$

where the estimated exposure E for subject s . Using equation (1), we can estimate monthly exposures of a for subject s for any given month m . Subtracting the gestational age from the birth date, we determined the number of days d that are covered by subject s 's first trimester for a given month m_i . We then weighed monthly exposure estimates E_{s,m_i} by the number of days in a given month covered by the first trimester to calculate our final estimates. We estimate first trimester exposures occurring prior to the incidence of IPD, making our study prospective in design.

Based on reported home addresses at enrollment and relocation dates (if applicable), we geocoded subject home locations using the Esri ArcGIS Address Locator via the Countywide Address Management System locator [40]. For addresses that failed to geocode properly, we used Google Maps via the ggmap R package [41].

2.4. Covariates

Using questionnaires, we collected data on covariates and potential IPD risk factors, including maternal age (years), maternal race (non-Hispanic White, Hispanic of any race, Black, Asian/Pacific Islander, or other), parity (continuous), maternal body-mass index (BMI, categorical), maternal and partner income (nominal), maternal education (categorical), and maternal smoking status prior to and during pregnancy (never/former smoker). We assessed pregnancy complications and other medical information, such as gestational diabetes (yes/no) and fetal sex (male/female) from medical records [42]. Subjects reported maternal and partner income as belonging to one of five annual salary ranges (under \$20 000, \$20 000–\$40 000, \$40 000–\$60 000, \$60 000–\$100,000, and over \$100 000). Based on reported incomes, we classified each household into low, middle, upper-middle, and high-income when applicable. Due the small sample size, we dichotomized race into non-Hispanic White and other.

We encountered missing data for some covariates. Six out of 178 subjects lacked maternal education data, five out of 178 lacked household income data, and 19 out of 178 lacked maternal smoking data prior to pregnancy. We addressed missing data using multivariate imputation using SAS [43]. Specifically, we created an imputation model based on exposure variables and complete covariates. We used the Markov Chain Monte Carlo method to assume a joint multivariate normal distributions for all variables included in the imputation model. After imputing five datasets, we randomly selected one for use in our final dataset.

2.5. Statistical analysis

2.5.1. Summary statistics

After assigning exposure data, we calculated the mean and interquartile range (IQR) of each exposure, stratified by IPD status. In an exploratory analysis, we calculated Pearson correlation coefficients between each exposure and checked for statistical significance ($p < 0.05$).

Prior to model fitting, we normalized exposure values by the corresponding IQR of the entire population, as has been done in previous studies that assessed air pollution and pregnancy outcomes [44–46].

2.5.2. Model fitting

To assess the impact of various exposures on the risk of developing IPD, we fitted unconditional logistic regression models for each of our exposures. We generated results based on three different models: (i) a crude model, (ii) a minimally adjusted model adjusting for age, fetal sex, and race, and (iii) a fully adjusted model additionally adjusting for parity, maternal BMI, maternal smoking, gestational diabetes, maternal education, and household income. We selected confounders in the minimally adjusted model based on information that would be available in large, administrative cohorts. The fully adjusted model incorporates confounders that were assessed using detailed medical records and subject interviews. We calculated log odds ratios and corresponding 95% confidence intervals representing the change in odds of IPD per IQR increase of each exposure.

2.5.3. Sensitivity analysis

Prior studies have demonstrated a relationship between diet and oxidative stress levels [47], and place of residence may affect both air quality as well as access to healthy food. In response we considered this potential effect of diet among a subset of 143 women who filled out the Diet History Questionnaire II, a food frequency questionnaire [48]. For the women who provided this information, we investigated whether adjustment for a healthy diet based on the United States Department of Agriculture 2015 Healthy Eating Index changed effect estimates. The Healthy Eating Index considers factors that may affect our study outcome, including sodium intake.

Additional sensitivity analyses included assessing alternate methods of exposure assessment i.e. weighing exposure estimates by each month of gestation. For a small subset of subjects who moved residences during the first trimester, we investigated whether maintaining their original address, i.e. assuming they did not move, affected effect estimates. Finally, during exploratory analyses we found that four subjects lived less than two miles outside of the boundaries of the exposure surface. Instead of excluding them, we assigned these four subjects exposure surface measures closest to their addresses.

3. Results

We screened 841 subjects for eligibility and willingness to participate in magnetic resonance imaging (MRI) examinations during mid-pregnancy and 234 did not respond to further inquiry (figure 1). There were 233 subjects who declined to enroll for reasons including time and/or travel ($n = 56$), lack of interest ($n = 50$), MRI safety concerns ($n = 62$) or doctor refusal ($n = 7$). An additional 58 women did not to provide a reason for declining participation. There were 166 women who were deemed ineligible due to late gestational age at enrollment ($n = 132$), twin pregnancy ($n = 5$), abortion or miscarriage ($n = 16$), discontinuation of care at UCLA ($n = 12$), or being too ill to continue ($n = 2$).

Thus, we initially enrolled 208 participants into the PARENTs study. After enrollment, we additionally excluded 30 subjects due to pregnancy complications or other illnesses resulting in MRI complications post-enrollment ($n = 7$); miscarriage or abortion post-enrollment ($n = 5$); patient withdrawal ($n = 4$); smoking during pregnancy ($n = 1$); exposure to Zika ($n = 1$); relocation outside the study area ($n = 1$); missing medical records ($n = 2$); or residing outside of the exposure surface boundaries ($n = 9$).

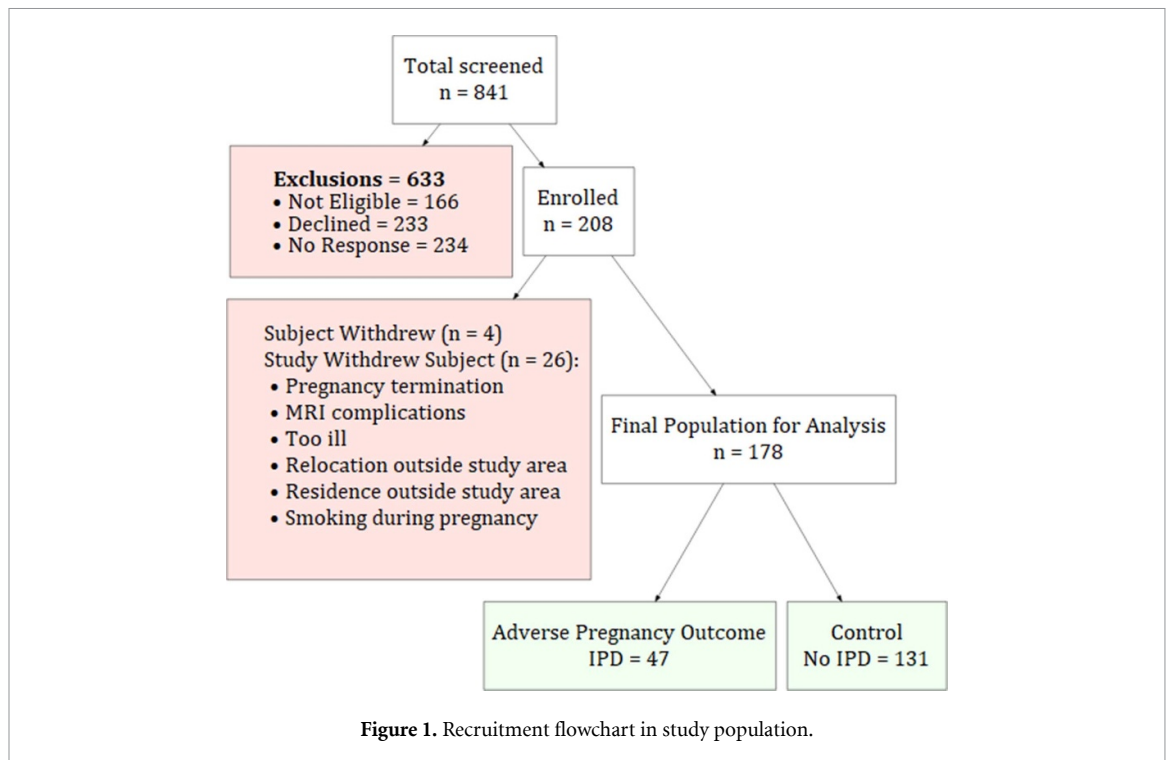
Baseline subject characteristics of the 47 cases and 131 non-cases are presented in table 1. Figure 2 Compared to non-cases, cases had a slightly higher mean age, BMI, and prevalence of gestational diabetes while non-cases were more often multiparous. There are also more former smokers and women missing information on smoking prior to pregnancy among cases.

Correlations between first trimester exposures are summarized in figure 3. All exposures were positively correlated with each other (Pearson ρ : 0.13–0.89). Overall, the estimated average first trimester $\text{PM}_{2.5}$ exposure was $9.75 \mu\text{g m}^{-3}$ with an IQR of $1.19 \mu\text{g m}^{-3}$, with higher mean concentration among cases ($9.85 \mu\text{g m}^{-3}$) compared to non-cases ($9.71 \mu\text{g m}^{-3}$). We also observed higher mean exposures to Ba, Zn, and oxidative potential markers among cases than non-cases, as shown in table 2.

The crude, minimal, and fully adjusted model display consistent effect direction. Odds ratios and 95% confidence intervals from logistic regression models shown in figure 4 suggest that higher levels of every exposure modeled were positively associated with IPD, with magnitudes of the ORs ranging in size from 1.1 (DTT loss) to 2.0 (KM-SUB-ELF ROS) for the fully adjusted model. Adjustment for covariates suggested some bias of crude estimated effects towards the null for the brake wear and tire wear marker Ba and Zn and also for KM-SUB-ELF ROS. The adjusted estimates for Ba and KM-SUB-ELF ROS the 95% confidence intervals exclude the null value of 1. While not necessarily statistically significant, all other exposure-IPD associations were positive and exhibited the same patterns.

Sensitivity analyses did not alter our main findings. Specifically, adjustment for diet-related variables, including sodium intake, did not significantly affect our effect direction or magnitude. Alcohol intake in the cohort was reported at very low levels in the cohort. While we did not adjust for alcohol in diet-related sensitivity analyses, less than 10% of women reported an average alcohol daily intake of greater than 0.5 grams per day. We would, as a result, not expect to observe differences when adjusting for alcohol intake.

Assigning alternate locations to subjects just outside the exposure surface not change effect estimates but increased standard errors. Alternate methods of exposure assessment resulted in increases in standard error, but no qualitative changes in effect estimate.



4. Discussion

We believe that this is the first study to examine the contributions from brake and tire wear-related $PM_{2.5}$ components and oxidative potential of the pollutant mixtures to IPD. Effect estimate directions were consistently positive whether adjusting for a minimal or full set of risk factors and potential confounders. While we cannot rule out the possibility of residual confounding, our results suggest that common risk factors known to adversely affect pregnancy did not confound the observed exposure-outcome associations except for strengthening the associations (figure 4) [11].

The positive relationships between oxidative potential markers and tracers of brake and tire wear and IPD are consistent with physiological mechanisms that are thought to drive placental disorders. The placenta plays a key role in fetal development and is essential for the transport and provision of nutrients, water, and oxygen to the fetus [49]. An imbalance of ROS induced by metals and organic species may lead to disruptions in placental trophoblast cell function, which has been hypothesized to play a key role in the physiologic mechanisms behind IPD [50].

We present results that further corroborate prior work investigating the relationship between TRAP and birth outcomes. Positive associations between increased maternal $PM_{2.5}$ exposure and negative health outcomes in children have been discussed widely in the literature [51]. Many studies employed black carbon as a tailpipe exhaust marker and evidence is mixed regarding associations with adverse birth outcomes [52–55]. Studies assessing exposures specifically associated with brake and tire wear are very limited, with most studies restricted to animal experiments [56–58]. Studies in larger administrative data using the same exposures as this study have found links between exposure to TRAP and adverse birth outcomes [39].

As shown in figure 3, Ba and Zn were highly correlated with Cu and Fe concentrations used to calculate the KM-SUB-ELF ROS measurement. As tracers of brake and tire wear, we interpret metals Ba and Zn as proxies for the mixture of brake and tire wear particle exposures directly involved in the production of ROS and not causal agents for IPD [36, 59]. In other words, we do not believe that reducing or replacing Ba and Zn emissions from brake and tire wear would necessarily lead to improved health outcomes. We also report the effects of various oxidative potential-related measures, which reflect the reactivity of water-soluble PM samples, and whose effect directions and magnitudes are consistent with the brake and tire wear tracers. Oxidative potential markers are positively correlated with source-specific measures in data and, thus, suggest that metals and related measures of non-tailpipe source exposures may be more effective than $PM_{2.5}$ or black carbon alone in predicting PM-related oxidative stress and adverse birth outcomes.

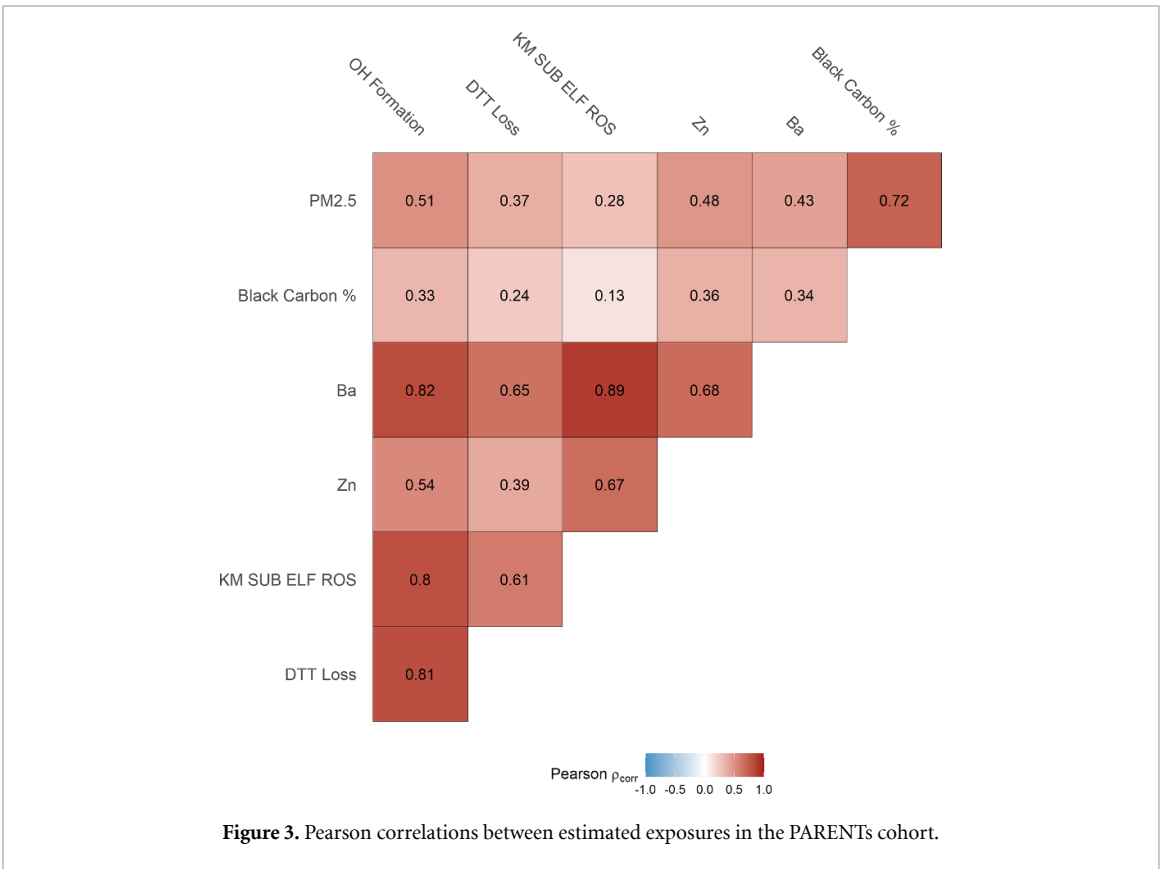
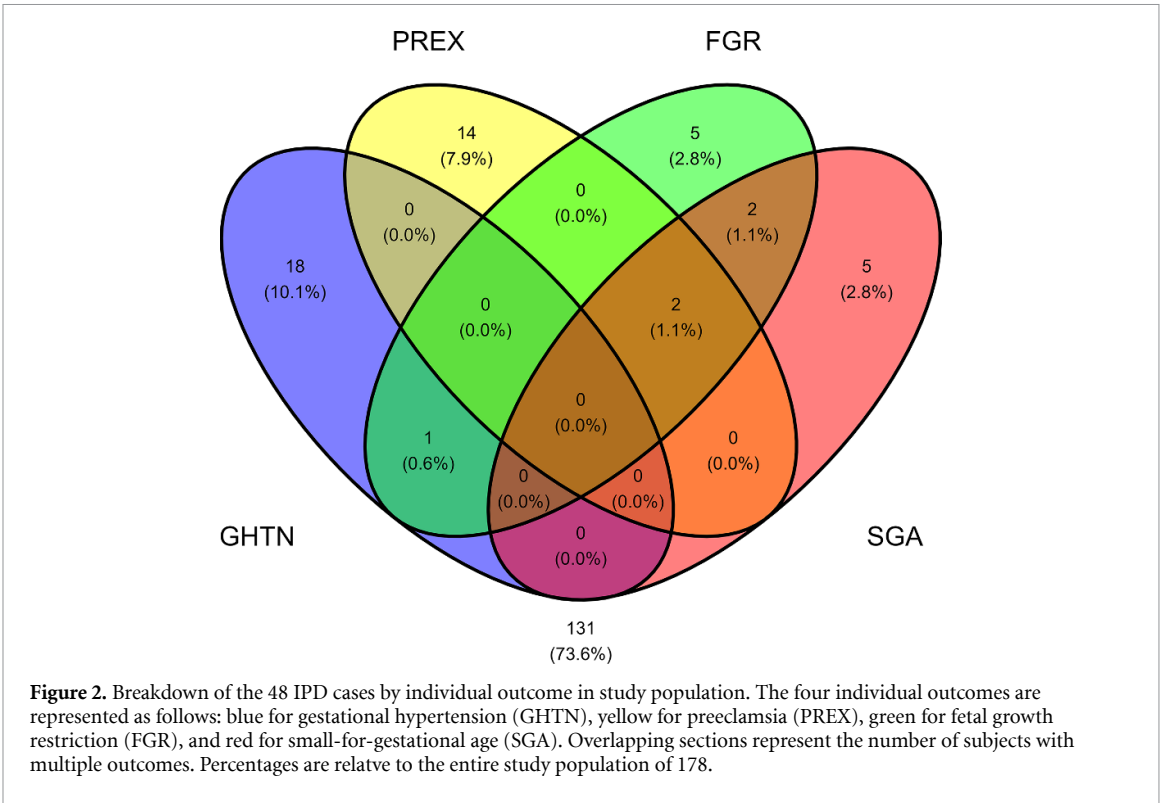
We estimated the highest point estimates in fully adjusted models for Ba, KM-SUB-ELF ROS, and OH formation. Although both DTT loss and OH formation assays measure oxidative potential, OH formation was more strongly correlated with the metals. This could reflect the DTT assay's relative insensitivity to Fe

Table 1. Selected characteristics of study population, Los Angeles, California.

	Cases (N = 47)	Non-cases (N = 131)	Overall (N = 178)
Maternal Age			
Mean (SD)	34 (4.4)	33 (3.9)	33 (4.0)
Race			
Asian	14 (29.8%)	34 (26.0%)	48 (27.0%)
Black or African American	3 (6.4%)	7 (5.3%)	10 (5.6%)
Hispanic	7 (14.9%)	27 (20.6%)	34 (19.1%)
White, non-Hispanic	23 (48.9%)	62 (47.3%)	85 (47.8%)
American Indian or Alaskan Native	0 (0%)	1 (0.8%)	1 (0.6%)
Maternal Education			
High School Graduate or GED	0 (0%)	1 (0.8%)	1 (0.6%)
Vocational, Technical, Associates, or other 2 year degree	0 (0%)	8 (6.1%)	8 (4.5%)
Some College	2 (4.3%)	6 (4.6%)	8 (4.5%)
Bachelors Degree (4 Years)	14 (29.8%)	44 (33.6%)	58 (32.6%)
Masters Degree	19 (40.4%)	34 (26.0%)	53 (29.8%)
Professional Degree (MD, JD, etc)	5 (10.6%)	20 (15.3%)	25 (14.0%)
Doctoral Degree	7 (14.9%)	12 (9.2%)	19 (10.7%)
Missing	0 (0%)	6 (4.6%)	6 (3.4%)
Household Income			
Low	1 (2.1%)	8 (6.1%)	9 (5.1%)
Middle	4 (8.5%)	10 (7.6%)	14 (7.9%)
Upper-middle	10 (21.3%)	20 (15.3%)	30 (16.9%)
High	30 (63.8%)	87 (66.4%)	117 (65.7%)
Don't know	1 (2.1%)	1 (0.8%)	2 (1.1%)
Refused to answer	1 (2.1%)	0 (0%)	1 (0.6%)
Missing	0 (0%)	5 (3.8%)	5 (2.8%)
Fetal Sex			
Female	22 (46.8%)	60 (45.8%)	82 (46.1%)
Male	25 (53.2%)	71 (54.2%)	96 (53.9%)
Parity			
0	26 (55.3%)	60 (45.8%)	86 (48.3%)
1	19 (40.4%)	55 (42.0%)	74 (41.6%)
2	1 (2.1%)	13 (9.9%)	14 (7.9%)
3	0 (0%)	2 (1.5%)	2 (1.1%)
4	0 (0%)	1 (0.8%)	1 (0.6%)
6	1 (2.1%)	0 (0%)	1 (0.6%)
Maternal BMI			
Mean (SD)	25 (5.6)	24 (4.4)	25 (4.7)
Gestational Diabetes			
No	38 (80.9%)	117 (89.3%)	155 (87.1%)
Yes	9 (19.1%)	14 (10.7%)	23 (12.9%)
Smoking			
I do not smoke and I never have	28 (59.6%)	96 (73.3%)	124 (69.7%)
I do not smoke anymore but I have in the past	12 (25.5%)	23 (17.6%)	35 (19.7%)
Missing	7 (14.9%)	12 (9.2%)	19 (10.7%)

[35, 60]. Fe and Cu play an important role in OH radical formation via Fenton reactions that occur in the human body [36, 61, 62]. Fe is a major component of brake wear and catalyzes the production of ROS; it is a component of the KM-SUB-ELF ROS model and highly correlates with Ba and Zn (figure 3) [5, 37]. Other research came to similar conclusions; a prior study assessing the relationship between oxidative potential markers and census tract-level health outcomes suggested that compared to PM_{2.5} mass, the OH formation assays may be better at predicting PM-related adverse health consequences [19].

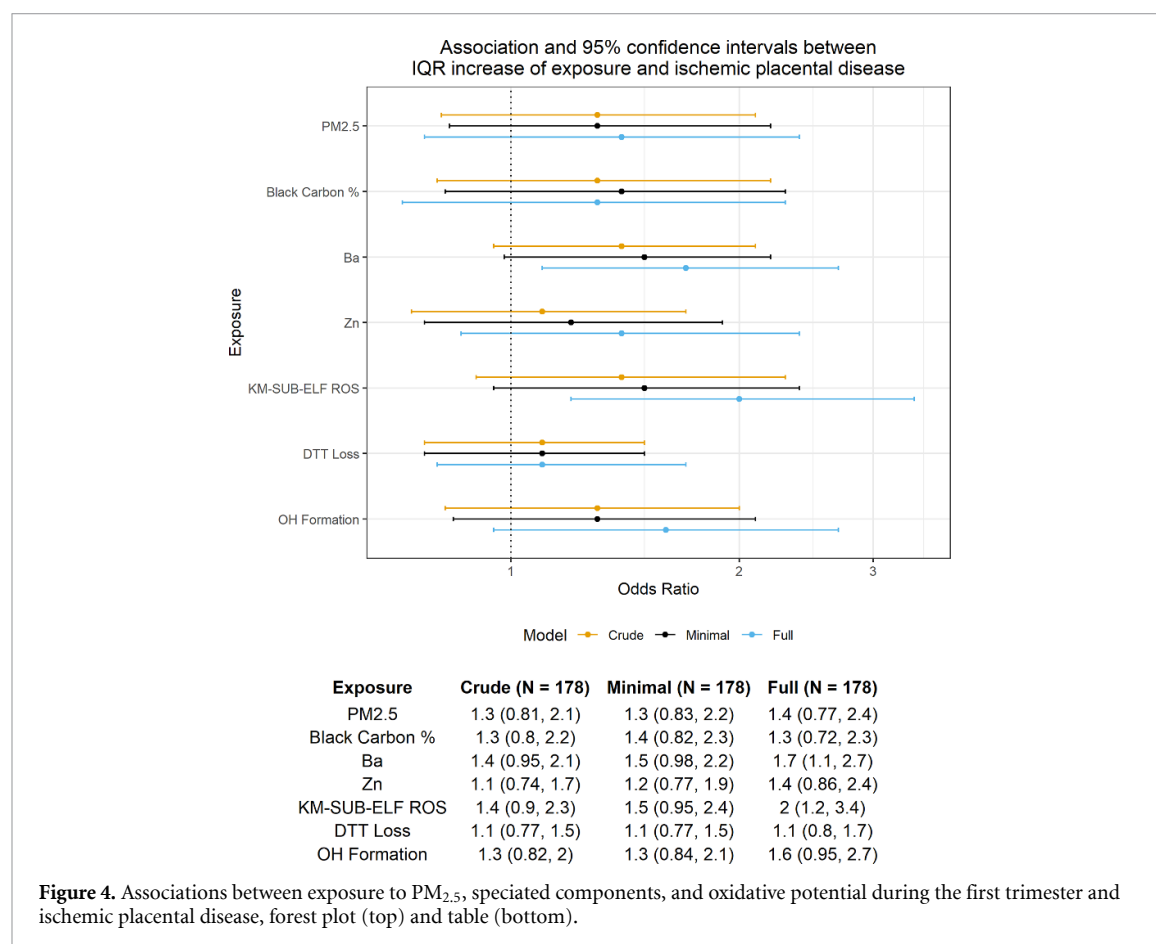
Prior studies have identified TRAP as a specific source of oxidative potential associated with adverse health effects [38, 63]. In our study, we found that Ba and Zn both are strongly correlated with OH radical formation and are more strongly associated with IPD compared to PM_{2.5} and black carbon. Increases in fuel efficiency and automobile electrification will likely increase the total share of PM from brake and tire wear



components [5, 64]. Consequently, health studies targeting TRAP with conventional metrics may underestimate exposure-outcome associations. Similarly, our findings suggest that future changes in fleet composition and reduction in tailpipe exhaust alone may not improve pregnancy outcomes.

Table 2. Mean (IQR) values of first trimester exposure estimates among cases and non-cases.

Exposure	Unit	Cases (N = 47)	Non-Cases (N = 131)>	Overall (N = 178)
PM _{2.5}	μg/m ³	9.83 (1)	9.68 (1)	9.72 (1)
Black Carbon %	%	4.85 (0)	4.74 (1)	4.77 (1)
Ba	ng/m ³	18.9 (6)	17.7 (4)	18.1 (4)
Zn	ng/m ³	9.91 (2)	9.76 (2)	9.8 (2)
KM-SUB-ELF ROS	nmol/L	119 (13.5)	116 (15.5)	117 (16)
DTT Loss	pmol/min/m ³	635 (108)	627 (119)	629 (119)
OH Formation	pmol/min/m ³	5.79 (1.5)	5.55 (1)	5.61 (1)



5. Strengths and limitations

Strengths include novel and robust exposure and outcome assessments. The relationship between air pollution and IPD is understudied, with only one previous study assessing IPD and distance to roads, which may have resulted in misclassification [17]. Our exposures include measurements which are more source-specific than conventional metrics compared to solely using PM_{2.5} mass concentration. Furthermore, around one-third of filter samples used in our exposure model were sampled at PARENTs subjects' homes, likely reducing exposure misclassification. Our close clinical follow-up enabled a detailed IPD outcome assessment, including criteria previously used by Wesselink *et al* [17] plus gestational hypertension, and fetal growth restriction. Comprehensive interviews also allowed us to conduct sensitivity analyses on factors such as diet. Consequently, we believe that the risk of outcome misclassification is very low.

This study has limitations regarding sample size and temporal alignment. With a small sample size of 178, our effect estimates exhibit consistent directions but have high uncertainty. As a result, comparisons between effect sizes among individual pollutants are not conclusive and should instead serve as starting point for further research. Likewise, low sample size may hamper inference using all the covariates used in the fully adjusted models. This study therefore presents the results of minimally adjusted models, which adjusts for confounders commonly found in large, administrative cohorts. Despite increased uncertainties associated with the fully adjusted models, changes in effect magnitude are mostly consistent. While the study's small

sample size limits the ability to draw specific comparisons between the minimal and adjusted model, the results nonetheless suggest that the effect sizes and direction observed in the crude and minimally adjusted models are not due to confounding due to variables including parity, maternal BMI, maternal smoking, gestational diabetes, maternal education, or household income. As stated elsewhere [25], we designed the PARENTs cohort to study placenta-related adverse outcomes in pregnancy, i.e. a high-risk population of pregnant women with a high prevalence of IPD. This likely allowed us to detect strong exposure-outcome associations despite limitations. Notably, our cohort does not represent the general population of pregnant women: they were older, more educated and of higher socio-economic status and sought specialized care at UCLA hospitals. Thus, on one hand, our subjects were at higher risk of pregnancy complications, on the other, higher SES, education, and levels of medical care may have protected them from some pregnancy complications [65]. Our exposure models were based on data collected 2–3 years after pregnancy. The main sources of our exposures, traffic and heavy industry, remained consistent during the time between recruitment and the air monitoring and sampling campaigns. Another limitation regarding time-varying exposure is that chemically speciated $PM_{2.5}$ data were only collected at two time points. This study used temporally-varying PurpleAir data to estimate month-to-month variation. That said, exposures across months were highly correlated with one another, and in the study area, activities such as automobile and train traffic remain relatively consistent throughout the year. We would expect spatial contrasts, which are well-captured by our exposure assessment, to play a more significant role.

Lastly, our sampling campaigns were not affected by the COVID-19 pandemic or wildfires in Southern California, such that spatial trends in pollution likely remained similar to those during time of the pregnancies, minimizing the impact of temporal misalignment.

6. Conclusion

For this Los Angeles birth cohort, we found consistent associations between IPD and oxidative potential markers for $PM_{2.5}$ and metals associated with brake and tire wear emissions. Our results suggest that compared to black carbon and $PM_{2.5}$, markers of brake and tire wear, namely Ba, KM-SUB-ELF ROS, and OH formation may have generated stronger size effect estimates even though 95% CIs overlapped. Although uncertainty remains regarding the true difference in effect between different pollutants, we believe that differences point estimates match toxicological concerns, and invite further study among larger cohorts. , Ba, KM-SUB-ELF ROS, and OH formation generated stronger effect estimates sizes that were stable or even increased after adjusting for important variables widely considered to be risk factors for IPD.

Our results indicate that the association between TRAP and these adverse pregnancy outcomes is at least partially attributable to brake and tire wear-related particulate matter and the toxicity of fine particulate matter. Clean air policy has successfully reduced tailpipe emissions but currently does not target brake and tire wear. Our results suggest that protecting public health may necessitate an expansion of vehicle emissions regulations that also address brake and tire wear PM exposures.

Data availability statement

The data cannot be made publicly available upon publication because they contain sensitive personal information. The data that support the findings of this study are available upon reasonable request from the authors.

6. Ethical statement

This research was approved by the UCLA IRB, and details are listed by ClinicalTrials.gov (NCT02786420).

The research was conducted in accordance with the principles embodied in the Declaration of Helsinki and in accordance with local statutory requirements. All participants gave written informed consent to participate in the study.

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