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Los Angeles

The Harmful Effects of Air Pollution
on Early and Late Life Outcomes

A dissertation submitted in partial satisfaction of the requirements
for the degree Doctor of Philosophy in Epidemiology

by

Sanjali Mitra

2026

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ABSTRACT OF THE DISSERTATION

The Harmful Effects of Air Pollution on Early and Late Life Outcomes

by

Sanjali Mitra

Doctor of Philosophy in Epidemiology

University of California, Los Angeles, 2026

Professor Beate R. Ritz, Chair

Air pollution can pose adverse health effects at any stage of life but can be especially detrimental at periods of heightened vulnerability — fetal growth in the womb and old age. Air pollution health impacts have been studied extensively but research on particulate matter $\leq 2.5\mu m$ (PM_{2.5}) constituents and volatile organic compounds are still lacking. We investigated the effect of a variety of air pollutants on adverse birth outcomes in California and in a smaller cohort explored the role of the placenta in explaining such associations. We also explored effects on

cardiometabolic health outcomes in a particularly vulnerable population of older Mexican Americans.

First, for Aim 1 of the dissertation, we analyzed California birth records from 1990 to 2021 to understand the trends in associations of gestational exposure to criteria air pollutants ($PM_{2.5}$, NO_2 , O_3) and traffic and industry-related air toxics (benzene, 1,3-butadiene, chromium, lead, nickel, zinc) with preterm birth (PTB) and low birth weight at term (TLBW). While $PM_{2.5}$ and NO_2 posed a lower threat in recent years, associations with nickel and zinc strengthened. Moreover, Black, Hispanic, and Asian and Pacific Islander mothers were vulnerable to the effect of zinc, nickel, and chromium on adverse birth outcomes.

Second, for Aim 2, we assessed the influence of gestational exposure to polycyclic aromatic hydrocarbons (PAHs) on placental volume, blood flow, deoxygenation during pregnancy; placental and birth weight at term; and hypertensive disorders of pregnancy in the Placental Assessment in Response to ENvironmental pollution study (PARENTs) cohort. We observed reduced mid-pregnancy placental volume in female fetuses, increased mid-pregnancy placental deoxygenation in male fetuses, and reduced placental and birth weight in both sexes, suggesting that the effects of PAH exposure may differ by sex of the fetus.

Lastly, for Aim 3, we explored the impact of exposure to the same pollutants as in the first study, on cardiometabolic disorders in the Sacramento Area Latino Study on Aging (SALSA) cohort. We found $PM_{2.5}$, NO_2 , and nickel to be strongly associated with the risk of developing hypertension and low HDL cholesterol in urban areas, highlighting the need for emission reduction policies targeting both exhaust and non-tailpipe pollutants.

The dissertation of Sanjali Mitra is approved.

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University of California, Los Angeles

2026

To Ma and Baba

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1. INTRODUCTION

The period of fetal growth is one of heightened susceptibility to environmental insults. Exposure to higher levels of air pollution during pregnancy has been linked to increased risk of low birth weight (LBW) and preterm birth (PTB)¹, outcomes that can leave a person vulnerable to health issues throughout life. These adverse birth outcomes are risk factors for neonatal death, stunted growth, poor neurodevelopment and neurological disorders, as well as adult-onset chronic diseases such as cancer and cardiovascular disease (CVD)²⁻⁴. Air pollution exposures later in life have also been related to cardiometabolic disorders like diabetes, hypertension, and CVD⁵⁻⁸. Identifying sources of air pollution that need to be regulated and vulnerable populations that are disproportionately affected, is critical in shaping targeted air pollution reduction policies. Further, an understanding of the biological mechanisms involved is important for accurate public health messaging and clinical advice.

Exploration of the impacts of air pollution have spanned the last several decades and while much has been learnt, knowledge gaps still remain. Federal and State regulations have been put in place to control the emissions from traffic exhaust. In California this has been successful in bringing down the levels of some key air pollutants such as particulate matter $\leq 2.5 \mu m$ (PM_{2.5}) and nitrogen dioxide (NO₂)⁹. However, components of PM_{2.5} and other air toxics such as gaseous volatile organic compounds have not been widely researched and regulated¹⁰. In this dissertation we investigated the impact of gestational exposure to ambient criteria air pollutants (PM_{2.5}, NO₂, O₃) and traffic and industry-related air toxics (benzene, 1,3-butadiene, chromium, lead, nickel, zinc) on PTB and low birth weight at term (TLBW) using 30 years of California birth records. Further we studied the effects of exposure to the same pollutants later in life on cardiometabolic

disorders including hypertension, low HDL cholesterol, hypertriglyceridemia, CVD, and stroke. This study was conducted in the Sacramento Area Latino Study on Aging (SALSA) cohort, consisting of elderly Mexican Americans, an ethnic group that is particularly vulnerable to these conditions as well as exposed to elevated levels of air pollution¹¹⁻¹⁴. Finally, we further explored underlying biological mechanisms that contribute to the harmful effects of air pollution exposure during pregnancy. Given the important role of the placenta in ensuring the fetus is well nourished and in producing growth-regulating hormones^{15,16}, we suspected that air pollution exposure may adversely affect placental growth and function, and subsequently result in suboptimal birthweight. To examine this, we looked at polycyclic aromatic hydrocarbons (PAHs), another class of air pollutants that have not been widely studied but are abundant in emissions from cooking, traffic and industries¹⁷⁻¹⁹. We measured levels of PAHs in the urine of pregnant women enrolled in the Placental Assessment in Response to ENvironmental pollution study (PARENTs) cohort. We tested associations with placental volume, blood flow, deoxygenation during pregnancy, placental and birth weight at term, as well as gestational hypertension and preeclampsia. Further, we assessed differences by sex of the fetus. To summarize, in this dissertation we investigated the harmful effects of air pollution at both the early and later stages in life, uncovered biological mechanisms in play, and identified vulnerable populations in need of special protection.

2. AIM 1: Association Of Prenatal Exposure to Criteria Air Pollutants and Traffic-Related Air Toxics with Adverse Birth Outcomes: A Population-Based Cohort Study in California (1990-2021)

2.1. Abstract

While traffic exhaust emissions remain the largest contributor of air pollution in California, levels have declined over time. Contrarily, non-tailpipe brake and tire wear and industrial emissions have persisted and remain a major health concern. Here we studied how air pollution levels have impacted adverse birth outcomes over a period of 30 years in California. Based on birth records (1990-2021) from the California Department of Public Health, we assessed associations of gestational exposure to criteria air pollutants (PM_{2.5}, NO₂, O₃) and traffic and industry-related air toxics (benzene, 1,3-butadiene, chromium, lead, nickel, zinc) with preterm birth (PTB) and low birth weight at term (TLBW). We used logistic regression to estimate odds ratios per interquartile range (IQR) increase in pollutants across four time periods (1990-1997, 1998-2005, 2006-2012, and 2013-2021). We also conducted analyses stratified by race/ethnicity and area-level socioeconomic status.

The estimated effect size for PM_{2.5} and NO₂ on PTB and TLBW declined over time, while those for nickel and zinc increased in the most recent period of 2013-2021 for PTB. We observed some of the strongest associations with adverse birth outcomes for zinc, nickel, and chromium, which may be from brake and tire-wear emissions, among Black and Hispanic mothers and low area-level SES populations.

Effect estimates for air pollutants in California changed over a 30-year period with important differences by race/ethnicity and area-level SES, highlighting the success of air pollution

reductions but also a need for additional interventions to mitigate remaining increases in risk from traffic and industry-related air toxics.

2.2. Introduction

Preterm Birth (PTB) is defined as birth before the completion of 37 weeks of gestation, and a newborn is considered low birth weight (LBW) if it weighs less than 2500g, or term LBW (TLBW) if the baby is born <2500g at term. In California, 7% of babies were born with LBW and 9% of babies were born preterm in 2022²⁰. Fetal development is a time of heightened susceptibility to maternal environmental exposures including air pollution, which may result in adverse birth outcomes with possible short- and long-term consequences such as increased infant mortality, child morbidity including poor neurodevelopment, and potentially even adult-onset chronic diseases such as hypertension and chronic kidney disease^{3,21–23}. There is an extensive literature on air pollution related adverse birth outcomes summarized in a recent umbrella review and a meta-analysis that concluded that particulate matter $\leq 2.5\mu m$ (PM_{2.5}) and nitrogen dioxide (NO₂) exposures are positively associated with LBW, TLBW and PTB^{1,24}. While PM_{2.5} mass encompasses a mixture from various sources and activities including combustion (e.g., vehicle exhaust, industrial activity, and forest fires), brake/tire wear²⁵, and atmospheric chemical reactions, much less is known about how such PM_{2.5} components and sources contribute to the adverse birth outcomes and whether they changed over time. Investigating the contributions of specific PM_{2.5} components to these sensitive outcomes can also help identify remaining sources that still are in need of mitigation. Regulations of fuel emissions over the past decades have generally reduced PM_{2.5} and NO₂ levels in California²⁶, yet some pollution sources have progressively become more prominent, such as wildfires and non-tailpipe brake and tire wear emissions. There are, however,

no studies yet that cover changing pollutions profiles with models that rely on a vast statewide monitoring network for criteria pollutants and air toxics spanning over three decades and a population as diverse as found in California. Here, we will use these unique resources to better understand the impact of changing pollution profiles on adverse birth outcomes while expanding beyond criteria air pollutants to include several air toxics.

The diversity of California will also allow us to address some racial/ethnic and socioeconomic disparities in these outcomes. For example, in 2022, Black mothers experienced the highest percentages of LBW and preterm births, and mothers residing in areas with less than 10% neighborhood poverty were affected the least in California²⁰. Studies have also found that exposure to PM_{2.5} and its chemical components are disproportionately higher in areas where low-income populations, racial minorities and people of color live¹²⁻¹⁴. One study found that despite overall reductions in PM_{2.5} levels in California, relative exposure disparities increased²⁷. However, studies on racial/ethnic disparities of air pollution related adverse birth outcomes remain limited even in California²⁸⁻³¹.

Thus, in the to date largest and longest ranging birth cohort study in California (1990 to 2021) we have utilized high-resolution (100m) exposure estimates for criteria air pollutants (PM_{2.5}, NO₂, O₃) and air toxics (1,3-butadiene, benzene, chlorine, lead, nickel, zinc) derived from a land use regression model, to examine patterns of associations between these pollutants and birth outcomes over time and explore whether there are racial/ethnic and area-level socioeconomic levels differences in estimated effects.

2.3. Methods

2.3.1. Study Population

We used California birth registry data from January 1st, 1990 to December 31st, 2021 obtained from the California Department of Public Health to identify preterm newborns and those born TLBW. There were 16,821,223 births in this time period, from which we excluded births with missing or extreme data for gestational length (less than 140 days or greater than 315 days) (N=729,956, 4.3%), missing or extreme data for birth weight in a viable infant (less than 500g or greater than 6800g) (N=15,445, 0.1%), missing information for year or month of last menses (N=3,449, 0.02%), non-singleton births (N=454,942, 2.8%), and those with less than 50% of daily ambient PM_{2.5}, NO₂, or O₃ observations available in all three trimesters (N=319,140, 2.0%). Our final analytical sample included 1,347,224 preterm births, 299,703 TLBW births, and 13,651,364 term births with normal birth weight (TNBW). A flowchart delineating the exclusion criteria and the process for arriving at the final analytical sample is shown in Figure S 2-1. A table comparing demographic characteristics of the final analytical sample and the excluded births records is provided in Table S 2-1.

2.3.2. Air Pollution Exposures

2.3.2.1. Criteria air pollutant surface generation

We employed land use regression (LUR) models integrated with a D/S/A algorithm for parameter selection³², a machine learning technique, to generate daily concentrations of PM_{2.5}, NO₂ and O₃ in California for the years 1989 to 2021. The methods employed have been outlined in detail elsewhere³³. Briefly, measured values for these air pollutants were obtained from Environmental Protection Agency (EPA) regulatory monitors, fixed-site saturation monitoring data, and Google-street car measurements. The daily EPA regulatory monitoring for PM_{2.5} began

in 1999 while for NO₂ and O₃ it began in 1990. Predictors used in our modelling process included daily traffic, land use and land cover, vegetation index, topography, distance to highways, major roadways, coast, and ports and remote sensing data for aerosol optical depth (AOD), and NO₂, and O₃ measurements from NASA's Ozone Monitoring Instrument (OMI). Measurements for some predictors, such as traffic and OMI- NO₂ and OMI-O₃ were unavailable prior to 2005 and vegetation and AOD data were not available before 2000. The daily LUR models for NO₂, PM_{2.5}, and O₃, were built based on available data for predictors and measured air pollutant concentration values. In addition, to allow us to predict daily NO₂, PM_{2.5} and O₃ concentrations for earlier periods when the above listed predictor data were unavailable, regression techniques were used to extended predictor data back to 1989. At the model development stage, predictor data were available at a resolution of up to 30m whereas the pollution surfaces were produced at a 100 m resolution. The adjusted R² values for the PM_{2.5}, NO₂ and O₃ LUR models were 0.65, 0.84, and 0.93 respectively.

2.3.2.2. Air toxics surface generation

Similar to criteria air pollutants, machine learning integrated LUR models were used to create 100m resolution surfaces for air toxics. The air toxics data used in our analysis were available from 1996 to 2021 and were sourced from the California Air Resources Board (CARB)'s speciation data and emissions estimates from the California Toxics Inventory (CTI), covering stationary sources, including point sources reported by facility operators or air districts under the Air Toxics "Hot Spots" Program and CARB and local air districts. In addition to the individual air toxics emissions, total organic gases (TOG) and reactive organic gases (ROG) data from CARB's emissions inventory were also included as predictors. Other predictors used for modelling included

traffic, land use and land cover, vegetation index, distance to ports, and remote sensing Sentinel-2 spectral bands and their ratios to account for the spatial distribution of surface characteristics such as land cover, vegetation, and urbanization. Predictor data was extended back to 1989 for the periods without observations using regression techniques. The adjusted R^2 values for the LUR models were 0.81 for benzene, 0.62 for 1,3-butadiene, 0.76 for chromium, 0.59 for lead, 0.70 for nickel, and 0.90 for zinc.

The Texas A&M Geoservices Geocoder^{34,35} was used to geocode maternal residential addresses. Prior to 1998 exact residential addresses were not available and the zipcode centroid was geocoded instead. Pollutant levels at these geocoded addresses were extracted, for each air pollutant from the LUR surfaces, specifically daily estimates for criteria air pollutants and annual ones for air toxics. The daily estimates for the criteria air pollutants were used to calculate entire pregnancy exposure averages. For the air toxics, we generated entire pregnancy exposure levels as a weighted average of the proportion of gestation time that was spent in each of two calendar years.

2.3.3. Outcome and Covariate Assessment

PTB was defined as a birth at gestational age ≥ 20 weeks but < 37 weeks, TLBW as infants born at term (≥ 37 weeks and ≤ 45 weeks of gestational age) with a birthweight of ≥ 500 g and < 2500 g, and TNBW as infants with a birthweight of ≥ 2500 g and ≤ 6800 g born at ≥ 37 weeks and ≤ 45 weeks of gestational age. Gestational age was calculated as the difference between last date of menses and the date of birth. Birth records provided by California Department of Public Health (CDPH) changed format in 2018. Prior to 2018, for records with incomplete last date of menses the gestational length was still provided. However, for the years 2018-2021, records with incomplete last date of menses, had missing gestational length. For these years, we used the mid-

month date, if month and year of last menses were known, to calculate the gestational length. Gestational age, birthweight, and most other covariates were obtained from the CDPH birth records, and area-level SES was additionally generated as quintiles of Yost's and Yang's indices of socioeconomic status at the census block group. The Yost index, based on the decennial Census, was used for birth records from 1990 to 2005, and the Yang index, based on the American Community Survey (2015-2019) data, was used for births from 2006 onward. These indices are described elsewhere^{36,37}, but briefly, the variables used to calculate them include the percentage of the population above a certain educational attainment level, above 200% of the poverty line, employed, with a blue-collar job, and the median rental value, median value of owned housing, and median household income.

2.3.4. *Statistical Analysis*

When processing the air toxic exposure data, we replaced zero values with half of the lowest non-zero value (Table S 2-2). We chose this approach as zero values likely represent measurements below the detection limit rather than the absence of the pollutant. Additionally, to reduce the influence of extreme or unrealistic values, we performed winsorization, a statistical technique used to limit the effect of outliers. We did this by replacing the air toxics concentration values that were greater than the 99th percentile of the distribution for each birth year, by the respective 99th percentile value. We used logistic regression to analyze the association between entire pregnancy average air pollutant exposure and each adverse birth outcome for the entire study period as well as stratified by time periods (1990-1997, 1998-2005, 2006-2012, and 2013-2021). We grouped the data into these time periods rather than analyzing individual years to avoid overinterpreting small, year-to-year fluctuations in the associations and to better capture overall temporal trends. Since prior to 1998, exact residential addresses were unavailable and PM_{2.5}

concentrations required back-casting because routine monitoring had not yet begun, we grouped years 1990-1997 together. To maintain comparability across periods, the remaining years were also divided into equal 7–8-year intervals. TNBW babies served as the reference for both outcomes. Estimates were reported per entire pregnancy interquartile range (IQR) for each pollutant (PM_{2.5}: 2.46 $\mu\text{g}/\text{m}^3$, NO₂: 5.07 ppb, O₃: 3.86 ppb, 1,3-butadiene: 0.58 ppb, benzene: 0.18 ppb, chromium: 1.10 ng/m³, lead: 0.55 ng/m³, nickel: 0.28 ng/m³, zinc: 0.78 ng/m³). As the range of pollutant concentrations differed across years, we used the IQR from the most recent period (2013-2021) allowing us to compare effect estimates over time. A Directed Acyclic Graph (DAG) was created a priori to help with determining potential confounding (Figure S 2-2), and all models were adjusted for sex of the child (male or female), and maternal parity (1,2, ≥ 3), age (<20, 20-24, 25-29, 30-35, >35 years), race and ethnicity (non-Hispanic White, Black, Asian and Pacific Islanders (API), and Hispanic mothers), birthplace (US-born vs foreign-born), payment type for prenatal care (no prenatal care, government insurance, private insurance, and self-payment), educational attainment ($\leq 8^{\text{th}}$ grade, 9th-12th grade without diploma, high school graduate or General Education Development (GED) completed, and at least some college or graduate education), area-level socioeconomic status (SES) (quintiles: 1 for lowest - 5 for highest), and birth year. As birth year correlated highly with the levels of some air toxics (resulting in high Variance Inflation Factor (VIF) values for the entire study period), we did not adjust for birth year for the entire study period when analyzing air toxics. Instead, we only adjusted for birth year within each of the four periods (1990-1997, 1998-2005, 2006-2012, and 2013-2021) and then conducted random effects meta-analyses of the effect estimates in these periods to generate the overall effect estimate for the entire study period. We tested for statistical significance of linear trend in associations across time periods. We also performed stratified analyses by race/ethnicity and area-level SES. To test if

statistically significant interaction exists with race/ethnicity or area-level SES, we used Likelihood Ratio Test to compare models without the interaction terms with the models without the interaction terms. In addition, we conducted two sensitivity analyses: i) for criteria air pollutants, we co-adjusted each criteria air pollutant model for the other two criteria pollutants and for air toxics, we co-adjusted for the two traffic-related criteria pollutants, PM_{2.5} and NO₂; and ii) to address concerns about the COVID-19 pandemic influencing study results towards the end of the study period, we excluded births in the years 2020 and 2021.

This research was approved by the University of California, Los Angeles, Office of the Human Research Protection Program IRB#22-000701, initial approval on 5/10/2022), and the California Committee for the Protection of Human Subjects (IRB#12-10-0861, initial approval on 12/7/2012). The study received an exemption from the requirement to obtain informed consent as no direct contact was made with study subjects. All analyses were conducted using R (version 4.3.3.; R Foundation for Statistical Computing, Vienna, Austria).

2.4. Results

2.4.1. Study Population Characteristics

Hispanics accounted for the largest racial/ethnic group overall (Table 2-1). Mothers of preterm compared to mothers of TNBW babies were more often Hispanic (52.4% vs 48.9%) or Black (9.2% vs 5.8%) and less often White (25.7% vs 32.1%) (Table 2-1). Similarly, mothers of TLBW babies compared to TNBW babies were more likely to be Black (11.8% vs 5.8%) and less likely to be White (24.1% vs 32.1%). Both PTB and TLBW mothers more commonly resided in the lowest area-level SES areas (32.4% vs 27.2% and 31.1% vs 27.2%, respectively) and less in the highest area-level SES areas (11.0% vs 14.3% and 11.9% vs 14.3%, respectively) compared to

TNBW mothers. Table S 2-1 shows the comparison of demographic characteristics between the final analytical sample and the birth records that were excluded from analyses. While the two are similar with respect to proportion of categories of infant sex, maternal age, maternal education, and area-level SES, some differences exist. The analytical sample has a lower percentage of non-Hispanic White mothers (31.4% vs 37.7%) and higher percentage of Hispanic mothers (49.1% vs 43.8%). The percentage of mothers who have government insurance in the analytical sample is also higher as compared to the excluded sample (46.3% vs 41.6%) and so is the percentage of mothers for who are giving birth for the first time (39.4% vs 32.3%).

2.4.2. Air Pollution Exposures

Entire pregnancy exposure averages for all pollutants we examined varied over time as well as by race/ethnicity and area-level SES (Table S 2-3). PM_{2.5}, NO₂, benzene, lead, and nickel concentrations decreased over time, with the highest measures recorded in 1990–1997 (13.52 µg/m³, 19.74 ppb, 1.11 ppb, 5.36 ng/m³, and 1.89 ng/m³ respectively) and the lowest in 2013–2021 (9.83 µg/m³, 9.88 ppb, 0.44 ppb, 4.46 ng/m³, and 1.22 ng/m³ respectively). However, upon examining exposure levels by individual years, we observed nickel levels to increase after 2016 (data not shown). Zinc, on the other hand, steadily increased from 0.8 ng/m³ in 1990-1997 to 4.16 ng/m³ in 2013-2021. O₃, 1,3-butadiene, and chromium levels fluctuated slightly but remained fairly stable across the entire study period. NO₂ exposure, a marker for traffic pollution, was highest among Black (16.06 ppb) and Hispanic mothers (16.27 ppb) and lowest in White (13.57 ppb) and API (14.58 ppb) mothers, while other pollutant exposure levels were relatively similar across race/ethnicity groups. The criteria air pollutants PM_{2.5}, NO₂, and O₃ exposures decreased with increasing area-level SES levels, ranging from 12.73 µg/m³, 16.42 ppb, and 38.39 ppb in the lowest area-level SES areas to 10.39 ppb, 13.61 ppb, and 36.96 ppb in the highest area-level SES

areas, respectively. Decreases with increasing area-level SES were also observed in some air toxics such as benzene (0.81 to 0.7 ppb) and lead (5.12 to 4.60 ng/m³).

Overall, moderate to high correlations were observed between PM_{2.5} and other traffic related pollutants, NO₂ (r=0.63), benzene (r=0.72), lead (r=0.60), and nickel (0.61) (Table S 2-4). Similarly, NO₂ displayed moderate to high correlations with benzene (r=0.79), lead (r=0.58), and nickel (r=0.56). Benzene was also strongly correlated with nickel (r=0.78) and lead (r=0.67). The correlation of PM_{2.5} with NO₂ decreased steadily, from 1990-1997 (r=0.57) to 2013-2021 (r=0.26), potentially suggesting a reduction in tail-pipe exhaust-related sources contributing to PM_{2.5} mass. Benzene remained consistently correlated with NO₂ across all four time periods. Zinc was observed to be negatively correlated with PM_{2.5} (r=-0.58), NO₂ (r=-0.56), benzene (r=-0.85), lead (-0.50), and nickel (r=-0.79), but the negative correlation with PM_{2.5} decreased from r=-0.38 in 1990-1997 to r=-0.11 in 2013-2021, highlighting the changing composition of PM_{2.5} over the last few decades.

2.4.3. Associations of Criteria Air Pollutant and Air Toxic Exposure with PTB

Time trend observation for the two traffic-related criteria air pollutants, PM_{2.5} and NO₂, were similar. We observed a positive effect estimate between PTB and PM_{2.5} in the single pollutant model for the entire study period (OR: 1.032, 95%CI: 1.030, 1.035). However, when modeling associations for PM_{2.5} within distinct periods, we saw positive associations in the three earlier periods but during the latest period 2013-2021 it was near null (Figure 2-1 and Table 2-2). For NO₂, the association for overall study period was close to null and very small associations were observed only in the three earlier periods. This time trend was also observed upon stratifying by race/ethnicity and area-level SES. Small to moderate elevated associations for PM_{2.5} and NO₂ in

the entire study period were observed in Whites, Hispanics, and Blacks, while among API mothers the association was slightly null or slightly negative (Table S 2-5). Associations of PM_{2.5} with PTB were elevated equally across area-level SES neighborhoods for the entire study period (Table S 2-7). For NO₂, a modest positive association was observed for the overall study period in the highest SES area (OR: 1.027, 95%CI 1.021, 1.033), and smaller associations were observed in the lower SES areas, however these association became null in the last period, with the exception of the lowest SES area, where a modest positive associations was observed (OR: 1.022, 95%CI: 1.011, 1.032).

There was a slight positive association between O₃ and PTB in the overall study period (OR: 1.015, 95%CI: 1.012, 1.017) (Table 2-2). However, associations for individual study periods were null, except for the 2006-2012 period. Overall study period associations were highest in White (OR: 1.024, 95%CI: 1.019, 1.029) and API (OR: 1.033, 95%CI: 1.025, 1.042) mothers and close to null for Hispanic and Black mothers (Table S 2-5). A null association was observed in the lowest area-level SES neighborhoods, but slightly elevated effect estimates were observed in higher area-level SES neighborhoods for the overall study period (Table S 2-7). Although the overall effect estimate for the last period was null, stratification revealed that White and API mothers and high SES area populations had higher odds of PTB even in 2013-2021 (Table S 2-5 and Table S 2-7).

There were similarities in our observations for the zinc and nickel components of PM_{2.5}, with an increase in association observed in the last 2013-2021 period (Figure 2-1 and Table 2-3). This was contrary to our observation for the criteria pollutants. While for zinc, a strong positive association was observed in the overall study period (OR: 1.065, 95% CI: 0.98, 1.158), for nickel

it was null. However, associations in individual study periods revealed that although for zinc we observed the effect estimate size decrease from strongly positive in 1990-1997 (OR: 1.201, 95%CI: 1.185, 1.236) to null in 2006-2012, it increased in 2013-2021 (OR: 1.031, 95%CI: 1.025, 1.038). For nickel, associations were slightly negative or null in earlier periods, but like zinc, there was an increase in association in the last period (OR: 1.054, 95%CI: 1.040, 1.068). Additionally, for these air toxics, Black, Hispanic, and low area-level SES populations were observed to be at higher odds of PTB (Figure 2-2, Table S 2-6 and Table S 2-8). For zinc, the strongest odds were observed in Black (OR: 1.131, 95%CI: 0.997, 1.282) and Hispanic (OR: 1.135, 95%CI: 1.002, 1.0285) mothers in the overall study period (Figure 2-2 and Table S 2-6). The overall study period associations also steadily declined with increasing area-level SES, with the strongest association observed in the lowest area-level SES neighborhoods (OR: 1.147, 95%CI: 0.997, 1.346) and no association in the highest area-level SES areas (OR: 0.993, 95%CI: 0.976, 1.01) (Table S 2-8). Interestingly an increase in association in the last period was only seen in Black and Hispanic mothers, and in mothers residing in the lowest, low-middle, and middle SES areas. For nickel, null associations were observed in earlier periods across race/ethnicities and SES categories, however, in 2013-2021, the strongest estimates were observed in Blacks (OR: 1.065, 95%CI: 1.012, 1.120) and Hispanics (OR: 1.060, 95%CI: 1.040, 1.080) while moderately positive associations were found across SES levels (Figure 2-2, Table S 2-6 and Table S 2-8).

The association for chromium was null for the overall as well as individual study periods and similar observations were made across race/ethnicity groups (Figure 2-2, Table 2-3 and Table S 2-6). Associations were also null in all area-level SES neighborhoods, except for 2013-2021, when we estimated a slightly positive association in the lowest area-level SES neighborhoods (OR:

1.022, 95%CI: 1.013, 1.03) (Figure 2-2 and Table S 2-8). For lead, benzene, and 1,3-butadiene, the pattern of effect estimates by period were similar to those for the criteria air pollutants PM_{2.5} and NO₂, with small to strong positive associations in earlier periods and no associations in the latest 2013-2021 period (Table 2-3). This trend held across race/ethnicities and across different area-level SES neighborhoods (Table S 2-6 and Table S 2-8).

2.4.4. Associations of Criteria Air Pollutant and Air Toxic Exposure with TLBW

Observations for the association of PM_{2.5} and NO₂ with TLBW were similar to that for PTB. We observed small positive associations for PM_{2.5} (OR: 1.019, 95%CI: 1.014, 1.024) and NO₂ (OR: 1.016, 95%CI: 1.012, 1.019) with TLBW for the entire study period in single pollutant models (Figure 2-1 and Table 2-4). For both of these pollutants, the associations were smaller in the last 2013-2021 period as compared to earlier periods. The temporal pattern was less obvious in the race/ethnicity and area-level SES stratified analyses. For both pollutants, small to moderately positive overall elevated association was found in White, Black, and Hispanic mothers, while the associations in API mothers were null or slightly below null (Table S 2-9). A small overall increased odds for TLBW with exposure to these pollutants was found in all area-level SES neighborhoods (Table S 2-11).

A modest positive association for the entire study period was also observed for O₃ (OR: 1.028, 95%CI: 1.023, 1.033), but unlike PM_{2.5} and NO₂, the association did not reduce in the last period (Table 2-4). The entire period associations were strongest in White (OR: 1.057, 95%CI: 1.046, 1.068) mothers and smaller positive associations were found API and Hispanic mothers while the association in Black mothers was null (Table S 2-9). Associations also increased with increasing area-level SES, with the smallest odds observed in the lowest area-level SES regions

(OR: 1.010, 95%CI: 1.002, 1.019) and the strongest odds in the highest area-level SES regions (OR: 1.046, 95%CI: 1.027, 1.065) (Table S 2-11).

Our observations for zinc's association with TLBW were similar in some aspects to that of PTB. While the entire study period association for zinc was close to null and a moderately positive association was only observed in 1990-1997 (Figure 2-1 and Table 2-5), stratification revealed that disadvantaged populations remained at higher risk in the last period. Increased odds were observed in Hispanic (OR: 1.052, 95%CI: 1.028, 1.076) and Black (OR: 1.054, 95%CI: 0.979, 1.136) mothers overall, as seen for PTB, although the odds in these groups attenuated over time, but remained positive for Hispanic mothers (OR: 1.030, 95%CI: 1.008, 1.052) in 2013-2021 (Figure 2-2 and Table S 2-10). The entire study period effect estimates steadily declined with increasing area-level SES, with the lowest area-level SES areas being most susceptible (OR: 1.04, 95%CI: 1.018, 1.063) and the high-middle and highest area-level SES areas showing null associations, similar to our observation for PTB (Figure 2-2 and Table S 2-12). Although associations in lower SES areas reduced over time, low SES area populations remained the most vulnerable across study periods.

For nickel, the overall entire study period association was null (Figure 2-1 and Table 2-5) but upon stratification we found a strong association only in Black mothers (OR: 1.03, 95%CI: 0.985, 1.077) (Figure 2-2 and Table S 2-10). On the other hand, a strong risk was observed in the highest area-level SES regions for the entire study period (OR: 1.05, 95%CI: 1.012, 1.089) while associations were null in other area-level SES neighborhoods (Figure 2-2 and Table S 2-12).

For chromium, lead, benzene, and 1,3-butadiene, the overall associations were close to null and while small positive associations were observed in earlier periods, associations were null by

2013-2021 (Table 2-5). Race/ethnicity stratification showed that for chromium, slightly positive overall odds were observed only in Black and Hispanic mothers, but these odds diminished over time, persisting only for Hispanic mothers in 2013–2021 (OR: 1.012, 95%CI: 0.999, 1.026) (Figure 2-2 and Table S 2-10). The entire study period associations were slightly elevated for all but API mothers for lead and benzene but there weren't any perceivable differences by race/ethnicity for 1,3-butadiene. Stratification by area-level SES does not reveal any notable trends in associations for these pollutants (Table S 2-12).

2.4.5. Sensitivity Analyses

Co-pollutant adjustment only slightly decreased the association size between NO₂ and PTB from a weak positive association (OR=1.009, 95%CI: 1.008, 1.011) to a null association, but did not meaningfully change the association size between other pollutants and PTB (Table S 2-13). For TLBW, co-pollutant adjustment reduced the association for PM_{2.5} from OR=1.019 (95%CI: 1.014, 1.024) to a null association and for benzene from a null association to a slightly negative association (Table S 2-14). Upon removing the birth records from 2020 and 2021, the association for nickel and PTB decreased from 1.054 (95%CI: 1.04, 1.068) in the 2013-2021 period to 1.016 (95%CI: 0.998, 1.034) in the 2013-2019 period (Table S 2-15), while the strength of associations between other pollutants and either outcome, PTB or TLBW, did not change, showing the robustness of our results (Table S 2-15 and Table S 2-16).

2.5. Discussion

We found notable variations in the associations of adverse birth outcomes with criteria and air toxic pollutants by type of pollutant, time period, race/ethnicities and area-level SES. Although the impact of some pollutants has diminished over time, possibly due to regulation-driven

reductions in pollutant levels, there are persisting associations that differ by race/ethnicity and are-level SES that need to be addressed. These findings highlight the complex interplay of pollutant sources, socioeconomic disadvantages, and temporal trends in pollutant levels.

The overall effect estimate we observed for PM_{2.5} on PTB (1.137, 95%CI: 1.128, 1.15 per 10µg/m³) falls within the range of estimates observed previously. A recent umbrella review summarizing prior meta-analyses reported ORs between 1.02 (95%CI: 0.93, 1.12, per 10µg/m³) and 1.16 (95%CI: 1.07, 1.26, per 10µg/m³)¹. A recent meta-analysis also reported a RR = 1.083 (95% CI: 1.038, 1.130, per 10µg/m³) for the association of PM_{2.5} with TLBW²⁴. This is consistent with our single pollutant effect estimate (OR: 1.08, 95%CI: 1.058, 1.101, per 10µg/m³). However, upon adjustment for NO₂ and O₃, the PM_{2.5} association became null likely indicating that much of the overall PM_{2.5} composition in California over the last three decades has come from combustion sources such as traffic which is well-represented by NO₂. For NO₂ we saw no overall associations with PTB, even though an umbrella review of prior meta-analyses reported positive associations¹. These inconsistencies may be attributed to studying diverse populations – as when we stratified by race/ethnicity we found a negative association in API mothers masking positive association in other race/ethnicities – but also methodological differences such as in exposure assessment and modelling techniques, and difference in study periods and pollutant levels. For TLBW, we found NO₂ to be slightly positively associated, though the few prior studies that have investigated this association found inconsistent results^{38–41}. Interestingly, for both PM_{2.5} and NO₂, we observed the associations with adverse birth outcomes to diminish over the years and even become null in the last period in some cases. The associations for air toxics such as lead, benzene, and 1,3-butadiene

with PTB and TLBW also diminished over time. This may be attributed to the reduction in the levels of pollution from traffic exhaust emissions as a result of successful regulatory policies.

While traffic exhaust emissions have been well regulated, non-exhaust sources of PM_{2.5} remain a concern. We observed a decline in correlation between PM_{2.5} with NO₂ over time, suggesting that non-exhaust sources of PM_{2.5} from traffic may be more relevant in recent years. This is also suggested by an increase in zinc exposure levels over time as well as an increase in nickel exposure levels since 2016 (data not shown). This is likely why a stronger association emerged between nickel exposure and PTB in 2013-2021 compared to earlier periods and the increase in the association between zinc and PTB in 2013-2021 compared to 2006-2012. While the association of nickel with PTB in the 2013-2021 period reduced upon removing birth records from 2020 and 2021, it still remained higher than study periods ranging from 1990-2012. Nickel and zinc possibly have an increasing role as markers of non-tailpipe sources of particles in recent years. Nickel has been found to be present in brake dust and tire wear debris and zinc is a prominent tire wear marker²⁵. In fact our LUR model for nickel shows nickel concentrations to be high near roadways throughout the state. Our study confirms the results of a previous study that also linked zinc with PTB in Los Angeles County⁴².

Stratification by race/ethnicity and by area-level SES revealed Black and Hispanic children and low area-level SES populations to be most vulnerable to the estimated associations for nickel, zinc, and chromium on PTB and TLBW. In addition to these air toxics being brake and tire wear markers^{25,43,44}, chromium is also prevalent in industrial emissions, such as those from metal processing and cement plants⁴⁵. Interestingly, an increase in association for zinc with PTB from 2006-2012 to 2013-2021 was noted only among Black and Hispanic mothers and low-SES areas,

indicating that increase in the impact of exposure to non-tailpipe sources of PM_{2.5} in recent years is being felt specifically by these communities. Low-income children of color have been found to be more likely to live in areas of high traffic density as compared to White children in California⁴⁶. Further, our group has previously shown that the associations between brake and tire wear markers, including zinc, on PTB and TLBW were strongest among Black and Hispanic mothers in Los Angeles County during the years 2017-2019⁴². Longstanding residential segregation policies in the US, such as redlining, has confined Black residents to less favorable neighborhoods, limiting access to education, income, and wealth, and hindering social mobility^{47,48}. Both Black and Hispanic populations, on average, achieve lower educational levels and incomes than White and Asian populations, often residing in poorer neighborhoods with higher pollutant levels⁴⁷. These SES areas also face poorer housing, nutrition, healthcare, less greenspace, and higher crime⁴⁹. The combined stress of social and environmental stress, during pregnancy in these communities increases vulnerability⁵⁰. We also found adverse impacts in White and API mothers and those living in high area-level SES communities, most consistently for O₃. This suggests that consequences of air pollution may be felt in more privileged communities as well, possibly due to secondary formation of pollutants O₃ further away from the primary sources of pollution, while in low SES urban areas high O₃ may simply be a marker for low traffic.

Several biological mechanisms have been suggested as being involved in mediating the association of air pollutants with PTB and LBW that may explain our results, including oxidative stress, inflammation, altered DNA methylation and damage, endothelial damage, placental dysfunction, immune and endocrine dysregulation, increased blood coagulation and hypertension⁵¹⁻⁵⁷.

Our study has several strengths. This is the first study to investigate this research question in a study period that spans over three decades, encompassing dramatic changes in air pollution levels due to regulatory policies. We used exposure data that has high spatial resolution, and we had access to residential addresses for most of the study period, allowing us to assign exposures to the homes of the mothers. Moreover, in this study we broadened our focus to understudied air toxics. Lastly, the large sample size of our study gave us the statistical power to investigate effect measure modification by race/ethnicity and area-level SES. Our study also had limitations. We were only able to estimate air pollution exposure levels at the mother's residential address as we did not have information on time spent away from home, most importantly at work. We also only had the residential address at the time of birth and did not have information on whether the mothers moved during their pregnancy. Therefore, we expect exposure misclassification that is likely non-differential, biasing our results towards the null. A comprehensive review on residential mobility during pregnancy and subsequent consequences for exposure assessment noted that while mobility varied by socioeconomic status and race, distances moved during pregnancy were on average short with the median often <10km⁵⁸. Owing to financial constraints, we think it is unlikely that pregnant women would move across regions with vastly different area-level SES. The same review also noted that some studies have found effect estimates to be underestimated due to lack of information regarding residential mobility⁵⁸. In the years 1990 to 1997, we did not have data on exact residential addresses and thus assigned exposure estimates based on zip codes only. In this period, we also needed to use back-casting to obtain the air pollution surfaces for PM_{2.5} that was not measured routinely before 1998. These issues likely led to additional non-differential misclassification. This may be why we sometimes observed effect estimates for 1990-1997 that were smaller than latter years during which exposure estimation was more accurate. We also want

to note that while we adjusted for potential confounders, residual confounding is still possible due to misclassification of covariates or unmeasured confounders. Another potential limitation is the method used to ascertain gestational age. Although first-trimester ultrasound provides more accurate dating, in our study PTB was defined using last date of menses, as this information is consistently available in birth certificates. A study comparing last menstrual period (LMP) with first-trimester ultrasound indicated that LMP performs well for distinguishing preterm from term births, with a similar proportion of births classified as preterm versus term across the two methods⁵⁹

Future studies with higher temporal granularity for air toxics may allow us to identify the most susceptible periods of exposure during pregnancy. A better characterization of the chemical composition of PM_{2.5} may help identify the contributions from tailpipe, non-tailpipe, and other sources such as wildfires and explain differences in effect estimates possibly due to composition changes.

2.6. Conclusion

This study highlights the complex interplay of air pollution, socio-economic factors, and racial-ethnic disparities in influencing PTB and TLBW, emphasizing the compounded vulnerability of disadvantaged populations. Pollutants such as nickel, zinc and chromium, air toxics found in non-tailpipe sources were found to be associated with adverse birth outcomes especially in Black and Hispanic mothers and mothers living in low SES neighborhoods. Our study suggests that while much has been done to control air pollution from fuel exhaust emissions, there is a pressing need to regulate emissions from non-tailpipe traffic sources such as from brake pad and tire abrasion and resuspended road dust. Further, targeted investment in low area-level SES

and Black and Hispanic communities, such as by improving housing ventilation or providing air purifiers to pregnant women in high-risk areas, may help reduce exposure to air toxics. Our results also suggest that higher area-level SES neighborhoods and White and Asian mothers might be at increased risk of adverse outcomes due to secondary pollutants such as ozone.

Main Figures and Tables

Table 2-1. Summary Statistics by Birth Outcomes in California (1990-2021)

		PTB	%	TLBW	%	TNBW	%
		1,347,224	8.8	299,703	2.0	13,651,364	89.2
Infant Sex							
	Male	736,410	54.7	128,186	42.8	6,970,788	51.1
	Female	610,751	45.3	171,501	57.2	6,680,524	48.9
	Missing	63		16		52	
Maternal Age							
	<20	150,298	11.2	35,858	12.0	1,165,446	8.5
	20-24	292,868	21.7	69,852	23.3	2,952,926	21.6
	25-29	328,534	24.4	74,198	24.8	3,709,341	27.2
	30-35	368,653	27.4	79,149	26.4	4,050,183	29.7
	>35	206,747	15.3	40,619	13.6	1,772,682	13.0
	Missing	124		27		786	
Maternal Race/Ethnicity							
	Non-Hispanic White	340,395	25.7	70,871	24.1	4,310,669	32.1
	Hispanic	694,379	52.4	137,185	46.6	6,561,784	48.9
	Non-Hispanic Black	122,081	9.2	34,809	11.8	774,557	5.8
	Non-Hispanic API	158,754	12.0	49,627	16.9	1,703,991	12.7

Other	8,689	0.7	1,770	0.6	73,011	0.5
Missing	22,926		5,441		227,352	
Nativity of Mother						
US Born	767,908	57.1	171,824	57.4	7,812,907	57.3
Foreign Born	577,712	42.9	127,530	42.6	5,827,098	42.7
Missing	1,604		349		11,359	
Mother's Education						
≤ 8th grade	159,484	12.2	28,961	10.0	1,334,394	10.0
9th – 12th	256,024	19.6	55,362	19.0	2,086,050	15.7
High School Grad	376,403	28.8	84,851	29.2	3,610,495	27.2
College or Graduation Education	515,963	39.5	121,563	41.8	6,250,634	47.1
Missing	39,350		8,966		369,791	
Parity						
First child	513,168	38.1	148,462	49.6	5,366,189	39.3
Second child	378,714	28.1	74,407	24.9	4,347,322	31.9
3 or more	453,530	33.7	76,449	25.5	3,927,621	28.8
Missing	1,812		385		10,232	
Principal Source of Payment for Prenatal Care						
No prenatal care	25,423	1.9	4,477	1.5	71,790	0.5
Government insurance	693,608	51.7	154,838	51.8	6,212,953	45.6

Private insurance	574,488	42.8	128,271	42.9	6,800,627	49.9
Self-pay	40,171	3.0	9,045	3.0	442,243	3.2
Other	8,642	0.6	2,073	0.7	93,412	0.7
Missing	4,892		999		30,339	
Area-level SES quintiles						
(Lowest SES) 1	432,875	32.4	92,435	31.1	3,688,593	27.2
2	317,941	23.8	70,290	23.6	3,053,214	22.5
3	241,514	18.1	53,923	18.1	2,554,117	18.8
4	198,801	14.9	45,402	15.3	2,322,202	17.1
(Highest SES) 5	146,476	11.0	35,340	11.9	1,938,841	14.3
Missing	9,617		2,313		94,397	
Birth Year						
1990-1997	380,873	28.3	81,201	27.1	3,620,925	26.5
1998-2005	357,886	26.6	73,052	24.4	3,389,171	24.8
2006-2012	303,843	22.6	66,979	22.3	3,066,292	22.5
2013-2021	304,622	22.6	78,471	26.2	3,574,976	26.2
Missing	0		0		0	

Note: PTB = Preterm Birth; TLBW = Term Low Birthweight; TNBW = Term Normal Birth Weight; API = Asian or Pacific Islander; SES = socioeconomic status

Table 2-2. Association between entire pregnancy average criteria air pollutants and PTB for children born between 1990-2021 in California

Time Period	PM_{2.5}	NO₂	O₃
1990-1997 (N= 4,001,798)	1.033 (1.028, 1.038)	1.016 (1.013, 1.019)	1.004 (0.999, 1.009)
1998-2005 (N= 3,747,057)	1.041 (1.035, 1.046)	1.007 (1.005, 1.010)	1.005 (1.000, 1.009)
2006-2012 (N= 3,370,135)	1.060 (1.054, 1.065)	1.010 (1.006, 1.013)	1.048 (1.043, 1.053)
2013-2021 (N= 3,879,598)	1.006 (1.001, 1.010)	0.997 (0.991, 1.003)	1.005 (1.000, 1.010)
Overall (N= 14,998,588)	1.032 (1.030, 1.035)	1.009 (1.008, 1.011)	1.015 (1.012, 1.017)
p for linear trend	<0.001	<0.001	<0.001

Notes: Results presented here are from single pollutants models; Effect estimates are OR (95% CI) per IQR. IQR values are as follows: PM_{2.5}: 2.46 µg/m³, NO₂: 5.07 ppb, O₃: 3.86 ppb

Table 2-3. Association between entire pregnancy average air toxics and PTB for children born between 1990-2021 in California

Time Period	Zinc	Nickel	Chromium	Lead	Benzene	1,3 Butadiene
1990-1997 (N=4,001,798)	1.210 (1.185, 1.236)	0.958 (0.947, 0.968)	0.998 (0.995, 1.000)	1.007 (1.005, 1.009)	1.012 (1.009, 1.016)	1.093 (1.086, 1.100)
1998-2005 (N=3,747,057)	1.031 (1.019, 1.043)	0.927 (0.914, 0.941)	1.000 (0.996, 1.005)	1.019 (1.015, 1.022)	1.010 (1.005, 1.014)	1.000 (0.997, 1.004)
2006-2012 (N=3,370,135)	1.003 (0.995, 1.012)	0.901 (0.885, 0.918)	0.990 (0.986, 0.994)	1.024 (1.020, 1.029)	1.030 (1.022, 1.037)	1.009 (1.005, 1.013)
2013-2021 (N=3,879,598)	1.031 (1.025, 1.038)	1.054 (1.040, 1.068)	0.998 (0.993, 1.003)	0.984 (0.980, 0.989)	0.917 (0.908, 0.925)	0.996 (0.994, 0.999)
Overall (N=14,998,588)	1.065 (0.98, 1.158)	0.958 (0.896, 1.025)	0.996 (0.992, 1.001)	1.008 (0.991, 1.026)	0.991 (0.942, 1.044)	1.024 (0.981, 1.069)
p for linear trend	<0.001	<0.001	0.100	<0.001	<0.001	<0.001
I ²	99.6%	98.9%	80%	99.1%	99.7%	99.8%
H ²	282.42	92.65	5	105.28	364.72	535.75

Notes: Results presented here are from single pollutants models; Effect estimates are OR (95% CI) per IQR. IQR values are as follows: zinc: 0.783 ng/m³, nickel: 0.284 ng/m³, chromium: 1.1 ng/m³, lead: 0.548 ng/m³, benzene: 0.183 ppb, 1,3-butadiene: 0.584 ppb; Overall ORs are from Random-Effects Meta-analysis. I²: Represents the proportion of variability due to true heterogeneity across time periods, not random error and H²: Measures the extent to which the observed variability reflects true differences rather than being due to random error

Table 2-4. Association between entire pregnancy average criteria air pollutants and TLBW in California for children born between 1990-2021 in California

Time Period	PM _{2.5}	NO ₂	O ₃
1990-1997 (N= 3,702,126)	1.022 (1.012, 1.033)	1.010 (1.004, 1.016)	1.010 (1.000, 1.021)
1998-2005 (N= 3,462,223)	1.024 (1.013, 1.035)	1.026 (1.019, 1.032)	1.030 (1.020, 1.041)
2006-2012 (N= 3,133,271)	1.027 (1.015, 1.038)	1.024 (1.016, 1.032)	1.042 (1.031, 1.053)
2013-2021 (N= 3,653,447)	1.011 (1.002, 1.020)	1.010 (0.999, 1.021)	1.035 (1.025, 1.045)
Overall (N= 13,951,067)	1.019 (1.014, 1.024)	1.016 (1.012, 1.019)	1.028 (1.023, 1.033)
p for linear trend	0.073	0.030	0.053

Notes: Results presented here are from single pollutants models; Effect estimates are OR (95% CI) per IQR. IQR values are as follows: PM_{2.5}: 2.46 µg/m³, NO₂: 5.07 ppb, O₃: 3.86 ppb

Table 2-5. Association between entire pregnancy average air toxics and TLBW in California for children born between 1990-2021 in California

Time Period	Zinc	Nickel	Chromium	Lead	Benzene	1,3 Butadiene
1990-1997 (N=3,702,126)	1.043 (0.998, 1.090)	1.004 (0.982, 1.027)	1.001 (0.996, 1.006)	1.000 (0.996, 1.005)	1.003 (0.996, 1.009)	1.014 (1.001, 1.028)
1998-2005 (N=3,462,223)	1.005 (0.981, 1.031)	1.013 (0.983, 1.045)	1.015 (1.006, 1.025)	1.014 (1.006, 1.022)	1.017 (1.007, 1.027)	1.012 (1.004, 1.019)
2006-2012 (N=3,133,271)	1.008 (0.990, 1.026)	0.993 (0.955, 1.031)	1.003 (0.994, 1.012)	1.017 (1.008, 1.025)	1.028 (1.013, 1.043)	1.011 (1.003, 1.019)
2013-2021 (N=3,653,447)	1.006 (0.993, 1.019)	0.999 (0.974, 1.025)	1.001 (0.992, 1.011)	0.999 (0.990, 1.008)	0.970 (0.953, 0.988)	1.006 (1.001, 1.011)
Overall (N=13,951,067)	1.008 (0.999, 1.018)	1.003 (0.989, 1.017)	1.004 (0.998, 1.011)	1.007 (0.998, 1.016)	1.005 (0.981, 1.029)	1.009 (1.005, 1.014)
p for linear trend	0.851	0.322	0.103	0.732	0.730	0.130
I ²	0.4%	0%	58.1%	84.1%	94.5%	23%
H ²	1	1	2.39	6.27	18.27	1.30

Notes: Results presented here are from single pollutants models; Effect estimates are OR (95% CI) per IQR. IQR values are as follows: zinc: 0.783 ng/m³, nickel: 0.284 ng/m³, chromium: 1.1 ng/m³, lead: 0.548 ng/m³, benzene: 0.183 ppb, 1,3-butadiene: 0.584 ppb; Overall ORs are from Random-Effects Meta-analysis. I²: Represents the proportion of variability due to true heterogeneity across time periods, not random error and H²: Measures the extent to which the observed variability reflects true differences rather than being due to random error

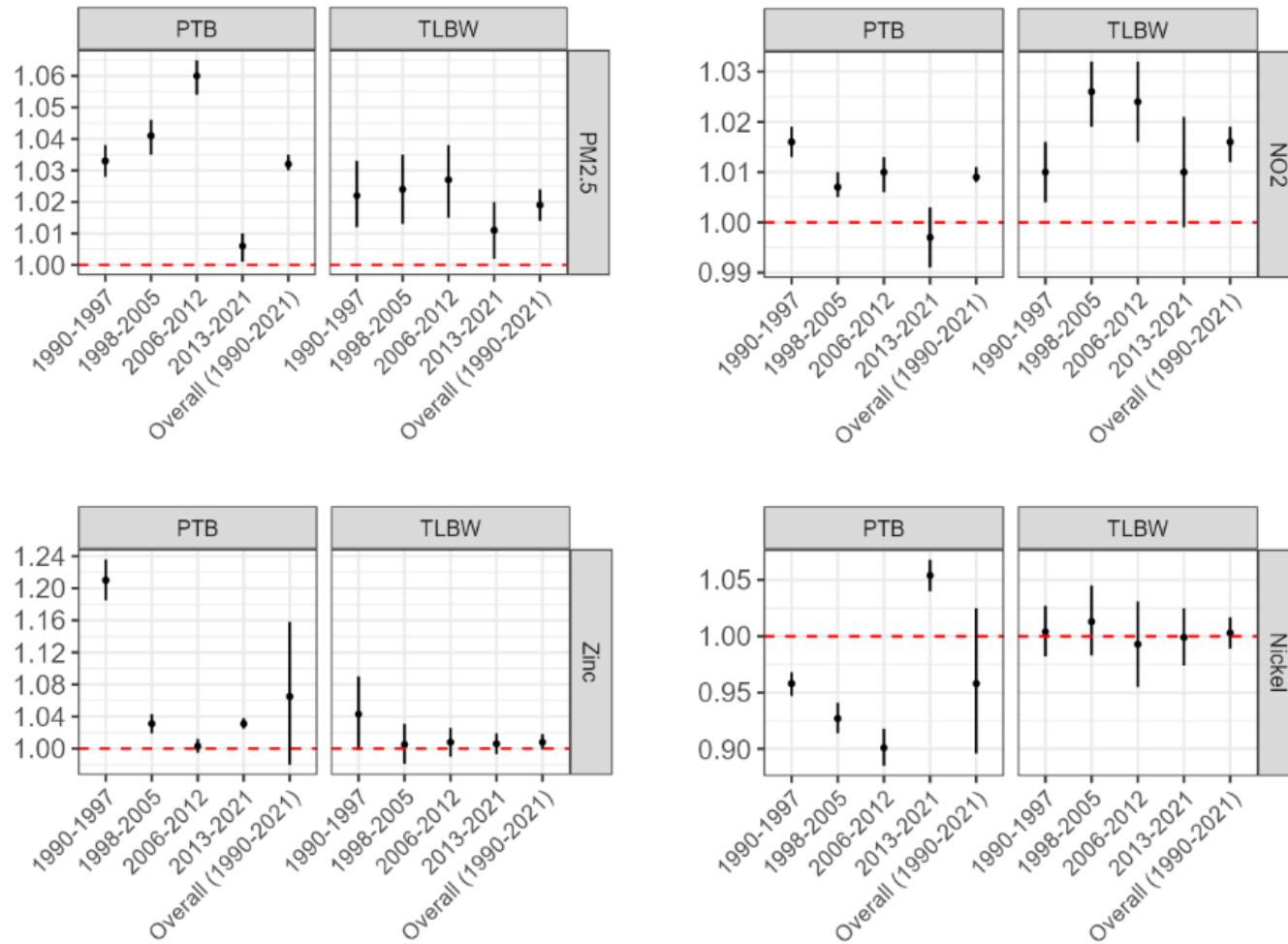


Figure 2-1. Association between entire pregnancy average pollutants and adverse birth outcomes for children born between 1990-2021 in California

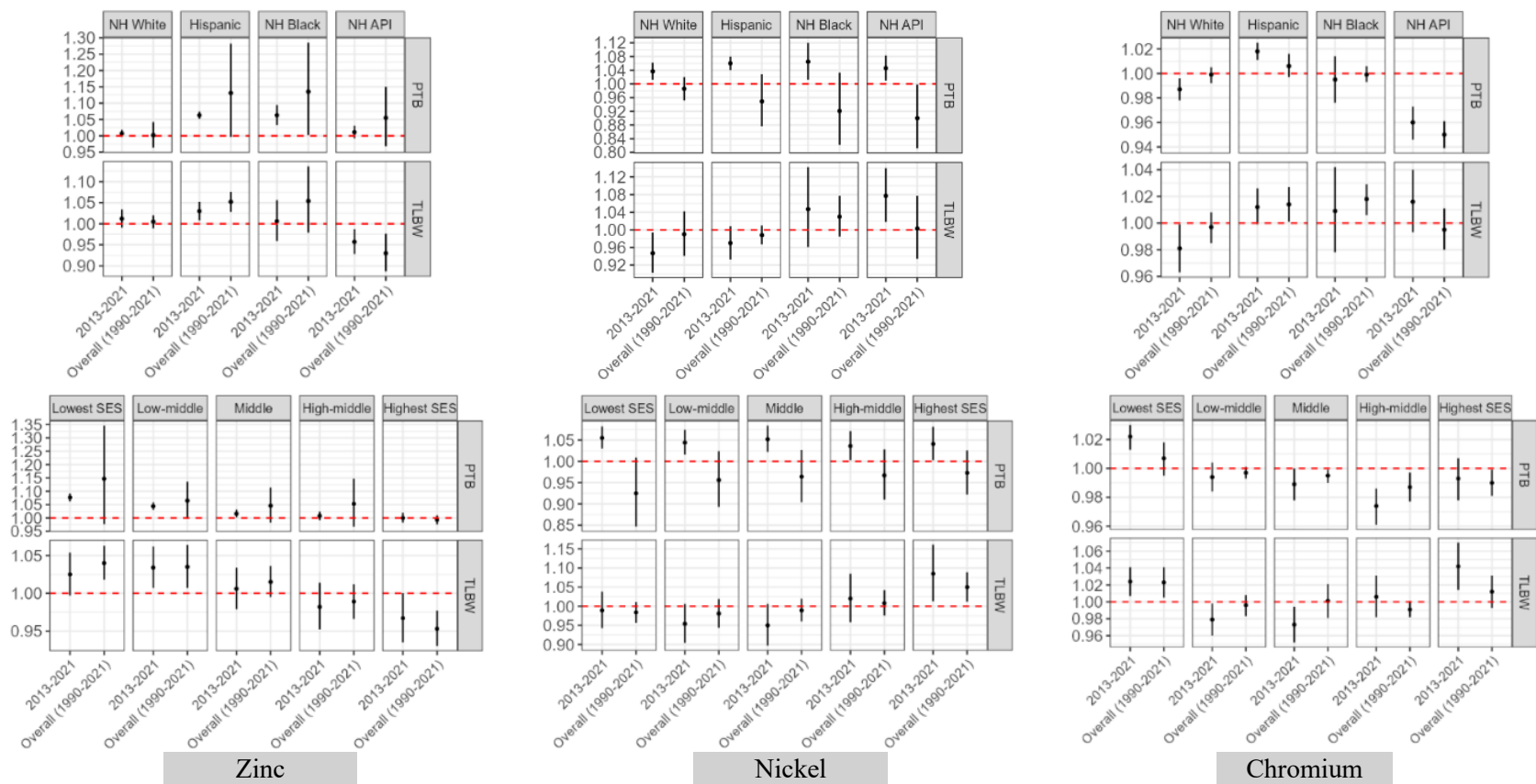


Figure 2-2. Association between entire pregnancy average pollutants and adverse birth outcomes for children born between 1990-2021 in California by race/ethnicity and area-level SES

Supplemental Figures and Tables

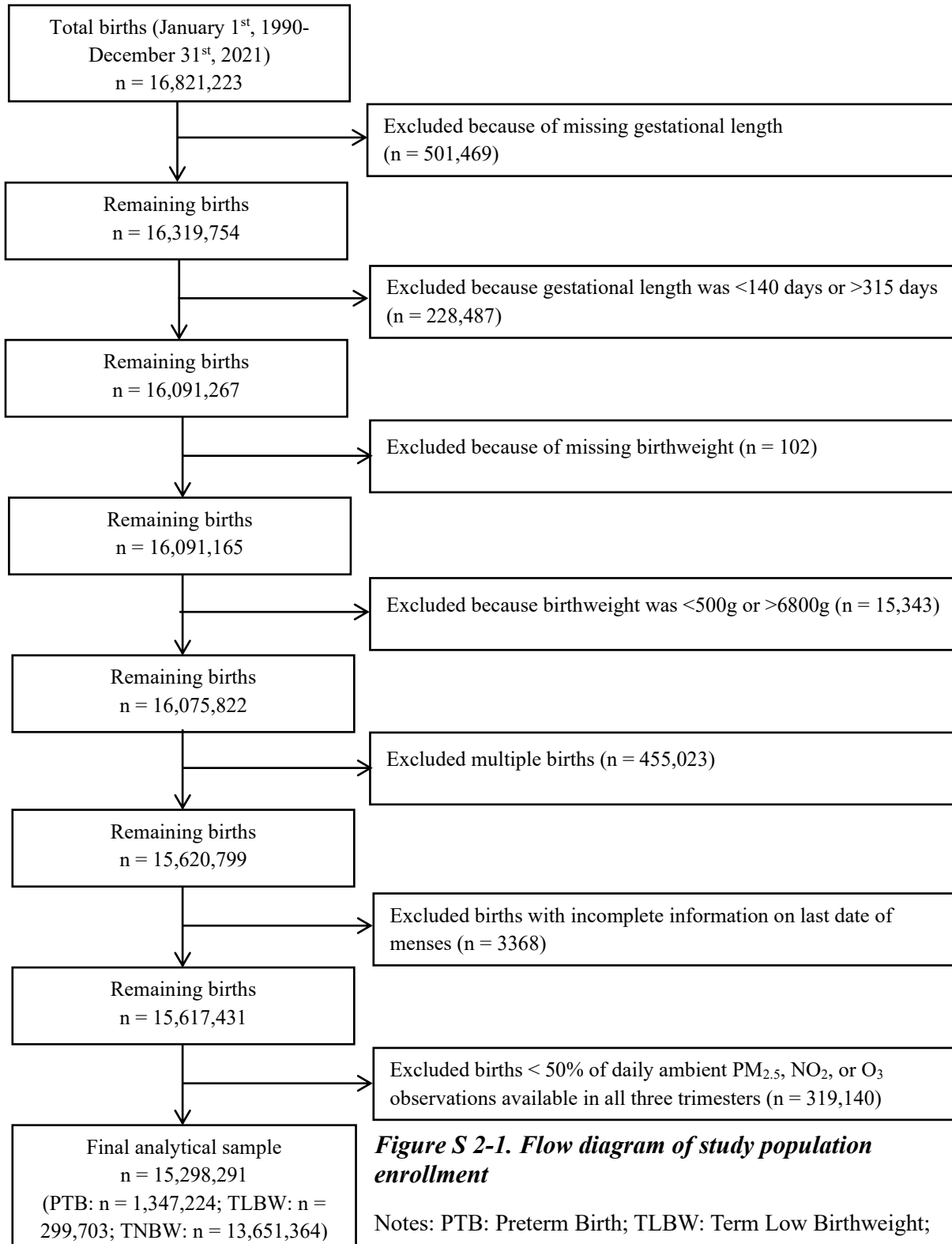


Table S 2-1. Summary Statistics of California birth records (1990-2021) comparing final analytical sample and excluded births records

		Final analytical Sample (N=15,298,291)		Excluded Births (N= 1,522,932)	
		N	%	N	%
Infant Sex					
	Male	7,835,384	51.2	773,799	50.8
	Female	7,462,776	48.8	749,012	49.2
	Missing	131		121	
Maternal Age					
	<20	1,351,602	8.8	136,283	9.0
	20-24	3,315,646	21.7	328,187	21.6
	25-29	4,112,073	26.9	392,090	25.8
	30-35	4,497,985	29.4	437,095	28.7
	>35	2,020,048	13.2	227,559	15.0
	Missing	937		1,718	
Maternal Race/Ethnicity					
	Non-Hispanic White	4,721,935	31.4	556,710	37.7
	Hispanic	7,393,348	49.1	647,845	43.8
	Non-Hispanic Black	931,447	6.2	109,957	7.4
	Non-Hispanic API	1,912,372	12.7	153,562	10.4
	Other	83,470	0.6	10,306	0.7
	Missing	255,719		44,552	
Nativity of Mother					
	US Born	8,752,639	57.3	937,694	61.9
	Foreign Born	6,532,340	42.7	578,369	38.1
	Missing	13,312		6,869	
Mother's Education					

≤ 8th grade	1,522,839	10.2	143,581	9.9
9th – 12th	2,397,436	16.1	236,717	16.3
High School Grad	4,071,749	27.4	408,831	28.1
College or Graduation Education	6,888,160	46.3	664,234	45.7
Missing	418,107		69,569	
Parity				
First child	6,027,819	39.4	486,620	32.3
Second child	4,800,443	31.4	484,260	32.1
3 or more	4,457,600	29.2	536,946	35.6
Missing	12,429		15,106	
Principal Source of Payment for Prenatal Care				
No prenatal care	101,690	0.7	36,326	2.4
Government insurance	7,061,399	46.3	624,535	41.6
Private insurance	7,503,386	49.2	761,234	50.6
Self-pay	491,459	3.2	71,725	4.8
Other	104,127	0.7	9,173	0.6
Missing	36,230		19,939	
Area-level SES quintiles				
(Lowest SES) 1	4,213,903	27.7	344,260	27.0
2	3,441,445	22.7	270,114	21.2
3	2,849,554	18.8	230,161	18.0
4	2,566,405	16.9	222,471	17.4
(Highest SES) 5	2,120,657	14.0	209,563	16.4
Missing	106,327		246,363	

Note: API = Asian or Pacific Islander; SES = socioeconomic status

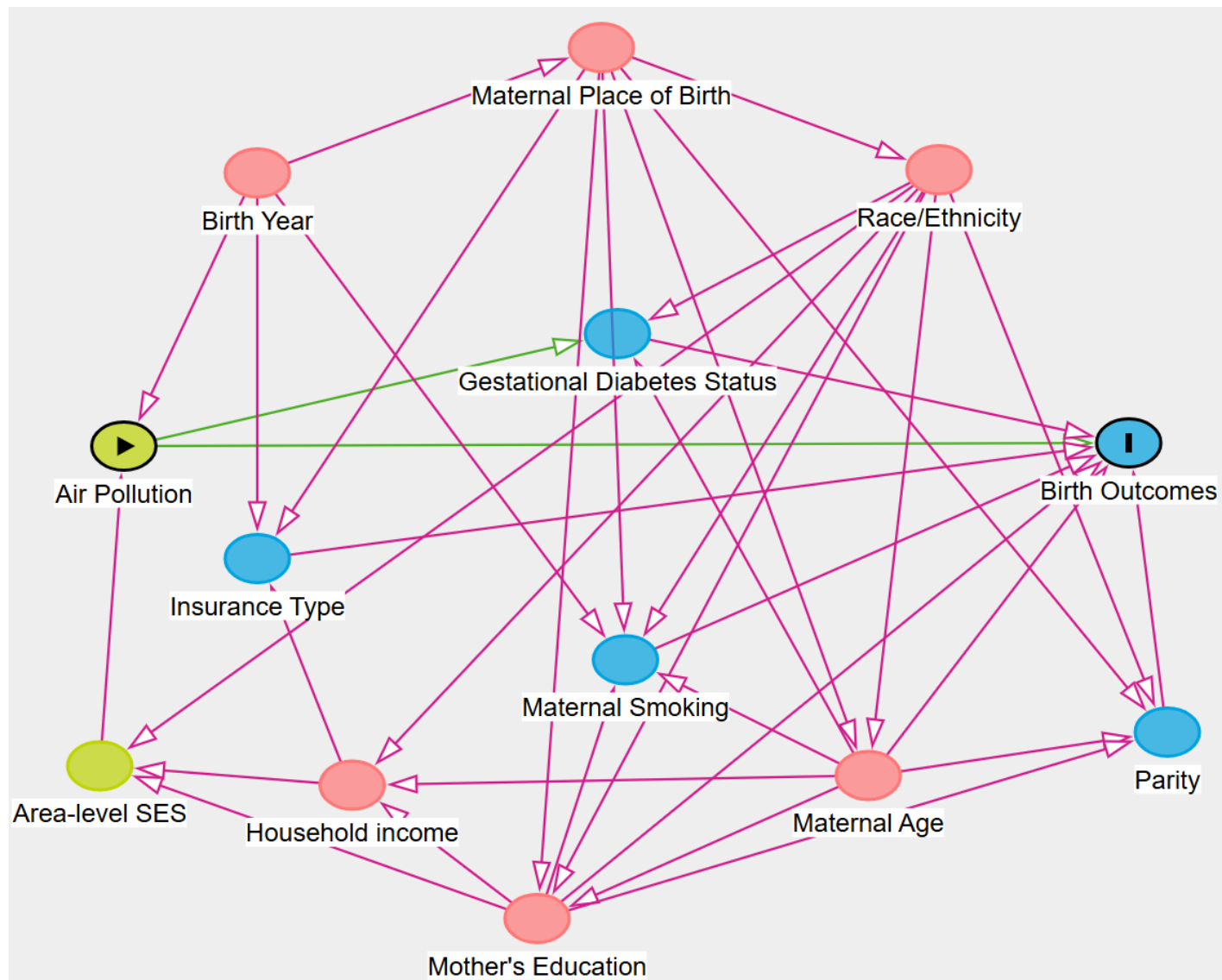


Figure S 2-2. Directed Acyclic Graph for selection of confounders

Table S 2-2. Number and percentage of air toxic measurements with 0 values prior to imputation with half of the lowest non-zero value

Air Toxic	Observations with 0 values	% with 0 values (N=15,298,291)
Zinc	11	<0.01%
Nickel	437	<0.01%
Chromium	4	<0.01%
Lead	11	<0.01%
Benzene	4	<0.01%
1,3- Butadiene	84896	0.55%

Table S 2-3. Entire pregnancy average pollutant exposure concentrations (birth years 1990-2021) in California

Pollutant		1990-1997	1998-2005	2006-2012	2013-2021	Overall
PM _{2.5} (ug/m3)		13.52 (2.06)	12.26 (2.09)	11.16 (2.03)	9.83 (2.30)	11.72 (2.54)
NO ₂ (ppb)		19.74 (6.74)	16.83 (6.44)	13.26 (5.31)	9.88 (3.72)	15.01 (6.84)
O ₃ (ppb)		37.58 (2.71)	37.25 (2.90)	38.09 (3.06)	38.61 (3.12)	37.88 (2.99)
Zinc (ng/m3)		0.80 (0.31)	1.79 (0.37)	2.67 (0.44)	4.16 (0.67)	2.36 (1.34)
Nickel (ng/m3)		1.89 (0.13)	1.57 (0.12)	1.28 (0.10)	1.22 (0.18)	1.49 (0.30)
Chromium (ng/m3)		3.95 (1.54)	3.88 (0.94)	3.86 (0.99)	3.85 (0.92)	3.89 (1.14)
Lead (ng/m3)		5.36 (0.91)	5.08 (0.59)	4.78 (0.55)	4.46 (0.50)	4.92 (0.75)
Benzene (ppb)		1.11 (0.21)	0.87 (0.16)	0.62 (0.12)	0.44 (0.12)	0.76 (0.30)
1,3-Butadiene (ppb)		4.85 (0.57)	5.54 (0.93)	4.70 (0.67)	4.61 (1.35)	4.93 (1.00)
Race/Ethnicity						
	Time Period	NH White	Hispanic	NH Black	NH API	
PM_{2.5} (ug/m3)	1990-1997	12.96 (2.16)	13.99 (1.90)	13.65 (1.80)	13.4 (1.95)	
	1998-2005	11.6 (2.12)	12.75 (1.99)	12.45 (1.84)	11.91 (1.91)	
	2006-2012	10.61 (2.18)	11.54 (1.93)	11.31 (1.79)	10.93 (1.83)	
	2013-2021	9.41 (2.46)	10.16 (2.23)	10.03 (2.08)	9.66 (2.03)	
	Overall	11.32 (2.61)	12.11 (2.47)	12.04 (2.33)	11.28 (2.38)	
NO₂ (ppb)	1990-1997	17.52 (6.08)	21.43 (6.87)	20.86 (6.04)	19.75 (6.50)	
	1998-2005	14.65 (5.73)	18.16 (6.63)	17.82 (5.75)	16.84 (6.16)	

	2006-2012	11.56 (4.75)	14.15 (5.49)	13.87 (4.82)	13.42 (5.12)
	2013-2021	8.81 (3.37)	10.43 (3.82)	10.44 (3.40)	10.27 (3.78)
	Overall	13.57 (6.20)	16.06 (7.16)	16.27 (6.60)	14.58 (6.46)
O₃ (ppb)	1990-1997	37.74 (2.72)	37.69 (2.72)	37.00 (2.58)	36.99 (2.52)
	1998-2005	37.44 (2.82)	37.35 (3.01)	36.79 (2.92)	36.62 (2.52)
	2006-2012	38.09 (2.96)	38.30 (3.17)	37.9 (3.12)	37.42 (2.67)
	2013-2021	38.53 (2.99)	38.91 (3.25)	38.53 (3.20)	37.99 (2.69)
	Overall	37.92 (2.89)	38.06 (3.10)	37.49 (3.01)	37.32 (2.66)
Zinc (ng/m3)	1990-1997	0.80 (0.32)	0.80 (0.30)	0.78 (0.30)	0.82 (0.31)
	1998-2005	1.82 (0.42)	1.77 (0.34)	1.75 (0.34)	1.80 (0.35)
	2006-2012	2.75 (0.52)	2.63 (0.39)	2.65 (0.38)	2.70 (0.41)
	2013-2021	4.25 (0.76)	4.10 (0.62)	4.09 (0.61)	4.17 (0.63)
	Overall	2.41 (1.40)	2.33 (1.29)	2.32 (1.31)	2.37 (1.35)
Nickel (ng/m3)	1990-1997	1.87 (0.14)	1.91 (0.13)	1.91 (0.12)	1.9 (0.13)
	1998-2005	1.55 (0.12)	1.58 (0.11)	1.58 (0.11)	1.57 (0.11)
	2006-2012	1.27 (0.10)	1.29 (0.09)	1.28 (0.09)	1.28 (0.09)
	2013-2021	1.21 (0.19)	1.22 (0.18)	1.23 (0.18)	1.22 (0.18)
	Overall	1.48 (0.31)	1.50 (0.30)	1.50 (0.31)	1.49 (0.30)
Chromium (ng/m3)	1990-1997	3.55 (1.49)	4.17 (1.54)	4.29 (1.39)	4.21 (1.47)
	1998-2005	3.49 (0.94)	4.07 (0.91)	4.15 (0.81)	4.01 (0.78)

	2006-2012	3.52 (1.01)	3.99 (0.97)	4.09 (0.90)	4.00 (0.86)	
	2013-2021	3.56 (0.97)	3.95 (0.90)	4.06 (0.83)	3.99 (0.79)	
	Overall	3.53 (1.16)	4.05 (1.11)	4.15 (1.05)	4.05 (0.99)	
Lead (ng/m3)	1990-1997	5.18 (0.94)	5.51 (0.86)	5.43 (0.82)	5.29 (0.93)	
	1998-2005	4.91 (0.64)	5.21 (0.52)	5.16 (0.51)	4.96 (0.56)	
	2006-2012	4.63 (0.61)	4.89 (0.50)	4.85 (0.47)	4.70 (0.52)	
	2013-2021	4.33 (0.55)	4.55 (0.45)	4.53 (0.42)	4.4 (0.47)	
	Overall	4.76 (0.80)	5.04 (0.70)	4.99 (0.70)	4.84 (0.71)	
Benzene (ppb)	1990-1997	1.05 (0.21)	1.16 (0.20)	1.13 (0.20)	1.09 (0.21)	
	1998-2005	0.82 (0.16)	0.9 (0.16)	0.88 (0.15)	0.84 (0.16)	
	2006-2012	0.60 (0.12)	0.64 (0.12)	0.63 (0.11)	0.61 (0.11)	
	2013-2021	0.42 (0.12)	0.45 (0.12)	0.45 (0.12)	0.44 (0.12)	
	Overall	0.72 (0.29)	0.79 (0.31)	0.77 (0.31)	0.75 (0.29)	
1,3-Butadiene (ppb)	1990-1997	4.76 (0.53)	4.91 (0.58)	4.84 (0.54)	4.83 (0.58)	
	1998-2005	5.48 (1.00)	5.59 (0.88)	5.60 (0.92)	5.45 (0.96)	
	2006-2012	4.61 (0.78)	4.75 (0.59)	4.71 (0.64)	4.66 (0.71)	
	2013-2021	4.54 (1.4)	4.68 (1.33)	4.64 (1.32)	4.58 (1.36)	
	Overall	4.85 (1.03)	4.99 (0.97)	4.95 (0.96)	4.88 (1.05)	
Area-level SES						
	Time Period	Lowest	Low-Middle	Middle	High-Middle	Highest

PM_{2.5} (ug/m3)	1990-1997	14.60 (1.79)	13.81 (1.83)	13.46 (1.96)	12.65 (2.03)	12.14 (1.79)
	1998-2005	13.36 (1.81)	12.46 (2.00)	11.97 (2.02)	11.52 (1.92)	10.76 (1.67)
	2006-2012	12.06 (1.90)	11.32 (1.98)	10.94 (2.00)	10.62 (1.88)	9.94 (1.66)
	2013-2021	10.74 (2.31)	10.09 (2.24)	9.67 (2.27)	9.25 (2.11)	8.63 (1.73)
	Overall	12.73 (2.42)	11.99 (2.45)	11.51 (2.51)	11.03 (2.37)	10.39 (2.16)
NO₂ (ppb)	1990-1997	21.66 (6.70)	19.87 (6.93)	19.51 (6.83)	17.95 (6.53)	18.26 (5.57)
	1998-2005	18.81 (6.51)	17.09 (6.63)	15.89 (6.48)	15.54 (5.95)	14.91 (5.17)
	2006-2012	14.22 (5.37)	13.52 (5.54)	12.87 (5.40)	12.59 (5.04)	12.12 (4.54)
	2013-2021	10.52 (3.64)	10.21 (3.90)	9.75 (3.83)	9.52 (3.63)	8.82 (3.21)
	Overall	16.42 (7.13)	15.35 (6.98)	14.51 (6.83)	13.95 (6.32)	13.61 (5.92)
O₃ (ppb)	1990-1997	37.95 (2.89)	37.72 (2.82)	37.62 (2.71)	37.39 (2.41)	36.84 (2.34)
	1998-2005	37.58 (3.14)	37.47 (2.99)	37.27 (2.93)	36.9 (2.65)	36.56 (2.21)
	2006-2012	38.67 (3.38)	38.22 (3.04)	38.01 (3.00)	37.72 (2.77)	37.14 (2.40)
	2013-2021	39.47 (3.52)	38.9 (3.13)	38.56 (2.92)	38.04 (2.72)	37.33 (2.34)
	Overall	38.39 (3.31)	38.06 (3.04)	37.88 (2.93)	37.52 (2.67)	36.96 (2.34)
Zinc (ng/m3)	1990-1997	0.77 (0.29)	0.78 (0.29)	0.8 (0.31)	0.83 (0.32)	0.86 (0.34)
	1998-2005	1.74 (0.33)	1.76 (0.36)	1.79 (0.39)	1.81 (0.38)	1.89 (0.40)
	2006-2012	2.61 (0.38)	2.66 (0.43)	2.68 (0.46)	2.7 (0.46)	2.81 (0.48)
	2013-2021	4.05 (0.61)	4.13 (0.66)	4.16 (0.69)	4.21 (0.67)	4.35 (0.69)
	Overall	2.29 (1.27)	2.33 (1.33)	2.36 (1.36)	2.39 (1.38)	2.48 (1.41)

Nickel (ng/m3)	1990-1997	1.92 (0.12)	1.90 (0.13)	1.88 (0.14)	1.87 (0.14)	1.86 (0.14)
	1998-2005	1.58 (0.11)	1.57 (0.11)	1.56 (0.12)	1.56 (0.12)	1.54 (0.12)
	2006-2012	1.29 (0.09)	1.28 (0.10)	1.28 (0.10)	1.27 (0.10)	1.26 (0.10)
	2013-2021	1.23 (0.18)	1.22 (0.18)	1.22 (0.19)	1.22 (0.18)	1.21 (0.18)
	Overall	1.51 (0.30)	1.49 (0.31)	1.49 (0.30)	1.48 (0.30)	1.47 (0.30)
Chromium (ng/m3)	1990-1997	4.39 (1.49)	3.98 (1.59)	3.85 (1.37)	3.7 (1.55)	3.55 (1.50)
	1998-2005	4.20 (0.93)	3.92 (0.96)	3.77 (0.94)	3.7 (0.85)	3.49 (0.80)
	2006-2012	4.11 (0.98)	3.92 (1.01)	3.78 (0.98)	3.7 (0.95)	3.55 (0.87)
	2013-2021	4.03 (0.93)	3.9 (0.93)	3.76 (0.92)	3.73 (0.86)	3.71 (0.87)
	Overall	4.18 (1.12)	3.93 (1.17)	3.79 (1.07)	3.71 (1.11)	3.58 (1.06)
Lead (ng/m3)	1990-1997	5.57 (0.82)	5.48 (0.88)	5.33 (0.88)	5.17 (0.93)	5.01 (0.97)
	1998-2005	5.31 (0.47)	5.14 (0.58)	5.02 (0.61)	4.91 (0.57)	4.72 (0.57)
	2006-2012	4.95 (0.47)	4.83 (0.56)	4.75 (0.57)	4.68 (0.54)	4.51 (0.53)
	2013-2021	4.63 (0.44)	4.51 (0.50)	4.44 (0.5)	4.38 (0.47)	4.17 (0.49)
	Overall	5.12 (0.67)	4.99 (0.75)	4.89 (0.74)	4.79 (0.73)	4.60 (0.75)
Benzene (ppb)	1990-1997	1.19 (0.19)	1.13 (0.20)	1.10 (0.21)	1.04 (0.22)	1.02 (0.19)
	1998-2005	0.93 (0.15)	0.87 (0.17)	0.85 (0.16)	0.83 (0.16)	0.79 (0.15)
	2006-2012	0.66 (0.11)	0.63 (0.12)	0.62 (0.12)	0.61 (0.11)	0.58 (0.11)
	2013-2021	0.46 (0.12)	0.45 (0.13)	0.44 (0.12)	0.43 (0.12)	0.40 (0.11)
	Overall	0.81 (0.31)	0.77 (0.31)	0.75 (0.30)	0.73 (0.29)	0.70 (0.28)

1,3-Butadiene (ppb)	1990-1997	4.94 (0.56)	4.86 (0.57)	4.82 (0.55)	4.78 (0.58)	4.74 (0.56)
	1998-2005	5.66 (0.85)	5.57 (0.88)	5.50 (0.93)	5.45 (0.99)	5.36 (1.08)
	2006-2012	4.80 (0.53)	4.73 (0.58)	4.68 (0.67)	4.63 (0.77)	4.52 (0.90)
	2013-2021	4.73 (1.31)	4.66 (1.31)	4.61 (1.34)	4.54 (1.38)	4.42 (1.44)
	Overall	5.04 (0.95)	4.96 (0.95)	4.90 (1.00)	4.85 (1.04)	4.76 (1.11)

Notes: NH: Non-Hispanic; API: Asian and Pacific Islanders; Pollutant concentrations provided as mean (SD)

Table S 2-4. Pearson correlation coefficients for entire-pregnancy average air pollutants by time period

Overall	PM _{2.5}	NO ₂	O ₃	Zinc	Nickel	Chromium	Lead	Benzene	1,3-Butadiene
PM _{2.5}	1.00	0.63	0.06	-0.58	0.61	0.20	0.60	0.72	0.15
NO ₂	0.63	1.00	-0.22	-0.56	0.56	0.36	0.58	0.79	0.21
O ₃	0.06	-0.22	1.00	0.13	-0.16	-0.29	0.03	-0.09	0.00
Zinc	-0.58	-0.56	0.13	1.00	-0.79	-0.03	-0.50	-0.85	-0.20
Nickel	0.61	0.56	-0.16	-0.79	1.00	0.13	0.44	0.78	0.06
Chromium	0.20	0.36	-0.29	-0.03	0.13	1.00	0.39	0.21	0.06
Lead	0.60	0.58	0.03	-0.50	0.44	0.39	1.00	0.67	0.19
Benzene	0.72	0.79	-0.09	-0.85	0.78	0.21	0.67	1.00	0.24
1,3-Butadiene	0.15	0.21	0.00	-0.20	0.06	0.06	0.19	0.24	1.00

1990-1997	PM _{2.5}	NO ₂	O ₃	Zinc	Nickel	Chromium	Lead	Benzene	1,3-Butadiene
PM _{2.5}	1.00	0.57	0.08	-0.38	0.53	0.30	0.47	0.76	0.06
NO ₂	0.57	1.00	-0.19	-0.17	0.41	0.42	0.37	0.78	0.15
O ₃	0.08	-0.19	1.00	0.01	-0.17	-0.26	0.10	0.04	0.12
Zinc	-0.38	-0.17	0.01	1.00	-0.67	0.06	-0.04	-0.31	0.41
Nickel	0.53	0.41	-0.17	-0.67	1.00	0.31	0.22	0.44	-0.26
Chromium	0.30	0.42	-0.26	0.06	0.31	1.00	0.61	0.37	0.13
Lead	0.47	0.37	0.10	-0.04	0.22	0.61	1.00	0.52	0.15
Benzene	0.76	0.78	0.04	-0.31	0.44	0.37	0.52	1.00	0.12
1,3-Butadiene	0.06	0.15	0.12	0.41	-0.26	0.13	0.15	0.12	1.00

1998-2005	PM _{2.5}	NO ₂	O ₃	Zinc	Nickel	Chromium	Lead	Benzene	1,3-Butadiene
PM _{2.5}	1.00	0.56	0.07	-0.31	0.36	0.27	0.67	0.75	0.18
NO ₂	0.56	1.00	-0.20	-0.14	0.31	0.45	0.53	0.73	0.20
O ₃	0.07	-0.20	1.00	0.02	-0.21	-0.35	0.08	0.02	-0.01
Zinc	-0.31	-0.14	0.02	1.00	-0.62	-0.05	-0.35	-0.40	-0.45
Nickel	0.36	0.31	-0.21	-0.62	1.00	0.26	0.30	0.43	0.51

Chromium	0.27	0.45	-0.35	-0.05	0.26	1.00	0.26	0.37	0.07
Lead	0.67	0.53	0.08	-0.35	0.30	0.26	1.00	0.76	0.22
Benzene	0.75	0.73	0.02	-0.40	0.43	0.37	0.76	1.00	0.33
1,3-Butadiene	0.18	0.20	-0.01	-0.45	0.51	0.07	0.22	0.33	1.00

2006-2012	PM _{2.5}	NO ₂	O ₃	Zinc	Nickel	Chromium	Lead	Benzene	1,3-Butadiene
PM _{2.5}	1.00	0.43	0.19	-0.32	0.35	0.17	0.53	0.62	0.16
NO ₂	0.43	1.00	-0.14	-0.18	0.37	0.42	0.45	0.73	0.18
O ₃	0.19	-0.14	1.00	-0.10	-0.14	-0.31	0.16	0.13	0.11
Zinc	-0.32	-0.18	-0.10	1.00	-0.47	0.02	-0.29	-0.35	-0.04
Nickel	0.35	0.37	-0.14	-0.47	1.00	0.22	0.20	0.43	0.04
Chromium	0.17	0.42	-0.31	0.02	0.22	1.00	0.26	0.33	0.05
Lead	0.53	0.45	0.16	-0.29	0.20	0.26	1.00	0.66	0.15
Benzene	0.62	0.73	0.13	-0.35	0.43	0.33	0.66	1.00	0.25
1,3-Butadiene	0.16	0.18	0.11	-0.04	0.04	0.05	0.15	0.25	1.00

2013-2021	PM _{2.5}	NO ₂	O ₃	Zinc	Nickel	Chromium	Lead	Benzene	1,3-Butadiene
PM _{2.5}	1.00	0.26	0.31	-0.11	0.31	0.08	0.33	0.22	0.01
NO ₂	0.26	1.00	-0.13	-0.25	-0.15	0.40	0.49	0.64	0.14
O ₃	0.31	-0.13	1.00	-0.08	-0.01	-0.31	0.16	0.08	0.05
Zinc	-0.11	-0.25	-0.08	1.00	0.43	-0.04	-0.34	-0.58	-0.13
Nickel	0.31	-0.15	-0.01	0.43	1.00	0.08	-0.12	-0.53	-0.40
Chromium	0.08	0.40	-0.31	-0.04	0.08	1.00	0.18	0.23	0.03
Lead	0.33	0.49	0.16	-0.34	-0.12	0.18	1.00	0.56	0.11
Benzene	0.22	0.64	0.08	-0.58	-0.53	0.23	0.56	1.00	0.27
1,3-Butadiene	0.01	0.14	0.05	-0.13	-0.40	0.03	0.11	0.27	1.00

Stratified analyses of air pollutants with PTB

Table S 2-5. Association between entire-pregnancy average criteria air pollutants and PTB in California for children born between 1990-2021 in California stratified by race-ethnicity

	Time Period	NH White (N=4,651,064)	Hispanic (N=7,256,163)	NH Black (N=896,638)	NH API (N=1,862,745)	p-value for interaction
PM_{2.5}	1990-1997	1.052 (1.044, 1.060)	1.026 (1.019, 1.034)	1.043 (1.026, 1.060)	0.962 (0.947, 0.978)	<0.001
	1998-2005	1.057 (1.048, 1.066)	1.040 (1.033, 1.047)	1.044 (1.026, 1.064)	1.002 (0.987, 1.018)	<0.001
	2006-2012	1.063 (1.052, 1.073)	1.067 (1.059, 1.075)	1.058 (1.036, 1.081)	1.014 (0.997, 1.031)	<0.001
	2013-2021	1.021 (1.012, 1.030)	1.001 (0.994, 1.007)	1.004 (0.986, 1.022)	0.996 (0.983, 1.009)	<0.001
	Overall	1.048 (1.043, 1.052)	1.031 (1.028, 1.035)	1.035 (1.026, 1.045)	0.994 (0.987, 1.002)	<0.001
NO₂	1990-1997	1.035 (1.030, 1.041)	1.012 (1.008, 1.016)	1.044 (1.034, 1.053)	0.975 (0.967, 0.984)	<0.001
	1998-2005	1.030 (1.023, 1.036)	1.008 (1.004, 1.012)	1.022 (1.011, 1.033)	0.971 (0.962, 0.979)	<0.001
	2006-2012	1.041 (1.032, 1.050)	1.009 (1.004, 1.014)	1.035 (1.019, 1.051)	0.972 (0.960, 0.983)	<0.001
	2013-2021	1.017 (1.005, 1.030)	1.017 (1.009, 1.025)	0.998 (0.975, 1.021)	0.931 (0.916, 0.945)	<0.001
	Overall	1.033 (1.029, 1.036)	1.010 (1.007, 1.012)	1.032 (1.026, 1.038)	0.968 (0.963, 0.973)	<0.001
O₃	1990-1997	1.018 (1.009, 1.027)	0.991 (0.984, 0.998)	0.982 (0.967, 0.997)	1.035 (1.018, 1.052)	<0.001
	1998-2005	1.001 (0.991, 1.010)	1.006 (1.000, 1.013)	0.990 (0.974, 1.006)	1.013 (0.997, 1.030)	0.173
	2006-2012	1.051 (1.040, 1.063)	1.045 (1.039, 1.052)	1.052 (1.034, 1.070)	1.054 (1.037, 1.071)	0.295
	2013-2021	1.033 (1.022, 1.044)	0.988 (0.982, 0.995)	0.998 (0.980, 1.015)	1.044 (1.029, 1.060)	<0.001
	Overall	1.024 (1.019, 1.029)	1.009 (1.006, 1.013)	1.002 (0.994, 1.010)	1.033 (1.025, 1.042)	<0.001

Notes: Results presented here are from single pollutants models; Effect estimates are OR (95% CI) per IQR. IQR values are as follows: PM_{2.5}: 2.46 $\mu\text{g}/\text{m}^3$, NO₂: 5.07 ppb, O₃: 3.86 ppb; p for interaction has been obtained using Likelihood Ratio Test.

Table S 2-6. Association between entire-pregnancy average air toxics and PTB in California for children born between 1990-2021 in California by race/ethnicity

	Time Period	NH White (N=4,651,064)	Hispanic (N=7,256,163)	NH Black (N=896,638)	NH API (N=1,862,745)	p-value for interaction
Zinc	1990-1997	1.064 (1.031, 1.098)	1.371 (1.325, 1.418)	1.380 (1.280, 1.487)	1.212 (1.129, 1.302)	<0.001
	1998-2005	0.979 (0.962, 0.996)	1.079 (1.060, 1.099)	1.106 (1.054, 1.160)	1.048 (1.009, 1.089)	<0.001
	2006-2012	0.969 (0.956, 0.983)	1.042 (1.029, 1.056)	1.036 (0.999, 1.074)	0.983 (0.956, 1.009)	<0.001
	2013-2021	1.007 (0.997, 1.018)	1.063 (1.052, 1.074)	1.063 (1.033, 1.094)	1.011 (0.992, 1.031)	<0.001
	Overall	1.002 (0.964, 1.042)	1.131 (0.997, 1.282)	1.135 (1.002, 1.285)	1.055 (0.968, 1.150)	<0.001
	I ²	95.8%	99.6%	97.1%	96.5%	
Nickel	H ²	24.03	257.43	35.01	28.71	
	1990-1997	0.981 (0.965, 0.996)	0.954 (0.937, 0.971)	0.959 (0.923, 0.996)	0.839 (0.809, 0.870)	<0.001
	1998-2005	0.967 (0.945, 0.990)	0.912 (0.893, 0.932)	0.832 (0.788, 0.880)	0.887 (0.849, 0.927)	0.001
	2006-2012	0.957 (0.926, 0.989)	0.878 (0.855, 0.901)	0.843 (0.783, 0.908)	0.841 (0.795, 0.889)	<0.001
	2013-2021	1.037 (1.012, 1.062)	1.060 (1.040, 1.080)	1.065 (1.012, 1.120)	1.046 (1.010, 1.083)	<0.001
	Overall	0.986 (0.952, 1.020)	0.949 (0.876, 1.028)	0.921 (0.822, 1.033)	0.900 (0.812, 0.998)	<0.001
Chromium	I ²	88.9%	98.3%	94.8%	95.9%	
	H ²	8.99	59.57	19.12	24.46	
	1990-1997	1.000 (0.996, 1.005)	1.004 (1.000, 1.008)	1.000 (0.991, 1.008)	0.958 (0.950, 0.967)	<0.001
	1998-2005	1.003 (0.995, 1.011)	1.010 (1.004, 1.016)	1.004 (0.987, 1.022)	0.942 (0.928, 0.956)	<0.001
	2006-2012	1.003 (0.994, 1.011)	0.994 (0.988, 0.999)	0.995 (0.978, 1.013)	0.938 (0.924, 0.951)	<0.001

	2013-2021	0.987 (0.978, 0.996)	1.018 (1.011, 1.025)	0.995 (0.976, 1.014)	0.960 (0.946, 0.973)	<0.001
	Overall	0.999 (0.992, 1.005)	1.006 (0.997, 1.016)	0.999 (0.993, 1.006)	0.950 (0.939, 0.961)	<0.001
	I ²	71.9%	92.1%	0%	68.2%	
	H ²	3.56	12.73	1	3.14	
Lead	1990-1997	1.017 (1.013, 1.020)	1.002 (0.999, 1.005)	1.005 (0.998, 1.013)	1.000 (0.994, 1.007)	<0.001
	1998-2005	1.032 (1.025, 1.038)	1.013 (1.007, 1.018)	1.018 (1.004, 1.033)	1.007 (0.996, 1.019)	<0.001
	2006-2012	1.040 (1.032, 1.047)	1.015 (1.009, 1.021)	1.029 (1.012, 1.047)	1.017 (1.005, 1.030)	<0.001
	2013-2021	1.000 (0.992, 1.009)	0.973 (0.966, 0.980)	1.006 (0.986, 1.026)	0.982 (0.969, 0.995)	<0.001
	Overall	1.022 (1.005, 1.039)	1.001 (0.982, 1.020)	1.013 (1.002, 1.025)	1.002 (0.988, 1.015)	<0.001
	I ²	96.8%	98.2%	59.7%	85.4%	
	H ²	31.16	55.57	2.48	6.85	
Benzene	1990-1997	1.025 (1.019, 1.031)	1.004 (0.999, 1.009)	1.028 (1.017, 1.039)	0.993 (0.982, 1.003)	<0.001
	1998-2005	1.032 (1.023, 1.041)	1.009 (1.002, 1.016)	1.006 (0.989, 1.024)	0.979 (0.965, 0.992)	<0.001
	2006-2012	1.073 (1.058, 1.088)	1.019 (1.009, 1.028)	1.053 (1.024, 1.083)	1.004 (0.983, 1.025)	<0.001
	2013-2021	0.940 (0.923, 0.958)	0.933 (0.921, 0.946)	0.923 (0.889, 0.959)	0.855 (0.833, 0.878)	<0.001
	Overall	1.017 (0.963, 1.073)	0.991 (0.953, 1.031)	1.003 (0.950, 1.058)	0.956 (0.889, 1.028)	<0.001
	I ²	99.1%	99%	96.5%	98.8%	
	H ²	113.78	101.64	28.83	80.78	
1,3-Butadiene	1990-1997	1.123 (1.109, 1.137)	1.074 (1.064, 1.083)	1.137 (1.114, 1.161)	1.085 (1.063, 1.106)	<0.001
	1998-2005	1.008 (1.002, 1.014)	0.999 (0.994, 1.004)	0.992 (0.980, 1.005)	0.995 (0.986, 1.004)	0.130

2006-2012	1.017 (1.010, 1.024)	1.007 (1.001, 1.013)	1.010 (0.996, 1.026)	0.996 (0.986, 1.007)	0.012
2013-2021	1.002 (0.997, 1.007)	0.996 (0.992, 1.000)	0.994 (0.984, 1.004)	0.993 (0.987, 1.000)	0.005
Overall	1.036 (0.983, 1.092)	1.018 (0.984, 1.054)	1.031 (0.968, 1.099)	1.016 (0.974, 1.059)	<0.001
I ²	99.6%	99.4%	98.8%	98.6%	
H ²	241.36	157.93	85.91	70.08	

Notes: Results presented here are from single pollutants models; Effect estimates are OR (95% CI) per IQR. IQR values are as follows: zinc: 0.783 ng/m³, nickel: 0.284 ng/m³, chromium: 1.1 ng/m³, lead: 0.548 ng/m³, benzene: 0.183 ppb, 1,3-butadiene: 0.584 ppb; Overall ORs are from Random-Effects Meta-analysis. I²: Represents the proportion of variability due to true heterogeneity across time periods, not random error and H²: Measures the extent to which the observed variability reflects true differences rather than being due to random error; p for interaction has been obtained using Likelihood Ratio Test.

Table S 2-7. Association between entire-pregnancy average criteria air pollutants and PTB in California for children born between 1990-2021 in California stratified by area-level SES

	Time Period	Lowest (N=4,121,468)	Low-Middle (N=3,371,155)	Middle (N=2,795,631)	High-Middle (N=2,521,003)	Highest (N=2,085,317)	p-value for interaction
PM_{2.5}	1990-1997	1.017 (1.008, 1.027)	1.049 (1.039, 1.060)	1.036 (1.025, 1.048)	1.029 (1.018, 1.040)	1.039 (1.023, 1.055)	<0.001
	1998-2005	1.043 (1.034, 1.052)	1.032 (1.022, 1.041)	1.042 (1.031, 1.053)	1.058 (1.044, 1.071)	1.033 (1.016, 1.050)	0.023
	2006-2012	1.077 (1.067, 1.087)	1.065 (1.054, 1.076)	1.053 (1.041, 1.066)	1.036 (1.021, 1.050)	1.039 (1.020, 1.059)	<0.001
	2013-2021	1.010 (1.002, 1.018)	1.003 (0.994, 1.013)	1.004 (0.994, 1.015)	0.999 (0.987, 1.011)	1.007 (0.989, 1.025)	0.044
	Overall	1.032 (1.028, 1.037)	1.035 (1.030, 1.040)	1.032 (1.026, 1.037)	1.029 (1.023, 1.035)	1.032 (1.023, 1.040)	0.158
NO₂	1990-1997	1.020 (1.015, 1.026)	1.015 (1.010, 1.021)	1.011 (1.005, 1.018)	1.017 (1.010, 1.023)	1.030 (1.020, 1.039)	0.031
	1998-2005	1.000 (0.995, 1.005)	1.010 (1.004, 1.016)	1.013 (1.006, 1.020)	1.021 (1.012, 1.029)	1.026 (1.016, 1.037)	<0.001
	2006-2012	1.001 (0.994, 1.007)	1.015 (1.008, 1.023)	1.014 (1.005, 1.023)	1.016 (1.005, 1.026)	1.041 (1.027, 1.055)	<0.001
	2013-2021	1.022 (1.011, 1.032)	0.988 (0.977, 0.999)	1.002 (0.989, 1.015)	0.986 (0.972, 1.001)	0.989 (0.970, 1.008)	0.001
	Overall	1.007 (1.004, 1.010)	1.011 (1.007, 1.014)	1.011 (1.007, 1.015)	1.015 (1.010, 1.019)	1.027 (1.021, 1.033)	<0.001
O₃	1990-1997	0.991 (0.982, 0.999)	1.014 (1.004, 1.024)	1.013 (1.002, 1.025)	1.010 (0.996, 1.024)	0.985 (0.968, 1.001)	<0.001
	1998-2005	0.999 (0.992, 1.007)	1.008 (0.999, 1.018)	1.014 (1.003, 1.026)	0.994 (0.980, 1.008)	1.004 (0.985, 1.022)	0.058
	2006-2012	1.044 (1.036, 1.052)	1.050 (1.039, 1.061)	1.049 (1.037, 1.061)	1.055 (1.040, 1.070)	1.052 (1.032, 1.072)	0.744
	2013-2021	0.993 (0.985, 1.001)	1.004 (0.994, 1.015)	1.014 (1.002, 1.027)	1.010 (0.996, 1.025)	1.054 (1.034, 1.074)	<0.001
	Overall	1.006 (1.002, 1.010)	1.019 (1.014, 1.024)	1.022 (1.016, 1.028)	1.015 (1.008, 1.022)	1.017 (1.008, 1.027)	<0.001

Notes: Results presented here are from single pollutants models; Effect estimates are OR (95% CI) per IQR. IQR values are as follows: PM_{2.5}: 2.46 µg/m³, NO₂: 5.07 ppb, O₃: 3.86 ppb; p for interaction has been obtained using Likelihood Ratio Test.

Table S 2-8. Association between entire-pregnancy average air toxics and PTB in California for children born between 1990-2021 in California stratified by area-level SES

	Time Period	Lowest (N=4,121,468)	Low-Middle (N=3,371,155)	Middle (N=2,795,631)	High-Middle (N=2,521,003)	Highest (N=2,085,317)	p-value for interaction
Zinc	1990-1997	1.466 (1.399, 1.536)	1.183 (1.131, 1.238)	1.160 (1.110, 1.213)	1.202 (1.147, 1.259)	1.041 (0.987, 1.098)	0.015
	1998-2005	1.079 (1.053, 1.105)	1.036 (1.011, 1.061)	1.020 (0.995, 1.046)	1.039 (1.010, 1.069)	0.980 (0.951, 1.010)	<0.001
	2006-2012	1.020 (1.003, 1.038)	1.017 (0.999, 1.035)	1.005 (0.987, 1.024)	0.985 (0.965, 1.006)	0.979 (0.957, 1.003)	<0.001
	2013-2021	1.077 (1.062, 1.092)	1.044 (1.030, 1.059)	1.016 (1.002, 1.031)	1.008 (0.992, 1.024)	1.000 (0.982, 1.019)	<0.001
	Overall	1.147 (0.977, 1.346)	1.065 (0.999, 1.136)	1.046 (0.982, 1.114)	1.053 (0.967, 1.147)	0.993 (0.976, 1.010)	<0.001
	I ²	99.6%	97.3%	97%	98%	34.1%	
	H ²	235.22	36.83	33.50	49.44	1.52	
Nickel	1990-1997	0.888 (0.867, 0.909)	0.978 (0.956, 1.000)	0.965 (0.943, 0.988)	0.984 (0.961, 1.008)	0.981 (0.955, 1.008)	0.061
	1998-2005	0.873 (0.850, 0.898)	0.907 (0.880, 0.935)	0.940 (0.912, 0.970)	0.961 (0.928, 0.995)	0.957 (0.921, 0.995)	<0.001
	2006-2012	0.893 (0.862, 0.925)	0.900 (0.866, 0.935)	0.900 (0.863, 0.938)	0.888 (0.848, 0.929)	0.909 (0.863, 0.957)	0.007
	2013-2021	1.055 (1.030, 1.082)	1.044 (1.016, 1.074)	1.052 (1.022, 1.084)	1.036 (1.003, 1.071)	1.041 (1.003, 1.081)	<0.001
	Overall	0.925 (0.847, 1.009)	0.956 (0.893, 1.024)	0.964 (0.904, 1.027)	0.967 (0.91, 1.028)	0.973 (0.922, 1.026)	<0.001
	I ²	97.6%	95.5%	94.4%	92.7%	87.7%	
	H ²	41.21	22.41	17.78	13.73	8.12	
Chromium	1990-1997	1.004 (0.999, 1.008)	0.999 (0.995, 1.004)	0.995 (0.989, 1.002)	0.991 (0.985, 0.997)	0.998 (0.991, 1.005)	0.113
	1998-2005	1.009 (1.002, 1.016)	1.000 (0.991, 1.009)	0.994 (0.984, 1.004)	1.000 (0.988, 1.013)	0.985 (0.971, 1.000)	0.530
	2006-2012	0.993 (0.985, 1.000)	0.990 (0.981, 0.999)	1.000 (0.989, 1.010)	0.982 (0.971, 0.994)	0.978 (0.963, 0.993)	0.120

	2013-2021	1.022 (1.013, 1.030)	0.994 (0.984, 1.004)	0.989 (0.978, 1.000)	0.974 (0.961, 0.986)	0.993 (0.978, 1.007)	<0.001
	Overall	1.007 (0.995, 1.018)	0.997 (0.993, 1.001)	0.995 (0.990, 0.999)	0.987 (0.977, 0.997)	0.990 (0.981, 0.999)	0.004
	I ²	91.6%	22.7%	0%	74.9%	55%	
	H ²	11.86	1.29	1	3.98	2.22	
Lead	1990-1997	1.006 (1.002, 1.010)	1.012 (1.008, 1.017)	1.007 (1.002, 1.012)	1.004 (0.998, 1.009)	1.007 (1.002, 1.013)	0.039
	1998-2005	1.007 (1.000, 1.015)	1.014 (1.007, 1.022)	1.024 (1.016, 1.032)	1.029 (1.019, 1.039)	1.040 (1.029, 1.051)	<0.001
	2006-2012	1.017 (1.009, 1.025)	1.021 (1.013, 1.029)	1.032 (1.023, 1.041)	1.022 (1.012, 1.033)	1.052 (1.039, 1.065)	<0.001
	2013-2021	0.986 (0.977, 0.996)	0.982 (0.972, 0.991)	0.984 (0.974, 0.994)	0.988 (0.976, 0.999)	0.999 (0.985, 1.012)	0.138
	Overall	1.004 (0.992, 1.017)	1.007 (0.991, 1.024)	1.012 (0.991, 1.033)	1.011 (0.993, 1.029)	1.024 (1.000, 1.049)	<0.001
	I ²	92.1%	95.5%	96.5%	93.6%	95.8%	
Benzene	H ²	12.66	22.32	28.88	15.69	24.04	
	1990-1997	1.016 (1.009, 1.023)	1.016 (1.009, 1.023)	1.012 (1.004, 1.019)	1.004 (0.997, 1.011)	1.025 (1.014, 1.035)	0.008
	1998-2005	0.999 (0.990, 1.007)	1.002 (0.993, 1.012)	1.019 (1.009, 1.030)	1.034 (1.021, 1.047)	1.040 (1.024, 1.055)	<0.001
	2006-2012	1.027 (1.013, 1.040)	1.031 (1.017, 1.045)	1.033 (1.016, 1.049)	1.025 (1.006, 1.044)	1.085 (1.060, 1.110)	<0.001
	2013-2021	0.937 (0.921, 0.954)	0.917 (0.901, 0.934)	0.920 (0.901, 0.940)	0.907 (0.885, 0.930)	0.931 (0.903, 0.960)	0.03
	Overall	0.995 (0.956, 1.035)	0.991 (0.941, 1.043)	0.995 (0.946, 1.048)	0.992 (0.936, 1.051)	1.019 (0.958, 1.085)	<0.001
1,3-Butadiene	I ²	98.3%	98.9%	98.6%	98.6%	98.1%	
	H ²	58.93	89.49	71.54	73.51	51.60	
	1990-1997	1.082 (1.069, 1.094)	1.096 (1.082, 1.111)	1.113 (1.096, 1.131)	1.093 (1.075, 1.110)	1.103 (1.083, 1.125)	<0.001
	1998-2005	0.996 (0.989, 1.003)	0.991 (0.984, 0.999)	1.000 (0.992, 1.008)	1.012 (1.004, 1.021)	1.006 (0.998, 1.014)	0.001

2006-2012	1.004 (0.995, 1.013)	1.009 (1.000, 1.019)	1.009 (1.000, 1.018)	1.010 (1.002, 1.019)	1.014 (1.005, 1.022)	0.374
2013-2021	0.996 (0.991, 1.001)	0.993 (0.987, 0.998)	1.000 (0.994, 1.006)	1.002 (0.996, 1.008)	0.994 (0.988, 1.001)	0.034
Overall	1.019 (0.980, 1.059)	1.021 (0.975, 1.070)	1.029 (0.978, 1.083)	1.028 (0.988, 1.069)	1.028 (0.982, 1.076)	<0.001
I ²	99.1%	99.2%	99.3%	98.8%	99.1%	
H ²	107.03	127.19	137.37	82.37	105.79	

Notes: Results presented here are from single pollutants models; Effect estimates are OR (95% CI) per IQR. IQR values are as follows: zinc: 0.783 ng/m³, nickel: 0.284 ng/m³, chromium: 1.1 ng/m³, lead: 0.548 ng/m³, benzene: 0.183 ppb, 1,3-butadiene: 0.584 ppb; Overall ORs are from Random-Effects Meta-analysis. I²: Represents the proportion of variability due to true heterogeneity across time periods, not random error and H²: Measures the extent to which the observed variability reflects true differences rather than being due to random error; p for interaction has been obtained using Likelihood Ratio Test.

Stratified analyses of air pollutants with TLBW

Table S 2-9. Association between entire-pregnancy average criteria air pollutants and TLBW in California for children born between 1990-2021 in California stratified by race-ethnicity

	Time Period	NH White (N=4,381,540)	Hispanic (N=6,698,969)	NH Black (N=809,366)	NH API (N=1,753,618)	p-value for interaction
PM_{2.5}	1990-1997	1.060 (1.042, 1.078)	1.008 (0.991, 1.025)	0.994 (0.966, 1.023)	1.000 (0.970, 1.030)	<0.001
	1998-2005	1.052 (1.031, 1.072)	1.021 (1.006, 1.037)	1.002 (0.969, 1.036)	1.005 (0.977, 1.034)	<0.001
	2006-2012	1.028 (1.007, 1.050)	1.027 (1.010, 1.043)	1.054 (1.014, 1.096)	1.019 (0.989, 1.049)	<0.001
	2013-2021	1.013 (0.996, 1.031)	1.007 (0.994, 1.021)	1.041 (1.009, 1.073)	1.003 (0.981, 1.026)	<0.001
	Overall	1.038 (1.029, 1.048)	1.014 (1.006, 1.021)	1.020 (1.003, 1.036)	1.007 (0.994, 1.021)	<0.001
NO₂	1990-1997	1.041 (1.029, 1.053)	1.003 (0.995, 1.012)	1.011 (0.995, 1.028)	0.974 (0.958, 0.990)	<0.001
	1998-2005	1.051 (1.037, 1.066)	1.032 (1.024, 1.041)	1.027 (1.006, 1.049)	0.992 (0.976, 1.008)	<0.001
	2006-2012	1.025 (1.006, 1.045)	1.040 (1.029, 1.051)	1.075 (1.046, 1.105)	0.967 (0.948, 0.987)	<0.001
	2013-2021	1.053 (1.028, 1.080)	1.029 (1.013, 1.044)	1.012 (0.974, 1.052)	0.955 (0.932, 0.979)	<0.001
	Overall	1.041 (1.034, 1.049)	1.021 (1.016, 1.026)	1.026 (1.015, 1.038)	0.977 (0.968, 0.986)	<0.001
O₃	1990-1997	1.026 (1.007, 1.046)	1.005 (0.990, 1.021)	0.965 (0.938, 0.993)	1.018 (0.986, 1.050)	<0.001
	1998-2005	1.082 (1.059, 1.105)	1.008 (0.994, 1.022)	1.009 (0.979, 1.040)	1.036 (1.006, 1.067)	<0.001
	2006-2012	1.081 (1.056, 1.107)	1.028 (1.014, 1.042)	1.001 (0.969, 1.033)	1.054 (1.025, 1.085)	<0.001
	2013-2021	1.047 (1.025, 1.070)	1.030 (1.016, 1.044)	1.036 (1.006, 1.068)	1.023 (0.999, 1.049)	<0.001
	Overall	1.057 (1.046, 1.068)	1.019 (1.012, 1.026)	1.002 (0.987, 1.017)	1.028 (1.014, 1.043)	<0.001

Notes: Results presented here are from single pollutants models; Effect estimates are OR (95% CI) per IQR. IQR values are as follows: PM_{2.5}: 2.46 µg/m³, NO₂: 5.07 ppb, O₃: 3.86 ppb; p for interaction has been obtained using Likelihood Ratio Test.

Table S 2-10. Association between entire-pregnancy average air toxics and TLBW in California for children born between 1990-2021 in California stratified by race-ethnicity

	Time Period	NH White (N=4,381,540)	Hispanic (N=6,698,969)	NH Black (N=809,366)	NH API (N=1,753,618)	p-value for interaction
Zinc	1990-1997	0.957 (0.894, 1.024)	1.110 (1.029, 1.197)	1.244 (1.088, 1.421)	1.027 (0.899, 1.173)	<0.001
	1998-2005	0.996 (0.958, 1.037)	1.066 (1.024, 1.110)	1.029 (0.942, 1.125)	0.879 (0.820, 0.942)	<0.001
	2006-2012	1.005 (0.976, 1.035)	1.055 (1.026, 1.085)	1.028 (0.963, 1.097)	0.908 (0.867, 0.952)	0.121
	2013-2021	1.012 (0.991, 1.034)	1.030 (1.008, 1.052)	1.006 (0.959, 1.056)	0.957 (0.928, 0.987)	0.480
	Overall	1.005 (0.989, 1.020)	1.052 (1.028, 1.076)	1.054 (0.979, 1.136)	0.930 (0.887, 0.976)	<0.001
	I ²	0%	43.5%	73.5%	64.3%	
	H ²	1	1.77	3.77	2.80	
Nickel	1990-1997	1.033 (0.998, 1.068)	0.995 (0.957, 1.035)	1.046 (0.978, 1.120)	0.919 (0.859, 0.984)	<0.001
	1998-2005	1.031 (0.978, 1.087)	0.997 (0.950, 1.045)	0.978 (0.883, 1.083)	0.989 (0.914, 1.070)	0.008
	2006-2012	0.938 (0.875, 1.007)	1.001 (0.945, 1.060)	1.019 (0.891, 1.166)	1.033 (0.938, 1.137)	0.470
	2013-2021	0.947 (0.903, 0.994)	0.970 (0.933, 1.008)	1.047 (0.961, 1.142)	1.077 (1.018, 1.140)	0.155
	Overall	0.990 (0.941, 1.042)	0.988 (0.967, 1.01)	1.030 (0.985, 1.077)	1.003 (0.934, 1.077)	<0.001
	I ²	76.7%	0%	0%	73.6%	
	H ²	4.30	1	1	3.79	

Chromium	1990-1997	1.007 (0.998, 1.017)	0.999 (0.991, 1.007)	1.017 (1.002, 1.031)	0.987 (0.972, 1.002)	0.002
	1998-2005	0.999 (0.982, 1.017)	1.030 (1.017, 1.044)	1.022 (0.991, 1.054)	1.003 (0.975, 1.030)	0.002
	2006-2012	0.993 (0.975, 1.012)	1.016 (1.003, 1.029)	1.025 (0.993, 1.057)	0.980 (0.956, 1.005)	0.010
	2013-2021	0.981 (0.963, 0.999)	1.012 (0.999, 1.026)	1.009 (0.978, 1.042)	1.016 (0.993, 1.040)	0.245
	Overall	0.997 (0.985, 1.008)	1.014 (1.001, 1.027)	1.018 (1.006, 1.029)	0.995 (0.98, 1.011)	<0.001
	I ²	54.9%	79.6%	0%	49.8%	
	H ²	2.22	4.90	1	1.99	
Lead	1990-1997	1.008 (1.001, 1.016)	0.994 (0.986, 1.001)	1.008 (0.996, 1.021)	0.996 (0.984, 1.008)	<0.001
	1998-2005	1.042 (1.028, 1.057)	1.006 (0.994, 1.018)	1.009 (0.983, 1.036)	0.996 (0.976, 1.017)	<0.001
	2006-2012	1.007 (0.992, 1.023)	1.031 (1.018, 1.044)	1.045 (1.014, 1.077)	0.999 (0.978, 1.020)	<0.001
	2013-2021	1.002 (0.987, 1.019)	1.013 (0.998, 1.027)	0.993 (0.960, 1.027)	0.989 (0.969, 1.010)	<0.001
	Overall	1.015 (0.997, 1.032)	1.010 (0.995, 1.026)	1.013 (0.996, 1.030)	0.995 (0.987, 1.004)	<0.001
	I ²	86.7%	86.5%	50%	0%	
	H ²	7.51	7.42	2	1	
Benzene	1990-1997	1.029 (1.016, 1.041)	0.993 (0.982, 1.004)	1.001 (0.982, 1.020)	0.986 (0.966, 1.005)	<0.001
	1998-2005	1.051 (1.030, 1.071)	1.026 (1.011, 1.041)	1.006 (0.975, 1.039)	0.984 (0.960, 1.009)	<0.001
	2006-2012	1.017 (0.987, 1.048)	1.058 (1.037, 1.080)	1.082 (1.028, 1.139)	0.982 (0.947, 1.017)	<0.001
	2013-2021	0.970 (0.935, 1.007)	1.021 (0.994, 1.048)	0.955 (0.896, 1.018)	0.933 (0.895, 0.973)	<0.001
	Overall	1.019 (0.989, 1.051)	1.023 (0.997, 1.051)	1.011 (0.968, 1.056)	0.976 (0.958, 0.995)	<0.001
	I ²	86.9%	89.7%	81.9%	43.5%	

	H ²	7.66	9.74	5.51	1.77	
	1990-1997	1.028 (1.001, 1.055)	1.014 (0.994, 1.034)	1.011 (0.974, 1.049)	1.002 (0.967, 1.038)	0.009
	1998-2005	1.018 (1.004, 1.032)	1.010 (0.998, 1.022)	0.993 (0.971, 1.017)	1.018 (1.001, 1.036)	0.124
1,3-Butadiene	2006-2012	1.007 (0.992, 1.021)	1.018 (1.004, 1.031)	1.009 (0.982, 1.037)	1.007 (0.990, 1.025)	0.255
	2013-2021	1.004 (0.995, 1.014)	1.004 (0.997, 1.012)	1.002 (0.986, 1.018)	1.014 (1.003, 1.024)	0.365
	Overall	1.011 (1.002, 1.020)	1.009 (1.003, 1.016)	1.002 (0.991, 1.013)	1.013 (1.005, 1.021)	0.591
	I ²	33.6%	26.2%	0%	0%	
	H ²	1.51	1.35	1	1	

Notes: Results presented here are from single pollutants models; Effect estimates are OR (95% CI) per IQR. IQR values are as follows: zinc: 0.783 ng/m³, nickel: 0.284 ng/m³, chromium: 1.1 ng/m³, lead: 0.548 ng/m³, benzene: 0.183 ppb, 1,3-butadiene: 0.584 ppb; Overall ORs are from Random-Effects Meta-analysis. I²: Represents the proportion of variability due to true heterogeneity across time periods, not random error and H²: Measures the extent to which the observed variability reflects true differences rather than being due to random error; p for interaction has been obtained using Likelihood Ratio Test.

Table S 2-11. Association between entire-pregnancy average criteria air pollutants and TLBW in California for children born between 1990-2021 in California stratified by area-level SES

	Time Period	Lowest (N=3,781,028)	Low-Middle (N=3,123,504)	Middle (N=2,608,040)	High-Middle (N=2,367,604)	Highest (N=1,974,181)	p-value for interaction
PM_{2.5}	1990-1997	1.008 (0.988, 1.028)	1.032 (1.010, 1.053)	1.030 (1.006, 1.054)	1.019 (0.996, 1.042)	1.053 (1.020, 1.087)	0.014
	1998-2005	1.030 (1.011, 1.050)	1.017 (0.997, 1.038)	1.018 (0.994, 1.041)	1.037 (1.008, 1.066)	1.038 (1.003, 1.075)	0.846
	2006-2012	1.022 (1.002, 1.042)	1.028 (1.006, 1.051)	1.061 (1.035, 1.088)	1.007 (0.979, 1.037)	1.011 (0.974, 1.051)	0.036
	2013-2021	1.017 (1.001, 1.032)	0.994 (0.976, 1.013)	1.007 (0.987, 1.027)	1.026 (1.002, 1.050)	1.003 (0.971, 1.035)	0.121
	Overall	1.016 (1.007, 1.025)	1.015 (1.005, 1.025)	1.023 (1.012, 1.035)	1.021 (1.008, 1.033)	1.028 (1.011, 1.046)	0.155
NO₂	1990-1997	1.005 (0.994, 1.016)	1.006 (0.994, 1.017)	1.022 (1.008, 1.035)	1.019 (1.005, 1.034)	1.022 (1.002, 1.042)	0.007
	1998-2005	1.040 (1.029, 1.051)	1.020 (1.007, 1.033)	1.027 (1.012, 1.042)	1.037 (1.019, 1.056)	1.023 (1.001, 1.046)	0.288
	2006-2012	1.043 (1.029, 1.058)	1.019 (1.003, 1.035)	1.041 (1.022, 1.060)	1.003 (0.982, 1.024)	1.013 (0.986, 1.041)	0.037
	2013-2021	1.030 (1.010, 1.052)	1.012 (0.990, 1.035)	0.992 (0.968, 1.017)	1.024 (0.996, 1.052)	1.022 (0.987, 1.058)	0.496
	Overall	1.026 (1.019, 1.032)	1.011 (1.004, 1.018)	1.021 (1.013, 1.029)	1.020 (1.010, 1.029)	1.018 (1.006, 1.031)	0.015
O₃	1990-1997	1.004 (0.986, 1.023)	1.005 (0.985, 1.025)	1.002 (0.978, 1.027)	1.030 (1.001, 1.061)	1.018 (0.983, 1.054)	0.461
	1998-2005	1.000 (0.983, 1.016)	1.033 (1.012, 1.054)	1.033 (1.008, 1.058)	1.061 (1.029, 1.093)	1.100 (1.058, 1.144)	0.001
	2006-2012	1.022 (1.005, 1.039)	1.051 (1.029, 1.073)	1.052 (1.027, 1.078)	1.051 (1.021, 1.082)	1.055 (1.015, 1.097)	0.199
	2013-2021	1.023 (1.008, 1.039)	1.041 (1.021, 1.062)	1.059 (1.034, 1.084)	1.013 (0.986, 1.041)	1.035 (1.000, 1.073)	0.022
	Overall	1.010 (1.002, 1.019)	1.032 (1.021, 1.042)	1.036 (1.023, 1.048)	1.036 (1.021, 1.051)	1.046 (1.027, 1.065)	0.004

Notes: Results presented here are from single pollutants models; Effect estimates are OR (95% CI) per IQR. IQR values are as follows: PM_{2.5}: 2.46 µg/m³, NO₂: 5.07 ppb, O₃: 3.86 ppb; p for interaction has been obtained using Likelihood Ratio Test.

Table S 2-12. Association between entire-pregnancy average air toxics and TLBW in California for children born between 1990-2021 in California stratified by area-level SES

		Lowest (N=3,781,028)	Low-Middle (N=3,123,504)	Middle (N=2,608,040)	High-Middle (N=2,367,604)	Highest (N=1,974,181)	p-value for interaction
Zinc	1990-1997	1.136 (1.029, 1.254)	1.151 (1.049, 1.263)	1.080 (0.984, 1.185)	0.924 (0.837, 1.021)	0.912 (0.814, 1.021)	0.021
	1998-2005	1.045 (0.992, 1.100)	1.036 (0.984, 1.090)	1.042 (0.988, 1.099)	0.985 (0.925, 1.048)	0.919 (0.861, 0.980)	0.059
	2006-2012	1.049 (1.011, 1.087)	1.008 (0.972, 1.046)	1.009 (0.971, 1.049)	1.016 (0.973, 1.061)	0.951 (0.907, 0.998)	0.017
	2013-2021	1.025 (0.997, 1.054)	1.034 (1.007, 1.062)	1.006 (0.979, 1.034)	0.982 (0.952, 1.014)	0.967 (0.935, 1.000)	0.121
	Overall	1.040 (1.018, 1.063)	1.035 (1.007, 1.064)	1.015 (0.995, 1.036)	0.989 (0.966, 1.012)	0.953 (0.930, 0.977)	0.084
	I ²	7.7%	37.3%	0.4%	0.1%	0%	
	H ²	1.08	1.59	1	1	1	
Nickel	1990-1997	0.982 (0.934, 1.031)	1.016 (0.969, 1.065)	0.997 (0.950, 1.046)	1.016 (0.967, 1.069)	1.026 (0.969, 1.085)	0.183
	1998-2005	1.010 (0.951, 1.073)	0.947 (0.889, 1.010)	1.009 (0.943, 1.079)	0.990 (0.917, 1.068)	1.084 (0.999, 1.178)	0.278
	2006-2012	0.937 (0.870, 1.009)	1.008 (0.930, 1.092)	1.023 (0.938, 1.115)	0.983 (0.894, 1.080)	0.997 (0.897, 1.107)	0.672
	2013-2021	0.989 (0.943, 1.038)	0.954 (0.904, 1.006)	0.950 (0.897, 1.006)	1.020 (0.958, 1.085)	1.085 (1.013, 1.161)	0.002
	Overall	0.984 (0.957, 1.011)	0.981 (0.944, 1.019)	0.989 (0.960, 1.020)	1.008 (0.976, 1.042)	1.050 (1.012, 1.089)	0.218
	I ²	0%	38.9%	0.3%	0%	3.1%	
	H ²	1	1.64	1	1	1.03	
Chromium	1990-1997	1.000 (0.990, 1.010)	1.007 (0.997, 1.018)	1.012 (0.999, 1.026)	0.987 (0.974, 1.000)	1.003 (0.988, 1.018)	0.049

	1998-2005	1.042 (1.025, 1.059)	1.000 (0.982, 1.019)	1.020 (0.997, 1.043)	0.996 (0.970, 1.024)	1.004 (0.974, 1.036)	0.018
	2006-2012	1.030 (1.014, 1.047)	0.990 (0.972, 1.009)	0.998 (0.976, 1.020)	0.988 (0.964, 1.013)	1.000 (0.970, 1.031)	0.077
	2013-2021	1.024 (1.007, 1.041)	0.979 (0.960, 0.998)	0.973 (0.952, 0.994)	1.006 (0.982, 1.031)	1.042 (1.014, 1.070)	<0.001
	Overall	1.023 (1.005, 1.041)	0.996 (0.983, 1.008)	1.001 (0.981, 1.021)	0.991 (0.982, 1.001)	1.012 (0.993, 1.031)	<0.001
	I ²	83.6%	57.8%	75.7%	0%	55%	
	H ²	6.100	2.37	4.12	1	2.22	
Lead	1990-1997	0.997 (0.988, 1.006)	0.998 (0.990, 1.007)	1.009 (0.999, 1.019)	0.999 (0.988, 1.009)	1.003 (0.992, 1.015)	0.188
	1998-2005	1.026 (1.009, 1.042)	1.014 (0.999, 1.030)	1.005 (0.988, 1.023)	1.008 (0.988, 1.029)	1.042 (1.019, 1.065)	0.278
	2006-2012	1.023 (1.006, 1.040)	1.014 (0.998, 1.031)	1.032 (1.013, 1.052)	0.999 (0.978, 1.021)	1.026 (1.000, 1.052)	0.163
	2013-2021	1.023 (1.005, 1.042)	0.986 (0.968, 1.004)	0.988 (0.968, 1.007)	1.028 (1.005, 1.051)	1.002 (0.978, 1.027)	0.001
	Overall	1.016 (1.001, 1.031)	1.003 (0.991, 1.015)	1.009 (0.992, 1.025)	1.006 (0.994, 1.019)	1.017 (0.998, 1.036)	0.209
	I ²	75.9%	66%	75.5%	44.7%	71.5%	
	H ²	4.16	2.94	4.08	1.81	3.50	
Benzene	1990-1997	1.001 (0.987, 1.015)	1.001 (0.986, 1.015)	1.010 (0.995, 1.026)	1.002 (0.987, 1.017)	1.026 (1.005, 1.048)	0.018
	1998-2005	1.052 (1.032, 1.073)	1.009 (0.990, 1.029)	1.004 (0.982, 1.027)	1.021 (0.995, 1.048)	1.042 (1.011, 1.074)	0.683
	2006-2012	1.061 (1.032, 1.091)	1.017 (0.989, 1.046)	1.048 (1.014, 1.082)	1.008 (0.971, 1.047)	1.040 (0.994, 1.088)	0.28
	2013-2021	1.012 (0.977, 1.047)	0.958 (0.924, 0.992)	0.954 (0.916, 0.993)	1.012 (0.966, 1.061)	0.999 (0.945, 1.056)	0.115
	Overall	1.031 (1.002, 1.061)	0.999 (0.979, 1.02)	1.005 (0.972, 1.04)	1.007 (0.995, 1.019)	1.030 (1.014, 1.046)	0.063
	I ²	85.1%	68.9%	85.8%	0%	0%	
	H ²	6.70	3.21	7.06	1	1	

	1990-1997	1.017 (0.992, 1.042)	1.014 (0.987, 1.041)	1.037 (1.004, 1.072)	0.999 (0.967, 1.033)	1.017 (0.978, 1.058)	0.262
	1998-2005	1.017 (1.001, 1.033)	0.998 (0.982, 1.014)	1.005 (0.988, 1.022)	1.021 (1.004, 1.039)	1.024 (1.006, 1.041)	0.710
1,3-Butadiene	2006-2012	1.015 (0.996, 1.034)	1.010 (0.991, 1.029)	1.017 (0.998, 1.036)	1.010 (0.993, 1.027)	1.008 (0.991, 1.024)	0.772
	2013-2021	1.002 (0.993, 1.012)	1.004 (0.993, 1.015)	1.006 (0.994, 1.017)	1.012 (1.001, 1.024)	1.010 (0.998, 1.022)	0.744
	Overall	1.010 (1.000, 1.020)	1.004 (0.997, 1.012)	1.010 (1.002, 1.018)	1.013 (1.005, 1.021)	1.013 (1.005, 1.021)	0.305
	I ²	34.3%	0%	1%	0%	0%	
	H ²	1.52	1	1.01	1	1	

Notes: Results presented here are from single pollutants models; Effect estimates are OR (95% CI) per IQR. IQR values are as follows: zinc: 0.783 ng/m³, nickel: 0.284 ng/m³, chromium: 1.1 ng/m³, lead: 0.548 ng/m³, benzene: 0.183 ppb, 1,3-butadiene: 0.584 ppb; Overall ORs are from Random-Effects Meta-analysis. I²: Represents the proportion of variability due to true heterogeneity across time periods, not random error and H²: Measures the extent to which the observed variability reflects true differences rather than being due to random error; p for interaction has been obtained using Likelihood Ratio Test.

Sensitivity analyses

Table S 2-13. Association of entire-pregnancy average criteria air pollutants and air toxics with PTB in California for children born between 1990-2021 in California in single pollutant and co-pollutant adjusted models (N= 14,998,588)

Pollutant	Single Pollutant	Adjusted for		
		NO ₂ , O ₃	PM _{2.5} , O ₃	PM _{2.5} , NO ₂
PM_{2.5}	1.032 (1.030, 1.035)	1.029 (1.026, 1.032)		
NO₂	1.009 (1.008, 1.011)		1.003 (1.001, 1.005)	
O₃	1.015 (1.012, 1.017)			1.012 (1.010, 1.015)
Zinc	1.065 (0.980, 1.158)			1.084 (0.992, 1.185)
Nickel	0.958 (0.896, 1.025)			0.920 (0.836, 1.011)
Chromium	0.996 (0.992, 1.001)			0.992 (0.986, 0.998)
Lead	1.008 (0.991, 1.026)			0.997 (0.985, 1.009)
Benzene	0.991 (0.942, 1.044)			0.931 (0.857, 1.010)
1,3-Butadiene	1.024 (0.981, 1.069)			1.020 (0.978, 1.063)

Notes: Effect estimates are OR (95% CI) per IQR. IQR values are as follows: PM_{2.5}: 2.46 µg/m³, NO₂: 5.07 ppb, O₃: 3.86 ppb, zinc: 0.783 ng/m³, nickel: 0.284 ng/m³, chromium: 1.1 ng/m³, lead: 0.548 ng/m³, benzene: 0.183 ppb, 1,3-butadiene: 0.584 ppb; Results for air toxics (zinc, nickel, chromium, lead, benzene, 1,3-butadiene) are Random-Effects Meta-analysis of time-period specific estimates.

Table S 2-14. Association of entire-pregnancy average criteria air pollutants and air toxics with TLBW in California for children born between 1990-2021 in California in single pollutant and co-pollutant adjusted models (N=13,951,067)

Pollutant	Adjusted for			
	Single Pollutant	NO ₂ , O ₃	PM _{2.5} , O ₃	PM _{2.5} , NO ₂
PM_{2.5}	1.019 (1.014, 1.024)	1.003 (0.997, 1.009)		
NO₂	1.016 (1.012, 1.019)		1.020 (1.015, 1.024)	
O₃	1.028 (1.023, 1.033)			1.033 (1.028, 1.039)
Zinc	1.008 (0.999, 1.018)			1.012 (1.002, 1.021)
Nickel	1.003 (0.989, 1.017)			0.976 (0.961, 0.990)
Chromium	1.004 (0.998, 1.011)			0.997 (0.993, 1.001)
Lead	1.007 (0.998, 1.016)			0.995 (0.992, 0.999)
Benzene	1.005 (0.981, 1.029)			0.949 (0.919, 0.981)
1,3-Butadiene	1.009 (1.005, 1.014)			1.006 (1.002, 1.009)

Notes: Effect estimates are OR (95% CI) per IQR. IQR values are as follows: PM_{2.5}: 2.46 µg/m³, NO₂: 5.07 ppb, O₃: 3.86 ppb, zinc: 0.783 ng/m³, nickel: 0.284 ng/m³, chromium: 1.1 ng/m³, lead: 0.548 ng/m³, benzene: 0.183 ppb, 1,3-butadiene: 0.584 ppb; Results for air toxics (zinc, nickel, chromium, lead, benzene, 1,3-butadiene) are Random-Effects Meta-analysis of time-period specific estimates.

Table S 2-15. Comparing the association of entire-pregnancy average criteria air pollutants and air toxics with PTB for children born between 2013-2021 with children born between 2013-2019* in California

Pollutant	2013-2021 (N=3,879,598)	2013-2019 (N=3,101,309)
PM_{2.5}	1.006 (1.001, 1.010)	1.002 (0.996, 1.009)
NO₂	0.997 (0.991, 1.003)	0.999 (0.993, 1.006)
O₃	1.005 (1.000, 1.010)	1.001 (0.995, 1.006)
Zinc	1.031 (1.025, 1.038)	1.038 (1.030, 1.046)
Nickel	1.054 (1.040, 1.068)	1.016 (0.998, 1.034)
Chromium	0.998 (0.993, 1.003)	1.001 (0.995, 1.006)
Lead	0.984 (0.980, 0.989)	0.993 (0.988, 0.998)
Benzene	0.917 (0.908, 0.925)	0.925 (0.916, 0.934)
1,3-Butadiene	0.996 (0.994, 0.999)	0.999 (0.997, 1.002)

Notes: Results presented here are from single-pollutant models; Effect estimates are OR (95% CI) per IQR. IQR values are as follows: PM_{2.5}: 2.46 µg/m³, NO₂: 5.07 ppb, O₃: 3.86 ppb, zinc: 0.783 ng/m³, nickel: 0.284 ng/m³, chromium: 1.1 ng/m³, lead: 0.548 ng/m³, benzene: 0.183 ppb, 1,3-butadiene: 0.584 ppb; *This time period excludes the years 2020 and 2021 when the COVID-19 pandemic was rampant.

Table S 2-16. Comparing the association of entire-pregnancy average criteria air pollutants and air toxics with TLBW for children born between 2013-2021 with children born between 2013-2019* in California

Pollutant	2013-2021 (N=3,653,447)	2013-2019 (N=2,930,070)
PM_{2.5}	1.011 (1.002, 1.020)	1.017 (1.005, 1.030)
NO₂	1.010 (0.999, 1.021)	1.009 (0.997, 1.021)
O₃	1.035 (1.025, 1.045)	1.036 (1.025, 1.048)
Zinc	1.006 (0.993, 1.019)	1.008 (0.993, 1.024)
Nickel	0.999 (0.974, 1.025)	0.986 (0.954, 1.020)
Chromium	1.001 (0.992, 1.011)	0.998 (0.988, 1.008)
Lead	0.999 (0.990, 1.008)	0.996 (0.986, 1.006)
Benzene	0.970 (0.953, 0.988)	0.970 (0.951, 0.989)
1,3-Butadiene	1.006 (1.001, 1.011)	1.007 (1.002, 1.012)

Notes: Results presented here are from single-pollutant models; Effect estimates are OR (95% CI) per IQR. IQR values are as follows: PM_{2.5}: 2.46 µg/m³, NO₂: 5.07 ppb, O₃: 3.86 ppb, zinc: 0.783 ng/m³, nickel: 0.284 ng/m³, chromium: 1.1 ng/m³, lead: 0.548 ng/m³, benzene: 0.183 ppb, 1,3-butadiene: 0.584 ppb; *This time period excludes the years 2020 and 2021 when the COVID-19 pandemic was rampant.

3. AIM 2: The Association of Polycyclic Aromatic Hydrocarbons with Adverse Placental and Birth outcomes in a Los Angeles Birth Cohort

3.1. Abstract

Polycyclic aromatic hydrocarbons (PAHs) have been linked to adverse pregnancy outcomes, but little is known about their influence on placental health as biological mechanisms impacting pregnancy complications. Here, we studied their association with placental volume, blood flow, deoxygenation, and weight as well as birth weight, preeclampsia and gestational hypertension.

We measured hydroxylated PAH metabolites (naphthalene, fluorene, pyrene, and phenanthrenes) in the urine of 159 pregnant women, as part of the Placental Assessment in Response to ENvironmental pollution study (PARENTs); samples were collected up to three times in pregnancy. Placental volume, blood flow, and deoxygenation were measured twice with MRI scans between the 14th and 24th gestational weeks. Placental and birth weight were recorded after delivery. We used linear regression and quantile g-computation to assess associations between these outcomes and the PAH mixture; additionally, we stratified by fetal sex.

PAH exposure in early pregnancy (9th-17th weeks) was associated with a *decrease* in 2nd MRI (19th-24th week) placental volume among female (PAH mixture association: -23.41cc, 95%CI: -47.25, 0.43) but not male fetuses, and this was complemented with a simultaneous *increase* in placental blood flow in female placentae. On the other hand, in male placentae, but not in female placenta, we observed an increase in 2nd sample PAH exposure (18th-29th weeks) to be associated with blood deoxygenation (R^2 value) at the 2nd MRI for the PAH mixture (0.98, 95%CI: -0.24, 2.21) and 1-PYR (1.82, 95%CI: 0.42, 3.22). PAH exposure was associated with a decrease in birth weight in both sexes, however in female fetuses 1st sample

exposure was most harmful (PAH mixture association: -106.10g, -206.31g, -5.89g) while in male fetuses in general 2nd sample PAH exposures were more strongly negatively associated with birthweight as compared to 1st sample exposures. Similar sex-based differences in observations were also made for placental weight.

Our findings suggest that PAHs may contribute to adverse pregnancy outcomes via the disruption in placental growth and function. While reduced fetal growth was observed in both sexes, the intermediate mechanisms and critical periods of PAH exposure may differ by sex.

3.2. Introduction

Polycyclic Aromatic Hydrocarbons (PAHs) are components of ambient air pollution emitted due to incomplete combustion from sources such as industrial combustion operations, engine exhaust, cooking, smoking, agricultural burning, and wildfires^{17–19,60–64}. PAHs were declared as priority pollutants by the United States Environmental Protection Agency (USEPA) in 1983. Exposure to PAHs during the prenatal period has been previously associated with reduced birth weight^{65–71}, however the underlying mechanisms are unclear.

The placenta plays an important role in regulating fetal growth by acting as the interface through which a pregnant mother and the fetus exchange oxygen and nutrients, produces fetal growth-regulating hormones, and protects the fetus from maternal stress hormones^{15,16}. Given the important role of the placenta in fetal development, we hypothesize that PAHs may in part negatively impact birth outcomes by affecting placental growth and function. There is limited evidence that PAHs may be associated with reduced placental weight at birth⁷². In vitro and animal studies have shown that PAH exposures can decrease placental vasculature, dysregulate growth hormones, and alter placental stem cell proliferation and differentiation^{73–76}. However, to our knowledge, no studies of human placental function under such exposure exist. Knowledge is also lacking on critical periods during which PAH exposure may contribute to adverse birth outcomes⁶⁵.

Here we use data collected as part of the PARENTs (Placental Assessment in Response to ENvironmental pollution study) project to study the association between PAH metabolites of naphthalene, fluorene, phenanthrenes, and pyrene, measured in urine samples of pregnant women collected at three time points during pregnancy with placental development and adverse birth outcomes. We examined PAH exposure associations with multi-parametric Magnetic Resonance Imaging (mp-MRI) measurements of placental volume, blood flow, and

oxygenation during early- and mid-pregnancy, as well as clinical diagnoses of gestational hypertension (GHTN) and preeclampsia, and placental and birth weight at term. Further, as human and animal studies have found sex-based differences in placental and fetal growth and development^{77,78}, we are also examining whether PAH exposures affect pregnancies of male or female fetuses and their placenta differently.

3.3. Material and Methods

3.3.1. Study Population

A prospective cohort study, Placental Assessment in Response to Environmental Exposures Study (PARENTs)¹, recruited 199 pregnant women, who were not smoking during their pregnancy, between 2016 and 2019 from antenatal clinics at the University of California, Los Angeles, and followed them throughout pregnancy until birth. For 159 participants, we were able to obtain PAH metabolite measures in the urine at least once but at most 3 times during pregnancy. A flow diagram of study participant recruitment is provided in Figure S 3-1. Demographic characteristics of the analytical sample are provided in Table 3-1.

3.3.2. Exposure Assessment

Urine of pregnant women was collected at most three times during the gestational period (Figure S 3-2). Study visits were scheduled to be optimal for Magnetic Resonance Imaging (MRI) evaluations. The three urine sample collection timepoints were between the 9th-17th gestational week, 18th-29th gestational week, and after the 30th gestational week and prior to delivery. After collection at UCLA, the urine samples were stored at -80 °C and then shipped on dry ice to the NIH-CHEAR (Children's Health Exposure Analysis Resource) center for measurement of the OH-PAHs. To minimize potential batch effects, all samples were randomized using a Fisher-Yates shuffling algorithm^{1,2}. The following PAH metabolites were measured in the urine samples using tandem mass spectrometry (MS/MS): i) 2-hydroxyfluorene and 3-hydroxyfluorene (2&3-FLUO) ii) 2-hydroxynaphthalene iii) 1-

hydroxyphenanthrene (1-PHEN) iv) 2-hydroxyphenanthrene v) 3-hydroxyphenanthrene (3-PHEN) vi) 4-hydroxyphenanthrene (4-PHEN) vii) 1-hydroxypyrene (1-PYR). Specific gravity was measured in the urine at the same facility using a Reichert AR200 refractometer to adjust the PAH measurements using the following formula:

$$Biomarker_{SG\ adjusted} = Biomarker_i * \left(\frac{SG_m - 1}{SG_i - 1} \right),$$

where $Biomarker_{SG\ adjusted}$ is the specific gravity adjusted biomarker concentration, $Biomarker_i$ is the observed biomarker concentration, SG_i is the specific gravity of the respective urine sample and SG_m is the median specific gravity of the entire study sample. Biomarker data for this analysis are publicly available in the Human Health Exposure Resource (HHEAR) Data Repository, which has been approved under Icahn School of Medicine at Mount Sinai IRB Protocol # 16-00947.

3.3.3. Outcome and Covariate Assessment

Participants were interviewed to obtain information on their age, parity, income, employment status, education level, race and ethnicity, and past smoking behavior. Fetal sex and maternal pre-pregnancy BMI were also recorded. Alternate Mediterranean Diet score (aMED) was calculated based on a food frequency questionnaire, the Diet History Questionnaire II (DHQ II) administered in mid-pregnancy. Gestational age was based on an obstetric estimate relying on a 1st trimester ultrasound exam.

Several outcomes were investigated in this study to assess placental and fetal growth and health. These include placental volume, perfusion, and oxygenation during gestation, and placental weight and birthweight at delivery⁴. To measure placental volume (cc), perfusion (ml/100g/min), and oxygenation, multi-parametric magnetic resonance imaging (mp-MRI) was performed during the first two clinic visits, between 14th-18th weeks and 19th-24th weeks respectively (Figure S 3-2). Placental blood flow was measured as mean maternal placental

blood flow throughout the entire placenta (MPBF), and in areas of maternal high placental blood flow (MhPBF). Placental deoxygenation measured blood hemoglobin saturation within the placenta, recorded as $R2^*$ measurements, with *higher* values indicating an increased amount of *deoxygenated* hemoglobin. Additionally, hypertensive diseases of pregnancy (preeclampsia and GHTN) were also assessed based on data obtained from electronic medical records.

3.3.4. Statistical Analysis

For 42 subjects, a specific gravity of 1 or below was recorded in at least one urine sample which is erroneous, specifically for 14, 18, and 16 samples at 1-3 sample collection timepoints respectively and these samples were removed from analysis.

PAH biomarkers with values below the limit of detection (LOD) were retained and not imputed to avoid falsely reducing the variability of the values. The percentage of PAH concentrations below the LOD are provided in Table S 3-1, and the distribution of PAH values and number of samples with a zero or missing value are provided in Table S 3-2. Placental volume was used as recorded during the MRIs. Additionally, we also generated a gestational length adjusted placental volume measure that was scaled per 100 days of gestational length completed at the time the MRI was performed.

Linear regression was performed to assess associations of urine PAH levels with all continuous outcome measures including placental weight at birth, birth weight, placental volume, perfusion, and oxygenation. For the categorical outcomes, GHTN and preeclampsia, we employed logistic regression. For regression models we used PAH-specific interquartile ranges (IQRs) calculated based on the average of PAH values across all three sample collection timepoints. Maternal age (years, continuous), maternal pre-pregnancy BMI (continuous), and parity (primiparous vs multiparous) were selected as potential confounders, a priori, based on

a DAG we made according to existing literature (Figure S 3-3). For birth weight and placental weight we additionally adjusted for gestational length (days, continuous). Additional adjustment for aMED scores to assess the influence of the maternal diet did not change our results and was therefore left out of the model. Analyses were also stratified by child sex (male vs female).

Several methods were used to assess the cumulative effect of all PAHs. First, we calculated the sum of 1-, 2-, 3-, 4- hydroxy phenanthrenes (Σ PHEN) for each sample. Second, we generated an index score for each sample in the following manner: 1) each individual PAH concentration was scored (1- 4) depending on into which quartile of the entire sample PAH distribution it belonged (n are listed in Table S 3-2); 2) we then summed across the individual PAH quartile-based scores for all 7 PAHs to generate a composite index score (ranging from 7 to 28). Third, we used quantile g-computation to estimate the association of the PAH mixture on the outcomes using the qqcomp package⁸³.

Spearman correlation coefficients were calculated to assess the correlation of specific gravity adjusted biomarker values in different exposure periods (Figure S 3-4) as well as the correlation among values in different exposure periods for each PAH (Figure S 3-5).

All analyses were performed on R version 4.3.3.

3.4. Results

3.4.1. Characteristics of Study Population

Our study participants were on average 33 years old; almost a third were overweight or obese (31.4%) and more than half multiparous (53.5%). The study sample consisted primarily of non-Hispanic White women (46.2%), followed by Asians (28.5%), Hispanics (18.4%), and Blacks (7.0%). The majority of our study population was of high socioeconomic status with 87.7% having completed at least a bachelor's degree, 83.2% being employed, 55.4% earning

\$60,000 or more annually and 66% having partners who earned \$60,000 or more annually. Our study sample also consisted of a high proportion of high-risk pregnancies with 9.6% getting a diagnosis of GHTN and 10.3% of preeclampsia (Table 3-1).

3.4.2. Correlation Among PAHs and Sampling Periods

All PAHs except 2-NAP and 4-PHEN were highly correlated with each other in all three sampling periods ($r=0.7-0.8$), while 2-NAP and 4-PHEN showed low to moderate correlation with the other PAHs ($r=0.1$ to 0.7) (Figure S 3-4) which could be due to a high proportion of samples being below the LOD as shown in Table S 3-1. As expected, Σ PHEN and the cumulative PAH index score were highly correlated with all PAHs except 4-PHEN and 2-NAP. Between sampling timepoint correlations in PAH biomarker values were low ($r=0-0.4$), except for 2-NAP for which it was moderate ($r=0.5-0.6$) (Figure S 3-5).

3.4.3. Associations between PAHs and Adverse Placental and Birth Outcomes

In Figure 3-1 we show the associations between PAH mixtures and the different outcome measures with the beta coefficients standardized by standard deviations for ease of comparability across outcomes (the non-standardized beta coefficient values are provided in Tables S 3 - S 15). Our observations differed by the sex of the fetus. Among women carrying female fetuses, but not among women carrying male fetuses, we saw a negative association (-23.41cc , 95% CI: -47.25cc , 0.43cc) between the 1st sample PAH mixture (9th-17th weeks) and the 2nd MRI placental volume (19th-24th weeks) (Figure 3-1 and Table S 3-4). These same associations were also seen for the PAH index, as well as 2-NAP and 1-PYR. Results remained consistent after scaling the placental volume per 100 days of gestational length completed at the time MRI (Table S 3-6). Further, a positive association between the 1st sample PAH mixture and maternal placental blood flow in the entire placenta (MPBF) measured at the 2nd MRI ($3.20\text{ ml}/100\text{g}/\text{min}$, 95%CI: $-0.09\text{ ml}/100\text{g}/\text{min}$, $6.48\text{ ml}/100\text{g}/\text{min}$) was mainly due to women carrying female fetuses ($4.13\text{ml}/100\text{g}/\text{min}$, 95% CI: $-1.68\text{ml}/100\text{g}/\text{min}$, $9.95\text{ml}/100\text{g}/\text{min}$).

For these associations in female fetuses, only 2&3-FLUO and 2-PHEN reached formal statistical significance (Figure 3-1 and Table S 3-8). Similar patterns were, however, not observed for perfusion in areas of high placental blood flow (MhPBF) (Figure 3-1 and Table S 3-10). On the other hand, in male fetuses, we observed a positive association between 2nd sample PAH mixture exposure (18th-29th weeks) and deoxygenation of placental blood, i.e. poorer blood hemoglobin saturation at the 2nd MRI (19th-24th weeks) (0.98, 95%CI: -0.24, 2.21), most strongly driven by an association with 1-PYR (1.82, 95%CI: 0.42, 3.22) (Figure 3-1 and Table S 3-12).

For measures of placental weight at birth and birth weight, negative associations were observed with PAH mixtures in the overall cohort but the critical exposure period for male fetuses was the 2nd timepoint (18th-29th week) whereas for female fetuses it was earlier i.e. the 1st exposure period (Figure 3-1, Table S 3-13, and Table S 3-14). In the overall cohort, a reduction in placental weight was found to be associated with PAH mixtures and PAH indices at all three timepoints, with the association for 1st sample 1-PYR reaching formal statistical significance. However, in women carrying male fetuses, PAH exposure measured during the 2nd timepoint (18th-29th weeks) seemed more harmful (2nd sample 2&3-FLUO, 1-PYR, 1-PHEN, 3-PHEN, and ΣPHEN were all negatively associated with placental weight with β s ranging from: -12.98g to -22.07g). For the 1st sample, only 1-PYR was negatively associated with placental weight (-17.45g, 95%CI :-34g, -0.9g) for male fetuses. For women carrying females fetuses, 1st sample 2-NAP (-30.62g, 95% CI: -61.75g, 0.50g) was negatively associated with placental weight but not the 2nd sample exposure measures (Table S 3-13). Similar observations were seen for birth weight (Figure 3-1 and Table S 3-14). In the overall sample, the 1st sample PAH mixture was strongly negatively associated with birth weight (-79.50g, 95% CI: -141.15g, -17.85g) and so was the 1st sample PAH index (-11.21g, 95% CI: -21.95g, -0.48g). The associations for birth weight remained negative with 2nd and 3rd

sample PAH mixtures and indices, but the effect sizes became weaker and the 95% confidence intervals straddled the null. All individual 1st sample PAH measures were also negatively associated with birth weight (2-NAP, 1-PYR, 2-PHEN, 4-PHEN associations reached formal statistical significance with β estimates ranging: -47.18g to -91.05g). This pattern was seen in both sexes, but the effect estimates for female babies were in general stronger while the effect estimates for male babies did not reach formal statistical significance. Specifically, we observed strong negative associations for female infant birthweights with the 1st sample PAH mixture (-106.10g, 95%CI: -206.31g, -5.89g), 2-NAP (-148.24g, 95%CI: -278.16g, -18.33g), 1-PYR (-104.76g, 95%CI: -192.55, -16.98), and 2-PHEN (-87.55g, 95%CI: -174.60g, -0.49g). For 2nd sample PAHs however, no negative associations with birth weight were seen in female babies, while negative associations were observed for this later exposure period in male babies, especially for pyrene (-130.01g, 95% CI: -218.27g, -41.76g) and phenanthrenes (eg. for Σ PHEN β estimate: -88.69g, 95% CI: -184.78g, 7.41).

For preeclampsia and gestational hypertension, we did not observe notable pregnancy sex differences. The 1st sample PAH mixture was slightly positively associated with the incidence of preeclampsia and gestational hypertension in women carrying fetuses of either sex, however, 95% confidence intervals included the null for the mixture measures as well as for individual PAHs (Figure 3-1 and Table S 3-15).

3.5. Discussion

In this study of highly educated women, some with high-risk pregnancies, we found sex-specific differences in the impact of PAH exposure on placental size and function. In female fetuses only, we observed reduced mid-pregnancy placental volume and a complimentary increased placental blood flow with PAH exposure. In males we observed a decrease in oxygen saturation in the placenta in mid-pregnancy in response to increased PAH

exposure. This sex-specific pattern parallels findings from our previous study in the same cohort that examined maternal dietary intake and placental volume, and found that a nutrient-rich diet did not affect placental volume in female fetuses but was associated with higher placental volume in male fetuses⁸⁴. Our findings suggest that male placental volume increases in response to beneficial dietary exposure but is resistant to harmful PAH exposure, whereas female placental volume shows the reverse pattern, decreasing in response to PAH exposure without a comparable increase from dietary quality. In fact, male fetuses have been shown to prioritize growth at the expense of their ability to adapt to adverse maternal environments, while female fetuses may sacrifice growth to preserve survival in anticipation of or to adjust to environmental insults in the womb⁸⁵. These differences are brought about by sex-based placental gene expression, placental structure and the preferential activation of distinct signaling pathways^{78,86}. Specifically, under stress, female fetuses prioritize glucocorticoid signaling and favor reduced growth while male fetuses are glucocorticoid-resistant and prioritize androgen signaling to maximize growth^{78,87}. Rodent models have demonstrated sex-specific placental structural and functional differences, with males having increased mid-pregnancy placental volume but a decrease in the labyrinth zone, which is involved in nutrient and oxygen exchange, while females showed upregulation of vasculogenesis related genes⁷⁸. Female fetal growth has been found to be more adaptable to placental size and structure, whereas male fetal growth appears to be more hormonally driven⁸⁸. Thus, the reduction in placental volume we observed in PAH exposed female fetuses may be an adaptive response to conserve resources and economize growth, but this needs further exploration. It is also possible that our results may not capture the harmful impact of PAHs on male fetuses if the most vulnerable and highly exposed male fetuses are selectively lost to spontaneous abortion and, thus, do not survive to birth, a condition for being included in this cohort.

Our observation that PAH exposure early in gestation (weeks 9–17) was negatively associated with mid-pregnancy placental volume but positively with placental blood flow in female fetuses, may suggest a compensatory response to ensure that female fetuses, who survive to be born alive, are adequately nourished and oxygenated. This pattern echoes findings from an animal model, in which female mice exposed to PAHs prior to conception went on to have fetuses with intrauterine growth restriction along with shrinkage of the arterial surface area and volume of placenta, but the blood vessels themselves were more extensively branched and enlarged⁷⁶. A greater abundance of RNA transcripts encoding luteinizing hormone (LH) and human chorionic gonadotropin (hCG) hormone, both of which promote vasculogenesis and angiogenesis, has previously been observed in female placentae at term⁸⁹. This compensatory increase in blood flow we saw in the MRI may partly reflect potential live-birth bias, as our cohort contained only the pregnancies that ended in a live birth. That is, those in whom successful vascular compensation allowed the pregnancy to continue to term, while pregnancies unable to compensate may have been lost earlier in pregnancy. In male fetuses, placental volume was not affected and did not require them to increase perfusion, but the concurrent PAH mixture exposure during the 18th-29th week period was associated with poorer blood hemoglobin oxygen saturation of the placenta at the 2nd MRI (19th-24th weeks) followed by low placental and birth weight.

Our results suggest that distinct periods of vulnerability underlie the association of PAH with low placental and birth weight in each sex. For these adverse outcomes, early pregnancy PAH exposure (9th-17th week) appears to be more harmful to female infants, while exposure during 18th to 29th week appeared more harmful to male infants. The earlier exposure window in females and the mid-pregnancy period in males was respectively associated with reduced placental volume and elevated deoxygenation levels. Ultrasound and MRI measurements of inadequate vasculature and reduced placental volume, blood flow, and oxygenation, have all

previously been shown to be predictive of fetal growth restriction and small-for-gestational age^{90–92}. Placental weight is also a well-established determinant of birth weight^{93–95} and has been shown to mediate the effect of harmful environmental exposures, such as temperature and chemical toxicants on birth weight^{96–98}. Reduced placental volume and improper vasculature have also been linked to gestational hypertension^{99–101}. In response to the lack of blood flow to the fetus and subsequent deprivation of nutrients and oxygen, the placenta secretes inflammatory cytokines and cells, reactive oxygen species, and antiangiogenic factors, which damage endothelial cells and lead to vasoconstriction and hypertension in the mother^{102,103}. Further, gestational hypoxia has been found to bring about morphological and cell-signaling changes that are characteristic of gestational hypertension and preeclampsia¹⁰⁴. These mechanisms explain our observations for reduced placental and birth weight with PAH exposures; however, we did not have sufficient sample size to estimate PAH effects on binary outcomes such as gestational hypertension and preeclampsia for which we saw positive but imprecise associations.

To our knowledge, there are no comparable studies with repeated urinary measurements of PAH metabolites throughout pregnancy that assessed associations with placental growth and MRI perfusion measures during pregnancy. There are however studies that explored the associations of PAH exposure with placental weight, birth weight, and hypertensive disorders of pregnancy, though in these studies PAHs were measured only once in pregnancy. A recent cohort of 5318 participants in the US found negative associations between birth weight and urinary metabolites of phenanthrenes, fluorenes, and 1-PYR measured in mid-gestation⁶⁶, agreeing with our findings for early and mid-pregnancy PAH exposure (see Table S 3-14). Another study conducted in China also found 2-NAP measured in urine in the third trimester to be associated with lower birth weight¹⁰⁵. However, a 2020 meta-analysis that reviewed 4 studies with urinary PAH measures mostly from late pregnancy¹⁰⁶ and a Czech study that

measured maternal urinary PAH at birth⁷² found no association of PAHs with birth weight concurring with our own results of late pregnancy samples. The Czech study also did not find statistically significant negative associations with placental weight for PAHs measured in the mother's urine, though inverse relationships were observed with PAH measurements in the newborn's urine⁷². While in general we observed negative associations with placental weight for all PAHs, a statistically significant negative association was only found for 1st sample 1-PYR (see Table S 3-13). Finally, a few cohort, case-control, and cross-sectional studies have been conducted to assess the link between PAH exposure and gestational hypertension and reported elevated risks, as did we, although the confidence intervals included the null value^{107–110}.

We observed the strongest associations with all outcomes studied with PAH exposures in early and mid-pregnancy. PAHs are highly lipophilic and thus bioavailable after inhalation⁶¹, allowing them to contribute to toxicity in various ways. Firstly, PAHs are endocrine disrupting chemicals that have been shown to alter levels of pregnancy-related hormones. An epidemiological study found PAH exposure to be associated increased concentrations of corticotropin releasing hormone, estriol and triiodothyronine, and decreased concentrations of testosterone and the progesterone:estriol ratio¹¹¹. In-vitro and animal studies of PAH also documented disruptions in hormone levels including estrogen, progesterone, and beta human chorionic gonadotropin (HCG) that play important roles in angiogenesis and placental circulation^{112–116}. Secondly, PAHs have been shown to form DNA-adducts in the human placenta^{117,118} that may interfere with DNA methylation, histone modification, and microRNA regulation¹¹⁹, all relevant to the epigenetic reprogramming during early fetal development¹²⁰. It has been shown that epigenetic alterations brought about by air pollution can affect fetal growth and angiogenesis¹²¹. Divergence from normal epigenetic regulation has also been linked to placental disorders such as preeclampsia¹²². Third, PAHs are also known to induce

oxidative damage. We previously reported on oxidative DNA damage and lipid peroxidation associated with urinary PAH levels in the PARENTs cohort¹²³. While a certain level of reactive oxygen species is needed for proper placental development, excessive oxidative stress can lead to shallow placentation such that the placenta does not attach deep enough into the lining of the uterus, preventing mother's blood vessels (spiral arteries) from widening properly and limiting blood flow and oxygen to the growing fetus. Oxidative stress also disrupts placental angiogenesis and increases the risk for intrauterine growth retardation (IUGR) and preeclampsia^{124,125}. Oxidative stress can further trigger inflammation. PAH exposure during pregnancy have been linked to increases in the level of inflammatory markers such as IL-6, IL-1 β , TNF- α , and IL-10^{126,127} some of which elevate the risk of preeclampsia¹²⁸.

Early and mid-pregnancy are periods important for placental formation and function, likely increasing susceptibility to PAH exposure during this period. Placenta formation begins in the 1st trimester and is fully functional by the 16th gestational week¹²⁹. Trophoblast invasion and remodeling of the spiral arteries of the uterus also occur in the first 22 weeks¹³⁰. Dysregulation of these processes results in poor utero-placental blood flow with consequences for fetal development and growth. We observed a sex-specific pattern in the critical early pregnancy window of exposure, with earlier exposures appearing more harmful to female and later exposures to male placentas and fetuses. A 2017 review summarized that early-pregnancy toxic exposures disrupted trophoblast differentiation and early placental growth in females, whereas exposures occurring in mid- to late-gestation, after the placenta has formed, more often affect male fetus viability¹³¹. Our findings align with this review and further add to a growing body of literature, underscoring the need for pregnancy research to investigate sex-based differences in windows of susceptibility.

The source of different PAHs found in indoor environments is indicated by their respective molecular structures and weights. Two- and three-ring aromatic structures, i.e. naphthalene, fluorenes, and phenanthrenes, are believed to be originating from indoor combustion related activities like cooking while heavier PAHs such as pyrenes are thought to be indicators of traffic related combustion^{18,64,132}. A study comparing modeled indoor and outdoor PAH concentrations with measured urine PAH metabolites found that for naphthalene, fluorene, and phenanthrenes, 97% of intake was due to indoor sources, whereas for pyrene, while indoor air inhalation remained a major route of exposure, outdoor air was also an important contributor to the total exposure¹³³. Another source of indoor PAH exposure is smoking^{80,81}. However, our study participants did not smoke during pregnancy, and this highly educated California study population is also unlikely to be exposed to second-hand smoke. Given the adverse placental and birth outcomes associated with PAH exposure in our study, this calls for policy interventions to reduce PAH exposure during pregnancy, informed by previous findings linking cooking fuel type and vehicle engine fuel type and mechanics to PAH emission levels^{63,136}, such as promoting electric stoves over gas and enforcing stricter vehicle emissions standards.

Our study has several strengths. Firstly, we took repeated measurements of PAH metabolites throughout pregnancy which made it possible to identify critical periods of exposure. Additionally, measuring the PAH metabolites in urine provided us with an estimate of internal dose. Secondly, measuring placental volume at two timepoints during pregnancy enabled us to assess the impact of exposure on the size of the placenta during pregnancy at different points. The use of MRI measurements of placental volume, perfusion, and oxygen saturation during pregnancy is novel¹³⁷. In sensitivity analyses we controlled for potential dietary intake of PAHs^{60,61,64,138} and the influence of a healthy diet by controlling for the Alternate Mediterranean Diet (aMED) score and this did not change our results (data not

shown). Finally, our cohort consisted of individuals who did not smoke during pregnancy, eliminating smoking as a risk factor for adverse outcomes in this cohort.

Some limitations also need to be acknowledged. As the half-lives of urine PAHs is only a few hours¹³⁹, our measurements reflect only recent exposures and assumes that they represent chronic exposures over longer periods. Inter-sample correlations for PAH biomarkers were low except for 2-NAP, for which it was moderate; this was also reported in another study¹⁴⁰. Second, our sample size was limited, especially for subgroup analyses, which resulted in effect estimates with low precision. Studies in larger prospective cohorts are needed. Further, our study population consisted mainly of mothers belonging to high socioeconomic status (SES), but this avoided some confounding due to competing risk factors for these outcomes.

3.6. Conclusion

PAH exposures in early to mid-pregnancy disrupted placental growth and function in a sex-specific manner and contributed to low infant and placental weight at birth in both sexes. Thus, reducing exposure through public health interventions is necessary. Our study provides evidence of critical windows of exposure and sex-specific differences in susceptibility that can help inform about risks and opportunities for prevention.

Main Figures and Tables

Table 3-1. Characteristics of PARENTs Study Population (N=159)

Variable	Mean (SD)	N (%)
Maternal age at baseline	33.3 (4.2)	
Maternal BMI class at baseline		
Underweight		6 (3.8%)
Normal		103 (64.8%)
Overweight		32 (20.1%)
Obese or extremely obese		18 (11.3%)
Parity		
0		74 (46.5%)
1 or more		85 (53.5%)
Child sex		
Female		67 (42.4%)
Male		91 (57.6%)
Missing		1
Race/Ethnicity		
White, non-Hispanic		73 (46.2%)
Asian		45 (28.5%)
Hispanic		29 (18.4%)
Black or African American		11 (7.0%)
American Indian or Alaskan Native		1 (0.6%)
Maternal Education		
Bachelor's degree or higher		136 (87.7%)
High school graduate, 2-year degree or some college		19 (12.3%)
Missing		4
Maternal Employment Status		
Employed		129 (83.2%)
Unemployed, student or other		26 (16.8%)
Missing		4
Maternal Income		
>\$100,000		40 (26.7%)
\$60,000 to \$100,000		43 (28.7%)
<\$60,000		67 (44.7%)
Missing		9
Partner's Income		
>\$100,000		61 (41.5%)
\$60,000 to \$100,000		36 (24.5%)
<\$60,000		50 (34.0%)
Missing		12
Placental volume (cc) (14-18 th week)	141.0 (49.9)	
Missing		9
Placental volume (cc) (19 th -24 th week)	264.0 (78.0)	
Missing		18

Maternal placental blood flow in the entire placenta (ml/100g/min) (14-18 th week)	62.9 (21.1)	
Missing		16
Maternal placental blood flow in the entire placenta (ml/100g/min) (19 th -24 th week)	71.9 (35.1)	
Missing		24
Placental blood flow in areas of maternal high placental blood flow (ml/100g/min) (14-18 th week)	220 (99.8)	
Missing		16
Placental blood flow in areas of maternal high placental blood flow (ml/100g/min) (19 th -24 th week)	252 (136)	
Missing		24
Placental deoxygenation (14-18 th week)	18.1 (5.57)	
Missing		41
Placental deoxygenation (19 th -24 th week)	18.7 (4.73)	
Missing		41
Placental weight at birth (grams)	449.0 (88.3)	
Missing		13
Birth weight (g)	3360 (486)	
Missing		2
Gestational Hypertension (GHTN)		
No		141 (90.4%)
Yes		15 (9.6%)
Missing		3
Preeclampsia		
No		140 (89.7%)
Yes		16 (10.3%)
Missing		3

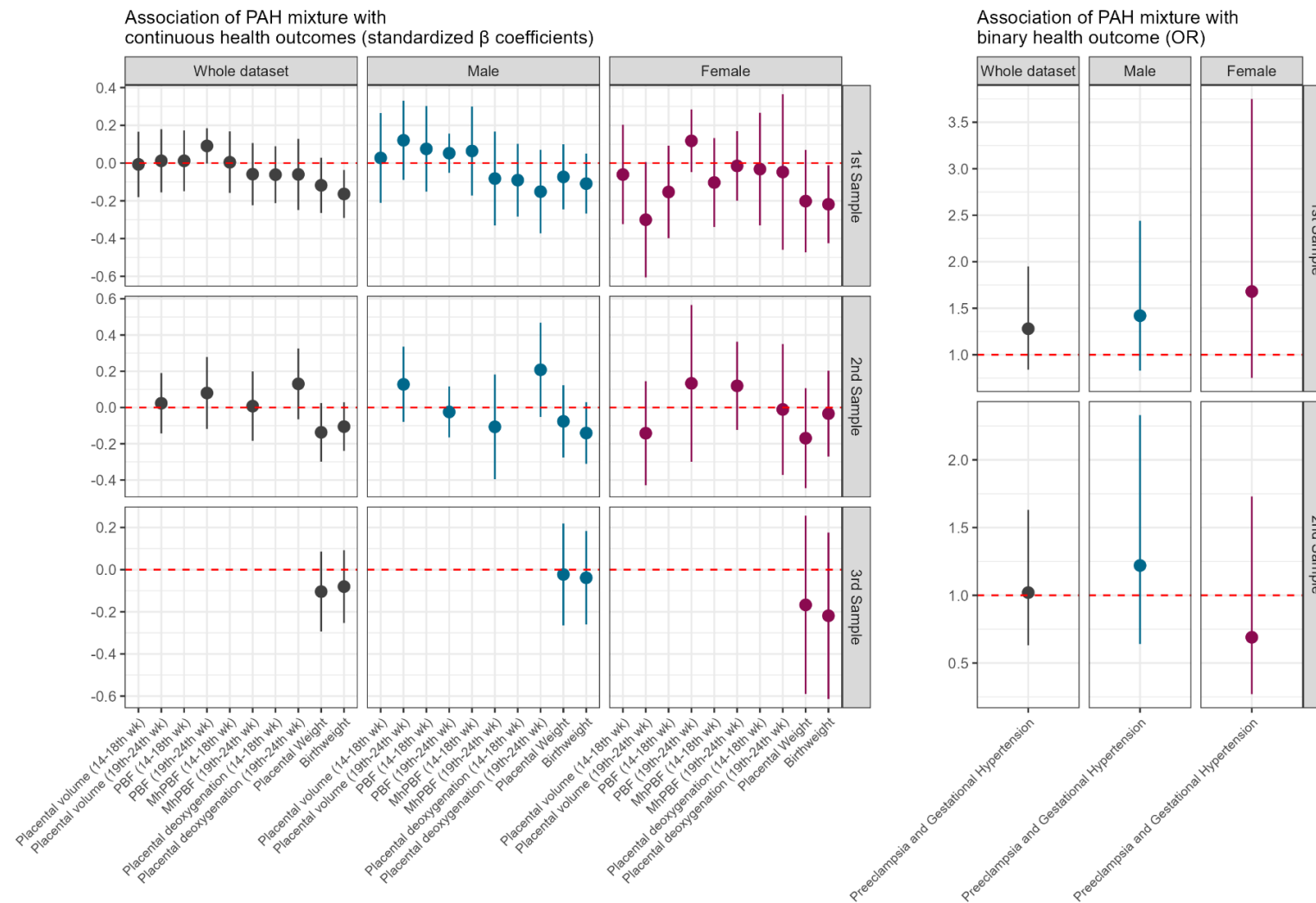


Figure 3-1. Association of placental and birth outcomes with PAH mixture (per IQR)

Note: 1st sample was collected between 9th-17th weeks, 2nd sample was collected between 18th-29th weeks, and 3rd sample was collected between the 30th week to prior to delivery

Supplemental Figures and Tables

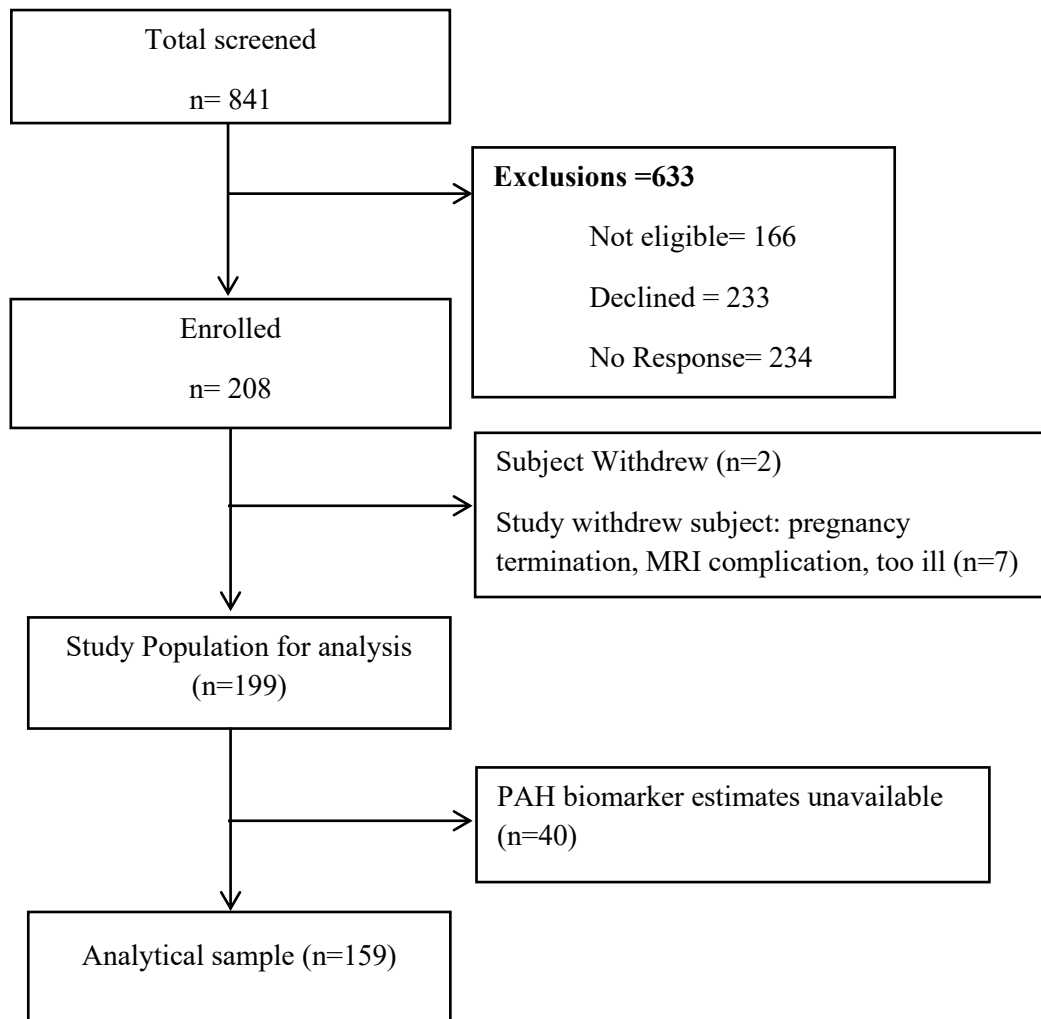


Figure S 3-1. Flow diagram of study participant recruitment for PARENTs

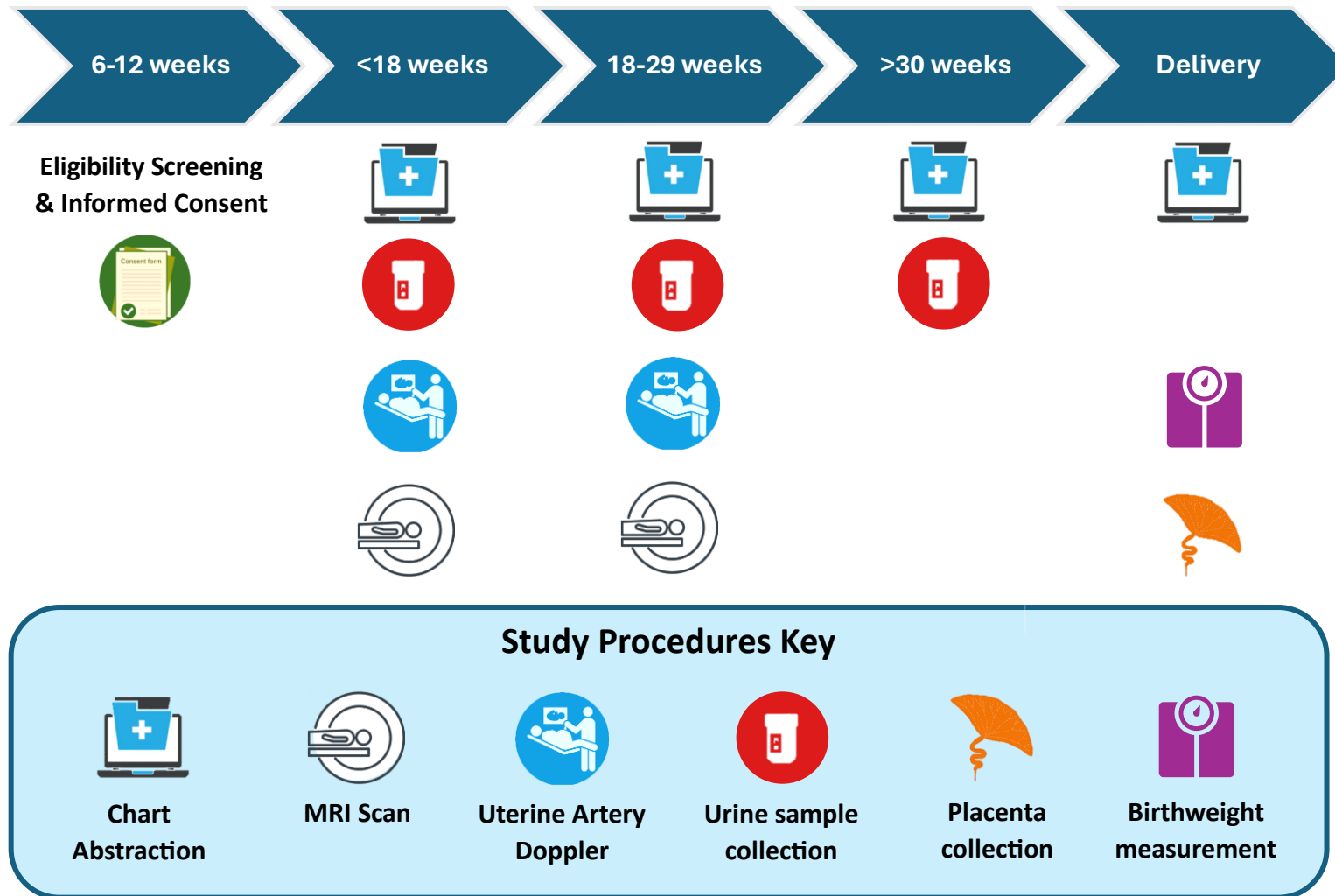


Figure S 3-2. Data collection timings for PARENTs

In this image we used icons from Flaticon.com.

Table S 3-1. Percentage of PAH Biomarkers below LOD

PAH	Sample	LOD	Samples < LOD (% of non-missing values)
2&3-FLUO	1	25 ng/L	25 (16.3%)
	2		12 (7.7%)
	3		22 (16.7%)
2-NAP	1	2500 ng/L	98 (64.1%)
	2		74 (47.4%)
	3		65 (49.2%)
1-PYR	1	12.5 ng/L	21 (13.7%)
	2		9 (5.8%)
	3		12 (9.2%)
1-PHEN	1	12.5 ng/L	11 (7.2%)
	2		7 (4.5%)
	3		7 (5.3%)
2-PHEN	1	12.5 ng/L	38 (25%)
	2		23 (14.7%)
	3		21 (15.9%)
3-PHEN	1	12.5 ng/L	45 (29.6%)
	2		33 (21.2%)
	3		38 (28.8%)
4-PHEN	1	12.5 ng/L	89 (58.2%)
	2		70 (44.9%)
	3		78 (59.5%)

Note: 1st sample was collected between 9th-17th weeks, 2nd sample was collected between 18th-29th weeks, and 3rd sample was collected between the 30th week to prior to delivery

Table S 3-2. Distribution of Specific Gravity Adjusted PAH Biomarkers

PAH (ng/L)	Sample	Mean (SD)	Median [Min, Max]	Samples = 0 (% of non- missing)	Missing (% of total)	Number of samples (n)
2&3-FLUO	1	166 (248)	96.1 [0, 2340]	1 (0.7%)	20 (12.6%)	139
	2	159 (154)	117 [10.2, 1150]	0 (0%)	21 (13.2%)	138
	3	161 (273)	92.2 [0, 2690]	1 (0.9%)	44 (27.7%)	115
2-NAP	1	4870 (7310)	1900 [0, 37100]	4 (2.9%)	20 (12.6%)	139
	2	6640 (13500)	2910 [0, 115000]	6 (4.3%)	21 (13.2%)	138
	3	8420 (26100)	2500 [0, 262000]	5 (4.3%)	44 (27.7%)	115
1-PYR	1	62.9 (125)	37.6 [1.67, 1430]	0 (0%)	20 (12.6%)	139
	2	68.3 (84.1)	45.4 [0, 747]	1 (0.7%)	21 (13.2%)	138
	3	108 (238)	54.1 [0, 2250]	3 (2.6%)	44 (27.7%)	115
1-PHEN	1	98.9 (170)	63.5 [0, 1670]	2 (1.4%)	20 (12.6%)	139
	2	96.5 (82.2)	70.1 [0, 450]	1 (0.7%)	21 (13.2%)	138
	3	154 (253)	81.4 [0, 1860]	3 (2.6%)	44 (27.7%)	115
2-PHEN	1	35.8 (42.1)	24.1 [0, 300]	2 (1.4%)	21 (13.2%)	138
	2	34.4 (27.7)	26.7 [0, 157]	1 (0.7%)	21 (13.2%)	138
	3	47.6 (64.7)	27.8 [0, 497]	2 (1.7%)	44 (27.7%)	115
3-PHEN	1	35.8 (35.6)	24.6 [2.75, 253]	0 (0%)	21 (13.2%)	138
	2	32.8 (26.7)	24.2 [0, 133]	1 (0.7%)	21 (13.2%)	138
	3	34.9 (44.0)	23.4 [0, 377]	3 (2.6%)	44 (27.7%)	115
4-PHEN	1	20.4 (28.0)	14.4 [0, 241]	24 (17.3%)	20 (12.6%)	139
	2	18.0 (18.5)	14.9 [0, 135]	21 (15.2%)	21 (13.2%)	138
	3	22.9 (38.1)	13.1 [0, 226]	43 (37.4%)	44 (27.7%)	115
Σ PHENs	1	191 (261)	127 [20.0, 2270]	0 (0%)	21 (13.2%)	138
	2	182 (143)	140 [36.0, 841]	0 (0%)	21 (13.2%)	138
	3	259 (379)	151 [0, 2430]	1 (0.9%)	44 (27.7%)	115
PAH index	1	17.6 (6.29)	17.0 [7.00, 28.0]	0 (0%)	21 (13.2%)	138
	2	17.5 (5.99)	17.0 [7.00, 28.0]	0 (0%)	21 (13.2%)	138
	3	17.8 (5.94)	18.0 [8.00, 28.0]	0 (0%)	44 (27.7%)	115

Note: 1st sample was collected between 9th-17th weeks, 2nd sample was collected between 18th-29th weeks, and 3rd sample was collected between the 30th week to prior to delivery

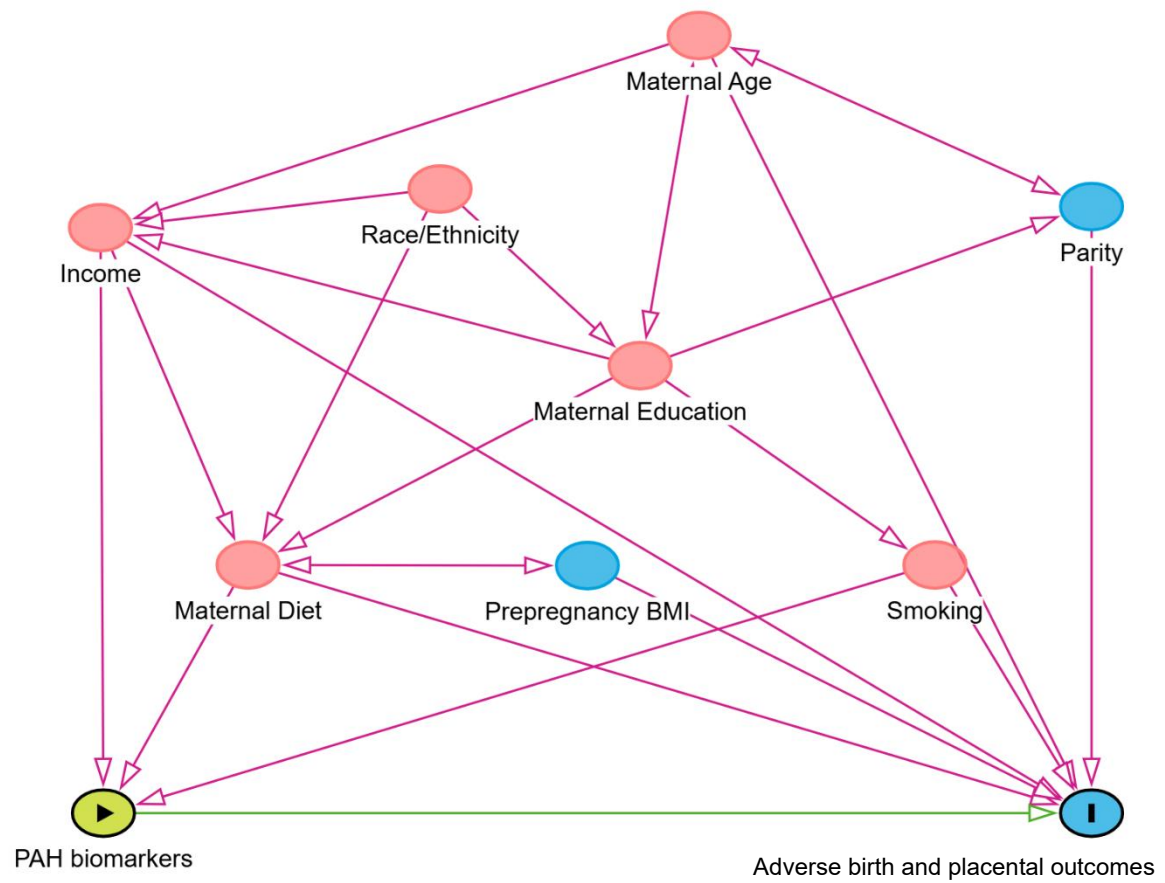
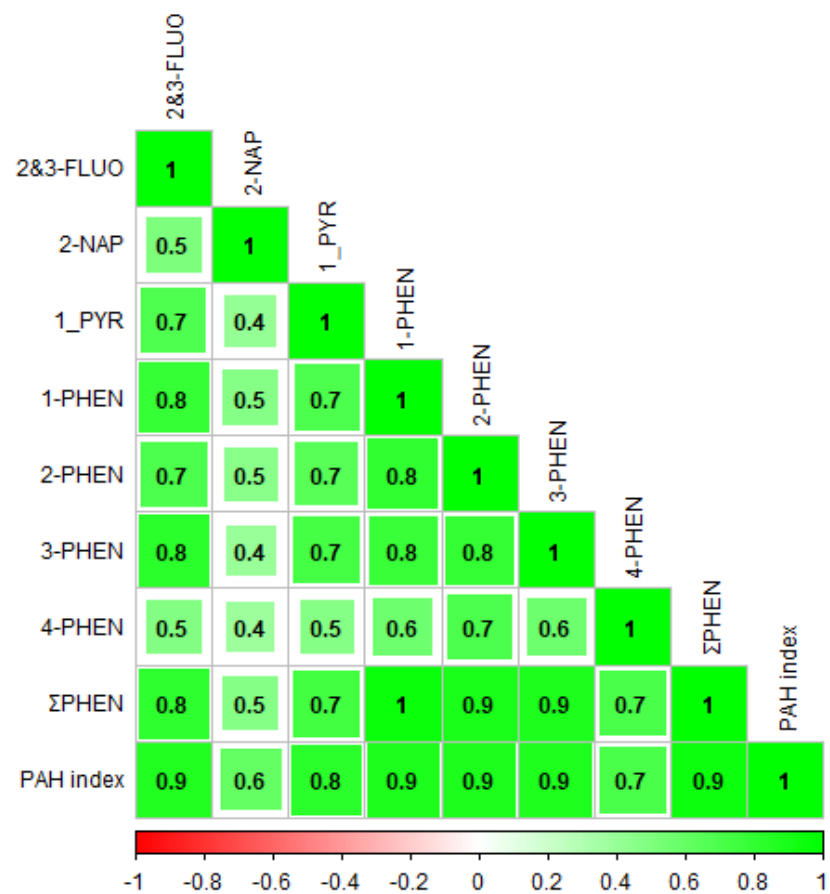
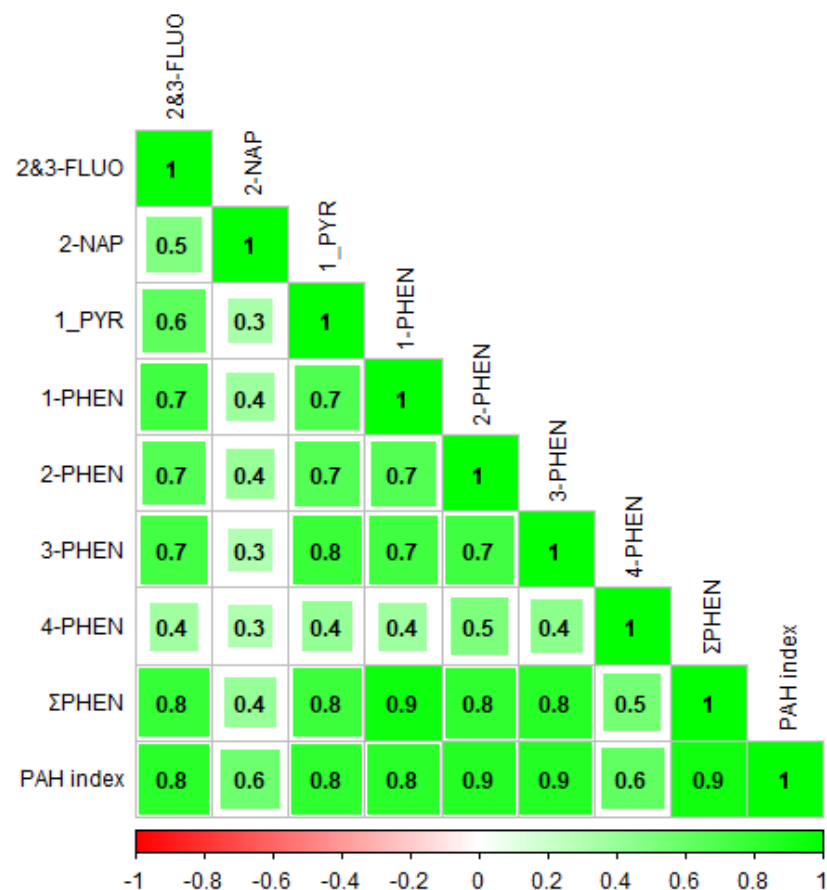


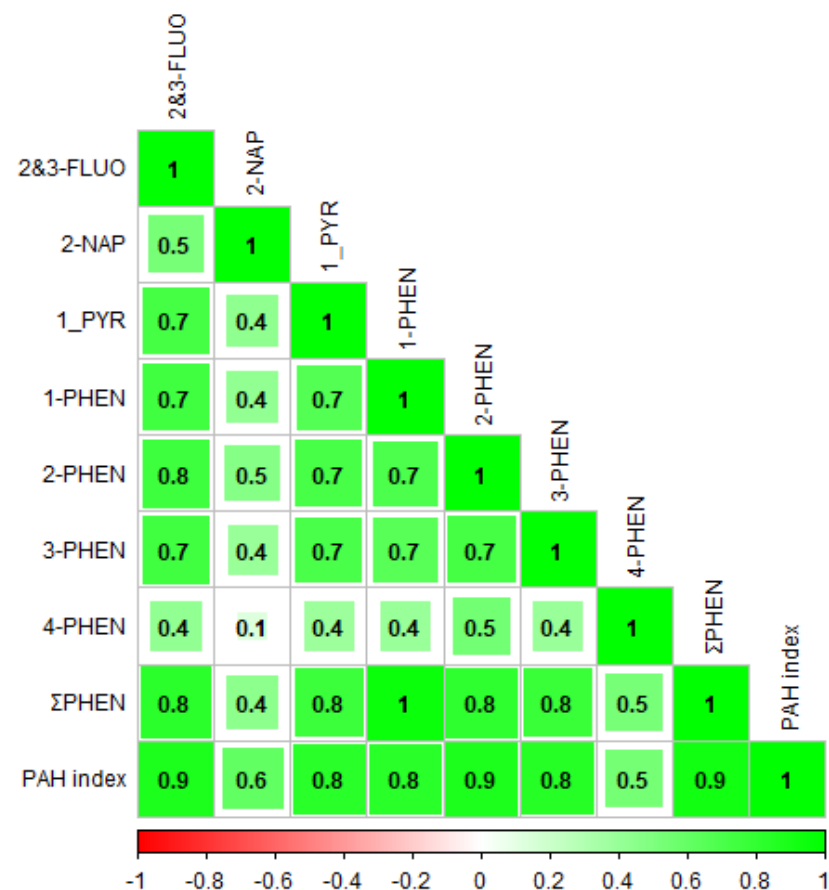
Figure S 3-3. Directed Acyclic Graph for the study



A: 1st Sample



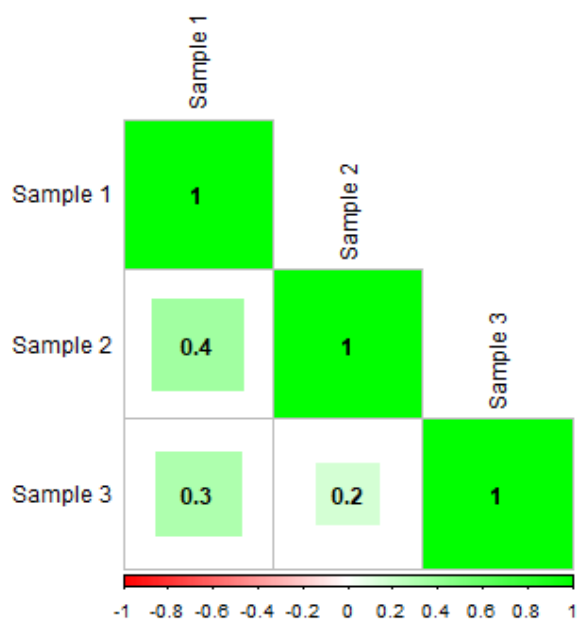
B: 2nd Sample



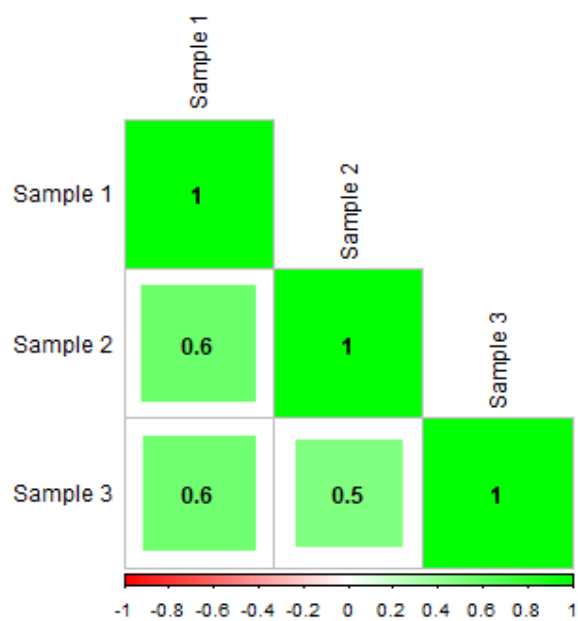
C: 3rd Sample

Figure S 3-4. Spearman Correlation Coefficients of Specific Gravity-Adjusted PAH Biomarker levels Stratified by Exposure Periods

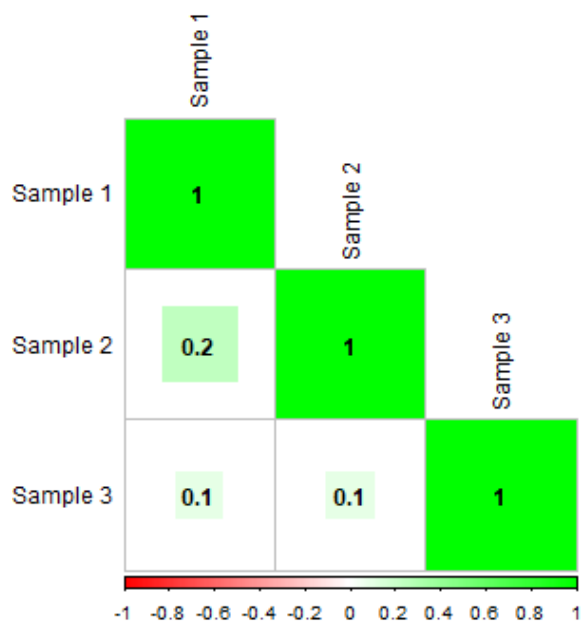
Note: 1st sample was collected between 9th-17th weeks, 2nd sample was collected between 18th-29th weeks, and 3rd sample was collected between the 30th week to prior to delivery



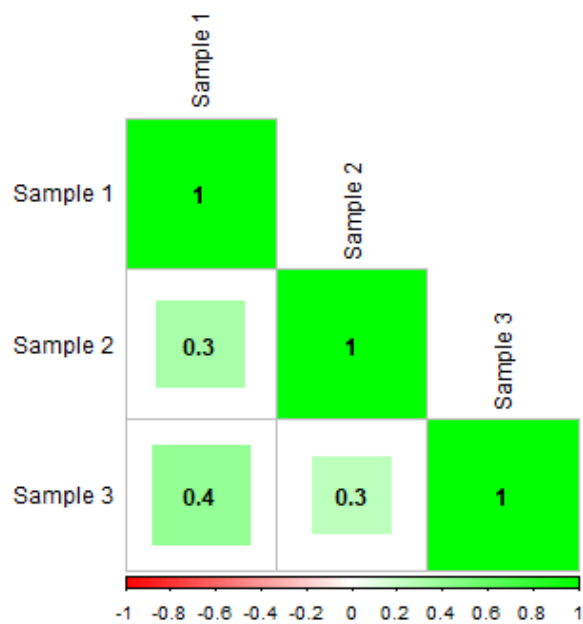
A: 2&3-FLUO



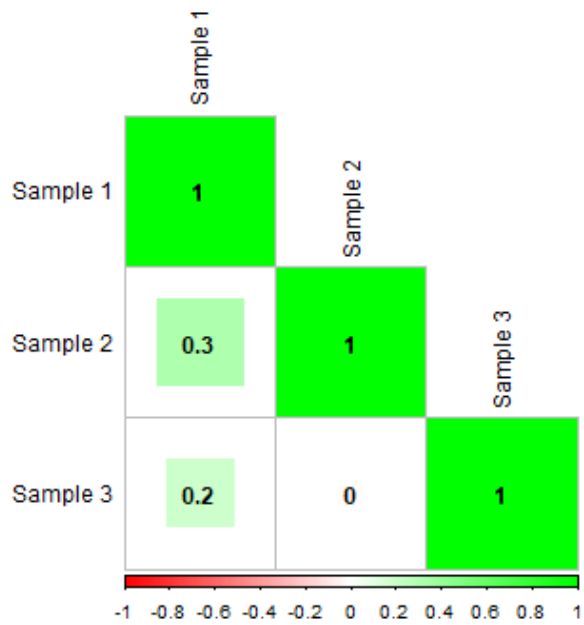
B: 2-NAP



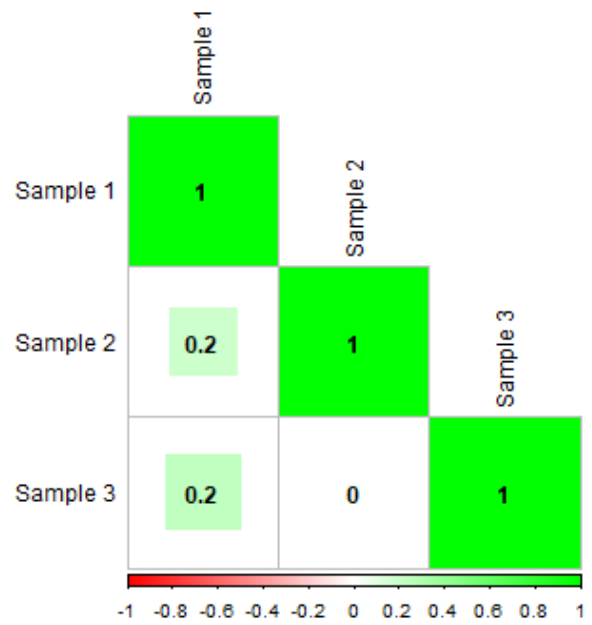
C: 1-PYR



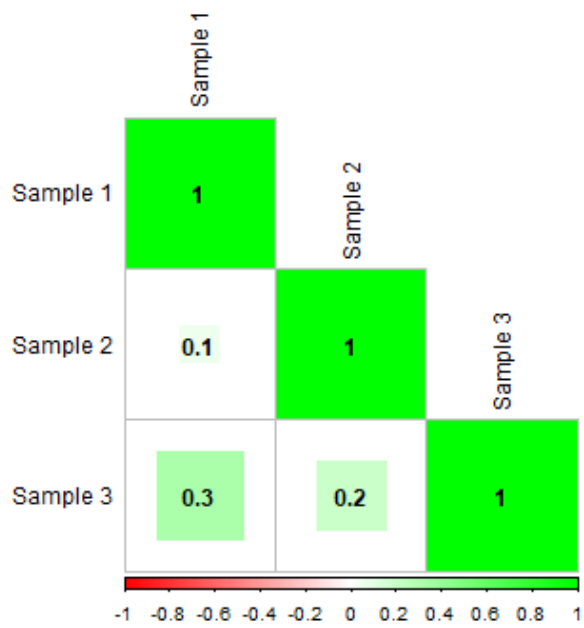
D: 1-PHEN



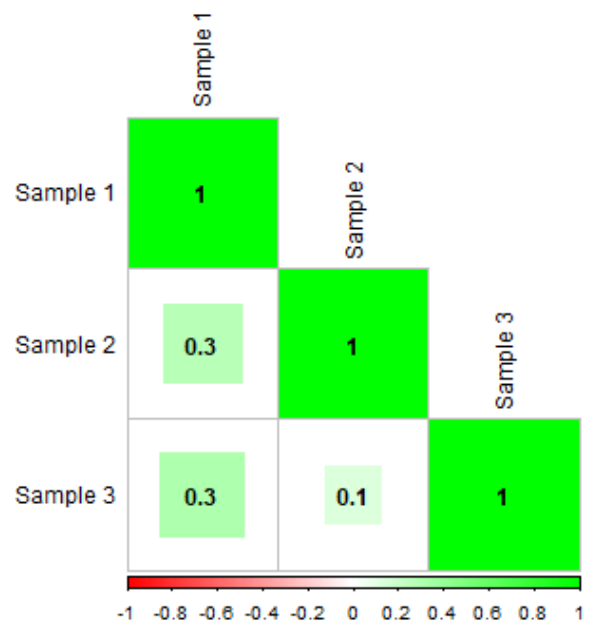
E: 2-PHEN



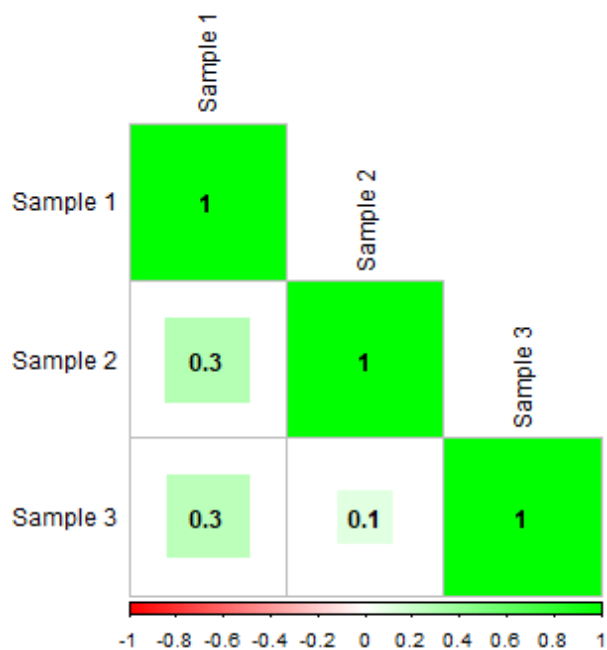
F: 3-PHEN



G: 4-PHEN



H: Σ PHENs



I: PAH index score

Figure S 3-5. Spearman Correlation Coefficients of Specific Gravity-adjusted PAH Biomarker Levels Among Exposure Periods Stratified by Biomarkers

Note: 1st sample was collected between 9th-17th weeks, 2nd sample was collected between 18th-29th weeks, and 3rd sample was collected between the 30th week to prior to delivery

Table S 3-3. Association of PAHs with placental volume (cc) measured between 14th-18th week

	1 st Sample PAH exposure (9 th -17 th week)		
	Overall	Male	Female
	5.24	7.49	0.89
2&3-FLUO	(-1.77, 12.25)	(-1.73, 16.72)	(-9.47, 11.26)
	-0.62	-0.14	0.37
2-NAP	(-12.09, 10.85)	(-17.78, 17.50)	(-13.70, 14.45)
	-1.66	-0.53	0.12
1-PYR	(-9.93, 6.62)	(-13.60, 12.54)	(-9.77, 10.01)
	0.39	0.79	0.55
1-PHEN	(-9.16, 9.95)	(-13.32, 14.90)	(-11.12, 12.22)
	0.24	1.35	-0.36
2-PHEN	(-6.93, 7.41)	(-8.45, 11.14)	(-10.22, 9.51)
	2.08	4.34	-1.44
3-PHEN	(-6.04, 10.21)	(-6.69, 15.35)	(-13.10, 10.22)
	-2.03	-3.66	1.68
4-PHEN	(-11.41, 7.34)	(-17.84, 10.51)	(-9.77, 13.13)
	0.41	1.53	-0.06
ΣPHEN	(-8.55, 9.37)	(-11.42, 14.47)	(-11.48, 11.37)
	0.02	0.46	-0.53
PAH index	(-1.48, 1.52)	(-1.64, 2.55)	(-2.54, 1.48)
	-0.34	1.36	-3.03
PAH mixture	(-8.98, 8.29)	(-10.49, 13.21)	(-16.17, 10.11)

Note: Effect estimates are beta estimates per IQR

Table S 3-4. Association of PAHs with placental volume (cc) measured between 19th-24th week

	1 st Sample PAH exposure (9 th -17 th week)			2 nd Sample PAH exposure (18 th -29 th week)		
	Overall	Male	Female	Overall	Male	Female
2&3-FLUO	5.82 (-4.54, 16.18)	7.01 (-5.48, 19.51)	-2.48 (-22.02, 17.06)	3.93 (-9.22, 17.08)	2.10 (-14.63, 18.83)	5.18 (-17.52, 27.88)
2-NAP	-1.83 (-19.48, 15.82)	14.17 (-10.29, 38.64)	-26.46 (-52.63, 0.29)	-0.58 (-14.26, 13.09)	1.94 (-13.68, 17.56)	-15.09 (-44.53, 14.35)
1-PYR	-6.64 (-19.54, 6.26)	0.55 (-17.10, 18.20)	-19.73 (-39.61, 0.14)	-2.95 (-17.22, 11.31)	5.18 (-14.81, 25.17)	-15.45 (-37.78, 6.89)
1-PHEN	2.35 (-12.60, 17.29)	3.57 (-15.95, 23.09)	-5.66 (-29.73, 18.42)	-0.07 (-16.65, 16.51)	5.14 (-19.54, 29.83)	-9.00 (-33.23, 15.23)
2-PHEN	6.23 (-4.52, 16.98)	8.18 (-4.88, 21.24)	-0.67 (-19.92, 18.58)	8.36 (-5.73, 22.44)	24.20 (5.16, 43.25)	-12.89 (-34.64, 8.86)
3-PHEN	2.24 (-10.21, 14.68)	2.62 (-12.37, 17.61)	-8.29 (-32.91, 16.32)	0.22 (-14.02, 14.45)	1.38 (-18.67, 21.44)	-5.42 (-27.28, 16.43)
4-PHEN	4.21 (-10.79, 19.22)	10.95 (-9.81, 31.71)	-3.99 (-26.43, 18.46)	-5.91 (-22.79, 10.97)	-0.29 (-22.21, 21.62)	-14.67 (-41.99, 12.66)
ΣPHEN	2.03 (-12.04, 16.09)	3.65 (-13.97, 21.27)	-9.25 (-33.73, 15.23)	3.14 (-13.57, 19.85)	10.55 (-12.66, 33.77)	-10.90 (-37.14, 15.34)
PAH index	0.44 (-1.85, 2.73)	1.37 (-1.56, 4.29)	-2.37 (-6.19, 1.46)	0.54 (-1.77, 2.85)	1.83 (-1.29, 4.95)	-1.55 (-5.21, 2.11)
PAH mixture	0.94 (-12.09, 13.96)	9.42 (-6.95, 25.78)	-23.41 (-47.25, 0.43)	1.83 (-11.18, 14.84)	9.97 (-6.22, 26.15)	-11.06 (-33.46, 11.33)

Note: Effect estimates are beta estimates per IQR

Table S 3-5. Association of PAHs with scaled placental volume (cc) measured between 14th-18th week

	1 st Sample PAH exposure (9 th -17 th week)		
	Overall	Male	Female
	4.32	5.41	2.16
2&3-FLUO	(-0.89, 9.53)	(-1.32, 12.14)	(-5.77, 10.08)
	0.27	1.27	0.42
2-NAP	(-8.26, 8.80)	(-11.60, 14.13)	(-10.38, 11.21)
	-0.20	-0.74	2.18
1-PYR	(-6.36, 5.96)	(-10.27, 8.80)	(-5.37, 9.74)
	3.51	3.83	3.43
1-PHEN	(-3.57, 10.59)	(-6.42, 14.08)	(-5.47, 12.32)
	1.35	1.59	1.92
2-PHEN	(-4.01, 6.70)	(-5.60, 8.77)	(-5.63, 9.46)
	2.87	2.69	3.36
3-PHEN	(-3.19, 8.93)	(-5.41, 10.79)	(-5.54, 12.25)
	-1.52	-2.36	0.86
4-PHEN	(-8.49, 5.46)	(-12.70, 7.99)	(-7.92, 9.64)
	2.61	2.54	3.21
ΣPHEN	(-4.08, 9.30)	(-6.95, 12.02)	(-5.50, 11.92)
	0.19	0.27	0.14
PAH index	(-0.93, 1.31)	(-1.27, 1.81)	(-1.41, 1.68)
	0.62	0.23	0.47
PAH mixture	(-5.88, 7.13)	(-8.53, 8.99)	(-9.55, 10.48)

Note: Effect estimates are beta estimates per IQR; scaled placental volume = (placental volume/gestational age at the time of measurement)*100

Table S 3-6. Association of PAHs with scaled placental volume (cc) measured between 19th-24th week

		1 st Sample PAH exposure (9 th -17 th week)		2 nd Sample PAH exposure (18 th -29 th week)		
	Overall	Male	Female	Overall	Male	Female
2&3-FLUO	3.56 (-2.67, 9.80)	4.14 (-3.53, 11.82)	-1.30 (-12.56, 9.96)	1.93 (-6.08, 9.94)	0.75 (-9.73, 11.23)	3.50 (-9.76, 16.76)
2-NAP	-0.54 (-11.16, 10.09)	10.19 (-4.77, 25.15)	-16.02 (-31.02, 1.01)	-2.19 (-10.50, 6.13)	-0.32 (-10.11, 9.46)	-10.68 (-27.80, 6.45)
1-PYR	-3.80 (-11.57, 3.97)	0.86 (-9.97, 11.69)	-12.82 (-24.14, 1.51)	-0.51 (-9.20, 8.18)	6.40 (-6.05, 18.84)	-8.92 (-21.98, 4.14)
1-PHEN	4.27 (-4.69, 13.24)	6.07 (-5.83, 17.97)	-2.29 (-16.17, 11.59)	1.41 (-8.69, 11.50)	4.59 (-10.84, 20.02)	-3.99 (-18.19, 10.21)
2-PHEN	3.99 (-2.54, 10.51)	5.62 (-2.54, 13.78)	-1.19 (-12.27, 9.89)	5.90 (-2.66, 14.46)	14.13 (2.14, 26.13)	-5.37 (-18.17, 7.44)
3-PHEN	1.62 (-5.94, 9.18)	1.38 (-8.01, 10.76)	-3.80 (-18.00, 10.41)	3.41 (-5.24, 12.06)	4.77 (-7.73, 17.27)	-0.19 (-13.00, 12.62)
4-PHEN	3.54 (-5.48, 12.56)	7.40 (-5.31, 20.12)	-1.55 (-14.49, 11.38)	-6.65 (-16.88, 3.58)	-4.35 (-18.03, 9.33)	-9.56 (-25.48, 6.37)
ΣPHEN	2.86 (-5.67, 11.39)	4.08 (-6.91, 15.08)	-4.55 (-18.68, 9.57)	3.14 (-7.03, 13.31)	7.05 (-7.47, 21.57)	-4.16 (-19.56, 11.24)
PAH index	0.34 (-1.05, 1.73)	0.88 (-0.95, 2.71)	-1.34 (-3.54, 0.87)	0.50 (-0.90, 1.90)	1.36 (-0.58, 3.31)	-0.79 (-2.93, 1.36)
PAH mixture	1.56 (-6.47, 9.60)	5.91 (-4.48, 16.30)	-11.61 (-25.60, 2.38)	0.88 (-7.14, 8.90)	6.09 (-4.39, 16.56)	-6.76 (-19.57, 6.05)

Note: Effect estimates are beta estimates per IQR; scaled placental volume = (placental volume/gestational age at the time of measurement)*100

Table S 3-7. Association of PAHs with maternal placental blood flow in the entire placenta (ml/100g/min) measured between 14th-18th week

	1 st Sample PAH exposure (9 th -17 th week)		
	Overall	Male	Female
	2.28	1.98	2.93
2&3-FLUO	(-0.46, 5.02)	(-1.58, 5.55)	(-1.72, 7.58)
	-0.51	0.53	-2.34
2-NAP	(-5.06, 4.05)	(-6.20, 7.26)	(-8.68, 3.99)
	0.82	1.19	-0.45
1-PYR	(-2.39, 4.02)	(-3.74, 6.12)	(-4.86, 3.97)
	0.78	0.90	0.09
1-PHEN	(-3.13, 4.69)	(-4.58, 6.38)	(-5.69, 5.88)
	0.06	0.38	-0.88
2-PHEN	(-2.83, 2.96)	(-3.37, 4.13)	(-5.95, 4.19)
	2.40	2.42	1.85
3-PHEN	(-0.79, 5.58)	(-1.81, 6.64)	(-3.54, 7.24)
	-1.53	1.02	-4.28
4-PHEN	(-5.33, 2.27)	(-4.64, 6.68)	(-9.33, 0.77)
	1.13	1.76	-0.37
ΣPHEN	(-2.44, 4.71)	(-3.22, 6.74)	(-5.75, 5.01)
	0.16	0.33	-0.17
PAH index	(-0.44, 0.76)	(-0.50, 1.16)	(-1.07, 0.73)
	0.25	1.59	-3.23
PAH mixture	(-3.14, 3.64)	(-3.19, 6.37)	(-8.40, 1.94)

Note: Effect estimates are beta estimates per IQR

Table S 3-8. Association of PAHs with maternal placental blood flow in the entire placenta (ml/100g/min) measured between 19th-24th week

	1 st Sample PAH exposure (9 th -17 th week)			2 nd Sample PAH exposure (18 th -29 th week)		
	Overall	Male	Female	Overall	Male	Female
2&3-FLUO	2.12 (-0.52, 4.76)	0.50 (-2.72, 3.72)	6.21 (1.44, 10.98)	2.12 (-0.52, 4.76)	0.50 (-2.72, 3.72)	3.87 (-12.00, 19.73)
2-NAP	4.91 (0.65, 9.16)	5.27 (-0.62, 11.15)	4.60 (-1.86, 11.06)	4.91 (0.65, 9.16)	5.27 (-0.62, 11.15)	0.30 (-15.52, 16.11)
1-PYR	1.03 (-2.07, 4.12)	0.86 (-3.71, 5.44)	2.81 (-1.74, 7.37)	1.03 (-2.07, 4.12)	0.86 (-3.71, 5.44)	6.69 (-9.87, 23.25)
1-PHEN	2.31 (-1.44, 6.05)	0.91 (-3.95, 5.77)	4.15 (-1.93, 10.24)	2.31 (-1.44, 6.05)	0.91 (-3.95, 5.77)	-4.62 (-21.72, 12.47)
2-PHEN	1.70 (-1.14, 4.54)	-0.02 (-3.43, 3.39)	5.96 (0.59, 11.34)	1.70 (-1.14, 4.54)	-0.02 (-3.43, 3.39)	1.94 (-14.80, 18.69)
3-PHEN	2.81 (-0.29, 5.90)	2.02 (-1.88, 5.91)	5.46 (-0.08, 11.00)	2.81 (-0.29, 5.90)	2.02 (-1.88, 5.91)	0.49 (-15.53, 16.51)
4-PHEN	0.65 (-2.92, 4.22)	-0.02 (-4.93, 4.90)	2.11 (-3.36, 7.57)	0.65 (-2.92, 4.22)	-0.02 (-4.93, 4.90)	3.46 (-15.83, 22.76)
ΣPHEN	2.73 (-0.75, 6.22)	1.65 (-2.92, 6.21)	4.83 (-0.84, 10.50)	2.73 (-0.75, 6.22)	1.65 (-2.92, 6.21)	-3.64 (-22.66, 15.38)
PAH index	0.44 (-0.13, 1.01)	0.23 (-0.52, 0.97)	0.77 (-0.16, 1.69)	0.44 (-0.13, 1.01)	0.23 (-0.52, 0.97)	0.37 (-2.28, 3.02)
PAH mixture	3.20 (-0.09, 6.48)	1.84 (-1.81, 5.49)	4.13 (-1.68, 9.95)	2.81 (-4.16, 9.77)	-0.86 (-5.79, 4.08)	4.68 (-10.50, 19.86)

Note: Effect estimates are beta estimates per IQR

Table S 3-9. Association of PAHs with placental blood flow in areas of maternal high placental blood flow (ml/100g/min) measured between 14th-18th week

	1 st Sample PAH exposure (9 th -17 th week)		
	Overall	Male	Female
	9.30	8.75	10.72
2&3-FLUO	(-3.80, 22.40)	(-8.93, 26.43)	(-9.34, 30.78)
	-2.13	3.47	-12.53
2-NAP	(-23.87, 19.60)	(-29.90, 36.83)	(-39.66, 14.59)
	3.70	5.31	3.36
1-PYR	(-11.59, 18.98)	(-19.13, 29.74)	(-15.59, 22.31)
	3.01	-1.30	6.77
1-PHEN	(-15.66, 21.67)	(-28.47, 25.88)	(-18.00, 31.54)
	0.64	-1.05	3.96
2-PHEN	(-13.18, 14.46)	(-19.64, 17.54)	(-17.79, 25.71)
	10.42	9.11	13.34
3-PHEN	(-4.79, 25.62)	(-11.93, 30.14)	(-9.59, 36.27)
	-10.13	-1.59	-17.70
4-PHEN	(-28.21, 7.95)	(-29.64, 26.46)	(-39.43, 4.03)
	3.70	2.01	5.26
ΣPHEN	(-13.37, 20.76)	(-22.76, 26.77)	(-17.81, 28.32)
	0.60	1.09	-0.42
PAH index	(-2.25, 3.45)	(-3.03, 5.21)	(-4.30, 3.45)
	0.43	6.39	-10.27
PAH mixture	(-15.84, 16.71)	(-17.15, 29.93)	(-33.77, 13.24)

Note: Effect estimates are beta estimates per IQR

Table S 3-10. Association of PAHs with placental blood flow in areas of maternal high placental blood flow (ml/100g/min) measured between 19th-24th week

	1 st Sample PAH exposure (9 th -17 th week)			2 nd Sample PAH exposure (18 th -29 th week)		
	Overall	Male	Female	Overall	Male	Female
2&3-FLUO	2.28 (-15.85, 20.41)	-0.07 (-26.94, 26.79)	12.18 (-8.74, 33.09)	4.39 (-23.29, 32.07)	-6.61 (-49.41, 36.20)	17.42 (-17.38, 52.23)
2-NAP	1.84 (-27.71, 31.39)	-4.31 (-54.61, 45.99)	12.43 (-14.74, 39.60)	6.87 (-17.18, 30.92)	10.83 (-22.81, 44.47)	-4.40 (-39.37, 30.56)
1-PYR	-5.74 (-26.76, 15.29)	-7.99 (-46.14, 30.15)	4.07 (-15.13, 23.27)	-6.16 (-35.33, 23.01)	-46.07 (-94.06, 1.91)	28.66 (-7.24, 64.56)
1-PHEN	-8.40 (-33.96, 17.16)	-16.59 (-56.93, 23.75)	5.72 (-19.99, 31.42)	-11.58 (-41.95, 18.78)	-34.29 (-82.73, 14.15)	6.29 (-31.60, 44.18)
2-PHEN	-7.20 (-26.56, 12.17)	-11.64 (-39.89, 16.61)	8.20 (-15.17, 31.56)	5.19 (-22.96, 33.35)	-9.64 (-55.33, 36.06)	16.15 (-20.60, 52.90)
3-PHEN	1.09 (-20.22, 22.40)	2.78 (-29.93, 35.49)	6.00 (-17.90, 29.89)	2.20 (-25.39, 29.78)	-12.42 (-56.80, 31.95)	15.49 (-19.64, 50.62)
4-PHEN	-23.70 (-47.57, 0.18)	-41.48 (-81.18, 1.77)	-3.25 (-26.08, 19.58)	5.59 (-26.85, 38.03)	-2.78 (-53.40, 47.85)	7.34 (-35.35, 50.02)
ΣPHEN	-7.10 (-30.97, 16.77)	-12.56 (-50.60, 25.48)	5.98 (-18.23, 30.18)	-8.72 (-40.11, 22.68)	-29.14 (-77.78, 19.51)	8.15 (-33.92, 50.23)
PAH index	-1.79 (-5.66, 2.08)	-2.75 (-8.90, 3.40)	0.20 (-3.76, 4.15)	-0.43 (-4.99, 4.13)	-3.41 (-10.39, 3.59)	2.55 (-3.27, 8.37)
PAH mixture	-7.98 (-30.35, 14.40)	-11.15 (-44.98, 22.68)	-2.02 (-27.13, 23.09)	1.04 (-24.99, 27.07)	-14.51 (-53.75, 24.73)	16.27 (-16.84, 49.39)

Note: Effect estimates are beta estimates per IQR

Table S 3-11. Association of PAHs with placental deoxygenation in the placenta measured between 14th-18th week

	1 st Sample PAH exposure (9 th -17 th week)		
	Overall	Male	Female
	-0.40	-0.55	-0.08
2&3-FLUO	(-1.10, 0.30)	(-1.39, 0.28)	(-1.46, 1.30)
	0.88	0.39	1.92
2-NAP	(-0.37, 2.12)	(-1.19, 1.98)	(-0.34, 4.17)
	-0.12	-0.72	0.47
1-PYR	(-0.93, 0.68)	(-1.83, 0.39)	(-0.82, 1.75)
	0.05	-0.14	0.39
1-PHEN	(-0.93, 1.03)	(-1.41, 1.12)	(-1.31, 2.09)
	-0.05	-0.17	0.29
2-PHEN	(-0.77, 0.68)	(-1.03, 0.68)	(-1.20, 1.79)
	-0.42	-0.72	0.22
3-PHEN	(-1.22, 0.39)	(-1.67, 0.24)	(-1.38, 1.82)
	-0.70	-0.58	-0.89
4-PHEN	(-1.67, 0.28)	(-1.92, 0.76)	(-2.43, 0.65)
	-0.19	-0.47	0.26
ΣPHEN	(-1.08, 0.71)	(-1.61, 0.67)	(-1.32, 1.83)
	-0.04	-0.09	0.03
PAH index	(-0.20, 0.11)	(-0.29, 0.10)	(-0.24, 0.31)
	-0.34	-0.50	-0.18
PAH mixture	(-1.18, 0.50)	(-1.58, 0.57)	(-1.84, 1.48)

Note: Effect estimates are beta estimates per IQR

Table S 3-12. Association of PAHs with placental deoxygenation in the placenta measured between 19th-24th week

	1 st Sample PAH exposure (9 th -17 th week)			2 nd Sample PAH exposure (18 th -29 th week)		
	Overall	Male	Female	Overall	Male	Female
2&3-FLUO	-0.07 (-0.74, 0.61)	-0.52 (-1.25, 0.22)	0.71 (-0.78, 2.19)	0.36 (-0.59, 1.31)	0.19 (-1.05, 1.44)	0.33 (-1.28, 1.93)
2-NAP	-0.23 (-1.41, 0.96)	-0.86 (-2.32, 0.60)	0.66 (-1.61, 2.92)	0.10 (-0.75, 0.95)	0.37 (-0.65, 1.39)	-0.48 (-2.02, 1.06)
1-PYR	0.12 (-0.66, 0.90)	-0.29 (-1.36, 0.79)	0.34 (-1.00, 1.68)	1.08 (0.06, 2.09)	1.82 (0.42, 3.22)	-0.17 (-1.98, 1.64)
1-PHEN	-0.40 (-1.33, 0.52)	-0.61 (-1.71, 0.49)	-0.38 (-2.10, 1.34)	0.47 (-0.59, 1.53)	0.53 (-0.87, 1.94)	0.31 (-1.55, 2.16)
2-PHEN	-0.61 (-1.30, 0.07)	-0.73 (-1.50, 0.03)	-0.68 (-2.10, 0.74)	-0.13 (-1.08, 0.82)	0.20 (-1.10, 1.49)	-0.96 (-2.56, 0.63)
3-PHEN	-0.01 (-0.81, 0.78)	-0.41 (-1.30, 0.47)	0.50 (-1.24, 2.24)	0.42 (-0.53, 1.37)	0.88 (-0.41, 2.16)	-0.28 (-1.89, 1.33)
4-PHEN	-0.51 (-1.41, 0.39)	-0.75 (-1.86, 0.35)	-0.63 (-2.30, 1.04)	-0.15 (-1.31, 1.00)	0.06 (-1.59, 1.71)	-1.06 (-2.83, 0.71)
ΣPHEN	-0.23 (-1.12, 0.65)	-0.46 (-1.50, 0.58)	-0.25 (-1.97, 1.47)	0.43 (-0.66, 1.52)	0.60 (-0.81, 2.01)	-0.21 (-2.27, 1.85)
PAH index	-0.01 (-0.16, 0.14)	-0.06 (-0.24, 0.12)	0.03 (-0.27, 0.33)	0.10 (-0.06, 0.26)	0.15 (-0.06, 0.36)	-0.03 (-0.32, 0.25)
PAH mixture	-0.28 (-1.17, 0.61)	-0.72 (-1.76, 0.33)	-0.22 (-2.17, 1.73)	0.62 (-0.31, 1.54)	0.98 (-0.24, 2.21)	-0.05 (-1.76, 1.66)

Note: Effect estimates are beta estimates per IQR

Table S 3-13. Association of PAHs with placental weight at birth (g)

	1 st Sample PAH exposure (9 th -17 th week)			2 nd Sample PAH exposure (18 th -29 th week)			3 rd Sample PAH exposure (30 th week-delivery)		
	Overall	Male	Female	Overall	Male	Female	Overall	Male	Female
2&3-FLUO	-3.52 (-14.45, 7.40)	-5.99 (-18.29, 6.32)	4.04 (-18.27, 26.36)	-8.78 (-23.27, 5.71)	-12.98 (-30.34, 4.39)	-2.66 (-29.05, 23.74)	-3.66 (-17.06, 9.73)	-9.47 (-25.77, 6.84)	8.16 (-17.25, 33.58)
2-NAP	-15.34 (-33.22, 2.54)	-9.05 (-31.45, 13.35)	-30.62 (-61.75, 0.50)	-6.98 (-20.38, 6.42)	-4.82 (-20.42, 10.78)	-12.82 (-37.84, 12.20)	-7.25 (-26.09, 11.58)	2.35 (-20.86, 25.56)	-26.44 (-59.62, 6.74)
1-PYR	-13.73 (-26.55, 0.91)	-17.45 (-34.00, 0.90)	-8.32 (-30.18, 13.54)	-11.01 (-26.93, 4.91)	-18.07 (-38.28, 2.13)	-1.08 (-28.17, 26.01)	0.22 (-11.93, 12.37)	-1.47 (-15.74, 12.80)	5.13 (-18.48, 28.74)
1-PHEN	-4.11 (-19.11, 10.89)	-6.65 (-25.42, 12.12)	1.92 (-23.45, 27.30)	-9.29 (-27.68, 9.09)	-22.07 (-44.46, 0.33)	4.21 (-27.67, 36.09)	-0.72 (-13.30, 11.86)	-3.78 (-19.80, 12.24)	4.46 (-17.60, 26.51)
2-PHEN	-2.27 (-13.42, 8.88)	-1.17 (-14.06, 11.73)	-4.32 (-26.19, 17.56)	1.11 (-14.50, 16.72)	-0.57 (-21.04, 19.89)	6.11 (-19.68, 31.91)	-1.28 (-13.40, 10.84)	-0.63 (-15.62, 14.36)	-0.46 (-26.08, 25.17)
3-PHEN	-4.86 (-16.95, 7.22)	-6.48 (-20.72, 7.77)	1.16 (-22.42, 24.74)	-3.25 (-18.77, 12.27)	-19.37 (-39.26, 0.53)	14.28 (-10.69, 39.25)	-0.55 (-12.70, 11.59)	-3.65 (-19.04, 11.74)	3.05 (-20.12, 26.22)
4-PHEN	-12.35 (-27.80, 3.09)	-4.57 (-25.49, 16.36)	-14.16 (-38.20, 9.88)	-12.07 (-30.38, 6.23)	-4.78 (-27.18, 17.63)	-16.71 (-48.41, 14.99)	-10.84 (-25.39, 3.71)	-2.58 (-20.29, 15.13)	-26.73 (-56.34, 2.87)
ΣPHEN	-5.45 (-19.04, 8.14)	-6.45 (-23.43, 10.52)	-1.31 (-24.66, 22.05)	-9.78 (-27.92, 8.36)	-18.98 (-41.25, 3.30)	1.90 (-29.93, 33.73)	-0.49 (-12.92, 11.95)	-2.10 (-17.81, 13.60)	3.74 (-20.06, 27.54)
PAH index	-1.07 (-3.35, 1.21)	-0.92 (-3.73, 1.88)	-0.95 (-5.00, 3.10)	-1.29 (-3.77, 1.19)	-1.71 (-4.83, 1.41)	-0.53 (-4.74, 3.69)	-0.02 (-2.71, 2.68)	-0.19 (-3.51, 3.13)	0.77 (-4.34, 5.88)
PAH mixture	-10.40 (-23.32, 2.52)	-6.46 (-21.65, 8.73)	-17.80 (-41.74, 6.13)	-12.09 (-26.37, 2.20)	-6.75 (-24.33, 10.84)	-14.95 (-39.31, 9.40)	-9.20 (-25.95, 7.55)	-2.02 (-23.36, 19.33)	-14.77 (-52.12, 22.58)

Note: Effect estimates are beta estimates per IQR

Table S 3-14. Association of PAHs with birth weight (g)

	1 st Sample PAH exposure (9 th -17 th week)			2 nd Sample PAH exposure (18 th -29 th week)			3 rd Sample PAH exposure (30 th week-delivery)		
	Overall	Male	Female	Overall	Male	Female	Overall	Male	Female
2&3-FLUO	-29.06 (-79.63, 21.51)	-50.14 (-107.74, 7.45)	21.57 (-74.75, 117.88)	-22.10 (-88.34, 44.15)	-36.60 (-115.69, 42.48)	15.43 (-105.50, 136.35)	-11.66 (-77.43, 54.11)	-27.45 (-107.36, 52.46)	-17.52 (-139.39, 104.36)
2-NAP	-91.05 (-171.38, -10.72)	-54.10 (-160.70, 52.49)	-148.24 (-278.16, 18.33)	-33.51 (-95.34, 28.32)	-32.87 (-105.17, 39.43)	-41.08 (-157.45, 75.28)	-2.89 (-93.98, 88.20)	-3.87 (-117.80, 110.06)	-34.48 (-190.27, 121.31)
1-PYR	-87.16 (-144.74, -29.58)	-74.34 (-154.14, 5.47)	-104.76 (-192.55, 16.98)	-63.57 (-134.99, 7.85)	-130.01 (-218.27, -41.76)	39.68 (-82.30, 161.65)	7.06 (-52.75, 66.88)	-24.45 (-94.15, 45.25)	44.80 (-66.96, 156.55)
1-PHEN	-50.03 (-119.70, 19.63)	-38.38 (-127.94, 51.19)	-59.27 (-168.78, 50.25)	-28.14 (-106.52, 50.24)	-83.69 (-182.88, 15.51)	24.37 (-105.80, 154.54)	2.89 (-58.41, 64.19)	9.63 (-69.27, 88.53)	-34.42 (-135.90, 67.06)
2-PHEN	-47.18 (-98.42, 4.06)	-18.84 (-81.13, 43.45)	-87.55 (-174.60, 0.49)	-26.45 (-96.77, 43.86)	-51.00 (-140.00, 38.01)	-5.29 (-125.77, 115.19)	20.22 (-36.70, 77.13)	-4.23 (-77.79, 69.32)	24.16 (-83.22, 131.54)
3-PHEN	-34.63 (-92.55, 23.29)	-41.37 (-109.68, 26.95)	-18.56 (-128.30, 91.17)	-18.64 (-88.43, 51.14)	-84.15 (-170.68, 2.39)	62.57 (-53.98, 179.12)	5.09 (-52.36, 62.54)	-22.59 (-97.94, 52.76)	-0.11 (-99.73, 99.51)
4-PHEN	-66.25 (-134.93, 2.43)	-42.12 (-134.45, 50.20)	-77.81 (-183.16, 27.54)	-75.99 (-158.42, 6.44)	-64.37 (-166.37, 37.63)	-75.72 (-217.39, 65.94)	-17.02 (-88.94, 54.91)	-5.87 (-93.16, 81.43)	-86.12 (-227.35, 55.11)
ΣPHEN	-54.81 (-119.18, 9.55)	-45.02 (-126.48, 36.44)	-63.47 (-168.90, 41.95)	-35.51 (-115.09, 44.07)	-88.69 (-184.78, 7.41)	35.94 (-105.64, 177.52)	1.66 (-59.24, 62.55)	-1.70 (-78.80, 75.39)	-40.91 (-151.14, 69.32)
PAH index	-11.21 (-21.95, 0.48)	-8.87 (-22.30, 4.57)	-15.30 (-33.53, 2.94)	-6.76 (-18.03, 4.52)	-12.92 (-26.97, 1.12)	2.19 (-17.35, 21.73)	-1.02 (-14.15, 12.12)	-6.48 (-22.40, 9.44)	-0.16 (-24.55, 24.22)
PAH mixture	-79.50 (-141.15, -17.85)	-52.86 (-130.03, 24.31)	-106.10 (-206.31, 5.89)	-51.26 (-116.47, 13.94)	-68.42 (-151.04, 14.20)	-16.41 (-131.53, 98.71)	-39.12 (-122.95, 44.70)	-18.74 (-126.53, 89.06)	-106.29 (-298.22, 85.64)

Note: Effect estimates are beta estimates per IQR

Table S 3-15. Association of PAHs with preeclampsia and gestational hypertension

	1 st Sample PAH exposure (9 th -17 th week)		
	Overall	Male	Female
2&3-FLUO	1.16 (0.84, 1.61)	1.06 (0.72, 1.57)	1.49 (0.80, 2.79)
2-NAP	1.24 (0.71, 2.16)	1.55 (0.73, 3.32)	1.02 (0.40, 2.65)
1-PYR	1.18 (0.81, 1.74)	1.04 (0.60, 1.80)	1.27 (0.69, 2.33)
1-PHEN	1.53 (0.96, 2.46)	1.32 (0.72, 2.41)	1.99 (0.87, 4.56)
2-PHEN	1.40 (0.98, 1.99)	1.24 (0.82, 1.89)	1.84 (0.95, 3.56)
3-PHEN	1.35 (0.94, 1.96)	1.26 (0.79, 1.99)	1.58 (0.81, 3.08)
4-PHEN	1.41 (0.84, 2.37)	1.17 (0.59, 2.31)	1.67 (0.69, 3.99)
ΣPHEN	1.47 (0.98, 2.23)	1.29 (0.76, 2.20)	1.84 (0.89, 3.79)
PAH index	1.04 (0.97, 1.12)	1.04 (0.95, 1.14)	1.06 (0.94, 1.19)
PAH mixture	1.28 (0.84, 1.95)	1.42 (0.83, 2.44)	1.68 (0.75, 3.75)

Note: Effect estimates are OR per IQR

4. AIM 3: Association of Criteria Air Pollutants and Air Toxics on Cardiometabolic Health in Older Mexican Americans in the SALSA Cohort

4.1. Abstract

Air pollutants, particularly PM_{2.5}, have shown associations with cardiometabolic health. However, studies on particulate matter components and volatile organic compounds are lacking. Further, vulnerable populations like the elderly and racial/ethnic groups who experience higher pollution levels are not well studied. Here we investigated the impact of such pollutants on the cardiometabolic health of older Mexican Americans.

We analyzed data from participants in the Sacramento Area Latino Study on Aging (SALSA, n=1789) from 1998 to 2007. Land use regression was used to estimate exposure to criteria air pollutants (NO₂, PM_{2.5}, and O₃) and air toxics (benzene, 1,3-butadiene, chromium, lead, nickel, and zinc). Cox proportional hazards regression was used to estimate hazards ratios (HR) for the impact of per inter-quartile range (IQR) increase in pollutants on hypertension, low HDL cholesterol, hypertriglyceridemia, cardiovascular disease, and stroke. Time-varying pollutant exposure averages were calculated over 1-, 5- and 10-years prior to the event. Quantile g-computation was used to estimate traffic-related multipollutant mixtures effects.

The risk of developing hypertension increased with NO₂, PM_{2.5}, and nickel exposures by 24% (95% CI: 1.00, 1.55), 28% (95% CI: 0.93, 1.76), and 59% (95% CI: 0.99, 2.56) respectively and with the traffic pollution mixture exposure (HR: 1.23, 95% CI: 0.99, 2.68). Low HDL cholesterol was associated with NO₂ (HR: 1.20, 95% CI: 0.99, 1.45), PM_{2.5} (HR: 1.39, 95% CI: 1.01, 1.91), and nickel exposures (HR: 1.76, 95% CI: 1.05, 2.94). NO₂, PM_{2.5}, nickel, and the traffic-related pollutant mixture were associated with an increased risk of hypertriglyceridemia,

ranging from 10% to 68%, and with CVD and stroke, ranging from 7% to 68%. Benzene was also associated with CVD and stroke. However, the confidence intervals for these associations were wide and included the null.

Traffic-related particles and volatile compounds represented by PM_{2.5}, NO₂, nickel, and benzene adversely affect cardiometabolic outcomes in older Mexican Americans, calling for air pollution reduction policies targeting both exhaust and non-tailpipe traffic related pollutants.

4.2. Introduction

Stroke and ischaemic heart disease are the leading causes of death in upper-middle-income and high-income countries¹⁴¹. These cardiovascular events can result from impaired lipid metabolism manifesting as low HDL cholesterol and hypertriglyceridemia, which in turn is influenced by impaired glucose metabolism^{142–144}. Defective glucose metabolism may also lead to hypertension, another major risk for heart disease¹⁴⁵. The cardiovascular system is therefore closely interconnected with glucose and lipid metabolism. A study National Health and Nutrition Examination Survey data (n=55,081). found a worsening trend of cardiometabolic health in the US from 1999 to 2018 with only 6.8% of the population having optimal cardiometabolic health at the end of the study period¹¹. The high prevalence of poor cardiometabolic health warrants investigations into modifiable risk factors associated with all of these conditions.

Prior literature has linked PM_{2.5} and NO₂ with cardiovascular outcomes and related risk factors such as insulin resistance, diabetes, hypertension, CVD, and stroke^{5–8}. Ambient air pollution has also been found to alter lipid profiles. A recent meta-analysis reporting positive associations of particulate matter and NO₂ with high triglyceride levels¹⁴⁶ and negative associations between PM_{2.5} and HDL-cholesterol (“good cholesterol”) levels¹⁴⁷. However, the

effect of specific components of PM_{2.5}, such as metals, or of volatile organic compounds (VOCs) remains to be researched^{5,148}. Another review stated that there is a need for assessing the impact of long-term exposure to air pollution on CVD¹⁴⁹ while an umbrella review pinpointed the need for studying multi-pollutant mixtures¹⁴⁸.

Further, special attention needs to be given to vulnerable populations in order to inform targeted public health policies. Hispanic populations in the US are disproportionately exposed to higher levels of air pollutants such as PM_{2.5} and NO₂^{12–14,150,151}. Moreover, a US-wide study found that a much smaller proportion of Mexican Americans had optimal cardiometabolic health (3.2%) as compared to non-Hispanic Whites (8.4%) highlighting important socioeconomic disparities. In addition, an umbrella review noted that older populations were more susceptible to the effect of air pollution on their cardiovascular health.¹⁴⁸ In this study, we used high resolution air pollution surfaces for criteria air pollutants (PM_{2.5}, NO₂, and O₃) as well as understudied air toxics (1,3-butadiene, benzene, nickel, lead, and chromium) to study the associations of long-term exposure to individual pollutants and pollutant mixtures with cardiometabolic health outcomes. The outcomes included hypertension, low HDL cholesterol, hypertriglyceridemia, cardiovascular disease (CVD), and stroke. Our study was conducted among older Mexican Americans enrolled in the Sacramento Area Latino Study on Aging (SALSA), a population that experiences dual compounded vulnerability due to their age and socioeconomic disadvantage.

4.3. Methods

4.3.1. Study Population

Our study population consists of participants enrolled in SALSA¹⁵², a longitudinal cohort of older Mexican Americans residing in the Sacramento Valley area from 1998 to 2007. Participants were recruited from the Sacramento metropolitan area and surrounding suburban and

rural counties via mail, telephone, and door-to-door neighborhood enumeration^{153,154}. Participants were eligible if they were (i) 60 years or older; (ii) lived in the six counties of the Sacramento Valley; (iii) self-identified as Latino, Mexican, Central American, or Mexican American; (iv) spoke Spanish or English; and (v) were living in a non-institutionalized setting. The participation rate was 85% among those who were contacted and 1,789 participants were enrolled at baseline. Interviews were conducted at baseline and during follow-up visits every 12-15 months. A maximum of six follow-up visits were completed. On average, annually 2.6% of participants died and 2.3% were lost to follow-up. We excluded those who either had no interview at baseline (n=3). Further for outcome-specific analysis, we excluded those who already had the respective outcome at baseline or for whom the baseline outcome status was unknown and if the participants did not have any of the follow-up visits (Figure S 4-1).

This study was approved by the Institutional Review Boards of the Universities of California, San Francisco, Los Angeles, and Davis; the University of North Carolina; and the University of Michigan. All participants provided written informed consent.

4.3.2. Exposure Assessment

4.3.2.1. Criteria Air Pollutant Surface Generation

We used land use regression (LUR) models with a deletion/substitution/addition machine learning algorithm^{3,4}, to generate daily concentration surfaces of PM_{2.5}, NO₂ and O₃ in California at high-resolution (100 m) for 1989-2007. A detailed description of the methods has been published previously¹⁵⁵. Briefly, air pollution measurement data for these pollutants were obtained from Environmental Protection Agency (EPA) regulatory monitors, fixed-site saturation monitoring, and Google-streetcar measurements. For PM_{2.5}, the daily EPA regulatory monitoring began in 1999 while for NO₂ and O₃ it began in 1990. The predictors included in our modelling process were

daily traffic data from 12 Caltrans districts, land use and land cover, vegetation index, topography, distance to highways, major roadways, coast, ports and remote sensing data for aerosol optical depth (AOD), NO₂, and O₃. The daily LUR models for NO₂, PM_{2.5}, and O₃, were constructed based on available existing data for both the predictors and the air quality monitoring measures. For some predictors (traffic, vegetation index, and remote sensing data) actual observations were not available in the earliest years, so we used regression techniques to extend the predictor data back to 1989. No algorithms of temporal extensions to the predictors were applied during the air pollution surface modeling process. The modeling results, however, were applied to all predictors across all years to predict daily NO₂, PM_{2.5} and O₃ concentrations across the entire study period, and these were averaged to generate annual average concentrations. The adjusted R² values for the PM_{2.5}, NO₂ and O₃ LUR models were 0.65, 0.84, and 0.93 respectively.

4.3.2.2. Air Toxics Surface Generation

Machine learning integrated LUR models, similar to those used for criteria air pollutants were used to create 100m resolution surfaces for air toxics including chromium, lead and nickel and the volatile organic compounds (VOCs) benzene and 1,3-butadiene. The air toxics measurements were available from 1996 to 2007 and were obtained from the California Air Resources Board (CARB)'s speciation data and emission estimates from the California Toxics Inventory (CTI). These data cover stationary sources, including point sources reported by facility operators or air districts under the Air Toxics "Hot Spots" Program and aggregated point sources estimated by CARB and local air districts. Further, total organic gases (TOG) and reactive organic gases (ROG) data from CARB's emissions inventory and data on traffic, land use and land cover, vegetation index, distance to ports, and remote sensing Sentinel-2 spectral bands and their ratios to account for the spatial distribution of surface characteristics such as land cover, vegetation, and

urbanization, served as predictors. For periods lacking measured predictor data, these were extrapolated back to 1989 using regression-based methods. The adjusted R^2 values for the LUR models were 0.81 for benzene, 0.62 for 1,3-butadiene, 0.76 for chromium, 0.59 for lead, and 0.70 for nickel.

Residential addresses were collected at the baseline interview and geocoded using global positioning system (GPS) readings obtained during home visits, ensuring high geolocation accuracy. For each pollutant, concentrations at the geocoded addresses were extracted from the LUR surfaces, with daily estimates for criteria air pollutants and annual estimates for air toxics. Annual averages were calculated for the criteria air pollutants using the daily values to be consistent with the air toxic measures.

4.3.3. Outcome Assessment

At baseline and each follow-up visit, systolic and diastolic blood pressure measurements were made with an automatic digital blood pressure monitor while the participant was seated and 2 measurements taken within a 5-minute interval were averaged^{156,157}. Hypertension was based on measured systolic blood pressure (≥ 140 mm Hg), diastolic blood pressure (≥ 90 mm Hg) and/or use of antihypertensive medication. Fasting blood draws were performed at baseline and most follow-up visits to measure lipid, triglyceride, and other biomarkers. Based on NCEP ATP III guidelines¹⁵⁸, low high-density lipoprotein (HDL) cholesterol was defined as <40 mg/dL for men and <50 mg/dL for women or use of statins, and hypertriglyceridemia was defined as elevated triglycerides (≥ 150 mg/dL) or use of statins. CVD events were ascertained by self-report at each visit; that is, participants were asked whether a physician had diagnosed any of the following: myocardial infarction, angina, catheterization or coronary artery bypass grafting, stroke, heart

failure, or atrial fibrillation. Stroke was also ascertained using self-report of physician's diagnosis¹⁵³.

4.3.4. Covariate Assessment

Demographic information including age, sex, monthly household income, years of education, longest held occupation during the lifetime, smoking status and alcohol consumption were collected at baseline. The outdoor leisure-time physical activity variable was computed based on seven physical activities (doing yardwork, taking walks, swimming or working out, dancing, hunting or camping or boating, golf or other moderate exercise games, walking around the neighborhood) that are likely to be performed outdoors. A metabolic equivalents of task (MET) value based on the Compendium of Physical Activities¹⁵⁹, was calculated for each activity. The MET value was multiplied by the reported time (hours/week) spent performing the activity. MET-hours/week values for all activities were added up to calculate a cumulative outdoor physical activity value, which was then categorized as a binary variable with the cutoff point of 74.5 MET-hours/week.

Based on residential address and US Department of Agriculture's Rural-Urban Commuting Area (RUCA) codes for the year 2000¹⁶⁰, subjects were classified as living in either rural or urban areas. Further, for each subject, an area-level socio-economic status (SES) variable is represented as a score ranging from 1 to 5 (low to high) depending on six 2000 U.S. Census estimates: percentage of a) individuals ≥ 25 years of age without a high school diploma; b) individuals below the poverty limit; c) individuals ≥ 16 years of age who had been in the workforce at one time but are unemployed; d) households owning their home; e) vacant housing units; and f) median number of rooms in a household³⁶. To avoid non-convergence of regression models, the 4th and 5th quintiles were grouped together. Finally, a 24-hr average noise exposure was estimated at each residential

address using the Federal Highway Administration (FHWA) Traffic Noise Model in the SoundPLAN (version 8.0; NAVCON, Fullerton, CA, USA) software package, which is implemented with the Federal Highway Administration Traffic Noise Model that uses annual average daily traffic data from Metropolitan Planning Organizations. More details have been described elsewhere¹⁶¹.

4.3.5. Statistical Analysis

We used Cox proportional hazards regression models with calendar time as the scale to estimate the association of the eight air pollutants on incident hypertension, low HDL cholesterol, hypertriglyceridemia, cardiovascular disease, and stroke. We estimated hazard ratios (HR) per inter-quartile range (IQR) increase in air pollutant concentration. IQR values are provided in Table S 4-1A and B. For each outcome, participants were censored when they developed the particular outcome, at their last date of contact if they were lost to follow-up, or the date of death if they passed away before the end of the study in 2007. Exposure to recent air pollution was calculated in a time-varying manner by averaging over 1-, 5- and 10-calendar years prior to the occurrence of an outcome event. Thus, for each year, the reference category consisted of everyone in the risk set without the outcome. As some of these outcomes were already commonly prevalent in these elderly subjects at enrolment, we also evaluated association between the prevalence of all cardiometabolic health outcomes at baseline and all 1-,5-,10-year average exposures to these pollutants at baseline in a cross-sectional manner. Based on a directed acyclic graph (DAG) drawn *a priori* using DAGitty web application¹⁶², as shown in Error! Reference source not found. we adjusted for baseline age (continuous), gender (male/female), years of education (continuous), area-level SES (4 levels ranging from low SES to middle-high or high SES), monthly household income (5 levels ranging from less than \$1000 to \$2500 or more), and urbanicity based on RUCA

codes (urban/rural). Then, in sensitivity analyses, we added 24-hr noise (continuous) followed by longest held occupation (manual/non-manual/other), outdoor physical activity (low/high), and smoking status (current smoker/former smoker/ never smoker). In further sensitivity analyses, we co-adjusted for each of the pollutants that are likely markers of traffic-related (exhaust) air pollution¹⁶³ — NO₂, PM_{2.5}, and benzene —as well as a prominent marker of brake and tire wear, nickel²⁵, to address confounding by co-pollutants. Finally, we used quantile g-computation to estimate the association of the air pollution mixtures on the various health outcomes of interest using the qgcomp package⁸³. In two separate models we included either all eight air pollutants or only the likely traffic-related pollutant markers, NO₂, PM_{2.5}, benzene, and nickel. Pearson correlation coefficients were computed to assess pollutant correlations. Lastly, we applied our regression models after stratification by RUCA status to identify vulnerable populations as well as likely sources of air pollution. In order to overcome issue of non-convergence, we combined levels of some confounders in stratified analyses. Area-level SES categories were combined into two levels (low or low-middle SES versus middle, middle-high, or high SES) and monthly household income into three levels (less than \$1000, \$1000-\$1499 versus \$1500 or more). Analyses were conducted using R (version 4.3.3.; R Foundation for Statistical Computing, Vienna, Austria).

4.4. Results

4.4.1. Study Population Characteristics

The characteristics of the study population are summarized in Table 4-1. Our study population consisted of elderly people who were on average 70 years of age at baseline, with 42% being male and 58% being female. A majority of the study participants were of low socioeconomic status with less than 8 average years of education completed, 60% having been employed in manual labor for most of their lives, and 45% having a monthly household income of less than

\$1000 in the late 1990s. Most of the study participants lived in urban areas (87%) and in areas characterized as low or low-middle SES (68%). A high percentage (80%) of subjects engaged only in low levels of outdoor physical activity. The majority either never smoked in their lives (46%) or had quit (42%) as well as never drank alcohol or did so only on rare occasions (72%). In general, the demographic characteristics of the analytical subpopulations according to outcome of interest were similar to the entire SALSA cohort, except that there was a higher proportion of males in the subgroups studied for low HDL and hypertriglyceridemia. Additionally, participants who returned for follow-up visits were comprised of a slightly lower proportion of individuals with monthly incomes below \$1,000. To assess selection bias, we also examined the demographic characteristics of the individuals who were excluded from at least one of the analytical samples shown in Figure S 4-1, i.e. those who either had one of the outcomes at baseline or for whom outcome status was unknown at baseline. Demographic characteristics of this group were nearly identical (data not shown) to the entire SALSA cohort (Table 4-1).

4.4.2. Air Pollution Exposures

The 1-, 5-, and 10-year average air pollution exposure levels prior to baseline are shown in Table S 4-2. In general, we observed a slight decline in exposure levels with decreasing exposure period length for NO₂, PM_{2.5}, O₃, benzene, and nickel reflecting the decrease in exposure over the decade of follow-up and correlations among air pollutants also followed expected patterns (Figure S 4-3). Traffic-related pollutants (NO₂, PM_{2.5}, benzene, and nickel) were positively correlated with each other and with noise ($r \approx 0.3$ – 0.84), with the strongest correlation observed between PM_{2.5} and benzene ($r = 0.84$). Chromium displayed moderate positive correlations with lead ($r = 0.58$) and NO₂ ($r = 0.42$), and slightly weaker positive correlations with PM_{2.5} ($r = 0.35$) and noise ($r = 0.32$). In contrast, O₃ was negatively correlated

with most pollutants, particularly NO₂ ($r = -0.80$), reflecting atmospheric chemistry, and PM_{2.5} ($r = -0.43$). 1,3-butadiene showed weak correlations with all other pollutants and so did lead except for its correlation with chromium.

Figure S 4-4 shows the spatial distribution of modeled annual average concentrations of the pollutants for the year 2000. NO₂ and nickel showed prominent roadway patterns, with the highest concentrations predicted near major roads. PM_{2.5} was elevated not only near roadways but across the urban area more broadly. Benzene was more dispersed and higher in urban areas. For lead and chromium there were a few largely overlapping hotspots reflecting industry, transportation and energy facilities, specifically areas where power plants, airports, rail yards, refineries, and other factories are located. The spatial distribution of air pollutants was largely the same across the years of the study period (data not shown).

4.4.3. Association of Air Pollutants with Cardiometabolic Outcomes

Cox model associations with time-varying 1-, 5-, and 10-year averages were similar and the confidence intervals for different exposure periods overlapped. Here we discuss results for the 5-year average exposures, but effect estimates for all period averages are provided in Table S 4-3 and shown in Figure S 4-5. Traffic-related pollutant markers showed positive associations with hypertension and low HDL cholesterol for the 5-year average traffic pollutant mixture (HR for hypertension: 1.23, 95% CI: 0.99, 2.68; and for low HDL cholesterol: 1.38, 95% CI: 1.06, 2.90) and for the individual pollutants (Figure 4-1 and in Table S 4-3). The strongest associations were seen per IQR increase in nickel with hypertension (HR: 1.59, 95% CI: 0.99, 2.56) and low HDL cholesterol (HR: 1.76, 95% CI: 1.05, 2.94), followed by PM_{2.5} (HR for hypertension: 1.28, 95% CI: 0.93, 1.76; and for low HDL cholesterol: 1.39, 95% CI: 1.01, 1.91). Similarly, each per IQR increase in NO₂ exposure was associated with a 24% increase in the incidence of hypertension

(95% CI: 1.00, 1.55) and with a 20% increase in the incidence of low HDL cholesterol (95% CI: 0.99, 1.45). Benzene associations were also positive for these outcomes but the confidence intervals included the null value. Stratifying by urbanicity, we observed that positive associations for traffic-pollutant mixture with hypertension and low HDL cholesterol were seen in urban but not rural areas (Figure S 4-5 and Table S 4-4) (HR for hypertension: 1.21, 95% CI: 0.95, 2.59; HR for low HDL cholesterol: 1.49, 95% CI: 1.10, 3.00). Similarly, in urban areas positive associations were found for exposure to PM_{2.5} with incident hypertension (1.73, 95% CI: 1.06, 2.83) and low HDL cholesterol (1.91, 95% CI: 1.17, 3.12). We also additionally adjusted the traffic-related air pollutants for co-pollutants to assess potential confounding (Table S 4-5) and found that the associations for NO₂, PM_{2.5}, and nickel with hypertension and low HDL cholesterol slightly reduced but remained positive. The association between nickel and HDL cholesterol also attenuated but was still strongly positive after PM_{2.5} or NO₂ co-adjustment. 1,3-butadiene, lead and chromium increased the occurrence of hypertension by 4-7%, but these effect estimates also did not reach formal statistical significance. For hypertriglyceridemia, we observed a 68% increase in risk associated with nickel exposure and positive but smaller increases in risk with NO₂ (10%), PM_{2.5} (11%) and the traffic-pollutant mixture (16%), though the confidence intervals crossed again the null. For CVD and stroke, traffic-pollutant mixture exposure as well as its components were associated with an increase in incidence, ranging from 7% to 68%, however, the effect estimates were very imprecise. As compared to the mixture of traffic-related pollutants only (NO₂, PM_{2.5}, benzene and nickel), when the mixture included all the pollutants, the effect estimate for hypertension strengthened (HR: 1.42, 95% CI: 1.05, 2.85), remained similar for low HDL cholesterol though lost statistical significance (HR: 1.31, 95%CI: 0.92, 2.51) but became null for hypertriglyceridemia, stroke, and CVD (Table S 4-6). After additionally adjusting for noise (Table

S 4-7, model 2), estimated effect size for the association between the traffic-pollution mixture and its individual components (NO₂, PM_{2.5}, benzene and nickel) with hypertension, low HDL cholesterol, and hypertriglyceridemia decreased while the association increased for CVD and stroke. Further adjustment for primary lifetime occupation, outdoor physical activity, smoking status, and alcohol consumption (Table S 4-7, model 3), made minimal difference except for strengthening the effect estimate for nickel and CVD.

As shown in Figure S 4-7 and Table S 4-8, there were similarities between the air pollutant associations with incident events during follow-up and prevalent outcomes at baseline. Positive ORs were observed for prevalent hypertension with the 5-year average exposure of the traffic-pollutant mixture (OR: 1.10, 95% CI: 0.97, 1.25), and component pollutants: NO₂ (OR: 1.12, 95% CI: 1.03, 1.22), PM_{2.5} (OR: 1.12, 95% CI: 1.04, 1.21), and benzene (OR: 1.12, 95% CI: 1.02, 1.24). However, no association was observed between nickel and prevalent hypertension. For low HDL cholesterol and hypertriglyceridemia, positive associations were observed for the traffic-pollutant mixture (OR: 1.11, 95% CI: 0.97, 1.26 and OR: 1.11, 95% CI: 0.98, 1.25, respectively) which were driven mainly by benzene. Prevalent low HDL cholesterol was also positively associated with O₃ exposure (OR 5-year period: 1.07. 95%CI: 1.00, 1.15).

4.5. Discussion

In our study we found long-term urban traffic air pollutant exposure, mainly nickel a marker of brake and tire wear and PM_{2.5}, and NO₂ to be associated with an increased risk for hypertension and low HDL cholesterol. While positive associations were also observed for the other cardiometabolic health outcomes—hypertriglyceridemia, CVD, and stroke—the confidence intervals were wide. Hypertension and low HDL cholesterol are precursors and major risk factors

of cardiovascular disease and stroke¹⁶⁴. While our cohort had enough statistical power to model these common outcomes with sufficient precision, fewer incident cases of CVD and stroke resulted in imprecise but consistent associations. PM_{2.5}, NO₂, and nickel share common sources such as traffic^{25,165,166}, as evidenced by the correlations we observed among these pollutants (Figure S 4-3), and, thus, it is not surprising that while effect estimates remained positive for these pollutants with hypertension and HDL cholesterol they were slightly attenuated after co-pollutant adjustment. Also, as synergistic effects are likely, a pollutant mixture model might be most appropriate. In the case of hypertension, we also observed a small 4-7% increase in incidence associated with 1,3-butadiene, lead and chromium exposures. This aligned with the stronger effect estimate size we observed for the mixture of all pollutants as compared to the effect estimate for the traffic pollution mixture only (PM_{2.5}, NO₂, nickel, and benzene). This supports toxicity of exhaust and non-exhaust traffic emissions as well as from industrial and other transportation related sources. Comparing the spatial distribution of lead and chromium (Figure S 4-4) with CARB's pollution mapping tool¹⁶⁷ and Google Maps, revealed high concentrations of these pollutants near power plants, airports, rail yards, refineries, and other factories releasing emissions. Lead and chromium concentrations have previously been shown to be high near these sources.¹⁶⁸⁻¹⁷³

An umbrella review published in 2022 found that long-term exposure to PM_{2.5} was associated with all cause CVD mortality and various types of cardiovascular disease outcomes such as heart attacks, atherosclerosis, hypertension, stroke, and stroke mortality¹⁴⁸. A meta-analysis that investigated hypertension specifically reported that long-term PM_{2.5} exposure was positively associated with hypertension (OR: 1.05, 95% CI: 1.01, 1.09, per 10 µg/m³).⁶ While this estimate is not directly comparable with ours, we found an elevated effect estimate size for this association as well (HR: 1.28, 95%CI: 0.93, 1.76, per 1.69 µg/m³). The same meta-analysis did

not find NO₂ to be associated with hypertension but with diastolic blood pressure (β : 0.77, 95%CI: 0.38, 1.17, per 10 $\mu\text{g}/\text{m}^3$).⁶ In our study, the modeled NO₂ exposure was strongly positively associated with hypertension (HR: 1.24, 95%CI: 1.00, 1.55, per 2.85ppb), possibly because we studied a particularly vulnerable group, elderly, Hispanic, and living in low SES areas. Another meta-analysis found a long-term NO₂ exposure to be associated with an increase in triglyceride levels (4.24%, 95%CI: 1.37%, 7.19%, per 10 $\mu\text{g}/\text{m}^3$) and a small and imprecisely measured decrease in HDL cholesterol (-0.45%, 95%CI: -2.65%, 1.81%, per 10 $\mu\text{g}/\text{m}^3$).¹⁷⁴ This somewhat corroborates our findings for the association of NO₂ exposure with these outcomes. Finally, another meta-analysis found suggestive positive association for stroke with long-term PM_{2.5} exposure (RR: 1.08, 95%CI: 0.89, 1.32, per 5 $\mu\text{g}/\text{m}^3$) but not with NO₂ exposure (RR: 0.98, 95%CI: 0.92, 1.05, per 10 $\mu\text{g}/\text{m}^3$).¹⁷⁵ In our study while we observed positive effect estimates for these associations, the confidence intervals were wide and included the null. Our observations therefore in general agreed with prior literature. Minor differences may be attributed to differences in the demographic characteristics of the populations studied and exposure assessment methods.

Traffic-related air pollution mixture (PM_{2.5}, NO₂, nickel, and benzene) and PM_{2.5} exposures were found to be more harmful in urban than in rural areas. This may be due to differences in the pollutant concentration levels as well as unmeasured difference in the composition of air pollution mixtures in the two environments. Concentrations of these pollutants tend to be higher in urban areas as shown in the spatial distribution of air pollution maps in Figure S 4-4. Most prominently nickel concentrations are highest along roadways, as has been reported before¹⁷⁶, owing to diesel exhaust emissions and brake and tire wear^{25,166}, and urban areas have a denser network of roads and more traffic. Prior literature has also highlighted differences in urban versus rural composition of PM_{2.5}. In general urban areas are characterized by higher levels of organic and elemental carbon,

secondary aerosol, and trace metals from automobiles and industries, while in rural areas, higher concentrations of crustal materials from agricultural activities and resuspended road dust are found^{177,178}, potentially resulting in differences in toxicity. It is important to note, however, that a majority of our population lived in urban areas and the rural population's sample size may have been too small to detect associations.

Cross-sectional analyses with prevalent outcomes at baseline revealed statistically significant positive associations between hypertension and traffic-related pollutants, PM_{2.5}, NO₂, and benzene although the effect estimate sizes were smaller than for incident hypertension. Similarly, positive associations with low HDL cholesterol and hypertriglyceridemia were observed for the traffic-related pollutant mixture and additionally, prevalent low HDL cholesterol was positively associated with O₃ exposure. We did not, however, find these air pollutants to be associated with prevalent stroke and CVD. Cross-sectional analyses are subject to selection bias as people with compromised cardiometabolic health may have been less likely to enroll into the baseline cohort if they were highly disabled or had already died as SALSA participants were on average 70 years of age at enrolment and cardiovascular diseases and stroke are leading causes of mortality in the US¹⁷⁹. More importantly, we do not know when the prevalent disease reported at baseline occurred such that the exposure windows we used might have been inappropriate. It is possible to live with hypertension with efficient clinical management and nearly half of the US adult population has hypertension¹⁸⁰. In our SALSA cohort, among the 1530 participants, 972 reported hypertension at baseline, which made studying incidence harder. Nevertheless, we observed positive associations with nickel, PM_{2.5}, and NO₂ as noted before.

Existing literature on air pollution delineates various biological mechanisms that may explain our observations^{5-8,147-149}, including oxidative stress, inflammation, epigenomic changes and circadian disruption. Particulate matter has been shown to induce oxidative stress, which chemically transforms thiols, fatty acids, and lipids that can then migrate and trigger insulin resistance and systemic inflammation. Similarly, local inflammation in the lungs after exposure may cause the release of pro-inflammatory mediators, allowing inflammatory signals to spill over into the blood circulation and contribute to systemic inflammation.^{181,182} Both particulate matter and gaseous air pollutants have been found to be associated with increases in inflammatory markers such as interleukin-6 and C-reactive protein.^{181,182} The downstream effects of oxidative stress and inflammation include dysregulation of the autonomic nervous system and sympathetic activation, hypothalamic–pituitary–adrenal axis activation, endothelial dysfunction, vasoconstriction, coagulation, atherosclerosis, and arterial stiffness that can then increase the risk of hypertension, ischemic heart disease, arrhythmias, atrial fibrillation, cardiac arrests, and other CVD outcomes.^{5,6,8,148,149} The relationship between air pollution and CVD may also be mediated through dysregulation of glucose and lipid metabolism. Air pollution has been linked with insulin resistance through mechanisms involving inflammation, oxidative stress, and activation of the sympathetic nervous system¹⁸³⁻¹⁸⁵. Insulin resistance can in turn increase the risk for hypertension¹⁸⁶⁻¹⁸⁸. Insulin resistance may also bring about an increase in triglyceride levels and a decrease in HDL cholesterol levels¹⁸⁹. Such altered lipid metabolism has also independently been found to be associated with particulate matter and NO₂^{146,147}. The disruption of lipid metabolism has in turn been linked to atherosclerosis and CVD^{164,190}. The associations for air pollutants and the mixtures observed in our study fit well within these biological pathways and also suggest

indirect effects mediated through related cardiovascular disease precursors (HDL cholesterol, high triglyceride levels and hypertension) and metabolic pathways.

Our study has noteworthy strengths. We used longitudinal cohort data to study the impact of air pollution in a Hispanic population, a group that is disproportionately exposed to higher levels of air pollution^{12–14,150,151}. The average PM_{2.5} levels that this cohort was exposed to (Table S 4-2) was higher than the 9 $\mu\text{g}/\text{m}^3$ primary annual standard recently set by the Environmental Protection Agency (EPA) for sensitive groups such as older population¹⁹¹. We used high resolution air pollution surfaces (100m) obtained through advanced machine learning techniques. The LUR models used various high quality predictor data including stationary and mobile air pollution monitoring, emissions inventories, traffic, land use and cover, vegetation index, topography, and satellite data. Further we derived surfaces for air toxics including PM_{2.5} metal components and volatile organic compounds which are not widely studied and for which no federal or state regulatory standards exist. Air pollution is by its nature a mixture and it is important to address synergistic effects of multiple pollutants from common sources. We evaluated the effects of air pollution mixtures using quantile g-computation to study the joint effect of mixture components. In order to accurately estimate exposure, we geocoded participant residences by global positioning system readings taken during baseline home visits. Blood samples were collected at baseline and at each follow-up visit to measure HDL cholesterol and triglyceride levels and blood pressure was noted at each visit for accurate outcome assessment. Finally, we utilized a DAG based on prior literature and had available a large list of potential confounders to adjust for including age, gender, education level, area-level SES, income, and urbanicity. We also conducted sensitivity analyses by further adjusting for noise, primary lifetime occupation, outdoor physical activity, smoking status, and alcohol consumption.

Some limitations should also be noted. Firstly, we estimated exposures based on residential address collected at baseline only. We did not have information on residential history, nor did we have air pollution exposure estimates prior to 1989. Thus, we were not able to assess the impacts of air pollution exposures for longer than 10 years. We did, however, assume that in the 10 years prior to baseline, participants lived in the same address as they did at baseline. While this may have resulted in some exposure misclassification, it was a reasonable assumption given that on average participants reported to have lived at their baseline addresses for 22 years. We also did not have detailed information about the participants' whereabouts during the day. However, given that this is aged population comprised of people who are mostly already retired, we assumed that they regularly spent time at home during the day. This is further evidenced by the fact that majority of the participants engaged in only low outdoor physical activity (Table 4-1). Another source of exposure misclassification could be the lower model prediction values for PM_{2.5} (0.65), 1,3-butadiene (0.62), and lead (0.59). However, such exposure misclassification is likely to be non-differential which would have pulled the effect estimates closer to the null. Despite this, we observed statistically significant associations for PM_{2.5} with low HDL cholesterol. Further, poor exposure contrast for 1,3-butadiene, as shown in Figure S 4-4B, also could have limited our ability to discern potential associations with cardiometabolic outcomes. An important potential confounder in the associations between air pollutants and cardiometabolic health outcomes is traffic noise. We performed sensitivity analysis to additionally control for traffic-related noise in our models and as expected, we observed that the effect estimate size for the association between the traffic-pollution mixture and its individual components (NO₂, PM_{2.5}, benzene and nickel) with hypertension, low HDL cholesterol, and hypertriglyceridemia decreased but remained positive. Caution is warranted in interpreting these results as they might be affected by collinearity issues

between noise exposure and traffic-related air pollutants as shown in Figure S 4-3 and discussed previously. Finally, outcome assessments did depend on recall of medical diagnoses and medication use. While misclassification is possible when relying on recall¹⁹², since proxies were allowed to help answer questions as well, and this would have helped to avoid some misclassification.

4.6. Conclusion

We found 1-, 5-, and 10-year exposure to PM_{2.5}, NO₂, and nickel to be associated with incidence of hypertension and low HDL cholesterol in a cohort of older Mexican Americans particularly in urban areas where the major pollution source is likely from traffic. We also found some indication that pollution from local hotspots such as from power plants, transportation hubs, or industry may increase the risk of hypertension. While positive associations were found for benzene with these outcomes as well as for other traffic-related pollutants with hypertriglyceridemia, CVD, and stroke, the confidence intervals were wide. Our study underscores the need for policies to regulate tail-pipe and non tail-pipe vehicular emissions as well as other combustion sources.

Main Figures and Tables

Table 4-1. Characteristics of the SALSA study population, 1998–2007

	Analytical sample for hypertension (N=558)	Analytical sample for low HDL cholesterol (N=967)	Analytical sample for Hyper- triglyceridemia (N=700)	Analytical sample for CVD (N=974)	Analytical sample for stroke (N=1385)	Sample with prevalent outcome or missing status at baseline (N=1553)	Entire SALSA cohort (N=1789)
	N (%) / <i>Mean (SD)</i>						
Age at baseline visit	68.8 (6.11)	70.3 (6.95)	70.9 (7.03)	69.9 (6.56)	70.2 (6.74)	70.7 (7.16)	70.6 (7.11)
Missing	0	0	0	0	0	3	3
Sex							
Male	221 (39.6%)	458 (47.4%)	316 (45.1%)	422 (43.3%)	575 (41.5%)	638 (41.1%)	745 (41.6%)
Female	337 (60.4%)	509 (52.6%)	384 (54.9%)	552 (56.7%)	810 (58.5%)	915 (58.9%)	1044 (58.4%)
Years of Education	7.72 (5.39)	7.79 (5.36)	7.28 (5.32)	7.89 (5.43)	7.60 (5.42)	7.28 (5.35)	7.24 (5.34)
Missing	4	4	4	0	0	10	10
Primary Lifetime Occupation							
Non-manual	127 (23.3%)	210 (22.2%)	144 (21.0%)	220 (23.0%)	310 (22.7%)	325 (21.3%)	372 (21.2)
Manual	317 (58.1%)	591 (62.3%)	415 (60.6%)	585 (61.1%)	813 (59.5%)	916 (59.9%)	1056 (60.1%)
Other (Housewives and Unemployed)	102 (18.68%)	147 (15.5%)	126 (18.4%)	153 (16.0%)	243 (17.8%)	287 (18.8%)	330 (18.8%)
Missing	12	19	15	16	19	25	31
Outdoor Physical Activity							
High	121 (23.0%)	221 (24.2%)	153 (23.1%)	227 (24.3%)	297 (22.4%)	308 (21.2%)	365 (21.8%)

Low Missing	406 (77%) 31	692 (75.8%) 54	510 (76.9%) 37	707 (75.7%) 40	1030 (77.6%) 58	1144 (78.8%) 101	1311 (78.2%) 113
Smoking status							
Never Smoker	264 (47.7%)	446 (46.4%)	338 (48.6%)	475 (48.8%)	648 (46.8%)	703 (45.6%)	820 (46.2%)
Former Smoker	215 (38.9%)	407 (42.3%)	278 (40.0%)	384 (39.5%)	581 (42.0%)	661 (42.9%)	746 (42.0%)
Current Smoker	74 (13.4%)	109 (11.3%)	79 (11.4%)	114 (11.7%)	155 (11.2%)	176 (11.4%)	209 (11.8%)
Missing	5	5	5	1	1	13	14
Alcohol Consumption							
Frequent (Daily) Drinker	51 (9.2%)	115 (12.0%)	77 (11.1%)	100 (10.3%)	129 (9.4%)	128 (8.4%)	155 (8.8%)
Moderate (Weekly) Drinker	67 (12.1%)	126 (13.2%)	77 (11.1%)	118 (12.2%)	159 (11.5%)	155 (10.1%)	185 (10.5%)
Occasional (Monthly) Drinker	57 (10.3%)	99 (10.3%)	70 (10.1%)	104 (10.7%)	145 (10.5%)	146 (9.5%)	163 (9.2%)
Yearly/Rarely/ Never Drinker	377 (68.3%)	617 (64.5%)	467 (67.6%)	646 (66.7%)	945 (68.6%)	1101 (72.0%)	1260 (71.5%)
Missing	6	10	9	6	7	23	26
Area-level SES							
Lowest SES	170 (30.5%)	322 (33.3%)	241 (34.4%)	311 (31.9%)	455 (32.9%)	526 (33.9%)	604 (33.8%)
Low-Middle SES	197 (35.3%)	318 (32.9%)	233 (33.3%)	343 (35.2%)	469 (33.9%)	531 (34.2%)	618 (34.5%)
Middle SES	137 (24.6%)	227 (23.5%)	159 (22.7%)	220 (22.6%)	318 (23.0%)	345 (22.2%)	394 (22.0%)
High-Middle or High SES	54 (9.7%)	100 (10.3%)	67 (9.6%)	100 (10.3%)	143 (10.3%)	151 (9.7%)	173 (9.7%)

Monthly household income								
Less than \$1000	221 (40.7%)	393 (41.5%)	288 (42.2%)	377 (39.1%)	568 (41.6%)	685 (45.1%)	784 (44.8%)	
\$1000 to \$1499	112 (20.6%)	194 (20.5%)	141 (20.7%)	196 (20.4%)	283 (20.7%)	309 (20.3%)	358 (20.5%)	
\$1500 to \$1999	77 (14.2%)	117 (12.3%)	88 (12.9%)	115 (11.9%)	154 (11.3%)	164 (10.8%)	199 (11.4%)	
\$2000 to \$2499	55 (10.1%)	93 (9.8%)	69 (10.1%)	116 (12.0%)	148 (10.8%)	148 (9.7%)	163 (9.3%)	
\$2500 or more	78 (14.4%)	151 (15.9%)	96 (14.1%)	159 (16.5%)	212 (15.5%)	214 (14.1%)	246 (14.1%)	
Missing	15	19	18	11	20	33	39	
Urbanicity (RUCS Status)								
Rural	68 (12.2%)	122 (12.6%)	86 (12.3%)	125 (12.8%)	176 (12.7%)	203 (13.1%)	234 (13.1%)	
Urban	490 (87.8%)	845 (87.4%)	614 (87.7%)	849 (87.2%)	1209 (87.3%)	1350 (86.9%)	1555 (86.9%)	

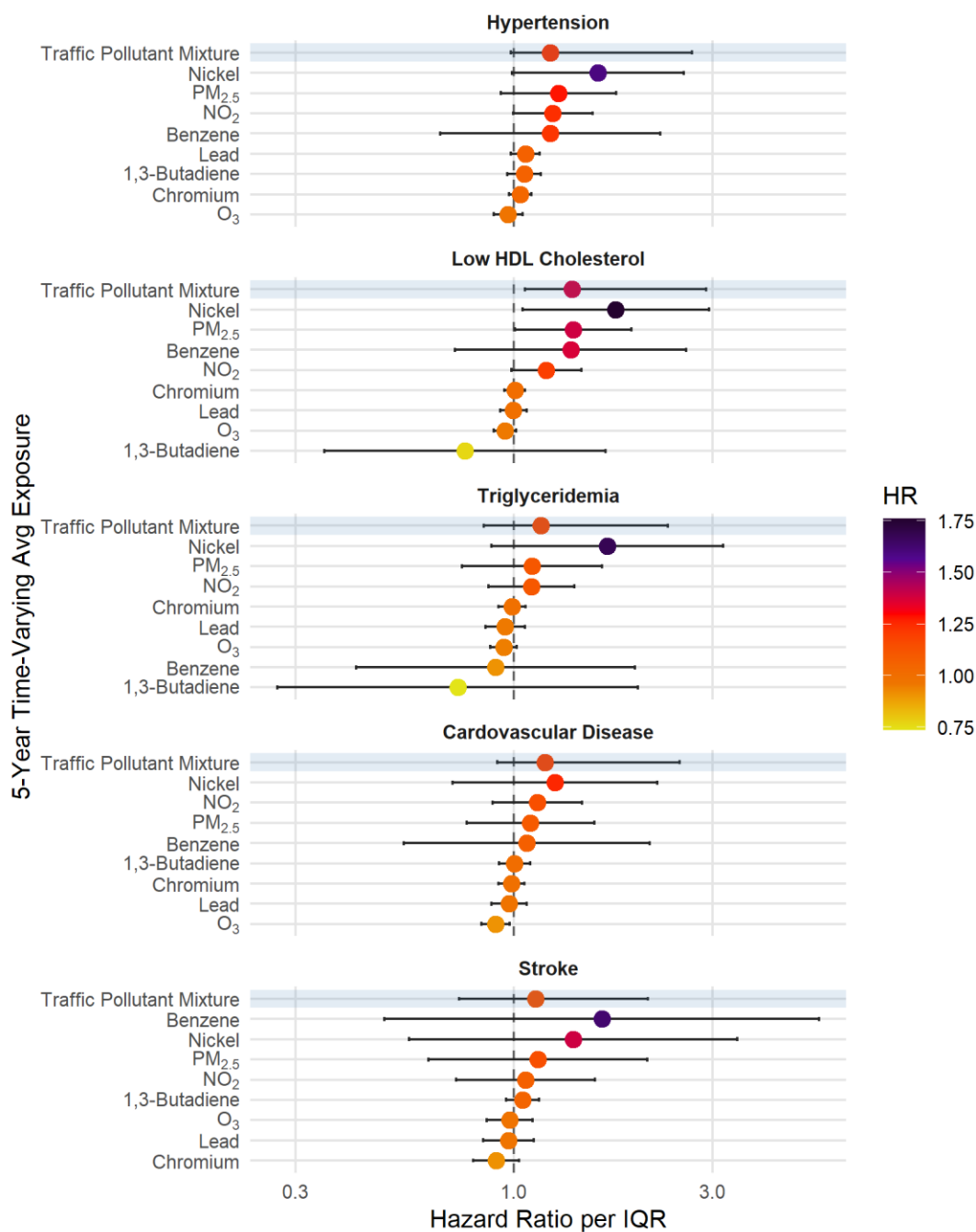


Figure 4-1. Association of 5-year time-varying air pollutant averages with cardiometabolic outcomes

Note: Here traffic pollution mixture consists of the pollutants NO₂, PM_{2.5}, benzene, and nickel. The models have been adjusted for age, sex, household income, years of education, area-level SES, and urbanicity based on demographic information and residential address collected at baseline. The effect estimates have been ordered in descending order of magnitude.

Supplemental Figures and Tables

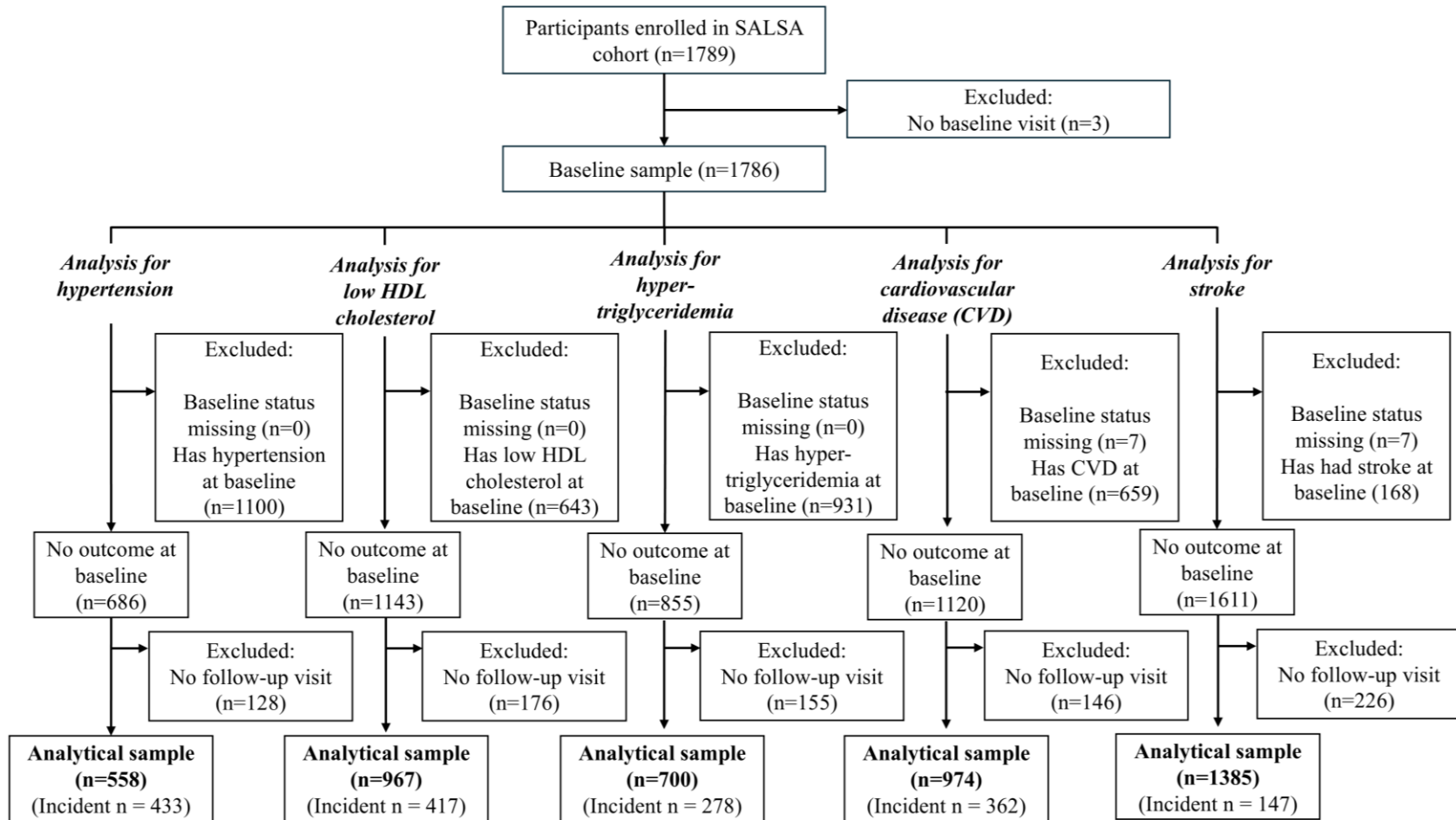


Figure S 4-1. Flow chart of SALSA study population, 1998–2007

Table S 4-1. Inter-quartile range (IQR) values of air pollutants

A. Time-varying exposure average periods (n=1530)

Pollutant	1-year average	5-year average	10-year average
NO ₂ (ppb)	3.64	2.85	2.08
PM _{2.5} (μg/m ³)	2.18	1.69	1.23
O ₃ (ppb)	0.91	0.46	0.41
1,3-Butadiene (ppb)	1.06	0.74	0.19
Benzene (ppb)	0.31	0.25	0.17
Nickel (ng/m ³)	0.38	0.30	0.20
Lead (ng/m ³)	0.41	0.35	0.29
Chromium (ng/m ³)	0.58	0.58	0.58

B. Exposure average periods prior to baseline (n=1530)

Pollutant	1-year average	5-year average	10-year average
NO ₂ (ppb)	1.10	1.09	1.10
PM _{2.5} (μg/m ³)	0.59	0.41	0.42
O ₃ (ppb)	1.27	0.42	0.41
1,3-Butadiene (ppb)	1.69	0.14	0.09
Benzene (ppb)	0.05	0.05	0.04
Nickel (ng/m ³)	0.10	0.10	0.10
Lead (ng/m ³)	0.29	0.24	0.25
Chromium (ng/m ³)	0.60	0.60	0.60

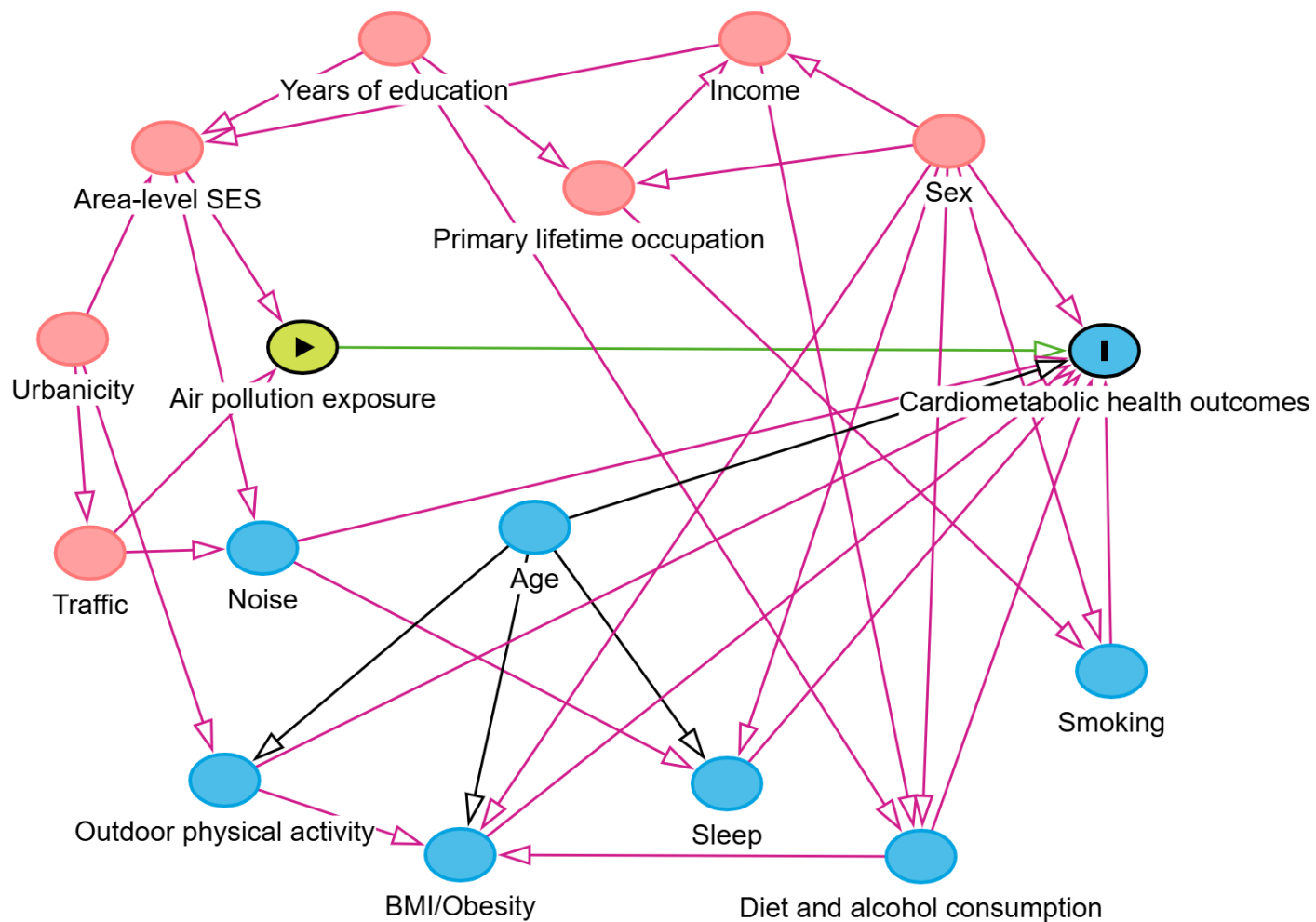


Figure S 4-2. Directed Acyclic Graph (DAG) showing potential covariates involved in the association between air pollution and cardiometabolic health

Table S 4-2. Mean (SD) values of air pollutants for different exposure average periods prior to baseline in the entire SALSA cohort (n=1789)

Pollutant	1-year average	5-year average	10-year average
NO ₂ (ppb)	13.20 (1.36)	14.00 (1.44)	15.20 (1.45)
PM _{2.5} (μg/m ³)	13.30 (0.59)	13.50 (0.59)	14.30 (0.61)
O ₃ (ppb)	37.30 (0.96)	38.10 (0.65)	38.20 (0.65)
1,3-Butadiene (ppb)	6.33 (1.10)	5.67 (0.53)	5.16 (0.28)
Benzene (ppb)	0.94 (0.05)	1.04 (0.06)	1.12 (0.06)
Nickel (ng/m ³)	1.67 (0.07)	1.75 (0.07)	1.85 (0.07)
Lead (ng/m ³)	5.38 (0.44)	5.35 (0.44)	5.38 (0.45)
Chromium (ng/m ³)	3.77 (0.90)	3.77 (0.90)	3.77 (0.90)

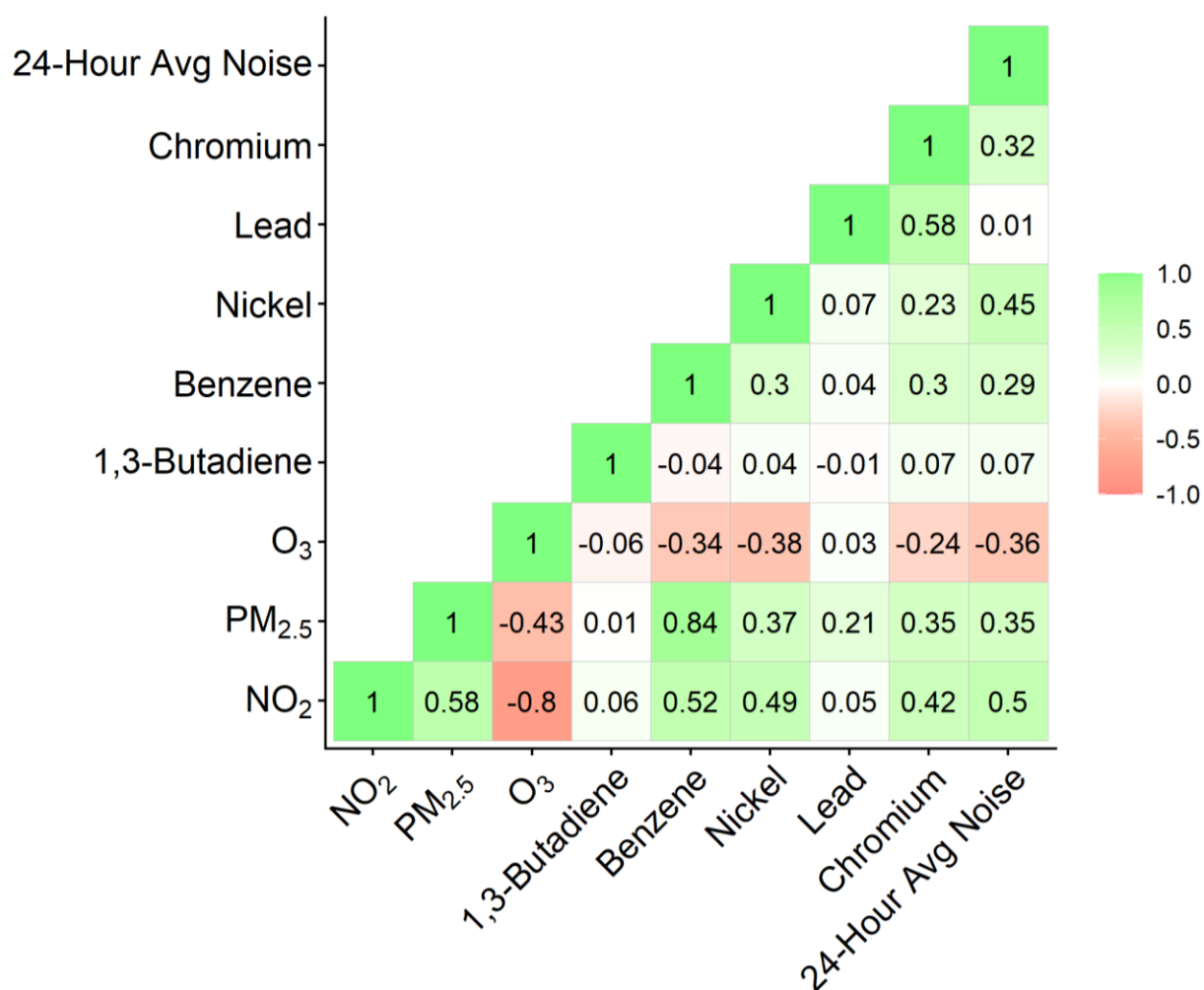
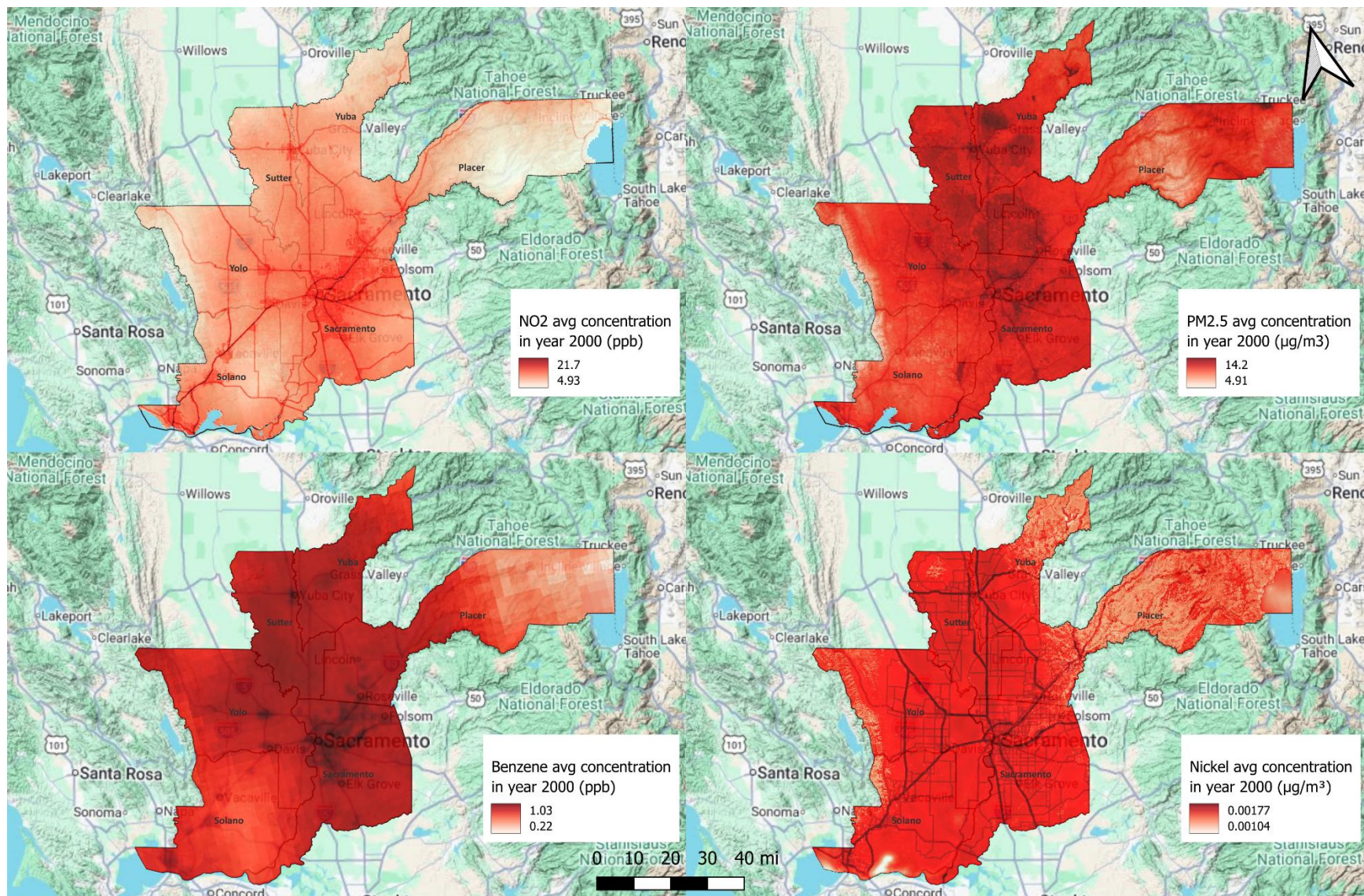


Figure S 4-3. Pearson correlation coefficients among 5-year average of air pollutant concentrations and annual average 24hr noise exposure at baseline

A.



B.

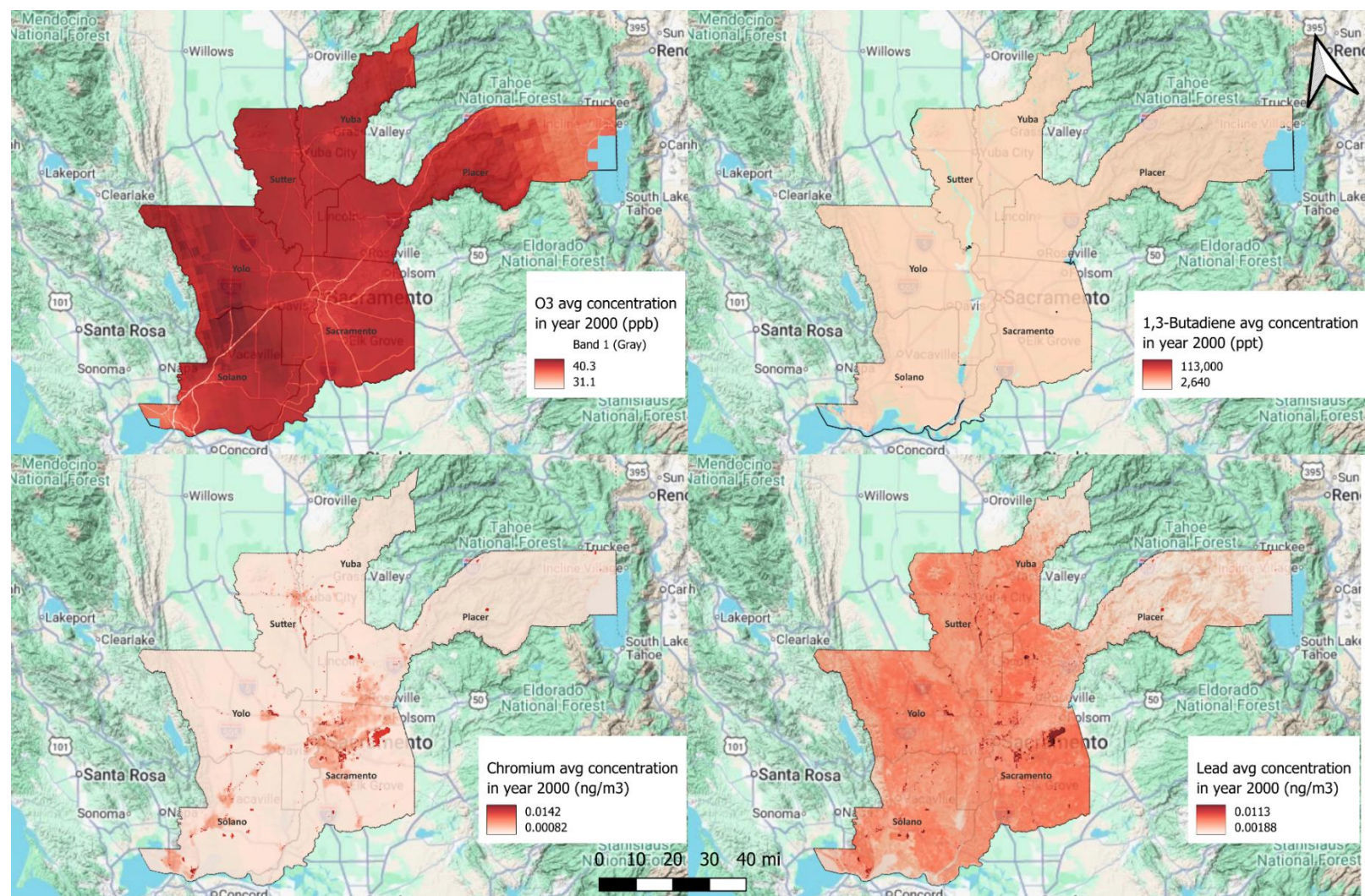


Figure S 4-4. Spatial distribution of modeled annual mean concentrations of air pollutants in the year 2000. (A) NO₂, PM_{2.5}, benzene, and nickel; (B) O₃, 1,3-butadiene, chromium, and lead.

Table S 4-3. Association of time-varying air pollutant averages over different periods with cardiometabolic outcomes

	Exposure period	Hypertension (total n=558 incident n=433)	Low HDL cholesterol (total n=967 incident n=417)	Hypertriglyceridemia (total n=700 incident n=278)	CVD (total n=974 incident n=362)	Stroke (total n=1385 incident n=147)
Traffic pollution mixture	1 year	1.21 (0.98, 2.66)	1.27 (0.97, 2.64)	1.08 (0.77, 2.17)	1.29 (0.98, 2.66)	1.18 (0.76, 2.13)
	5 years	1.23 (0.99, 2.68)	1.38 (1.06, 2.90)	1.16 (0.85, 2.34)	1.19 (0.92, 2.50)	1.13 (0.74, 2.10)
	10 years	1.26 (1.02, 2.76)	1.34 (1.04, 2.84)	1.13 (0.83, 2.30)	1.18 (0.91, 2.49)	1.09 (0.72, 2.06)
NO ₂	1 year	1.33 (1.01, 1.74)	1.27 (1.00, 1.62)	1.14 (0.84, 1.54)	1.21 (0.88, 1.65)	1.12 (0.70, 1.82)
	5 years	1.24 (1.00, 1.55)	1.20 (0.99, 1.45)	1.10 (0.87, 1.40)	1.14 (0.89, 1.46)	1.07 (0.73, 1.57)
	10 years	1.17 (1.00, 1.38)	1.14 (0.99, 1.32)	1.08 (0.90, 1.29)	1.11 (0.93, 1.34)	1.05 (0.79, 1.40)
PM _{2.5}	1 year	1.35 (0.91, 2.02)	1.43 (0.96, 2.13)	1.18 (0.72, 1.92)	1.14 (0.73, 1.78)	1.16 (0.54, 2.48)
	5 years	1.28 (0.93, 1.76)	1.39 (1.01, 1.91)	1.11 (0.75, 1.63)	1.10 (0.77, 1.56)	1.14 (0.63, 2.09)
	10 years	1.20 (0.95, 1.51)	1.25 (0.99, 1.58)	1.09 (0.82, 1.45)	1.06 (0.82, 1.38)	1.07 (0.69, 1.65)
O ₃	1 year	0.94 (0.81, 1.09)	0.91 (0.81, 1.03)	0.90 (0.78, 1.04)	0.82 (0.70, 0.95)	0.92 (0.73, 1.16)
	5 years	0.97 (0.90, 1.05)	0.95 (0.90, 1.02)	0.95 (0.88, 1.02)	0.91 (0.84, 0.98)	0.98 (0.86, 1.11)
	10 years	0.97 (0.91, 1.05)	0.96 (0.91, 1.02)	0.95 (0.89, 1.02)	0.91 (0.85, 0.97)	0.98 (0.87, 1.10)
1,3- Butadiene	1 year	1.06 (0.95, 1.19)	0.49 (0.14, 1.70)	0.46 (0.10, 2.10)	1.01 (0.89, 1.14)	1.04 (0.88, 1.22)
	5 years	1.06 (0.97, 1.16)	0.76 (0.35, 1.66)	0.74 (0.27, 1.99)	1.01 (0.92, 1.10)	1.05 (0.96, 1.15)
	10 years	1.03 (0.99, 1.08)	0.91 (0.73, 1.13)	0.91 (0.69, 1.22)	1.00 (0.97, 1.03)	1.02 (0.99, 1.05)

Benzene	1 year	1.32 (0.60, 2.92)	1.47 (0.63, 3.42)	0.91 (0.33, 2.55)	1.18 (0.48, 2.89)	1.85 (0.38, 8.92)
	5 years	1.23 (0.67, 2.25)	1.37 (0.72, 2.59)	0.91 (0.42, 1.95)	1.08 (0.55, 2.12)	1.63 (0.49, 5.39)
	10 years	1.13 (0.77, 1.64)	1.21 (0.81, 1.80)	0.94 (0.58, 1.53)	1.07 (0.70, 1.63)	1.39 (0.65, 2.94)
Nickel	1 year	1.85 (0.99, 3.45)	2.12 (1.08, 4.17)	1.96 (0.85, 4.55)	1.36 (0.65, 2.86)	1.54 (0.47, 5.07)
	5 years	1.59 (0.99, 2.56)	1.76 (1.05, 2.94)	1.68 (0.89, 3.18)	1.26 (0.71, 2.21)	1.39 (0.56, 3.44)
	10 years	1.34 (1.00, 1.81)	1.42 (1.03, 1.96)	1.39 (0.93, 2.07)	1.15 (0.81, 1.65)	1.23 (0.70, 2.17)
Lead	1 year	1.08 (0.98, 1.18)	1.00 (0.92, 1.09)	0.95 (0.83, 1.08)	0.97 (0.87, 1.09)	0.97 (0.82, 1.14)
	5 years	1.07 (0.99, 1.15)	1.00 (0.93, 1.07)	0.95 (0.86, 1.06)	0.98 (0.89, 1.08)	0.97 (0.85, 1.12)
	10 years	1.05 (0.99, 1.12)	1.00 (0.94, 1.06)	0.96 (0.88, 1.05)	0.98 (0.91, 1.06)	0.98 (0.87, 1.10)
Chromium	1 year	1.04 (0.98, 1.11)	1.01 (0.95, 1.07)	0.99 (0.92, 1.07)	0.99 (0.92, 1.06)	0.91 (0.80, 1.03)
	5 years	1.04 (0.97, 1.10)	1.01 (0.95, 1.07)	0.99 (0.92, 1.07)	0.99 (0.92, 1.06)	0.91 (0.80, 1.03)
	10 years	1.04 (0.97, 1.10)	1.01 (0.95, 1.07)	0.99 (0.92, 1.07)	0.99 (0.92, 1.06)	0.91 (0.80, 1.03)

Note: Effect estimates are HR (95% CI). For single pollutant models the effect estimates represent the effect per IQR. The results for traffic pollution mixture (NO₂, PM_{2.5}, benzene, and nickel) are obtained from quantile g-computation, and the effect estimate represents the effect of increasing all exposures by one quantile simultaneously. The models have been adjusted for age, sex, household income, years of education, area-level SES, and urbanicity based on demographic information and residential address collected at baseline.

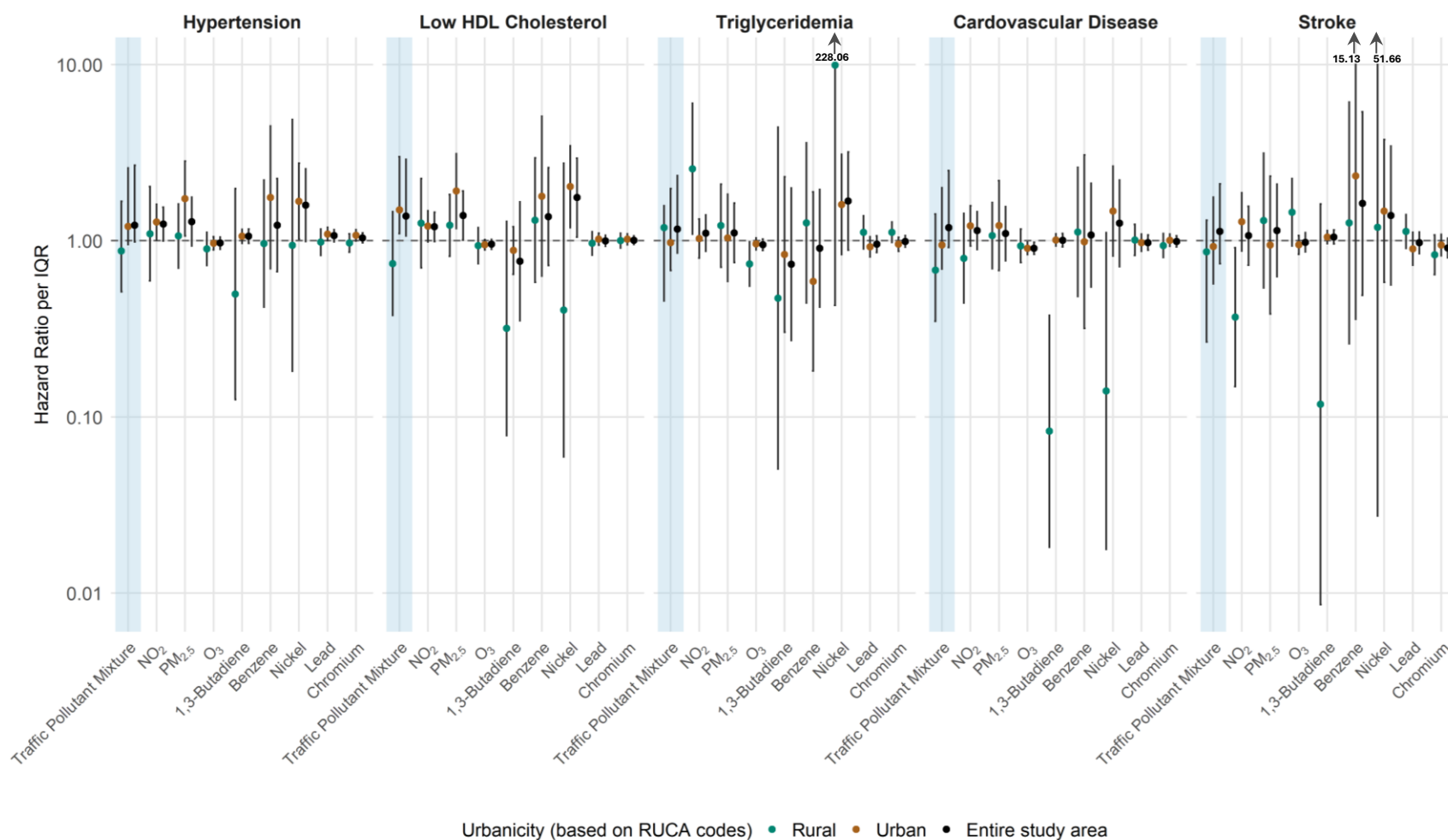


Figure S 4-5. Association of 5-year time-varying air pollutant averages with cardiometabolic outcomes stratified by residence in urban vs entire study area

Note: Here traffic pollution mixture consists of the pollutants NO₂, PM_{2.5}, benzene, and nickel. The models have been adjusted for age, sex, household income, years of education, area-level SES, and urbanicity based on demographic information and residential address collected at baseline.

Table S 4-4. Association of 5-year time-varying air pollutant averages with cardiometabolic outcomes stratified by residence in urban vs rural area

Outcome	Pollutant	Rural	Urban	Entire study area
Hypertension (total n=558 incident n=433)	Traffic pollution mixture	0.88 (0.51, 1.67)	1.21 (0.95, 2.59)	1.23 (0.99, 2.68)
	NO ₂	1.10 (0.59, 2.03)	1.28 (1.01, 1.61)	1.24 (1.00, 1.55)
	PM _{2.5}	1.06 (0.70, 1.62)	1.73 (1.06, 2.83)	1.28 (0.93, 1.76)
	O ₃	0.90 (0.72, 1.11)	0.97 (0.89, 1.05)	0.97 (0.90, 1.05)
	1,3-Butadiene	0.50 (0.13, 1.98)	1.06 (0.97, 1.16)	1.06 (0.97, 1.16)
	Benzene	0.96 (0.42, 2.21)	1.76 (0.69, 4.47)	1.23 (0.67, 2.25)
	Nickel	0.94 (0.18, 4.87)	1.67 (1.02, 2.75)	1.59 (0.99, 2.56)
	Lead	0.98 (0.83, 1.16)	1.09 (1.00, 1.19)	1.07 (0.99, 1.15)
	Chromium	0.97 (0.86, 1.10)	1.07 (1.00, 1.15)	1.04 (0.97, 1.10)
Low HDL cholesterol (total n=967 incident n=417)	Traffic pollution mixture	0.74 (0.38, 1.46)	1.49 (1.10, 3.00)	1.38 (1.06, 2.90)
	NO ₂	1.26 (0.70, 2.25)	1.21 (0.99, 1.48)	1.20 (0.99, 1.45)
	PM _{2.5}	1.22 (0.82, 1.83)	1.91 (1.17, 3.12)	1.39 (1.01, 1.91)
	O ₃	0.94 (0.74, 1.19)	0.95 (0.89, 1.01)	0.95 (0.90, 1.02)
	1,3-Butadiene	0.32 (0.08, 1.29)	0.88 (0.64, 1.20)	0.76 (0.35, 1.66)

	Benzene	1.31 (0.58, 2.95)	1.79 (0.63, 5.07)	1.37 (0.72, 2.59)
	Nickel	0.40 (0.06, 2.75)	2.02 (1.19, 3.46)	1.76 (1.05, 2.94)
	Lead	0.97 (0.83, 1.12)	1.02 (0.94, 1.10)	1.00 (0.93, 1.07)
	Chromium	1.00 (0.91, 1.10)	1.02 (0.95, 1.09)	1.01 (0.95, 1.07)
Hypertriglyceridemia (total n=700 incident n=278)	Traffic pollution mixture	1.18 (0.45, 1.58)	0.97 (0.68, 1.97)	1.16 (0.85, 2.34)
	NO ₂	2.56 (1.09, 6.02)	1.03 (0.80, 1.33)	1.10 (0.87, 1.40)
	PM _{2.5}	1.22 (0.71, 2.10)	1.04 (0.59, 1.83)	1.11 (0.75, 1.63)
	O ₃	0.74 (0.55, 0.99)	0.96 (0.89, 1.04)	0.95 (0.88, 1.02)
	1,3-Butadiene	0.47 (0.05, 4.40)	0.83 (0.30, 2.30)	0.74 (0.27, 1.99)
	Benzene	1.26 (0.44, 3.59)	0.59 (0.18, 1.89)	0.91 (0.42, 1.95)
	Nickel	9.91 (0.43, 228.06)	1.61 (0.83, 3.09)	1.68 (0.89, 3.18)
	Lead	1.11 (0.90, 1.38)	0.92 (0.81, 1.05)	0.95 (0.86, 1.06)
	Chromium	1.12 (0.98, 1.28)	0.95 (0.87, 1.05)	0.99 (0.92, 1.07)
	Traffic pollution mixture	0.68 (0.35, 1.42)	0.95 (0.69, 2.00)	1.19 (0.92, 2.50)
CVD (total n=974 incident n=362)	NO ₂	0.80 (0.44, 1.43)	1.21 (0.93, 1.58)	1.14 (0.89, 1.46)
	PM _{2.5}	1.07 (0.69, 1.65)	1.22 (0.68, 2.19)	1.10 (0.77, 1.56)
	O ₃	0.94 (0.75, 1.16)	0.91 (0.84, 0.98)	0.91 (0.84, 0.98)
	1,3-Butadiene	0.08 (0.02, 0.38)	1.01 (0.93, 1.09)	1.01 (0.92, 1.10)
	Benzene	1.12 (0.48, 2.61)	0.99 (0.32, 3.06)	1.08 (0.55, 2.12)

	Nickel	0.14 (0.02, 1.11)	1.47 (0.82, 2.65)	1.26 (0.71, 2.21)
	Lead	1.01 (0.82, 1.24)	0.98 (0.87, 1.09)	0.98 (0.89, 1.08)
	Chromium	0.94 (0.80, 1.10)	1.01 (0.93, 1.09)	0.99 (0.92, 1.06)
Stroke (total n=1385 incident n=147)	Traffic pollution mixture	0.86 (0.27, 1.31)	0.93 (0.57, 1.77)	1.13 (0.74, 2.10)
	NO ₂	0.37 (0.15, 0.91)	1.28 (0.87, 1.87)	1.07 (0.73, 1.57)
	PM _{2.5}	1.30 (0.54, 3.14)	0.95 (0.38, 2.33)	1.14 (0.63, 2.09)
	O ₃	1.45 (0.93, 2.26)	0.95 (0.84, 1.07)	0.98 (0.86, 1.11)
	1,3-Butadiene	0.12 (0.01, 1.62)	1.05 (0.96, 1.14)	1.05 (0.96, 1.15)
	Benzene	1.26 (0.26, 6.11)	2.33 (0.36, 15.13)	1.63 (0.49, 5.39)
	Nickel	1.19 (0.03, 51.66)	1.47 (0.58, 3.74)	1.39 (0.56, 3.44)
	Lead	1.13 (0.91, 1.41)	0.90 (0.73, 1.11)	0.97 (0.85, 1.12)
	Chromium	0.83 (0.64, 1.08)	0.95 (0.82, 1.09)	0.91 (0.80, 1.03)

Note: Effect estimates are HR (95% CI). For single pollutant models the effect estimates represent the effect per IQR. The results for traffic pollution mixture (NO₂, PM_{2.5}, benzene, and nickel) are obtained from quantile g-computation, and the effect estimate represents the effect of increasing all exposures by one quantile simultaneously. The models have been adjusted for age, sex, household income, years of education, and area-level SES based on demographic information and residential address collected at baseline.

Table S 4-5. Association of 5-year time-varying air pollutant averages with cardiometabolic outcomes adjusted for co-pollutants

Outcome	Pollutant	Adjusted for NO ₂	Adjusted for PM _{2.5}	Adjusted for Benzene	Adjusted for Nickel
Hypertension (total n=558 incident n=433)	NO ₂	1.24 (1.00, 1.55)	1.19 (0.92, 1.53)	1.25 (0.99, 1.60)	1.16 (0.91, 1.48)
	PM _{2.5}	1.13 (0.79, 1.64)	1.28 (0.93, 1.76)	1.49 (0.92, 2.40)	1.17 (0.84, 1.64)
	Benzene	0.93 (0.48, 1.83)	0.68 (0.27, 1.73)	1.23 (0.67, 2.25)	1.10 (0.59, 2.04)
	Nickel	1.39 (0.82, 2.34)	1.46 (0.88, 2.43)	1.57 (0.97, 2.54)	1.59 (0.99, 2.56)
Low HDL cholesterol (total n=967 incident n=417)	NO ₂	1.20 (0.99, 1.45)	1.11 (0.88, 1.39)	1.18 (0.96, 1.46)	1.11 (0.89, 1.38)
	PM _{2.5}	1.27 (0.88, 1.85)	1.39 (1.01, 1.91)	1.63 (1.01, 2.63)	1.28 (0.92, 1.78)
	Benzene	1.10 (0.55, 2.19)	0.64 (0.24, 1.70)	1.37 (0.72, 2.59)	1.23 (0.65, 2.35)
	Nickel	1.55 (0.86, 2.78)	1.56 (0.91, 2.67)	1.71 (1.02, 2.89)	1.76 (1.05, 2.94)
Hypertriglyceridemia (total n=700 incident n=278)	NO ₂	1.10 (0.87, 1.40)	1.10 (0.82, 1.46)	1.15 (0.88, 1.48)	1.02 (0.78, 1.32)
	PM _{2.5}	1.02 (0.65, 1.62)	1.11 (0.75, 1.63)	1.39 (0.78, 2.48)	1.02 (0.68, 1.51)
	Benzene	0.75 (0.32, 1.75)	0.55 (0.17, 1.77)	0.91 (0.42, 1.95)	0.82 (0.38, 1.78)
	Nickel	1.64 (0.81, 3.34)	1.67 (0.85, 3.25)	1.72 (0.90, 3.29)	1.68 (0.89, 3.18)
CVD (total n=974 incident n=362)	NO ₂	1.14 (0.89, 1.46)	1.14 (0.86, 1.52)	1.15 (0.88, 1.51)	1.11 (0.85, 1.46)
	PM _{2.5}	1.00 (0.67, 1.50)	1.10 (0.77, 1.56)	1.18 (0.67, 2.08)	1.06 (0.74, 1.53)
	Benzene	0.92 (0.44, 1.92)	0.83 (0.28, 2.50)	1.08 (0.55, 2.12)	1.03 (0.52, 2.04)
	Nickel	1.13 (0.61, 2.11)	1.22 (0.68, 2.20)	1.25 (0.71, 2.21)	1.26 (0.71, 2.21)

Stroke (total n=1385 incident n=147)	NO ₂	1.07 (0.73, 1.57)	1.03 (0.66, 1.61)	1.01 (0.66, 1.54)	1.01 (0.66, 1.54)
	PM _{2.5}	1.12 (0.56, 2.23)	1.14 (0.63, 2.09)	0.89 (0.35, 2.23)	1.08 (0.58, 2.01)
	Benzene	1.61 (0.44, 5.82)	1.93 (0.32, 11.57)	1.63 (0.49, 5.39)	1.54 (0.46, 5.15)
	Nickel	1.38 (0.51, 3.77)	1.35 (0.53, 3.44)	1.33 (0.53, 3.31)	1.39 (0.56, 3.44)

Note: Effect estimates are HR (95% CI per IQR. The models have been adjusted for age, sex, household income, years of education, area-level SES, and urbanicity based on demographic information and residential address collected at baseline. The effect estimates in grey boxes are single pollutant estimates without adjustment for any co-pollutants.

Table S 4-6. Association of 5-year time-varying air pollutant average mixtures with cardiometabolic outcomes

Outcome	All pollutants	Traffic pollutant mixture
Hypertension (total n=558 incident n=433)	1.42 (1.05, 2.85)	1.23 (0.99, 2.68)
Low HDL cholesterol (total n=967 incident n=417)	1.31 (0.92, 2.51)	1.38 (1.06, 2.90)
Hypertriglyceridemia (total n=700 incident n=278)	0.98 (0.65, 1.91)	1.16 (0.85, 2.34)
CVD (total n=974 incident n=362)	0.89 (0.62, 1.86)	1.19 (0.92, 2.50)
Stroke (total n=1385 incident n=147)	0.81 (0.45, 1.57)	1.13 (0.74, 2.10)

Note: Effect estimates are HR (95% CI). The results are obtained from quantile g-computation, and the effect estimate represents the effect of increasing all exposures by one quantile simultaneously. The models have been adjusted for age, sex, household income, years of education, area-level SES, and urbanicity based on demographic information and residential address collected at baseline. Here traffic pollution mixture consists of NO₂, PM_{2.5}, benzene, and nickel.

Table S 4-7. Association of 5-year time-varying air pollutant averages with cardiometabolic outcomes across differently adjusted models

Outcome	Pollutant	Model 1 (main model)	Model 2	Model 3
Hypertension (total n=558 incident n=433)	Traffic pollution mixture	1.23 (0.99, 2.68)	1.19 (0.94, 2.56)	1.17 (0.91, 2.49)
	NO ₂	1.24 (1.00, 1.55)	1.16 (0.90, 1.48)	1.19 (0.92, 1.54)
	PM _{2.5}	1.28 (0.93, 1.76)	1.17 (0.84, 1.64)	1.14 (0.81, 1.61)
	O ₃	0.97 (0.90, 1.05)	0.99 (0.91, 1.07)	0.99 (0.91, 1.07)
	1,3-Butadiene	1.06 (0.97, 1.16)	1.05 (0.96, 1.16)	1.05 (0.95, 1.15)
	Benzene	1.23 (0.67, 2.25)	1.00 (0.52, 1.90)	1.02 (0.53, 1.99)
	Nickel	1.59 (0.99, 2.56)	1.39 (0.83, 2.33)	1.24 (0.72, 2.14)
	Lead	1.07 (0.99, 1.15)	1.07 (0.99, 1.15)	1.05 (0.97, 1.15)
	Chromium	1.04 (0.97, 1.10)	1.02 (0.95, 1.09)	1.03 (0.96, 1.10)
Low HDL cholesterol (total n=967 incident n=417)	Traffic pollution mixture	1.38 (1.06, 2.90)	1.34 (1.01, 2.75)	1.43 (1.07, 2.91)
	NO ₂	1.20 (0.99, 1.45)	1.14 (0.91, 1.43)	1.19 (0.94, 1.50)
	PM _{2.5}	1.39 (1.01, 1.91)	1.31 (0.94, 1.83)	1.34 (0.95, 1.90)
	O ₃	0.95 (0.90, 1.02)	0.97 (0.91, 1.04)	0.96 (0.89, 1.03)
	1,3-Butadiene	0.76 (0.35, 1.66)	0.65 (0.26, 1.63)	0.70 (0.28, 1.75)
	Benzene	1.37 (0.72, 2.59)	1.20 (0.62, 2.32)	1.18 (0.60, 2.34)
	Nickel	1.76 (1.05, 2.94)	1.59 (0.89, 2.83)	1.70 (0.93, 3.11)

	Lead	1.00 (0.93, 1.07)	1.00 (0.93, 1.08)	0.99 (0.91, 1.07)
	Chromium	1.01 (0.95, 1.07)	0.99 (0.93, 1.06)	0.98 (0.92, 1.05)
Hypertriglyceridemia (total n=700 incident n=278)	Traffic pollution mixture	1.16 (0.85, 2.34)	1.06 (0.76, 2.13)	1.09 (0.77, 2.17)
	NO ₂	1.10 (0.87, 1.40)	1.00 (0.76, 1.33)	0.95 (0.71, 1.26)
	PM _{2.5}	1.11 (0.75, 1.63)	1.01 (0.67, 1.51)	0.99 (0.65, 1.50)
	O ₃	0.95 (0.88, 1.02)	0.96 (0.89, 1.05)	0.99 (0.91, 1.07)
	1,3-Butadiene	0.74 (0.27, 1.99)	0.60 (0.20, 1.86)	0.47 (0.13, 1.64)
	Benzene	0.91 (0.42, 1.95)	0.76 (0.35, 1.69)	0.79 (0.34, 1.81)
	Nickel	1.68 (0.89, 3.18)	1.45 (0.71, 2.96)	1.58 (0.76, 3.29)
	Lead	0.95 (0.86, 1.06)	0.96 (0.86, 1.06)	0.96 (0.86, 1.06)
	Chromium	0.99 (0.92, 1.07)	0.97 (0.90, 1.05)	0.97 (0.90, 1.05)
	Traffic pollution mixture	1.19 (0.92, 2.50)	1.30 (0.97, 2.65)	1.35 (1.01, 2.74)
CVD (total n=974 incident n=362)	NO ₂	1.14 (0.89, 1.46)	1.29 (0.97, 1.71)	1.28 (0.96, 1.71)
	PM _{2.5}	1.10 (0.77, 1.56)	1.16 (0.80, 1.67)	1.14 (0.78, 1.65)
	O ₃	0.91 (0.84, 0.98)	0.87 (0.80, 0.95)	0.88 (0.81, 0.95)
	1,3-Butadiene	1.01 (0.92, 1.10)	1.01 (0.93, 1.10)	1.01 (0.92, 1.10)
	Benzene	1.08 (0.55, 2.12)	1.17 (0.58, 2.36)	1.08 (0.53, 2.19)
	Nickel	1.26 (0.71, 2.21)	1.55 (0.82, 2.90)	2.02 (1.05, 3.87)
	Lead	0.98 (0.89, 1.08)	0.97 (0.88, 1.08)	0.99 (0.89, 1.10)

	Chromium	0.99 (0.92, 1.06)	1.00 (0.93, 1.08)	1.02 (0.94, 1.10)
	Traffic pollution mixture	1.13 (0.74, 2.10)	1.27 (0.79, 2.21)	1.28 (0.79, 2.20)
	NO ₂	1.07 (0.73, 1.57)	1.22 (0.79, 1.90)	1.29 (0.82, 2.03)
	PM _{2.5}	1.14 (0.63, 2.09)	1.25 (0.66, 2.38)	1.19 (0.61, 2.33)
Stroke	O ₃	0.98 (0.86, 1.11)	0.95 (0.83, 1.09)	0.94 (0.82, 1.08)
(total n=1385 incident n=147)	1,3-Butadiene	1.05 (0.96, 1.15)	1.06 (0.96, 1.16)	1.05 (0.96, 1.15)
	Benzene	1.63 (0.49, 5.39)	1.91 (0.55, 6.63)	1.57 (0.42, 5.85)
	Nickel	1.39 (0.56, 3.44)	1.90 (0.69, 5.25)	2.01 (0.70, 5.79)
	Lead	0.97 (0.85, 1.12)	0.97 (0.84, 1.12)	0.99 (0.84, 1.15)
	Chromium	0.91 (0.80, 1.03)	0.92 (0.80, 1.05)	0.93 (0.81, 1.07)

Note: Model 1 was adjusted for age, sex, household income, years of education, area-level SES, and urbanicity based on demographic information and residential address collected at baseline; model 2 was adjusted for variables in model 1 plus baseline annual average 24hr noise exposure; and model 3 was adjusted for variables in model 2 plus primary lifetime occupation, outdoor physical activity, smoking status, and alcohol consumption. Effect estimates are HR (95% CI). For single pollutant models the effect estimates represent the effect per IQR. The results for traffic pollution mixture (NO₂, PM_{2.5}, benzene, and nickel) are obtained from quantile g-computation, and the effect estimate represents the effect of increasing all exposures by one quantile simultaneously.

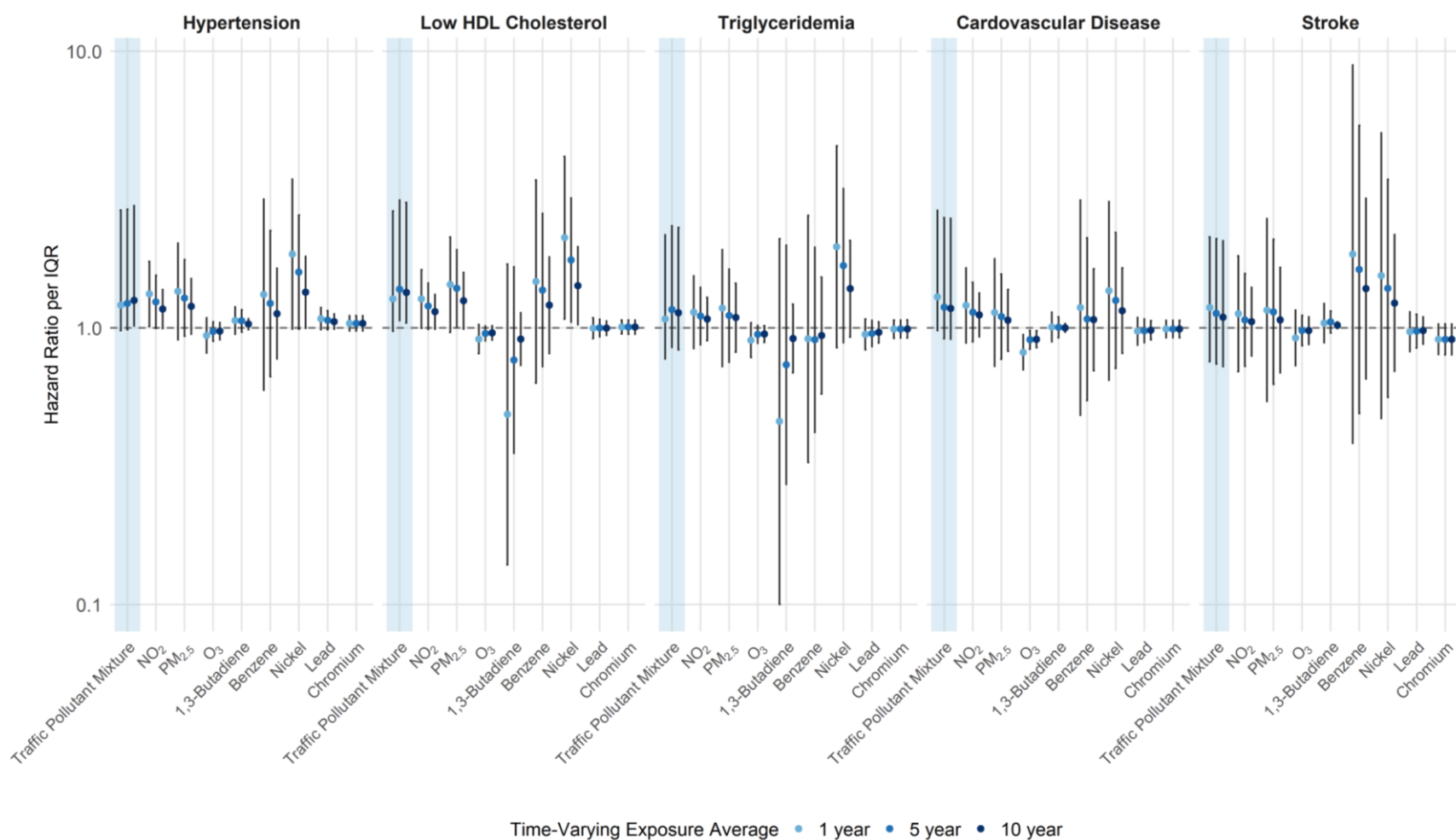


Figure S 4-6. Association of time-varying air pollutant averages over different periods with cardiometabolic outcomes

Note: Here traffic pollution mixture consists of the pollutants NO₂, PM_{2.5}, benzene, and nickel. The models have been adjusted for age, sex, household income, years of education, area-level SES, and urbanicity based on demographic information and residential address collected at baseline.

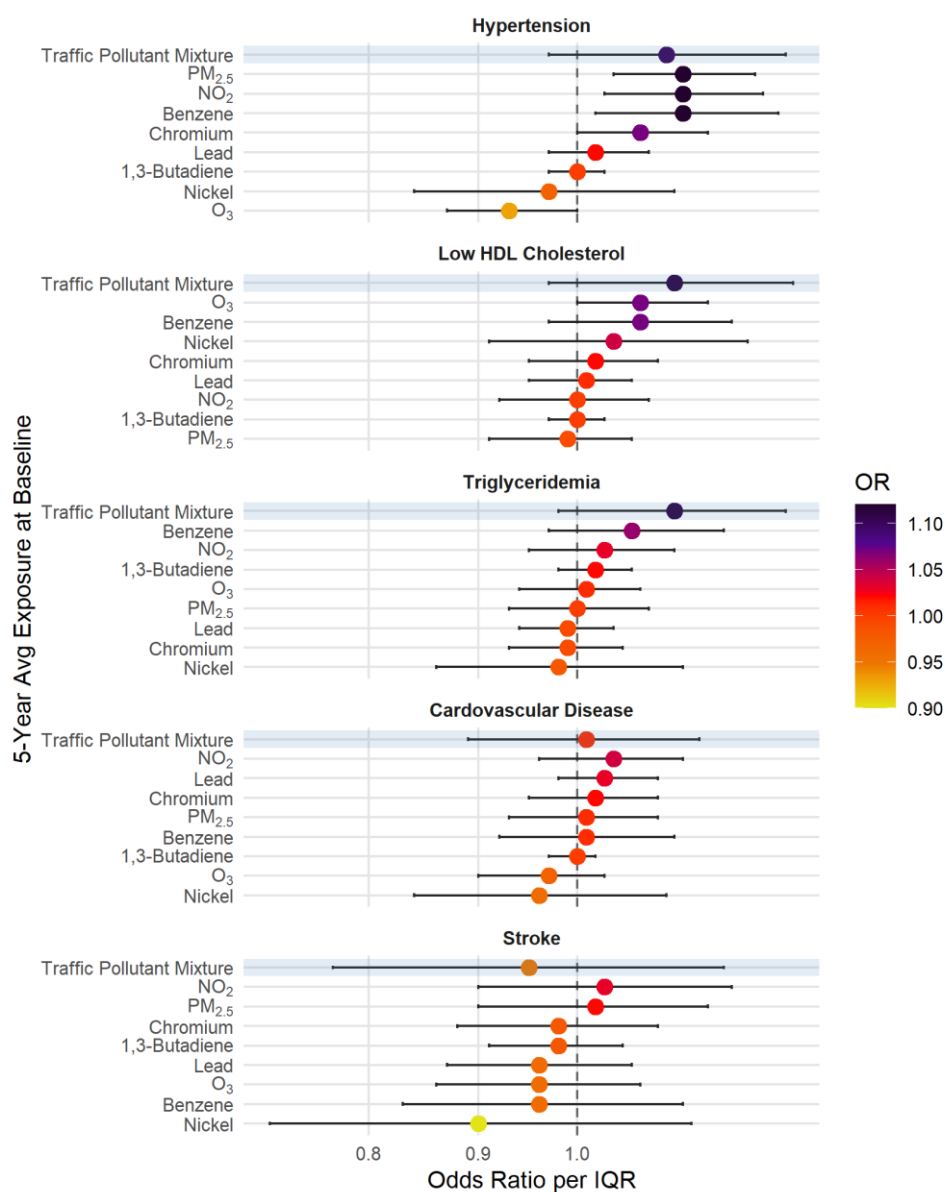


Figure S 4-7. Association of 5-year average air pollutant exposures at baseline with cardiometabolic outcomes

Note: Here traffic pollution mixture consists of the pollutants NO₂, PM_{2.5}, benzene, and nickel. The models have been adjusted for age, sex, household income, years of education, area-level SES, and urbanicity based on demographic information and residential address collected at baseline.

Table S 4-8. Association of average air pollutant exposures at baseline with prevalent cardiometabolic outcomes

	Exposure period	Hypertension (total n=1786 incident n=1100)	Low HDL cholesterol (total n=1786 incident n=643)	Hypertriglyceridemia (total n=1786 incident n=931)	CVD (total n=1779 incident n=659)	Stroke (total n=1779 incident n=168)
Traffic pollution mixture	1 year	1.12 (0.97, 1.28)	0.97 (0.85, 1.12)	0.98 (0.85, 1.12)	0.96 (0.83, 1.10)	1.03 (0.82, 1.30)
	5 years	1.10 (0.97, 1.25)	1.11 (0.97, 1.26)	1.11 (0.98, 1.25)	1.01 (0.89, 1.14)	0.95 (0.77, 1.17)
	10 years	1.10 (0.97, 1.25)	1.10 (0.97, 1.25)	1.11 (0.98, 1.25)	1.00 (0.88, 1.14)	0.95 (0.77, 1.17)
NO ₂	1 year	1.12 (1.03, 1.22)	0.96 (0.88, 1.04)	0.99 (0.91, 1.07)	1.02 (0.94, 1.11)	1.05 (0.92, 1.20)
	5 years	1.12 (1.03, 1.22)	1.00 (0.92, 1.08)	1.03 (0.95, 1.11)	1.04 (0.96, 1.12)	1.03 (0.90, 1.18)
	10 years	1.12 (1.03, 1.22)	1.00 (0.92, 1.08)	1.03 (0.95, 1.11)	1.04 (0.96, 1.12)	1.04 (0.91, 1.18)
PM _{2.5}	1 year	1.15 (1.04, 1.27)	0.91 (0.82, 1.01)	0.93 (0.84, 1.02)	0.98 (0.88, 1.08)	1.05 (0.89, 1.24)
	5 years	1.12 (1.04, 1.21)	0.99 (0.91, 1.06)	1.00 (0.93, 1.08)	1.01 (0.93, 1.09)	1.02 (0.90, 1.15)
	10 years	1.12 (1.04, 1.21)	0.98 (0.91, 1.06)	1.00 (0.93, 1.08)	1.00 (0.93, 1.09)	1.02 (0.90, 1.15)
O ₃	1 year	0.88 (0.75, 1.02)	0.96 (0.82, 1.13)	0.88 (0.76, 1.02)	0.89 (0.76, 1.04)	0.98 (0.75, 1.27)
	5 years	0.93 (0.87, 1.00)	1.07 (1.00, 1.15)	1.01 (0.94, 1.07)	0.97 (0.90, 1.03)	0.96 (0.86, 1.07)
	10 years	0.93 (0.87, 1.00)	1.06 (0.99, 1.14)	1.00 (0.94, 1.07)	0.96 (0.90, 1.03)	0.97 (0.87, 1.07)
1,3- Butadiene	1 year	1.00 (0.84, 1.18)	1.19 (1.00, 1.41)	1.40 (1.14, 1.73)	1.06 (0.90, 1.24)	0.86 (0.63, 1.18)
	5 years	1.00 (0.97, 1.03)	1.00 (0.97, 1.03)	1.02 (0.98, 1.06)	1.00 (0.97, 1.02)	0.98 (0.91, 1.05)
	10 years	1.01 (0.97, 1.04)	1.00 (0.97, 1.03)	1.02 (0.98, 1.07)	1.00 (0.97, 1.03)	0.98 (0.92, 1.05)

Benzene	1 year	1.15 (1.02, 1.30)	0.94 (0.84, 1.06)	0.93 (0.83, 1.04)	0.96 (0.85, 1.08)	1.00 (0.83, 1.20)
	5 years	1.12 (1.02, 1.24)	1.07 (0.97, 1.18)	1.06 (0.97, 1.17)	1.01 (0.92, 1.11)	0.96 (0.83, 1.12)
	10 years	1.11 (1.02, 1.21)	1.05 (0.97, 1.15)	1.04 (0.96, 1.13)	1.00 (0.92, 1.09)	0.97 (0.85, 1.11)
Nickel	1 year	0.97 (0.85, 1.11)	1.09 (0.95, 1.25)	1.04 (0.91, 1.18)	0.98 (0.85, 1.12)	0.89 (0.71, 1.12)
	5 years	0.97 (0.84, 1.11)	1.04 (0.91, 1.20)	0.98 (0.86, 1.12)	0.96 (0.84, 1.10)	0.90 (0.72, 1.13)
	10 years	0.97 (0.85, 1.11)	1.04 (0.91, 1.19)	0.98 (0.86, 1.12)	0.96 (0.84, 1.10)	0.90 (0.72, 1.13)
Lead	1 year	1.03 (0.96, 1.10)	1.02 (0.96, 1.09)	1.00 (0.94, 1.07)	1.04 (0.98, 1.11)	0.94 (0.83, 1.07)
	5 years	1.02 (0.97, 1.08)	1.01 (0.95, 1.06)	0.99 (0.94, 1.04)	1.03 (0.98, 1.09)	0.96 (0.87, 1.06)
	10 years	1.02 (0.97, 1.08)	1.00 (0.95, 1.06)	0.99 (0.94, 1.04)	1.03 (0.98, 1.09)	0.96 (0.87, 1.06)
Chromium	1 year	1.07 (1.00, 1.15)	1.02 (0.95, 1.09)	0.99 (0.93, 1.05)	1.02 (0.95, 1.09)	0.98 (0.88, 1.09)
	5 years	1.07 (1.00, 1.15)	1.02 (0.95, 1.09)	0.99 (0.93, 1.05)	1.02 (0.95, 1.09)	0.98 (0.88, 1.09)
	10 years	1.07 (1.00, 1.15)	1.02 (0.95, 1.09)	0.99 (0.93, 1.05)	1.02 (0.95, 1.09)	0.98 (0.88, 1.09)

Note: Effect estimates are HR (95% CI). For single pollutant models the effect estimates represent the effect per IQR. The results for traffic pollution mixture (NO₂, PM_{2.5}, benzene, and nickel) are obtained from quantile g-computation, and the effect estimate represents the effect of increasing all exposures by one quantile simultaneously. The models have been adjusted for age, sex, household income, years of education, area-level SES, and urbanicity based on demographic information and residential address collected at baseline.

5. PUBLIC HEALTH IMPLICATIONS

Regulations aimed at reducing traffic exhaust emissions over the last few decades were successful in California, and our results indicated declining effect estimates for the associations between PM_{2.5} and NO₂ exposure and PTB and TLBW over the last 30 years. However, we also observed an increase in the effects of zinc and nickel on PTB in recent years, pointing to non-tailpipe emissions, such as brake and tire wear, and industrial emissions as looming dangers. Furthermore, stronger associations were observed among Black, Hispanic and Asian and Pacific Islander populations, who often lived in areas of higher concentrations of metal exposures. These findings underscore the need for further regulation of emissions from non-tailpipe and industrial sources.

Our exploration of the biological mechanisms underlying the effect of gestational air pollution exposure on low birth weight, using polycyclic aromatic hydrocarbons (PAHs) as the studied pollutant, revealed that PAH exposure affected mid-pregnancy placental volume in female fetuses and mid-pregnancy oxygenation of placental blood. These mechanisms may have contributed to subsequent low birth weight. In this cohort, PAH exposure was likely attributable to cooking and traffic sources. These findings highlight the need for public health policies and public health awareness campaigns on ways to reduce PAH exposure, such as switching to electricity for cooking, and using fuels and technologically advanced engines that emit less PAHs. Additionally, our results suggest sex-specific differences in critical windows of vulnerability during gestation, which can help guide clinical advice for expecting parents to prevent adverse birth outcomes.

Results from our third study found strong positive associations between traffic-related pollutants including nickel, PM_{2.5}, and NO₂, and hypertension and low HDL cholesterol in urban areas, with suggestive associations for hypertriglyceridemia, stroke, and CVD. We also found that exposure to lead, chromium, and 1,3-butadiene slightly increased the risk of developing hypertension. Examination of the spatial distribution of lead and chromium concentrations revealed that these pollutants originated primarily from power plants and transportation hubs. Thus, traffic exhaust, non-tailpipe emissions, and industrial sources were all harmful in this vulnerable population of elderly Mexican Americans. These results point to the need for further regulation of emissions from all these sources to protect the most vulnerable populations.

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