Research Report 236, *Traffic-Related Air Pollution and Birth Weight: The Roles of Noise, Placental Function, Green Space, Physical Activity, and Socioeconomic Status (FRONTIER)*, by Dadvand and Sunyer et al.

INTRODUCTION

Traffic-related air pollution is a complex mixture of gases and particles emitted from the use of motor vehicles and includes a variety of pollutants such as nitrogen oxides (NO_x), fine particulate matter ($PM_{2.5}$), heavy metals, elemental carbon, and organic carbon. Sources include tailpipe emissions from vehicle exhaust and nontailpipe emissions such as tire and brake wear and resuspended road dust. Traffic-related air pollution is associated with numerous health effects, including adverse birth outcomes and slower fetal growth.[1]

In a systematic review, the Health Effects Institute (HEI) reported that maternal exposure to traffic-related air pollution, particularly $PM_{2.5}$, was associated with measures of fetal growth restriction, including low birth weight (LBW) at full term, and the newborn being small for its gestational age (SGA).[1] Depending on which pollutant and birth outcome were considered, the strength of the evidence was rated as low to moderate, primarily due to the lack of adjustment for maternal smoking and body mass index (BMI). HEI's systematic review also noted that few birth outcome studies have assessed interactions with spatially correlated factors, such as traffic noise.

HEI issued *Request for Applications 17-1*: *Assessing Adverse Health Effects of Exposure to Traffic-Related Air Pollution, Noise, and Their Interactions with Socioeconomic Status* in 2017 (see Preface). Its goal was to assess the health effects of exposure to traffic-related air pollution, and how these effects might be influenced by spatially correlated factors such as noise, socioeconomic status, and the built environment. Drs. Payam Dadvand and Jordi Sunyer proposed to examine the effects of exposure to traffic-related air pollutants in pregnant women on fetal growth trajectories and birth weight in Barcelona, Spain. They planned to recruit a new cohort of 800 mother–infant pairs and evaluate the influence of noise, green space, stress, physical activity, and socioeconomic status, and the potential role of placental function.

HEI's Research Committee recommended funding the application by Drs. Dadvand and Sunyer because the study was well designed and would incorporate robust assessments of both exposure and health outcomes. The Committee liked the fact that the investigators proposed establishing a new cohort where detailed information could be collected that was not available in previous studies. The Committee appreciated the overall approach, with the use of hybrid air pollution models, personal monitoring, and time–activity information to develop a detailed assessment of traffic-related air pollution exposure, and the assessment of fetal growth using prenatal and postnatal measures.

This Commentary provides the HEI Review Committee's independent evaluation of the study. It is intended to aid the sponsors of HEI and the public by highlighting both the strengths and limitations of the study and by placing the results presented in the Investigators' Report into a broader scientific and regulatory context.

SCIENTIFIC AND REGULATORY BACKGROUND

Birth weight is the most widely used indicator of fetal growth and infant health. LBW is defined as being born weighing 2,500 g (5 pounds, 8 ounces) or less. In Spain and the United States, 8% of babies are born with LBW, and worldwide the statistic reaches 15%.[2,3] LBW can have long-term health ramifications, including increased risk of poor growth, lower lung function, and altered neurodevelopment in childhood and the increased risk of developing chronic respiratory and metabolic diseases in adulthood.[3,4] Thus, preventing fetal growth restriction is of great public health concern.

Environmental influences in early life during critical developmental windows have the potential to alter development and health permanently.[5] Among the most widely studied examples is the effect of maternal smoking during pregnancy, which can change lifetime lung function trajectories. Prenatal tobacco smoke exposure is associated with impaired lung development, decreased function, childhood asthma, and many adult respiratory diseases.[6–8] Other well-known causes

Dr. Payam Dadvand's and Jordi Sunyer's 4.5-year study, "Traffic-Related Air Pollution and Birth Weight: The Roles of Noise, Placental Function, Green Space, Physical Activity, and Socioeconomic Status (FRONTIER)," began in June 2018. Total expenditures were $1,019,015. The draft Investigators' Report from Dadvand, Sunyer, and colleagues was received for review in December 2023. A revised report, received in March 2025, was accepted for publication in April 2025. During the review process, the HEI Review Committee and the investigators had the opportunity to exchange comments and clarify issues in the Investigators' Report and its Commentary. Note: Review Committee member Michael Jerrett was not involved in the review of this report due to a conflict of interest.

* A list of abbreviations and other terms appears at the end of this volume.

of poor fetal growth include malnutrition in both underweight and overweight mothers, disease, and environmental exposures, including air pollution.[3,9]

Traffic-related air pollution has also been associated with poor birth outcomes. It is estimated that a 10 μg/m^3 increase in traffic-related air pollutants, such as $PM_{2.5}$ and NO_2, is equivalent to 5.5 and 2.5 passively smoked cigarettes per day, respectively.[10] The mechanisms by which traffic-related air pollution leads to poor birth outcomes are not fully understood, but are likely multifactorial — involving effects on the mother's health, placental function, or the fetus directly. Animal and human studies suggest that potential mechanisms include alterations in growth and development, increased inflammation and stress responses, and epigenetic modifications.[11]

To protect the public from the health effects of traffic-related air pollution, governments have implemented a variety of regulations primarily aimed at controlling vehicle emissions of specific pollutants, such as $PM_{2.5}$ and NO_x. They include emission standards for new cars and trucks, rules for adherence to emission limits for the useful life of the vehicle, and rules for fuels and fuel additives that reduce emissions. Additional regulations focus on setting fuel efficiency standards or managing transportation plans and infrastructure to support air quality more generally.[1] Broadly, the regulations can facilitate regional compliance with limits set for specific pollutants, such as the US National Ambient Air Quality Standards or the World Health Organization Air Quality Guidelines.

The United States began implementing air quality regulations in 1970 with the Clean Air Act. Although individual European countries started adopting such regulations around the same time, the European Union (EU) has been slower to adopt vehicle emissions controls and set its first directive in 1990. Implementation and enforcement also vary across EU countries. Nevertheless, EU standards are adopted by many countries around the world.[1]

Air quality regulations are mostly based on effects on the respiratory and cardiovascular systems. However, new evidence on developmental outcomes is emerging and is being incorporated into regulatory decision-making so that the most vulnerable members of society, including pregnant women and children, are protected. As an example, the US Environmental Protection Agency has determined that the associations of birth outcomes with $PM_{2.5}$ and NO_X are suggestive of but not sufficient to infer causality.[12,13]

In addition to air pollution, other factors in the urban environment, such as traffic noise and green space (e.g., live green plant life present in tree-lined streets, gardens, and parks) can either confound or modify the health effects of traffic-related air pollution. Prior research suggests that prenatal exposure to traffic noise is associated with lower birth weight and SGA, although there are only a few studies.[14,15] In 2018, the WHO released environmental noise guidelines for Europe, which included recommendations for reducing road traffic noise.[16] In contrast, green space is associated with decreased risk of LBW.[17] The mechanisms by which noise and green space influence health outcomes are likely, in part, mediated by biological stress responses.[14,17] The study described in this report adds valuable information on the health effects of traffic-related air pollutants and noise that can be considered in future scientific reviews used to inform air quality regulations.

STUDY OBJECTIVES

The study aimed to accomplish the following:

1. Establish a new pregnancy cohort in Barcelona, Spain
2. Assess maternal exposure to traffic-related air pollution and noise, and characterize tree canopies and greenness surrounding participants' homes
3. Collect detailed information on maternal stress, physical activity, and placental function
4. Evaluate the association between maternal exposure to traffic-related air pollution and fetal growth while separating the effect of noise, identify relevant windows of vulnerability during pregnancy, and identify modifiers, mediators, and mitigators of this association

Between 2018–2021, Dadvand and Sunyer and colleagues established a new cohort of 1,080 pregnant women in Barcelona, Spain. They conducted a comprehensive exposure assessment to estimate the inhaled dose of traffic-related air pollutants by calculating breathing rates based on measures of physical activity and combining them with pollutant concentration data from land use regression, dispersion, and hybrid air quality models; personal and home monitoring; and time–activity patterns based on time spent at home, work, and commuting. Health and lifestyle data were obtained several times throughout the pregnancy via interviews, questionnaires, and medical records.

They evaluated air pollution exposure in relation to both fetal ultrasound measurements and birth weight and evaluated whether the associations were influenced by numerous neighborhood factors (such as noise and green space) and individual factors (such as maternal stress and physical activity). They also evaluated whether air pollution might affect fetal growth through changes in placental function, which was assessed by ultrasound measurements of blood flow.

SUMMARY OF METHODS AND STUDY DESIGN

STUDY POPULATION

The study recruited 1,080 pregnant women during their first prenatal visit at about 12 weeks of gestation at three major

university hospitals and their affiliated primary care centers in the Barcelona metropolitan area between October 2018 and March 2021. Additional external funds were leveraged to increase the sample size from the originally proposed 800, and the study timeline was extended to accommodate additional recruitment and delays due to the COVID-19 pandemic. Inclusion criteria restricted the study participants to pregnant women, 18–45 years old, with a singleton pregnancy, who were pregnant with a fetus without congenital abnormalities, were living in the hospital catchment area, and were literate in Spanish or Catalan.

Dadvand, Sunyer, and colleagues conducted interviews and collected participant information during two hospital visits at about 12 and 32 weeks of gestation and at two home visits shortly after the two hospital visits (**Commentary Figure 1**). They also used online surveys and collected information from medical records. The home visits included the implementation of personal, in-home, and outside-home air quality monitoring, the implementation of outside-home noise monitoring, and documentation of the home characteristics. They also implemented personal physical activity and geolocation sensors to quantify time–activity patterns. Details are provided below.

EXPOSURE ASSESSMENT

Traffic-Related Air Pollution

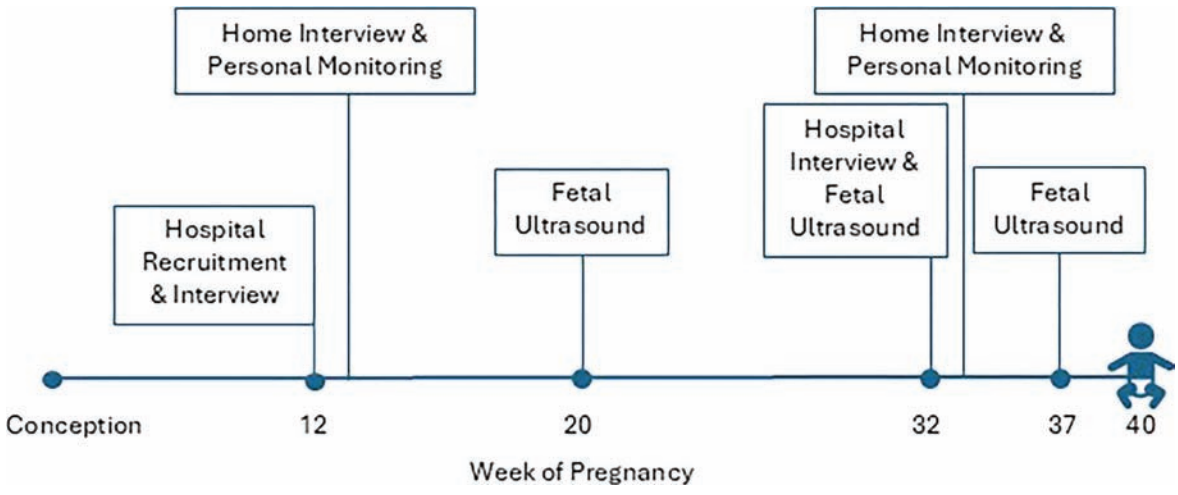
Maternal exposure to traffic-related air pollutants included assessment of black carbon (BC), nitrogen dioxide (NO_2), and fine particulate matter ($PM_{2.5}$), and its metal components of copper (Cu), iron (Fe), and zinc (Zn). Dadvand and Sunyer considered BC and NO_2 to be markers of tailpipe emissions and the $PM_{2.5}$ metal components to be markers of nontailpipe emissions.

Between January 2021 and February 2022, Dadvand and Sunyer conducted four campaigns to measure BC and NO_2 and three campaigns to measure $PM_{2.5}$ and its metal components at 34 urban traffic and background sites across Barcelona. Monitors were placed at street level and away from exhaust outlets, air conditioners, tree lines, and designated outdoor smoking areas. Each campaign lasted an average of 9 days. $PM_{2.5}$ mass was quantified using gravimetric analysis, and $PM_{2.5}$ components were quantified using inductively coupled plasma atomic emission spectrometry and inductively coupled plasma mass spectrometry.

Moreover, home and personal NO_2 concentrations were measured using passive monitoring for one week in the first and third trimesters. In-home monitors were placed in the bedroom, outside-home monitors were placed at the most traffic-exposed window or balcony, and personal monitors were worn around the neck or attached to a backpack with the air inlet near the face. Measurements were processed to remove the effects of short-term meteorological and seasonal variations and averaged across the two monitored weeks.

Simultaneously, physical activity monitoring was used to classify participants' activity level as sedentary, light, moderate, or vigorous, and geolocation monitoring tracked time spent in three microenvironments of home, work, and commuting. Participants also self-reported physical activity using a standardized questionnaire from which average daily total energy expenditure was calculated. They were also asked to document their main commuting route using an interactive map and report the modes of transportation used.

Dadvand and Sunyer applied the monitoring data to develop exposure estimates using three modeling methods: land use regression, dispersion, and hybrid models. For the land use regression models, they followed the European Study of Cohorts for Air Pollution Effects (ESCAPE) protocol.



Commentary Figure 1. Approximate timing of study recruitment and data collection.

They obtained data for 101 potential predictors of traffic-related air pollution at each monitoring location and used a supervised forward selection approach to develop multiple linear regression models for each pollutant using annual average concentrations obtained from the monitoring campaigns as the dependent variable. For NO_2, the models also applied data from the outside-home monitoring. Exposure estimates were then adjusted using the ratio method to estimate hourly exposure.

Dispersion models were developed using ADMS-Urban (Cambridge Environmental Research Consultants), which models the chemical transport and dispersion of pollutants. Hybrid models incorporated the same predictor variables as the land use regression model, the exposure estimates from the dispersion models, monitoring data, and meteorological variables. Random forest algorithms were then applied to capture nonlinearity and interactions between the predictor variables and the pollutants. Validation indicated good performance for all exposure modeling methods. However, dispersion model performance for NO_2 was lower when compared to outside-home and personal measurements.

They estimated hourly exposure during pregnancy for the three microenvironments and then averaged the data over each week, each trimester, and the total pregnancy. They estimated total exposure by incorporating time–activity patterns and calculated the inhaled dose by incorporating the monitored physical activity level and published ventilation rates.[18]

Noise

Dadvand and Sunyer estimated average day, evening, nighttime, and total noise levels using data from their monitoring campaigns and data collected by the government. Noise monitors outside the home were placed next to NO_2 monitors for one week. Participants logged noise events (e.g., construction and parties) in a diary that was used to clean the monitoring data and ensure noise levels were mainly traffic-related. They also assessed home and work road traffic noise using government-based 2017–2022 Strategic Noise Maps for Catalonia. They used standardized questionnaires to assess participant sensitivity and annoyance to noise and protection efforts (e.g., earplugs).

Green Space

Green space within 50-m and 300-m buffers from participant homes was estimated by using two measures. Investigators used the Normalized Difference Vegetation Index based on 2020 aerial photos to provide a two-dimensional measure of live green vegetation at a 1-meter resolution. They also assessed tree canopy volume, a three-dimensional measure of vegetation, using 2016–2017 Light Detection and Ranging data.

FETAL GROWTH ASSESSMENT

Birth weight and SGA were the primary health outcomes and were determined by medical records. SGA was defined as birth weight under the 10th percentile for the gestational age and sex in Barcelona.[19] They also calculated age- and sex-specific birth weight z-scores, which measure how much the baby's weight deviates from population norms. Fetal growth trajectories were considered as a secondary outcome and were determined by transabdominal ultrasound measurements of fetal body dimensions at 20, 32, and 37 weeks of gestation. Placental function was assessed using Doppler ultrasound indicators for fetoplacental hemodynamics at 32 weeks of gestation. Specifically, they quantified the pulsatility index (a measure of resistance to blood flow) in the uterine, umbilical, and fetal cerebral arteries.

MATERNAL STRESS ASSESSMENT

Dadvand and Sunyer evaluated maternal stress in the third trimester of pregnancy using subjective and objective biomarker-based methods. Subjective stress was assessed using the self-administered 10-item Perceived Stress Scale. Hair samples were collected during the third trimester using established guidelines and analyzed for cortisol levels using liquid chromatography with tandem mass spectrometry.

MAIN HEALTH ANALYSES

To assess the effect of traffic-related air pollutants on fetal growth, Dadvand and Sunyer applied single-pollutant mixed effects regression models that accounted for potential differences between hospitals (e.g., the hospital the mother attended was treated as a random effect in the model). Models for trajectories of fetal growth evaluated changes in fetal growth over time by evaluating the interaction between pollutants and gestational age, and allowed the trajectories to vary by participant (e.g., treated as random effects). The main analysis applied the land use regression–based exposure estimates.

To evaluate potential windows of elevated vulnerability, they used distributed lag nonlinear models to assess weekly traffic-related air pollution exposure. To assess the effect of multiple exposures (including traffic-related noise), they applied Lasso, Ridge regression, and Bayesian hierarchical models that are each suitable for accounting for collinearity and evaluated the impact of BC, NO_2, and $PM_{2.5}$ exposures, with and without noise exposure. They also used the monitored NO_2 concentrations to adjust for potential exposure measurement error in the modeled NO_2 exposure estimates.

Dadvand and Sunyer adjusted models for a priori selected covariates that included maternal age, education, first trimester BMI, number of prior births, smoking and alcohol use during pregnancy, environmental tobacco smoke exposure, history of LBW in previous pregnancies, gestational age at birth, and the child's sex. Models for SGA were not adjusted

for gestational age or sex because these variables were used to define SGA. Models that included noise exposure were also adjusted for reported noise sensitivity and noise protection. Missing values were imputed for smoking, alcohol use, maternal weight, and height using multiple imputations with chained equations; all listed variables had less than 7% of data missing. Due to the large number of analyses, they adjusted for multiple statistical comparisons.

ADDITIONAL ANALYSES

Dadvand and Sunyer assessed modification of the associations between traffic-related air pollutants and fetal growth by green space, maternal socioeconomic status, stress (cortisol levels and perceived stress), physical activity (monitored and self-reported), and the pregnancy's timing related to the onset of the COVID-19 pandemic (fully before, fully after, or split). They also used model-based causal mediation analyses to assess whether traffic-related air pollution affects fetal growth by altering placental function.

To evaluate the robustness of the results, Dadvand and Sunyer performed several sensitivity analyses. These included evaluating the complete case analyses without imputation, adjusting the main analyses by removing outliers, removing gestational age at delivery, evaluating hospital of admission as a fixed effect rather than a random effect, using birth weight z-scores, as the outcome variable, adjusting for additional covariates (e.g., child ethnicity, cook stove type, kitchen hood use), and applying exposure estimates derived from the dispersion and hybrid models.

Commentary Table 1. Study Population Characteristics (*N* = 1,024 mother-child pairs)[a]

	Median (IQR)
Maternal age (years)	34.4 (5.8)
Maternal body mass index (kg/m^2)	23.5 (4.9)
Gestational age at birth (weeks)	40 (1.7)
Newborn birth weight (g)	3,310 (580)
	***N* (%)**
European ethnicity	688 (67.2%)
Maternal university degree	713 (69.6%)
Maternal active smoking	79 (8.0%)
Maternal environmental tobacco smoke	422 (43.0%)
Maternal alcohol use	294 (30.2%)
Previous births	450 (43.9%)
Previous LBW baby	37 (3.6%)
Vaginal delivery	767 (74.9%)
Newborn SGA	136 (13.3%)

[a]Values are expressed as median (interquartile range) for continuous variables and N (%) for categorical variables.

SUMMARY OF KEY RESULTS

STUDY POPULATION

The final sample included 1,024 live births. Median maternal age was 34 years, and most mothers were of European ethnicity (67%) (**Commentary Table 1**). Few mothers reported smoking during pregnancy (8%), but 43% reported environmental tobacco smoke exposure, and 30% reported alcohol use. Most babies were born by vaginal delivery (75%). At birth, the median gestational age was 40 weeks, and the median weight was 3,310 g (7 lb 5 oz). Thirteen percent of children were classified as SGA. There were no statistically significant sociodemographic or lifestyle differences between participants included in the study sample compared to those who were lost to follow-up.

TRAFFIC-RELATED AIR POLLUTION AND NOISE EXPOSURE

Traffic-related air pollution and noise exposure estimates based on the land use regression models are presented in **Commentary Table 2**. Median total pregnancy exposure estimates for BC, NO_2, and $PM_{2.5}$ were 1.4, 37.2, and 17.1 µg/m^3, respectively. Median total pregnancy exposure estimates for $PM_{2.5}$ metal components were 6.0 ng/m^3 for Cu, 0.2 µg/m^3 for Fe, and 34.9 ng/m^3 for Zn. Exposures to all pollutants were generally lowest at home and highest during commuting. Dispersion model-based exposure estimates for BC, NO_2, and $PM_{2.5}$ were lower, and hybrid model-based estimates for Fe and Zn were higher than land use regression–based estimates. Traffic-related noise levels at home and work were about 65 decibels, which is above the World Health Organization's recommended 53 decibel limit for traffic noise.[20]

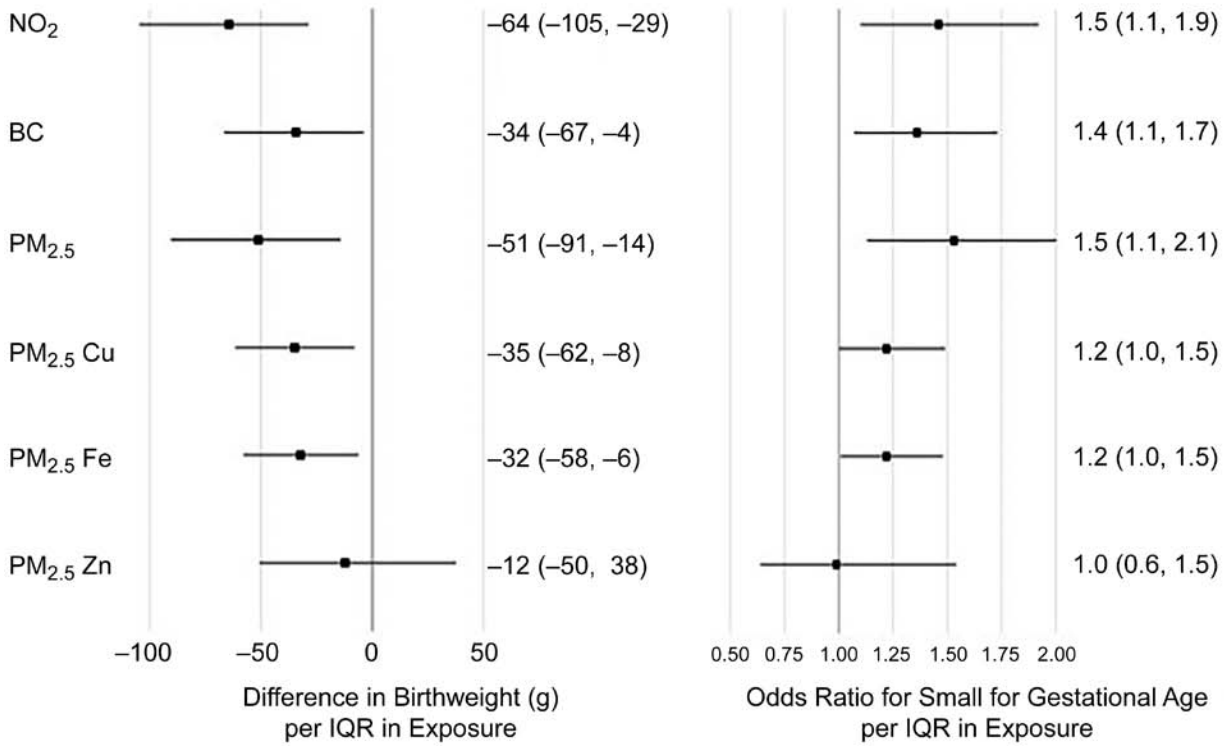
TRAFFIC-RELATED AIR POLLUTION RELATED TO RESTRICTED FETAL GROWTH

Higher exposure to outdoor NO_2, BC, $PM_{2.5}$, and the Cu and Fe fractions of $PM_{2.5}$ during pregnancy was associated with lower birth weight and increased odds of SGA when considering the total exposure across all three microenvironments combined (**Commentary Figure 2**). An interquartile range increase in total exposure to NO_2 (15 µg/m^3) was associated with a birth weight reduction of 64 g and a 46% increased odds of SGA. Similarly, interquartile range increases in total exposure to BC (0.5 µg/m^3) and $PM_{2.5}$ (4.5 µg/m^3) were associated with birth weight reductions of 34 g and 51 g, respectively, and increased the odds of SGA by 36% and 53%, respectively.

Commentary Table 2. Median (IQR) Traffic-Related Air Pollution and Noise Exposure Estimates[a]

	Microenvironment			
	Home	Work	Commute	Total
BC (μg/m³)	1.4 (0.6)	1.6 (0.8)	2.1 (0.9)	1.4 (0.5)
NO_2 (μg/m³)	36.2 (15.1)	46.6 (18.5)	56.0 (21.8)	37.2 (15.0)
$PM_{2.5}$ (μg/m³)	16.8 (5.1)	18.1 (4.5)	18.9 (5.0)	17.1 (4.5)
Cu (ng/m³)	6.0 (2.0)	5.9 (2.5)	6.9 (2.4)	6.0 (2.0)
Fe (μg/m³)	0.2 (0.1)	0.2 (0.1)	0.3 (0.1)	0.2 (0.1)
Zn (ng/m³)	34.3 (25.1)	36.4 (21.7)	36.6 (18.9)	34.9 (22.9)
Noise (dB(A))	64.6 (8.9)	64.7 (8.1)	–	–

[a]Air pollution estimates are based on land use regression. Values are expressed as the median (interquartile range) over the entire pregnancy.



Commentary Figure 2. Association between an interquartile range increase in traffic-related air pollution and fetal growth across all three microenvironments combined (home, commuting, and workplace) based on the land use regression model exposure estimates.
BC = black carbon; IQR = interquartile ratio.

For the microenvironment-specific analyses, higher exposure to traffic-related air pollutants at home was generally associated with statistically significantly lower birth weight and increased risk of SGA. Similar associations were observed for workplace and commuting exposures, although they were generally not statistically significant. This finding might suggest that duration of exposure was more important than intensity, but one should note that estimates for the different microenvironments are not directly comparable because they were reported for an interquartile range change in exposure, which differed across the microenvironments. In contrast, associations for the Zn component of $PM_{2.5}$ were generally weak for total and home exposure. There was a trend for a potential protective effect of the Zn fraction of $PM_{2.5}$ for workplace and commuting exposures, but this effect did not reach significance.

A similar pattern of associations was observed for exposure based on estimated inhaled dose. Additionally, models of NO_2 that were adjusted for exposure measurement error yielded associations that were larger in magnitude (e.g., larger decreases in birth weight) and had wider confidence intervals.

The windows of heightened vulnerability to traffic-related air pollution included the late first to early second trimesters and the late third trimester. Exposure to NO_2, $PM_{2.5}$ (**Commentary Figure 3**), and the Cu and Fe fractions of $PM_{2.5}$ (not shown) during the late first to early second trimesters were associated with lower birth weight. BC exposure during the late third trimester was also associated with lower birth weight (Commentary Figure 3).

In evaluating fetal weight trajectories over time, higher maternal exposure to outdoor NO_2 and BC was generally associated with slower fetal growth, although the associations did not reach statistical significance. The Zn fraction of $PM_{2.5}$ was associated with faster fetal growth. Results were consistent for multiple fetal anthropometric measurements.

In models of traffic-related air pollution and noise exposure combined, similar associations were observed between the air pollutants and fetal growth outcomes. In these models, noise exposure itself was generally associated with lower birth weight and increased risk of SGA, but those estimates were not statistically significant, suggesting that traffic noise was less important than traffic pollution. Adjustment for noise annoyance and protection efforts (such as earplugs) yielded similar results.

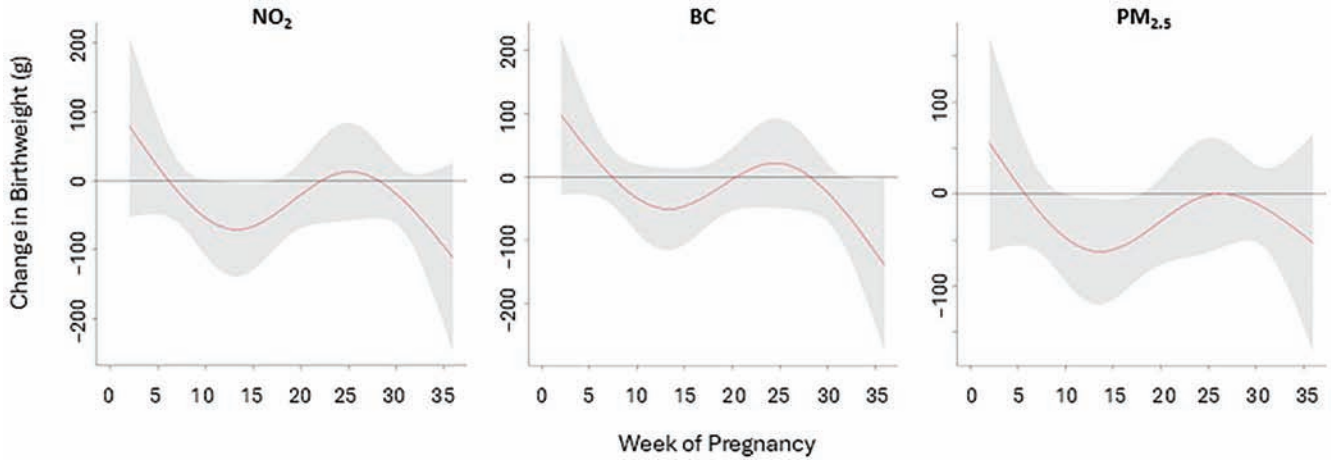
Multipollutant analyses that included NO_2, $PM_{2.5}$, and BC in the models suggested that NO_2 was associated with decreased birth weight, whereas the associations for $PM_{2.5}$ and BC were inconclusive. In contrast, the models suggested that $PM_{2.5}$ was associated with SGA, whereas NO_2 and BC were not.

Role of Placental Function

Higher exposure to outdoor $PM_{2.5}$ during pregnancy was associated with a higher pulsatility index (i.e., higher resistance to blood flow) in the umbilical artery (which delivers blood between the fetus and placenta) during the third trimester of pregnancy. Thus, Dadvand and Sunyer evaluated this measure of placental function as a potential intermediate biological step between traffic-related air pollution exposure and fetal growth using mediation analysis. They estimated that umbilical artery pulsatility explained 9.1% and 3.5% of the association of $PM_{2.5}$ with birth weight and SGA, respectively.

ADDITIONAL ANALYSES

Stratified analyses suggested that the associations between traffic-related air pollutants and both birth weight and SGA were larger in magnitude among families with higher socioeconomic status, as measured by maternal education level and neighborhood-level household income. Associations were also generally larger in magnitude for mothers with higher levels of the stress hormone cortisol, but not for perceived stress. Associations with birth weight tended to be slightly attenuated for mothers living in areas with higher levels of green space within a 300-m buffer of the home, but this trend was not observed for other measures of green space. There was no consistent trend demonstrating differences in associations by maternal physical activity level or timing of the pregnancy with respect to the COVID-19 pandemic. The sensitivity analyses generally yielded similar results to the main analysis.



Commentary Figure 3. Traffic-related air pollution exposure effects on LBW across pregnancy. The red line represents the effect estimate, and the shaded area represents the 95% confidence interval. Exposure estimates are derived from the land use regression model.

HEI REVIEW COMMITTEE'S EVALUATION

This study recruited 1,080 pregnant women in Barcelona, Spain, to evaluate the effect of prenatal traffic-related air pollution exposure on fetal growth. Dadvand and Sunyer and colleagues found that NO_2, BC, $PM_{2.5}$, and the Cu and Fe fractions of $PM_{2.5}$ were associated with lower birth weight and increased odds of SGA. They found that the most vulnerable periods of exposure were during the late first to early second trimester and the late third trimester of pregnancy. NO_2 and BC were also related to slower fetal growth throughout gestation. They also found that the associations between $PM_{2.5}$ and decreased fetal growth might be partly mediated by higher resistance to blood flow in the umbilical artery. These results suggested that prenatal exposure to both tailpipe emissions, as indicated by NO_2 and BC, and nontailpipe emissions, as indicated by $PM_{2.5}$ and its Cu and Fe metal components, can negatively affect fetal growth.

In its independent review of the study, the HEI Review Committee concluded that this report presents a thorough investigation into associations between exposure to traffic-related air pollution and fetal growth. Details on the strengths and limitations of the study are discussed below.

STUDY DESIGN, DATASETS, AND ANALYTICAL APPROACHES

The Committee noted that the study implemented a high-quality design, including the recruitment of a new cohort of pregnant women, the documentation of detailed health and lifestyle information, and the repeated follow-up throughout pregnancy. Multiple measures of fetal growth were used, including prenatal ultrasound measurements of the fetus and weight-based measures at birth. The Committee appreciated the comprehensive exposure assessment, which implemented home and personal monitoring and three contrasting air pollution exposure modeling methods (land use regression, dispersion, and hybrid), included information on noise and green space, evaluated the potential for exposure measurement error, and incorporated information on time–activity patterns in the home, workplace, and during commuting. Findings were similar, although not always statistically significant, across the different exposure modeling methods and microenvironments.

The results suggest that exposure measurement bias in epidemiological studies based on outdoor concentrations at residential locations might be small and that accounting for different microenvironments (including commuting) might not be an important consideration in certain contexts. Similar findings have been documented by de Hoogh and colleagues in their HEI-funded study.[21] A recent review also reported similar findings in five of six identified health studies.[22]

The thorough statistical analysis included a detailed evaluation of windows of vulnerability, multipollutant modeling, and effect modification by a range of factors such as socioeconomic status, physical activity, and green space. The detailed data collection allowed the investigators to adjust for maternal smoking and prepregnancy BMI, both of which were noted in the HEI review on traffic-related pollution[1] as lacking in many prior studies and a major reason for uncertainty in establishing a causal association. Additionally, few prior studies adjusted for traffic-related noise in their assessments of traffic-related air pollution and birth outcomes. Thus, this study helped fill important gaps in the scientific literature and will be useful in future systematic reviews and regulatory science assessments.

The Committee noted that a limitation of the analyses included that the multipollutant analysis did not account for potential nonlinearity or interactions among the pollutants. They also noted that the procedure to adjust for seasonality of exposures might remove important variability in the exposure that might relate to known seasonal variability in birth outcomes.[23–25]

FINDINGS AND INTERPRETATION

The median (and interquartile range) estimated air pollution exposures based on the land use regression models during the 40-week pregnancy were 37.2 (15.0) $\mu g/m^3$ for NO_2 and 17.1 (4.5) $\mu g/m^3$ for $PM_{2.5}$. For context, the EU one-year limit values are 40 $\mu g/m^3$ for NO_2 and 20 $\mu g/m^3$ for $PM_{2.5}$.[26] By 2030, the EU limit values will be lowered to 20 $\mu g/m^3$ for NO_2 and 10 $\mu g/m^3$ for $PM_{2.5,}$ which align more closely with the 2021 World Health Organization Air Quality Guidelines.[27,28] In the United States, the one-year National Ambient Air Quality Standards are 53 ppb for NO_2 (annual average) and 9 $\mu g/m^3$ for primary $PM_{2.5}$ (averaged over three years).[29,30]

Results in this study were largely consistent with prior research demonstrating that traffic-related air pollutants, including $PM_{2.5}$ and NO_2, are related to slower fetal growth.[1] Interquartile range increases in total exposure to NO_2 and $PM_{2.5}$ during pregnancy were associated with a birth weight reduction of 64 g and 51 g, respectively. As a reference, these reductions were smaller than reductions in birth weight reported for active maternal smoking during pregnancy, which ranged from 86 g to 755 g, depending on the frequency and duration of smoking.[31,32] However, the results in this study were similar to some of the birth weight reductions reported for environmental tobacco smoke exposure during pregnancy, ranging from 18 g to 129 g.[31,32]

This study also evaluated the metal components of $PM_{2.5}$; this evaluation is important because $PM_{2.5}$ is a complex mixture, and different components might elicit different effects. Indeed, Dadvand and Sunyer reported that exposure to the Cu and Fe fractions of $PM_{2.5}$ was generally related to decreased fetal growth, whereas Zn fractions suggested a protective association. Prior studies on $PM_{2.5}$ and birth outcomes, including birth weight, have reported inconsistent results and were sensitive to the variables selected for adjustment and the statistical model formulation.[33,34] However, a meta-analysis

focused on trace metal levels (and not air pollution exposures specifically) reported that Cu levels measured in cord blood were associated with an increased risk of SGA, and that Zn levels measured in the maternal and cord blood were related to increased birth weight.[35] Both Cu and Zn are essential trace minerals that are required for human health, but can be toxic in higher doses. Research also demonstrates that prenatal Zn deficiency can be catastrophic to normal development and that a healthy pregnancy requires higher nutritional Zn.[35] Future studies are needed to further clarify the effects of $PM_{2.5}$ components.

CONCLUSIONS

In summary, Dadvand and Sunyer and colleagues examined whether traffic-related air pollution exposure during pregnancy was associated with fetal growth. They observed that NO_2, BC, $PM_{2.5}$, and certain PM components were associated with multiple measures of fetal growth, including slower fetal growth trajectories, lower birth weight, and increased risk of infants being born small for their gestational age. This study adds to the existing body of literature demonstrating that traffic-related air pollution during pregnancy can alter fetal development.

This study found that results were similar when analyses used fairly simple versus complicated exposure estimates. This indicates that future studies in similar urban environments might reasonably simplify exposure assessments when resources are limited. Additional research is needed to clarify the effects of $PM_{2.5}$ components, such as metals, and particularly those metals that can be beneficial in small doses and harmful in larger doses.

ACKNOWLEDGMENTS

The HEI Review Committee thanks the ad hoc reviewers for their help in evaluating the scientific merit of the Investigators' Report. The Committee is also grateful to Hanna Boogaard for oversight of the study, to Eva Tanner for assistance with the review of the Investigators' Report and preparation of its Commentary, to Tom Zaczkiewicz for editing the Investigators' Report and its Commentary, and to Kristin Eckles for her role in preparing this Research Report for publication.

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