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RESEARCH REPORT

Traffic-Related Air Pollution and Birth Weight: The Roles of Noise, Placental Function, Green Space, Physical Activity, and Socioeconomic Status (FRONTIER)

Payam Dadvand (co-principal investigator), Jordi Sunyer (co-principal investigator), Ioar Rivas, Maria Dolores Gómez-Roig, Elisa Llurba, Maria Foraster, Gustavo Arévalo, Lluís Barril, Mariona Bustamante, Xavier Basagaña, Marta Cirach, Alan Domínguez, Toni Galmés, Mireia Gascon, Jose Lao, Edurne Mazarico Gallego, Teresa Moreno, Mark J. Nieuwenhuijsen, Cecilia Persavento, Bruno Raimbault, Xavier Querol, and Cathryn Tonne

INCLUDES A COMMENTARY BY THE INSTITUTE'S REVIEW COMMITTEE

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with a Commentary by the HEI Review Committee

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ABOUT HEI

The Health Effects Institute is a nonprofit corporation chartered in 1980 as an independent research organization to provide high-quality, impartial, and relevant science on the effects of air pollution on health. To accomplish its mission, the Institute

- identifies the highest-priority areas for health effects research
- competitively funds and oversees research projects
- provides an intensive independent review of HEI-supported studies and related research
- integrates HEI's research results with those of other institutions into broader evaluations
- communicates the results of HEI's research and analyses to public and private decision-makers.

HEI typically receives balanced funding from the US Environmental Protection Agency and the worldwide motor vehicle industry. Frequently, other public and private organizations in the United States and around the world also support major projects or research programs. HEI has funded more than 390 research projects in North America, Europe, Asia, and Latin America, the results of which have informed decisions regarding carbon monoxide, air toxics, nitrogen oxides, diesel exhaust, ozone, particulate matter, and other pollutants. These results have appeared in more than 275 comprehensive reports published by HEI, as well as in more than 2,500 articles in peer-reviewed literature.

HEI's independent Board of Directors consists of leaders in science and policy who are committed to fostering the public–private partnership that is central to the organization. The Research Committee solicits input from HEI sponsors and other stakeholders and works with scientific staff to develop a Five-Year Strategic Plan, select research projects for funding, and oversee their conduct. The Review Committee or Panel, which has no role in selecting or overseeing studies, works with staff to evaluate and interpret the results of funded studies and related research.

All project results and accompanying comments by the Review Committee or Panel are widely disseminated through HEI's website (*www.healtheffects.org*), reports, newsletters, annual conferences, and presentations to legislative bodies and public agencies.

ABOUT THIS REPORT

Research Report 236, *Traffic-Related Air Pollution and Birth Weight: The Roles of Noise, Placental Function, Green Space, Physical Activity, and Socioeconomic Status (FRONTIER)*, presents a research project funded by the Health Effects Institute and conducted by Dr. Payam Dadvand and Dr. Jordi Sunyer at the Barcelona Institute for Global Health (ISGlobal), Barcelona, Spain, and colleagues. The report contains three main sections:

The **HEI Statement**, prepared by staff at HEI, is a brief, nontechnical summary of the study and its findings; it also briefly describes the Review Committee's comments on the study.

The **Investigators' Report**, prepared by Dadvand, Sunyer, and colleagues, describes the scientific background, aims, methods, results, and conclusions of the study.

The **Commentary**, prepared by members of the Review Committee with the assistance of HEI staff, places the study in a broader scientific context, points out its strengths and limitations, and discusses remaining uncertainties and implications of the study's findings for public health and future research.

This report has gone through HEI's rigorous review process. When an HEI-funded study is completed, the investigators submit a draft final report presenting the background and results of the study. Outside technical reviewers first examine this draft report. The report and the reviewers' comments are then evaluated by members of the Review Committee, an independent panel of distinguished scientists who are not involved in selecting or overseeing HEI studies. During the review process, the investigators have an opportunity to exchange comments with the Review Committee and, as necessary, to revise their report. The Commentary reflects the information provided in the final version of the report.

Although this report was produced with partial funding by the United States Environmental Protection Agency under Assistance Award CR–83998101 to the Health Effects Institute, it has not been subjected to the Agency's peer and administrative review and may not necessarily reflect the views of the Agency; thus, no official endorsement by it should be inferred. The contents of this report have also not been reviewed by private party institutions, including those that support the Health Effects Institute, and may not reflect the views or policies of these parties; thus, no endorsement by them should be inferred.

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* Herring, Berhane, and Kelly rotated off the Committee before this report's publication.

† Review Committee member Jerrett did not participate in the review of this report due to a conflict of interest.

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PREFACE

HEI's Research to Assess Health Effects of Traffic-Related Air Pollution and to Improve Exposure Assessment for Health Studies

INTRODUCTION

Traffic emissions are an important source of urban air pollution and have been linked to various adverse health outcomes (Atkinson et al. 2018; Health Canada 2016; HEI 2010; HEI 2022a; Huangfu and Atkinson 2020; US Environmental Protection Agency [US EPA] 2016). Over the last several decades, air quality regulations and improvements in vehicular emission control technologies have steadily decreased emissions from motor vehicles. As a result, ambient concentrations of several major traffic-related air pollutants have decreased in most high-income countries, even as vehicle miles traveled and economic activity have increased, and older or malfunctioning vehicles have remained on the roads (HEI 2022a; US EPA 2023).

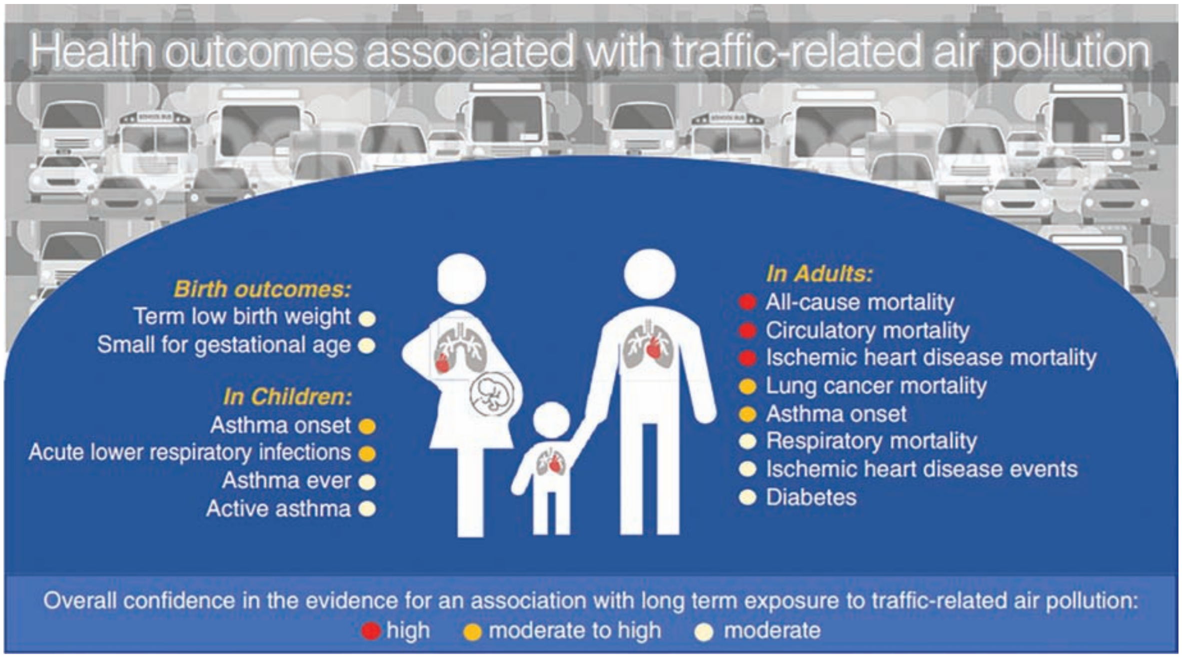
Following HEI's widely cited 2010 Report (HEI 2010), HEI published *Special Report 23*, a systematic review of more than 350 epidemiological studies on the health effects of long-term exposure to emissions of primary traffic-related air pollutants (HEI 2022a). The report found a high level of confidence that strong connections exist between traffic-related air pollution and early death due to cardiovascular diseases. A strong connection was also found between traffic-related air pollution and lung cancer mortality, asthma onset in children and adults, and acute lower respiratory infections in children (**Preface Figure**). The confidence in the evidence was considered moderate, low, or very low for the other selected outcomes, such as coronary events, diabetes, and adverse birth outcomes.

Although traffic-related emissions have decreased over the past decades, further research is warranted in several areas. Emerging evidence suggests that transportation can affect health through many intertwined pathways such as collisions, noise, climate change, temperature, stress, and the lack of physical activity and green space (Glazener et al. 2021). As tailpipe emissions from internal combustion engines decrease and electric vehicles increase market share, more studies are needed to quantify human exposures to nontailpipe particulate matter better and to assess the health effects associated with those exposures. Relatively few studies evaluate how influential factors such as green space, heat exposure, noise pollution, and physical activity interact with or modify air pollution health effects. Evaluation of those factors and exposures are critical because they reflect real-world conditions and might further advance our understanding of the implications of transportation activities on traffic-related air pollution and health (Khreis et al. 2020).

Moreover, better understanding is needed of the role of specific pollutants including nitrogen dioxide (NO_2) and ultrafine particles (UFPs), the health effects of short-term exposures versus long-term exposures, the effects on a broader range of health outcomes (such as neurological and birth outcomes) that have not been extensively examined, and the ways in which marginalized communities are affected. However, a challenge for exposure assessment of traffic-related air pollution is that traffic emits a complex mixture of pollutants in particulate and gaseous forms, many of which are also emitted by other sources. In addition, traffic-related air pollution is characterized by high spatial and temporal variability, with the highest concentrations occurring at or near major roads. Therefore, it has been difficult to identify an appropriate exposure metric that uniquely indicates traffic-related air pollution and to model the distribution of exposure at a sufficiently high degree of spatial and temporal resolution.

Various air quality models — such as dispersion, land use regression, and hybrid models — have been developed to estimate long-term exposure to air pollution (HEI 2022a; Hoek 2017; Jerrett et al. 2005). Recent developments in measurement technologies and approaches to modeling long-term exposure to air pollution have increasingly been used to provide air pollution estimates at fine spatial scales for epidemiological studies of large populations. Advances include novel air pollution sensors, mobile monitoring, satellite data, hybrid models, and machine-learning approaches (Hoek 2017).

Moreover, many improvements in exposure models have occurred over time with the advance of geographic information system approaches and the application of more sophisticated statistical methods; see, for example, several studies previously funded by HEI: Apte et al. 2024, Barratt et al. 2018, Batterman et al. 2020, Frey et al. 2022, and Sarnat et al. 2018. However, the usefulness of exposure estimates still depends on the model assumptions and input data quality, and there remain limitations and challenges when predicting air pollution exposure, particularly for such



Preface Figure. Overall confidence in the evidence for an association between long-term exposure to traffic-related air pollution and selected health outcomes. Health outcomes for which the overall confidence in the evidence was low to moderate, low, or very low are not in the figure. Reproduced from HEI 2022a.

pollutants as UFPs, NO_2, and black carbon (BC) that vary highly in space and time. Few studies have compared the performance of different models and evaluated exposure measurement error and possible bias in health estimations.

Thus, HEI issued complementary requests for applications in 2017 (RFA 17-1) and 2019 (RFA 19-1) to evaluate traffic-related health effects in the context of spatially correlated factors — specifically traffic noise, socioeconomic status, and green space — and to improve exposure assessment for health studies.

OBJECTIVES OF THE RFAs

OBJECTIVES OF RFA 17-1

RFA 17-1, Assessing Adverse Health Effects of Exposure to Traffic-Related Air Pollution, Noise, and Their Interactions with Socioeconomic Status, solicited studies that sought to assess adverse health effects from exposure to traffic-related air pollution and to disentangle the effects from spatially correlated confounding or modifying factors — most notably, traffic noise, socioeconomic status, and the built environment, including green space. The RFA had five major objectives:

1. In the proposed health studies, develop, validate, and apply improved exposure assessment methods and models suitable for estimating exposure to traffic-related air pollution that take into account other air pollution sources in urban areas (such as airports, [sea]ports, industries, and other local point sources) and that would be able to distinguish between tailpipe and nontailpipe traffic emissions.
2. Propose ways in these studies to disentangle the relationship between the adverse health effects of traffic-related air pollution and traffic noise.
3. Develop, evaluate, and apply indicators of socioeconomic status at the individual and community levels in the proposed health studies; if such indicators are novel, compare with socioeconomic status indicators commonly used in the literature.
4. Explore the role of other factors that might confound or modify the health effects of traffic-related air pollution at the individual (e.g., age, smoking status, diet, physical activity, and health status) and community levels (e.g., presence of green space, other factors related to the built environment, and walkability).
5. Investigate — to the extent that the measurements and patterns of a range of different indicators of traffic-related air pollution allow it (e.g., NO_2, UFPs, BC, and indicators of nontailpipe emissions) — whether one or more of them can be shown to have health effects independent of the other pollutants.

OBJECTIVES OF RFA 19-1

RFA 19-1, Applying Novel Approaches to Improve Long-Term Exposure Assessment of Outdoor Air Pollution for Health Studies, solicited studies to assess exposures to air pollution using new and conventional exposure assessment approaches, to evaluate quantitatively exposure measurement error to determine the added value of the novel approaches, and to apply the exposure estimates in epidemiological analyses to evaluate the potential effect of exposure measurement error on chronic health estimates. The RFA had four major objectives:

1. Conduct a new monitoring campaign designed to determine long-term exposure to outdoor air pollutants with high spatial and temporal variability by using sensors, mobile monitoring, location tracking, or other approaches.
2. Develop several exposure assessment approaches suitable to estimate long-term exposure to air pollution at relevant spatial and temporal scales for use in an ongoing or future health study.
3. Quantify exposure measurement error by evaluating and comparing the performance of models of long-term air pollution exposure developed under this RFA to the performance of previous models.
4. Apply the various exposure estimates in an ongoing health study to evaluate the potential impact of exposure measurement error in health estimates or explain how the exposure assessments would be directly applicable to future health studies.

DESCRIPTION OF THE RESEARCH PROGRAM

Three 4-year studies were funded under RFA 17-1, and five 3-year studies were funded under RFA 19-1 to cover the various RFA objectives; they are summarized below (**Preface Table**). The study by Dadvand and Sunyer and colleagues described in this report (Research Report 236) is the sixth to be published.

STUDIES FUNDED UNDER RFA 17-1

HEI funded two studies in Europe and one study in the United States to evaluate various aspects of the association between long-term traffic-related air pollution and health by using existing cohorts (Denmark, USA) and a newly recruited cohort (Spain). Two studies focused on health outcomes during pregnancy (Dadvand) and childhood (Franklin), and one study focused on cardiometabolic outcomes in adults (Raaschou-Nielsen).

"Traffic-Related Air Pollution and Birth Weight: The Roles of Noise, Placental Function, Green Space, Physical Activity, and Socioeconomic Status (FRONTIER)," Payam Dadvand and Jordi Sunyer, Barcelona Institute for Global Health (ISGlobal), Spain Dadvand, Sunyer, and colleagues established a new cohort, named Barcelona Life Study Cohort (BiSC) of 1,080 healthy pregnant women in Barcelona, Spain, in 2018. They estimated exposure to various traffic-related pollutants by using hybrid models that included dispersion models, land use data, time-activity data, and personal and home-outdoor air pollution monitoring data. They linked the exposure to various birth outcomes including birth weight, small for gestational age, and fetal growth trajectories. They evaluated the role of traffic noise and green space and also took into account socioeconomic status and maternal stress (current report).

"Intersections as Hot Spots: Assessing the Contribution of Localized Non-Tailpipe Emissions and Noise on the Association between Traffic and Children's Respiratory Health," Meredith Franklin, University of Southern California, Los Angeles Franklin and colleagues developed novel exposure models of tailpipe and nontailpipe air pollutants and noise and applied those models to children's respiratory health in a large Southern California cohort that was also studied in a previous HEI-funded study led by Frank Gilliland; see *HEI Research Report 190*. They made use of the most recent Children's Health Study (CHS) cohort that was initiated in 2003 and included about 2,000 children in eight communities. Longitudinal data on asthma and lung function were collected at various time points (2008–2012) at ages 11 through 16. Air pollution models were supported by particulate matter filters at more than 200 locations in the eight Southern California communities (in press).

"Cardiometabolic Health Effects of Air Pollution, Noise, Green Space and Socioeconomic Status: The HERMES Study," Ole Raaschou-Nielsen, Danish Cancer Institute, Copenhagen, Denmark Raaschou-Nielsen and colleagues evaluated effects of traffic-related air pollution, traffic noise, lack of green space, and other factors on myocardial infarction, stroke, diabetes, and related biomarkers in three cohorts, including an administrative cohort of about 2.6 million Danish adults in the period 2005–2017. They assessed traffic-related air pollution using a chemical transport model for various pollutants, including UFPs and NO_2. In addition, they assessed noise, individual- and neighborhood-level socioeconomic status, and various residential green space exposure metrics (Research Report 222).

STUDIES FUNDED UNDER RFA 19-1

HEI funded five studies in North America and Europe to evaluate different aspects of improvements to exposure assessment and the application of different exposure assessment approaches to existing cohorts. Three studies are focused on combining novel methods for measuring air pollution and diverse exposure assessment approaches to improve exposure assignment, including machine learning and mobile monitoring (Weichenthal and Hoek) and mobility (de Hoogh). Two studies are testing the added value of incrementally more complex statistical modeling approaches to improving exposure assessment in London (Katsouyanni) and Seattle (Sheppard) and applying their findings to estimating health effects in epidemiological studies.

"Long-Term Exposure to Outdoor Ultrafine Particles and Black Carbon and Effects on Mortality in Montreal and Toronto, Canada," Scott Weichenthal, McGill University, Montreal, Canada Weichenthal and colleagues estimated associations between long-term exposures to UFPs, BC, and other pollutants and mortality in Toronto and Montreal, Canada, using several exposure modeling approaches. They conducted mobile monitoring campaigns in both cities and used those newly collected data to develop various high-resolution exposure models, including land use regression and machine learning. They then evaluated how the effect estimates for nonaccidental and cause-specific mortality in the Canadian Census Health and Environment Cohort (CanCHEC) are influenced by different exposure models (Research Report 217).

"Comparison of Long-Term Air Pollution Exposure Assessment Based on Mobile Monitoring, Low-Cost Sensors, Dispersion Modelling and Routine Monitoring-Based Exposure Models (CLAIRE)," Gerard Hoek, Utrecht University, The

Preface Table. Key Characteristics of HEI's Research to Assess Health Effects of Traffic-Related Air Pollution and to Improve Exposure Assessment for Health Studies

Principal Investigator	Study Name	Location	Study Period	Study Population	Sample Size	Outcomes	Main Air Pollutants	Monitoring Data	Exposure Assessment
RFA 17-1, *Assessing Adverse Health Effects of Exposure to Traffic-Related Air Pollution, Noise, and Their Interactions with Socioeconomic Status*									
Dadvand and Sunyer (current report)	FRONTIER (BiSC)	Barcelona, Spain	2018–2022	Newborns	1,080	Birth weight, small for gestational age, fetal growth trajectories, and placental function	BC, NO_2, $PM_{2.5}$, Cu, Fe, and Zn	Personal, indoor, and outdoor home measurements	LUR, dispersion, and hybrid models
Franklin	CHS	Southern California	2008–2012	Children	2,000	Asthma and lung function	PM_{coarse}, $PM_{2.5}$, Cu, Fe, Zn, and many other elemental components	Outdoor home and school measurements and measurements near road intersections	Machine learning and LUR models
Raaschou-Nielsen	HERMES (DK-POP, DNHS, DCH–NG)	Denmark	2005–2017	Adults	2.9 million	Myocardial infarction, stroke, and diabetes	UFPs, EC, NO_2, and $PM_{2.5}$	NA	Chemical transport model
RFA 19-1, *Applying Novel Approaches to Improve Long-Term Exposure Assessment of Outdoor Air Pollution for Health Studies*									
Weichenthal	CanCHEC	Montreal and Toronto, Canada	1991–2016	Adults	1.5 million	Mortality	UFPs, BC	Mobile	Machine learning and LUR models
Hoek	CLAIRE (DUELS, EPIC-NL, PIAMA)	Netherlands	1993–2019	Children and adults	10 million	Mortality, cardiovascular disease, lung function, and asthma	UFPs, NO_2, BC, and $PM_{2.5}$	Mobile, outdoor low-cost sensors, regulatory monitors	LUR, dispersion, machine-learning, and hybrid models

Continues next page

Preface Table *(continued)***.** Key Characteristics of HEI's Research to Assess Health Effects of Traffic-Related Air Pollution and to Improve Exposure Assessment for Health Studies

Principal Investigator	Study Name	Location	Study Period	Study Population	Sample Size	Outcomes	Main Air Pollutants	Monitoring Data	Exposure Assessment
de Hoogh	MOBI-AIR (EPIC-NL, SAPALDIA, SNC)	Netherlands, Switzerland	1991–2018	Adults	3.5 million	Mortality, cardiovascular disease, lung function, and, blood pressure	NO_2, $PM_{2.5}$	Personal measurements, location tracking	Agent-based, LUR, and machine-learning models
Katsouyanni	MELONS (BLW, COPE, DEMiSt, PASTA, London segment of UK Biobank)	London, UK	2006–2024	Adults	62,000	Mortality	BC, NO_2, $PM_{2.5}$, and O_3	Personal measurements, regulatory monitors	LUR, dispersion, machine learning, and hybrid models
Sheppard	ACT Air pollution study	Seattle	1994–2020	Older adults	5,400	Cognitive function	UFPs, NO_2	Mobile, outdoor low-cost sensors	Universal kriging and machine-learning models

ACT = Adult Changes in Thought; BiSC = Barcelona Life Study Cohort; BLW = Breathe London Wearables; CanCHEC = Canadian Census Health and Environment Cohort; CHS = Children's Health Study; COPE = Characterisation of COPD Exacerbations using Environmental Exposure Modelling; DCH–NG = Diet, Cancer and Health–Next Generations cohort; DEMiSt = Driver Diesel Exposure Mitigation Study; DK–POP = Danish Population cohort; DNHS = Danish National Health Survey; DUELS = Dutch Environmental Longitudinal Study; EPIC–NL = European Prospective Investigation on Cancer and Nutrition–Netherlands; PIAMA = Prevention and Incidence of Asthma and Mite Allergy; NA = not applicable; PASTA = Physical Activity through Sustainable Transport Approaches; SAPALDIA = Swiss Study on Air Pollution and Lung Disease in Adults; SNC = Swiss National Cohort.

Netherlands Hoek and colleagues prepared maps of modeled annual average air pollution across the Netherlands, validated the maps using new measurements from 90 sites, and evaluated the performance of several exposure models. They conducted cross-comparisons to evaluate how different exposure assessment methods compare in their ability to predict long-term pollutant concentrations, with a particular focus on spatial variability of pollutants. They applied the various models to three major cohorts in the Netherlands — an administrative cohort of about 10 million adults (DUELS), the European Prospective Investigation into Cancer and Nutrition Netherlands (EPIC-NL), and the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort — to evaluate how they influence health effect estimates in epidemiological studies (Research Report 226).

"Accounting for Mobility in Air Pollution Exposure Estimates in Studies on Long-Term Health Effects (MOBI-AIR)," Kees de Hoogh, Swiss Tropical and Public Health Institute, Basel, Switzerland Kees de Hoogh and colleagues used location tracking using a mobile phone application and GPS units for about 700 individuals in the Netherlands and Switzerland. They then compared exposure estimates accounting for individual mobility to those accounting only for home addresses in three major cohorts: the Study on Air Pollution and Lung Disease in Adults (SAPALDIA) in Switzerland, participants in the European Prospective Investigation into Cancer and Nutrition Netherlands (EPIC-NL), and the Swiss National Cohort (SNC) (Research Report 229).

"Investigating the Consequences of Measurement Error of Gradually More Sophisticated Long-Term Personal Exposure Models in Assessing Health Effects: The London Study (MELONS)," Klea Katsouyanni, Imperial College, United Kingdom Katsouyanni and colleagues evaluated whether increasingly detailed estimates of long-term exposures to outdoor air pollution yielded different estimates of the health effects. They leveraged personal exposure data from four earlier studies in London. They compared predictions from various exposure models that accounted for exposure to indoor sources and mobility by using several types of air pollution models (dispersion, land use regression, machine learning, and hybrid models). Finally, exposures were applied to the London segment of the UK Biobank study with about 62,000 participants to evaluate associations with mortality (Research Report 227).

"Optimizing Exposure Assessment for Inference about Air Pollution Effects with Application to the Aging Brain," Lianne Sheppard, University of Washington, Seattle Sheppard and colleagues compared and contrasted scientific and logistic benefits of different study designs to develop air pollution exposure estimates. They leveraged detailed air pollution data and cognitive function data from about 5,000 participants in the Adult Changes in Thought (ACT) Air Pollution study in Seattle. They developed several exposure models that used air pollution data from mobile monitoring of UFPs, NO_2, and other pollutants, and low-cost sensors. In particular, they used statistical techniques to assess the bias and precision of health effect estimates and compared the time and costs spent on more sophisticated exposure assessment activities to guide future studies in efficient selection of exposure assessment methods (Research Report 228).

FURTHER RESEARCH UNDERWAY

Given the large number of people exposed to traffic-related air pollution — both in and beyond the near-road environment — exposures to traffic-related air pollution remain an important public health concern and deserve greater attention from the public and from policymakers.

Although emissions from automobile exhaust systems have decreased in recent years, emissions from the use and wear of brakes, tires, and other nontailpipe sources now contribute a higher fraction of the particulate emissions. Therefore, HEI funded two ongoing studies funded under *RFA 21-1*, Quantifying Real-World Impacts of Non-Tailpipe Particulate Matter Emissions. The two studies involve measurements of mass and composition of ambient particles from nontailpipe motor vehicle sources to disentangle nontailpipe and tailpipe pollution and better understand how each effects human health. One study is measuring concentrations of nontailpipe particulate matter across Toronto, Canada, to determine how much nontailpipe pollution people might breathe in everyday life and how to improve measurement of these exposures in the future. The other study is a panel study in which asthmatic adults rode stationary bicycles on sidewalks in three different exposure environments in London, United Kingdom, to measure how exposure to traffic with different mixtures of nontailpipe and tailpipe emissions affects lung function.

Building on its prior and ongoing research and the recommendations from its systematic traffic review, HEI issued *RFA 23-1*, Assessing Health Effects of Traffic-Related Air Pollution in a Changing Urban Transportation Landscape. Investigators funded under RFA 23-1 will conduct epidemiological and health impact assessment studies to assess current and potential future population-level health effects and health burdens associated with current and future transportation systems and traffic-related air pollution. The studies began in late spring 2024. HEI also publishes reports on the State of Global Air to communicate the relationship between air quality and health around the world; see, for example, a recent report on cities and NO_2 (HEI 2022b).

Looking ahead, HEI continues to support improvements in exposure assessment via the use of new technologies, such as satellite remote sensing data. HEI held a *workshop* to discuss applications of high-quality satellite remote sensing data, which have opportunities for increased use in large epidemiological studies, studying the health effects of wildfires, and addressing environmental justice concerns. Challenges include the complexities of data assimilation and accessibility, and current data and algorithmic limitations. HEI is developing an RFA to support research using or assessing the limitations of new approaches to incorporate satellite data products in health studies.

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HEI STATEMENT

Synopsis of Research Report 236

Traffic-Related Air Pollution Associated with Restricted Fetal Growth

BACKGROUND

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, fine particulate matter, 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. However, many earlier studies of prenatal exposure lacked information on important confounding factors, including maternal smoking, body mass index, and traffic noise.

To evaluate the effects of prenatal exposure to traffic-related air pollution on fetal growth, HEI funded a study by Drs. Payam Dadvand and Jordi Sunyer of ISGlobal titled "Traffic-Related Air Pollution and Birth Weight: The Roles of Noise, Placental Function, Green Space, Physical Activity, and Socioeconomic Status (FRONTIER)" in response to HEI's *Request for Applications 17-1*: *Assessing Adverse Health Effects of Exposure to Traffic-Related Air Pollution, Noise, and Their Interactions with Socioeconomic Status*. Drs. Dadvand and 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, and to identify relevant windows of exposure during pregnancy. They planned to recruit a new cohort of 800 mother–infant pairs and evaluate the influence of noise, greenspace, stress, physical activity, and socioeconomic status, as well as the potential role of placental function.

APPROACH

Between 2018 and 2021, Dadvand, Sunyer, and colleagues recruited 1,080 women with singleton pregnancies during their first prenatal visit at about

What This Study Adds

- This study examined the effects of prenatal exposure to traffic-related air pollution on fetal growth and placental function in a newly established cohort of 1,080 women living in Barcelona, Spain.
- Exposure to nitrogen dioxide, black carbon, fine particles, and components of fine particles (copper, iron, and zinc) at home, at work, and during the commute was assessed using personal and home monitoring and land use regression and other modeling methods throughout pregnancy.
- The study found that increased exposure to all pollutants, except zinc, was associated with lower birth weight and increased odds of the infant being considered small for its gestation age. Changes in placental function suggest that fine particle exposure might affect fetal growth by increasing resistance to blood flow between the fetus and placenta.
- Results were similar after adjusting for traffic-related noise, or when evaluating personal home, workplace, and commute exposures separately, or when using land use regression models versus other exposure models. Future studies set in similar urban environments might consider simplifying exposure assessment measures when resources are limited.
- The most vulnerable periods of exposure were during the late first to early second trimesters and the late third trimester of pregnancy. The results confirm other research on birth outcomes and stress the importance of reducing air pollution exposures of pregnant women.

This Statement, prepared by the Health Effects Institute, summarizes a research project funded by HEI and conducted by Drs. Payam Dadvand and Jordi Sunyer at the Barcelona Institute for Global Health (ISGlobal), Barcelona, Spain, and colleagues. Research Report 236 contains the detailed Investigators' Report and a Commentary on the study prepared by the HEI Review Committee.

12 weeks of gestation in Barcelona, Spain. They collected extensive information on participant health, lifestyle, and exposures from interviews, online surveys, and medical records. Fetal and newborn body size measurements were taken during two hospital visits at about 12 and 32 weeks of gestation and at two home visits shortly after the two hospital visits.

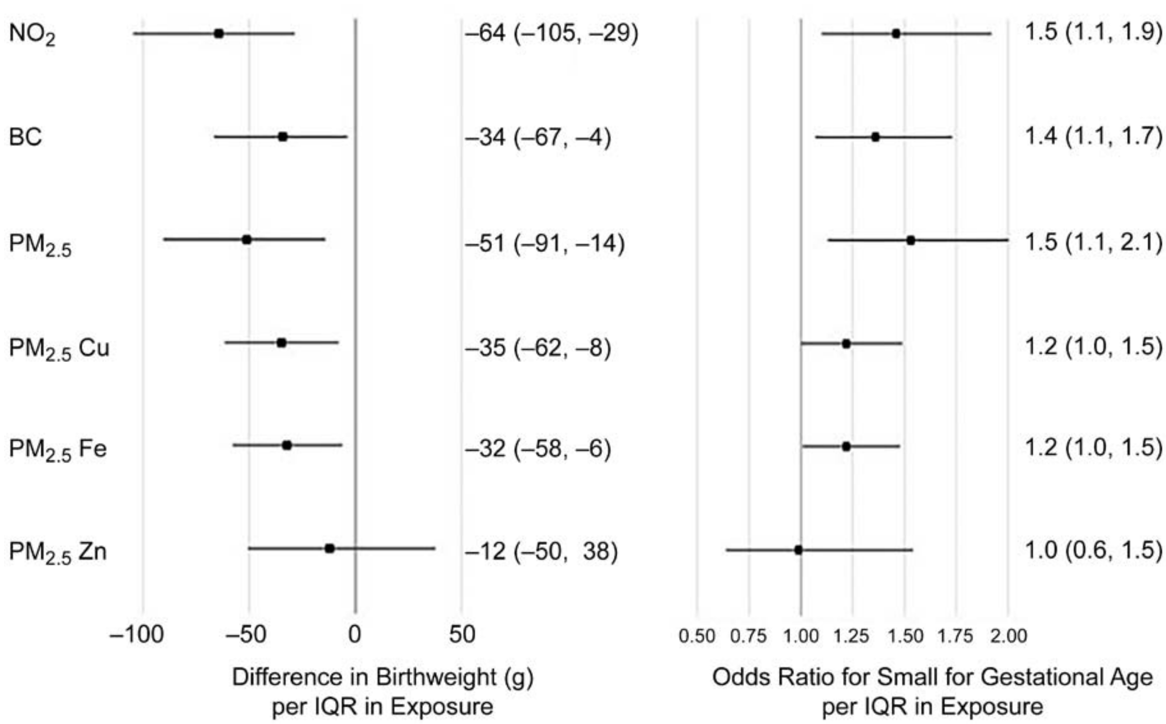
Dadvand and Sunyer conducted a comprehensive assessment to estimate exposure to traffic-related air pollutants. They used multiple exposure modeling methods (including land use regression models, dispersion modeling, and hybrid models), incorporated personal and home monitoring, and estimated time–activity patterns based on time spent at home, work, and commuting. For the entire pregnancy, they estimated exposure to nitrogen dioxide, black carbon, fine particles, and fine particle metal components, copper, iron, and zinc. They also estimated exposure to traffic-related noise, which might confound the association between traffic-related air pollution and fetal development.

They evaluated air pollution exposure in relation to birth weight measurements and whether the fetus was more susceptible to exposure during specific periods of gestation. They adjusted for numerous health and socioeconomic indicators, including body mass index and tobacco smoke exposure. Using mediation analysis, they also evaluated whether air pollution might affect fetal growth through changes in placental function, which was assessed by ultrasound measurements of blood flow.

KEY RESULTS

The final sample included 1,024 live births with complete data on exposure and outcomes. The median exposures during pregnancy for women who participated in the study were 37.2 μg/m³ for nitrogen oxides and 17.1 μg/m³ for fine particles. Their exposures to all pollutants were generally lowest at home and highest during commuting. The median traffic-related noise levels at home and work were about 65 decibels, which is a moderate noise level.

Higher exposure during pregnancy to outdoor concentrations of all pollutants except the zinc component of fine particles was associated with lower birth weight and increased odds of the baby being classified as small for their gestational age (**Statement Figure**). For context, the associations for nitrogen dioxide translate to a 64-g reduction in birth weight and 46% increased odds of being small for gestational age for every 15 μg/m³ increase in exposure.



Statement Figure. Association between an interquartile range increase in traffic-related air pollutants and fetal growth based on the land use regression model exposure estimates. BC = black carbon; IQR = interquartile range.

The late first trimester to early second trimester was the most vulnerable window of exposure for all pollutants except black carbon and zinc. For black carbon, the late third trimester was the most vulnerable window. Findings were similar when traffic-related air pollutant exposure at home, at work, and during commuting were evaluated separately and when estimates from different exposure modeling methods were used, including estimates based only on residential address.

In models accounting for both traffic-related air pollution and noise exposure, similar associations were observed between the air pollutants and fetal growth outcomes. In those models, noise exposure itself was generally associated with lower birth weight, but the results were not statistically significant, suggesting that traffic noise was less important than traffic pollution.

Higher exposure to outdoor fine particle concentrations during pregnancy was associated with higher resistance to blood flow in the umbilical artery (which delivers blood between the fetus and placenta) during the third trimester of pregnancy. Dadvand and Sunyer estimated that this blood flow resistance explained 9.1% and 3.5% of the association of $PM_{2.5}$ with birth weight and being small for gestational age, respectively.

INTERPRETATION AND CONCLUSIONS

In its independent review of the study, the HEI Review 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. Importantly, the investigators were able to adjust for smoking and body mass index, information that was lacking in many earlier studies and considered a major limitation in prior research. The results from this study will be useful in future systematic reviews and regulatory science assessments.

The Committee appreciated the comprehensive exposure assessment with information on noise, commuting patterns, and various modeling approaches. Findings were consistent, although not always statistically significant, across the various exposure assessment methods. The results suggested that exposure measurements based on outdoor concentrations at residential locations, as used in many epidemiological studies (thus without capturing work and commuting patterns), might capture exposures adequately.

Results in this study largely confirmed prior research demonstrating that traffic-related air pollutants are related to decreased fetal growth. Their effects on birth weight were smaller than the effects of active maternal smoking but were similar to the effects of environmental tobacco smoke exposure during pregnancy. This study adds to the limited literature on fine particle metal components; the association between iron and copper with lower birth weight confirms the role of metals in general, but needs further study, given that these are essential trace elements.

In summary, Dadvand, Sunyer, and colleagues observed that nitrogen dioxide, black carbon, fine particles, and iron and copper components of fine particles were associated with slower fetal growth. This study adds to the existing body of literature demonstrating that traffic-related air pollution during pregnancy can alter fetal development. The results stress the importance of reducing exposures to pregnant women. Future studies in similar urban environments might be able to simplify exposure assessments when resources are limited. Additional research is needed to clarify the effects of fine particle components.

Traffic-Related Air Pollution and Birth Weight: The Roles of Noise, Placental Function, Green Space, Physical Activity, and Socioeconomic Status (FRONTIER)

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ABSTRACT

Introduction FRONTIER aimed to provide a robust and comprehensive evaluation of the impact of maternal exposure to traffic-related air pollution (TRAP*) on fetal growth. Toward this aim it (1) disentangled the effects of noise as a co-exposure; (2) identified the relevant window(s) of vulnerability for this impact; (3) evaluated its modification by household and neighborhood level socioeconomic status (SES), stress, physical activity, and the timing of conception and delivery in relation to the COVID-19 pandemic lockdown; (4) elucidated the role of placental function as an underlying mechanism; and (5) explored the potential of urban tree canopies and green spaces to mitigate it.

Methods FRONTIER established a new pregnancy cohort of 1,080 pregnant women in Barcelona, Spain — Barcelona Life Study Cohort (BiSC). Fetal growth was characterized by anthropometric measures at birth, together with ultrasound-based trajectories of fetal development. We developed an innovative exposure assessment framework integrating objective data on time–activity patterns with dispersion, land use regression, and hybrid models, with campaigns of personal and home-outdoor air pollution monitoring to estimate maternal exposure levels as well as inhaled dose of black carbon (BC), nitrogen dioxide (NO_2), fine particulate matter ($PM_{2.5}$), and $PM_{2.5}$ copper, iron, and zinc in the main microenvironments for pregnant women (home, workplace, and commuting routes). We also assessed maternal exposure to noise by integrating measurements at participants' homes and outdoors using noise monitors with modeled microenvironmental noise levels, data on noise sensitivity, annoyance, and protections against noise. We developed single- and multipollutant models to evaluate the impact of TRAP exposure and inhaled dose on fetal growth while also correcting for the exposure measurement error. We further evaluated the modification of associations by SES, stress (cortisol levels and perceived stress), physical activity (objective and subjective measures), their mitigation by urban greenness and canopy volume, and their mediation by Doppler ultrasound measures of placental function.

Results We found that higher pregnancy exposure to NO_2, BC, $PM_{2.5}$, and $PM_{2.5}$ copper and iron contents, particularly at home and all microenvironments combined, were generally associated with lower birth weight, higher risk of small for gestational age (SGA), and a decelerated trajectory of fetal growth, although some of these associations were not statistically significant. These associations appeared to be stronger for mothers with higher SES and those with higher objective measures of psychological stress. For the COVID-19 pandemic and physical activity, as effect modifiers, and urban greenness and canopy cover, as effect mitigators, we observed mixed patterns. In multipollutant models that include different measures of exposure to noise in addition to TRAP, the associations between TRAP and fetal growth generally remained consistent with those that we observed in our main analyses. We found two potential windows of vulnerability for the association of TRAP with fetal growth: one at the end of the first trimester and the beginning of the second trimester, and another at the end of the third trimester. Finally, we observed that a small proportion of the associations between $PM_{2.5}$ and fetal growth could be mediated through the impact of these pollutants on placental function (i.e., umbilical artery pulsatility index).

Conclusions Exposure to TRAP is associated with impaired fetal growth.

This Investigators' Report is one part of Health Effects Institute Research Report 236, which also includes a Commentary by the Review Committee and an HEI Statement about the research project. Correspondence concerning the Investigators' Report may be addressed to Dr. Payam Dadvand, Barcelona Institute for Global Health (ISGlobal), Doctor Aiguader 88, 08003 Barcelona, Spain; email: *payam.dadvand@isglobal.org*. No potential conflict of interest was reported by the authors.

Although this report was produced with partial funding by the United States Environmental Protection Agency under Assistance Award CR–83998101 to the Health Effects Institute, it has not been subjected to the Agency's peer and administrative review and may not necessarily reflect the views of the Agency; thus, no official endorsement by it should be inferred. This report has also not been reviewed by private party institutions, including those that support the Health Effects Institute, and may not reflect the views or policies of these parties; thus, no endorsement by them should be inferred.

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

INTRODUCTION

It is well established that the fetus and infant are especially vulnerable to the effects of socioenvironmental factors.[1] Exposures during pregnancy not only affect reproductive and childhood outcomes, but their effects also extend over the rest of the child's life stages; a corpus of evidence embodied by the DOHaD (Developmental Origins of Health and Diseases) concept.[2,3] DOHaD suggests that exposures during prenatal and early postnatal periods may permanently change the structure, physiology, and metabolism of the body, and such changes can promote disease long after the environmental exposure has ceased. In this context, impaired fetal growth has been associated not only with poorer health and development in children but also with adverse health outcomes in later life. For example, low birth weight (LBW, birth weight <2,500 g) is, directly or indirectly, responsible for 60% to 80% of all neonatal deaths and is associated with higher risks of infections, growth and developmental delays, and mortality during infancy and childhood.[4] At the same time, LBW has been linked to enhanced risk of noncommunicable diseases, such as ischemic heart disease, chronic hypertension, insulin resistance and metabolic syndrome, and chronic kidney disease in adults.[5,6] Overall, impaired fetal growth is estimated to result in about 1.9 million deaths and 178 million disability-adjusted life years globally each year, and accordingly is the sixth highest contributor to the global burden of disease.[7]

Traffic-related air pollution (TRAP) is one of the most studied environmental exposures during pregnancy. This exposure has been associated with several pregnancy complications and adverse pregnancy outcomes, but it has been more consistently related to impaired fetal growth. Several systematic reviews and meta-analyses of available literature have related maternal exposure to TRAP with different indicators of impaired fetal growth, such as LBW or small for gestational age (SGA).[8,9] However, to date, a vast majority of epidemiological studies of the impacts of TRAP on pregnancy outcomes have assessed exposure mainly at the home, overlooking the contribution of other microenvironments (e.g., workplace and commuting) to personal exposure. Moreover, they have not characterized and accounted for exposure misclassification, and have also relied on exposure levels (ambient concentrations of pollution to which the individual is exposed) instead of dose (amount of pollution inhaled by the individual). Furthermore, although traffic is the main source of both TRAP and noise in urban areas, air pollution studies on pregnancy have rarely accounted for the potential impact of noise to separate the impacts of these two important traffic-related hazards on fetal growth. Additionally, socioeconomic status (SES) has been generally treated as a confounder in studies relating TRAP and fetal growth. A very limited body of evidence has also evaluated the modification of this impact by SES, suggesting more vulnerability among pregnant women from lower SES.[10] It is still not clear which factors explain the SES-related vulnerability to TRAP.

Psychological stress has been suggested to be involved in such vulnerability;[11] however, there is no available epidemiological study in humans on the role of stress in this vulnerability among pregnant women. Such a role is supported by a study in mice showing that maternal stress during pregnancy enhances fetal vulnerability to the adverse effects of maternal exposure to TRAP.[12] Similarly, the potential modification of the association of TRAP with fetal growth by physical activity is yet to be evaluated. Physical activity, on one hand, is associated with a wide range of health benefits (including better pregnancy outcomes), but on the other hand, it enhances uptake and deposition of air pollutants, possibly augmenting their harmful effects.[13,14] Green spaces are increasingly recognized as a measure to mitigate the adverse impacts of TRAP in urban areas. The only available study on the impact of green space on personal exposure to TRAP[15] showed that pregnant women living in greener areas were exposed to lower levels of particulate air pollution. Although this observation could be suggestive for the mitigation of the association of TRAP with fetal growth, there is no available evidence evaluating such a mitigation effect.

The placenta is the gate between the mother and the fetus. The impairment of placental function and reduced transplacental oxygen and nutrient transport have been suggested as a potential mechanism through which TRAP may affect fetal growth. For example, a study has shown that around 10% of the observed association between TRAP exposure and birth weight could be explained by a reduction in placental mitochondrial DNA content, which is an indicator of placental stress.[16] A few studies have also reported an adverse impact of TRAP on placental function;[17–19] however, available evidence evaluating whether such an impact can mediate the association between TRAP and fetal growth remains very scarce.

SPECIFIC AIMS

FRONTIER aimed to provide a robust and comprehensive evaluation of the impact of maternal exposure to TRAP on fetal growth. Toward this aim it (1) disentangled the effects of noise as a co-exposure; (2) identified the relevant window(s) of vulnerability for this impact; (3) evaluated its modification by household and neighborhood level socioeconomic status (SES), stress, physical activity, and the timing of conception and delivery in relation to the COVID-19 pandemic lockdown; (4) elucidated the role of placental function as an underlying mechanism; and (5) explored the potential of urban tree canopies and green spaces to mitigate it. Accordingly, the specific aims of FRONTIER were as follows:

Aim 1: Establishing a new pregnancy cohort.

Aim 2: Assessing maternal exposure to TRAP and noise and characterizing canopies and greenness surrounding participants' homes.

Aim 3: Objectively characterizing maternal stress, physical activity, and placental function.

Aim 4: Evaluating the association between maternal exposure to TRAP and fetal growth while separating the effect of noise, and identifying relevant window(s) of vulnerability during pregnancy, as well as modifiers, mediators, and mitigators of this association.

STUDY DESIGN AND METHODS

We followed the research roadmap as described in **Table 1**.

STUDY DESIGN, SETTING, AND POPULATION

FRONTIER was a prospective cohort study conducted in Barcelona, Spain, and its metropolitan area. Barcelona, situated on the Northeastern Iberian Peninsula, has a Mediterranean climate characterized by mild winters and hot and dry summers. The city faces a significant air pollution challenge, ranking among the worst in Spain and Western Europe. This issue can be attributed, in part, to the high traffic density and a large proportion of diesel-powered vehicles, as well as high population density, relatively low precipitation, and an urban landscape characterized by tall buildings and narrow streets, which hampers the dispersion of pollutants.

To conduct FRONTIER, we set up a new birth cohort, named the Barcelona Life Study Cohort (BiSC). Pregnant women were recruited during their first routine hospital visit (weeks 11–14 of gestation) at three tertiary university hospitals in Barcelona, Spain: Hospital de la Santa Creu i Sant Pau, Hospital Sant Joan de Déu, and Hospital Clínic de Barcelona, along with their corresponding primary healthcare centers. The obstetrics departments of Hospital Sant Joan de Déu (located in the Esplugues de Llobregat, which is in the west of Barcelona) and Hospital Clínic de Barcelona (located in the southwestern part of Barcelona) are part of the BCNatal, a center of excellence in maternal–fetal and neonatal medicine that collectively manages a total of 6,500 births annually. Hospital de la Santa Creu i Sant Pau is in the northeastern part of Barcelona, and manages around 2,000 deliveries per year. The detailed description of the recruitment process, data collection, and follow-up visits of the BiSC has been reported elsewhere.[20] Briefly, we distributed posters and flyers about the study in the aforementioned centers to inform potential participants about the study. At the time of the first routine hospital visit, a trained nurse approached the pregnant women attending the visit, explained the study aims and objectives, the study procedures, the expected tasks from the participants, and their right to withdraw from the study at any point without any consequence. If the pregnant woman agreed to participate and met the inclusion criteria, she was enrolled in the cohort after signing informed consents. We included pregnant women between 18 and 45 years old with a singleton pregnancy from the general population who were living in the catchment area of the aforementioned three hospitals and were able to communicate in Spanish or Catalan. We excluded those women residing outside the catchment area, aged <18 years or >45 years, illiterate, with a multiparous pregnancy, or having a fetus with congenital anomalies. The enrolment of the BiSC participants started in October 2018 and ended in March 2021, with a total of 1,080 pregnant women recruited. Of these recruited pregnant women at baseline, seven experienced abortion, two experienced stillbirth, and 1,032 remained in the cohort till the time of delivery with live birth, of whom we had valid data on birth weight for 1,024 of the original 1,080 (94.8%) participants that were included in the FRONTIER analyses.

Ethic approvals were obtained from the corresponding authorities in all the participating institutions and hospitals, including the Clinical Research Ethics Committee of the Parc de Salut Mar (2018/8050/I), the Medical Research Committee of the Fundació de Gestió Sanitària del Hospital de la Santa Creu i Sant Pau de Barcelona (EC/18/206/5272), and the Ethics Committee of the Fundació Sant Joan de Déu (PIC-27-18).

Table 1. FRONTIER's Research Road Map

Aims and Research Conducted	Methods Description
Aim 1	• Study Design, Setting, and Population • FRONTIER Data Collection Follow-Ups • Health Outcomes
Aim 2	• Exposure Assessment
Aim 3	• Covariate and Modifier Data • Mediators
Aim 4	• Data Analysis

FRONTIER DATA COLLECTION FOLLOW-UPS

During the pregnancy period, in addition to two hospital visits — one in the first (at the recruitment time, around week 12 of gestation) and one in the third (around week 32 of gestation) trimester — we conducted one-week personal and home environmental measurement campaigns that were carried out through home visits right after the hospital visits in the first and third trimesters. During the hospital visits, we conducted face-to-face interviews to collect sociodemographic, lifestyle, and clinical data, and we also conducted ultrasound examinations of placental function and fetal anthropometry. (Note: We also obtained hospital records on routine ultrasound examination of fetal anthropometry during the second and third trimesters as described below.)

In the home visits, the BiSC fieldworkers (1) implemented sensors to simultaneously measure TRAP (personal, home-indoor, and home-outdoor levels) and noise (home-outdoor level), (2) implemented personal physical activity and geolocation sensors and applied an interactive Geographic Information System (GIS) platform to characterize participants' time–activity patterns and commuting mode, (3) generated a detailed record of the participant's home characteristics, and (4) conducted face-to-face interviews to collect questionnaire data. In addition to these visits, we asked participants to fill out online questionnaires on sociodemographic and lifestyle factors in the first and third trimesters, coinciding with the hospital and home visits.

EXPOSURE ASSESSMENT

Air Pollution

We assessed participants' exposure to particulate matter with an aerodynamic diameter ≤2.5 µm ($PM_{2.5}$), black carbon (BC), and nitrogen dioxide (NO_2). Furthermore, we assessed exposure to $PM_{2.5}$ copper (Cu), iron (Fe), and zinc (Zn) contents as markers of nontailpipe emissions.[21] On the other hand, in Barcelona, BC could be considered a marker of tailpipe traffic emissions.

Home and Personal NO_2 Measurements For NO_2, we measured personal, home-indoor, and home-outdoor levels using passive samplers (NO_2 diffusion tube, Gradko International Ltd., UK) for one week during the first and one week during the third trimesters (two weeks in total) (**Figure 1**). Indoor NO_2 samplers were placed in the participant's bedroom next to their bed. They were placed in the bedrooms (versus the living room or other spaces) because pregnant women were expected to spend a considerable amount of time there while resting, and also the NO_2 levels there were likely to be less affected by the NO_2 generated due to gas cooking at home, so our measured NO_2 levels could be more representative of the traffic-related sources. The samplers monitoring home-outdoor air were attached to a window or balcony on the most traffic-exposed façade, or on its exterior wall. For personal measurements, the samplers were worn by the participants either in a necklace or attached to backpack straps close to the breathing zone.

For analyses of the associations between these exposures and fetal growth, we first deseasonalized the measured levels using the ratio method to remove short-term (e.g., due to meteorological conditions such as precipitation, storms, and inversions) and long-term (e.g., seasonal variations) temporal fluctuations in background levels from our measured levels and hence make them more comparable among participants whose measurements were conducted in different weeks. We then averaged the levels of two measurements made in the first and third trimesters. Following the method applied in our previous works,[22,23] separately for each sample, we calculated the ratio between the average concentrations of NO_2 in the urban background reference station of Palau Reial (PR) for the same period as the exposure of the passive sampler tube in visit w ($C_{w,PR}$) and the pregnancy period of the participant i ($C_{i,PR(avg)}$). Finally, we divided the concentration measured by the sampler for participant i in visit w ($C_{i,w}$) by the previously computed ratio at the reference station. The following equation summarizes the procedure to obtain the deseasonalized concentration for each sample ($C_{i,w,des}$):$C_{i,w,des} = C_{i,w}/(C_{w,PR}/C_{i,PR(avg)})$.[24]

BiSCAPE Air Pollution Monitoring Campaigns To develop land use regression (LUR) models for estimating exposures to air pollutants for BiSC participants, we conducted campaigns of monitoring $PM_{2.5}$ and its chemical inorganic components (37 mm Polytetrafluoroethylene-Teflon-filters collected using a BGI-400 pump [working at 4 L/min] and a PCIS impactor), BC (MicroAeth AE51), and NO_2 (Gradko NO_2 diffusion tubes). To cover intra-annual variability in the pollution surface, we carried out three monitoring campaigns in different seasons

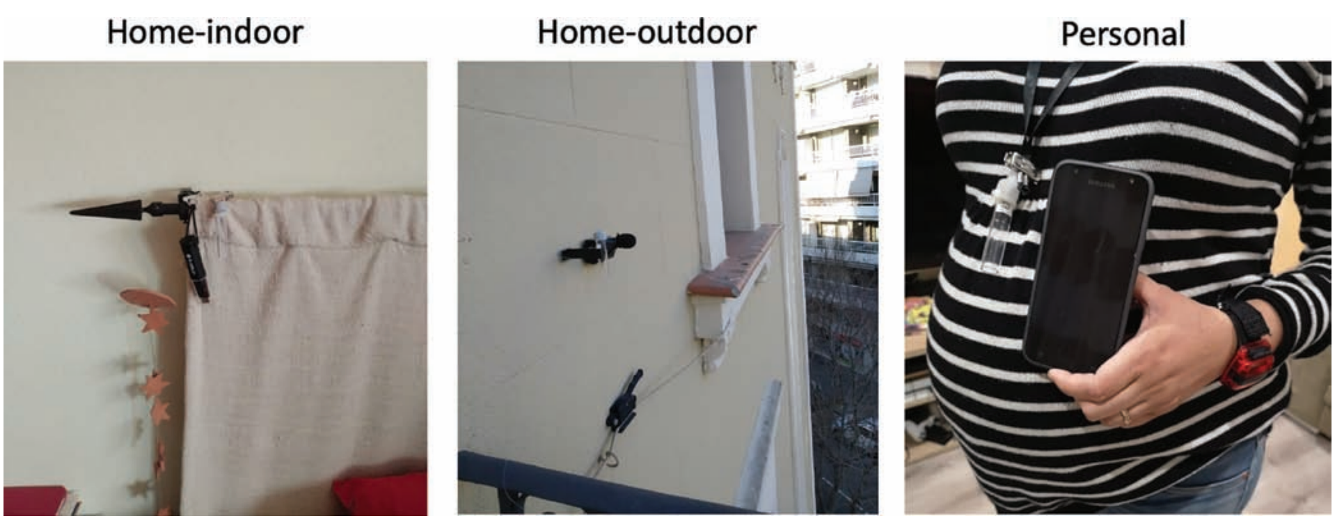

Figure 1. Examples of the installation of home-outdoor, home-indoor, and personal NO_2 passive samplers.

from June 2021 to February 2022 (first campaign: June 28 to July 28, 2021; second campaign: October 11 to November 12, 2021; third campaign: January 12 to February 16, 2022). We also had an extra campaign from February 16 to March 29, 2021, where we collected data on NO_2 and BC. Following the European Study of Cohorts for Air Pollution Effects (ESCAPE) protocols,[25–27] we selected 34 representative sites including urban traffic and background sites, as well as one reference urban background station, all of which represented the gradient of various land use, emission sources, and traffic characteristics across the BiSC study area (i.e., cities of Barcelona, Cornellà de Llobregat, Esplugues de Llobregat, Hospitalet de Llobregat, and Sant Just Desvern) (**Figure 2**).

We monitored air pollutant levels in these sites for an average period of nine days in each campaign. Sites were located approximately at a first-floor height. The following criteria were also fulfilled when placing the samplers: (1) not to be placed near exhaust flues, chimneys, air conditioning devices, or drip line of trees; (2) location should be a smoking-free area; (3) they should be placed at approximately 0.5–1.5 m above the floor. Trained fieldworkers logged the GPS coordinates (exact location) and installation height relative to the ground. Moreover, the fieldworkers collected data on installation and collection times of the different samplers, and registered (and corrected if needed) $PM_{2.5}$ pump flow at the beginning, middle, and end of each data collection period in each location. In addition, any incidents that may have affected the measurements were also recorded (e.g., the power supply was turned off during the data collection).

Gravimetry and Chemical Analysis of $PM_{2.5}$ Filters We performed a gravimetric determination of $PM_{2.5}$ mass concentrations by weighing the filters before and after sampling. Filters were weighed using an MX5 Mettler Toledo microbalance together with a Mettler Toledo antistatic bar at the University of Lleida. Filters were conditioned (at least 24 hours at a constant relative humidity between 30% to 40% and a constant temperature between 20°C to 23°C) both before and after sampling, before the weighing. $PM_{2.5}$ concentrations were the result of the difference in weights (after sampling minus before sampling) divided by the total volume of air sampled.

A complete chemical characterization (>50 components) was carried out through a close research collaboration at the Environmental Geochemistry and Atmospheric Research Group (EGAR) of the Institute of Environmental Assessment and Water Research (IDAEA) from the Spanish National Research Council (CSIC), following the methodology described previously.[28] Particles collected in the 37-mm Teflon filters were washed from the filter and digested using an acidic solution of 2.5 mL 65% nitric acid (HNO_3), 2.5 mL 40% hydrofluoric acid (HF), and 1.25 mL of 60% perchloric acid ($HClO_4$). The resulting solution was then analyzed with both inductively coupled plasma atomic emission spectrom-

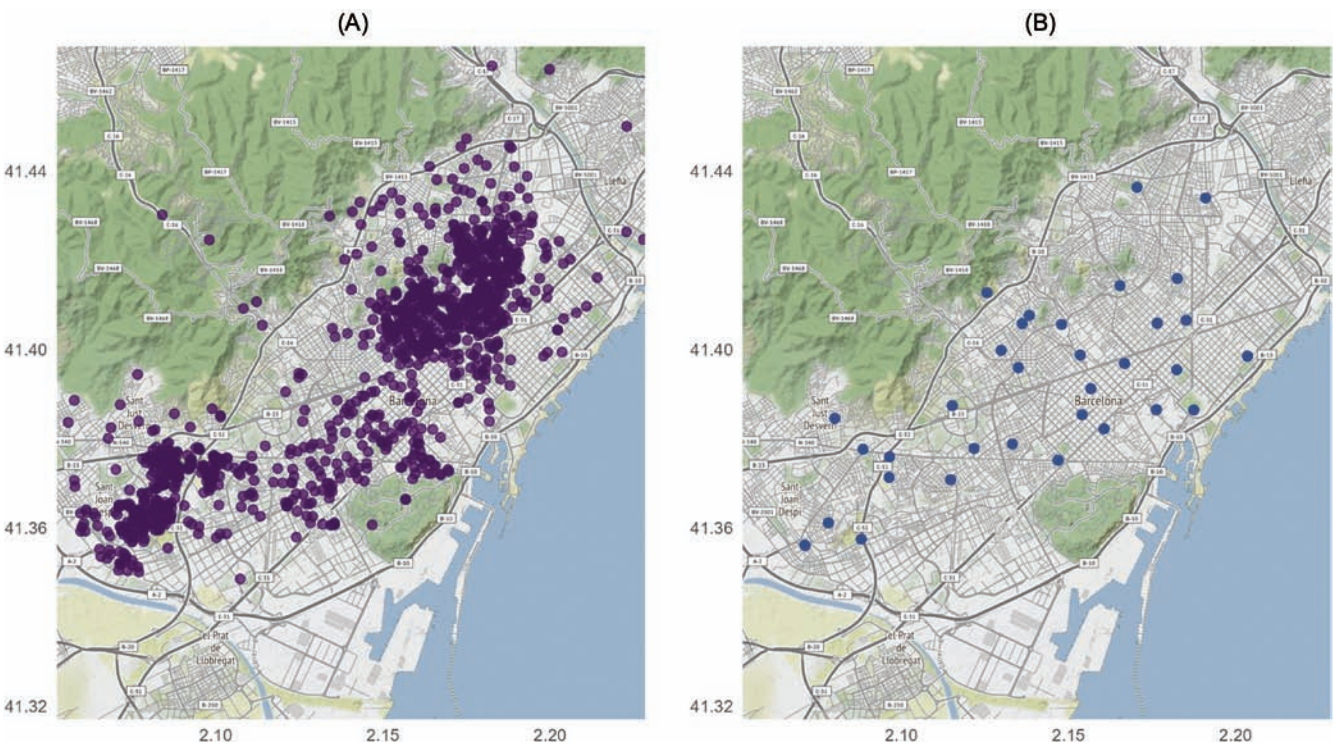

Figure 2. Locations of the home-outdoor NO_2 sampling at BiSC participants' homes (A) and NO_2, BC, and $PM_{2.5}$ sampling sites for BiSCAPE campaigns (B). BC = black carbon; BiSC = Barcelona Life Study Cohort.

etry and inductively coupled plasma mass spectrometry to obtain the elemental composition. The same procedure was carried out for blank filters (to subtract potential impurities or contamination of the batches) and for blank filters with the NBS-1633a reference material to ensure analysis quality for the same levels of the sample digestion concentrations. Relative analytical errors were between 3% and 10% for the elements studied.

Air Pollution Models To estimate the exposure to different air pollutants for each week of the pregnancy, we obtained or developed three different types of models: LUR models, dispersion models, and hybrid LUR-dispersion models.

Land Use Regression Models Using the data collected in the BiSCAPE campaigns, we developed LUR models for NO_2, BC, $PM_{2.5}$, and $PM_{2.5}$ Cu, Zn, and Fe content following the ESCAPE protocols.[25–27] For NO_2, in addition to data from BiSCAPE campaigns, we applied data on home-outdoor measurements for those participants who had two repeated measurements in the first and third trimesters ($n = 489$). The detailed description of the development of the LUR models is presented as *Additional Materials 1* on the HEI website. Briefly, for each sampling site, data on 101 potential predictors of TRAP (e.g., street type, greenness coverage, distance to major road, high population density, traffic density, land use, building density and height, etc.) were obtained according to the ESCAPE guidelines. We then followed the ESCAPE supervised forward selection approach to develop multiple linear regression models separately for each pollutant using annual average concentrations obtained from the sampling campaign as outcomes. The description of the final models, including the predictor variables, the coefficients of determination (R^2), and residual standard error, as well as their corresponding leave-one-out cross-validated R^2 values, is presented in **Table 2**.

Using ESCAPE's ratio method, we then temporally adjusted the estimations to estimate hourly exposure levels of each pollutant for each participant's entire pregnancy for (1) outdoor levels at home address, and (2) outdoor levels considering the time–activity pattern of the participant in different microenvironments, using the average of the outdoor concentrations at home, the workplace, and the commuting route between these two, weighted by the time the participant spent in each of these microenvironments to estimate total personal exposure.

Dispersion Models We applied dispersion models to estimate hourly outdoor levels of $PM_{2.5}$, BC, and NO_2 for each participant for her entire pregnancy period, separately for (1) the home, (2) the combined home, workplace, and commuting route exposure weighted by the time that they usually spent in each of these microenvironments. Moreover, we estimated hourly levels of these pollutants for 34 BiSCAPE monitoring sites during the monitoring campaign periods. The detailed description of the development of the dispersion models is presented in *Additional Materials 2*. Briefly, dispersion

Table 2. Description for the BiSC LUR Models Pollutant in Terms of the Years of Data Collection (year), Number of Data Points Used to Develop the Model (N), the Adjusted Coefficient of Determination, Cross-Validation R^2, Residual Standard Error, and Predictor Variables That Remained in the Final Model

Pollutant	Year	*N*	Adj-R^2	CV-R^2	RSE	Predictor Variables[a]
NO_2	2018–2021	489	0.62	0.62	4.03	trafload25 – sqralt + majorroadlength50 + roadlength25 + majorroadlength300
$PM_{2.5}$	2021	34	0.47	0.45	1.47	hdres500 + trafnear + LEZ
BC	2021	30	0.85	0.83	0.18	hdres50 + linesnear + pop300 + trafload500 + roads500
$PM_{2.5}$ Cu	2021	31	0.90	0.87	0.72	trafnear + roads1000 + ind1000 + pop25
$PM_{2.5}$ Fe	2021	34	0.91	0.89	0.03	trafnear – lat + pop50 – LEZ
$PM_{2.5}$ Zn	2021	31	0.89	0.85	6.99	LEZ + roads50 + ind1000 + build25

Adj-R^2 = adjusted coefficient of determination; BC = black carbon; BiSC = Barcelona Life Study Cohort;
CV-R^2 = cross-validation R^2; LUR = land use regression; RSE = residual standard error.
[a] Predictor variable definitions — roadlength25: total roads of indicated length (m) within 25-m buffer, majorroadlength50: total major roads of indicated length (m) within 50-m buffer, majorroadlength300: total major roads of indicated length (m) within 300-m buffer, trafload25: total traffic intensity (vehicles/day) within 25-m buffer, trafload500: total traffic intensity (vehicles/day) within 500-m buffer, trafnear: traffic intensity at the nearest road (vehicles/day), linesnear: number of traffic lines on nearest street, LEZ: Low Emissions Zone (Yes/No, ref value = No), hdres50: high-density residential areas of indicated size (m^2) within 50m buffer, hdres500: high-density residential areas of indicated size (m^2) within 500-m buffer, roads50: roads of indicated surface area (m^2) within 50-m buffer, roads500: roads of indicated surface area (m^2) within 500-m buffer, roads1000: roads of indicated surface area (m^2) within 1000-m buffer, ind1000: industry areas of indicated size (m^2) within 1000-m buffer, pop25: population density (inhabitants/km^2) within 25-m buffer, pop50: population density (inhabitants/km^2) within 50-m buffer, pop300: population density (inhabitants/km^2) within 300-m buffer, build25: buildings of indicated floor area (m^2) within 25-m buffer, lat: latitude (m), sqralt: squared root altitude ($m^{0.5}$).

models were developed and validated using ADMS-Urban (Cambridge Environmental Research Consultants), which is based on a Gaussian dispersion model with integrated photochemical reaction models, street canyon models, and a meteorological preprocessing model.[29,30] ADMS-Urban employs various algorithms to assess the chemical transportation and dispersion of pollutants, factoring in ground-level turbulence and turbulence induced by the surrounding topography.[31] A detailed emission inventory at street level for road traffic, industry, power plants, residential and commercial sources, the port of Barcelona, the airport, and other sources, together with topographic and meteorological data and regional air transport models, was applied as inputs to this model. The results of the external validation of the dispersion model estimates for NO_2 levels against measured NO_2 levels at BiSCAPE sampling sites, as well as measured BiSC home-outdoor and personal levels, are presented in **Table 3**.

Hybrid (LUR-Dispersion) Models For the hybrid models, we sought to improve the predictive performance of the outdoor air pollution models by integrating comprehensive data from multiple sources of information and leveraging machine learning algorithms. We used a Random Forest algorithm to capture nonlinear relationships and potential interactions between predictor variables and the response variable.[32] The detailed description of the development of the hybrid models is presented in *Additional Materials 3*. Briefly, the models combined data on all the potential predictors used in the LUR model development, the exposure estimates from the dispersion models, routine air pollution monitoring data, and meteorological variables to estimate weekly exposure levels of NO_2, BC, $PM_{2.5}$, and $PM_{2.5}$ Cu, Fe, and Zn content both at home and the workplace, considering the time spent at home and work (i.e., the hybrid models did not estimate the exposure during commuting). We assessed the performance of each hybrid model by contrasting predictions with observations. Two distinct validation approaches were employed: 10-fold cross-validation and external validation with 20% of the data. While both methods differ in the sample size designed for testing, their fundamental distinction lies in the data-splitting strategy. For the 10-fold cross-validation, the model was trained on 9 out of the 10 data partitions and then validated against the remaining 1. In contrast, during the external validation procedure, we reserved 20% of the initial dataset, which had not been used for training, to provide an unbiased evaluation of the final model fit. This approach allowed us to assess how well the model will perform when predicting new, unseen data. We employed a grid search for hyperparameter tuning to select the best configuration to obtain the optimal model based on the R^2. The description of the final models, including the predictor variables as well as their performance metrics, is presented in **Table 4**.

Inhaled Dose We integrated microenvironmental TRAP levels with physical activity data collected in the first and third trimesters using the personal physical activity monitor (ActiGraph wGT3X-BT, ActiGraph Ltd., USA) to estimate the inhaled dose for each study participant (for more details about the collection of time–activity data, please see the subsection on this topic below). For each participant and microenvironment, we computed the average Euclidean norm minus one (ENMO) metric[33] and used the cut-off points obtained by Hildebrand[34,35] to classify the activities performed in each environment into sedentary, light, moderate, and vigorous. Afterward, we used the ventilation rates for each level of physical activity published by the US EPA (2009)[36] (which considers sex, age, and body weight) to compute the inhaled dose as the multiplication of the concentration (μg/m^3) and the participant-specific minute ventilation (m^3/min).

Exposure Estimates We estimated exposure to as well as inhaled dose of NO_2, BC, $PM_{2.5}$, and $PM_{2.5}$ Cu, Fe, and Zn content for each participant for each hour (LUR and dispersion models) and week (hybrid models) of her pregnancy, separately for each microenvironment (i.e., home, workplace, and commuting route), and also all microenvironments combined (i.e., total exposure), given their time–activity pattern.

Table 3. External Validation of NO_2 Level Estimates by the Dispersion Model

Validation Dataset	Number of Validation Observations[a]	Adjustment	External Validation R^2
BiSCAPE sampling sites	98	Unadjusted	**0.65**
Participants' home-outdoor measurements	1,554	Unadjusted	**0.44**
Participants' personal measurements	1,660	Unadjusted	**0.10**
	1,515	Adjusted for the indoor/outdoor ratio[a]	**0.32**

BiSCAPE = Barcelona Life Cohort Study Air Pollution Exposure.
[a] The number of datapoint-weeks.
[b] For all times that the participant was at home, we multiplied the ambient NO_2 level predicted by the dispersion model by the home-indoor/home-outdoor ratio for that participant. (The NO_2 levels at home-indoor and home-outdoor were collected during the same campaign of collecting personal NO_2 and time–activity data.)

Table 4. Description for the BiSC Hybrid Models for Each Pollutant's Contents in Terms of the Number of Data Points Used to Develop the Model (*N*), 10-Fold-Cross-Validation R^2 (10-CV R^2), and Root Mean Square Error (10-CV RMSE), and Predictor Variables

			Performance Metrics		
Pollutant	**Year**	***N***	**10-CV R^2**	**10-CV RMSE**	**Predictor Variables**[a]
NO_2	2018–2021	1,232	0.64	7.5	NO2_Dispersion + idw_no2_monitoring_station + distinvmajor1 + majorroadlength100 +majorroadlength50 + trafload25 + trafnear + avg_traffic_stations + avg_solar_radiation + sqralt + ldres1000 + ldres500 + hdres1000 + build1000 + roads100 + lat + lon
$PM_{2.5}$	2021	161	0.66	3.45	PM25_Dispersion + idw_pm25monitoring_stations + avg_traffic_stations + ldres1000 + build25 + pop1000 + roads25 + sqralt + majorroadlength25 + trafload300 + build_height_25 + lat + lon
BC	2021	74	0.86	0.23	BC_Dispersion + idw_nox_monitoring_stations + avg_atmospheric_pressure + avg_bc_palau_reial + pop100 + hdres300 + roads25 + avg_wind_speed + roadlength25 + hdres50 + distinvmajor1 + avg_traffic_stations + linesnear + pop300 + trafload500 + roads500
$PM_{2.5\text{-}Fe}$	2021	161	0.54	0.08	PM25_road_nonexhaust + idw_pm25monitoring_stations + roads300 + roads1000 + ldres500 + sqralt + LEZ + lat + lon
$PM_{2.5\text{-}Cu}$	2021	154	0.70	2.15	PM25_road_nonexhaust + idw_pm25monitoring_stations + linesnear + industry1000 + roads300 + ldres1000 + roads1000 + avg_traffic_stations + LEZ + lat + lon
$PM_{2.5\text{-}Zn}$	2021	141	0.44	27.7	PM25_road_nonexhaust + PM25_background + idw_pm25 + linesnear + industry1000 + roads50 + build25 + roads300 + ldres1000 + roads1000 + avg_traffic_stations + trafmajor + trafmajorload1000 + trafload1000 + hdres25 + LEZ + lat + lon

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[a] Predictor variable definitions — NO2_Dispersion: dispersion estimates (μg/m³), PM25_Dispersion: dispersion estimates $PM_{2.5}$ (μg/m³), BC_Dispersion: dispersion estimates BC (μg/m³), PM25_road_nonexhaust: dispersion estimates for nonexhaust $PM_{2.5}$, PM25_background: dispersion estimates for background $PM_{2.5}$, idw_no2_monitoring_station: weekly NO_2 inverse distance weighting interpolation estimates from XVCPA (μg/m³), idw_pm25_monitoring_station: weekly $PM_{2.5}$ inverse distance weighting interpolation estimates from XVCPA (μg/m³), idw_nox_monitoring_station: weekly NO_x inverse distance weighting interpolation estimates from XVCPA (μg/m³), avg_bc_palau_reial: weekly BC average concentration from Palau Reial monitoring station (μg/m³), avg_traffic_stations: weekly average count of vehicles in AMB (count), avg_solar_radiation: weekly average solar radiation from Raval station (MJ/m²), avg_wind_speed: weekly average wind speed from Raval station (km/h), avg_atmospheric_pressure: atmospheric pressure from Raval station (hPA), distinvmajor1: inverse distance to the nearest major road (m^{-1}), roadlength25: total road length (m) within 25 m, majorroadlength25: total major road length (m) within 25 m, majorroadlength50: total major road length (m) within 50 m, majorroadlength100: total major road length (m) within 100 m, trafload25: total traffic intensity (vehicles/day) within 25 m, trafload300: total traffic intensity (vehicles/day) within 300 m, trafload500: total traffic intensity (vehicles/day) within 500 m, trafload1000: total traffic intensity (vehicles/day) within 1,000 m, trafmajorload1000: total major road traffic intensity (vehicles/day) within 1,000 m, trafnear: traffic intensity at the nearest road (vehicles/day), linesnear: number traffic lines on nearest street, LEZ: Low Emissions Zone (Yes/No, ref value=No), hdres25: high-density residential area (m²) within 25 m, hdres50: high-density residential area (m²) within 300 m, hdres300: high-density residential area (m²) within 500 m, hdres1000: high-density residential area (m²) within 1,000 m, roads25: road surface area (m²) within 25m, roads50: road surface area (m²) within 50 m, roads100: road surface area (m²) within 100 m, roads300: road surface area (m²) within 300 m, roads500: road surface area (m²) within 500 m, roads1000: road surface area (m²) within 1,000 m, pop100: population density (inhabitants) within 100 m, pop300: population density (inhabitants) within 300 m, pop1000: population density (inhabitants) within 1,000 m, build25: building area (m²) within 25 m, build1000: building area (m²) within 1,000 m, ldres500: low-density residential area (m²) within 500 m, ldres1000: low-density residential area (m²) within 1,000 m, industry1000: industrial area (m²) within 1,000 m, trafmajor: traffic intensity at the nearest major road (vehicles/day), build_height_25: averaged building height (meters) within 25 m, lat: latitude (m), lon: longitude (m), sqralt: squared root altitude ($m^{0.5}$).

Noise

Home Measurement Campaigns As part of our home visits, we measured home-outdoor noise levels at the most traffic-exposed façade of each participant for one week during the first or third trimester of pregnancy (coinciding with the air pollution measurement campaign). This one-week campaign was expected to provide representative long-term equivalent sound pressure levels in dB(A) according to standard measurement guidelines.[37] We conducted these measurements using a high-quality (Class I) long-life noise level meter (Noise Sentry RT). Sound level meters were placed next to the NO_2 samplers. The exact locations of the noise meters were recorded on GIS software (QGIS) by the fieldworkers. We also asked participants to fill out a diary regarding the noise-generating incidents (e.g., construction work, public celebrations, neighbors' home parties, etc.), which were then used to clean the measured noise level data. After cleaning the measured data, we derived the average noise levels in dB(A) for the daytime (L_d), evening-time (L_e), night-time (L_n), and the day-evening-night combined (L_{den}; EU indicator for the 24h with 5 and 10 dB[A] weights for the evening and night, respectively, under Directive 2002/49/EC), as well as noise intermittency ratio. Noise intermittency ratio, as an indicator of noise events, was defined as the ratio (i.e., percentage) of the event-based noise energy to the total noise energy.[38]

Noise Maps To generate comparable exposure estimates with those of TRAP (estimated at home and the workplace), we supplemented the home-outdoor measurements with levels of road traffic noise (L_d, L_e, L_n, L_{den}) at home and workplace address façades derived from the Strategic Noise Maps across BiSC areas that were developed under EU Directive 2002/49/EC for the period of 2017–2022.[39] The Strategic Noise Maps were generated by the urban agglomerations of more than 100,000 inhabitants. These maps adhere to the best practices outlined by the European Commission and comply with regional regulations.[39] The underlying noise levels either came from predictive models for acoustic simulation, for instance in Barcelona, or representative measurements (both short- and long-term to ensure accuracy and comprehensiveness), in smaller municipalities such as Sant Adrià del Besòs. Estimated noise levels depict exposure levels at 4 m on building façades. As such, it was not possible to assign noise exposure levels during commuting (e.g., at the sidewalk or road) to the BiSC participants. These maps provide noise levels encompassing road traffic, other sources, and totals. For the FRONTIER analyses, we used the estimates of noise due to road traffic.

Noise Perception, Sensitivity, and Protection We applied standardized questions to assess noise sensitivity[40,41] and noise annoyance.[42] To account for outdoor and indoor noise differences, as previously done by our team,[43] we also obtained data on protections against noise used at home by participants, including using earplugs and closing window blinds or windows.

Exposure Estimates For each participant, we assigned home exposure indicators, including L_d, L_e, L_n, and L_{den}, as well as the noise intermittency ratio at home, based on the home-outdoor measurements. Moreover, we assigned each participant indicators of noise exposure (L_d, L_e, L_n, and L_{den}) at home and the workplace based on the noise maps.

Green Space

Greenness We used the Normalized Difference Vegetation Index (NDVI),[44] derived from 2020 aerial images by the Cartographic and Geological Institute of Catalonia (ICGC) at a 1 m × 1 m resolution, as a two-dimensional indicator of greenness. NDVI values range between −1 and 1, with higher numbers indicating more greenness (i.e., photosynthetic activity).

Canopy Volume We applied a Light Detection and Ranging (LiDAR)-based 3D indicator of the volume of green features such as shrubs and trees (Green volume [m^3/m^2]).[45] We used LiDAR data acquired by the Catalan Institute of Cartography between April 2016 and October 2017 with a point density of >0.5/m^2, coupled with auxiliary data (Barcelona topographic map and NDVI from Planet satellite), to derive a Canopy Height Model from which we obtained the Canopy Volume. Given that the building footprint layer — used as auxiliary data to calculate the canopy volume — only covered the city of Barcelona, the canopy volume was assigned only to a subset of 741 participants residing in the city of Barcelona.

Exposure Estimates We abstracted surrounding greenness and canopy volume separately for each participant's home (50-m and 300-m buffers).[46] We also characterized the surrounding greenness around the major roads (i.e., roads with annual average traffic over 5,000 vehicles per day) within 200 m of each participant's home, and retrieved greenspace indicators for a buffer area of 50 m surrounding these roads.[47]

We characterized maternal physical activity (1) objectively using personal physical activity monitors (ActiGraph wGT3X-BT, ActiGraph Ltd., US) during the two-week personal measurement campaigns (i.e., home visits) in the first and third trimesters, and (2) subjectively using a Pregnancy Physical Activity Questionnaire[48] filled by the women in the first and third trimesters. We converted the raw tri-axial acceleration data (ActiGraph) into ENMO,[33] a measure that represents the vectorial magnitude of dynamic acceleration over the three axes, using the GGIR R-package.[49] From the questionnaire, we obtained information on the average daily total energy expenditure in Metabolic Equivalent for Task-hours per day.[50]

During the same measurement campaign weeks, we collected data on the time–activity patterns of pregnant women using a smartphone with a validated geolocation application (ExpoApp, Ateknea Solutions, Spain).[51] Moreover, during the home visits, the participants were asked to identify and mark the main commuting route to and from work on the map using an interactive GIS environment (QGIS Time–Activity Pattern platform).[52] We also obtained data on modes of transportation and used this data to either estimate the time spent in each commuting segment when we did not have ExpoApp data, or to determine a probable commuting route using home and work location data when neither ExpoApp nor QGIS data were available. These data together enabled us to characterize the time spent and the level of physical activity that the BiSC participants had in each microenvironment (home, workplace, and commuting between these two).

HEALTH OUTCOMES

Main Health Outcomes

Birth weight and small for gestational age (SGA) were the main health outcomes of the FRONTIER study. Data on birth weight were extracted from the hospital records. SGA was defined as birth weight below the 10th percentile for the gestational age and sex according to reference tables for the Spanish population.[53] The gestational age was determined objectively based on ultrasound measurement of the fetal crown–rump length during the first trimester (weeks 11–13).[54]

Secondary Health Outcomes

We considered trajectories of fetal growth as our secondary outcomes. We applied transabdominal ultrasound measurements of fetal head (biparietal diameter and head circumference), abdominal circumference, femur length, and estimated fetal weight (Hadlock formula)[55] at weeks 20 (range: weeks 19–26), 32 (range: weeks 28–36), and 37 (range: weeks 28–41) of gestation.[56] All the ultrasound examinations were performed by well-trained and experienced operators. To minimize the inter-rater variability, we applied the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) guideline.[57]

COVARIATE AND MODIFIER DATA

Socioeconomic and Demographic Data

We collected demographic data (e.g., age and ethnicity) through questionnaires and face-to-face interviews at the recruitment visit. We also collected data on maternal education as an indicator of household socioeconomic status (SES), and annual average household income at the census tract level as an indicator of neighborhood SES. Data on maternal education were collected using the following categories: (1) no education or incomplete primary school, (2) primary school, (3) secondary school or professional education, (4) university undergraduate education, and (5) university postgraduate education. Given the small number of participants in some of these categories, we reclassified these categories into two categories: having a university degree (yes/no). The data on annual average household income at the census tract level was obtained from the 2020 Standard of Living and Living Conditions survey conducted by the Spanish National Institute of Statistics (INE), which is based on fiscal data including wages, pensions, unemployment benefits, other benefits, and other income.[58] This data was extracted in Euros and linked to participants based on the census tract in which their residential address was located. In instances of change in home address during pregnancy, values were proportionally weighted according to the time spent at each census tract.

Maternal Lifestyle

Data on active and passive smoking as well as alcohol consumption during pregnancy were collected through questionnaires[59] administered during the first and third trimesters. During these trimesters, we also collected data on maternal time–activity patterns as described before.

Maternal Stress

We characterized maternal stress during the third trimester objectively, using maternal hair cortisol levels, and subjectively, using a self-administered questionnaire. During the third-trimester hospital visit, we collected maternal hair from the posterior vertex close to the scalp following the guidelines of the Society of Hair Testing.[60] We then measured cortisol level in these hair samples using liquid chromatography with tandem mass spectrometry, carried out at the Hospital del Mar Research Institute as described elsewhere.[61]

We also applied the widely used 10-item Perceived Stress Scale (PSS-10),[62,63] filled by the women during the third trimester, to subjectively characterize their perceived stress.

Clinical Data

We collected clinical data on past and current pregnancies (e.g., parity, history of low birth weight, and use of artificial reproductive techniques) during the first and third trimesters of pregnancy through face-to-face interviews and hospital records.

MEDIATORS

Placental Function

Placental function was characterized at week 32 (range: weeks 28–36) of gestation, based on Doppler ultrasound indicators for fetoplacental hemodynamics including (1) uterine artery pulsatility index (PI), (2) umbilical artery PI, (3) middle cerebral artery PI, and (4) cerebroplacental ratio as the ratio of the middle cerebral artery PI divided by the uterine artery PI.[64] We followed the established guidelines[65] to conduct the ultrasound examinations to minimize the inter-rater variability. Briefly, for uterine artery assessment, the ultrasound probe was placed on the lower quadrant of the abdomen, angled medially, and color Doppler imaging was used to identify the uterine artery at the apparent crossover with the external iliac artery. Measurements were taken approximately 1 cm distal to the crossover point. The umbilical artery PI was calculated from a free-floating portion of the umbilical cord. To minimize variability, the middle cerebral artery PI was measured in a transverse view of the fetal head, at the level of its origin from the circle of Willis. Doppler readings were recorded during the absence of fetal movements and voluntarily suspended maternal breathing. All pulsed Doppler parameters were recorded automatically from at least three consecutive waveforms, with the angle of insonation as close to 0 as possible and always below 30°. We calculated z-scores for each of the aforementioned indicators based on the gestational age at the time of the ultrasound examination, and used these z-scores in our analyses.[66–69]

COVID-19 PANDEMIC IMPACT

On March 14, 2020, Catalonia, alongside the rest of Spain, started a strict lockdown due to the COVID-19 pandemic, essentially halting all nonessential work and severely limiting the freedom of movement of its residents. As part of these measures, hospitals across Catalonia halted all the ongoing research activities apart from those that were dealing with COVID-19. These measures stayed in place until they were gradually phased out during three phases in June 2020. During this period, all the BiSC fieldworks, including recruitments, clinical visits at the hospitals, and environmental fieldwork at participants' homes, were put on hold. After the lockdown, the recruitment and clinical and environmental fieldworks were restarted, using amended inclusion criteria and a short version of home visits to accommodate the situation imposed by the pandemic.

Inclusion Criteria

We restarted the recruitment of the participants through phone in early May 2020. Before the pandemic, we recruited pregnant women with a gestational age up to week 16 of pregnancy. Given the fact that, due to the pandemic, our nurses were not able to go to the primary healthcare centers where some of our pregnant women were approached to be recruited in the study, we extended the eligibility to women with gestational age up to week 24 of pregnancy. The reason was that in our study region, all pregnant women have to go to the hospital for their routine ultrasound measures around week 20 of their pregnancy, and these visits were not stopped during the pandemic, so we could therefore approach these women and recruit them.

Home Visits

We restarted the environmental fieldwork (i.e., home visits) on June 8, 2020. We opted for a short version of the home visits that included the personal, home-indoor, and home-outdoor NO_2 passive samplers; the personal physical activity monitor; and the smartphone. Our environmental fieldworkers delivered the monitors and instructions to the doorstep of the participants. The instructions consisted of a dossier with step-by-step installation instructions, including images and a video detailing how to install and use the aforementioned samplers and sensors. During the remission time of the epidemic, our fieldworkers were also offering the participants the possibility of the installation of the monitors by the fieldworkers (which could take less than 15 minutes). For those participants who were willing to allow our fieldworkers in, our fieldworkers entered their homes and installed the monitors.

These shortened visits did not include using the QGIS platform to collect information about the main commuting route to and from the workplace. Moreover, due to the complexity of installing noise meters, their installation was done only when the pandemic situation allowed fieldworkers to enter the homes. For those participants (n = 116) for whom we could not install the noise meters during their pregnancy, we installed the noise meter postnatally up to 6 months after their delivery. To validate that the noise measurements taken at 6 months were representative of those of the third trimester visit, we repeated measurements at 6 months in 38 participants who also had measurements at the third trimester. The Spearman's correlation between these two measures was 0.91.

DATA ANALYSIS

The main steps to conduct statistical analyses of the FRONTIER project included the following:

1. Managing, curating, and cleaning the data
2. Dealing with missing data
3. Descriptive analyses of the different variables included in the project
4. Conducting analyses that evaluate the association between maternal exposure to TRAP and fetal growth while separating the effect of noise; evaluating modifiers, mediators, and mitigators of this association; and identifying relevant window(s) of vulnerability
5. Conducting sensitivity analyses to explore the robustness of the findings of the main analyses to a number of assumptions or under different scenarios

DATA PREPARATION

Quality Assurance/Quality Control Procedures

The procedures for quality assurance and quality control of the FRONTIER study are described in *Appendix 1*.

Dealing with Missing Data

To prevent a loss of information and the introduction of potential selection bias, missing values of smoking (5.9% missing), alcohol consumption (6.5% missing), maternal weight (6.7% missing), and height (0.9% missing) were imputed. No imputation was done for outcome and exposure variables because no gain in power is expected from such a procedure.[70] To impute missing variables, we applied multiple imputation by a chained equations procedure[70] using the *mice* R package,[71] which is a commonly used and accepted method to deal with missing data. A total of 100 imputed datasets were created for each analysis. After imputation, all variables with missing values were inspected. In particular, the imputed and nonmissing observations were compared using density plots and strip plots as described by van Buuren and Groothuis-Oudshoorn,[71] and no anomalies were observed in the distribution of new data.

ASSOCIATION OF TRAP WITH FETAL GROWTH

A summary description of the FRONTIER study's statistical analyses is presented in **Table 5**.

SINGLE-POLLUTANT MODELS

We first checked the linearity of associations between the different exposures and outcomes, using generalized additive models by means of the *mgcv* R package,[72] which did not show a notable deviation from linearity. We then estimated the association of each air pollutant (i.e., one exposure variable at a time) on both anthropometric measures at birth (primary outcomes) and the longitudinal trajectories of fetal growth (secondary outcomes). These analyses were conducted separately for exposure levels in each microenvironment (i.e., home, workplace, and commuting route between these two), as well as all microenvironments combined. Moreover, separate analyses were conducted for exposure estimates based on LUR models, dispersion models, and hybrid models, as well as personal measurement (only for NO_2) levels and inhaled dose of traffic-related air pollutants. For estimating the associations between TRAP and birth outcomes using these analyses, we developed linear mixed effects models for birth weight and fetal growth trajectories (continuous outcome variables), and logistic mixed effects models for SGA (binary outcome variable). For the main outcomes (birth weight and SGA), we set the hospital as the random effect, while for the secondary outcome (trajectories of fetal growth), we considered both participant and hospital as random effects. In latter models, we included a multiplicative interaction term between TRAP and gestational age (i.e., time) to estimate the association of TRAP exposure (time-varying variable) on trajectories of fetal growth.[22] All these models were adjusted for a priori sets of covariates selected based on the available literature, which included maternal age (continuous, years), education level (categorical, university degree: yes/no), body mass index (BMI)[73] at the first trimester (continuous, kg/m^2), parity (categorical, nulliparous: yes/no), active smoking during pregnancy (categorical, yes/no), exposure to environmental tobacco smoke (categorical, yes/no), alcohol consumption during pregnancy (categorical, yes/no), gestational age at delivery (continuous, day), history of low birth weight in previous pregnancies (categorical, yes/no), and sex of the neonate (girl or boy). Several of these variables were not classical confounders for our analyses; however, given that they were strong determinants of fetal growth (i.e., our study outcome), adjusting our linear regression models for them could result in more precise association estimates.[74] The analyses of SGA were not controlled for gestational age at delivery and sex of the neonate because they had already been used to define SGA. For the aforementioned models, we explored the distribution of residuals using histograms and q-q plots, as well as graphs of residuals versus predicted values to assess departures from model assumptions. No notable anomalies were observed. These mixed effects models were conducted using the R package *lme4*.[75]

Table 5. Overview of the FRONTIER Main Analyses

Statistical Analysis	Applied Methodology	R Package	Imputation Method
Single pollutant models	Generalized Additive Models	mgcv	Multiple Imputation by Chain Equations (MICE)
	Linear and Logistic Mixed Effects Models	lme4	Multiple Imputation by Chain Equations (MICE)
	Mediation analysis	mediation	Multiple Imputation by Chain Equations (MICE)
Multiple pollutant models	Lasso and Ridge regression	glmnet	Multiple Imputation by Chain Equations (MICE)
	Bayesian hierarchical models	R2jags	Multiple Imputation by Chain Equations (MICE)
Windows of vulnerability	Distributed Lag Nonlinear Models	dlnm	Multiple Imputation by Chain Equations (MICE)
Correction for exposure measurement error	Regression calibration	mecor	–
Sensitivity analyses	Similar to the corresponding main analyses	Similar to the corresponding main analyses	Similar to the corresponding main analyses

Sensitivity Analyses

We conducted a wide range of sensitivity analyses to evaluate the robustness of our findings:

1. We conducted complete case analyses to evaluate any issues related to missing data and compared the findings with those observed for the multiple imputation datasets.

2. We further adjusted our analyses for potentially relevant covariates including neonate's ethnicity (categorical, European vs. other), type of cooking stove (categorical, gas vs. electric), having kitchen hood (categorical, yes/no), and using kitchen hood during cooking (categorical, always vs. sometimes or never) that were not included in the main analyses.

3. We repeated the analyses after removing gestational age at delivery from our models. We adjusted our analyses for gestational age at delivery, given that it is a very strong predictor of birth weight, and also by doing so, we were in line with the vast majority of previous studies on the association of air pollution with birth weight that have controlled their analyses for it. However, given the potential impact of air pollution on gestational age at delivery, it might act as a mediator of the association between air pollution and birth weight, and if this is the case, the analyses of the association of air pollution and birth weight should not be controlled for the gestational age at delivery.

4. In our main analyses, to account for the multilevel structure of our data (i.e., participants within hospitals), we applied mixed effects models with hospital as a random effect. As a sensitivity analysis, we developed linear and logistic regression models with hospital as an independent fixed effect categorical variable in the models to evaluate the robustness of our results to the choice of our models, and also provide comparable results for analyses of multipollutant models and exposure measurement error models, for which we used hospital as an independent fixed effect categorical variable. Fixed effect models control for any potential differences between the hospitals in the study by providing within-hospital estimates, while random effect models also control for differences between hospitals and provide results that can be more generalizable.

5. We repeated our analyses after removing the outliers and compared the results with those of the main analyses to explore whether there are any influential observations in our association estimates. We defined outliers as those values that were more than 1.5 times the interquartile range (IQR) above the upper quartile or below the lower quartile.

6. We developed z-scores for birth weight based on sex and gestational age at delivery, using birth weight standards for the Spanish population developed based on the data from one of the hospitals participating in BiSC.[53] We repeated the main analyses for birth weight using the z-scores as the outcome variable and removing sex and gestational age at delivery from the models.

7. Given the relatively large number of comparisons, we adjusted our *P* values for multiple comparisons using the method developed by Nyholt.[76] Based on this method, we estimated the effective number of independent tests based on the correlation between exposure variables grouped by model (LUR, dispersion, and hybrid models) and by microenvironment (all microenvironments combined, home, workplace, and commuting). To run this analysis, we used the *meff* function from the R Package *poolr*.[77]

Note: For analyses of effect modification and mitigation, incorporation of exposure measurement errors, and mediation analyses that are described below, we applied the estimated TRAP levels from LUR models for all microenvironments and the entire pregnancy. For the analyses of the window(s) of vulnerability, we applied estimates from LUR models for all microenvironments and each week of pregnancy. The reasons for this selection were that the LUR models showed a superior performance compared to dispersion models, and we also had estimates for all microenvironments (i.e., home, workplace, and commuting route), which contrasts with the hybrid models that did not have estimates for the commuting route.

Modification by Maternal Socioeconomic Status, Stress, Physical Activity, and COVID-19 Pandemic

We assessed the modification of the association between TRAP exposure and fetal growth by maternal stress (both cortisol levels and maternal perceived stress), maternal education (a household-level indicator of SES), annual average household income at the census tract (a neighborhood-level indicator of SES), physical activity (both objective and subjective measures), and the timing of conception and delivery in relation to the COVID-19 pandemic lockdown. The continuous effect modifiers were categorized into three categories based on their tertiles. For the COVID-19 pandemic, we generated a categorical variable by allocating participants into three groups: (1) those who had their entire pregnancy (conception and delivery) before the beginning of the state of emergency in Spain (March 14, 2020) (n = 350), (2) those who had their conception before the state of emergency and their delivery afterward (n = 308), and (3) those who had their entire pregnancy after the state of emergency (n = 366). We first tested the statistical significance of the multiplicative interaction term between each air pollutant and each potential effect modifier (one exposure and one modifier at a time) using a likelihood ratio test comparing models with and without interaction terms. Afterward, we stratified the main effect analyses based on the strata of each modifier (one at a time) to explore the potential variation in our observed associations across the strata of these modifiers.

Mitigation by Urban Canopy or Greenness

We evaluated the mitigation of the impact of TRAP on fetal growth by urban greenness or canopy (one at a time).

We first evaluated the statistical significance of the multiplicative interaction term between each air pollutant and each canopy or greenness indicator (expressed as tertiles), using a likelihood ratio test. We then stratified analyses of TRAP and fetal growth based on tertiles of the canopy or greenness indicators to explore whether the associations vary across different amounts of canopy or greenness.

Incorporating Exposure Measurement Error

We treated our measured personal NO_2 exposure levels (using passive samplers) as our gold standard and applied regression calibration to correct for the effect of measurement error on the estimates produced when using modeled exposure.[78] Accordingly, we followed these steps:

Step 1: We estimated the regression coefficients and variances using the modeled exposure (uncorrected models) and the covariates.

Step 2: The measurement-error-model parameters were estimated by regressing the personal exposure on the modeled exposure during the personal NO_2 sampling period, adjusting for all other covariates included in the primary regression model.

Step 3: The estimates were adjusted for measurement error by the two sets (those of Steps 1 and 2) of estimates and their variance–covariances, using bootstrapping to estimate proper standard errors.[79]

For these analyses, instead of mixed effects models with hospital as the random effect, we applied linear regression models with hospital as a fixed effect categorical predictor. We used the *mecor* R package[79] to conduct these analyses, and within the *mecor()* function, we used the *MeasErrorExt* object, which is applied for external validation studies.

Window(s) of Vulnerability

We applied distributed lag nonlinear models to assess the associations of exposure to TRAP, separately during each week of pregnancy, with fetal growth.[80] To avoid variation in the length of gestation, we restricted these analyses to those births with a minimum gestation of 37 weeks (i.e., excluding preterm births).[81] We then included in the model the weekly exposure estimated at weeks 1–36 of pregnancy using a *cross-basis* function in the *dlnm* R package,[82] which constrained the estimates for each week to vary smoothly across lags. Specifically, the cross-basis was defined using a linear function to model the exposure–response function at different lags.[83] The lagged associations were constrained with natural splines, using equidistant knots in the lag space. We tried between two and six degrees of freedom for the spline, and selected the one that minimized the Akaike information criterion of the model. For these analyses, models were adjusted for the same covariates used in the main analysis. We also conducted a sensitivity analysis without adjustment for gestational age at delivery.

Mediation Analyses

We assessed the potential mediatory role of placental function in the association between TRAP and fetal growth (birth weight and SGA) using the *mediation* R package. The mediation analysis consisted of two steps: We first established the potential mediatory role of placental function for those air pollutants for which we found a statistically significant association with fetal growth in our main analyses. Then, if we could establish such a mediatory role, we quantified this role. We followed the steps set by Baron and Kenny[84] to establish the mediation role of placental function (separately for each Doppler ultrasound indicator of placental function) in the association between TRAP exposure and fetal growth. More contemporary mediation analysis approaches, such as the four-way decomposition approach proposed by VanderWeele,[85] include both mediated effects and interactive effects; however, in our setting, we did not find it plausible to assume an interaction between air pollution and placental function in relation to fetal growth. We note that if the interaction is absent, the counterfactual approach to mediation is equivalent to the Baron and Kenny approach.[86] Briefly, these steps included establishing the association(s) between (1) TRAP and fetal growth (i.e., our main analyses); (2) TRAP and placental function using mixed effects models with hospital as the random effect, the z-score of the Doppler indicators of placental function (based on gestational age at the time of ultrasound examination) as the outcome variable, TRAP (based on LUR model estimates for all microenvironments averaged between conception and the time of the Doppler ultrasound examination) as the main exposure variable, and the same set of covariates as the main analyses (all but gestational age) plus pregnancy-induced hypertensive disorders in the current pregnancy; and (3 and 4) fetal growth and placental function adjusted for TRAP along with fetal growth and TRAP adjusted for placental function, essentially by adding mediators (one at a time) to our main analyses models without gestational age. For these latter models, the TRAP exposure was based on LUR model estimates for all microenvironments averaged between conception and the time of the Doppler ultrasound examination. We then calculated, for each mediator and association separately, the proportion mediated as the percentage of the total effect of the exposure on the outcome that is explained by the mediator (i.e., indirect effect). We used bootstrapping to obtain percentile-based 95% confidence intervals (CIs) for the contribution of each mediator.

MULTIPOLLUTANT MODELS

We developed two types of multipollutant models: models simultaneously including NO_2, BC, and $PM_{2.5}$ to provide a comprehensive picture of the association between TRAP and fetal growth, and models that in addition to an air pollutant also included measures of noise exposure, including modeled traffic-related noise exposure (L_{den}) in all microenvironments combined, measured noise levels (L_{den}) at home, measured noise intermittency ratio at home, and noise annoyance due to traffic sources at home (one at a time). To limit the number of conducted analyses, we did not conduct bipollutant models for air pollutants (i.e., including two air pollutants instead of three air pollutants).

We first checked the multiple collinearity in our multipollutant models by abstracting the variance inflation factor (VIF) for each exposure variable and comparing it to a cut-off value of 2.5. If we detected indications of multicollinearity, we turned to estimating the associations using Ridge and Lasso regression models,[87] as well as Bayesian techniques that have been recommended for correlated exposure data.[88] These methods could produce association estimates for individual pollutants that were easy to interpret and could be compared with the results of single-pollutant models applied in our main analyses. We did not apply analytical methods such as Bayesian Kernel Machine Regression or Weighted Quantile Sum regression models because these methods could provide estimates for a mixture of pollutants that were difficult to interpret or compare with findings of single-pollutant models.

Ridge and Lasso regression models are regularization techniques used to reduce model complexity and prevent overfitting and collinearity.[87] Their processes are based on introducing a regularization parameter λ on the magnitude of the model coefficients. Ridge penalizes the sum of the coefficients squared. This regularization, known as L2, proportionally reduces the values of all coefficients without setting them to zero. Lasso uses L1 regularization, which penalizes the sum of the absolute values of coefficients, forcing the coefficients to tend toward zero. We conducted all these analyses using *glmnet* R package.[87] To find the optimal λ parameter, we applied a cross-validation that balances model complexity and predictive accuracy, using the function *cv.glmnet*.[87] We applied bootstrapping to obtain percentile-based 95% CIs for the coefficient of each air pollutant.

JAGS (Just Another Gibbs Sampler)[89] is purpose-built software designed to implement Bayesian hierarchical models using Markov Chain Monte Carlo techniques.[90] The strength of this methodology is that it guarantees convergence to the quantity (or quantities) of interest with minimal requirements on the targeted distribution behind such quantities.[90] We used the *R2jags* R package[91] to conduct these analyses.

For multipollutant analyses and for the joint air pollution and noise analyses that were based on the modeled traffic-related noise data for all microenvironments, we applied the estimated air pollution levels by LUR models for all microenvironments and the entire pregnancy. On the other hand, for the joint air pollution and noise analyses that used the home-outdoor measured noise data and noise annoyance, we used the estimated air pollution levels by LUR models for only the home and the entire pregnancy. For the two-pollutant models, including TRAP, modeled and measured noise levels, and noise intermittency ratio, as a sensitivity analysis, we further adjust our analyses for noise sensitivity and noise protection (one at a time).

RESULTS

DESCRIPTION OF THE STUDY POPULATION

Socioeconomic, Demographic, and Lifestyle Characteristics

The description of sociodemographic, lifestyle, and home characteristics of study participants at recruitment (n = 1,080) and delivery (n = 1,024) time are presented in **Table 6**. The average age of the participants was 34 years, with the majority of them being European and having a university degree. There was no statistically significant difference between those participants included in FRONTIER and those who were lost to follow-up in terms of sociodemographic and lifestyle characteristics.

Physical Examination and Clinical Data

Table 7 presents the description of the physical examination and clinical characteristics of the study participants included in the frontier analyses.

DESCRIPTION OF HEALTH OUTCOMES

The descriptive statistics of the delivery aspects and fetal growth are presented in **Table 8**. The median (IQR) of birth weight and gestational age at delivery were 3,310 (580) g and 40 (1.7) weeks, respectively, and there were 136 (13.3% of babies) cases of SGA.

DESCRIPTION OF EXPOSURES

Air Pollution

Personal and Home Measurements The description of measured personal, home-indoor, and home-outdoor NO_2 levels (using passive samplers), separately for the first trimester and third trimester campaigns, is presented in **Figure 3**.

Moreover, as presented in **Figure 4**, the personal NO_2 levels in both trimesters had stronger correlations with home-indoor levels than home-outdoor levels. There were also moderate correlations between levels measured in the first and third trimesters.

Modeled Air Pollution Levels The description of estimated exposure levels separately for each pollutant, model, and microenvironment is presented in **Table 9** and depicted in **Figure 5**. The correlations between the air pollution exposure estimates are presented in *Appendix 2*.

Noise

The median (IQR) of the modeled traffic-related noise exposure (L_{den}) at home, workplace, and commuting combined, and measured home-outdoor noise level (L_{den}) were 64.6 dB(A) (8.9) and 64.7 dB(A) (8.1), respectively. As presented in *Appendix 3*, there were weak to moderate correlations between indicators of noise and TRAP exposure.

Table 6. Description of Socioeconomic, Demographic, and Lifestyle Characteristics of the Recruited BiSC Participants (n = 1,080), Those with Valid Data Included in the FRONTIER Analyses (n = 1,024), and Those Who Were Lost to Follow-Up

Maternal Characteristics[a]	BiSC Participants (n = 1,080)	FRONTIER Participants (n = 1,024)	Loss to Follow-Up (n = 56)	P Value of Difference[b]
Maternal age (years)	34.4 (5.8)	34.4 (5.8)	34.8 (5.3)	0.56
Ethnicity (%)				0.98
European	725 (67.1)	688 (67.2)	37 (66.1)	
Non-European	355 (32.9)	336 (32.8)	19 (33.9)	
Education level (%)				0.21
Primary/secondary school	333 (30.8)	311 (30.4)	22 (39.3)	
University	747 (69.2)	713 (69.6)	34 (60.7)	
Active smoking (%)				0.48
Yes	83 (8.2)	79 (8.0)	4 (13.3)	
No	932 (91.8)	906 (92.0)	26 (86.7)	
Missing	65	39	26	
Passive smoking (%)				1.00
Yes	435 (43.0)	422 (43.0)	13 (43.3)	
No	576 (57.0)	559 (57.0)	17 (56.7)	
Missing	69	43	26	
Alcohol consumption (%)				1.00
Yes	303 (30.1)	294 (30.2)	9 (30.0)	
No	702 (69.9)	681 (69.8)	21 (70.0)	
Missing	75	49	26	
Maternal Metabolic Equivalent for Task (MET)-hours per day	152.2 (98)	152.3 (95.7)	125.1 (165.9)	0.19
Maternal Euclidean norm minus one (ENMO) (milligravity)	25 (7.3)	25 (7.3)	25.4 (6.4)	0.76

BiSC = Barcelona Life Study Cohort.
[a] Continuous variables are described by median (interquartile range), and categorical variables are described by n (%).
[b] Test for the difference between BiSC participants that were included (n = 1,024) and not included (n = 56) in FRONTIER analyses using the Mann-Whitney U test for the continuous variables and Chi-squared test for the categorical variables.

Greenness and Canopy

Appendix 4 presents the descriptive statistics of greenness and canopy indicators.

ASSOCIATION OF TRAP WITH FETAL GROWTH

Main Outcomes

Higher exposure to NO_2 and BC at all microenvironments was associated with lower birth weight across all exposure models, with statistically significant associations for the home and all microenvironments combined (**Figure 6**). For $PM_{2.5}$, we observed a similar pattern with statistically significant associations for the LUR and dispersion model estimates at all microenvironments combined, and for LUR model estimates at home (Figure 6). For $PM_{2.5}$ Cu content, we observed inverse associations with birth weight in all microenvironments, and the associations were statistically significant for exposure in all microenvironments combined, home, and workplace for the estimates made by the LUR model (Figure 6). For the $PM_{2.5}$ Fe content, we observed a similar pattern of associations, and these associations were statistically significant for the estimates made by the LUR model at home and all microenvironments combined (Figure 6). On the other hand, for the $PM_{2.5}$ Zn content, we observed a mixed pattern of associations with birth weight, with a statistically significant direct association

Table 7. Description of Maternal Physical Examination and Clinical Data (n = 1,024)

Variable[a]	Description
Parity	
Multiparous	450 (43.9%)
Nulliparous	574 (56.1%)
Body mass index (kg/m²)	23.5 (4.9)
Missing	63 (6.2%)
Previous low birth weight	
No	987 (96.4%)
Yes	37 (3.6%)
Hair cortisol level (pg/mg)	3.8 (3.2)
Missing	208 (20.3%)
Perceived stress[b]	12 (8)
Missing	397 (38.8%)

[a] Continuous variables are described by median (interquartile range), and categorical variables are described by n (%).
[b] Total score of 10-item Perceived Stress Scale (PSS-10).[62,63]

Table 8. Description of Fetal Growth and Pregnancy Outcomes (n = 1,024)

Variable[a]	Delivery Data (n = 1,024)
Delivery type	
Cesarean	255 (24.9%)
Vaginal	767 (74.9%)
Missing	2 (0.2%)
Gestational age at birth (weeks)	40 (1.7)
Birth weight (g)	3,310 (580)
Small for Gestational Age	
No	888 (86.7%)
Yes	136 (13.3%)
Biparietal diameter (mm) 20 weeks	48 (4)
Missing	18 (1.8%)
Biparietal diameter (mm) 32 weeks	80 (6)
Missing	83 (8.1%)
Biparietal diameter (mm) 37 weeks	88 (5)
Missing	135 (13.2%)
Head circumference (mm) 20 weeks	179 (12)
Missing	19 (1.9%)
Head circumference (mm) 32 weeks	293 (17)
Missing	83 (8.1%)
Head circumference (mm) 37 weeks	320 (17)
Missing	135 (13.2%)
Estimated fetal weight (g) 20 weeks	369 (66)
Missing	86 (8.4%)
Estimated fetal weight (g) 32 weeks	1,894 (352)
Missing	83 (8.1%)
Estimated fetal weight (g) 37 weeks	2,741 (445.8)
Missing	118 (11.5%)
Abdominal circumference (mm) 20 weeks	158 (14)
Missing	21 (2.1%)
Abdominal circumference (mm) 32 weeks	282 (21)
Missing	84 (8.2%)
Abdominal circumference (mm) 37 weeks	320 (23)
Missing	136 (13.3%)
Femur length (mm) 20 weeks	33 (3)
Missing	20 (2%)
Femur length (mm) 32 weeks	60 (5)
Missing	83 (8.1%)
Femur length (mm) 37 weeks	68 (4)
Missing	136 (13.3%)

[a] Continuous variables are described by median (interquartile range), and categorical variables are described by n (%).

for exposure at the workplace estimated by the hybrid model (Figure 6). For the directly measured NO_2 levels (using passive samplers), we observed inverse associations between measured home-indoor, home-outdoor, and personal NO_2 levels and birth weight, which were statistically significant for personal and home-outdoor exposures (Figure 6).

We found an increased risk of SGA associated with NO_2 in all microenvironments, which was statistically significant for home and all microenvironments combined for all exposure models **(Figure 7)**. There was also a statistically significant increase in the risk of SGA in association with NO_2 exposure during commuting for NO_2 levels estimated by dispersion models. Higher exposure to BC was generally associated with an increased risk of SGA, which was statistically significant for LUR and hybrid models at home and all microenvironments combined (Figure 7). Similarly, higher exposure to $PM_{2.5}$ was related to increased risk of SGA in all microenvironments, with statistically significant associations for exposure estimates by LUR and hybrid models in all microenvironments combined and by the LUR model at home (Figure 7). $PM_{2.5}$ Cu and Fe contents were generally associated with a higher risk of SGA, with the association for the LUR model-estimated exposure to $PM_{2.5}$ Fe content in all microenvironments combined being statistically significant (Figure 7). For the $PM_{2.5}$ Zn content, we observed a mixed pattern with no statistically significant associations (Figure 7). For the directly measured NO_2 levels, we observed an increased risk of SGA in association with home-outdoor, home-indoor, and personal levels, and the association was statistically significant for the home-outdoor exposure (Figure 7).

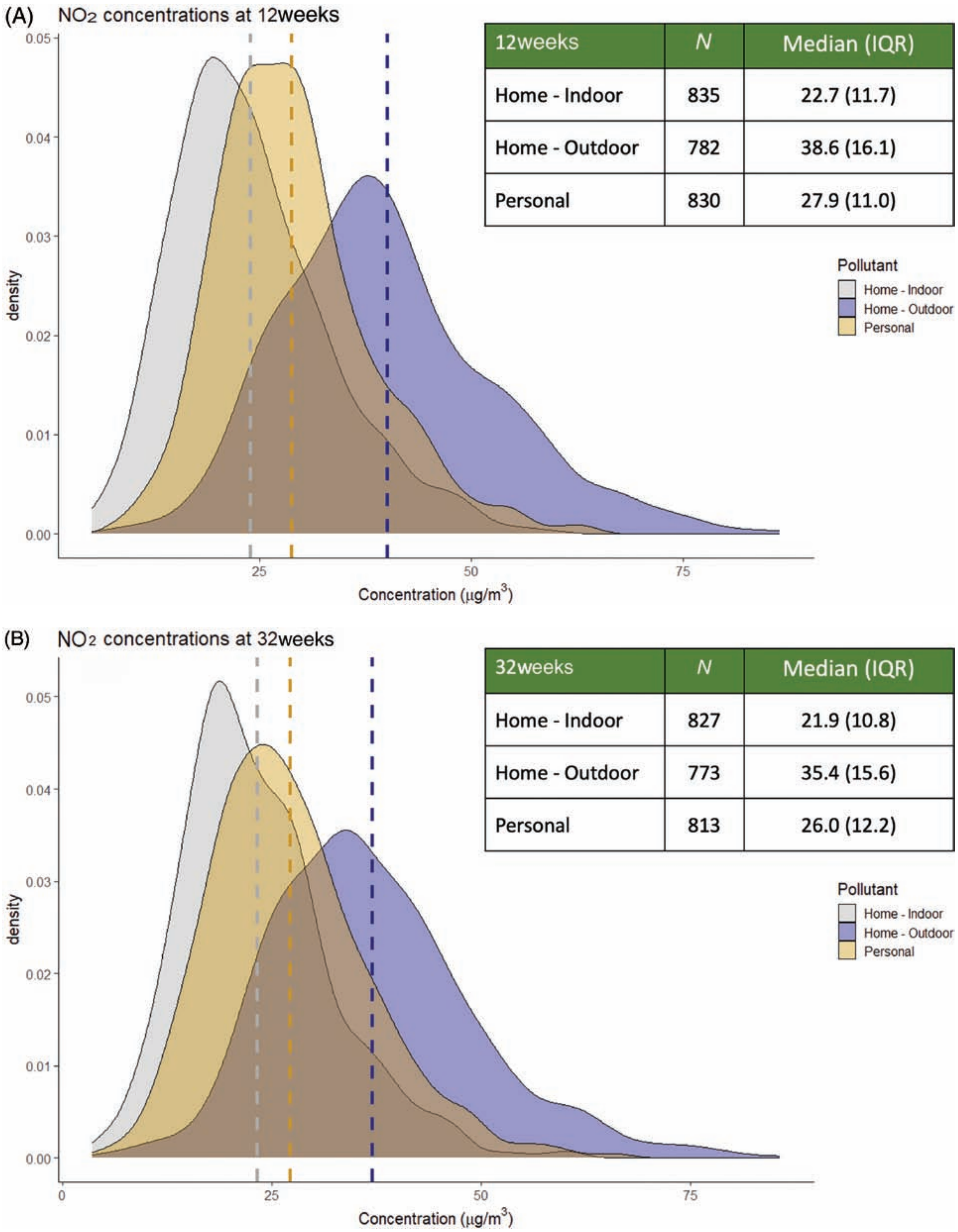


Figure 3. Descriptive statistics of the measured personal, home-indoor, and home-outdoor NO_2 levels in BiSC participants during the first trimester (A) and third trimester (B) of pregnancy. BiSC = Barcelona Life Study Cohort.

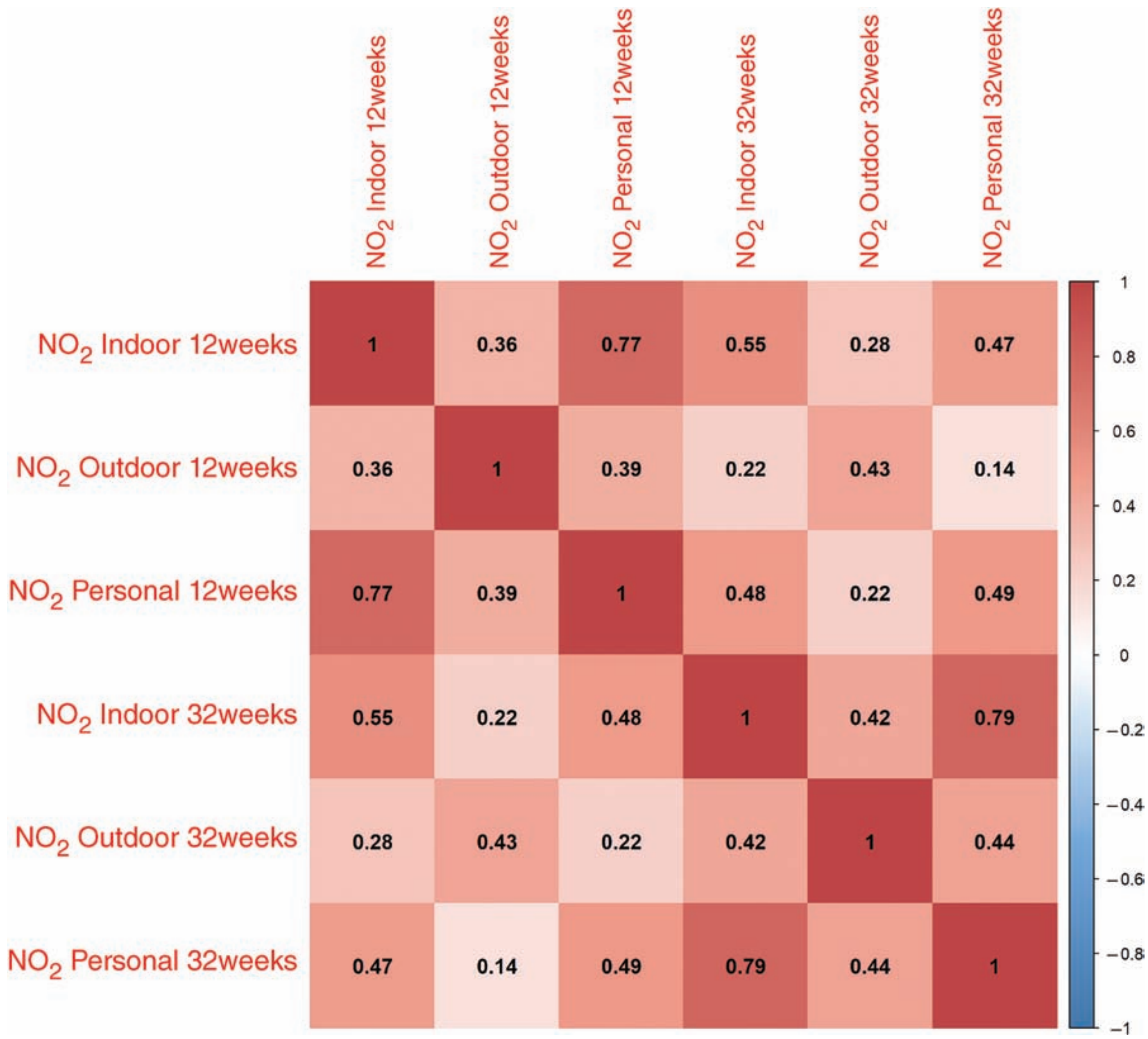


Figure 4. Spearman's correlation coefficients among measured personal, home-indoor, and home-outdoor NO_2 levels in BiSC participants in the first (~week 12 of gestation) and third (~week 32 of gestation) trimesters.

For the inhaled dose, we observed a similar pattern of associations as the main analyses, with associations for birth weight being statistically significant for the inhaled dose of NO_2 at home (–38.2 g [95% CI: –77.5 to –1.8]) and all microenvironments combined (–42.8 g [–82.8 to –6.1]) as presented in *Appendix 5*. For SGA, we generally observed a direct association with exposure in all microenvironments but commuting, with statistically significant associations for NO_2 in all microenvironments combined (odds ratio: 1.38 [95% CI: 1.01–1.89]), $PM_{2.5}$ Cu content at workplace (odds ratio: 1.39 [1.02–1.89]), and $PM_{2.5}$ Fe content at workplace (odds ratio: 1.33 [1.00–1.76]) (*Appendix 6*).

Secondary Outcomes

Higher exposure to NO_2, BC, and $PM_{2.5}$ was generally associated with decelerated fetal growth in terms of estimated fetal weight, and the associations were statistically significant for the workplace (hybrid model) for NO_2, and all microenvironments combined, home, and workplace (dispersion models) for $PM_{2.5}$. For $PM_{2.5}$ Fe, Cu, and Zn contents, the pattern of associations with the estimated fetal weight was mixed (**Figure 8**). Higher $PM_{2.5}$ Zn exposure in all microenvironments combined (LUR and hybrid models), home (hybrid model), and workplace (hybrid model) was statistically significantly associated with accelerated fetal growth. The other associations did not attain statistical significance.

The associations between TRAP exposures and growth trajectories of head circumference, biparietal diameter, abdominal circumference, and femur length are presented in *Appendices 7–10*. These associations were generally in line with the findings for the estimated fetal weight.

Table 9. Estimated Levels of NO_2 (µg/m³), BC (µg/m³), $PM_{2.5}$ (µg/m³), $PM_{2.5}$ Cu Content (ng/m³), $PM_{2.5}$ Fe Content (µg/m³), and $PM_{2.5}$ Zn Content (ng/m³) at Home, Workplace, Commuting Route, and All Microenvironments Combined (Total) by Land Use Regression, Dispersion, and Hybrid Models

Variable	Median (IQR)
Total NO_2 (LUR)	37.2 (15.0)
Home NO_2 (LUR)	36.2 (15.1)
Workplace NO_2 (LUR)	46.6 (18.5)
Commuting NO_2 (LUR)	56.0 (21.8)
Total NO_2 (DM)	28.3 (9.9)
Home NO_2 (DM)	27.8 (9.8)
Workplace NO_2 (DM)	31.8 (12.8)
Commuting NO_2 (DM)	49.1 (18.7)
Total NO_2 (Hybrid)	37.1 (9.6)
Home NO_2 (Hybrid)	36.9 (9.6)
Workplace NO_2 (Hybrid)	39.4 (10.2)
Total BC (LUR)	1.4 (0.5)
Home BC (LUR)	1.4 (0.6)
Workplace BC (LUR)	1.6 (0.8)
Commuting BC (LUR)	2.1 (0.9)
Total BC (DM)	0.8 (0.4)
Home BC (DM)	0.8 (0.4)
Workplace BC (DM)	1.0 (0.5)
Commuting BC (DM)	2.3 (1.4)
Total BC (Hybrid)	1.2 (0.2)
Home BC (Hybrid)	1.2 (0.2)
Workplace BC (Hybrid)	1.1 (0.3)
Total $PM_{2.5}$ (LUR)	17.1 (4.5)
Home $PM_{2.5}$ (LUR)	16.8 (5.1)
Workplace $PM_{2.5}$ (LUR)	18.1 (4.5)
Commuting $PM_{2.5}$ (LUR)	18.9 (5.0)
Total $PM_{2.5}$ (DM)	12.2 (3.6)
Home $PM_{2.5}$ (DM)	12.0 (3.6)
Workplace $PM_{2.5}$ (DM)	13.9 (3.9)
Commuting $PM_{2.5}$ (DM)	18.4 (5.9)
Total $PM_{2.5}$ (Hybrid)	12.5 (1.4)
Home $PM_{2.5}$ (Hybrid)	12.5 (1.4)
Workplace $PM_{2.5}$ (Hybrid)	12.6 (1.5)
Total $PM_{2.5}$ Cu (LUR)	6.0 (2.0)
Home $PM_{2.5}$ Cu (LUR)	6.0 (2.0)
Workplace $PM_{2.5}$ Cu (LUR)	5.9 (2.5)
Commuting $PM_{2.5}$ Cu (LUR)	6.9 (2.4)
Total $PM_{2.5}$ Cu (Hybrid)	6.7 (1.4)
Home $PM_{2.5}$ Cu (Hybrid)	6.6 (1.5)
Workplace $PM_{2.5}$ Cu (Hybrid)	6.8 (1.6)
Total $PM_{2.5}$ Fe (LUR)	0.2 (0.1)
Home $PM_{2.5}$ Fe (LUR)	0.2 (0.1)
Workplace $PM_{2.5}$ Fe (LUR)	0.2 (0.1)
Commuting $PM_{2.5}$ Fe (LUR)	0.3 (0.1)
Total $PM_{2.5}$ Fe (Hybrid)	0.2 (0.1)
Home $PM_{2.5}$ Fe (Hybrid)	0.2 (0.1)
Workplace $PM_{2.5}$ Fe (Hybrid)	0.3 (0.1)
Total $PM_{2.5}$ Zn (LUR)	34.9 (22.9)
Home $PM_{2.5}$ Zn (LUR)	34.3 (25.1)
Workplace $PM_{2.5}$ Zn (LUR)	36.4 (21.7)
Commuting $PM_{2.5}$ Zn (LUR)	36.6 (18.9)
Total $PM_{2.5}$ Zn (Hybrid)	39.8 (21.9)
Home $PM_{2.5}$ Zn (Hybrid)	39.0 (22.8)
Workplace $PM_{2.5}$ Zn (Hybrid)	38.5 (19.3)

Continues next column

Table 9. *(continued)*

DM = dispersion model; hybrid = LUR-DM; IQR = interquartile range; LUR = land use regression.

SENSITIVITY ANALYSES

The results of the complete case analyses were generally in line with the results of the main analyses that were based on the multiple imputation datasets in terms of the direction and strength of the associations (*Appendices 11 and 12*); however, fewer associations reached statistical significance.

After further adjustment of our analyses for ethnicity (*Appendices 13 and 14*), type of cooking stove (*Appendices 15 and 16*), having kitchen hood (*Appendices 17 and 18*), and using kitchen hood during cooking (*Appendices 19 and 20*), the pattern of associations stayed generally similar to the main analyses; however, there were some changes in the associations that reached statistical significance. The sample size for some analyses was smaller based on available data (915, 787, and 783 participants for the models adjusting for type of cooking stove, having a kitchen hood, and using a kitchen hood during cooking, respectively).

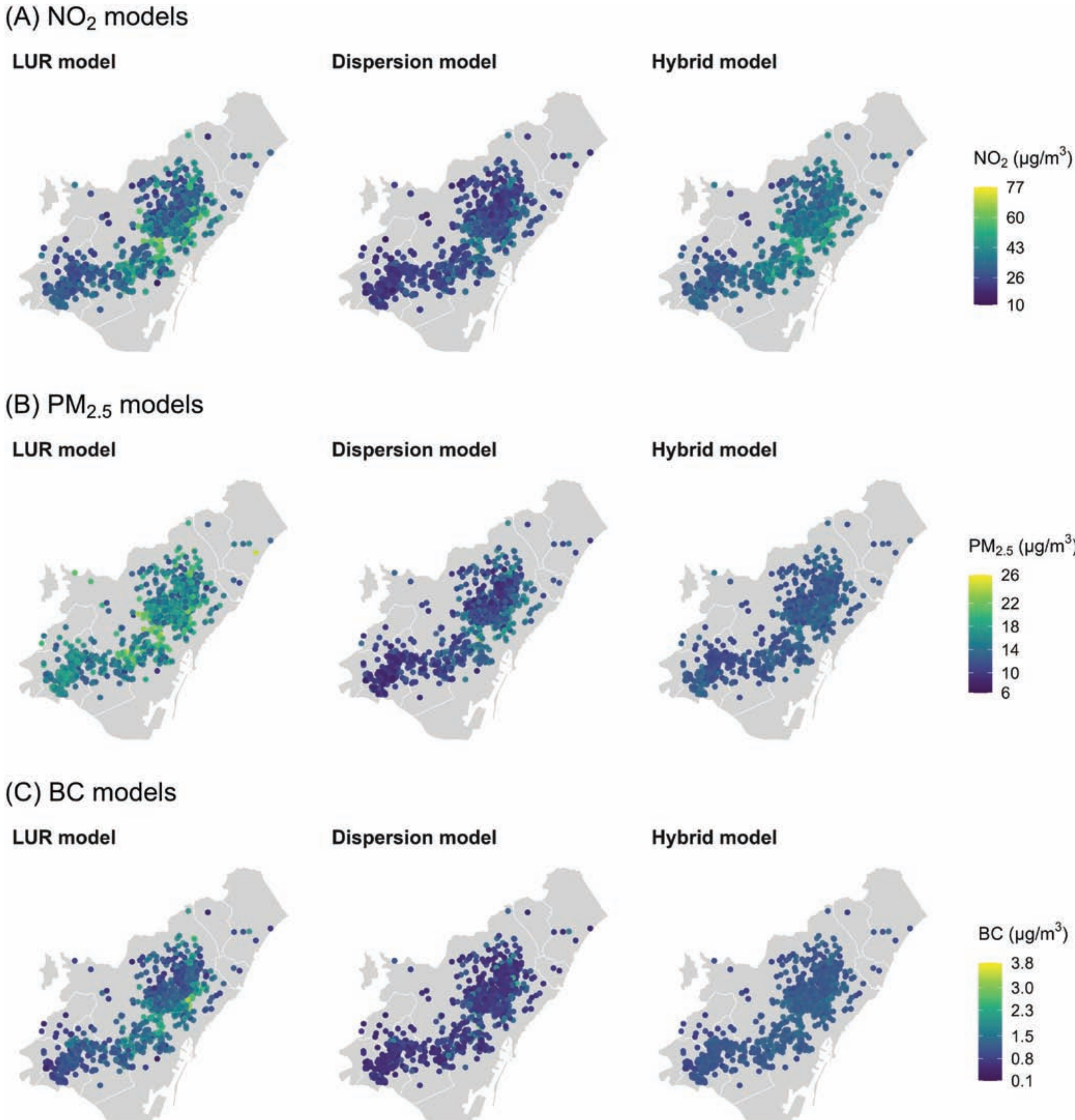


Figure 5. Map of estimated exposures. Color gradient shows (A) NO_2, (B) $PM_{2.5}$, (C) BC, and $PM_{2.5}$, (D) Fe, (E) Cu, and (F) Zn content during the entire pregnancy for the BiSC participants (points in the map) using LUR models, dispersion models, and hybrid models. BC = black carbon; BiSC = Barcelona Life Study Cohort; hybrid = hybrid LUR-DM model; LUR = land use regression.

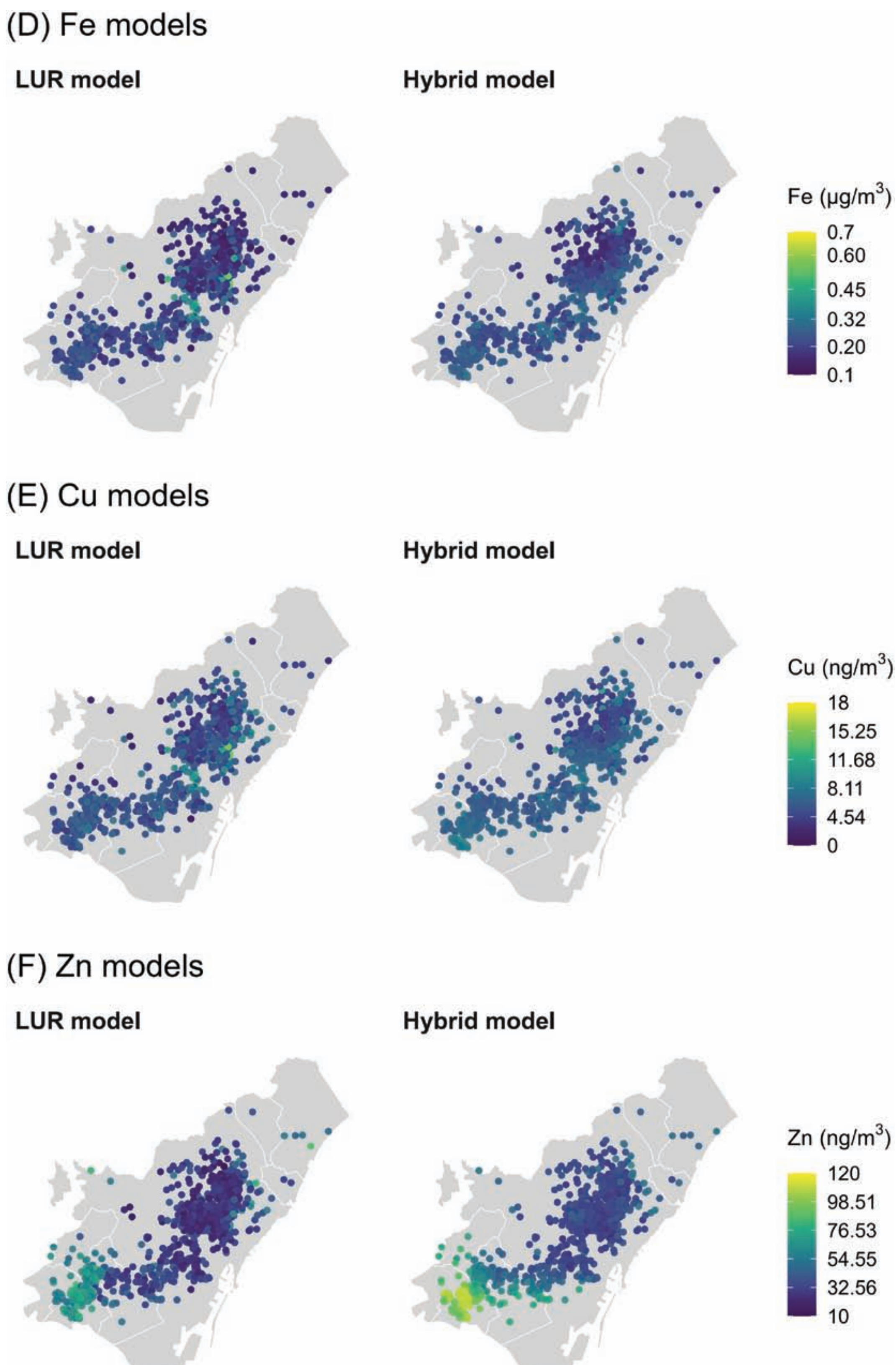


Figure 5. *(continued)*

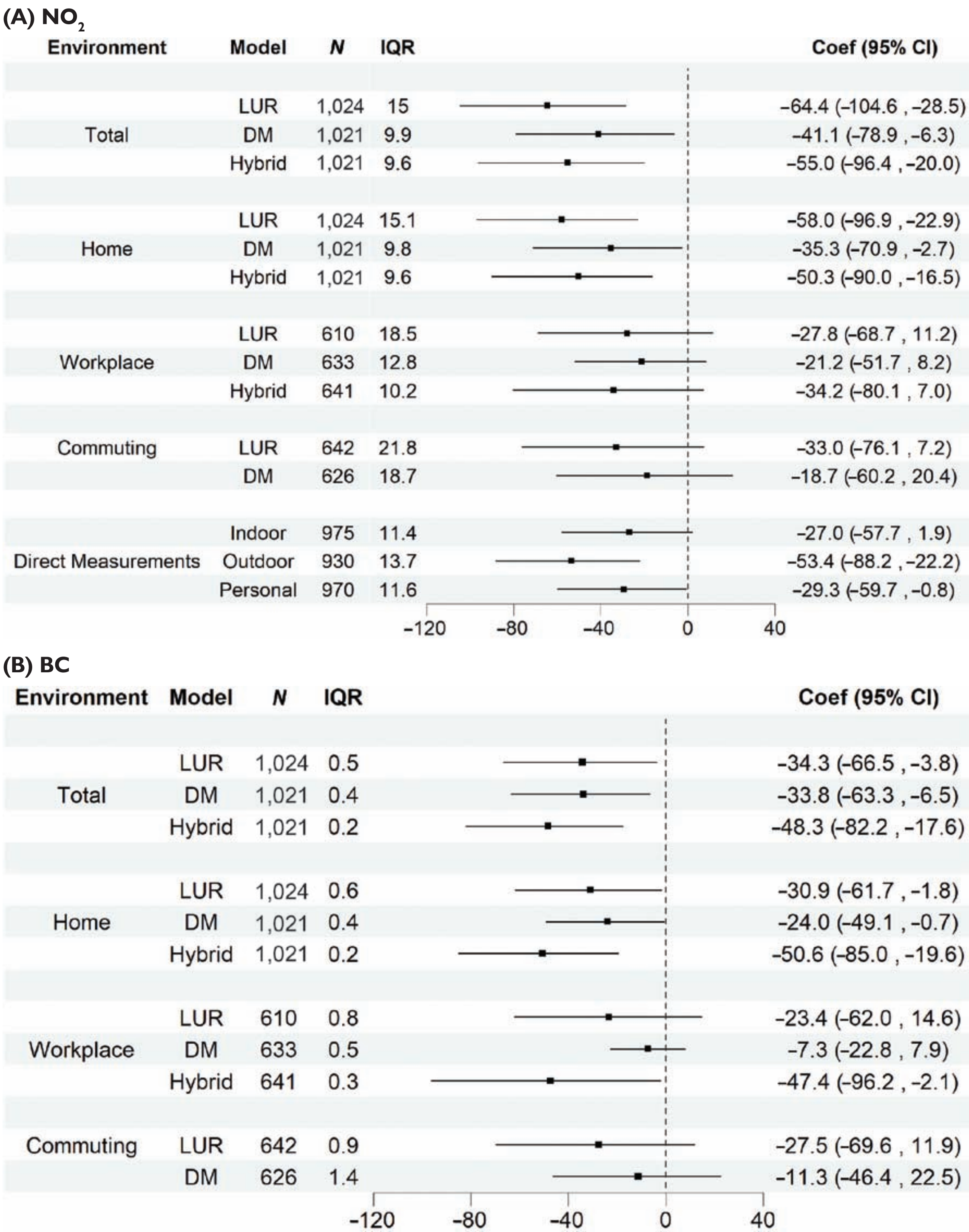
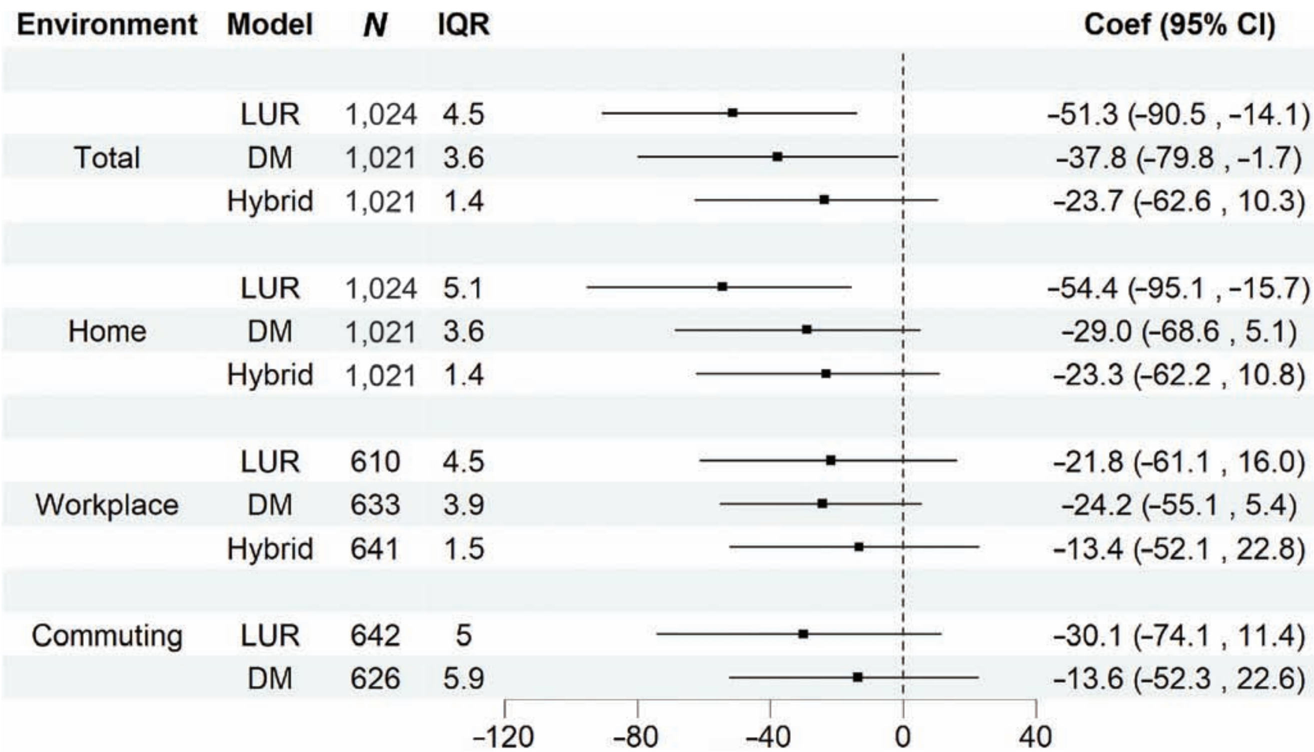


Figure 6. Adjusted change in birth weight (g) associated with one IQR increase in exposure to (A) NO_2 (μg/m³), (B) BC (μg/m³), (C) $PM_{2.5}$ (μg/m³), (D) $PM_{2.5}$ Cu content (ng/m³), (E) $PM_{2.5}$ Fe content (μg/m³), and (F) $PM_{2.5}$ Zn content (ng/m³). Change in birth weight is adjusted for maternal age (continuous, years), education level (categorical, university degree: yes/no), body mass index (BMI) at the first trimester (continuous, kg/m²), parity (categorical, nulliparous: yes/no), active smoking during pregnancy (categorical, yes/no), exposure to environmental tobacco smoke (categorical, yes/no), alcohol consumption during pregnancy (categorical, yes/no), gestational age at delivery (continuous, days), history of low birth weight in previous pregnancies (categorical, yes/no), and sex of the neonate (girl vs. boy). BC = black carbon; CI = confidence interval; DM = dispersion model; hybrid = hybrid LUR-DM model; indoor = measured home-indoor NO_2 level using passive samplers; IQR = interquartile range; LUR = land use regression; OR = odds ratio; outdoor = measured home-outdoor NO_2 level using passive samplers; personal = measured personal NO_2 level using passive samplers.

(C) $PM_{2.5}$



(D) $PM_{2.5}$ Cu content

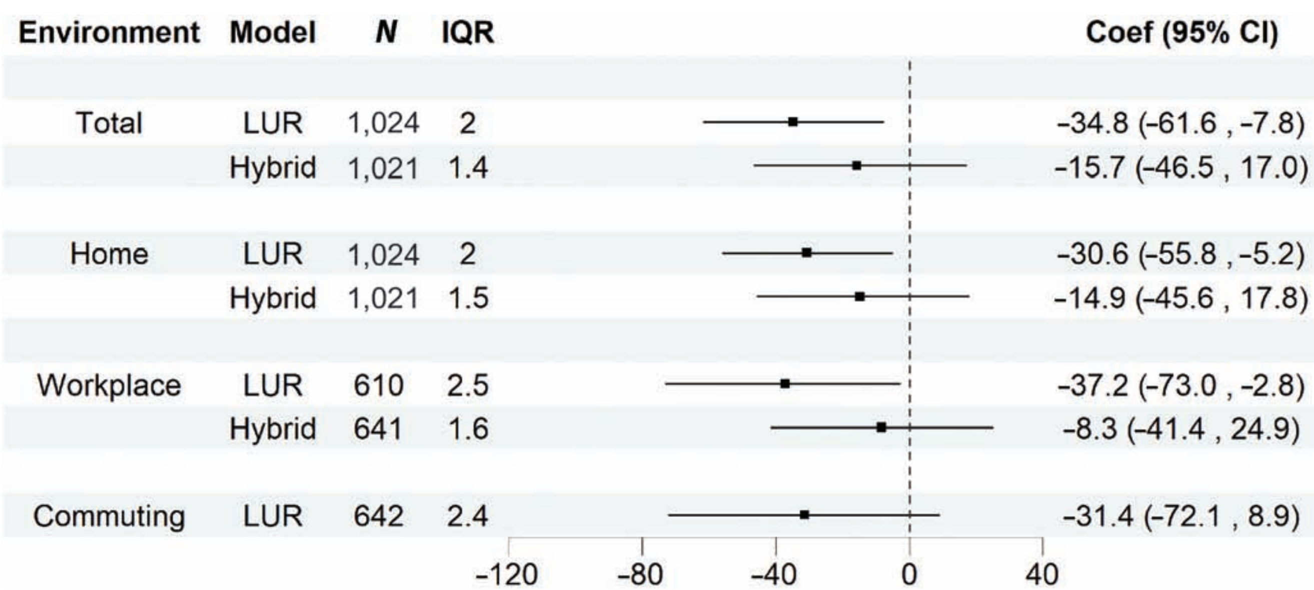


Figure 6. *(continued)*

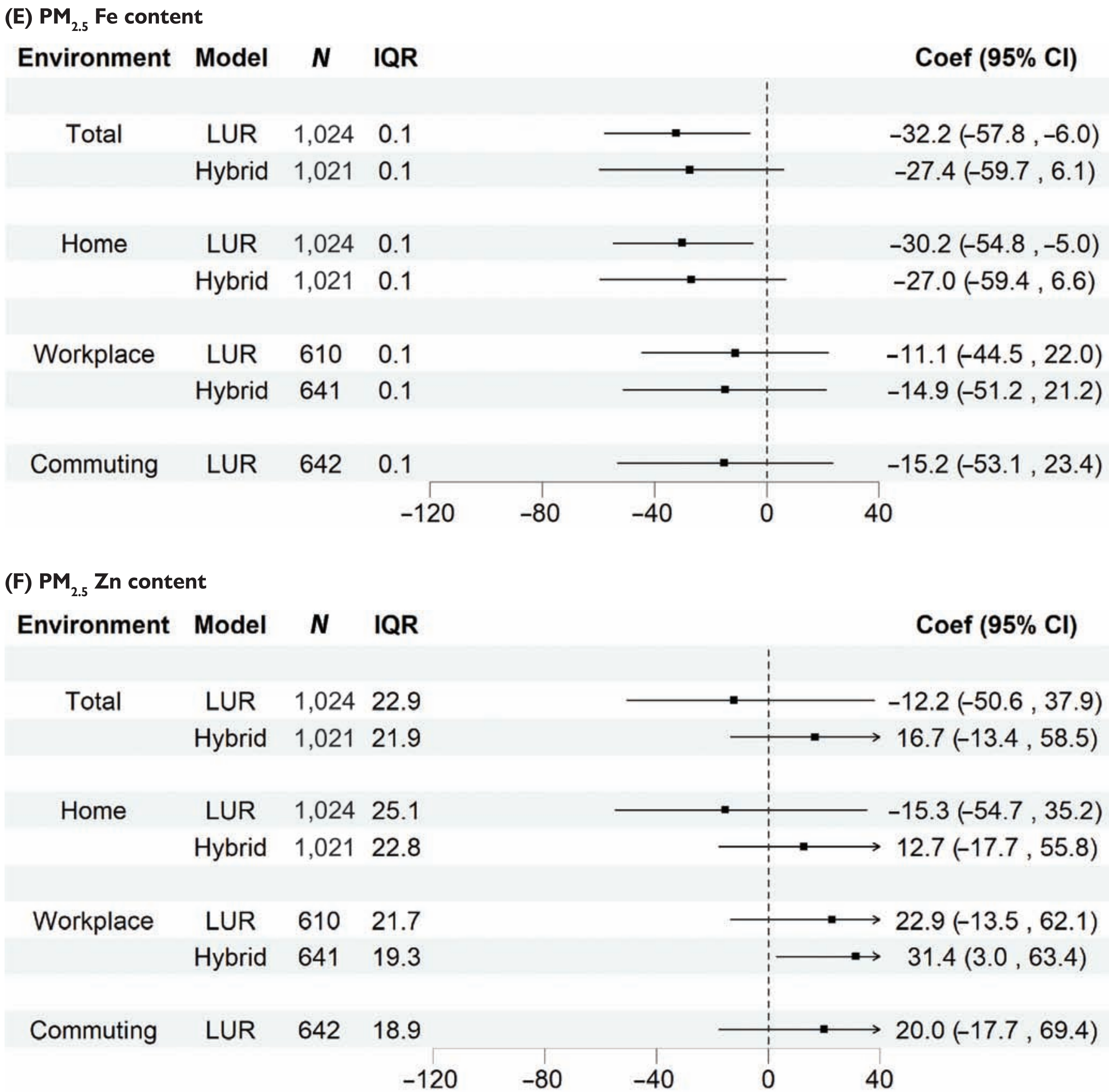


Figure 6. *(continued)*

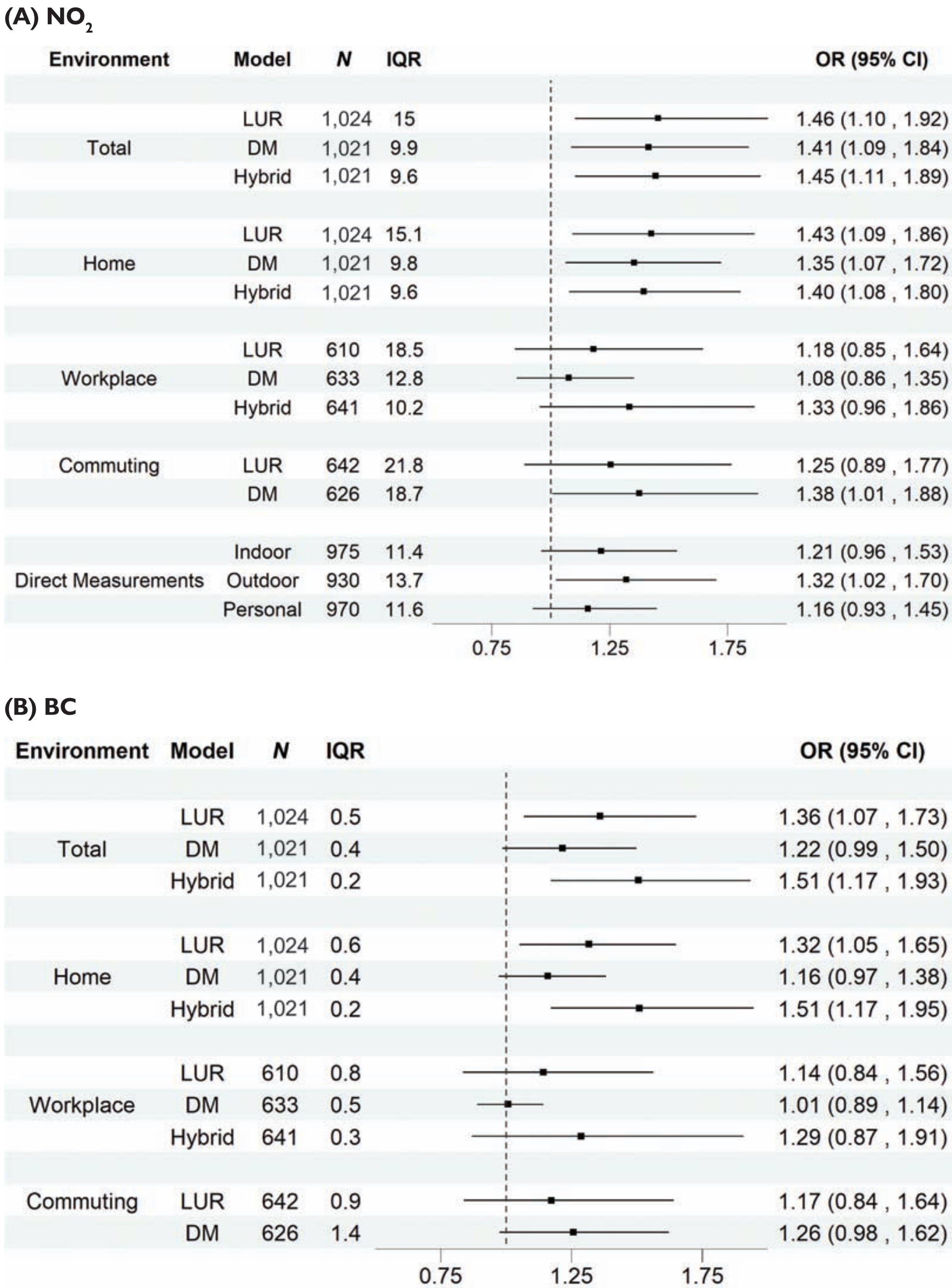


Figure 7. Adjusted odds ratio of SGA with a single IQR increase in exposure to (A) NO_2 (μg/m³), (B) BC (μg/m³), (C) $PM_{2.5}$ (μg/m³), (D) $PM_{2.5}$ Cu content (ng/m³), (E) $PM_{2.5}$ Fe content (μg/m³), and (F) $PM_{2.5}$ Zn content (ng/m³). The OR of SGA is adjusted for maternal age (continuous, years), education level (categorical, university degree: yes/no), body mass index (BMI) at the first trimester (continuous, kg/m²), parity (categorical, nulliparous: yes/no), active smoking during pregnancy (categorical, yes/no), exposure to environmental tobacco smoke (categorical, yes/no), alcohol consumption during pregnancy (categorical, yes/no), and history of low birth weight in previous pregnancies (categorical, yes/no). BC = black carbon; CI = confidence interval; DM = dispersion model; hybrid = hybrid LUR-DM model; indoor = measured home-indoor NO_2 level using passive samplers; IQR = interquartile range; LUR = land use regression; outdoor = measured home-outdoor NO_2 level using passive samplers; OR = odds ratio; personal = measured personal NO_2 level using passive samplers; SGA = small for gestational age.

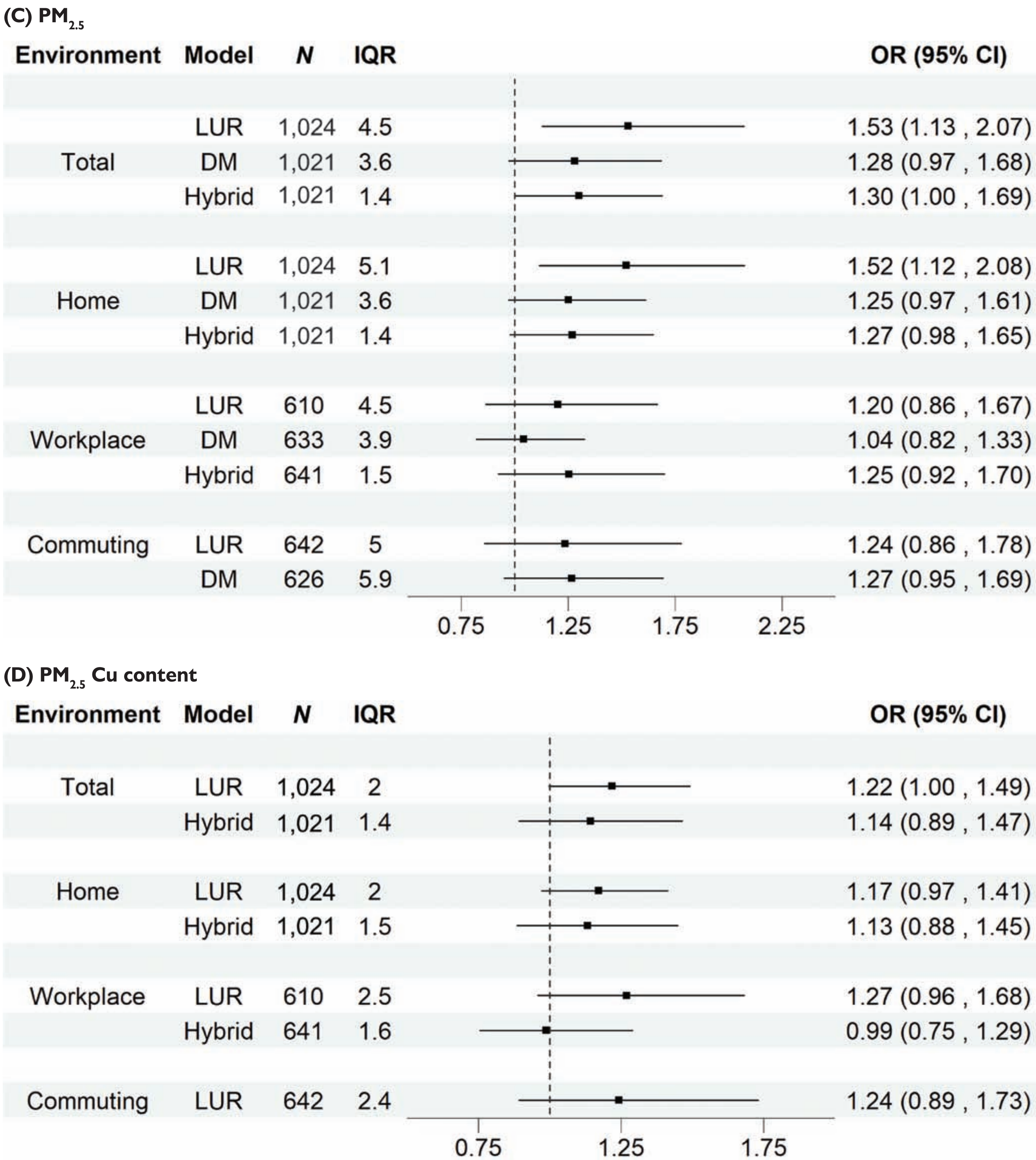
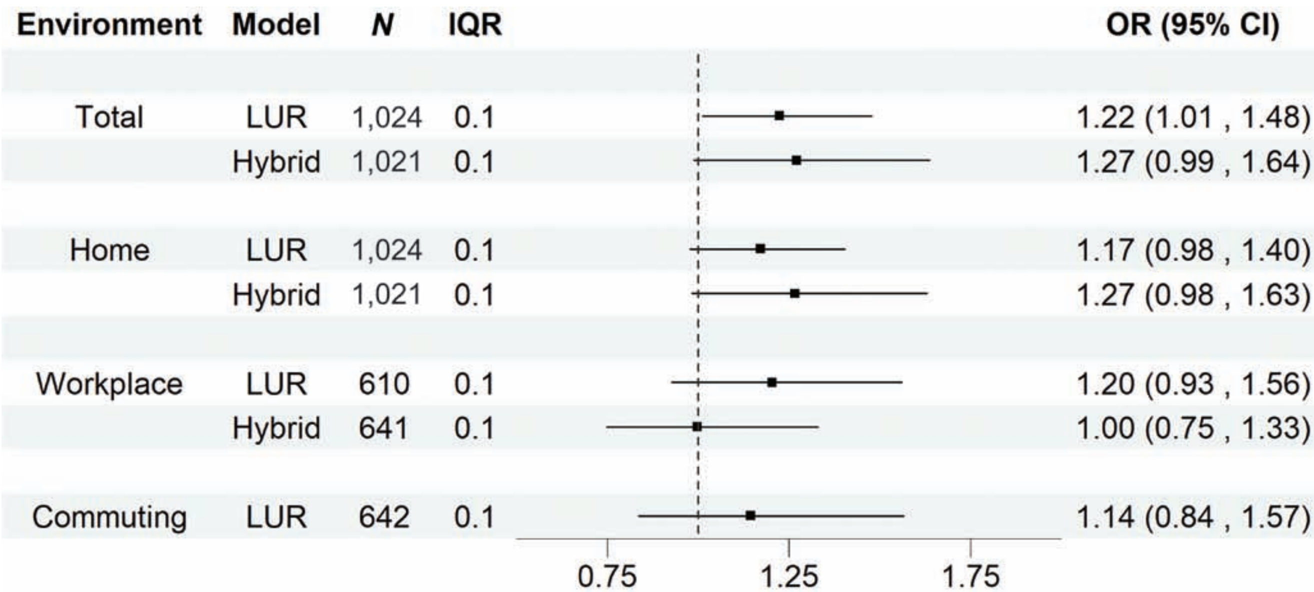


Figure 7. *(continued)*

(E) $PM_{2.5}$ Fe content



(F) $PM_{2.5}$ Zn content

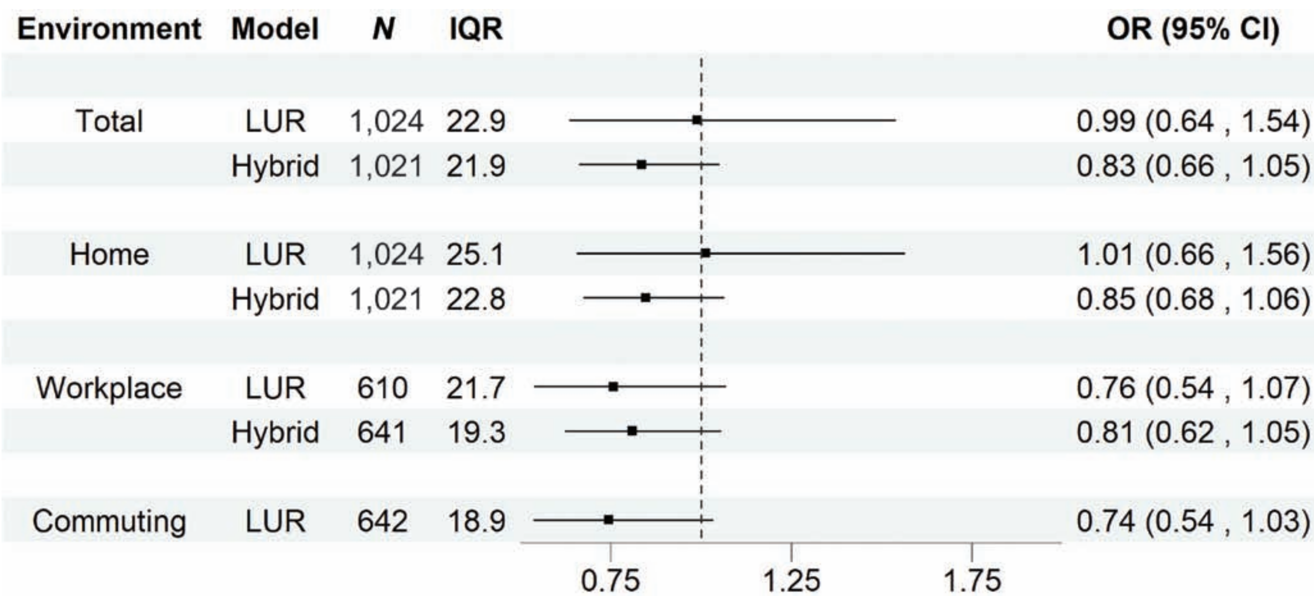


Figure 7. *(continued)*

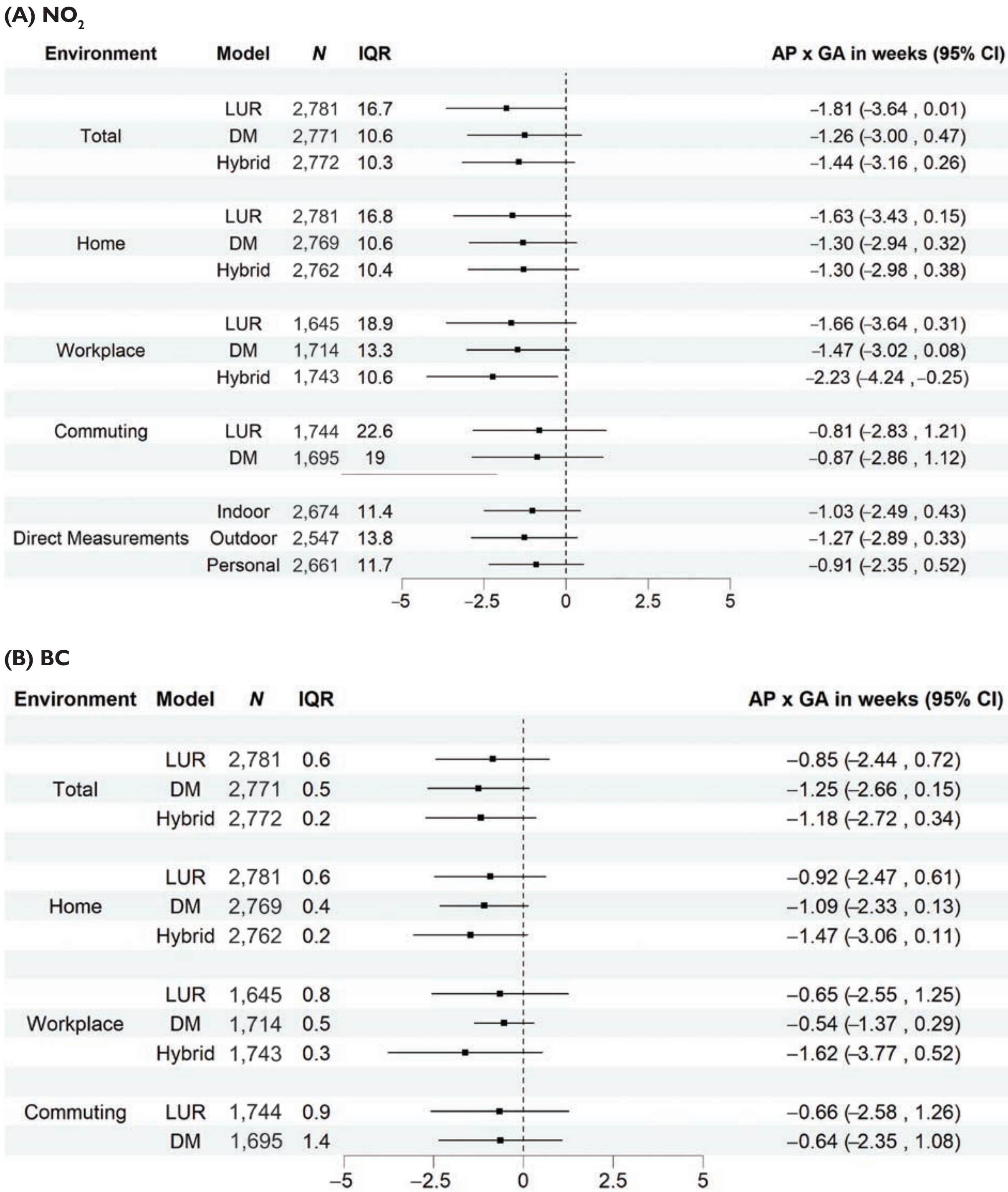


Figure 8. Adjusted change in the trajectory of the estimated fetal weight (g) associated with one IQR increase in exposure to (A) NO_2 (μg/m³), (B) BC (μg/m³), (C) $PM_{2.5}$ (μg/m³), (D) $PM_{2.5}$ Cu content (ng/m³), (E) $PM_{2.5}$ Fe content (μg/m³), and (F) $PM_{2.5}$ Zn content (ng/m³). The trajectory of the estimated fetal weight is adjusted for maternal age (continuous, years), education level (categorical, university degree: yes/no), body mass index (BMI) at the first trimester (continuous, kg/m2), parity (categorical, nulliparous: yes/no), active smoking during pregnancy (categorical, yes/no), exposure to environmental tobacco smoke (categorical, yes/no), alcohol consumption during pregnancy (categorical, yes/no), gestational age at the time of ultrasound examination (continuous, day), history of low birth weight in previous pregnancies (categorical, yes/no), and sex of the neonate (girl vs. boy). AP × GA = air pollution levels multiplied by gestational age; BC = black carbon; CI = confidence interval; DM = dispersion model; hybrid = hybrid LUR-DM model; indoor = measured home-indoor NO_2 level using passive samplers; IQR = interquartile range; LUR = land use regression; OR = odds ratio; outdoor = measured home-outdoor NO_2 level using passive samplers; personal = measured personal NO_2 level using passive samplers.

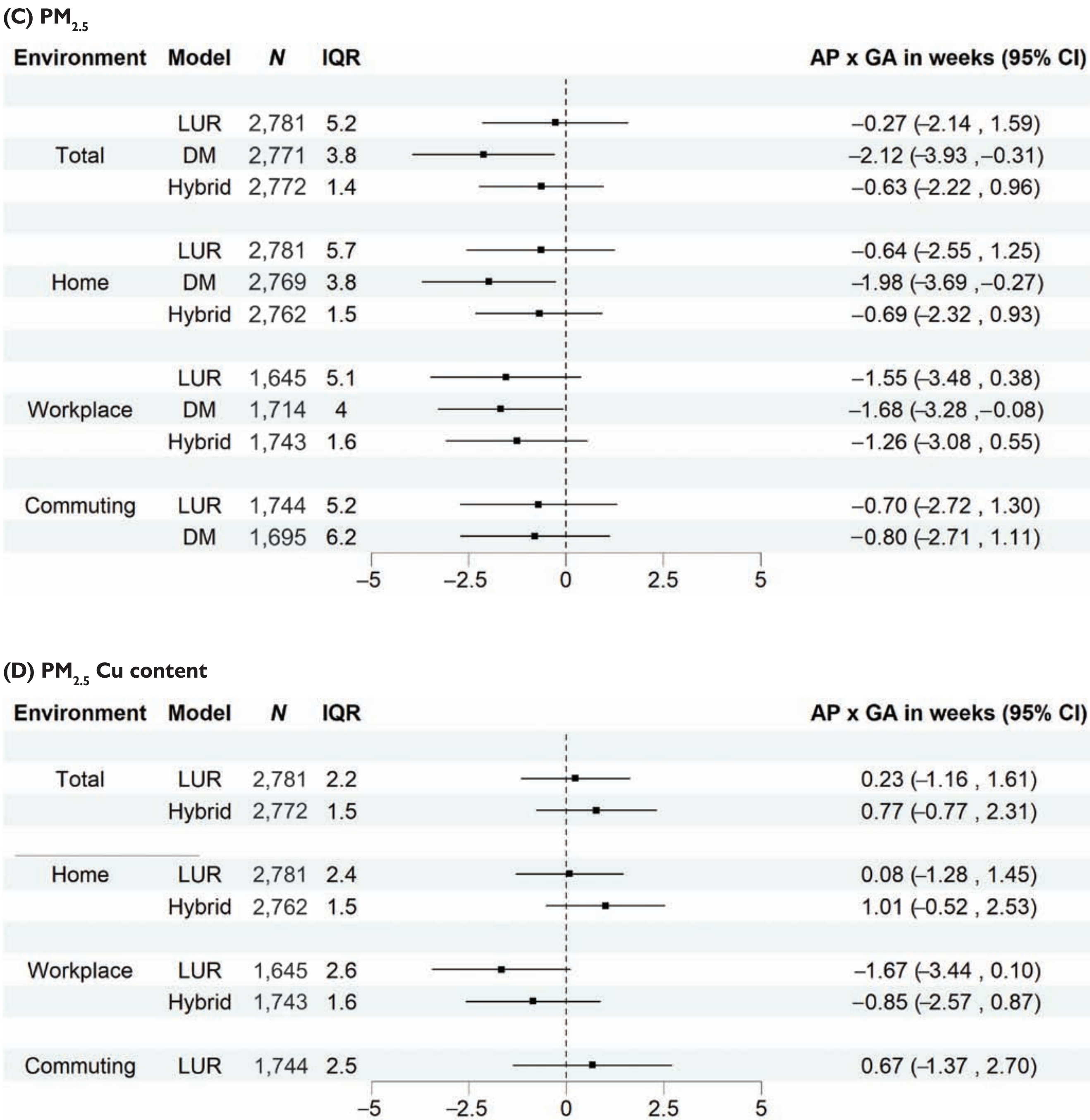


Figure 8. *(continued)*

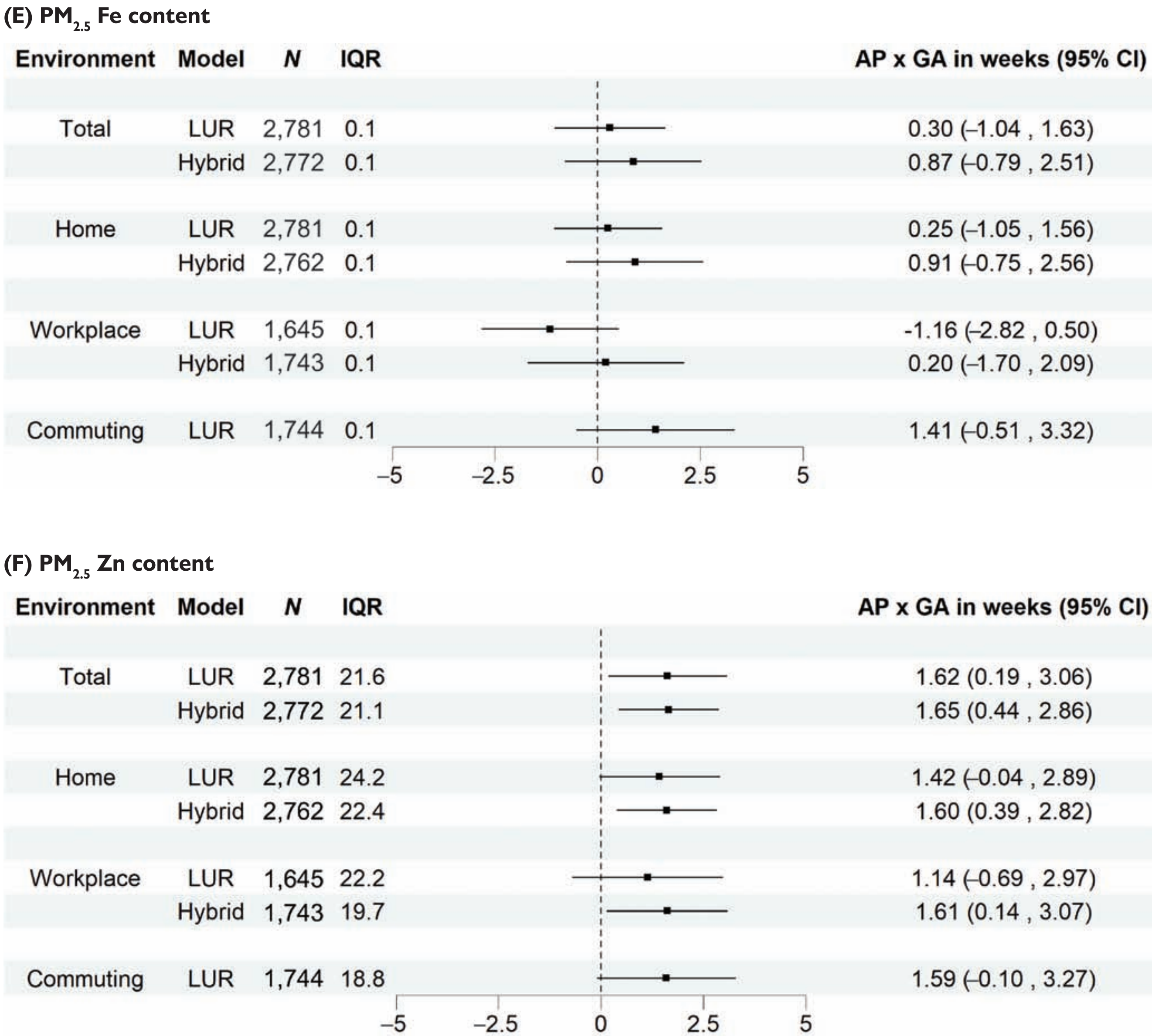


Figure 8. *(continued)*

Using the hospital as a categorical independent variable in the models instead of a random effect did not change our findings considerably (*Appendices 21 and 22*); however, fewer associations reached statistical significance.

Additionally, after removing the outliers in exposure or outcome, the associations were similar to the main analysis, but there were some changes in the associations that reached statistical significance *(Appendices 23 and 24)*.

Our analyses with z-score of birth weight as the outcome (*Appendix 25*) and after removing gestational age at delivery as a covariate from birth weight models (*Appendix 26*), we observed a similar pattern of associations with the main analyses of birth weight (*Appendix 25*). However, there were some changes in the associations that reached statistical significance.

Finally, after adjustment of the *P* values of our analyses for multiple comparisons, 12 of the associations lost their statistical significance (*Appendices 27 and 28*).

MODIFICATION BY MATERNAL SOCIOECONOMIC STATUS, STRESS, PHYSICAL ACTIVITY, AND COVID-19 PANDEMIC

For the interaction between $PM_{2.5}$ and $PM_{2.5}$ Cu content and self-reported physical activity (Metabolic Equivalent for Task) in relation with birth weight (Figure 13A), between $PM_{2.5}$ and BC and neighborhood SES in association with SGA (Figure 10B), and between $PM_{2.5}$ Zn content and hair cortisol level in association with SGA (Figure 12A), the *P* value of interaction term was less than 0.1, and for the rest of our evaluated interaction terms between effect modifiers and TRAP, the *P* values for the interaction term were more than 0.1 (**Figures 9–14).**

After stratifying the analyses, we observed some suggestions for a potentially stronger association of TRAP (all but $PM_{2.5}$ Zn content) with lower birth weight and SGA for women with a university degree (i.e., higher household SES). We found a similar pattern for the neighborhood SES, with generally stronger

Text continues on page 48

(A) Maternal education

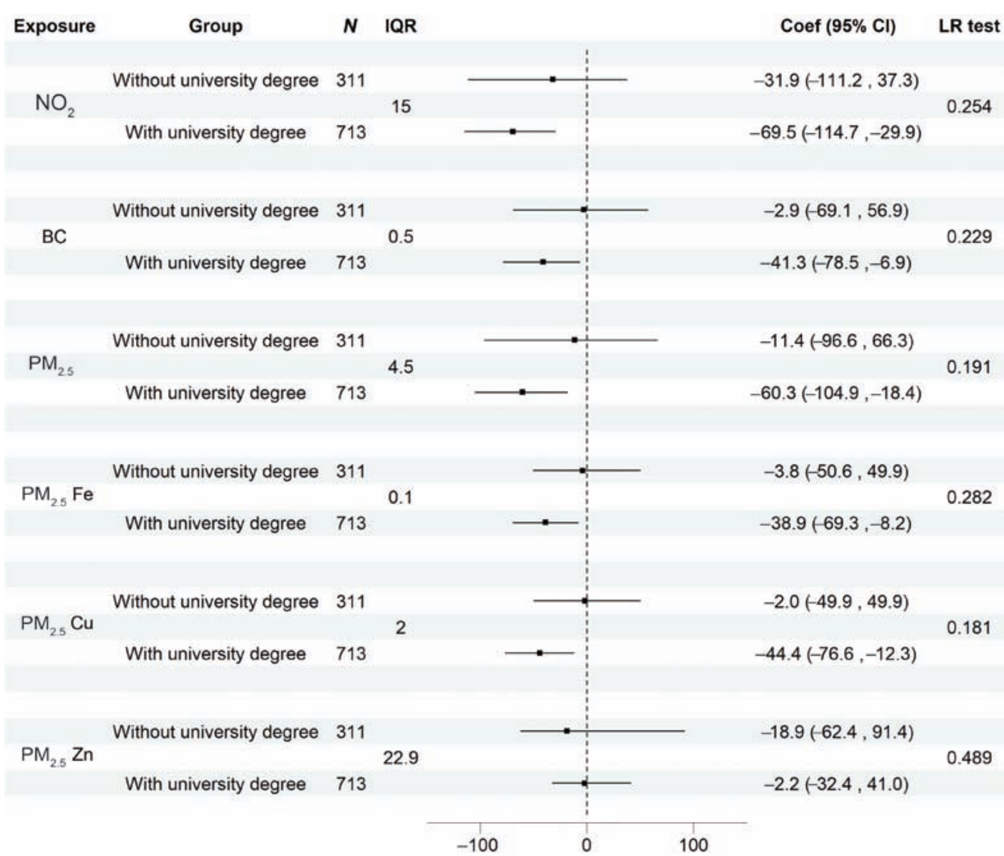


Figure 9. Adjusted change in birth weight (g) associated with one IQR increase in exposure to NO_2 (µg/m³), BC (µg/m³), $PM_{2.5}$ (µg/m³), $PM_{2.5}$ Cu content (ng/m³), $PM_{2.5}$ Fe content (µg/m³), and $PM_{2.5}$ Zn content (ng/m³) stratified by (A) maternal education, and (B) tertiles of the annual average household income at census tract. Change in birth weight is adjusted for maternal age (continuous, years), education level (categorical, university degree: yes/no), body mass index (BMI) at the first trimester (continuous, kg/m²), parity (categorical, nulliparous: yes/no), active smoking during pregnancy (categorical, yes/no), exposure to environmental tobacco smoke (categorical, yes/no), alcohol consumption during pregnancy (categorical, yes/no), gestational age at delivery (continuous, days), history of low birth weight in previous pregnancies (categorical, yes/no), and sex of the neonate (girl vs. boy). BC = black carbon; CI = confidence interval; IQR = interquartile range; LR test = likelihood ratio test.

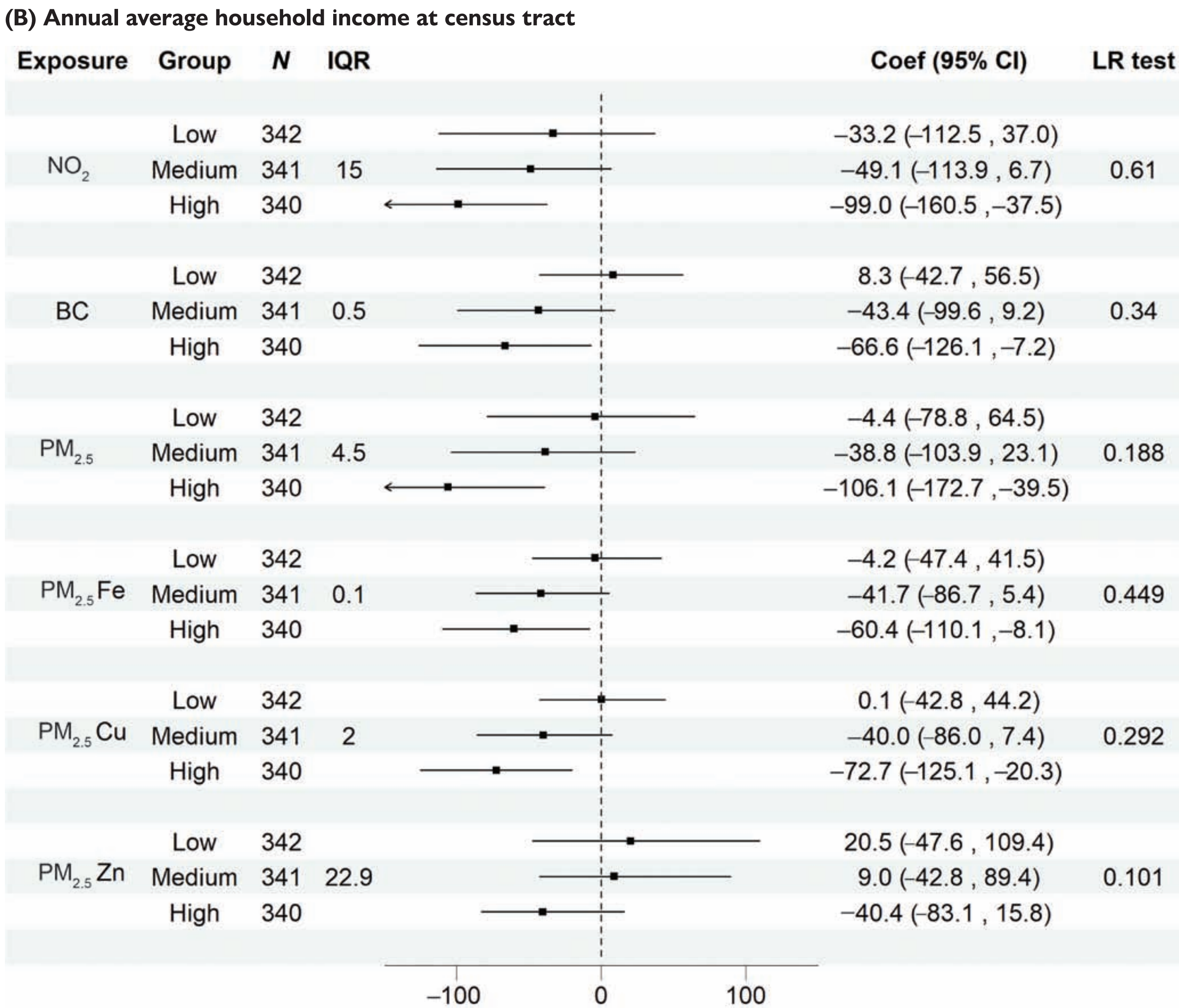


Figure 9. *(continued)*

(A) Maternal education

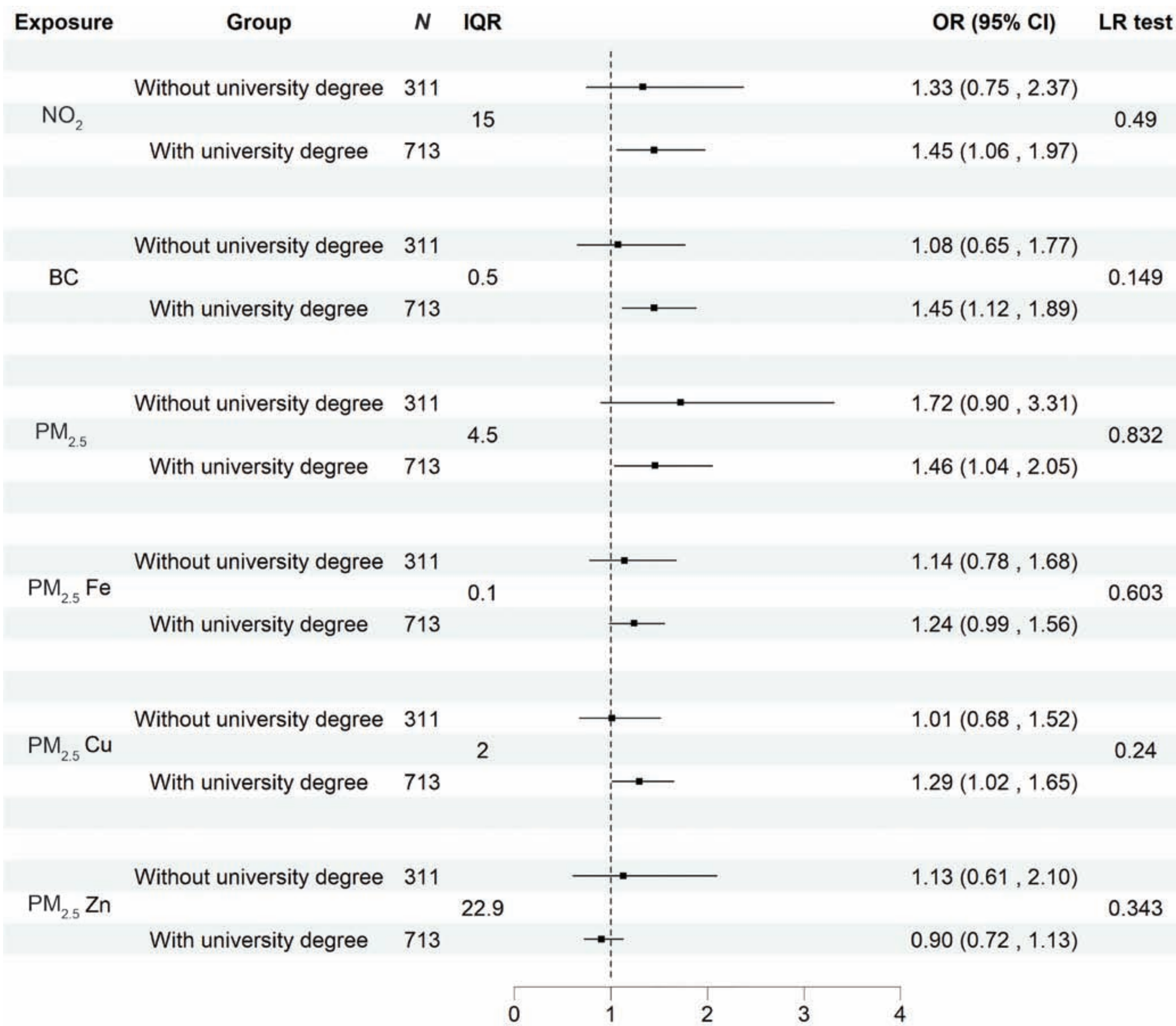


Figure 10. Adjusted OR of the SGA associated with one IQR increase exposure to NO_2 (μg/m³), BC (μg/m³), $PM_{2.5}$ (μg/m³), $PM_{2.5}$ Cu content (ng/m³), $PM_{2.5}$ Fe content (μg/m³), and $PM_{2.5}$ Zn content (ng/m³) stratified by (A) maternal education, and (B) tertiles of the annual average household income at census tract. The OR of SGA is adjusted for maternal age (continuous, years), education level (categorical, university degree: yes/no), body mass index (BMI) at the first trimester (continuous, kg/m²), parity (categorical, nulliparous: yes/no), active smoking during pregnancy (categorical, yes/no), exposure to environmental tobacco smoke (categorical, yes/no), alcohol consumption during pregnancy (categorical, yes/no), and history of low birth weight in previous pregnancies (categorical, yes/no). BC = black carbon; CI = confidence interval; IQR = interquartile range; LR test = likelihood ratio test; OR = odds ratio; SGA = small for gestational age.

(B) Annual average household income at census tract

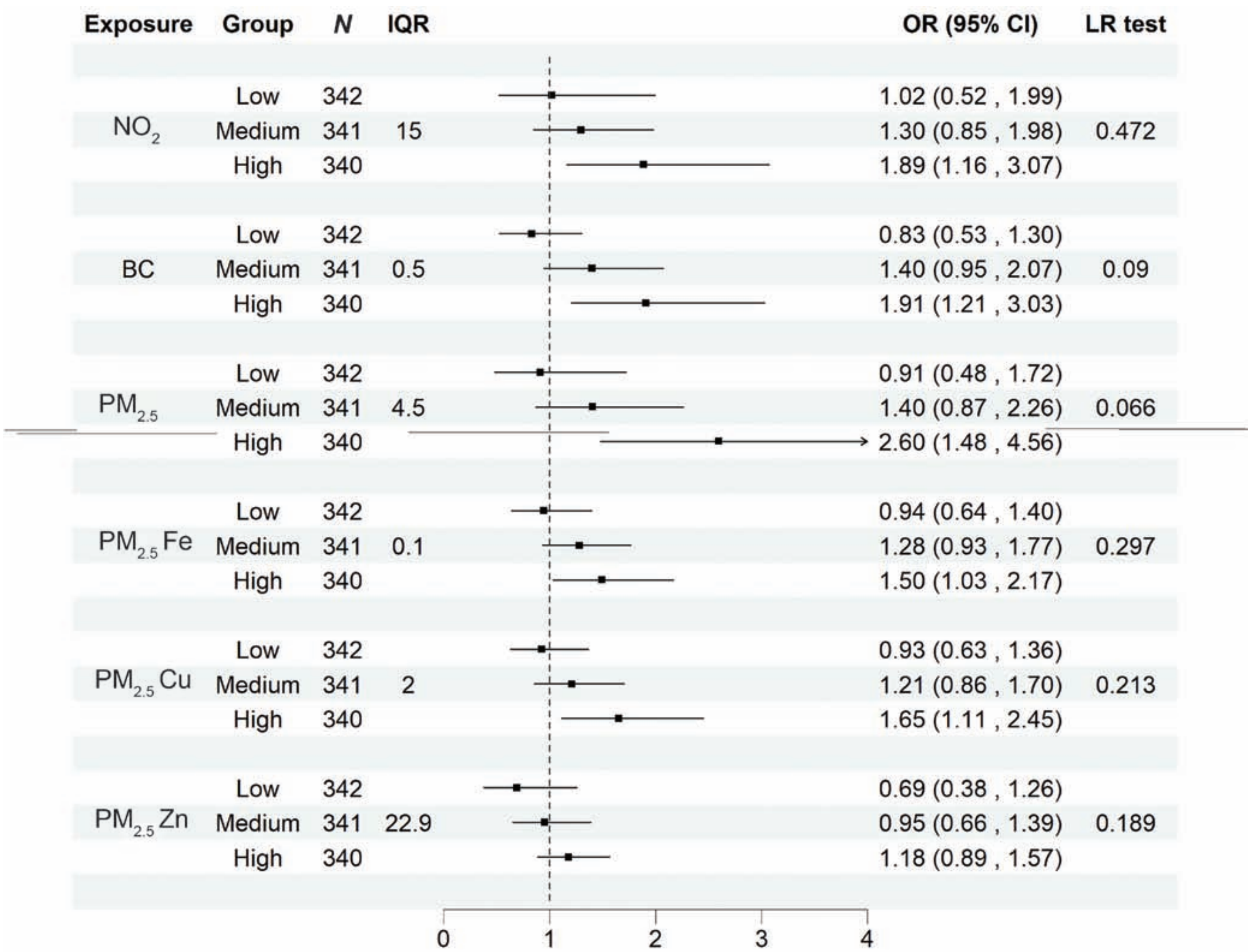


Figure 10. *(continued)*

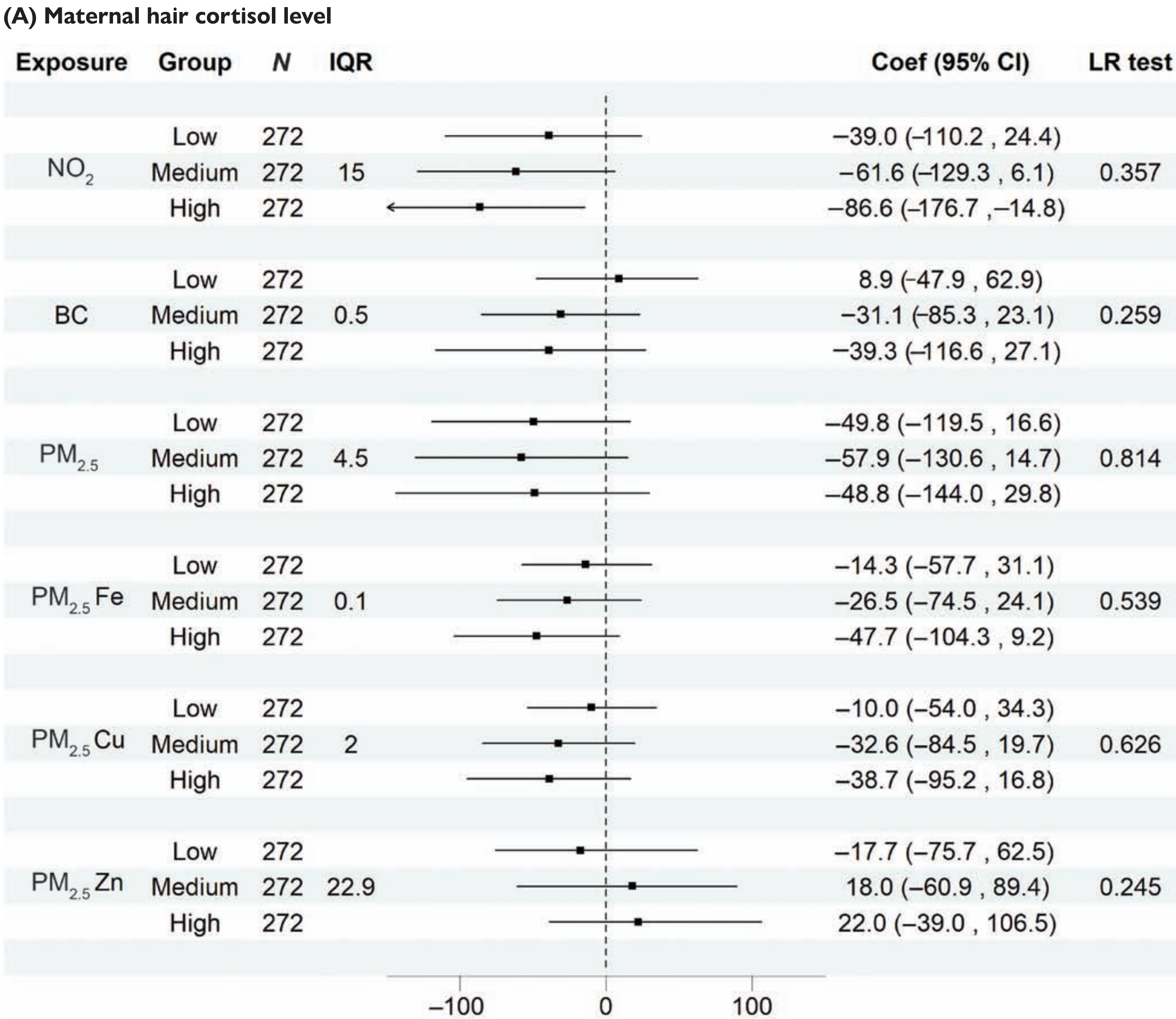


Figure 11. Adjusted change in birth weight (g) associated with one IQR increase exposure to NO_2 (μg/m³), BC (μg/m³), $PM_{2.5}$ (μg/m³), $PM_{2.5}$ Cu content (ng/m³), $PM_{2.5}$ Fe content (μg/m³), and $PM_{2.5}$ Zn content (ng/m³) stratified by (A) tertiles of maternal hair cortisol level, and (B) tertiles of perceived stress score. Change in birth weight is adjusted for maternal age (continuous, years), education level (categorical, university degree: yes/no), body mass index (BMI) at the first trimester (continuous, kg/m²), parity (categorical, nulliparous: yes/no), active smoking during pregnancy (categorical, yes/no), exposure to environmental tobacco smoke (categorical, yes/no), alcohol consumption during pregnancy (categorical, yes/no), gestational age at delivery (continuous, days), history of low birth weight in previous pregnancies (categorical, yes/no), and sex of the neonate (girl vs. boy). BC = black carbon; CI = confidence interval; IQR = interquartile range; LR test = likelihood ratio test.

(B) Maternal perceived stress

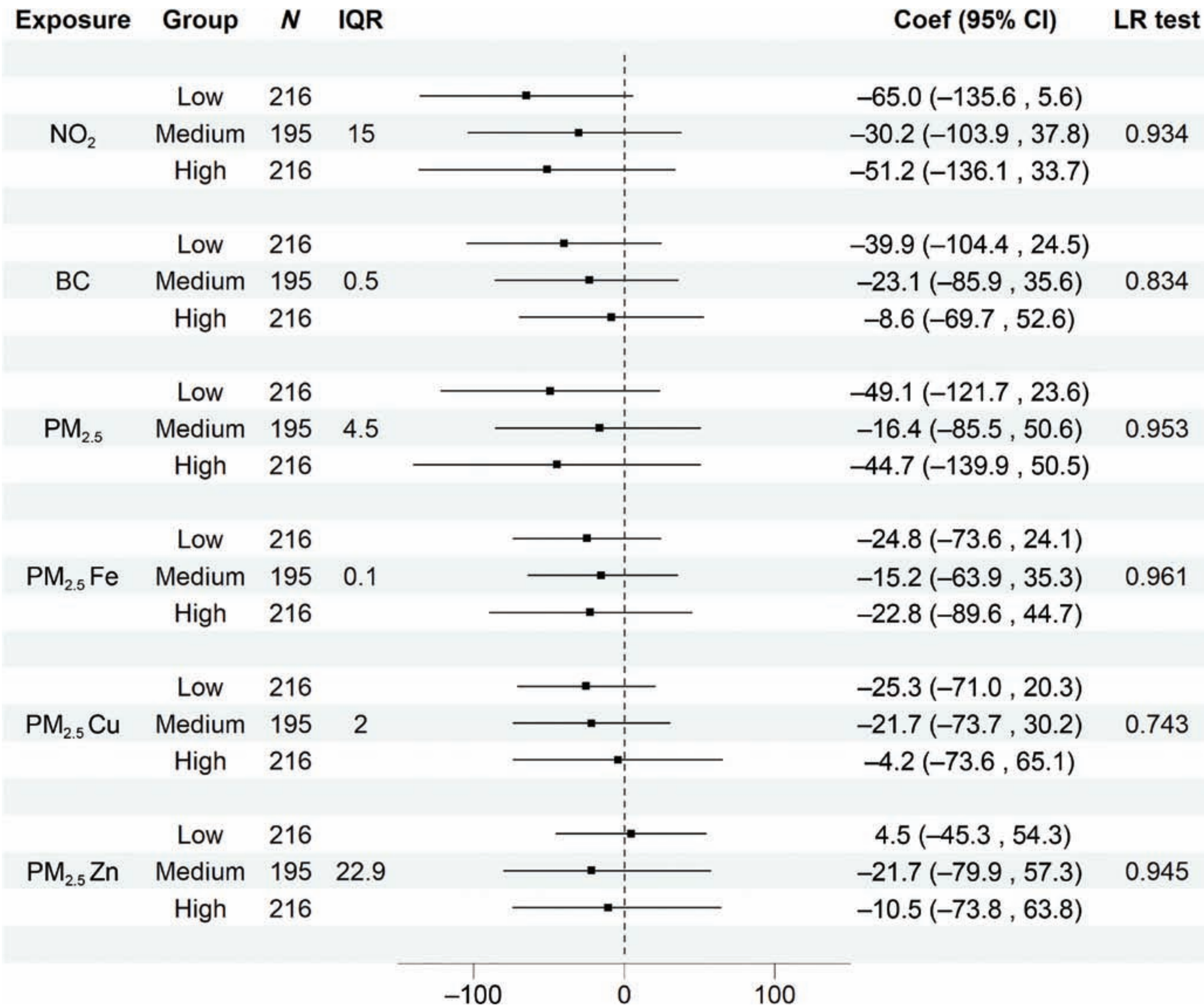


Figure 11. *(continued)*

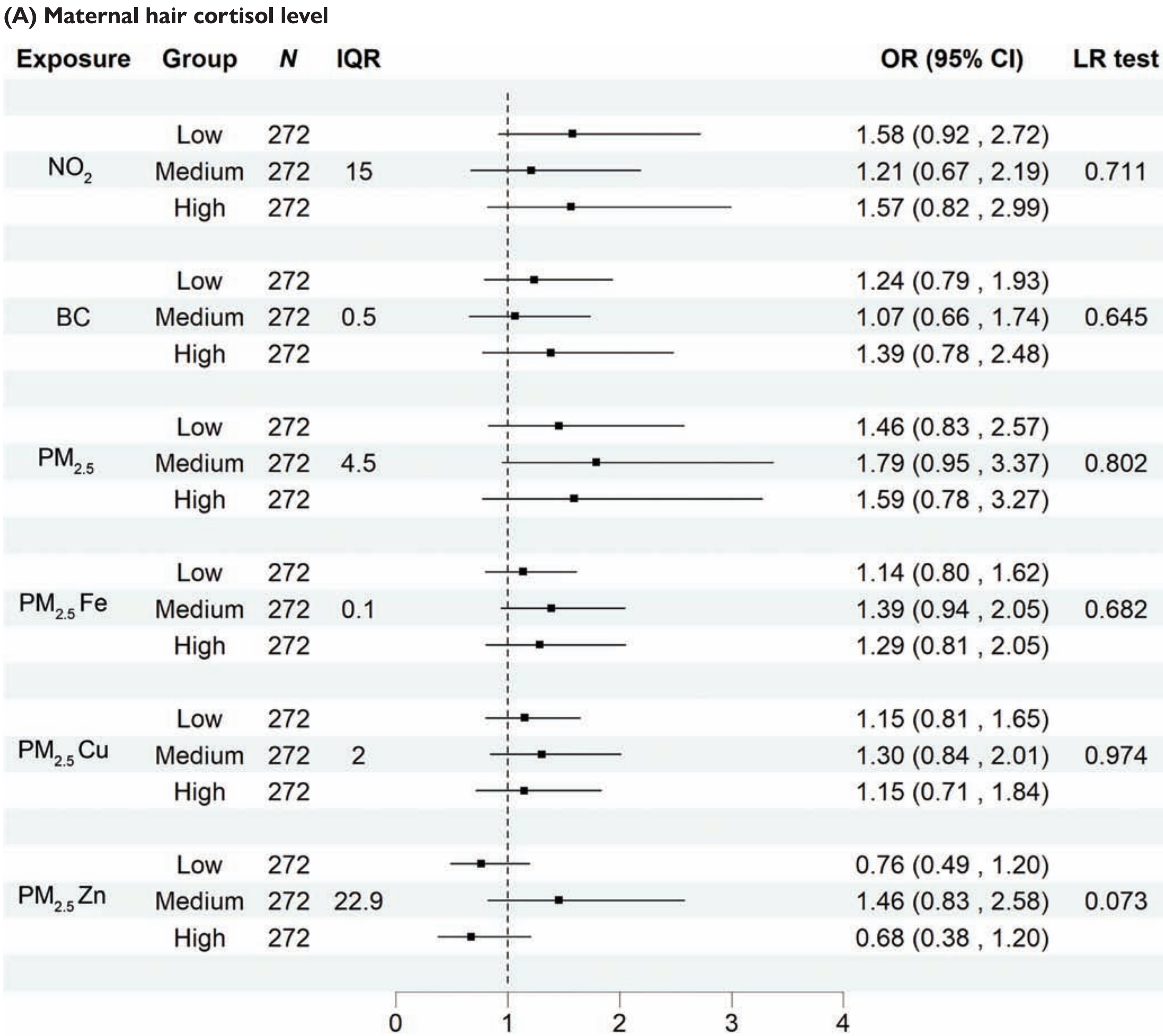


Figure 12. Adjusted OR of SGA associated with one IQR increase in exposure to NO_2 (µg/m³), BC (µg/m³), $PM_{2.5}$ (µg/m³), $PM_{2.5}$ Cu content (ng/m³), $PM_{2.5}$ Fe content (µg/m³), and $PM_{2.5}$ Zn content (ng/m³) stratified by (A) tertiles of maternal hair cortisol level, and (B) tertiles of perceived stress score. The OR of SGA is adjusted for maternal age (continuous, years), education level (categorical, university degree: yes/no), body mass index (BMI) at the first trimester (continuous, kg/m²), parity (categorical, nulliparous: yes/no), active smoking during pregnancy (categorical, yes/no), exposure to environmental tobacco smoke (categorical, yes/no), alcohol consumption during pregnancy (categorical, yes/no), and history of low birth weight in previous pregnancies (categorical, yes/no). BC = black carbon; CI = confidence interval; IQR = interquartile range; LR test = likelihood ratio test; OR = odds ratio; SGA = small for gestational age.

(B) Maternal perceived stress

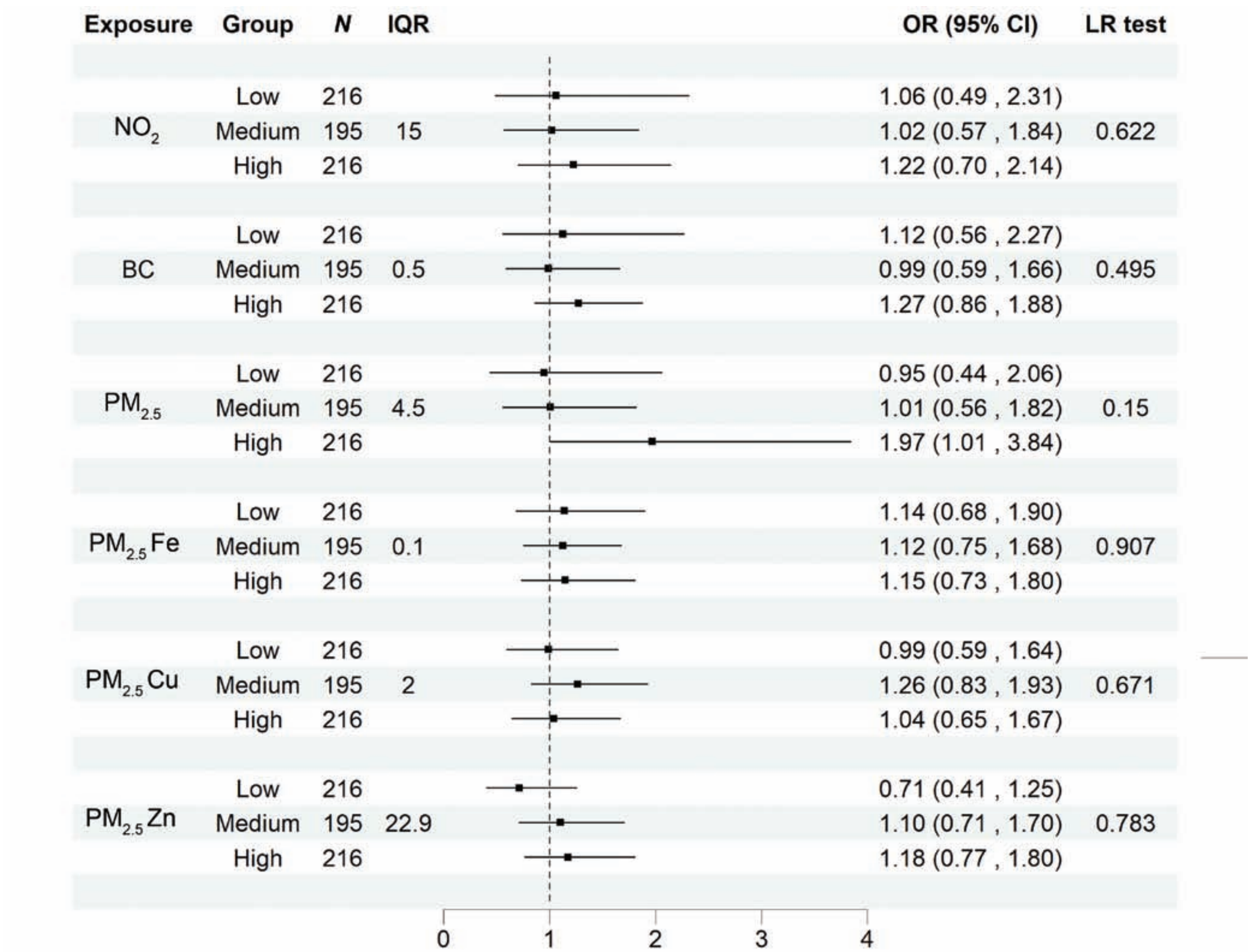


Figure 12. *(continued)*

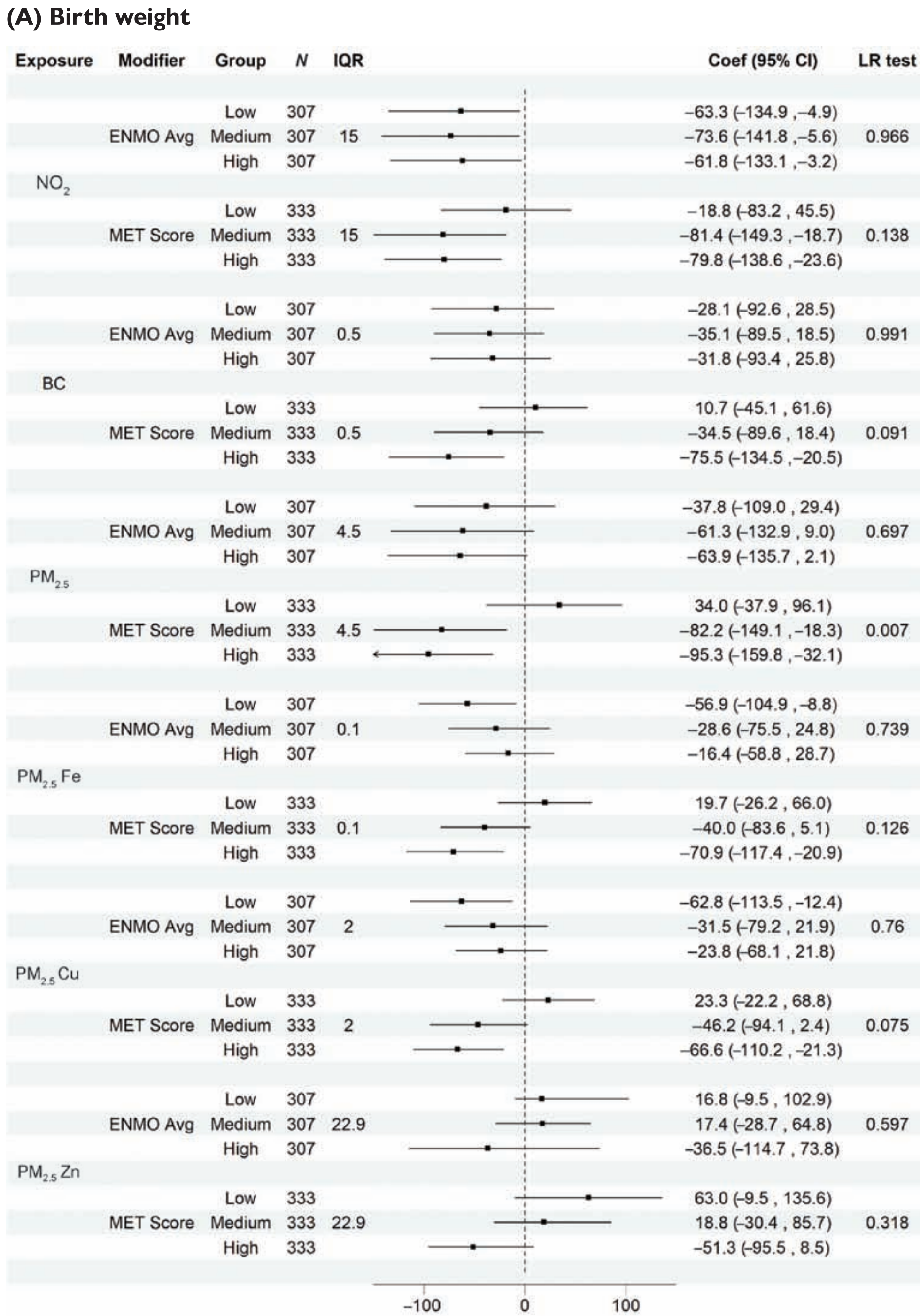


Figure 13. (A) Adjusted change in birth weight (g), and (B) adjusted OR of SGA associated with one IQR increase in exposure to NO_2 (μg/m³), BC (μg/m³), $PM_{2.5}$ (μg/m³), $PM_{2.5}$ Cu content (ng/m³), $PM_{2.5}$ Fe content (μg/m³), and $PM_{2.5}$ Zn content (ng/m³), stratified by tertiles of questionnaire-based Metabolic Equivalent for Task hours per day and tertiles of sensor-based Euclidean norm minus one. Change in birth weight is adjusted for maternal age (continuous, years), education level (categorical, university degree: yes/no), body mass index (BMI) at the first trimester (continuous, kg/m²), parity (categorical, nulliparous: yes/no), active smoking during pregnancy (categorical, yes/no), exposure to environmental tobacco smoke (categorical, yes/no), alcohol consumption during pregnancy (categorical, yes/no), gestational age at delivery (continuous, days), history of low birth weight in previous pregnancies (categorical, yes/no), and sex of the neonate (girl vs. boy). The OR for SGA is adjusted for maternal age (continuous, years), education level (categorical, university degree: yes/no), body mass index (BMI) at the first trimester (continuous, kg/m²), parity (categorical, nulliparous: yes/no), active smoking during pregnancy (categorical, yes/no), exposure to environmental tobacco smoke (categorical, yes/no), alcohol consumption during pregnancy (categorical, yes/no), and history of low birth weight in previous pregnancies (categorical, yes/no). BC = black carbon; CI = confidence interval; ENMO = Euclidean norm minus one; IQR = interquartile range; LR test = likelihood ratio test; OR = odds ratio; MET = metabolic equivalent for task; SGA = small for gestational age.

(B) SGA

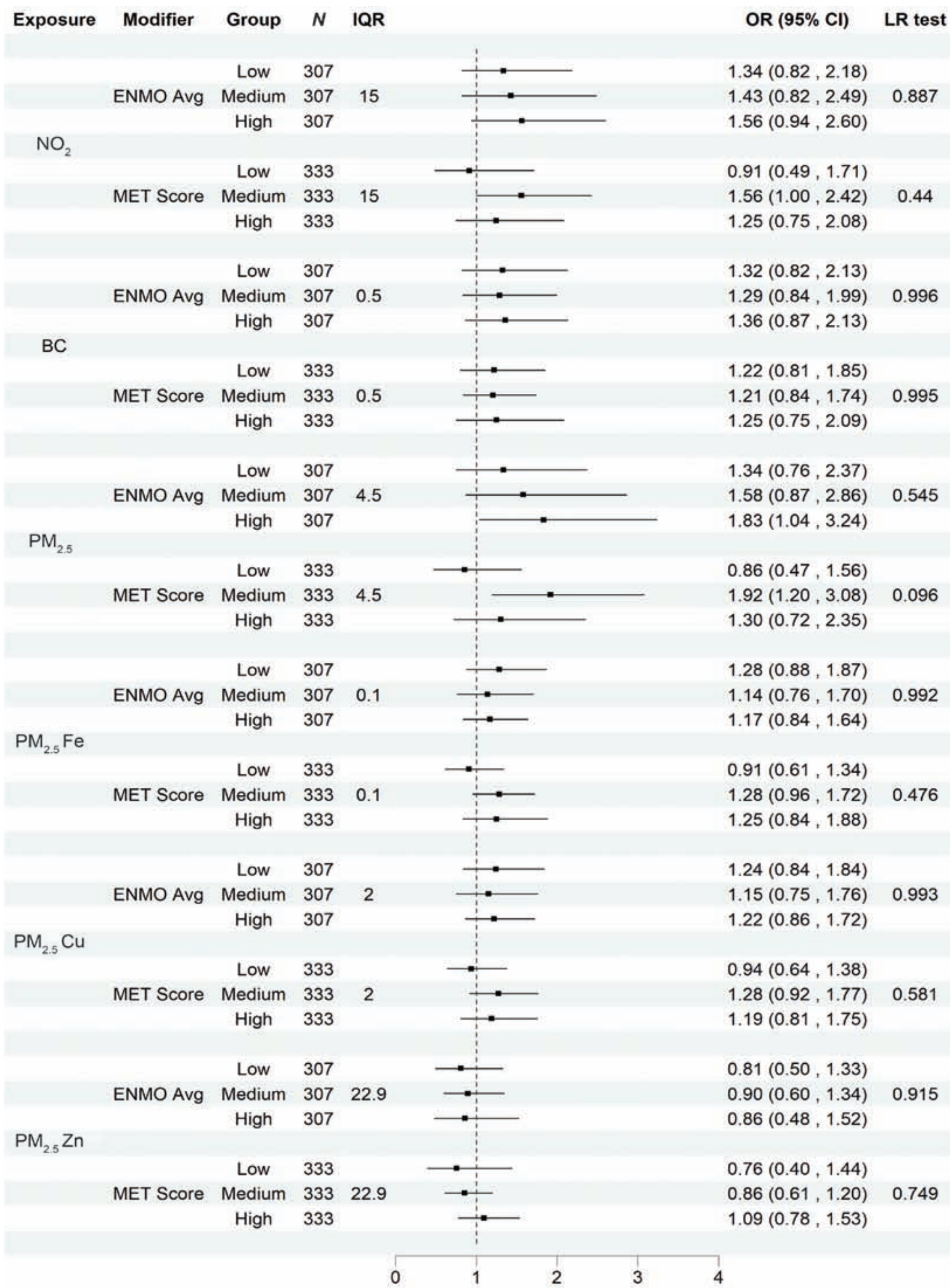


Figure 13. *(continued)*

(A) Birth weight

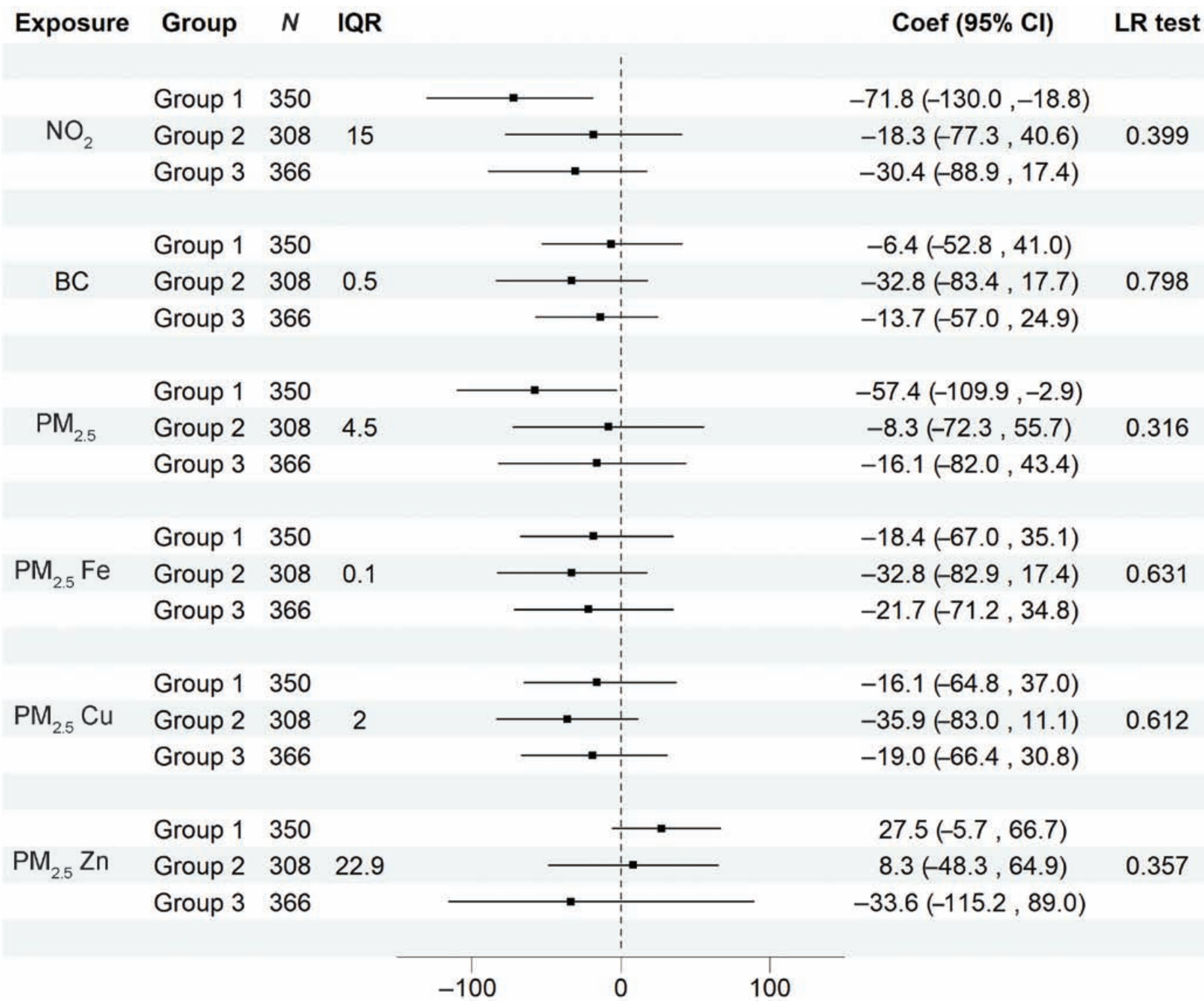


Figure 14. (A) Adjusted change in birth weight (g) and (B) the adjusted odds ratio of SGA associated with one IQR increase in exposure to NO_2 (μg/m³), BC (μg/m³), $PM_{2.5}$ (μg/m³), $PM_{2.5}$ Cu content (ng/m³), $PM_{2.5}$ Fe content (μg/m³), and $PM_{2.5}$ Zn content (ng/m³), separately for pregnancies that were entirely before the start of the COVID-19 pandemic (group 1), those whose conception was before the start of the pandemic and their delivery was afterward (group 2), and those whose conception and delivery were after the start of the pandemic (group 3). Change in birth weight is adjusted for maternal age (continuous, years), education level (categorical, university degree: yes/no), body mass index (BMI) at the first trimester (continuous, kg/m²), parity (categorical, nulliparous: yes/no), active smoking during pregnancy (categorical, yes/no), exposure to environmental tobacco smoke (categorical, yes/no), alcohol consumption during pregnancy (categorical, yes/no), gestational age at delivery (continuous, days), history of low birth weight in previous pregnancies (categorical, yes/no), and sex of the neonate (girl vs. boy). The OR of SGA is adjusted for maternal age (continuous, years), education level (categorical, university degree: yes/no), body mass index (BMI) at the first trimester (continuous, kg/m²), parity (categorical, nulliparous: yes/no), active smoking during pregnancy (categorical, yes/no), exposure to environmental tobacco smoke (categorical, yes/no), alcohol consumption during pregnancy (categorical, yes/no), and history of low birth weight in previous pregnancies (categorical, yes/no). BC = black carbon; CI = confidence interval; IQR = interquartile range; LR test = likelihood ratio test; OR = odds ratio; SGA = small for gestational age.

(B) SGA

Exposure	Group	*N*	IQR	OR (95% CI)	LR test
NO_2	Group 1	350	15	1.39 (0.93 , 2.06)	0.386
	Group 2	308		0.94 (0.58 , 1.52)	
	Group 3	366		0.89 (0.56 , 1.42)	
BC	Group 1	350	0.5	1.10 (0.79 , 1.54)	0.595
	Group 2	308		1.36 (0.89 , 2.07)	
	Group 3	366		1.08 (0.76 , 1.52)	
$PM_{2.5}$	Group 1	350	4.5	1.32 (0.90 , 1.95)	0.705
	Group 2	308		1.19 (0.71 , 2.01)	
	Group 3	366		1.26 (0.73 , 2.16)	
$PM_{2.5}$ Fe	Group 1	350	0.1	1.05 (0.74 , 1.50)	0.609
	Group 2	308		1.29 (0.89 , 1.87)	
	Group 3	366		1.14 (0.74 , 1.77)	
$PM_{2.5}$ Cu	Group 1	350	2	1.05 (0.73 , 1.50)	0.647
	Group 2	308		1.27 (0.89 , 1.83)	
	Group 3	366		1.01 (0.67 , 1.52)	
$PM_{2.5}$ Zn	Group 1	350	22.9	0.88 (0.68 , 1.14)	0.743
	Group 2	308		1.18 (0.73 , 1.89)	
	Group 3	366		0.77 (0.40 , 1.47)	

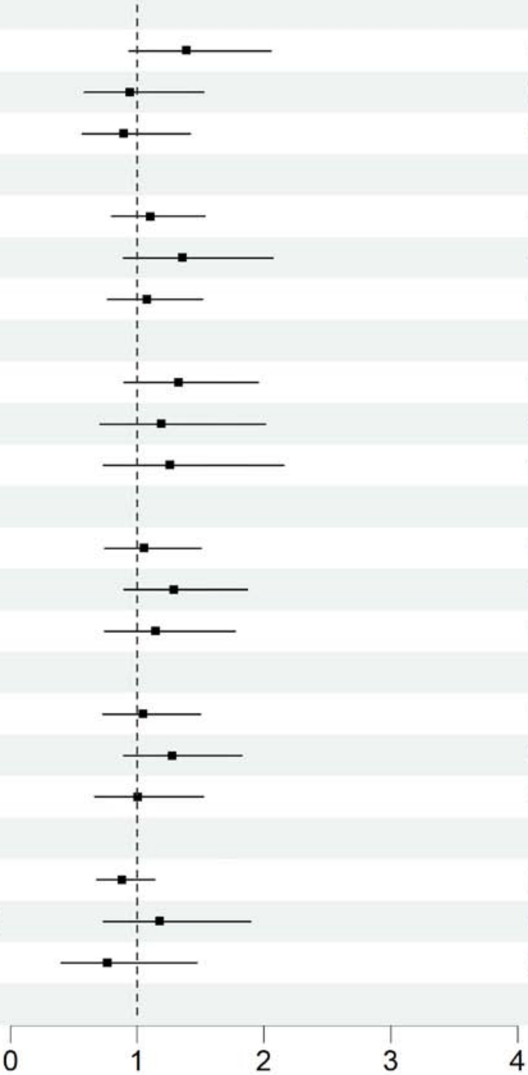


Figure 14. *(continued)*

associations for the women residing in neighborhoods with higher annual average household income (Figures 9 and 10). We also observed some indications of stronger associations for women with higher hair cortisol levels (i.e., higher stress); however, for the associations involving SGA, this pattern was less clear. For the self-reported perceived stress, we did not observe a clear pattern (Figures 11 and 12).

For the associations of birth weight and SGA with physical activity, the patterns tended to vary across different air pollutants and between the subjective and objective measures of physical activity. For birth weight, while we observed that exposure to NO_2 and BC had indications of potentially stronger associations for women with higher self-reported physical activity level (i.e., questionnaire-based Metabolic Equivalent for Task), we did not observe a clear pattern for the objectively measured physical activity level (i.e., monitoring-based ENMO). On the other hand, for the $PM_{2.5}$ exposure, we found consistent patterns for objective and subjective measures of physical activity, with both indicating potentially stronger associations among more physically active women. For $PM_{2.5}$ Fe and Cu content, while the objectively measured physical activity had some suggestions for a potentially stronger association for less physically active women, for the subjective measure of physical activity, we observed an opposite pattern with stronger associations for those who were more physically active. For SGA, we observed indications of a potentially stronger association for NO_2 and $PM_{2.5}$ exposure among more physically active women based on the objective measure of physical activity. For the rest of the air pollutants, we did not observe any clear pattern (Figure 13).

With regards to the COVID-19 pandemic, while we observed a suggestion for a potentially stronger association of NO_2 and $PM_{2.5}$ exposure with birth weight and SGA for those pregnancies that were entirely before the start of the pandemic (i.e., Group 1), there was no clear pattern for other air pollutants (Figure 14).

MITIGATION BY URBAN GREENNESS AND CANOPY

For birth weight, we observed some suggestions for potentially weaker associations with NO_2, BC, and $PM_{2.5}$ Fe and Cu contents for participants with higher greenness (i.e., NDVI) across a 300-m buffer around their home; however, for the greenness across 50 m around their home, we observed such a pattern only for BC. Moreover, for the greenness surrounding the road, while we observed a similar pattern for BC, for NO_2, $PM_{2.5}$, and $PM_{2.5}$ Fe contents, we found an opposite pattern with potentially stronger associations for participants with higher greenness **(Figure 15)**. For SGA, there were indications of a potentially weaker association with NO_2, BC, and $PM_{2.5}$ for pregnant women with higher greenness in a 300-m buffer around their homes; we did not observe a similar pattern for greenness in a 50-m buffer around their homes. Furthermore, there were suggestions for a potentially stronger association between $PM_{2.5}$ and SGA for participants with higher greenness around major roads in the vicinity of their home **(Figure 16)**. None of the interaction terms between TRAP and greenness indicators were statistically significant (*P* values >0.1).

With regards to the canopy cover, while we found that the association between birth weight and BC exposure suggested weaker associations for the women with higher canopy volume within a 50-m buffer around their homes, we did not observe such a pattern for the canopy volume within a 300-m buffer around the home. In contrast, for $PM_{2.5}$ Fe content, while we observed a potentially stronger association for women with higher canopy volume within a 300-m buffer around their home, we did not observe such a pattern for the canopy volume within a 50-m buffer (Figure 15). For the association of SGA with NO_2, BC, $PM_{2.5}$, and $PM_{2.5}$ Fe and Cu contents, there were indications of stronger associations for participants with higher canopy volume within a 50-m buffer of their homes; however, for the canopy cover within a 300-m buffer around the home, there was an opposite pattern for BC and no clear pattern for $PM_{2.5}$. For the canopy volume around the major roads in the vicinity of women's homes, there were suggestions for potentially stronger associations of exposure to NO_2, $PM_{2.5}$, and $PM_{2.5}$ Fe and Zn content with birth weight, and $PM_{2.5}$ with SGA for women with higher canopy volume. For the rest of the associations between TRAP and birth weight and SGA, we did not find any clear pattern across the strata of home- and road-surrounding canopy cover (Figure 16). None of the interaction terms between TRAP and canopy volume indicators were statistically significant (Figures 15 and 16).

INCORPORATING EXPOSURE MEASUREMENT ERROR

Given the availability of the measured personal exposure to NO_2, using passive samplers that could be used as the gold standard measure of personal exposure to NO_2, we evaluated the impact of measurement error on the association of NO_2 with birth weight. These analyses were conducted using linear regression models with hospital as a categorical predictor (instead of mixed effects models with hospital as the random effect as used in the main analyses), and based on them, an IQR (i.e., 15.0 μg/m^3) increase in the modeled NO_2 exposure during the entire pregnancy (LUR model and for all microenvironments combined) was associated with a decrease of –65.1 g (95% CI: –102.0 to –28.3) in birth weight. After controlling for the exposure measurement error, the estimated association became stronger with a wider confidence interval: –242.5 g (–384.5 to –113.7).

WINDOW(S) OF VULNERABILITY

There were generally two windows of vulnerability: one at the end of the first trimester and the beginning of the second trimester, and the other at the end of the third trimester. While we observed statistically significant associations with lower birth weight during the first vulnerability window period for exposures to NO_2, $PM_{2.5}$, and $PM_{2.5}$ Cu and Fe contents, for BC exposure, we observed statistically significant associations during the second vulnerability window period (**Figure 17).** After removing gestational age at delivery from

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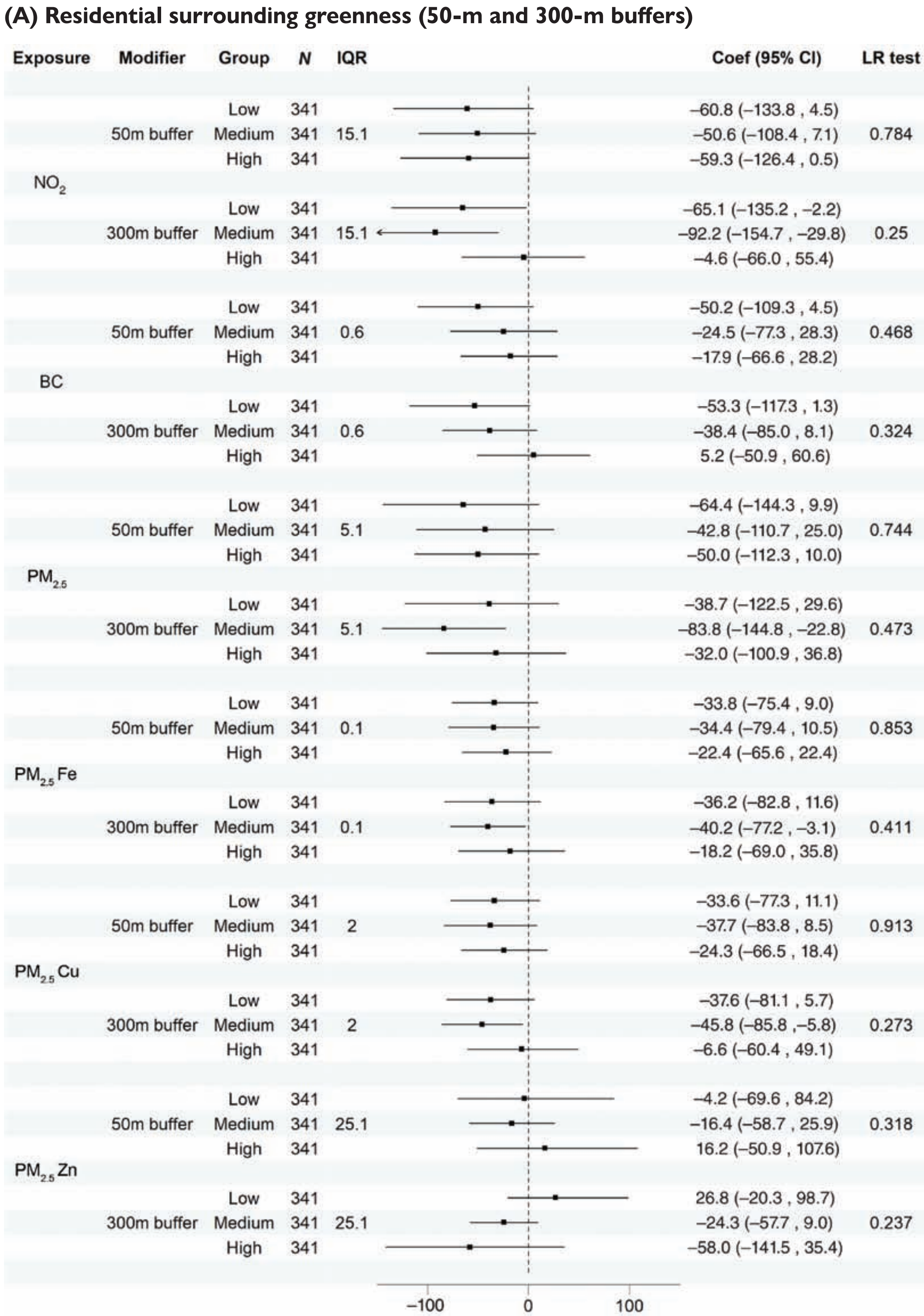

Figure 15. Adjusted change in birth weight (g) associated with one IQR increase in exposure to NO_2 (μg/m³), BC (μg/m³), $PM_{2.5}$ (μg/m³), $PM_{2.5}$ Cu content (ng/m³), $PM_{2.5}$ Fe content (μg/m³), and $PM_{2.5}$ Zn content (ng/m³) stratified by (A) tertiles of residential surrounding greenness, (B) tertiles of greenness surrounding major roads within 200 m from the residential address, (C) tertiles of residential surrounding canopy volume, and (D) tertiles of canopy volume surrounding major roads within 200 m from the residential address. Change in birth weight is adjusted for maternal age (continuous, years), education level (categorical, university degree: yes/no), body mass index (BMI) at the first trimester (continuous, kg/m²), parity (categorical, nulliparous: yes/no), active smoking during pregnancy (categorical, yes/no), exposure to environmental tobacco smoke (categorical, yes/no), alcohol consumption during pregnancy (categorical, yes/no), gestational age at delivery (continuous, days), history of low birth weight in previous pregnancies (categorical, yes/no), and sex of the neonate (girl vs. boy). BC = black carbon; CI = confidence interval; IQR = interquartile range; LR test = likelihood ratio test.

(B) Greenness surrounding major roads in vicinity of residential address

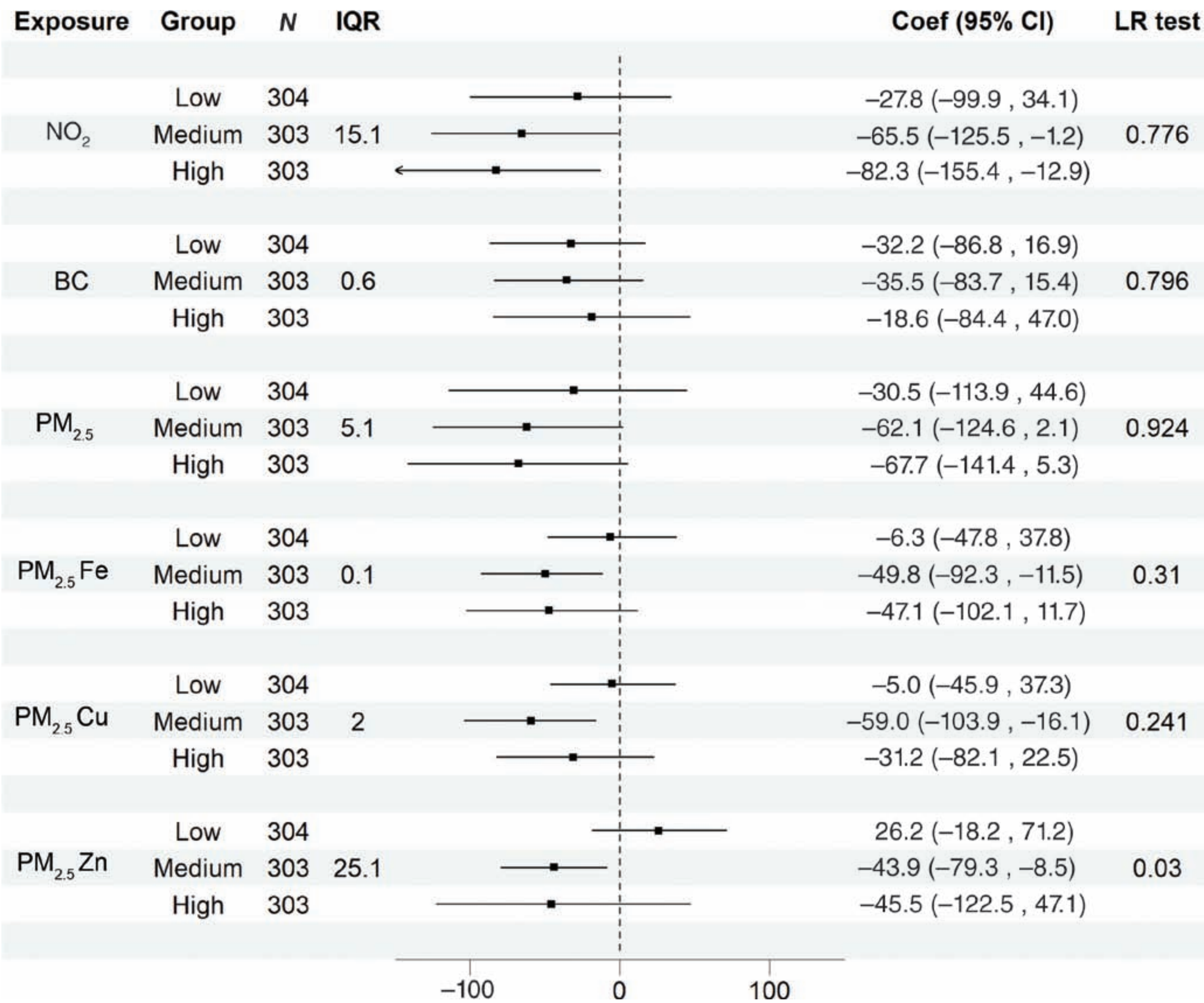

Figure 15. *(continued)*

(C) Residential surrounding canopy volume (50-m and 300-m buffers)

Exposure	Modifier	Group	*N*	IQR	Coef (95% CI)	LR test
NO_2	50m buffer	Low	235	15.1	–36.5 (–104.1 , 31.1)	0.719
		Medium	234		–114.8 (–196.7 , –36.8)	
		High	235		–66.3 (–137.1 , 4.4)	
	300m buffer	Low	235	15.1	–41.7 (–115.6 , 32.2)	0.678
		Medium	234		–93.6 (–167.6 , –21.6)	
		High	235		–89.3 (–173.1 , –7.5)	
BC	50m buffer	Low	235	0.6	–64.3 (–127.8 , –0.7)	0.587
		Medium	234		–64.9 (–135.2 , 1.9)	
		High	235		–35.7 (–94.0 , 22.7)	
	300m buffer	Low	235	0.6	–44.1 (–113.5 , 25.2)	0.844
		Medium	234		–66.1 (–125.5 , –6.3)	
		High	235		–43.8 (–113.7 , 23.6)	
$PM_{2.5}$	50m buffer	Low	235	5.1	–30.9 (–113.3 , 51.5)	0.49
		Medium	234		–122.8 (–215.7 , –34.5)	
		High	235		–75.6 (–153.4 , 0.0)	
	300m buffer	Low	235	5.1	–37.6 (–116.6 , 41.5)	0.484
		Medium	234		–108.6 (–192.0 , –30.7)	
		High	235		–82.2 (–168.1 , 1.1)	
$PM_{2.5}$ Fe	50m buffer	Low	235	0.1	–1.2 (–50.0 , 47.6)	0.252
		Medium	234		–80.4 (–135.8 , –26.5)	
		High	235		–21.9 (–72.5 , 29.4)	
	300m buffer	Low	235	0.1	–10.5 (–66.1 , 45.1)	0.844
		Medium	234		–43.0 (–87.8 , 4.4)	
		High	235		–52.3 (–110.0 , 4.7)	
$PM_{2.5}$ Cu	50m buffer	Low	235	2	–13.4 (–72.1 , 45.3)	0.572
		Medium	234		–77.2 (–136.6 , –20.3)	
		High	235		–33.9 (–84.9 , 18.6)	
	300m buffer	Low	235	2	–8.7 (–68.7 , 51.3)	0.526
		Medium	234		–65.4 (–115.5 , –12.0)	
		High	235		–48.8 (–110.2 , 12.3)	
$PM_{2.5}$ Zn	50m buffer	Low	235	25.1	16.7 (–41.2 , 74.4)	0.522
		Medium	234		–21.3 (–78.5 , 43.1)	
		High	235		–26.4 (–80.3 , 33.1)	
	300m buffer	Low	235	25.1	9.2 (–48.9 , 67.2)	0.403
		Medium	234		–53.2 (–114.9 , 17.6)	
		High	235		–17.3 (–71.8 , 40.9)	

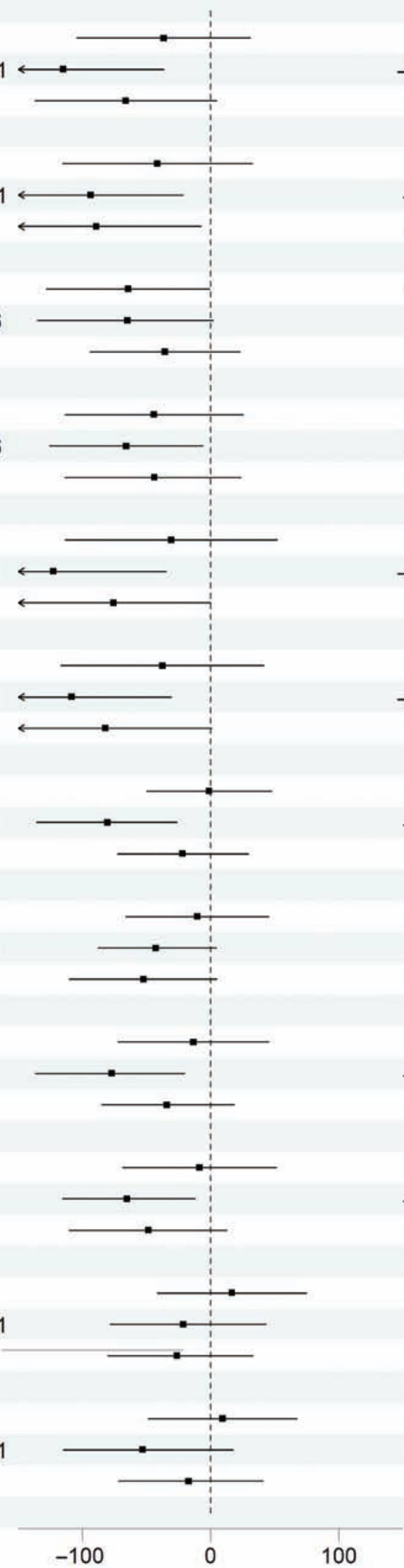

Figure 15. *(continued)*

(D) Canopy volume surrounding major roads in vicinity of residential address

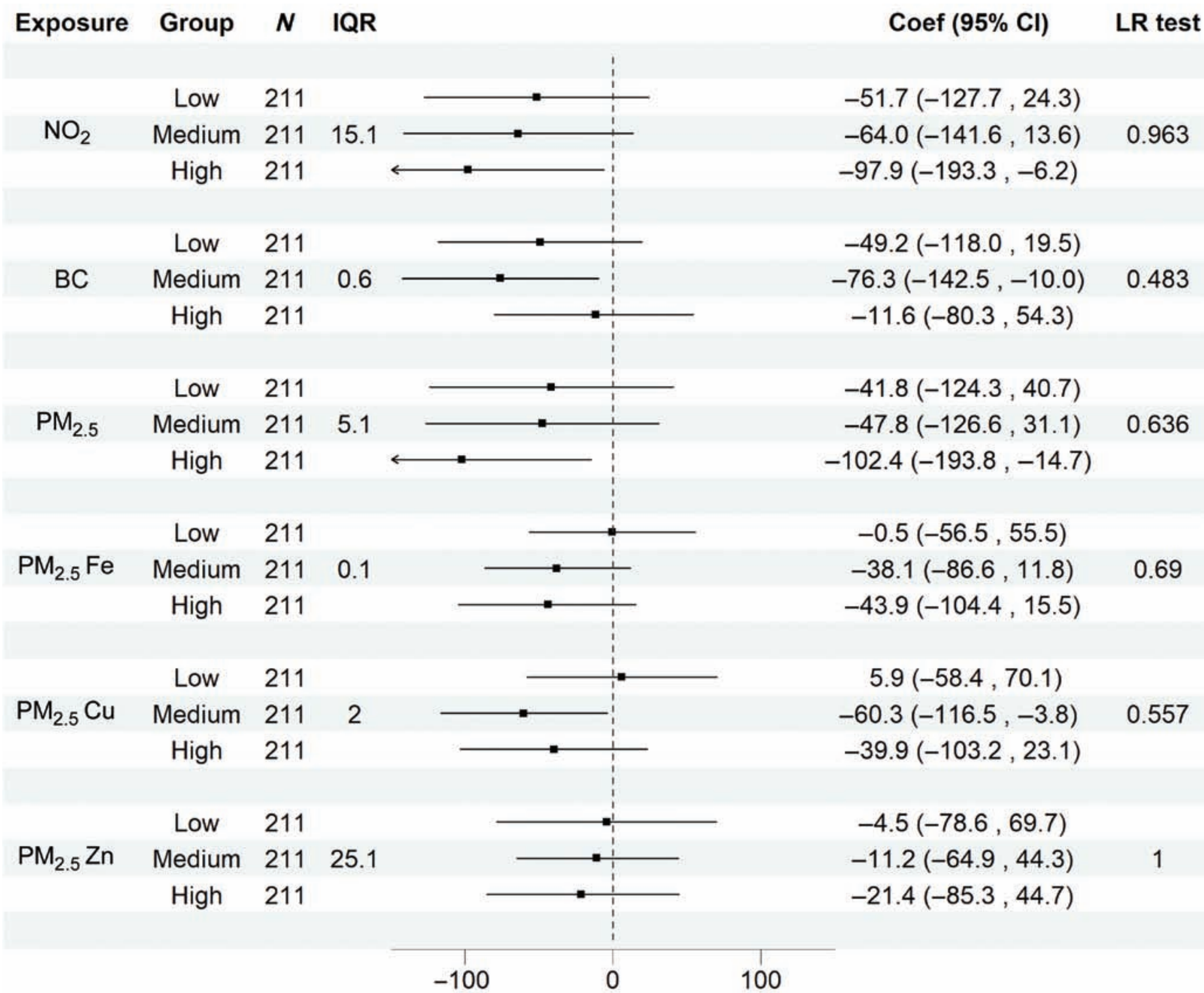

Figure 15. *(continued)*

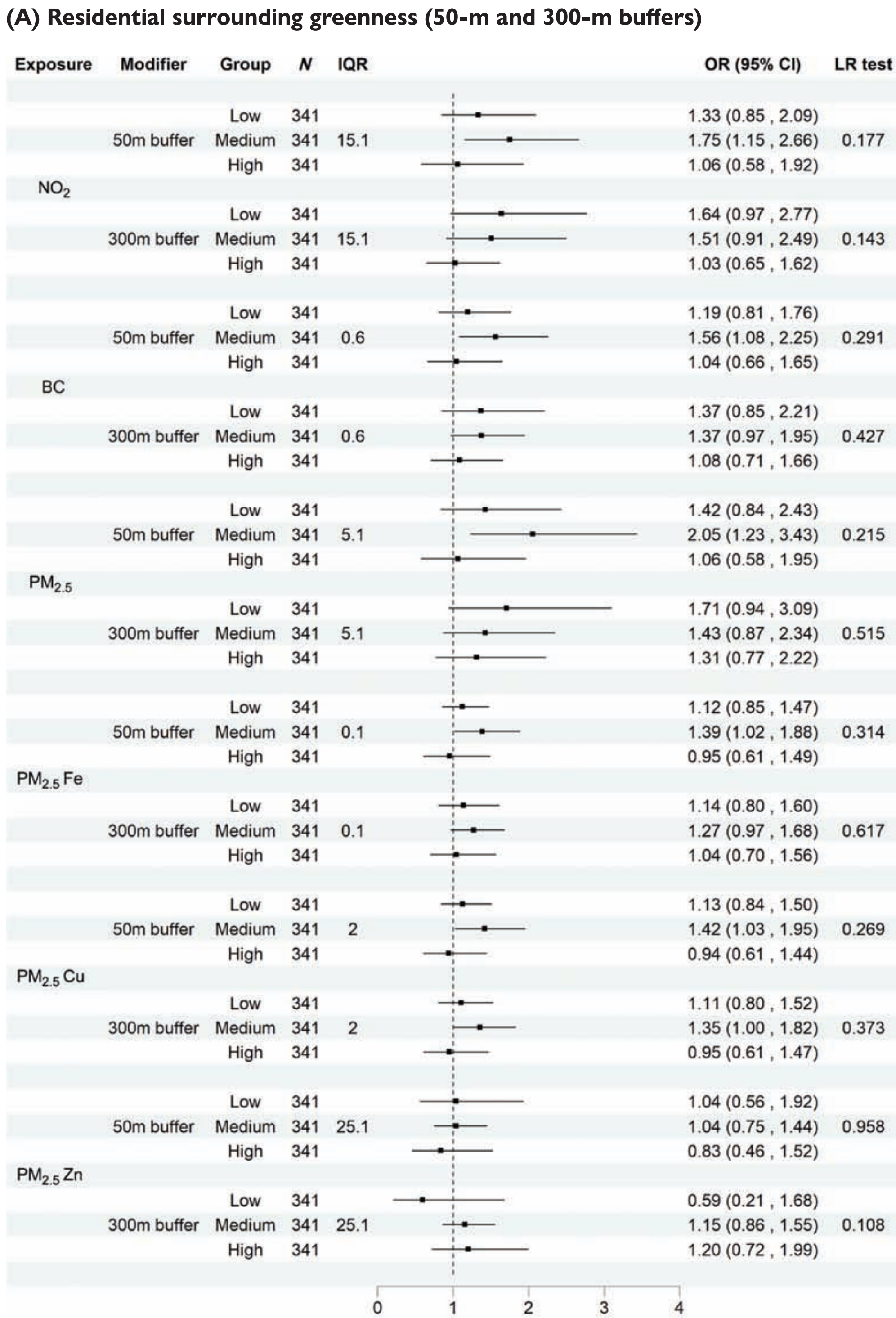

Figure 16. The adjusted odds ratio of SGA associated with one IQR increase in exposure to NO_2 (μg/m³), BC (μg/m³), $PM_{2.5}$ (μg/m³), $PM_{2.5}$ Cu content (ng/m³), $PM_{2.5}$ Fe content (μg/m³), and $PM_{2.5}$ Zn content (ng/m³) stratified by (A) tertiles of residential surrounding greenness, (B) tertiles of greenness surrounding major roads within 200 m from the residential address, (C) tertiles of residential surrounding canopy volume, and (D) tertiles of canopy volume surrounding major roads within 200 m from the residential address. The OR of SGA is adjusted for maternal age (continuous, years), education level (categorical, university degree: yes/no), body mass index (BMI) at the first trimester (continuous, kg/m²), parity (categorical, nulliparous: yes/no), active smoking during pregnancy (categorical, yes/no), exposure to environmental tobacco smoke (categorical, yes/no), alcohol consumption during pregnancy (categorical, yes/no), and history of low birth weight in previous pregnancies (categorical, yes/no). BC = black carbon; CI = confidence interval; IQR = interquartile range; LR test = likelihood ratio test; OR = odds ratio; SGA = small for gestational age.

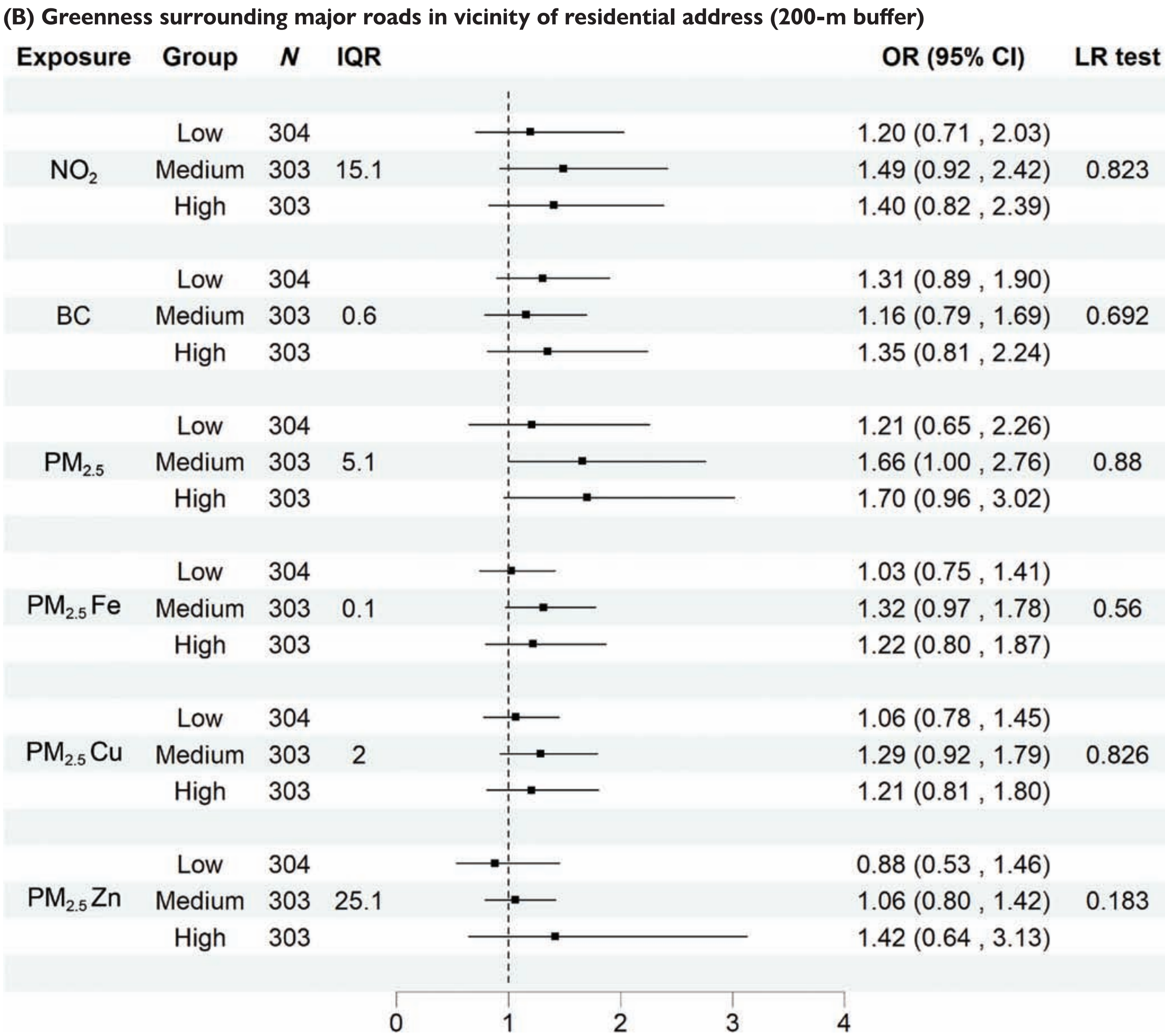

Figure 16. *(continued)*

(C) Residential surrounding canopy volume (50-m and 300-m buffer)

Exposure	Modifier	Group	*N*	IQR	OR (95% CI)	LR test
		Low	235		1.19 (0.71 , 1.99)	
	50m buffer	Medium	234	15.1	1.39 (0.77 , 2.53)	0.565
		High	235		1.74 (0.97 , 3.12)	
NO_2						
		Low	235		1.35 (0.73 , 2.48)	
	300m buffer	Medium	234	15.1	1.47 (0.83 , 2.61)	0.854
		High	235		1.57 (0.85 , 2.91)	
		Low	235		1.18 (0.73 , 1.92)	
	50m buffer	Medium	234	0.6	1.28 (0.78 , 2.09)	0.496
		High	235		1.58 (1.01 , 2.47)	
BC						
		Low	235		1.69 (0.94 , 3.04)	
	300m buffer	Medium	234	0.6	1.46 (0.95 , 2.25)	0.425
		High	235		1.26 (0.74 , 2.12)	
		Low	235		1.10 (0.58 , 2.07)	
	50m buffer	Medium	234	5.1	1.43 (0.73 , 2.81)	0.217
		High	235		2.04 (1.08 , 3.86)	
$PM_{2.5}$						
		Low	235		1.42 (0.73 , 2.79)	
	300m buffer	Medium	234	5.1	1.59 (0.84 , 3.00)	0.632
		High	235		1.47 (0.80 , 2.72)	
		Low	235		1.06 (0.73 , 1.53)	
	50m buffer	Medium	234	0.1	1.20 (0.82 , 1.76)	0.808
		High	235		1.22 (0.83 , 1.80)	
$PM_{2.5}$ Fe						
		Low	235		1.04 (0.66 , 1.63)	
	300m buffer	Medium	234	0.1	1.14 (0.81 , 1.61)	0.952
		High	235		1.44 (0.95 , 2.17)	
		Low	235		1.13 (0.73 , 1.75)	
	50m buffer	Medium	234	2	1.20 (0.80 , 1.80)	0.695
		High	235		1.31 (0.87 , 1.95)	
$PM_{2.5}$ Cu						
		Low	235		1.04 (0.63 , 1.71)	
	300m buffer	Medium	234	2	1.26 (0.87 , 1.83)	0.878
		High	235		1.39 (0.87 , 2.22)	
		Low	235		0.87 (0.55 , 1.36)	
	50m buffer	Medium	234	25.1	0.65 (0.37 , 1.13)	0.242
		High	235		1.08 (0.69 , 1.69)	
$PM_{2.5}$ Zn						
		Low	235		0.64 (0.39 , 1.07)	
	300m buffer	Medium	234	25.1	1.20 (0.73 , 1.97)	0.309
		High	235		0.86 (0.55 , 1.34)	

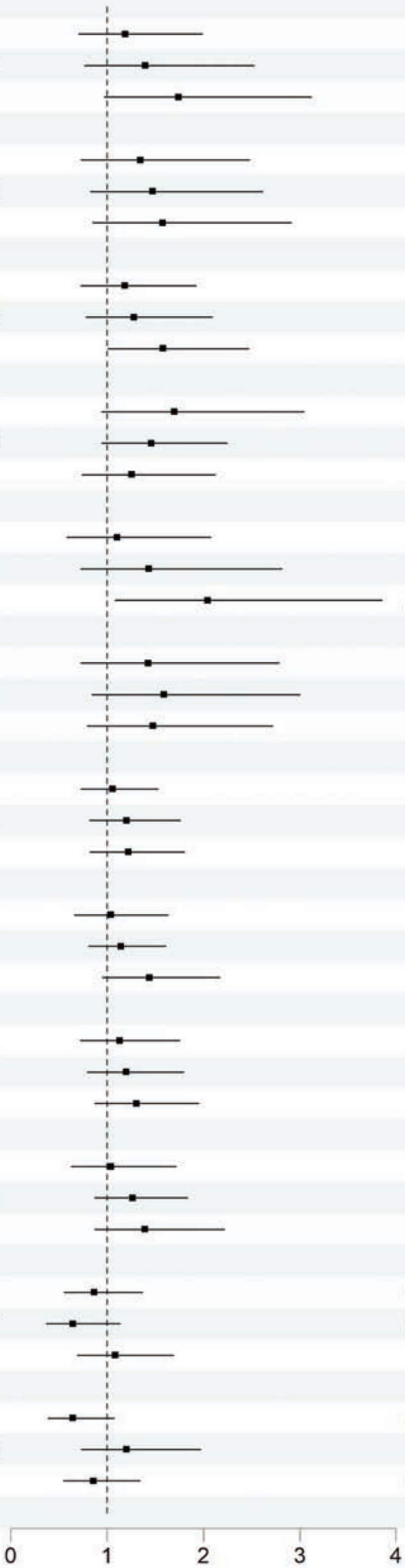

Figure 16. *(continued)*

(D) Canopy volume surrounding major roads in vicinity of residential address

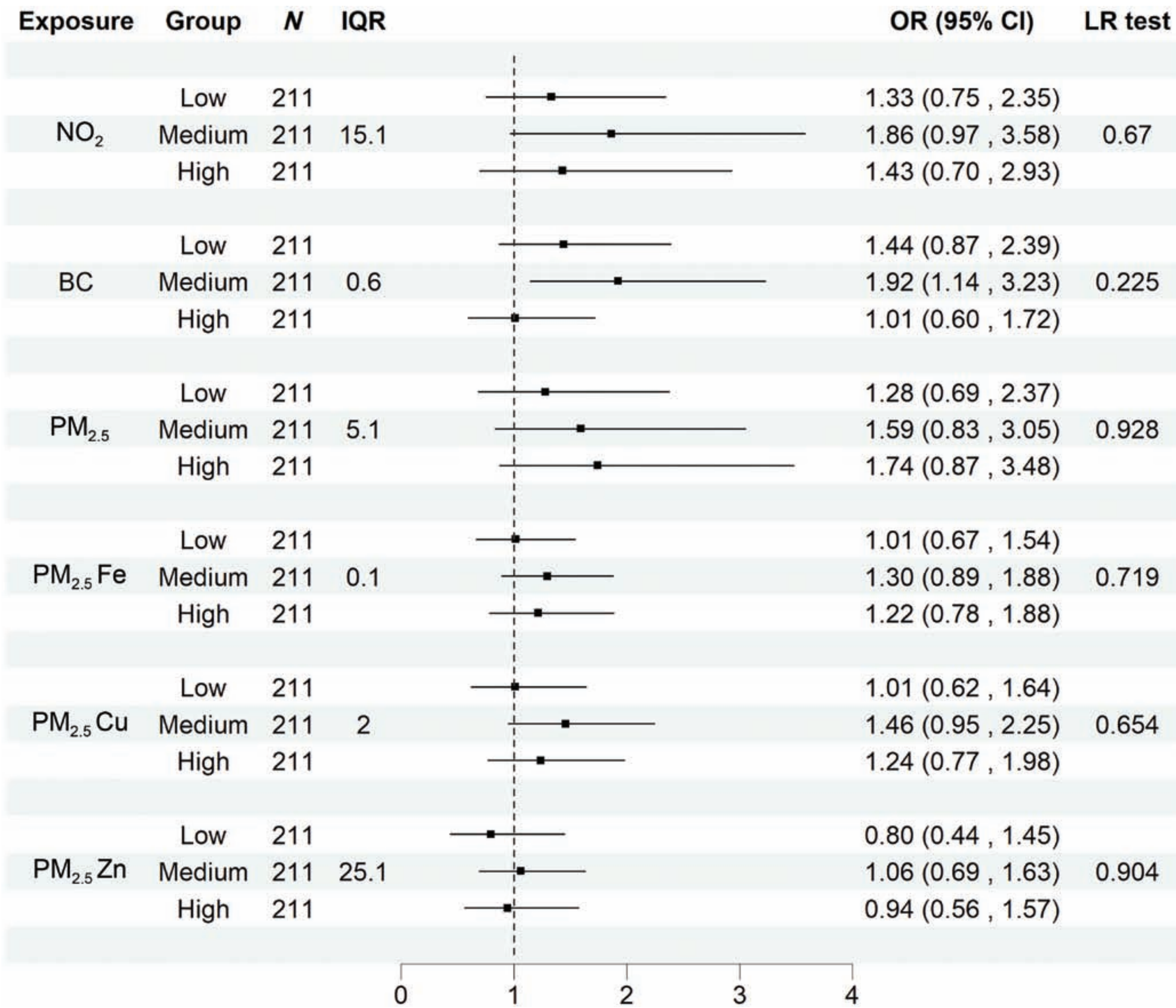

Figure 16. *(continued)*

(A) NO_2

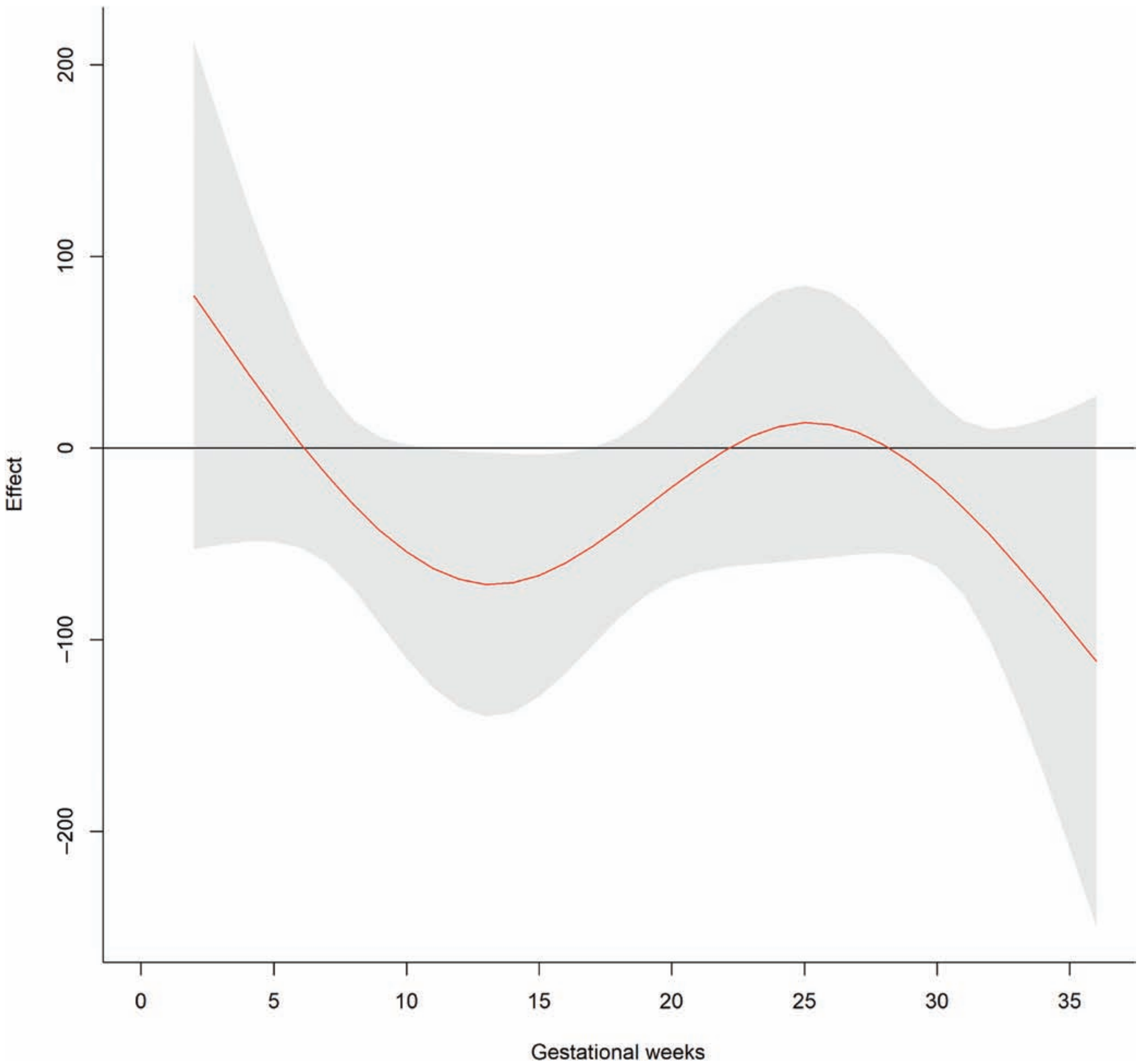

Figure 17. Adjusted change in birth weight (g) associated with one IQR increase in exposure to (A) NO_2 (µg/m³), (B) BC (µg/m³), (C) $PM_{2.5}$ (µg/m³), (D) $PM_{2.5}$ Cu content (ng/m³), (E) $PM_{2.5}$ Fe content (µg/m³), and (F) $PM_{2.5}$ Zn content (ng/m³) during each week of pregnancy. Change in birth weight is adjusted for maternal age (continuous, years), education level (categorical, university degree: yes/no), body mass index (BMI) at the first trimester (continuous, kg/m²), parity (categorical, nulliparous: yes/no), active smoking during pregnancy (categorical, yes/no), exposure to environmental tobacco smoke (categorical, yes/no), alcohol consumption during pregnancy (categorical, yes/no), gestational age at delivery (continuous, days), history of low birth weight in previous pregnancies (categorical, yes/no), and sex of the neonate (girl vs. boy). BC = black carbon; IQR = interquartile range.

(B) BC

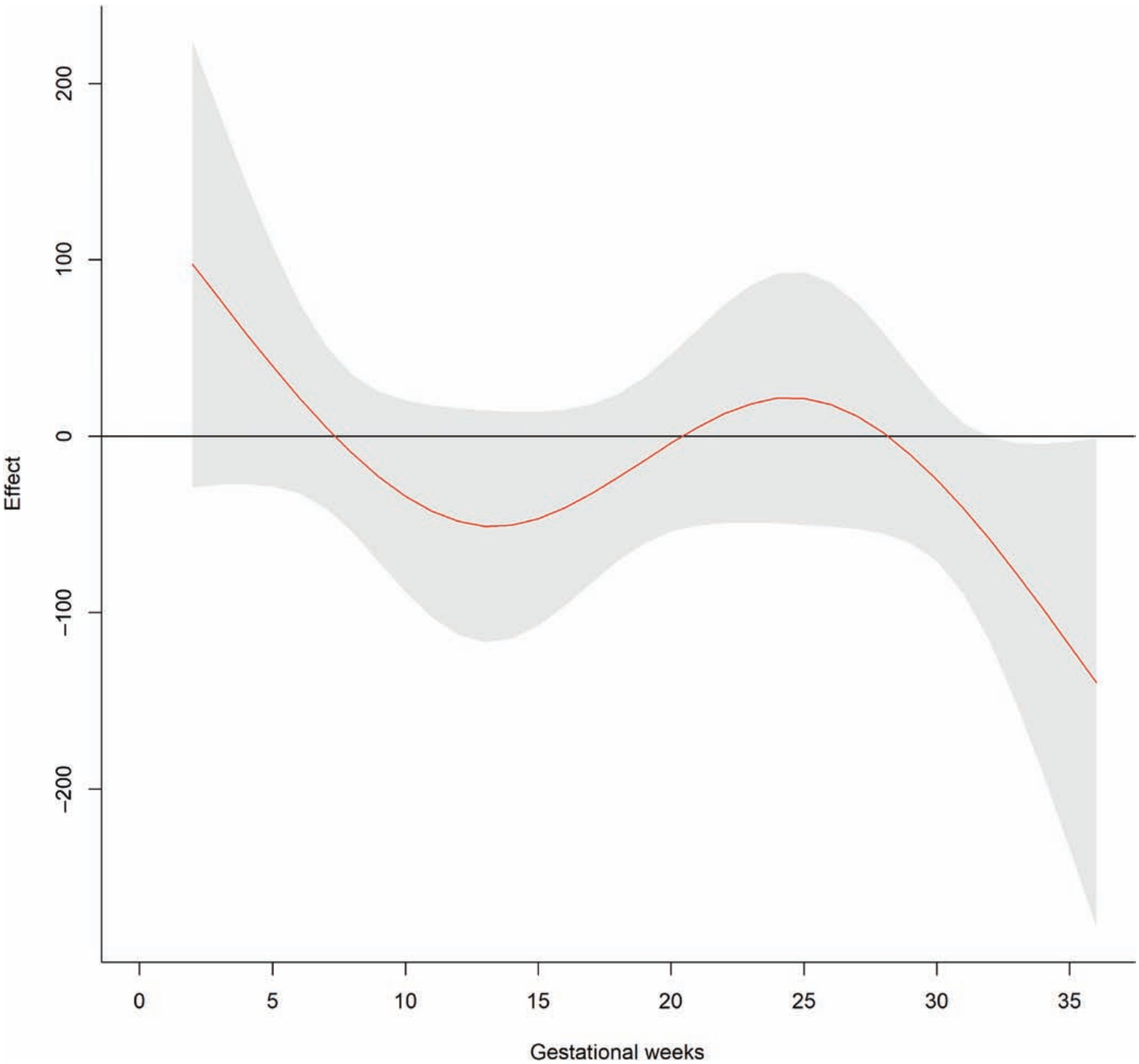

Figure 17. *(continued)*

(C) $PM_{2.5}$

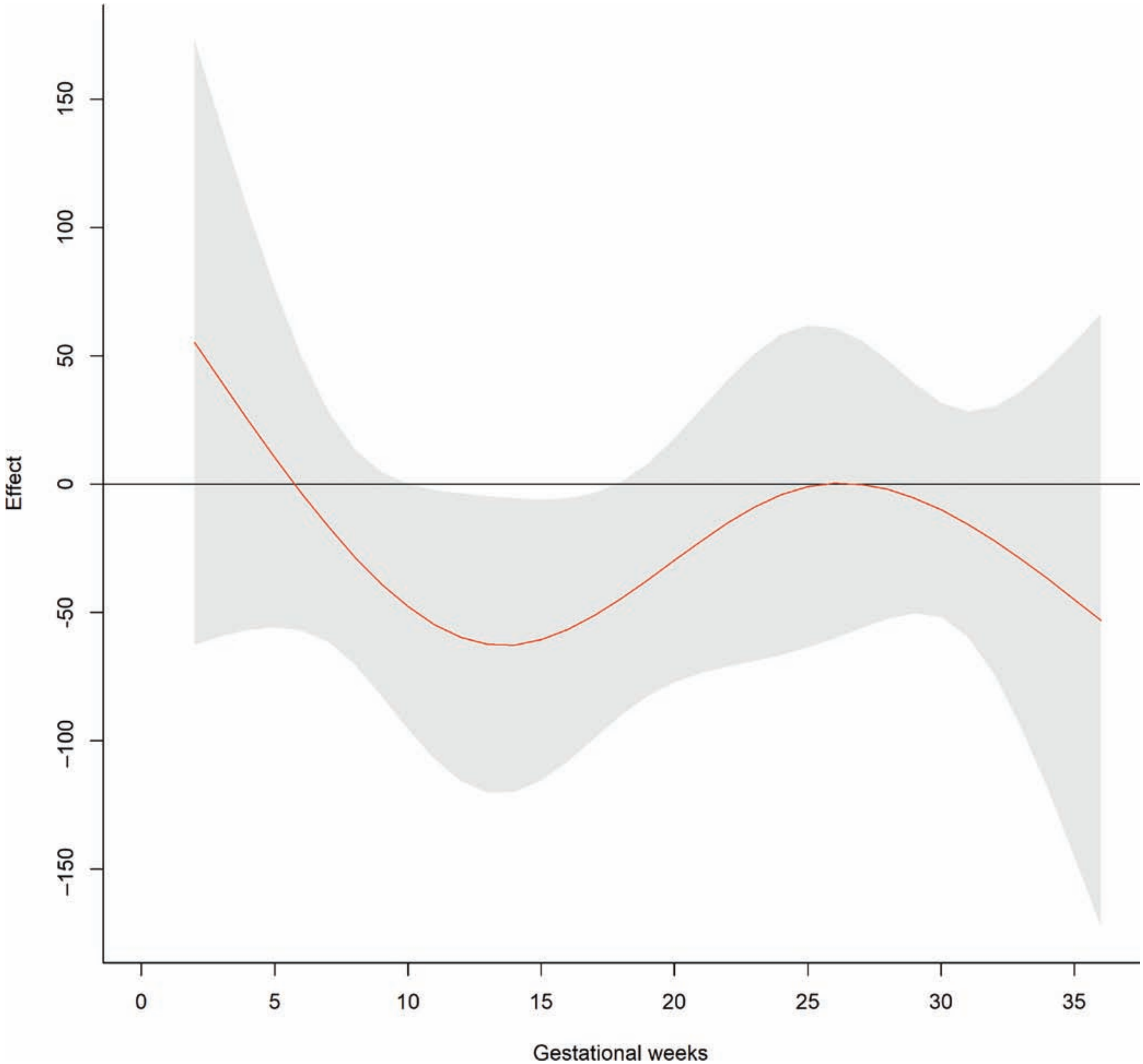

Figure 17. *(continued)*

(D) $PM_{2.5}$ Cu content

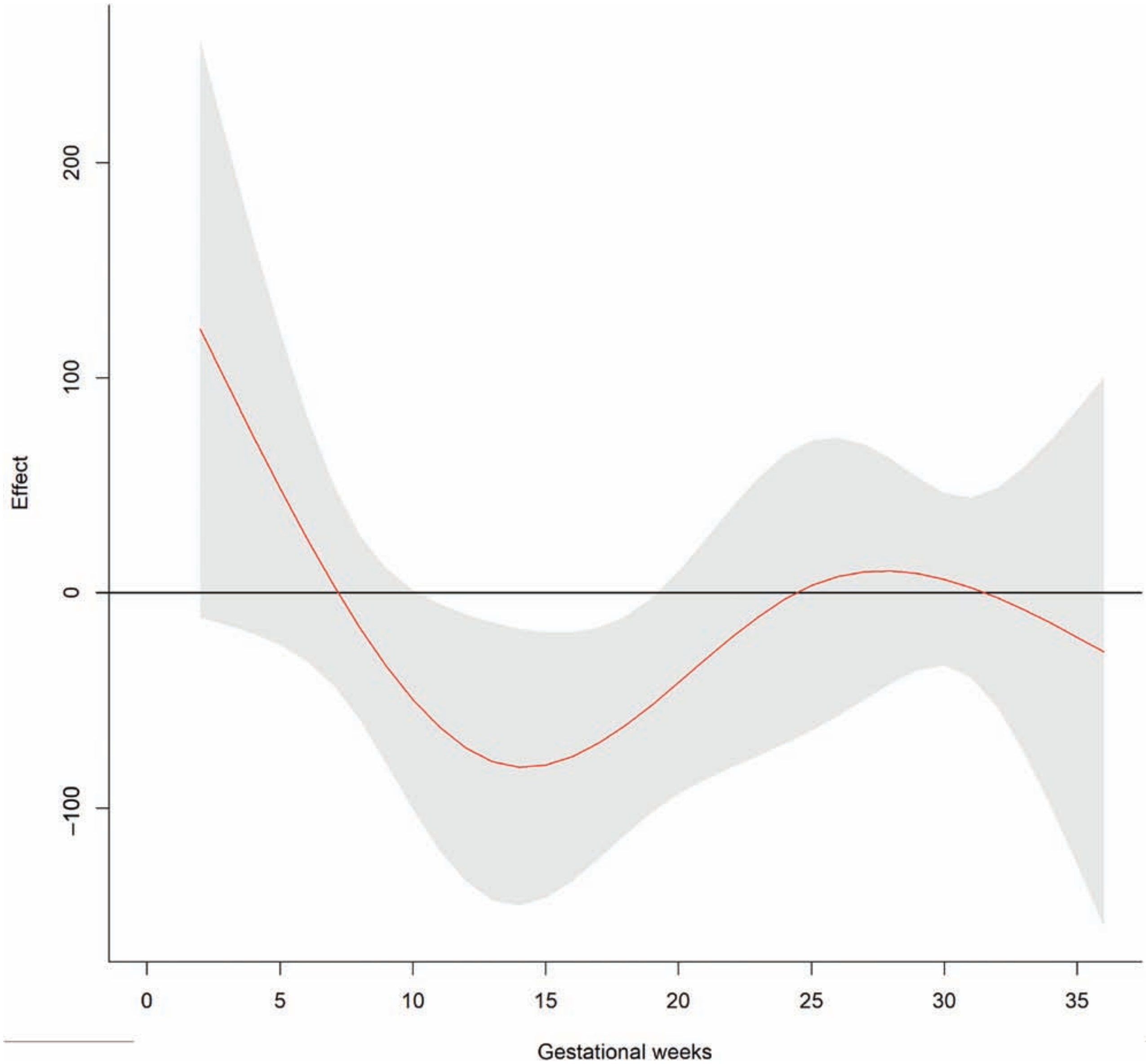

Figure 17. *(continued)*

(E) $PM_{2.5}$ Fe content

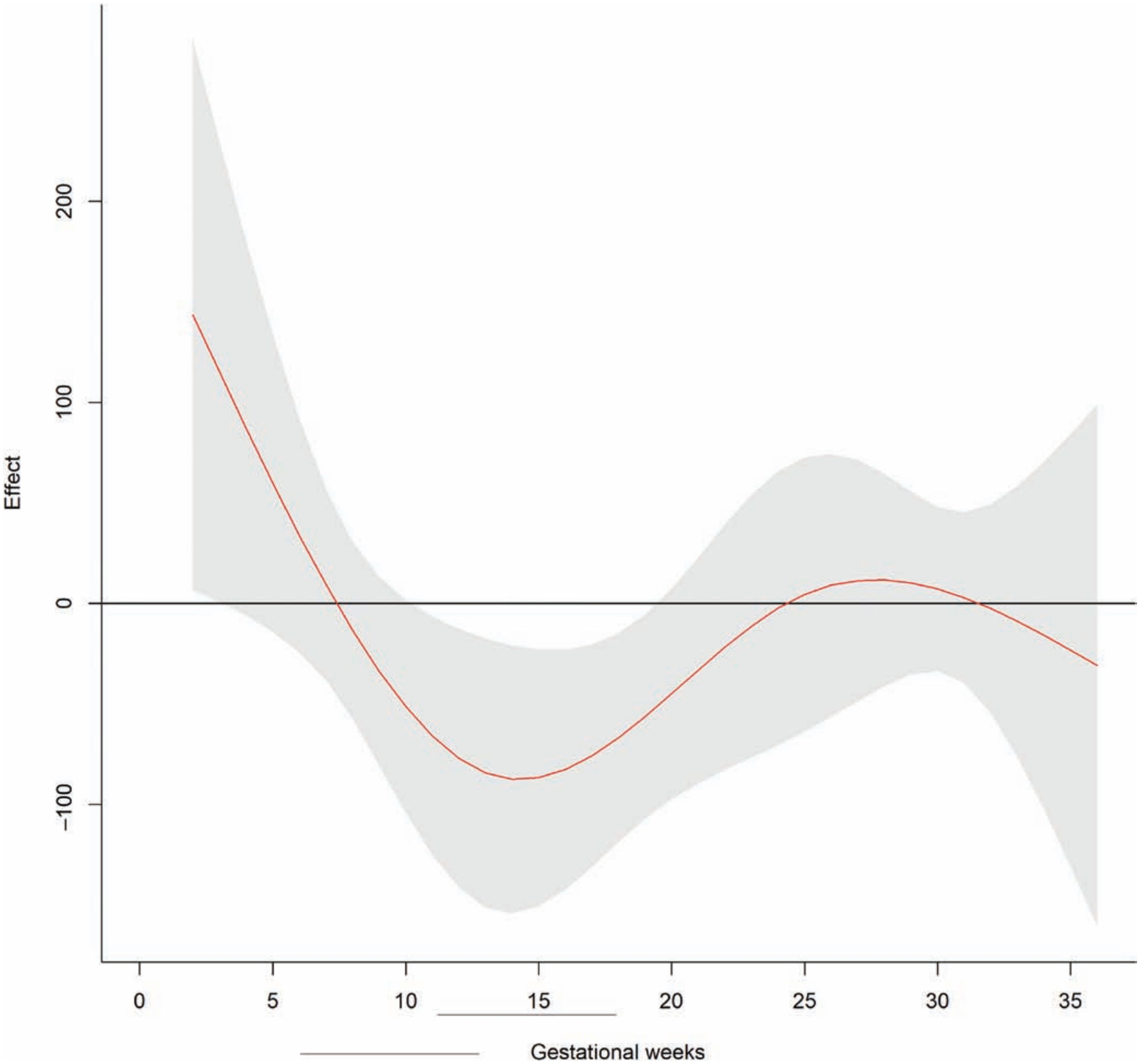

Figure 17. *(continued)*

(F) $PM_{2.5}$ Zn content

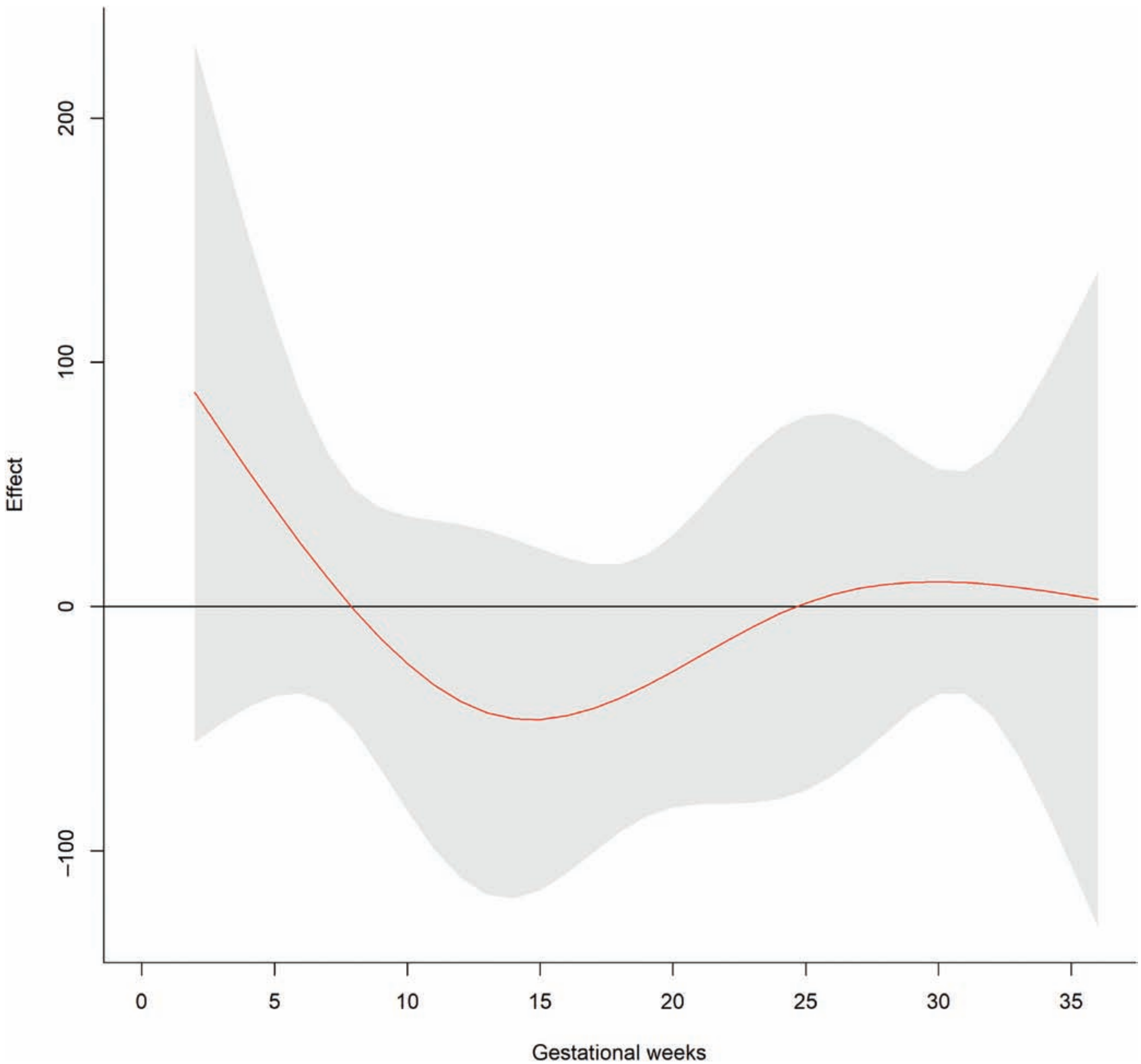

Figure 17. *(continued)*

our distributed lag nonlinear models, these two windows of vulnerability were still evident; however, the associations for NO_2 in the first window and BC in the second window lost their statistical significance. On the other hand, we observed statistically significant inverse associations for $PM_{2.5}$ Zn content in the first window (*Appendix 29*). For SGA, we observed a similar pattern of associations to those for birth weight except for NO_2, for which we did not observe any statistically significant associations (*Appendix 30*).

MEDIATION ANALYSES

In the first step, we evaluated the associations of TRAP exposure between conception and the time of the Doppler ultrasound examination in the third trimester (based on LUR models and all microenvironments combined) with Doppler measures of placental function. Among all these evaluated associations, we found a statistically significant detrimental association between $PM_{2.5}$ and umbilical artery PI (**Figure 18**). In the next step, we evaluated the statistical significance of the interaction term between $PM_{2.5}$ and umbilical artery PI using a likelihood ratio test, which showed no statistically significant interactions (interaction *P* values of 0.26 and 0.46 for associations with birth weight and SGA, respectively). Finally, we evaluated the proportion of our observed associations of $PM_{2.5}$ with birth weight and SGA that was mediated by the umbilical artery PI. We estimated that umbilical artery PI could explain 9.1% (95% CI: −0.5% to 35.4%) and 3.5% (−0.6% to 18.0%) of the associations of $PM_{2.5}$ with birth weight and SGA, respectively.

MULTIPOLLUTANT MODELS

Three Air Pollutants

For birth weight as the outcome, when we included NO_2, BC, and $PM_{2.5}$ as predictors in the same mixed effects model, we observed VIF values of 3.74, 2.43, and 2.71 for these exposures, respectively, which could indicate a potential multiple collinearity issue. We therefore applied alternative methods to assess their associations. As presented in **Figure 19**, all three methods indicated an association between NO_2 and birth weight (although the association in the Bayesian JAGS analysis was not statistically significant), whereas the associations for BC and $PM_{2.5}$ became inconclusive.

For SGA, we also observed indications of multiple collinearity, with VIF values of 3.97, 2.53, and 2.78 for NO_2, BC, and $PM_{2.5}$, respectively. When using the alternative methods, we generally observed some suggestions for a potentially slightly stronger association for $PM_{2.5}$ (**Figure 20**).

Disentangling Effects of TRAP and Noise on Fetal Growth

In models with one air pollutant and one indicator of noise exposure, the VIF values were not indicative of a high likelihood of multiple collinearity (**Figures 21–24** and *Appendices 31–59*). We therefore applied the mixed effect models that were used in our main analyses of TRAP and fetal growth association to develop our bipollutant models, including both TRAP and noise exposures.

Models including both modeled TRAP exposure (LUR models) in all microenvironments combined and modeled traffic-related noise levels (L_{den}) at home and the workplace showed that after controlling for the noise exposure, the inverse associations of exposure to NO_2, $PM_{2.5}$, and $PM_{2.5}$ Cu and Fe content with birth weight stayed statistically significant. Noise exposure was also inversely associated with birth weight, but none of its associations attained statistical significance (Figure 21). For SGA, while higher exposures to NO_2, BC, and $PM_{2.5}$ were associated with a statistically significant increased risk of SGA, the associations for the noise exposure were not statistically significant (*Appendix 31*). After further adjustment of these models for the noise sensitivity (n = 886 participants) or noise protection (i.e., using earplugs [n = 874 participants], closing window blinds [n = 875 participants], or closing windows, n = 878 participants]), we generally observed similar patterns in terms of direction and strength of associations (*Appendices 32–39*); however, associations of exposure to BC and $PM_{2.5}$ Fe content with birth weight and exposure to BC and NO_2 with SGA lost their statistical significance after further adjustment of models for using earplugs and closing window blinds or windows. Additionally, the association of $PM_{2.5}$ and SGA lost its statistical significance after further adjustment of the analysis for closing windows (*Appendix 39*). Moreover, in models further adjusted for noise sensitivity, the associations of exposure to $PM_{2.5}$ Fe content with birth weight (compared to those in Figure 21) and exposure to NO_2, BC, and $PM_{2.5}$ with SGA lost their statistical significance. On the other hand, the inverse association of modeled noise exposure and birth weight attained statistical significance in the joint models with $PM_{2.5}$ Zn content, after further adjustment for noise sensitivity, using earplugs, and closing window blinds or windows. Additionally, limiting the analyses to 999 participants who had modeled noise data for at least 75% of their pregnancy periods (*Appendices 40–41*), the pattern of associations was similar to the models including all participants; however, the association of BC with SGA lost its statistical significance.

In models including modeled TRAP at home (LUR models) and measured noise levels (L_{den}) at home in the subset of participants that had data on both exposures (n = 490), we generally observed inverse associations between birth weight and the exposure to TRAP and noise, with associations for $PM_{2.5}$ being statistically significant (Figure 22). For SGA, we found an increased risk of SGA associated with exposure to noise in models including $PM_{2.5}$ Cu or Fe content (*Appendix 42*). The results of these analyses after further adjustment of models for noise sensitivity and noise protection (i.e., using earplugs and closing window blinds or windows) were generally in line of the findings of the main analyses; however, the associations of noise exposure with SGA in models including $PM_{2.5}$ Cu or Fe content lost their statistical significance (*Appendices 43–50*).

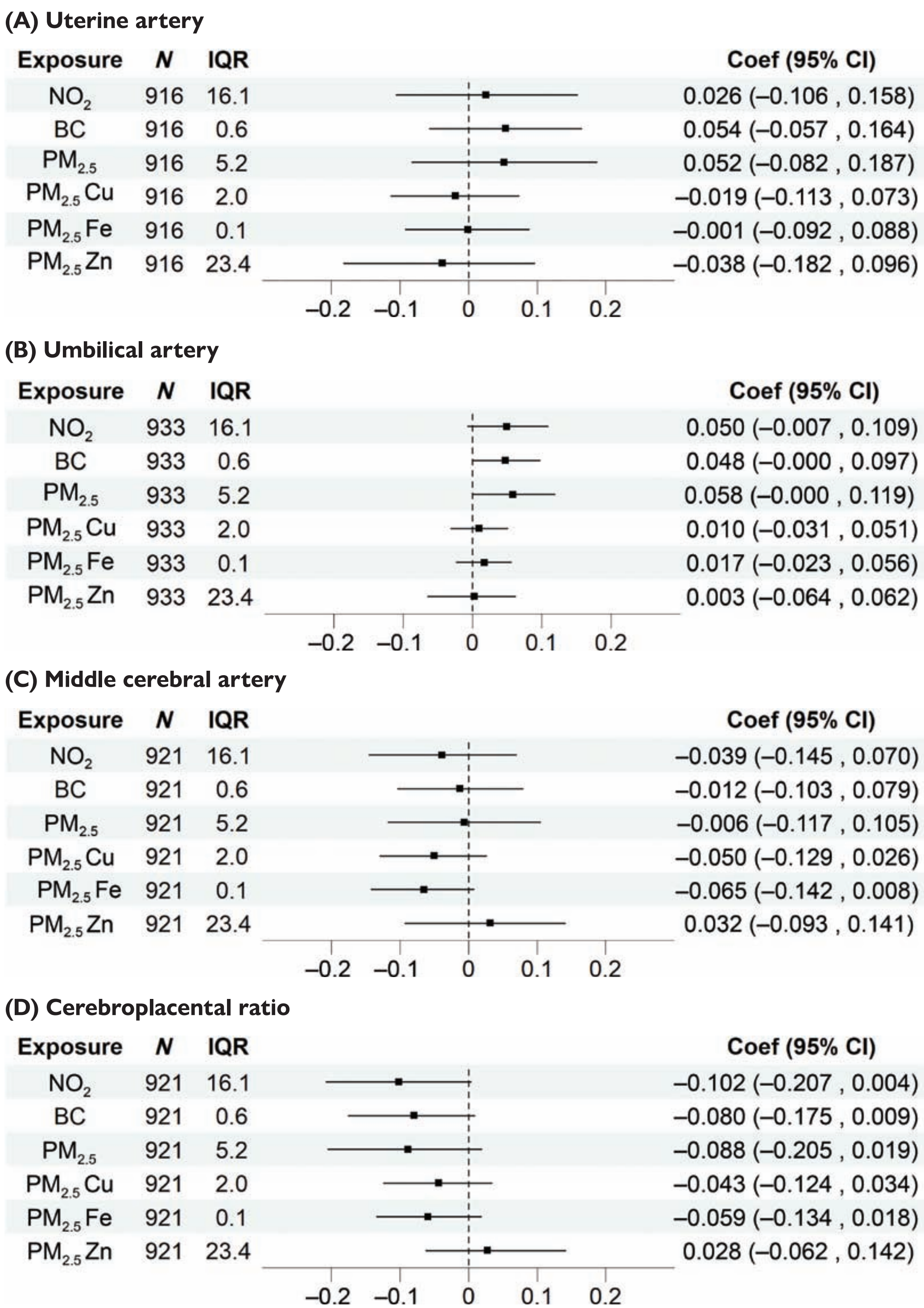

Figure 18. The adjusted change in pulsatility index associated with one IQR increase in exposure to NO_2 (μg/m³), BC (μg/m³), $PM_{2.5}$ (μg/m³), $PM_{2.5}$ Cu content (ng/m³), $PM_{2.5}$ Fe content (μg/m³), and $PM_{2.5}$ Zn content (ng/m³) between conception and the time of Doppler ultrasound examination, separately for the (A) uterine artery, (B) umbilical artery, (C) middle cerebral artery, and (D) cerebroplacental ratio. The change in pulsatility index is adjusted for maternal age (continuous, years), education level (categorical, university degree: yes/no), body mass index (BMI) at the first trimester (continuous, kg/m²), parity (categorical, nulliparous: yes/no), active smoking during pregnancy (categorical, yes/no), exposure to environmental tobacco smoke (categorical, yes/no), alcohol consumption during pregnancy (categorical, yes/no), history of low birth weight in previous pregnancies (categorical, yes/no), and sex of the neonate (girl vs. boy). BC = black carbon; CI = confidence interval; IQR = interquartile range.

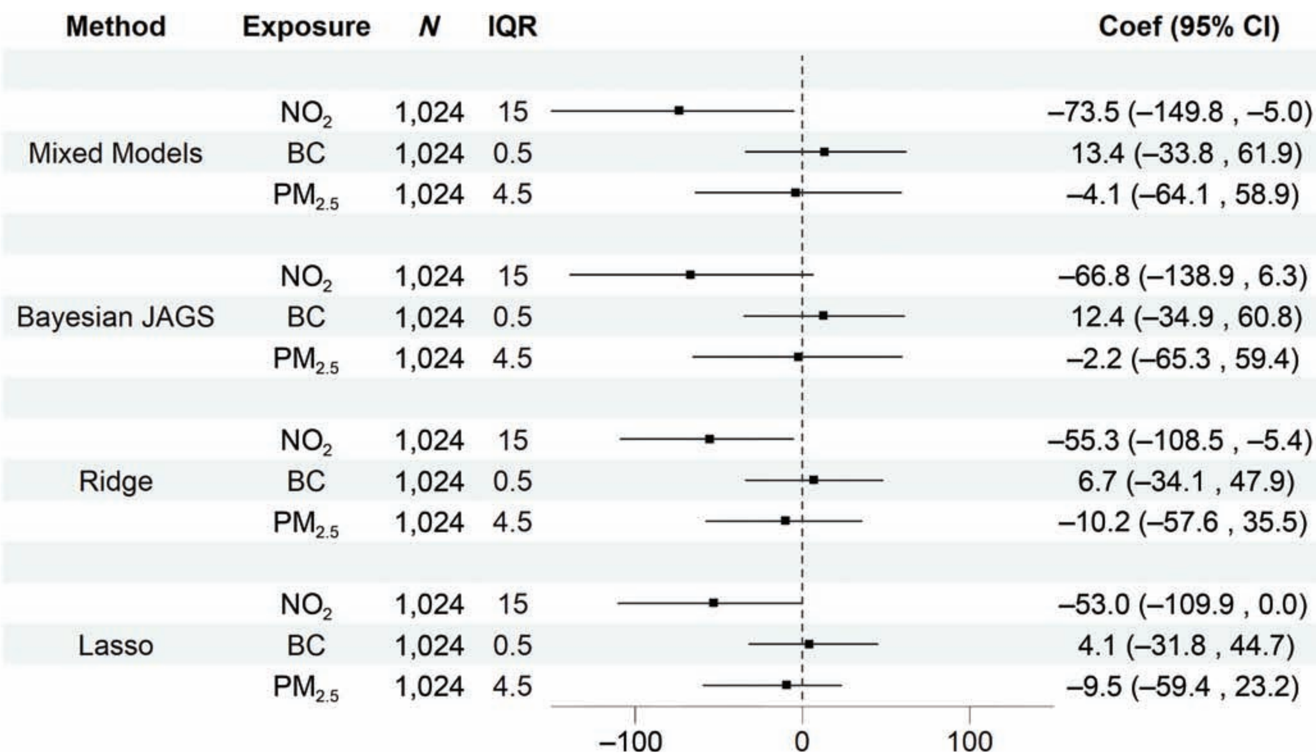

Figure 19. Adjusted change in birth weight (g) associated with one IQR increase in exposure to NO_2 (μg/m³), BC (μg/m³), and $PM_{2.5}$ (μg/m³) in the three-pollutant models. Change in birth weight is adjusted for maternal age (continuous, years), education level (categorical, university degree: yes/no), body mass index (BMI) at the first trimester (continuous, kg/m²), parity (categorical, nulliparous: yes/no), active smoking during pregnancy (categorical, yes/no), exposure to environmental tobacco smoke (categorical, yes/no), alcohol consumption during pregnancy (categorical, yes/no), gestational age at delivery (continuous, days), history of low birth weight in previous pregnancies (categorical, yes/no), and sex of the neonate (girl vs. boy). BC = black carbon; CI = confidence interval; IQR = interquartile range; mixed models = mixed effects models as used in the main analyses, but including all three air pollutants simultaneously for comparison; JAGS = Just Another Gibbs Sampler; ridge = Ridge regression model; Lasso = least absolute shrinkage and selection operator regression model. For NO_2 using the Lasso method, the upper CI <0 at 3 decimals.

Models including modeled TRAP at home (LUR models) and measured noise intermittency ratio at home (in the subset of participants that had data on both exposures [$n = 507$]) generally showed inverse associations for the exposure to air pollutants and noise with birth weight, where associations of NO_2 and $PM_{2.5}$ with birth weight were statistically significant (Figure 23). For SGA, none of the associations were statistically significant for the traffic-related air pollutants; however, there was a statistically significant increased risk of SGA associated with the noise intermittency ratio in the model that included BC (*Appendix 51*). The inverse association between $PM_{2.5}$ exposure and birth weight retained statistical significance after we further adjusted the models for noise sensitivity and noise protection (i.e., using earplugs, closing window blinds or windows) (*Appendices 52–55*). The rest of the associations between TRAP and noise intermittency ratio and birth weight were similar to those of the main analyses. The association of the noise intermittency ratio and SGA in models including BC lost its statistical significance after further adjustment of analyses for using earplugs or closing windows (*Appendices 56–59*). On the other hand, the association between the noise intermittency ratio and SGA gained statistical significance in the model including NO_2 after further adjustment for the noise sensitivity (*Appendix 56*).

Models including both modeled air pollutant exposure (LUR models) at home and noise annoyance due to traffic at home showed inverse associations for TRAP exposures and noise annoyance with birth weight, with statistically significant associations for exposure to all air pollutants besides $PM_{2.5}$ Zn content. Noise annoyance was also inversely associated with birth weight, but none of these associations were statistically significant (Figure 24). For SGA, higher exposures to NO_2, BC, and $PM_{2.5}$ were associated with a statistically significant increased risk of SGA; however, the associations for noise annoyance were not statistically significant (*Appendix 60*).

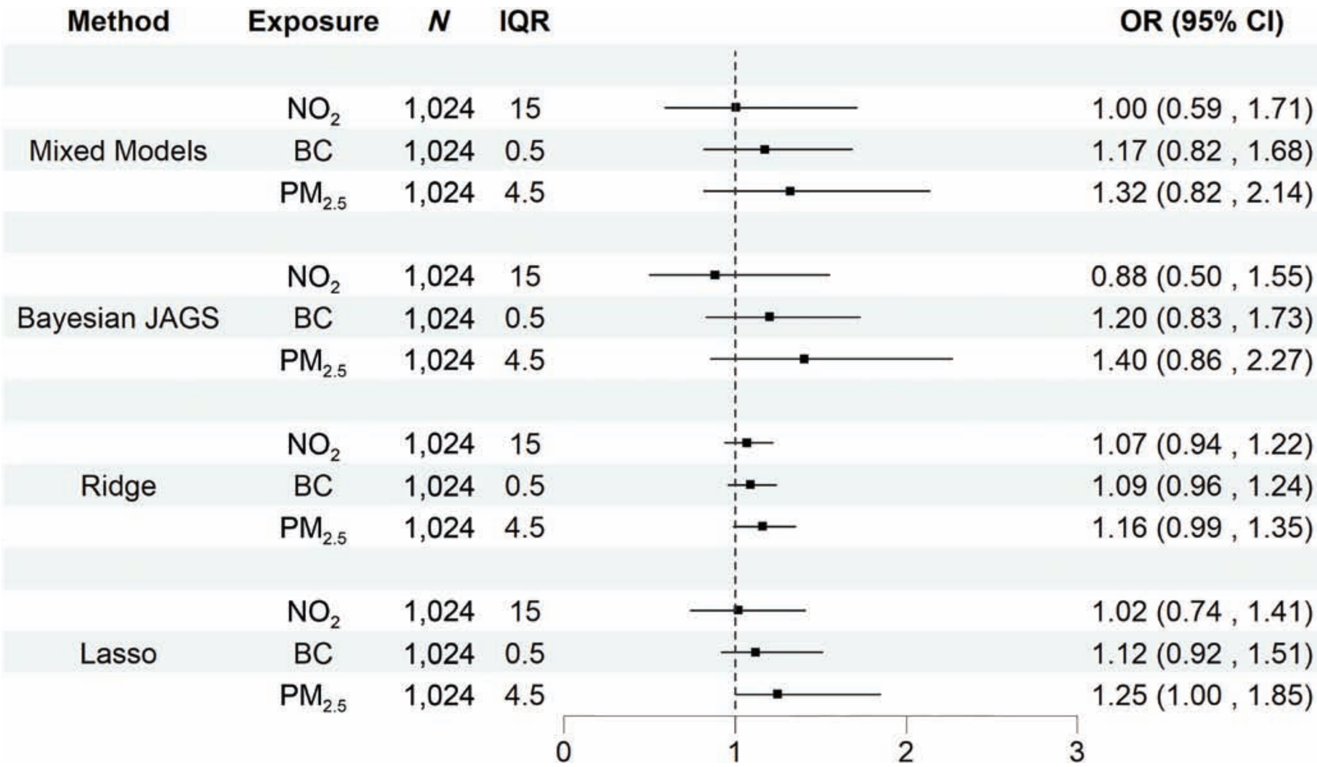

Figure 20. Adjusted OR of SGA associated with one IQR increase in exposure to NO_2 (μg/m³), BC (μg/m³), and $PM_{2.5}$ (μg/m³) in the three-pollutant models. The OR of SGA is adjusted for maternal age (continuous, years), education level (categorical, university degree: yes/no), body mass index (BMI) at the first trimester (continuous, kg/m²), parity (categorical, nulliparous: yes/no), active smoking during pregnancy (categorical, yes/no), exposure to environmental tobacco smoke (categorical, yes/no), alcohol consumption during pregnancy (categorical, yes/no), and history of low birth weight in previous pregnancies (categorical, yes/no). BC = black carbon; CI = confidence interval; IQR = interquartile range; JAGS = Just Another Gibbs Sampler; mixed models = mixed effects models as used in the main analyses, but including all three air pollutants simultaneously for comparison; OR = odds ratio; ridge = Ridge regression model; Lasso = least absolute shrinkage and selection operator regression model; SGA = small for gestational age.

DISCUSSION AND CONCLUSIONS

SUMMARY OF MAIN FINDINGS

We established a cohort of pregnant women in Barcelona, Spain (2018–2021), and comprehensively evaluated the association of maternal exposure to TRAP with fetal growth, identified the relevant windows of exposure for this association, evaluated its modification by household- and neighborhood-level SES, stress, physical activity, and the timing of conception and delivery in relation to the COVID-19 pandemic lockdown, disentangled the association of noise as a co-exposure, explored the role of placental function as an underlying mechanism, and evaluated the potential of urban green as a mitigating factor.

- We found that higher exposure to NO_2, BC, $PM_{2.5}$, and $PM_{2.5}$ Cu and Fe contents were generally associated with reduced birth weight, with statistically significant associations mainly observed for exposure at home and all microenvironments combined. For NO_2 and BC, we found statistically significant associations for exposure estimates by all models (dispersion, LUR, and hybrid models) in these two microenvironments. For $PM_{2.5}$ and its Cu and Fe contents, we observed statistically significant associations only for estimates made by LUR models.
- On the other hand, exposure to the $PM_{2.5}$ Zn content at the workplace was associated with an increased birth weight only when this exposure was estimated based on the hybrid model.
- In addition to the modeled TRAP, we also observed reduced birth weight in association with objective measurements of home-outdoor, home-indoor, and personal NO_2 exposure levels.
- We observed a similar pattern of associations for an inhaled dose of these pollutants as well as for SGA and trajectories of fetal growth, but with a lower number of statistically significant associations.

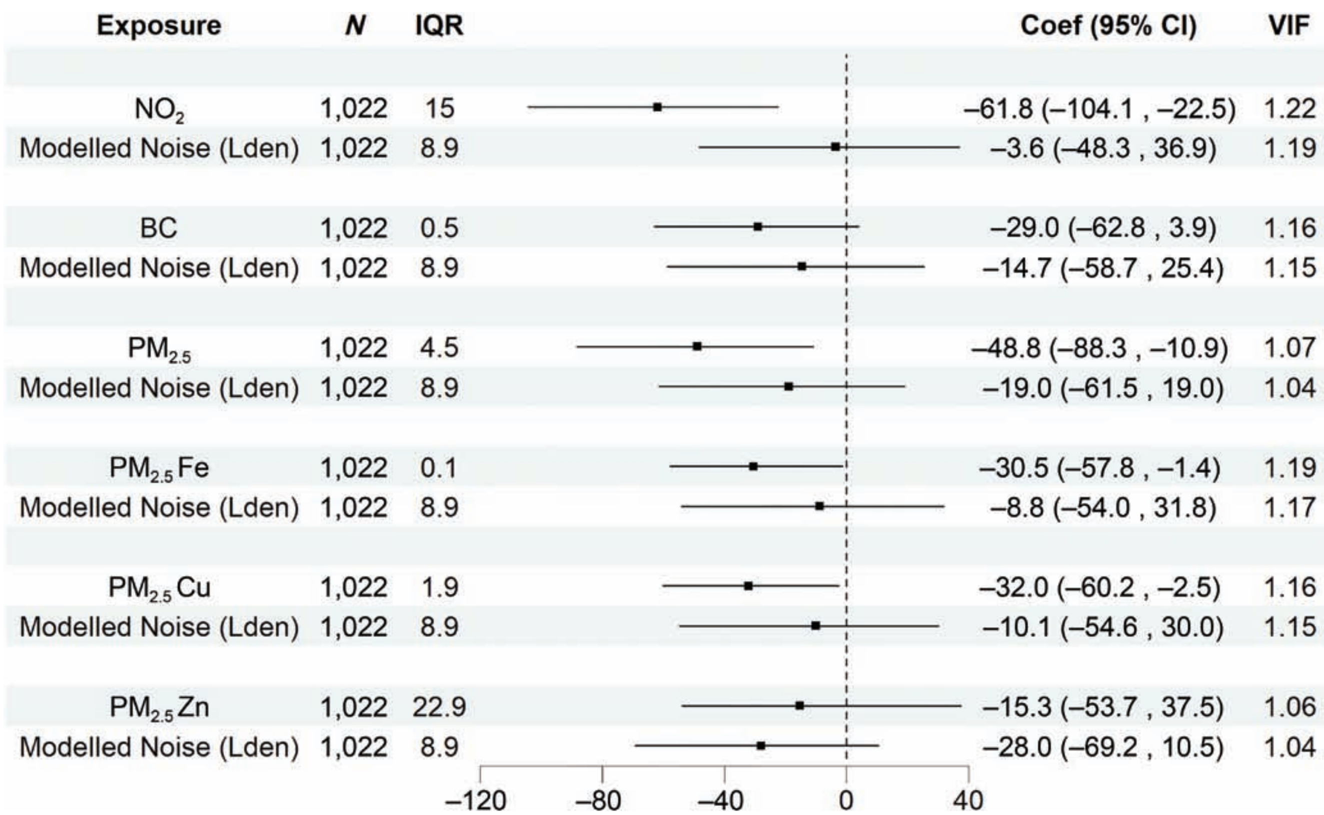

Figure 21. Adjusted change in birth weight (g) associated with one IQR increase in exposure to NO_2 (µg/m³), BC (µg/m³), $PM_{2.5}$ (µg/m³), $PM_{2.5}$ Cu content (ng/m³), $PM_{2.5}$ Fe content (µg/m³), $PM_{2.5}$ Zn content (ng/m³), and noise (L_{den}) in the two-pollutant models, including modeled air pollutants and modeled traffic-related noise levels (both at all microenvironments combined). Change in birth weight is adjusted for maternal age (continuous, years), education level (categorical, university degree: yes/no), body mass index (BMI) at the first trimester (continuous, kg/m²), parity (categorical, nulliparous: yes/no), active smoking during pregnancy (categorical, yes/no), exposure to environmental tobacco smoke (categorical, yes/no), alcohol consumption during pregnancy (categorical, yes/no), gestational age at delivery (continuous, days), history of low birth weight in previous pregnancies (categorical, yes/no), and sex of the neonate (girl vs. boy). BC = black carbon; CI = confidence interval; IQR = interquartile range; L_{den} = average noise levels for day+evening+night; VIF = variance inflation factor.

- All in all, in the single-pollutant models, we observed a consistent pattern of associations for the NO_2 exposures, which was in line with the findings of our multipollutant (i.e., NO_2, BC, and $PM_{2.5}$) models, which showed that NO_2 was the only air pollutant to remain statistically significantly associated with birth weight. However, for SGA, in the multipollutant models, none of the air pollutants showed a statistically significant association.
- When including one air pollutant and one noise exposure metric at a time, our multipollutant models revealed that the detrimental association of air pollutants with birth weight was generally present after controlling for the noise exposure. The results of these models with SGA as the outcome were less conclusive.
- We found suggestions for a potentially stronger association between TRAP and fetal growth for pregnant women with a university degree (i.e., higher household SES), those residing in neighborhoods with higher annual average household income, and those having higher hair cortisol levels (i.e., higher stress).
- We also observed a potentially stronger association between NO_2 exposure and fetal growth for those pregnancies that were entirely before the start of the pandemic; however, for BC and $PM_{2.5}$, we did not observe such a pattern.
- For physical activity as an effect modifier, and urban greenness and canopy cover as effect mitigators, we observed mixed patterns, depending on air pollutant, indicator of fetal growth, and the method or metrics used to characterize physical activity (i.e., objective vs. subjective methods) and urban green (i.e., greenness vs. canopy cover and surrounding home vs. surrounding nearby major roads).
- Similarly, we did not observe a clear variation in the associations by the timing of the pregnancy with regard to the COVID-19 pandemic; however, there were some

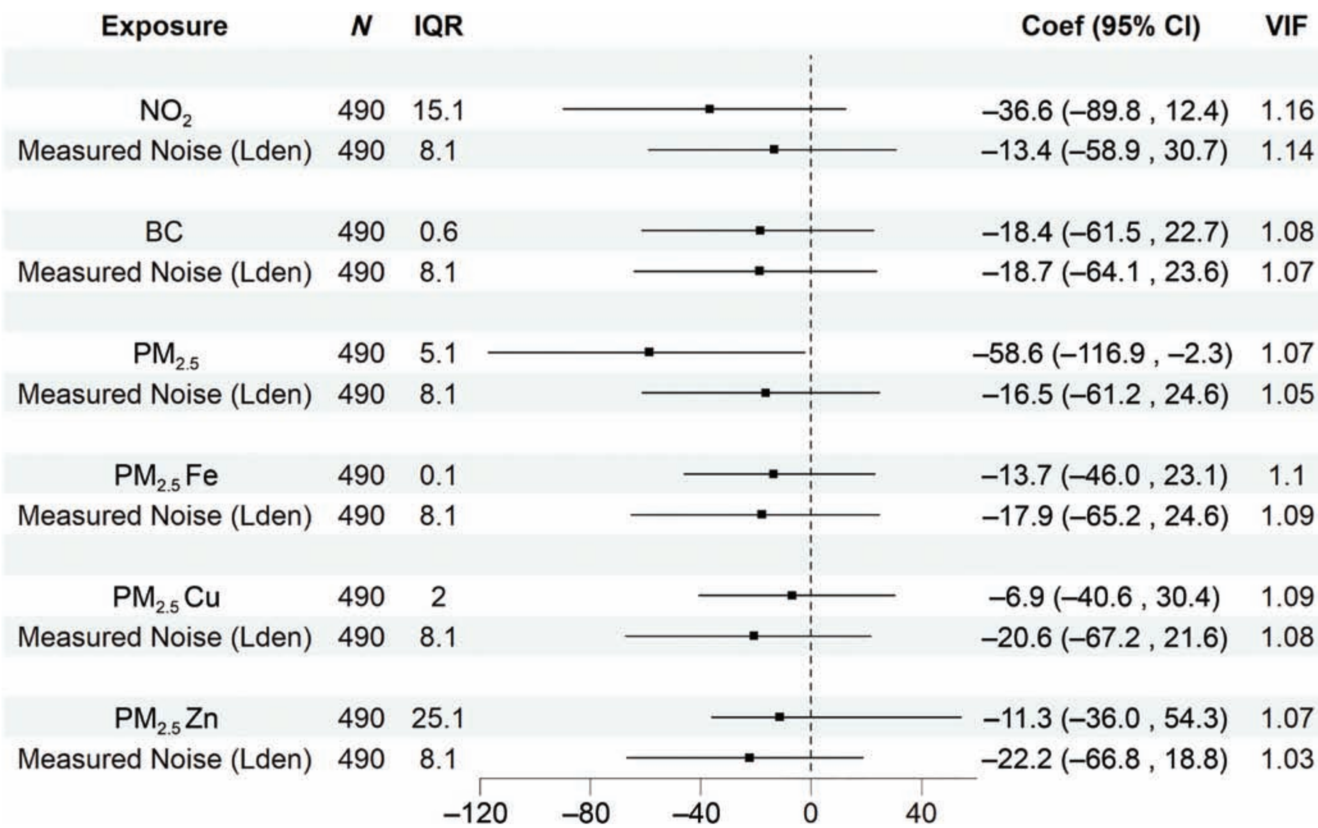

Figure 22. Adjusted change in birth weight (g) associated with one IQR increase in exposure to NO_2 (µg/m^3), BC (µg/m^3), $PM_{2.5}$ (µg/m^3), $PM_{2.5}$ Cu content (ng/m^3), $PM_{2.5}$ Fe content (µg/m^3), $PM_{2.5}$ Zn content (ng/m^3), and noise (L_{den}) in the two-pollutant models, including modeled air pollution and measured noise levels (both at home and outdoor). Change in birth weight is adjusted for maternal age (continuous, years), education level (categorical, university degree: yes/no), body mass index (BMI) at the first trimester (continuous, kg/m^2), parity (categorical, nulliparous: yes/no), active smoking during pregnancy (categorical, yes/no), exposure to environmental tobacco smoke (categorical, yes/no), alcohol consumption during pregnancy (categorical, yes/no), gestational age at delivery (continuous, days), history of low birth weight in previous pregnancies (categorical, yes/no), and sex of the neonate (girl vs. boy). BC = black carbon; CI = confidence interval; IQR = interquartile range; L_{den} = average noise levels for day+evening+night; VIF = variance inflation factor.

suggestions for potentially stronger associations of NO_2 and perhaps $PM_{2.5}$ exposure with fetal growth for those pregnancies that were entirely before the start of the pandemic.

- With regards to the windows of vulnerability, we found two potential windows: one at the end of the first and beginning of the second trimester, and one at the end of the third trimester, which were consistent for associations of different pollutants with both birth weight and SGA.
- Our mediation analyses suggested that just a tiny proportion of the association between TRAP and fetal growth could be explained by changes in the placenta's function.

OUR FINDINGS IN THE BROADER CONTEXT

Our measured home-indoor and personal levels of NO_2 were generally lower compared to those of our previous study in Barcelona (2008–2009).[92] That study included 65 pregnant women recruited from Hospital Clínic de Barcelona (one of the BiSC recruiting hospitals) in their second or third trimester.[92] We conducted campaigns of seven-day sampling of home-outdoor, home-indoor, and personal NO_2 levels (using passive NO_2 samplers) between November 2008 and October 2009. The average (SD) of the home-outdoor, home-indoor, and personal NO_2 levels were 36.5 (11.1) µg/m^3, 38.8 (17.0) µg/m^3, and 34.9 (12.3) µg/m^3, respectively. In comparison, these levels for our third trimester campaign were 37.1 (12.2) µg/m^3, 23.3 (8.9) µg/m^3, and 27.2 (9.6) µg/m^3, respectively. With respect to our modeled air pollution levels, we observed relatively higher estimated exposure levels by LUR models compared to dispersion models, with hybrid models' estimates being between these two levels. Given that hybrid models were essentially a combination of dispersion and LUR models, we could expect that their estimated levels fall within the range of levels estimated by dispersion and LUR models. Our observed higher estimated levels by LUR models

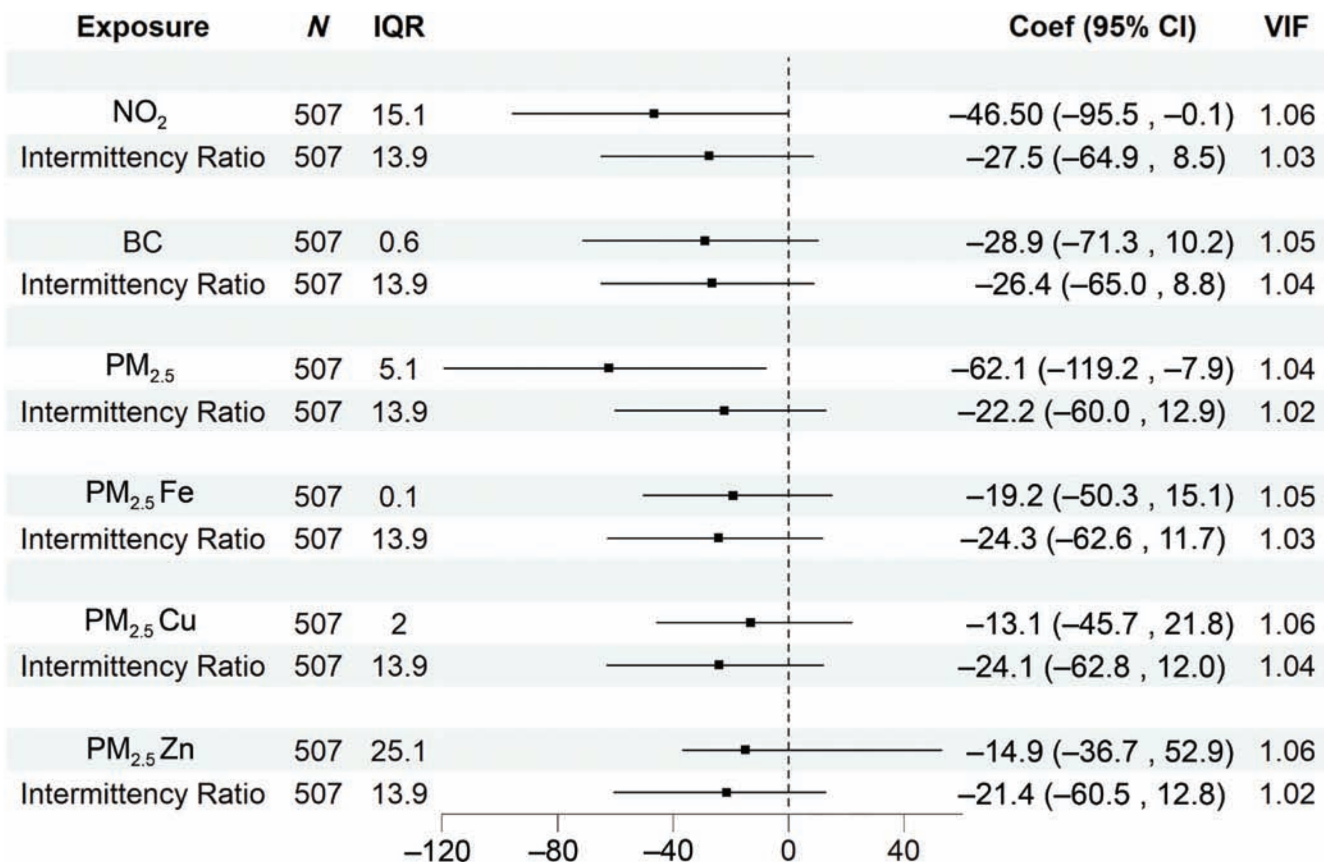

Figure 23. Adjusted change in birth weight (g) associated with one IQR increase in exposure to NO_2 (μg/m^3), BC (μg/m^3), $PM_{2.5}$ (μg/m^3), $PM_{2.5}$ Cu content (ng/m^3), $PM_{2.5}$ Fe content (μg/m^3), $PM_{2.5}$ Zn content (ng/m^3), and noise intermittency ratio in the two-pollutant models including modeled air pollution and measured noise intermittency ratio (both at home-outdoor). Change in birth weight is adjusted for maternal age (continuous, years), education level (categorical, university degree: yes/no), body mass index (BMI) at the first trimester (continuous, kg/m^2), parity (categorical, nulliparous: yes/no), active smoking during pregnancy (categorical, yes/no), exposure to environmental tobacco smoke (categorical, yes/no), alcohol consumption during pregnancy (categorical, yes/no), gestational age at delivery (continuous, days), history of low birth weight in previous pregnancies (categorical, yes/no), and sex of the neonate (girl vs. boy). BC = black carbon; CI = confidence interval; IQR = interquartile range; VIF = variance inflation factor.

compared to dispersion models were also observed in previous studies, including two comparing ESCAPE LUR models with dispersion models[93,94] and one comparing the ELAPSE (Effects of Low-level Air Pollution: A Study in Europe) project's hybrid LUR models with interpolation-dispersion models.[95] Differences in predicted exposure concentrations between LUR and dispersion models can be attributed to inherent distinctions in their methodologies.[30,96,97]

Our observed detrimental associations between exposure to TRAP and fetal growth are in line with the available evidence. A systematic review and meta-analysis by Boogaard and colleagues (2022) found a reduction in term birth weight associated with exposure to $PM_{2.5}$, NO_2, and elemental carbon; however, the combined estimate was statistically significant only for the $PM_{2.5}$ exposure (combined estimate of –17.3 g [95% CI: –33.2 to –1.5] per 5-μg/m^3 increase in $PM_{2.5}$, –3.2 g [–11.0 to 4.6] per 10-μg/m^3 increase in NO_2, and –2.6 g [–6.1 to 0.9] per 1-μg/m^3 increase in elemental carbon).[9] In comparison, we found a reduction in birth weight of –57.1 g (–97.4 to –18.5) per 5.1-μg/m^3 increase in exposure to $PM_{2.5}$, –60.0 g (–98.6 to –25.4) per 15.3-μg/m^3 increase in exposure NO_2, and –32.3 g (–63.0 to –3.0) per 0.6-μg/m^3 increase in exposure to BC at home (based on LUR models). Similarly, their meta-analyses showed an increased risk of SGA (combined relative risk of 1.09 [1.04–1.14]) associated with exposure to $PM_{2.5}$; however, the combined estimates for exposure to NO_2 (1.00 [0.98–1.02]) and elemental carbon (1.02 [0.92–1.14]) were not statistically significant. In comparison, we found odds ratios of 1.47 (1.09–1.99), 1.37 (1.05–1.79), and 1.28 (1.03–1.58) for home exposure to $PM_{2.5}$, NO_2, and BC, respectively. Our observed stronger associations could be due to contextual differences in the study setting between our study and the included studies in the meta-analyses, or methodological differences, such as a more refined exposure assessment in our study. We also found that higher exposures to NO_2, BC, $PM_{2.5}$, and $PM_{2.5}$ Cu and Fe contents were generally associated with a decelerated trajectory of fetal growth; however, the strength

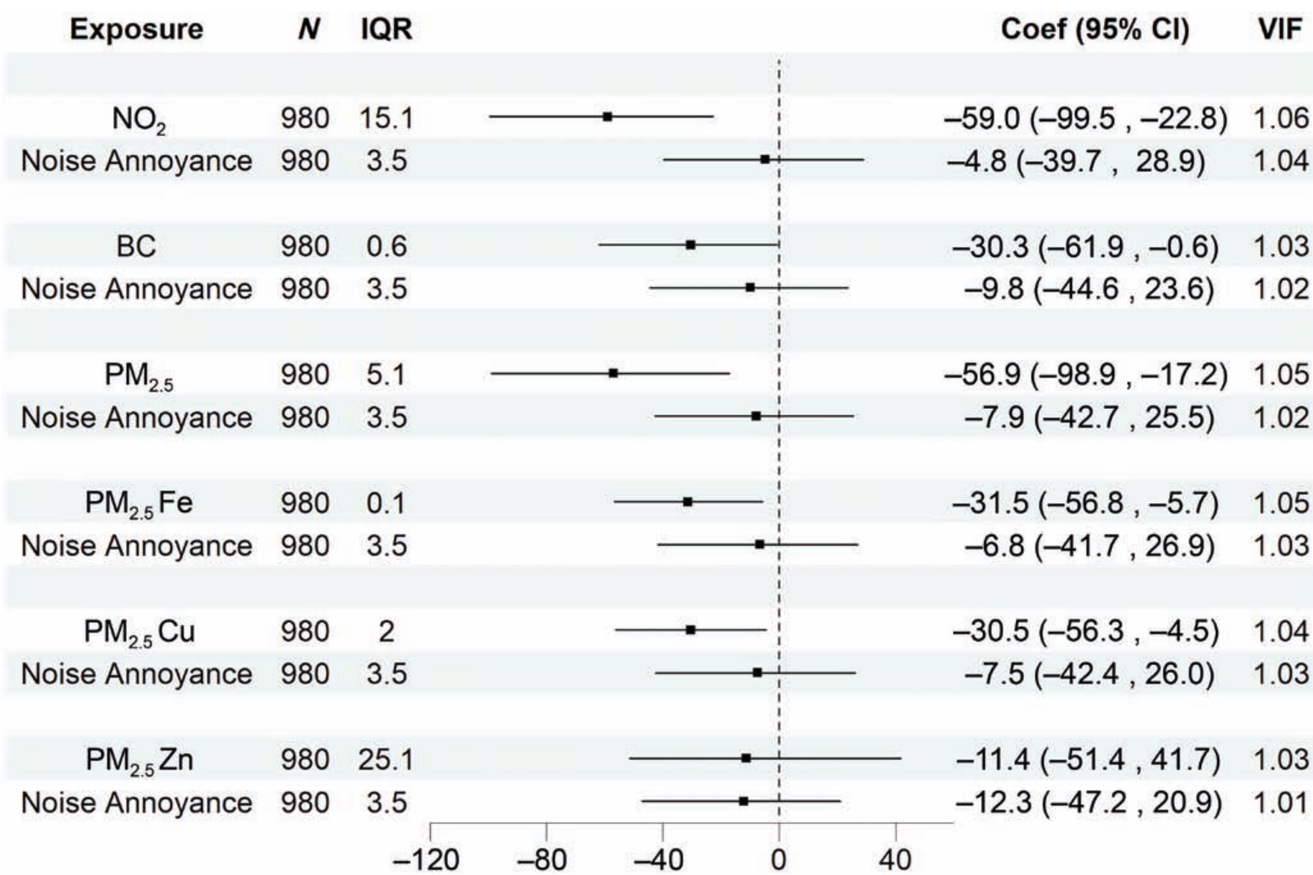

Figure 24. Adjusted change in birth weight (g) associated with one IQR increase in exposure to NO_2 (μg/m³), BC (μg/m³), $PM_{2.5}$ (μg/m³), $PM_{2.5}$ Cu content (ng/m³), $PM_{2.5}$ Fe content (μg/m³), and $PM_{2.5}$ Zn content (ng/m³) and traffic-related noise annoyance in the two-pollutant models, including modeled air pollution and noise annoyance (both at home). Change in birth weight is adjusted for maternal age (continuous, years), education level (categorical, university degree: yes/no), body mass index (BMI) at the first trimester (continuous, kg/m²), parity (categorical, nulliparous: yes/no), active smoking during pregnancy (categorical, yes/no), exposure to environmental tobacco smoke (categorical, yes/no), alcohol consumption during pregnancy (categorical, yes/no), gestational age at delivery (continuous, days), history of low birth weight in previous pregnancies (categorical, yes/no), and sex of the neonate (girl vs. boy). BC = black carbon; CI = confidence interval; IQR = interquartile range; VIF = variance inflation factor.

and statistical significance of the associations varied for different indicators of fetal growth, air pollutants, exposure modeling methods, and microenvironments. In our previous study (2004–2006) with a sample of 562 pregnant women in Sabadell, a city close to Barcelona, we observed that a higher exposure to NO_2 was associated with a decelerated growth of head circumference, abdominal circumference, biparietal diameter, and estimated fetal weight only among pregnant women who spent the majority of their time (>22 hours a day) at home.[98] Other studies have also associated maternal exposure to NO_2 and $PM_{2.5}$ with slower fetal growth, although these results are heterogeneous.[99–102]

In addition to NO_2 and BC, which could be considered as indicators of tailpipe emissions, we also evaluated the association with fetal growth of $PM_{2.5}$ Fe, Cu, and Zn contents, which could be considered as indicators of nontailpipe emissions. Our observed detrimental associations between $PM_{2.5}$ Fe, and Cu contents were in line with three previous studies reporting that these exposures were associated with decreased birth weight and increased risk of LBW.[103–105] Similarly, a large study including eight birth cohorts across Europe reported an inverse association between exposure to $PM_{2.5}$ Fe and Cu contents and head circumference; however, they did not find any statistically significant associations between these two exposures and birth weight or term LBW.[106] A large study in California reported an increased risk of term LBW in association with $PM_{2.5}$ reactive oxygen species based on measured $PM_{2.5}$ Cu and Fe contents combined.[107] In line with these findings, another large study in Atlanta reported a reduction in birth weight in association with the third-trimester exposure to $PM_{2.5}$ "water-soluble metal index," including $PM_{2.5}$ Cu, Fe, Cr, Mn, Ni, and V contents combined.[108] For exposure to $PM_{2.5}$ Zn content, we generally observed beneficial associations with fetal growth; however, the associations were statistically nonsignificant. While some of the previous studies have reported detrimental associations between this exposure and birth weight,[103,109] head circumference,[106] and higher risk of LBW,[109,110] others did not find any statistically significant association for birth weight[106] or term LBW.[103,105–107] A part of this inconsistency in the reported associations could be explained by the heterogeneity in the available evidence on the effect of Zn on fetal growth, as reported by a recent systematic review and meta-analysis of this evidence with regard to the association of Zn levels in biological samples of pregnant women and their fetuses with fetal growth.[111] Their meta-analyses showed that while maternal as well as cord blood Zn levels were beneficially associated with birth weight, their associations with SGA were not statistically significant.[111]

Apart from a few exceptions, we mainly observed statistically significant associations between TRAP exposure at home and all microenvironments combined. This observation could be, in part, explained by the fact that participants spent much of their time at home; therefore, they received a considerable part of their daily exposure at home. In this context, the findings for all microenvironments combined could also be influenced by the exposure at home, which contributed the most to this total exposure. For the exposure at the workplace and during commuting, we also observed mainly detrimental associations, which were not statistically significant. The lack of statistical significance for these associations could be because of the potentially larger exposure misclassification in these two microenvironments due to, for example, occupational sources of air pollution and the shorter exposure periods in these environments, and also because of the smaller sample size and hence lower statistical power of these analyses. All in all, while assessing exposure in microenvironments other than home by combining time–activity patterns with modeling approaches could potentially reduce exposure misclassification, our findings suggested that relying on exposure levels at only home could provide similar association estimates. This might indicate that future studies can apply home-outdoor levels for assessing air pollution exposure when data on time–activity patterns or the location of other relevant microenvironments and commuting routes are not available. For NO_2, we also observed that association estimates for home-outdoor levels (measured during two weeks in the entire pregnancy) were comparable with those of modeled home-outdoor and total exposure levels. These findings could suggest that, in the lack of enough resources or necessary infrastructure and data, where elaborate modeling approaches are not feasible, measuring home-outdoor NO_2 levels for a few weeks distributed across the pregnancy (e.g., one week during each trimester) can be considered as an alternative way to assess prenatal exposure to air pollution.

We are not aware of any previous study reporting on the association of the inhaled dose of TRAP with fetal growth. It is, therefore, not possible to compare our findings with those of previous studies. With regard to personal exposure to NO_2, a previous study included 288 Brazilian pregnant women who used passive samplers to measure personal NO_2 levels for 7–18 days during each trimester found no association between NO_2 exposure and birth weight.[18]

Our findings suggested a potentially stronger association between TRAP and fetal growth for pregnant women from higher SES groups in terms of maternal education and neighborhood average household income. In a systematic review of the available evidence on the potential modification of the impact of particulate air pollution on pregnancy outcomes, the authors found that while three studies had reported stronger associations with LBW and SGA for women with lower education, one study had reported a stronger association with LBW for women with higher education, and seven studies had not reported a notable difference in the associations with LBW and SGA across strata of maternal education.[112] For neighborhood SES, they found two studies reporting on the modification of the association between particulate air pollution and LBW, both of which suggested a stronger association for women residing in more deprived neighborhoods, in contrast with our findings.[112] We do not have a clear explanation for our observed pattern; however, it is worth mentioning that in Barcelona, neighborhoods with higher income tend to be in the center of the city and have higher levels of air pollution, including NO_2 and $PM_{2.5}$.[113]

To our knowledge, there is no available study on the modification of the TRAP and fetal growth association by physical activity, or by the COVID-19 pandemic. Our findings, therefore, require further confirmation by future studies. The association of physical activity with fetal growth is complex. While moderate physical activity during pregnancy has been reported to be associated with higher birth weight, vigorous physical activity has been associated with lower birth weight.[114] Another potential facet is that physical activity enhances uptake and deposition of air pollutants, possibly augmenting their harmful effects.[13,14] This complexity might explain, at least in part, the heterogeneous results that we observed in our stratified analyses for the physical activity. Similarly, the COVID-19 pandemic and its resulting changes in TRAP levels and maternal lifestyle (e.g., time–activity patterns, diet, and stress) could theoretically influence the association between TRAP and fetal growth.

Regarding maternal stress, while we found some indications of a potentially stronger association between TRAP and birth weight for those women with higher hair cortisol levels, for perceived stress (measured by the PSS-10), we did not observe such a pattern. Psychological stress has been suggested to be involved in vulnerability to the adverse health effects of air pollution;[11] however, there is no available epidemiological study on the modification of the association between TRAP and fetal growth by maternal cortisol levels. A recent study in the United States reported stronger associations of $PM_{2.5}$ and NO_2 exposure with reduced birth weight among women with higher perceived stress (measured by the PSS-10).[115] They also found a longer window of vulnerability for women with high perceived stress.[115] Although the hair cortisol level has been shown to increase in response to stressors, the correlation between hair cortisol and self-reports of perceived stress could be low, especially in moderately stressed individuals like our study participants.[116] Part of this low correlation could be explained by subjectivity issues due to differences among individuals and their perception of stress. On the other hand, the association between hair cortisol and stress is more evident when less subjective measures of stress, such as the number of stressful or negative life events, are used.[116] However, the substantial body of evidence based on self-reported validated questionnaires of perceived stress (e.g., PSS-10) supports the usefulness of such data. In this sense, mainly in studies of moderately stressed participants, perceived stress and hair cortisol levels may reveal complementary processes related to the pathology of stress.

For the potential mitigation of the association between TRAP and fetal growth by urban green, we observed a mixed pattern. In our previous study in Barcelona (2001–2005), we found some suggestions for a weaker association between residential proximity to major roads (i.e., living within 200 m of a major road) and term LBW when there was a higher number of trees around that road.[47] A study across the Alpine region in Austria and Italy did not find a clear pattern of the modification of the association between NO_2 exposure and birth weight by residential surrounding greenness measured as average NDVI.[117] Similarly, two other studies in the Greater Taipei Area,[118] Taiwan, and California[119] did not find any interaction between air pollution and greenness in association with fetal growth.

With respect to the window of vulnerability, a recent (2023) systematic review and meta-analysis of the available evidence on the association of $PM_{2.5}$ exposure with adverse pregnancy outcomes showed statistically significant combined associations between birth weight and $PM_{2.5}$ exposure during the entire pregnancy as well as the third trimester, and also between SGA and $PM_{2.5}$ exposure during the entire pregnancy as well as the second trimester.[120] These findings are in line with our findings indicating two windows of vulnerability: one at the end of the first and beginning of the second trimester, and another one at the end of the third trimester. Our identified first window corresponds to the latest stages of the formation of the placenta,[121] while the second window corresponds to the time when the highest fetal weight gain occurs.[122]

We found that higher exposure to $PM_{2.5}$ was associated with higher umbilical artery PI, which could indicate an increased fetoplacental vascular resistance.[123] Normally, umbilical artery PI decreases as pregnancy advances,[124] and a high umbilical artery PI in the second[125] and third[126] trimesters has been associated with impaired fetal growth, including reduced birth weight and higher risk of SGA. In this context, our mediation analysis showed that only 9% of our observed associations between $PM_{2.5}$ and birth weight could be explained by higher umbilical artery PI associated with these exposures. Our previous study (2017–2018), based on personal measurements of NO_2 exposure (using passive samplers) in a sample of 85 pregnant women in Barcelona, did not find a statistically significant association between NO_2 and umbilical artery PI, while it detected an association between this exposure and uterine artery PI.[19] A study in the Netherlands did not find any association between NO_2 exposure and umbilical artery PI or uterine artery PI; however, it found an association between PM_{10} exposure and umbilical artery PI.[17] Similarly, a study in Brazilian women did not detect any association between NO_2 exposure and umbilical artery PI, but it found an association between ozone exposure and umbilical artery PI.[18] On the other hand, a study[127] in China has shown an increased umbilical artery PI in association with $PM_{2.5}$ oxidative potential, which is in line with our observed direct association between $PM_{2.5}$ exposure and umbilical artery PI. They also found that 33% (95% CI: 9% to 87%) of their observed association between $PM_{2.5}$ oxidative potential and estimated fetal weight could be explained by the association between this exposure with the umbilical artery PI.[127] We are not aware of any previous studies on the association of BC or $PM_{2.5}$ Cu, Fe, or Zn content with placental function, or on the mediation of the association between our evaluated air pollutants and fetal growth by placental function.

Our multipollutant models, including modeled TRAP and noise exposure (in all microenvironments combined), together showed that while air pollutants (all but $PM_{2.5}$ Zn content) remained statistically significantly associated with birth weight, the associations for noise exposure were not statistically significant. In our previous study that included 6,438 pregnant women in Barcelona (2001–2005), we developed multipollutant models including TRAP ($PM_{2.5}$), noise (based on the strategic noise map of Barcelona), and heat (based on land surface temperature), and we found that while exposure to TRAP was associated with increased risk of term LBW, the associations for noise and heat were not statistically significant.[47] Similarly, a study in France found that in their two-pollutant models, while higher exposure to PM_{10} was associated with a higher risk of SGA, the association for the noise exposure was not statistically significant.[128] Likewise, a large study conducted in London, UK, found an increased risk of SGA associated with exposure to NO_2, $PM_{2.5}$, traffic exhaust-$PM_{2.5}$, and traffic nonexhaust-$PM_{2.5}$.[129] Further adjustment of their analyses for noise exposure did not result in a notable change in these findings. In line with these findings, a systematic review and meta-analysis of the evidence on the impact of noise exposure on pregnancy outcomes showed that there was no statistically significant association between noise exposure and birth weight or SGA, particularly after combining the analyses that were adjusted for air pollution.[130] These observations could indicate a more important impact of TRAP on fetal growth compared to noise; however, they could also be due to a potentially higher degree of exposure misclassification for the noise exposure, which is more challenging to characterize. In this context, after further adjustment of our analyses for noise sensitivity and noise protection (i.e., using earplugs, closing window blinds or windows), our results were generally in line with the main analyses.

LIMITATIONS

FRONTIER faced some limitations and challenges. BiSC participants had slightly higher educational attainment compared to the general population. While 69% of BiSC participants had a university degree, 64% of the Barcelona general population of 20–44-year-old women in Barcelona had a university degree in 2019. This difference could have slightly influenced the external validity of our findings. Moreover, the small number of LBW cases (n = 52) in the BiSC prevented us from analyzing LBW as one of our outcomes. Similarly, our stratified analyses had limited statistical power due to the relatively modest sample size in each stratum. With regards to our exposure assessment, while our dispersion models for NO_2 could predict 65% of the variation in monitored NO_2 levels during BiSCAPE campaigns, they could predict only 44% and 10% of our measured home-outdoor and personal NO_2 levels. In comparison, LUR models had an R^2 of 56% when predicting our measured home-outdoor NO_2 levels. The relatively low R^2 for dispersion models when predicting home-outdoor and particularly personal NO_2 levels could have resulted in exposure misclassification, which, in turn, could have influenced our association estimates. This misclassification could be an explanation for the relatively weaker associations that we observed for NO_2 exposure predicted by dispersion models compared to those of LUR and hybrid models. Furthermore, to measure home-indoor NO_2 levels, we had placed NO_2 passive samplers in the bedroom. However, the placement in the bedroom might not properly reflect actual personal exposure because NO_2 levels might be higher in the living room or cooking area in those homes that have gas cooking stoves. Moreover, for the exposure measurement error correction, we used the personal NO_2 exposure measurements as the gold standard; however, these measures were limited in that they were only assessed for a relatively short period and might not have been representative of the entire pregnancy. In our bipollutant models, including one that modeled TRAP exposure and noise pollution in all microenvironments combined, while each microenvironment had estimates for TRAP, the modeled noise levels were only recorded for the home and workplace, and thus the models did not include noise exposure during commuting. This discrepancy could have affected these bipollutant analyses. However, we also conducted other bipollutant TRAP and noise analyses, including three other measures of noise, and the results of all these analyses were generally consistent. Moreover, our multipollutant analyses did not account for potential nonlinear associations or interactions, which could have been relevant in our analyses. Finally, the COVID-19 pandemic imposed challenges on all aspects of our participant recruitment and data collection. It also forced us to change some of the data collection protocols. Even though these changes and the pandemic itself could have influenced our findings, our stratified analyses based on the timing of pregnancy during the pandemic did not show a consistent pattern of differences for different air pollutants and outcomes.

CONCLUDING REMARKS

In a cohort of 1,024 pregnant women in Barcelona, Spain (2018–2021), we found that higher maternal exposure to NO_2, BC, $PM_{2.5}$, and $PM_{2.5}$ Cu and Fe, particularly at home and all microenvironments (i.e., home, workplace, and commuting route) combined, was generally associated with lower birth weight, higher risk of SGA, and a decelerated trajectory of fetal growth, although some of these associations were not statistically significant. These associations appeared to be stronger for women with higher SES and those with higher objective measures of psychological stress. For the COVID-19 pandemic and physical activity, as effect modifiers, and urban greenness and canopy cover, as effect mitigators, we observed mixed patterns. In multipollutant models that included different measures of exposure to noise in addition to TRAP, the associations between TRAP and fetal outcomes remained consistent with those we observed in our main analyses. We found two potential windows of vulnerability for the association of TRAP with fetal growth: one at the end of the first trimester and the beginning of the second trimester, and another at the end of the third trimester. Finally, we observed that a tiny proportion of the associations between TRAP and fetal growth could be mediated through the impact of these air pollutants on fetoplacental hemodynamics (i.e., umbilical artery PI) as an indicator of placental function.

IMPLICATIONS OF FINDINGS

A recent systematic review and meta-analysis of the available evidence on the health effects of TRAP conducted by the *HEI Panel on the Health Effects of Long-Term Exposure to Traffic-Related Air Pollution*[9,73] concluded that the overall level of confidence for the association of TRAP with term LBW and SGA was moderate, and the association of TRAP with term birth weight was low. For individual associations, they assigned a (1) high level of confidence for the association of $PM_{2.5}$ with term birth weight, (2) moderate level of confidence for the association of NO_2 and SGA, (3) low level of confidence for the associations of NO_2 and elemental carbon (highly correlated with BC as both terms refer to the same pollutant, although the measurement technique differs) with term birth weight, and $PM_{2.5}$ with SGA, and (4) very low level of confidence for the association of elemental carbon and SGA. The panel identified a lack of adjustment for important covariates, including maternal BMI and smoking, as one of the main sources of the risk of bias in their evaluated studies.[73] In this context, FRONTIER controlled its analyses for these two factors together with a large array of other potentially important covariates. The panel also identified a lack of accounting for residential mobility during pregnancy as a common source of the risk of bias in the exposure assessment.[73] FRONTIER not only accounted for residential mobility in the assessment of exposure, but also improved exposure assessment on other aspects as well. To date, a vast majority of epidemiological studies of the impacts of TRAP on fetal growth have: (1) relied on assessment of exposure in only one microenvironment (mainly the home), overlooking the contribution of other microenvironments (e.g., workplace and commuting) to personal exposure; (2) not characterized and accounted for exposure misclassification; and (3) have relied on exposure levels (level of pollution to which the individual is exposed) instead of dose (level of pollution inhaled by the individual). FRONTIER developed an innovative framework integrating an objective characterization of time–activity patterns with three modeling approaches and personal and home-outdoor monitoring of TRAP, to personalize exposure to TRAP at main microenvironments (home, work, and commuting), and transform exposure levels in each microenvironment to inhaled dose. It also used personal exposure measures to characterize exposure misclassification and account for it in the analyses. This approach provided a full-chain perspective from transport and emissions to exposure to inhaled dose, which has important regulatory implications by enabling policymakers to implement finely targeted interventions. In this context, the evaluation of the associations for tailpipe and nontailpipe emissions, separating the impact of these pollutants from that of noise, identifying the more susceptible pregnancies and windows of vulnerability, and potential mitigation factors by FRONTIER, could help further fine-tune such interventions. Taken together, the vigorous evidence generated by FRONTIER could also support the inclusion of the impact of air pollution on fetal growth in the next estimations of the global burden of disease attributable to ambient air pollution.

DATA AVAILABILITY STATEMENT

FRONTIER welcomes external collaborations and provides gated access to its data. Data requests for analyses or grant applications should be submitted following the instructions available on the BiSC website.[131] BiSC Steering Committee will evaluate the requests, and in the case of the approval of the request, for data access, a data transfer agreement (DTA) will be signed with the applicant's institution. Further details about the process and the information for the contact person are presented on the BiSC website.[131]

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HEI QUALITY ASSURANCE STATEMENT

The conduct of this study was subjected to independent audits by RTI International staff members Dr. Linda Brown, Dr. David Wilson, and Mr. Ryan Chartier. These staff members are experienced in quality assurance (QA) oversight for air quality monitoring, modeling, and exposure assessment, epidemiological methods, and statistical modeling.

The QA oversight program consisted of a remote audit of the final report and the data processing steps. Key details of the dates of the audit and the reviews performed are listed below.

Audit: Final Remote Audit

Date: May 2025 – July 2025

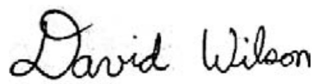
Remarks: The final remote audit consisted of two parts: (1) review of the final project report, and (2) audit of data processing steps. The review of the final report focused on ensuring that the methods are well documented and the report is easy to understand. The review also examined if the key study findings reported were supported by the data presented and if study limitations were discussed. The data audit included a review of the codes and a live virtual demonstration of data reduction, processing and analysis, and comparison of the generated data outputs with reported data. This portion of the audit was restricted to the key components of the study and associated findings. Selected codes for epidemiological model development of the impacts of TRAP on pregnancy outcomes were sent to RTI, but it was not possible for the audit team to review the underlying data due to data restrictions.

The codes were reviewed at RTI to verify, to the extent feasible, linkages between the various scripts, confirmation of model functionality, model documentation, and verification of reported model variables. Verification of key tables, figures, and data outputs was performed using data outputs generated by the study team during a virtual demonstration with the auditors. The codes and data outputs appear to be largely consistent with the models described in the report and follow the overall model development procedure described.

A few minor discrepancies between data outputs and the final report were noted, which were attributable to predictor variable naming consistency and did not impact study findings. No major quality-related issues were identified from the review of the codes, data outputs, and the final report. Recommendations were made to address noted discrepancies and typographical errors, and included general edits for improved clarity. Those recommendations were addressed in the final report.

A written report was provided to HEI. The QA oversight audit demonstrated that the study was conducted according to the study protocol. The final report appears to be representative of the study conducted.

Linda Morris Brown, MPH, DrPH, Epidemiologist, Quality Assurance Auditor



David Wilson, PhD, Statistician, Quality Assurance Auditor

Ryan Chartier, MS, Air Quality and Exposure Scientist, Quality Assurance Auditor

Date: July 23, 2025

APPENDICES AND ADDITIONAL MATERIALS ON THE HEI WEBSITE

Appendices 1–60 and Additional Materials 1–3 contain material not included in the main report. They are available on the *HEI website*.

ABOUT THE AUTHORS

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Maria Foraster, PhD, was an assistant research professor at the Barcelona Institute for Global Health (ISGlobal) in Barcelona, Spain. She coordinated the protocol and quality control as well as the data management of the project and collection, curation, and analyses of noise exposure. She is currently at RTI Health Solutions, Barcelona, Spain.

Gustavo Arévalo, PhD, is a senior technician at the Air Quality and Energy Efficiency Department at Barcelona Regional in Barcelona, Spain. He was involved in developing the dispersion models of air pollutants.

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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.

This report has not been reviewed by public or private party institutions, including those that support the Health Effects Institute, and may not reflect the views of these parties; thus, no endorsements by them should be inferred.

* 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

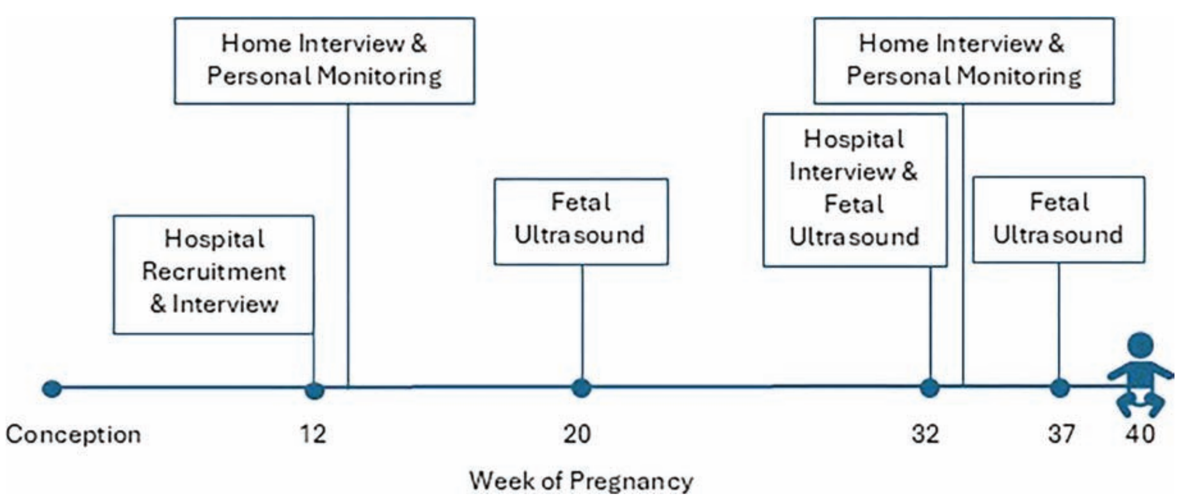
Maternal exposure to traffic-related air pollutants included assessment of black carbon (BC), nitrogen dioxide (NO_2), and fine particulate matter ($PM_{2.5}$), and its metal components of copper (Cu), iron (Fe), and zinc (Zn). Dadvand and Sunyer considered BC and NO_2 to be markers of tailpipe emissions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

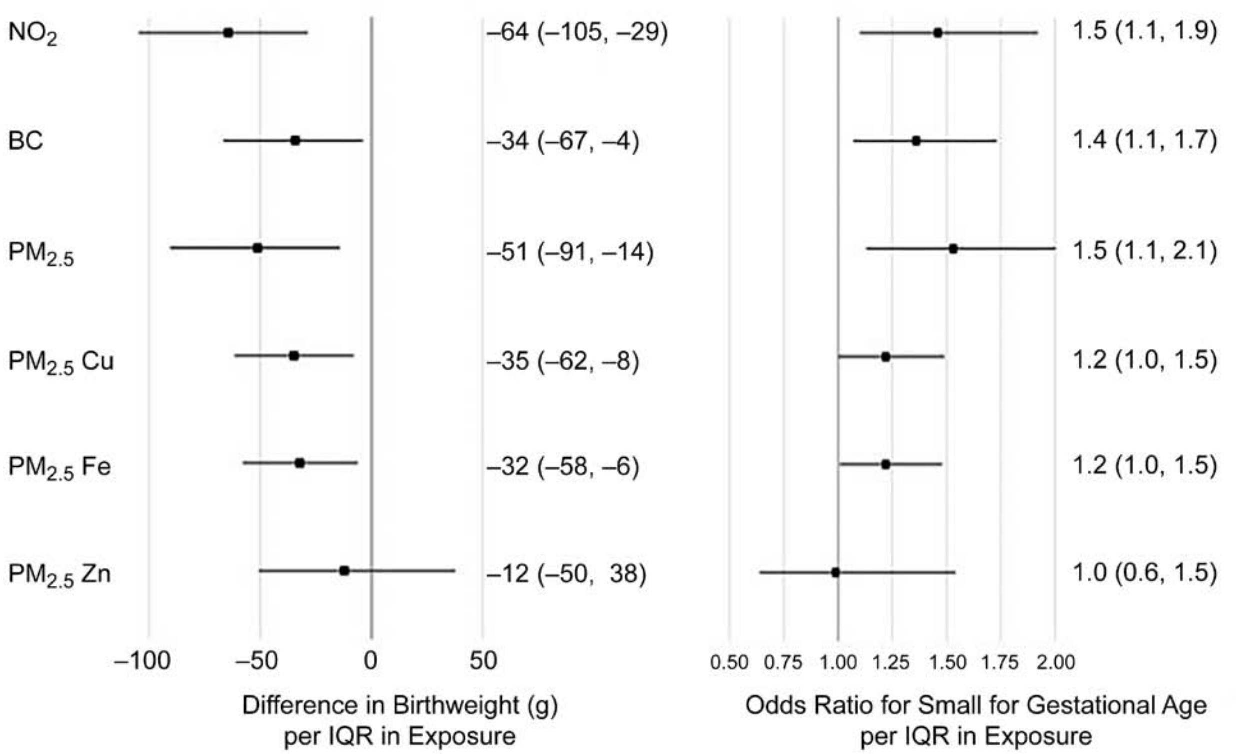
TRAFFIC-RELATED AIR POLLUTION RELATED TO RESTRICTED FETAL GROWTH

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.

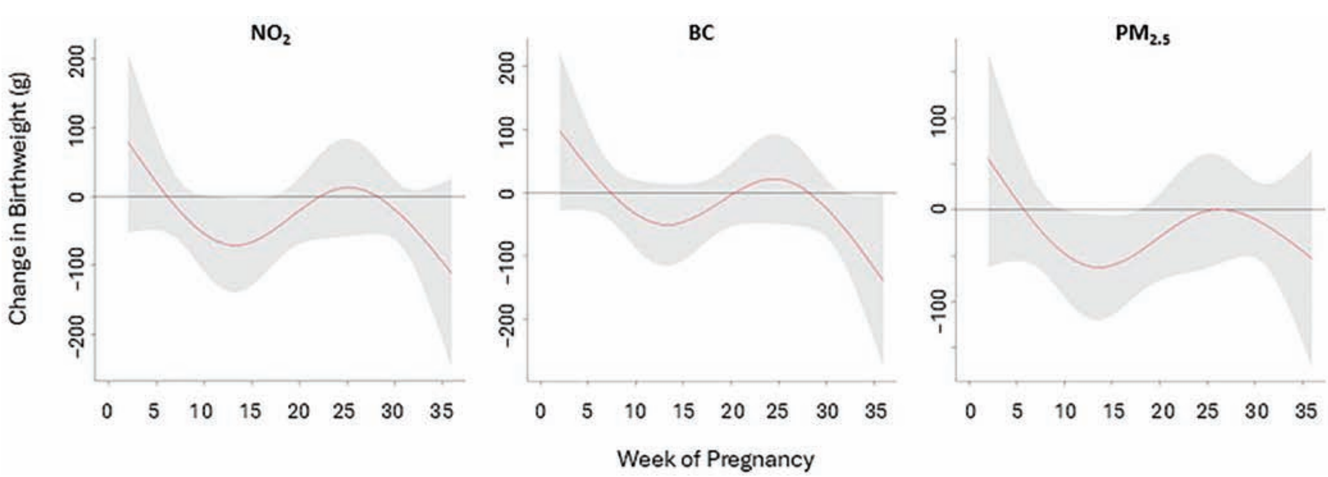
Multipollutant analyses that included NO_2, $PM_{2.5}$, and BC in the models suggested that NO_2 was associated with decreased birth weight, whereas the associations for $PM_{2.5}$ and BC were inconclusive. In contrast, the models suggested that $PM_{2.5}$ was associated with SGA, whereas NO_2 and BC 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) µg/m^3 for NO_2 and 17.1 (4.5) µg/m^3 for $PM_{2.5}$. For context, the EU one-year limit values are 40 µg/m^3 for NO_2 and 20 µg/m^3 for $PM_{2.5}$.[26] By 2030, the EU limit values will be lowered to 20 µg/m^3 for NO_2 and 10 µg/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 µg/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

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ABBREVIATIONS AND OTHER TERMS

BC	black carbon
BiSC	Barcelona Life Study Cohort
BiSCAPE	Barcelona Life Cohort Study Air Pollution Exposure
BMI	body mass index
CI	confidence interval
Cu	copper
dB(A)	A-weighted (human perceivable) decibels
DOHaD	Developmental Origins of Health and Diseases
ENMO	Euclidean norm minus one
ESCAPE	European Study of Cohorts for Air Pollution Effects
Fe	iron
GIS	Geographic Information System
$HClO_4$	perchloric acid
HF	hydrofluoric acid
HNO_3	nitric acid
IQR	interquartile range
JAGS	Just Another Gibbs Sampler
Lasso	least absolute shrinkage and selection operator regression model
LBW	low birth weight
L_{den}	average noise levels for day+evening+night
LR test	likelihood ratio test
LUR	land use regression
NDVI	Normalized Difference Vegetation Index
NO_2	nitrogen dioxide
OR	odds ratio
PI	pulsatility index
$PM_{2.5}$	particulate matter with an aerodynamic diameter <2.5 μm
PR	Palau Reial
PSS	perceived stress scale
RMSE	root mean square error
SES	socioeconomic status
SGA	small for gestational age
TRAP	traffic-related air pollution
VIF	variance inflation factor
Zn	zinc

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