Environmental Pollution 410 (2026) 129046

Contents lists available at ScienceDirect

Environmental Pollution

journal homepage: www.elsevier.com/locate/envpol

Maternal exposure to air pollution and fetoplacental Doppler markers during pregnancy

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ARTICLE INFO

Keywords:
Placenta
Fetoplacental hemodynamics
Air quality
Spatiotemporal modelling

ABSTRACT

Maternal exposure to air pollution has been associated with a wide range of adverse perinatal outcomes; however, the evidence on its influence on the placenta has remained limited. We studied the association of maternal exposure to air pollution with fetoplacental Doppler markers in a cohort of pregnant women recruited in three tertiary hospitals and their primary care centers in Barcelona, Spain (2018- 2021). Maternal exposure to nitrogen dioxide (NO_2), black carbon (BC), and particulate matter <2.5 μm ($PM_{2.5}$) was assessed at home, workplace, commuting route, and all these microenvironments combined using different modelling techniques: land use regression (LUR), dispersion (DM), and Hybrid LUR-DM (HM) models. Doppler examination of the Uterine artery (UtA) mean pulsatility index (PI) was assessed in the first, second, and third trimester of pregnancy, while the umbilical artery (UA) PI, middle cerebral artery (MCA) PI, and cerebroplacental ratio (CPR) were examined in the third trimester. Mixed effects linear regression models with recruiting hospital as the random effect were used to estimate associations, controlled for relevant covariates. Higher maternal exposure to NO_2 and BC was consistently associated with increased UtA mean PI, particularly for home and total exposure estimates by all three exposure models, while $PM_{2.5}$ showed similar associations in some exposure models (DM). We also

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https://doi.org/10.1016/j.envpol.2026.129046
Received 17 April 2026; Received in revised form 7 August 2026; Accepted 25 August 2026
Available online 2 September 2026
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observed a significant association between home NO_2 exposure and lower CPR, suggesting subtle fetal hemodynamic adaptation to impaired placental function. Overall, our findings provide evidence that maternal exposure to ambient air pollution may adversely affect uteroplacental vascular function. Further prospective studies are needed to confirm these associations and assess their clinical relevance for maternal and fetal outcomes.

1. Introduction

Normal placental development is critical for securing proper fetal growth and development; hence, any factor that interferes with this process in early stages of placentation or its function later in pregnancy may increase the risk of placental-related complications. Maternal exposure to air pollution has been associated with an increased risk of pregnancy complications and adverse outcomes such as pregnancy-induced hypertensive disorders, low birth weight (LBW), and small for gestational age (Bai et al., 2018; L. Q. Guo et al., 2019; Song et al., 2023; Wang et al., 2018). A limited number of previous studies have investigated the association of air pollutants and placental function markers (Cahuana-Bartra et al., 2022; Carvalho et al., 2016; Contreras et al., 2018; Hettfleisch et al., 2017; Ouidir et al., 2021; van den Hooven et al., 2012), suggesting a potential pathway through which air pollution could contribute to the adverse perinatal outcomes. However, the majority of these studies have relied on exposure assessed at residential address, overlooking the exposure that occurs in other microenvironments, like the workplace or during commuting periods, or have based on short-term exposure, which may lead to small associations, failing to capture the effects of long-term exposure.

Doppler ultrasound is a valuable non-invasive tool for assessing fetoplacental circulation (Alfirevic et al., 2017; Enakpene et al., 2023; O'Gorman et al., 2016; Vollgraff Heidweiller-Schreurs et al., 2018), with the pulsatility index (PI) being the most commonly used Doppler index to evaluate vascular flow resistance. This study aimed to investigate the association of maternal air pollution exposure with fetoplacental Doppler markers during pregnancy, applying three exposure modelling approaches to assess the exposures occurring in relevant microenvironments for pregnant women (home, workplace, and commuting), and Doppler examinations of fetoplacental circulation.

2. Materials and methods

2.1. Study population and setting

This study was conducted in the context of the Barcelona Life Study Cohort (BiSC), a prospective birth cohort of 1080 pregnant women recruited between October 2018 and April 2021, in Barcelona, Spain. A detailed description of the cohort has been provided elsewhere (Dadvand et al., 2024). Briefly, pregnant women were recruited at their first routine hospital visit (around week 12 of gestation) at three main tertiary university hospitals: Hospital Sant Joan de Déu, Hospital de la Santa Creu i Sant Pau, and Hospital Clínic de Barcelona, and their corresponding primary healthcare centers. BiSC included pregnant women between 18 and 45 years old with 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/Catalan. Women carrying out multiple pregnancy or fetus with congenital or chromosomal abnormalities were excluded. Information about socio-demographic characteristics was obtained through face-to-face interviews and questionnaires provided at enrolment. Maternal medical history and previous and current obstetrical history were also collected through questionnaires and hospital records. Gestational age was calculated by crown-rump length (CRL) at the first-trimester ultrasound (Robinson and Fleming, 1975).

Ethics approvals were obtained from the corresponding authorities in all the participating institutions and hospitals including Clinical Research Ethics Committee of the Parc de Salut Mar (2018/8050/I), 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 Ethics Committee of the Fundació Sant Joan de Déu (PIC-27–18). All participants received detailed information about the study from one of the BiSC nurses before providing written informed consent to participate.

2.2. Air pollution exposure assessment

We evaluated the exposure to nitrogen dioxide (NO_2), black carbon (BC), and particulate matter with an aerodynamic diameter <2.5 μm ($PM_{2.5}$). The exposure assessment has been previously described in detail (Domínguez et al., 2024). In brief, we developed three types of models, namely land use regression models (LUR), dispersion models (DM), and hybrid models (HM), to predict the exposure in three relevant microenvironments for pregnant women (i.e., home, workplace, and commuting route between these two) and then combined these microenvironmental levels (i.e., total). LUR models were developed using data from four BiSCAPE monitoring campaigns at 34 representative locations across the BiSC study area following the ESCAPE (European Study of Cohorts for Air pollution Effect) guidelines (Beelen et al., 2013; Beelen R, 2010; Eeftens et al., 2012). The DM were built applying the ADMS-Urban software (Cambridge Environmental Research Consultants, UK), which is based on a Gaussian dispersion model incorporating photochemical reactions, street canyon effects, and a meteorological pre-processing module (CERC, 2025); McHugh et al., 1997). For the HM, we applied Random Forest algorithms (Breiman, 2001) to combine LUR predictors, DM estimates, routine air pollution monitoring data, and meteorological variables to estimate air pollutant levels. Indicators of model performance are presented in Supplementary Tables 1 and 2

We abstracted weekly average pollutants levels during the entire pregnancy at home, workplace, and commuting routes (except for the HM, which lacked the temporal resolution necessary to estimate commuting exposures). Total exposure was computed as the average of air pollutant levels at the microenvironments weighted by the time that the participant spent in each of them. For those participants who started their maternity leave before delivery (mean 36 ± SD 7.6 weeks of gestation), we included all three microenvironmental exposures in the calculation of the total exposure, and from the starting date of maternity leave, we only included exposure at residential address. The time-activity patterns were derived from a validated smartphone-based geolocation application (ExpoApp, Ateknea Solutions, Barcelona, Spain) (Donaire-Gonzalez et al., 2019) and face-to-face interviews (Supplementary Appendix 1).

2.3. Fetoplacental circulation assessment

Doppler ultrasound examinations were performed by four trained obstetricians strictly following the techniques and device settings establish by the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) guidelines ("ISUOG practice guidelines: Use of Doppler ultrasonography in obstetrics," 2013) to minimize the inter-rater variability, and using GE Voluson E6 or E8 expert (GE Healthcare, London, United Kingdom), and Phillips Affiniti 50 or Phillips EPIQ 7 (Philips, Amsterdam, the Netherlands), equipped with multifrequency transabdominal probes. Pulsatility indices (PIs) of the uterine arteries (UtAs) were obtained at the first and second trimester

routine pregnancy visits, and also at the BiSC-organized third-trimester visit (around 12, 20, and 32 weeks of gestation, respectively). The PI of the left and right UtAs were averaged to obtain the UtA mean PI. The umbilical artery (UA) PI, middle cerebral artery (MCA) PI, and cerebroplacental ratio (CPR) were assessed only in the third trimester during the BiSC-organized visit. The mean gestational age (GA) (in weeks) at the Doppler ultrasound examinations was 12.5 (±0.6), 20.3 (±0.7), and 31.3 (±1.1) for each trimester visit, respectively.

In the first trimester, uterine artery PI was obtained transabdominally by a midsagittal section of the uterus at the level of the cervical canal, then the probe was moved laterally, and the uterine artery was identified by Color Doppler at the level of the internal cervical os (Gómez et al., 2008; "ISUOG practice guidelines: Use of Doppler ultrasonography in obstetrics," 2013). Measurements by pulsed Doppler were taken at this point. From the second trimester onwards, the probe was placed on the lower quadrant of the abdomen on the right and left sides, angled medially, and color Doppler was used to identify the UtA at the apparent crossover with the external iliac artery. Measurements by pulsed Doppler were taken approximately 1 cm distal to the crossover point, with an angle of less than 30° (Gómez et al., 2008; "ISUOG practice guidelines: Use of Doppler ultrasonography in obstetrics," 2013). Umbilical artery PI was measured from a free-floating cord loop. The MCA PI was obtained at the proximal part of the circle of Willis in a transverse view of the fetal head, including the thalami and the sphenoid bone wings. In both cases, measurements were averaged from three consecutive waveforms, obtained in the absence of fetal breathing and movements, and with the angle of insonation as close to 0° as possible ("ISUOG practice guidelines: Use of Doppler ultrasonography in obstetrics," 2013). The cerebroplacental ratio was calculated between the MCA PI and UA PI.

2.4. Data analysis

We applied mixed effects linear regression models to estimate the association of air pollutant levels with placental function markers. The models were adjusted for an *a priori* set of covariates, including gestational age at ultrasound examination, maternal age at conception, body mass index (BMI) at the first trimester, parity, educational level, active smoking, and alcohol consumption during pregnancy.

First, we performed a main analysis to estimate the association of each pollutant and each fetoplacental Doppler marker (main outcomes). In the case of UtA, the estimate considered the measurements obtained at 12, 20, and 32 weeks of gestation. The analyses were conducted separately for NO_2, BC and $PM_{2.5}$ estimates made by LUR, DM and Hybrid models, and also separately for each microenvironment (home, workplace, and commuting routes), as well as all microenvironments combined (i.e., total). The pollutant's average levels were estimated from conception until the outcome's measurement. The hospital was considered as a random effect, in order to account for between-hospital variation in outcome measures and other potentially relevant unmeasured covariates; and in the case of UtA mean PI, we also used participant as another random effect to take account of repeated measurements for each participant.

Second, we conducted a further analysis in which we explored possible susceptibility windows by assessing the effects of average air pollutant levels during the first (from conception until week 12) and second trimesters (from week 13 to week 28) with fetoplacental Doppler markers measured in the third trimester.

To enable comparison of estimated associations across different pollutants, modelling approaches, and microenvironments, we reported the association estimates for one interquartile range (IQR) increase in exposure. To minimize bias, we imputed missing covariate data (all <4% of missing), applying Multiple Imputations (White et al., 2011) using *mice* R package (Buuren and Groothuis-Oudshoorn, 2011). All statistical analyses were performed using R version 4.4.1. The results with *p*-values <0.05 were considered statistically significant.

2.4.1. Sensitivity analysis

We further adjusted our analyses for ethnicity, type of conception, maternal blood pressure (systolic and diastolic) at the visit, personal history of preeclampsia, history of LBW (<2500gr at birth) in previous pregnancies, fetal sex, aspirin intake during pregnancy, chronic hypertension, and other co-morbidities (i.e., chronic kidney disease, pregestational diabetes, antiphospholipid syndrome, and systemic lupus erythematosus), passive smoking, season of conception, year of the visit, neighborhood-level socioeconomic status (i.e. census-tract average household income), and noise exposure. Outdoor noise levels (L_{den}) at home and workplace were abstracted using Strategic Noise Maps across BiSC areas developed under EU Directive 2002/49/EC for the period 2017–2022 (Ministry for Ecological Transition and the Demographic Challenge, 2021). Adjustment for maternal blood pressure in the analyses of UtA mean PI was done only for the first and third trimester measurements, due to a lack of data for the second trimester. For the rest of the outcomes, the analyses were adjusted for the blood pressure at the time of the third-trimester visit when those outcomes were measured. Moreover, we performed a sensitivity analysis using hospital as a fixed effect. We also conducted a complete case analysis by removing participants with missing covariate data from analyses (i.e., not using imputed data), and we repeated the analysis after excluding participants with pregnancy-induced hypertensive disorders (i.e., preeclampsia, eclampsia, and HELLP syndrome) during their current pregnancy. Given the relatively large number of comparisons, we applied Nyholt method (Nyholt, 2004) to adjust our *p*-values based on the effective number of comparisons. Lastly, we developed bi-pollutant models to explore the associations between them and the main outcomes.

3. Results

3.1. Maternal characteristics and air pollution exposure

Of 1080 pregnant women initially recruited in the BiSC, 1039 had data on air pollution exposure and fetoplacental Doppler markers and were included in this study. There was no statistically significant difference in sociodemographic, lifestyle, and clinical characteristics of the BiSC participants included and excluded in the current study (Table 1). The mothers' average age was 34 years, most of them were European (67.9%), with a university degree (69.3%), and non-smokers (92%).

The estimated exposure levels of NO_2, BC, and $PM_{2.5}$ until the third trimester visit by the different models (mean, IQR) are presented in Supplementary Table 3. Correlations between air pollutants levels for BiSC participants in the third trimester (n = 944) for each exposure model and in each microenvironment and all microenvironments combined (i.e., total) are presented in Supplementary Fig. 1. Table 2 presents the number of Doppler examinations performed and the mean ± SD values for the pulsatility indices and cerebroplacental ratio.

3.2. Main analyses

The cross-sectional associations between each pollutant and the UtA mean PI at around 12, 20, and 32 weeks of gestation are presented in Fig. 1. NO_2 total exposure was statistically significantly positively associated with an increase in the UtA mean PI across the three models assessed (LUR: β = 0.04; 95% confidence intervals (CI): 0.01, 0.06, DM: β = 0.03; 95% CI: 0.01, 0.06, HM: β = 0.03; 95% CI: 0.01, 0.06) (Fig. 1A). We also found statistically significant associations for NO_2 at home assessed by LUR and Hybrid models with UtA mean PI (LUR: β = 0.03; 95% CI: 0.01, 0.06, HM: β = 0.03; 95% CI: 0.01, 0.06). For BC, total exposure levels showed a statistically significant association with UtA mean PI across the three exposure models (LUR: β = 0.03; 95% CI: 0.00, 0.05, DM: β = 0.04; 95% CI: 0.02, 0.06, HM: β = 0.03; 95% CI: 0.01, 0.05) (Fig. 1B). We also observed a statistically significant increase in UtA mean PI associated with BC exposure at home across the three models (LUR: β = 0.02; 95% CI: 0.00, 0.04, DM: β = 0.02; 95% CI: 0.00,

Table 1
Sociodemographic, lifestyle and clinical characteristics of the BiSC participants and those included and excluded from the current study.

Variable description	BiSC (n = 1080)	Included (n = 1039)	Excluded (n = 41)	ASMD	p-values[a]
Maternal age at conception	34.4 (5.8)	34.4 (5.9)	34.7 (5)	0.13	0.57
Ethnicity					
European	725 (67.1)	705 (67.9)	20 (48.8)		
Non-European	355 (32.9)	334 (32.1)	21 (51.2)	0.39	0.17
BMI at first trimester	23.6 (4.9)	23.5 (4.9)	25.3 (5.3)	0.35	0.06
Parity					
Nulliparous	606 (56.1)	586 (56.4)	20 (48.8)		
Multiparous	474 (43.9)	453 (43.6)	21 (51.2)	0.15	0.42
Educational Level					
University degree	747 (69.2)	720 (69.3)	27 (65.9)		
Non-University degree	333 (30.8)	319 (30.7)	14 (34.1)	0.07	0.77
Active smoking					
No	932 (91.8)	909 (92)	23 (85.2)		
Yes	83 (8.2)	79 (8)	4 (14.8)		
NA	65	51	14	0.79	0.36
Alcohol consumption					
No	702 (69.9)	687 (70.2)	15 (55.6)		
Yes	303 (30.1)	291 (29.8)	12 (44.4)		
NA	75	61	14	0.76	0.15
ASA treatment					
No	899 (93.5)	874 (93.4)	25 (96.2)		
Yes	63 (6.5)	62 (6.6)	1 (43.8)		
NA	118	103	15	0.66	0.87
Chronic Hypertension					
No	1068 (99)	1027 (98.9)	41 (100)		
Yes	11 (1)	11 (1.1)	0 (0)		
NA	1	1	0	0.04	1
Others concomitant diseases[b]					
No	1058 (98)	1017 (97.9)	41 (100)		
Yes	22 (2)	22 (2.1)	0 (0)	0.21	0.71
History of LBW					
No	1043 (96.6)	1004 (96.6)	39 (95.1)		
Yes	37 (3.4)	35 (3.4)	2 (4.9)	0.08	0.93
History of SGA					
No	1062 (98.3)	1021 (98.3)	41 (100)		
Yes	18 (1.7)	18 (1.7)	(0)	0.19	0.82
History of PE					
No	1045 (96.8)	1005 (96.7)	40 (97.6)		
Yes	35 (3.2)	34 (3.3)	1 (2.4)	0.05	1
Fetal sex					
Male	523 (50.7)	512 (51)	11 (39.3)		
Female	509 (49.3)	492 (49)	17 (60.7)		
NA	48	35	13	0.24	0.30
Active worker					
No	264 (24.4)	250 (24.1)	14 (34.1)		
Yes	816 (75.6)	789 (75.9)	27 (65.9)	0.22	0.20

Continuous variables are described by median (interquartile range) and categorical variables are described by n (%).
ASMD = absolute standardize mean difference, BMI = body mass index, NA = missings, ASA = aspirin, PE = preeclampsia, SGA = small for gestational age, LBW = low birth weight.
[a] *p*-values for the difference between BiSC participants that were included (n = 1039) and excluded (n = 41) in the analysis.
[b] Chronic kidney disease, pregestational diabetes, thrombophilia, systemic lupus erythematosus (SLE).

Table 2
Fetoplacental Doppler markers' values (mean ± SD) and sample size (*n*).

Assessment – time	UtA PI	UA PI	MCA PI	CPR
12 w	1.6 (0.40) (n = 965)	-	-	-
20 w	1 (0.30) (n = 912)	-	-	-
32 w	0.8 (0.20) (n = 925)	0.99 (0.17) (n = 937)	2.04 (0.39) (n = 924)	2.1 (0.51) (n = 924)

UtA = uterine artery, PI = pulsatility index, UA = umbilical artery, MCA = middle cerebral artery, CPR = cerebroplacental ratio, w = weeks of gestation.

0.04, HM: β = 0.03; 95% CI: 0.01, 0.05). For $PM_{2.5}$, we only found a statistically significant positive association for total (β = 0.04; 95% CI: 0.01, 0.06) and home exposure (β = 0.03; 95% CI: 0.01, 0.05) estimated by DM (Fig. 1C).

Umbilical artery PI showed a consistent trend toward positive associations with air pollutants; however, none of these associations reached statistical significance (Fig. 2). No statistically significant associations were also observed between air pollution exposure and MCA PI (Fig. 3). Although home and total exposure estimates generally showed inverse associations with CPR, only home NO_2 exposure estimated by HM was significantly associated with a lower CPR (β = −0.05; 95% CI: −0.10, −0.00) (Fig. 4).

3.3. Further analyses

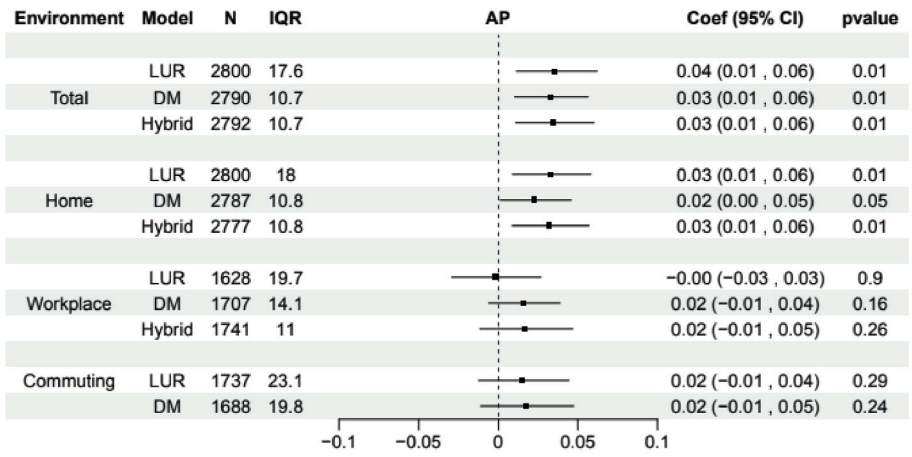
Overall, the associations of air pollution exposure during the first trimester with fetoplacental Doppler markers at the third trimester showed patterns of association consistent with those observed in the main analyses (Supplementary Fig. 2–5), although the associations with UtA mean PI were generally attenuated. We only found significant associations for $PM_{2.5}$, particularly for first-trimester home and total $PM_{2.5}$ exposure levels in association with higher UtA mean PI when estimated using LUR models (Supplementary Fig. 2); and for first-trimester $PM_{2.5}$ exposure with higher UA PI in total exposure estimated by LUR and DM, home exposure estimated by LUR, and at workplace exposure estimated by DM (Supplementary Fig. 3).

We observed no associations between second-trimester exposures and UtA mean PI in the third trimester (Supplementary Fig.6). Likewise, in the associations with UA PI, MCA PI, and CPR, we found similar patterns compared to the main analyses, but none of them were statistically significant (Supplementary Fig.7-9).

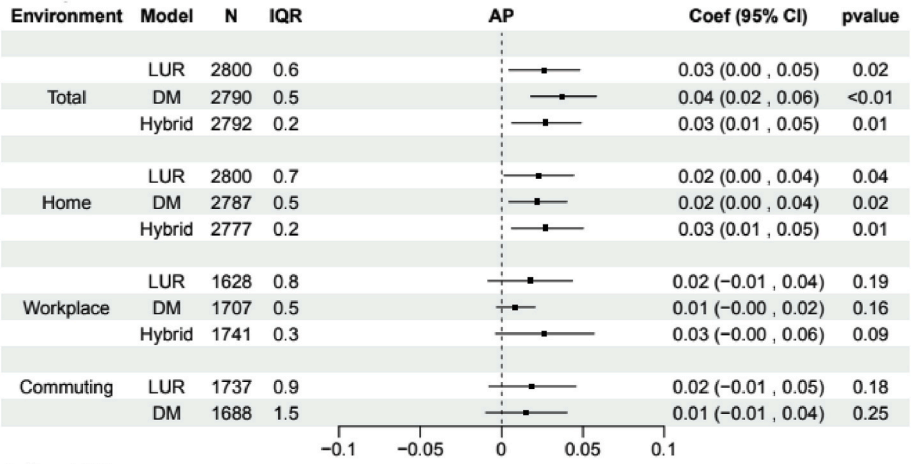
3.4. Sensitivity analyses

Additional adjustment for the aforementioned covariates generally did not alter the direction of the associations observed in the main analyses (Supplementary Fig. 10-89). Most changes involved an attenuation or strengthening of statistical significance rather than changes in the direction of the associations. However, after adjustment for maternal systolic and diastolic blood pressure, the associations between home NO_2 exposure, and total and home BC exposures assessed by LUR models with UtA mean PI lost their statistical significance (Supplementary Fig. 18,22). In contrast, the associations of the total exposure to BC (by HM) and to $PM_{2.5}$ (by DM) with UA PI gained statistical significance after adjustment for maternal diastolic blood pressure (Supplementary Fig. 23). Similarly, total NO_2 exposure by HM in relation to CPR

1.A. NO_2 exposure



1.B. BC exposure



1.C. $PM_{2.5}$ exposure

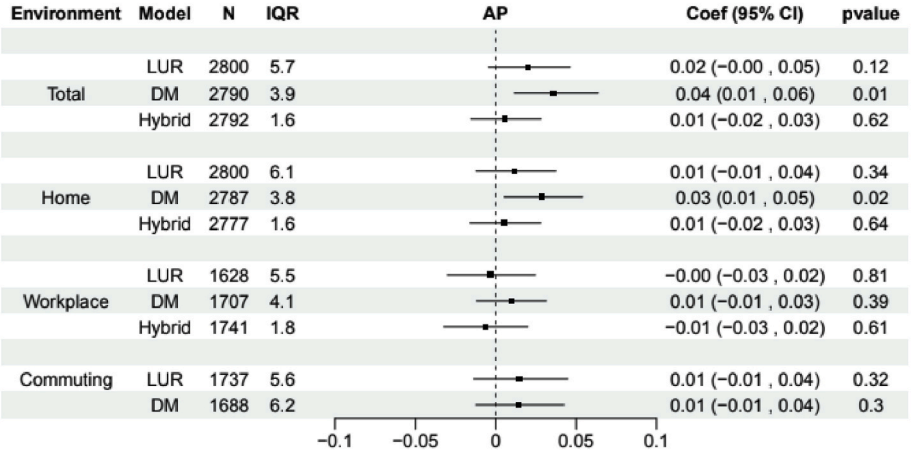


Fig. 1. Main analysis of uterine artery mean PI at 12, 20 and 32 weeks of gestation vs. air pollution levels (from conception until the outcome measurement). Adjusted* change in uterine arteries mean PI associated with one interquartile (IQR) increase exposure to NO_2 (μg/m^3) (1.A), black carbon (μg/m^3) (1.B), $PM_{2.5}$ (μg/m^3) (1.C).

*Adjusted for gestational age at visit, maternal age at conception, BMI at the first trimester, parity, educational level, active smoking during pregnancy, alcohol consumption during pregnancy.

PI: pulsatility index; LUR: Land use regression model; DM: Dispersion model; Hybrid: Hybrid model; NO_2: nitrogen dioxide; BC: black carbon; $PM_{2.5}$: Particulate matter with an aerodynamic diameter < 2.5 μm; AP: Air pollution.

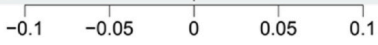
2.A. NO_2 exposure

Environment	Model	N	IQR	Coef (95% CI)	pvalue
Total	LUR	937	16.1	0.01 (−0.01 , 0.03)	0.23
	DM	934	10.2	0.01 (−0.00 , 0.03)	0.18
	Hybrid	934	10.1	0.01 (−0.00 , 0.03)	0.18
Home	LUR	937	16	0.01 (−0.01 , 0.03)	0.27
	DM	933	10.1	0.01 (−0.01 , 0.02)	0.42
	Hybrid	932	10	0.01 (−0.01 , 0.03)	0.23
Workplace	LUR	569	18.3	−0.00 (−0.02 , 0.01)	0.62
	DM	585	13.3	0.01 (−0.01 , 0.02)	0.48
	Hybrid	592	10.4	0.01 (−0.01 , 0.03)	0.35
Commuting	LUR	594	22.6	0.00 (−0.02 , 0.02)	0.68
	DM	579	19.2	−0.00 (−0.02 , 0.02)	0.68



2.B. BC exposure

Environment	Model	N	IQR	Coef (95% CI)	pvalue
Total	LUR	937	0.6	0.01 (−0.00 , 0.03)	0.15
	DM	934	0.5	0.01 (−0.01 , 0.02)	0.31
	Hybrid	934	0.2	0.01 (−0.00 , 0.03)	0.13
Home	LUR	937	0.6	0.01 (−0.01 , 0.02)	0.27
	DM	933	0.4	0.00 (−0.01 , 0.01)	0.74
	Hybrid	932	0.2	0.01 (−0.00 , 0.03)	0.15
Workplace	LUR	569	0.8	0.00 (−0.02 , 0.02)	0.87
	DM	585	0.5	0.00 (−0.01 , 0.01)	0.8
	Hybrid	592	0.3	0.00 (−0.02 , 0.02)	0.81
Commuting	LUR	594	0.9	0.01 (−0.01 , 0.03)	0.32
	DM	579	1.4	−0.01 (−0.02 , 0.01)	0.36



2.C. $PM_{2.5}$ exposure

Environment	Model	N	IQR	Coef (95% CI)	pvalue
Total	LUR	937	5.2	0.01 (−0.00 , 0.03)	0.12
	DM	934	3.8	0.02 (−0.00 , 0.03)	0.07
	Hybrid	934	1.4	0.01 (−0.01 , 0.02)	0.36
Home	LUR	937	5.6	0.02 (−0.00 , 0.03)	0.1
	DM	933	3.8	0.01 (−0.00 , 0.03)	0.19
	Hybrid	932	1.5	0.01 (−0.01 , 0.02)	0.39
Workplace	LUR	569	5.4	0.01 (−0.02 , 0.03)	0.62
	DM	585	3.9	0.01 (−0.00 , 0.02)	0.18
	Hybrid	592	1.5	0.01 (−0.01 , 0.03)	0.29
Commuting	LUR	594	5.6	0.01 (−0.02 , 0.03)	0.64
	DM	579	6.2	0.00 (−0.02 , 0.02)	0.98



(caption on next page)

Fig. 2. Main analysis of umbilical artery (UA) PI at around 32 weeks of gestation vs. air pollution levels (from conception until the outcome measurement). Adjusted* regression coefficients of change in UA PI associated with one interquartile (IQR) increase exposure to NO_2 (μg/m^3) (2.A), black carbon (μg/m^3) (2.B), $PM_{2.5}$ (μg/m^3) (2.C).
*Adjusted for Adjusted for gestational age at visit, maternal age at conception, BMI at the first trimester, parity, educational level, active smoking during pregnancy, alcohol consumption during pregnancy.
PI: pulsatility index; LUR: Land use regression model; DM: Dispersion model; Hybrid: Hybrid model; NO_2: nitrogen dioxide; BC: black carbon; $PM_{2.5}$: Particulate matter with an aerodynamic diameter < 2.5 μm; AP: Air pollution.

became statistically significant after adjustment for maternal systolic and diastolic blood pressure (Supplementary Fig. 21,25).

For some of the covariates, we observed minor changes as in the case of the association between total NO_2 exposure assessed by HM with CPR which gained statistical significance after adjustment for maternal history of preeclampsia (Supplementary Fig. 29). Home NO_2 exposure assessed by DM and UtA mean PI, and total NO_2 exposure assessed by HM and CPR also became statistical significance after adjustment for previous pregnancy with LBW (Supplementary Fig. 30, 33), whereas the association of home exposure to BC by LUR model with UtA mean PI lost statistical significance after adjustment by fetal sex (Supplementary Fig. 34). Similarly, BC exposures in total (by LUR and HM) and home (by LUR and DM) estimates and UtA mean PI, and home NO_2 exposure (by HM) and CPR lost their statistical significance after adjustment by aspirin intake (Supplementary Fig. 38, 41). Likewise, the association of home exposure to BC by LUR model with UtA mean PI lost statistical significance after adjustment for season of conception (Supplementary Fig. 54); while after adjustment for this covariate resulted in significant associations between total BC exposure by HM and UA PI, and between commuting $PM_{2.5}$ exposure by LUR model and MCA PI (Supplementary Fig. 55, 56).

When considering the year of the visit as a covariate, home NO_2 exposure assessed by LUR model became marginally significant, while BC exposure in total (by LUR and HM) and home (assessed by the three models) estimates, and home $PM_{2.5}$ exposure (by DM) in association with UtA mean PI lost their statistical significance (Supplementary Fig. 58). Adjustment for this covariate also resulted in a loss of statistical significance of the association between home NO_2 exposure assessed by HM and CPR, whereas the associations between workplace and commuting $PM_{2.5}$ exposures by LUR models and CPR became statistically significant (Supplementary Fig. 61).

Further adjustment of the main analysis for noise exposure levels showed variance inflation factor (VIF) values between 1.02 and 1.42, not indicating a high likelihood of multiple collinearity (Supplementary Fig. 66-69). After controlling for this covariate, only the associations between home BC exposure (by LUR) and UtA mean PI, and between home NO_2 exposure (by HM) and CPR lost their statistical significance (Supplementary Fig. 66, 69).

Using hospital as a fixed effect, resulted in a loss of statistical significance of the association between home BC exposure (by LUR) and UtA mean PI (Supplementary Fig. 70), and home NO_2 exposure (by HM) and CPR (Supplementary Fig. 73). The results of the complete case analysis were generally consistent with those of the main analyses (Supplementary Fig. 74-77); however, the association of home BC exposure estimated by LUR and DM with UtA mean PI lost their statistical significance (Supplementary Fig. 74). On the contrary, the associations of total and home exposures to $PM_{2.5}$ estimated by LUR models with UA PI, and total NO_2 exposure by HM with CPR attained statistical significance (Supplementary Fig. 75, 77). Similarly, after excluding participants with pregnancy-induced hypertensive disorders, the associations of NO_2 exposure at home by DM, and total $PM_{2.5}$ exposure by LUR model with UtA mean PI became statistically significant (Supplementary Fig. 78); whereas the association of home NO_2 exposure by HM with CPR lost statistical significance (Supplementary Fig. 81). We did not observe any change in terms of statistical significance after correcting our main analysis for multiple comparisons (Supplementary Fig. 82-85).

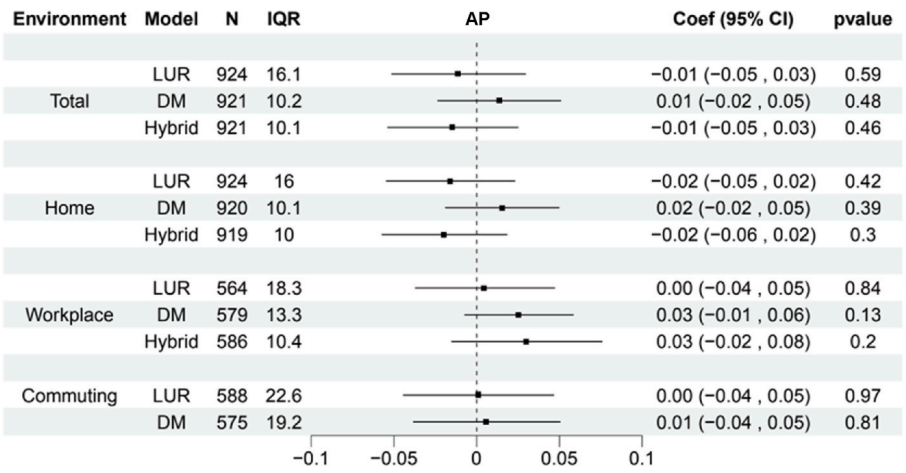
Our bi-pollutant models based on the main analyses of the fetoplacental Doppler markers showed moderate VIF in LUR and Hybrid models (1.25-3.55), while DM showed mainly high correlation (2.70-8.13), indicating a potential multicollinearity issue (Supplementary Fig. 86-89). In these models, some of the previous associations attained statistical significance, such as the association of workplace BC exposure with UtA mean PI (by HM) and with CPR (by DM), when including BC and $PM_{2.5}$ in the model (Supplementary Fig. 86, 89); and the associations of workplace $PM_{2.5}$ exposure and commuting BC exposure by DM and UA PI, when incorporating BC and $PM_{2.5}$, respectively (Supplementary Fig. 87). Commuting $PM_{2.5}$ exposure by LUR and MCA PI, when including NO_2 in the model, also gained statistical significance (Supplementary Fig. 88). Similarly, the relation between total and home exposures to NO_2 and BC by HM with MCA PI, when including both pollutants in the model became statistically significant (Supplementary Fig. 88). On the other hand, several other associations lost their statistical significance, such as the association of total and home exposures to NO_2 and BC with UtA mean PI in the bi-pollutant LUR models comprising both pollutants, and the association of total and home exposure to BC with UtA mean PI when including $PM_{2.5}$ in the aforementioned model (Supplementary Fig. 86). In the bi-pollutant DM, we observed non-significant associations between total exposure to NO_2 and $PM_{2.5}$ and UtA mean PI when including both pollutants in the model, or when each pollutant was modeled separately alongside BC; moreover, non-significant associations were found in home exposure in this model (Supplementary Fig. 86). Lastly, in the bi-pollutant HM, the associations of total and home exposures to NO_2 and BC with UtA mean PI when comprising both pollutants (Supplementary Fig. 86), and of home NO_2 exposure with CPR, when incorporating $PM_{2.5}$ in the model, all lost their statistical significance (Supplementary Fig. 89).

4. Discussion

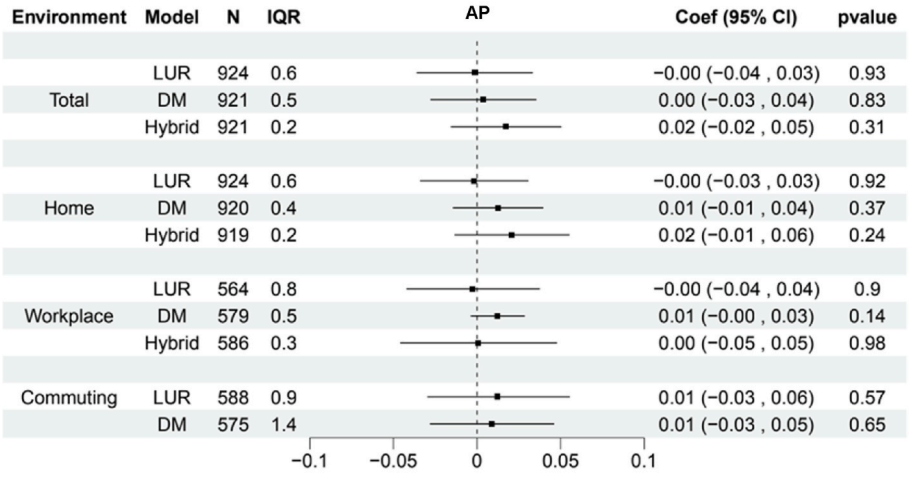
We explored the association of maternal air pollution exposure in different microenvironments, based on three exposure modelling approaches, with fetoplacental Doppler markers in a population-based cohort of pregnant women. Our main finding was that higher maternal exposure to air pollution, particularly total and home exposures, was positively associated with uterine artery PI. Although we also found that NO_2 exposure was associated with a lower CPR, most of the associations between air pollution and fetal Doppler markers in the third trimester were heterogeneous.

UtA Doppler ultrasound is considered a surrogate marker of vascular remodeling and placental function (Gómez et al., 2006; Pedroso et al., 2018; Plasencia et al., 2008), and a tool for screening pregnancies at risk of placental-related complications due to a remaining high resistance in the uterine vasculature (Enakpene et al., 2023; Sciscione and Hayes, 2009; Stampalija et al., 2010). Our main analyses showed direct associations between total and home air pollution exposures and the UtA mean PI. The more consistent findings for exposure at home compared to other microenvironments could be explained by pregnant women spending more time at their residences (Samuelsson et al., 2025). Therefore, home microenvironment could be considered the major contributor to total exposure, even though the exposure levels were generally higher on the commuting route. The available evidence on the association between air pollution exposure and placental Doppler markers remains limited. Cahuana-Bartra et al. investigated the impact of short-term NO_2 exposure in the third trimester and the UtA mean PI in 101 pregnant women. In contrast to our findings, they observed an

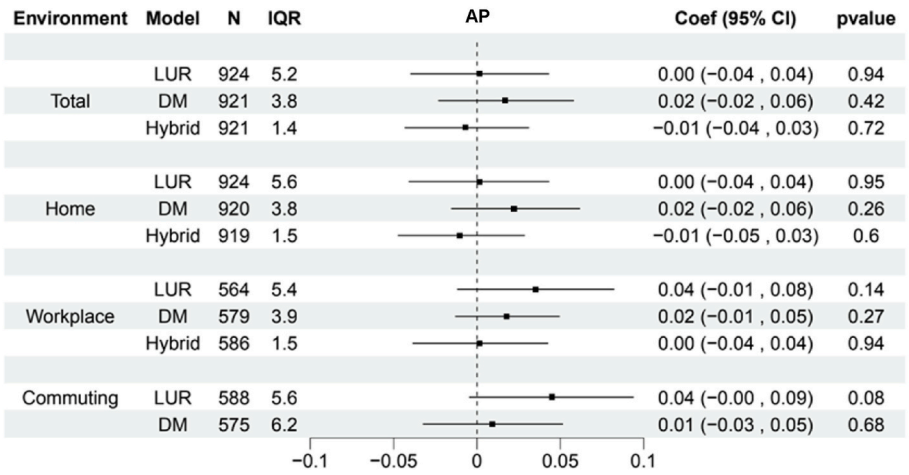
3.A. NO_2 exposure



3.B. BC exposure



3.C. $PM_{2.5}$ exposure



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Fig. 3. Main analysis of middle cerebral artery (MCA) PI around 32 weeks of gestation vs. air pollution levels (from conception until the outcome measurement). Adjusted* regression coefficients of change in MCA PI associated with one interquartile (IQR) increase exposure to NO_2 (μg/m^3) (3.A), black carbon (μg/m^3) (3.B), $PM_{2.5}$ (μg/m^3) (3.C).
*Adjusted for Adjusted for gestational age at visit, maternal age at conception, BMI at the first trimester, parity, educational level, active smoking during pregnancy, alcohol consumption during pregnancy.
PI: pulsatility index; LUR: Land use regression model; DM: Dispersion model; Hybrid: Hybrid model; NO_2: nitrogen dioxide; BC: black carbon; $PM_{2.5}$: Particulate matter with an aerodynamic diameter < 2.5 μm; AP: Air pollution.

inverse association between NO_2 exposure and UtA PI (β = −0.07; 95% CI: −0.12, −0.02 for an IQR increase in NO_2 exposure) (Cahuana-Bartra et al., 2022). This discrepancy might be, in part, explained by the differences in the sample size, the exposure assessment method (i.e., personal sampling vs. modelling), and also the evaluated exposure window and duration (i.e., short-term in the third trimester vs. long-term during the entire pregnancy). In this context, long-term exposure could primarily reflect the cumulative effect on placental implantation and spiral artery remodeling rather than an acute physiological response to a short-term exposure immediately preceding ultrasound assessment. Van den Hooven et al., within the Generation R study (n = 7801), evaluated the association of short and long-term exposure to particulate matter <10 μm (PM_{10}) and NO_2 with UtA PI in the second and third trimesters of pregnancy, finding no consistent associations (van den Hooven et al., 2012). Carvalho et al. studied personal exposure to NO_2 and placental hemodynamics in the three trimesters of pregnancy in 366 pregnant women. They did not find any association between NO_2 and the UtA mean PI (Carvalho et al., 2016). Similar to our study, Contreras et al., in a study of 566 pregnant women, found a positive association between NO_2 levels assessed by LUR and UtA PI at 35–37 weeks of gestation (β = 0.12 SD, 95% CI: 0.02, 0.23; for an IQR increase in NO_2 exposure). They also observed an increased risk of UtA PI above the 90th percentile in association with NO_2 exposure (Contreras et al., 2018).

Whereas UA Doppler reflects the placental vascular resistance on the fetal side (Sciscione and Hayes, 2009), MCA PI and CPR are markers of fetal cardiovascular adaptation to placental dysfunction, reflecting the redistribution of blood flow towards the brain in response to a relative hypoxic status (Ali et al., 2022; Everett and Peebles, 2015; L.-N. Guo et al., 2019; Vollgraff Heidweiller-Schreurs et al., 2018). Although the associations of air pollution with fetal Doppler markers in the third trimester were mostly non-significant, we observed a positive trend in the association of the air pollutants, mainly total and home exposures, with UA PI across the models. We also observed a negative trend in the associations of the pollutants with CPR, which could be explained, in part, by the rise in the UA PI. These patterns are consistent with early fetal circulatory adaptation in response to impaired placental function. Moreover, abnormal CPR values have been previously related to poor neurodevelopmental and academic outcomes in infants (Bellido-González et al., 2016; Monteith et al., 2019).

The available evidence on the association of air pollution exposure with these Doppler markers is heterogeneous. Van den Hooven et al. in the Generation R study observed an inverse association between PM_{10} exposure averaged from conception and 2 months prior to the Doppler ultrasound examination and UA PI in the second trimester; however, they observed no association between NO_2 exposure and UA PI in the same periods (van den Hooven et al., 2012). In their study, Carvalho et al. reported no association between NO_2 and ozone (O_3) exposures and MCA; however, they found inconsistent results for the association of O_3 exposure with UA PI. While O_3 exposure in the second trimester was associated with increased UA PI (β = 0.017; standard error = 0.007, p = 0.013), the third-trimester O_3 exposure showed an inverse association (β = −0.021; standard error = 0.008, p = 0.011) (Carvalho et al., 2016). Lastly, Cahuana-Bartra et al. in their study of short-term exposure to NO_2 in the third trimester, found a decrease in CPR in relation with this pollutant levels (β = − 0.18; 95% CI: − 0.37, 0.01, p < 0.1 for one IQR increase in NO_2 exposure) (Cahuana-Bartra et al., 2022).

In our further analyses of first-trimester air pollution exposure and fetoplacental Doppler markers at the third trimester, the overall pattern of associations remained consistent with the main analyses; however, we only found statistically significant associations between $PM_{2.5}$ exposure and UA PI. To our knowledge, there is only one previous study conducted by Carvalho et al. that explores trimester-specific air pollutants exposure and fetoplacental Doppler markers later in pregnancy. Similar to our study, the authors found no association between NO_2 exposure in each trimester with fetoplacental Doppler markers at the third trimester (Carvalho et al., 2016).

A strength of our study was the use of three exposure assessment models, which could provide more confidence in the observed associations. Moreover, in contrast to previous studies, which mainly estimated air pollution exposure at home, overlooking the exposures at other microenvironments, we estimated exposure levels at home, workplace, and commuting route. By combining these exposure levels with time-activity data, we could generate potentially more realistic exposure estimates. Additionally, the wealth of available data in BiSC allowed us to account for a vast number of covariates, including low aspirin intake, which has demonstrated to reduce placental-related complications (Rolnik et al., 2017).

Our study faced a number of limitations. BiSC participants had slightly higher educational attainment (69.3% vs 64% Barcelona general population in 2019), which could have influenced the external validity of our findings. Furthermore, our $PM_{2.5}$ and BC LUR models relied on data from 34 to 30 monitoring stations, respectively, while the cross-validation R^2 for $PM_{2.5}$ models was relatively modest. These could have resulted in exposure misclassification in our study. However, consistency of our observed associations across three different exposure modelling frameworks that had different inherent limitations could provide more confidence in our findings. Lastly, fetal Doppler markers were only evaluated at the third trimester, preventing us from investigating the potential association of air pollution exposure on their trajectories.

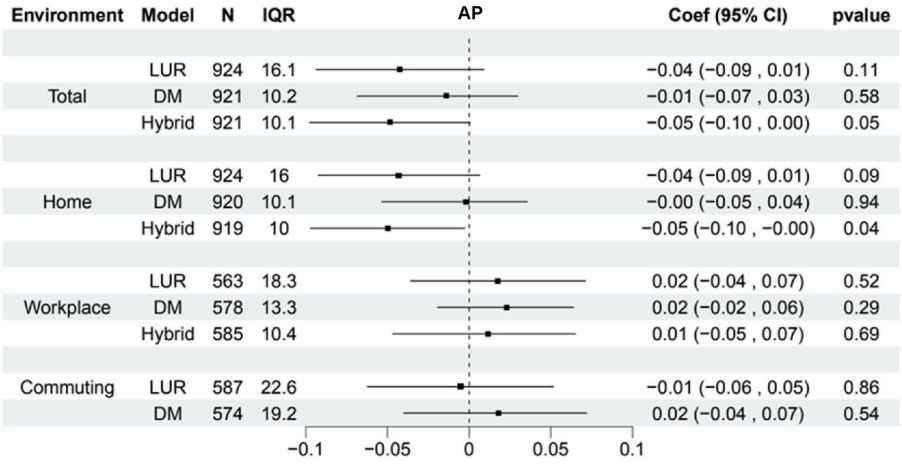
5. Conclusion

In our study, we found that maternal exposure to ambient air pollution, particularly NO_2 and BC, was associated with increased uteroplacental vascular resistance, as reflected by higher UtA mean PI. In addition, the observed reduction in CPR with increasing NO_2 exposure suggests that maternal air pollution may also induce subtle fetal hemodynamic adaptation. Together, these findings provide evidence that ambient air pollution may influence placental vascular function, even in a cohort of predominantly low-risk pregnancies. Confirmation in larger prospective studies is needed to determine whether these subclinical vascular changes translate into adverse obstetric and long-term child health outcomes.

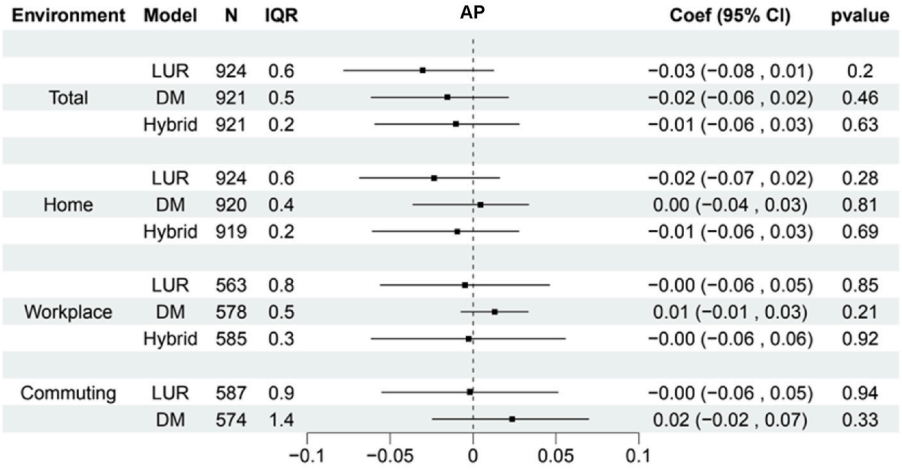
CRediT authorship contribution statement

Maria Julia Zanini: Writing – original draft, Resources, Data curation. **Toni Galmés:** Writing – review & editing, Validation, Formal analysis, Data curation. **Bethany Knox:** Writing – review & editing, Resources, Data curation. **Yana Luo:** Writing – review & editing, Resources. **Laura Gómez-Herrera:** Writing – review & editing, Resources, Data curation. **Marta Cirach:** Writing – review & editing, Resources. **Alan Domínguez:** Writing – review & editing, Resources. **Carla Domínguez-Gallardo:** Writing – review & editing, Resources, Data curation. **Marta Muniesa:** Writing – review & editing, Resources, Data curation.

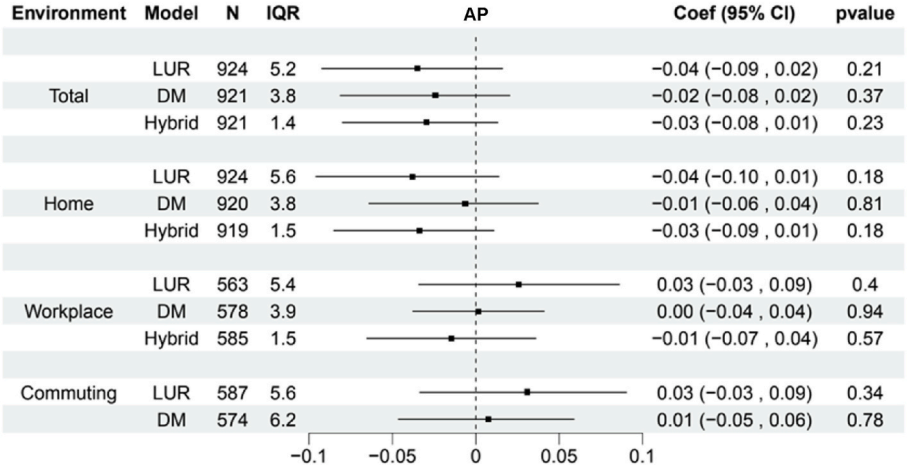
4.A. NO_2 exposure



4.B. BC exposure



4.C. $PM_{2.5}$ exposure



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Fig. 4. Main analysis of cerebroplacental ratio (CPR) at around 32 weeks of gestation vs. air pollution levels (from conception until the outcome measurement). Adjusted* regression coefficients of change in CPR associated with one interquartile (IQR) increase exposure to NO_2 (μg/m^3) (4.A), black carbon (μg/m^3) (4.B), $PM_{2.5}$ (μg/m^3) (4.C).
*Adjusted for Adjusted for gestational age at visit, maternal age at conception, BMI at the first trimester, parity, educational level, active smoking during pregnancy, alcohol consumption during pregnancy.
PI: pulsatility index; LUR: Land use regression model; DM: Dispersion model; Hybrid: Hybrid model; NO_2: nitrogen dioxide; BC: black carbon; $PM_{2.5}$: Particulate matter with an aerodynamic diameter < 2.5 μm; AP: Air pollution.

Giulia Casu: Writing – review & editing, Resources, Data curation. **Mónica Cruz-Lemini:** Writing – review & editing, Resources. **Yu Zhao:** Writing – review & editing, Resources. **Gustavo Arévalo Roa:** Writing – review & editing, Validation, Resources. **Glòria Carrasco-Turigas:** Writing – review & editing, Resources. **Xavier Basagaña:** Writing – review & editing, Validation, Methodology, Investigation. **Maria Foraster:** Writing – review & editing, Resources. **Mireia Gascon:** Writing – review & editing, Resources. **Olga Sánchez:** Writing – review & editing, Resources. **Mariona Bustamante:** Writing – review & editing, Resources, Investigation. **Ioar Rivas:** Writing – review & editing, Resources. **Maria Dolores Gómez-Roig:** Writing – review & editing, Resources, Methodology, Conceptualization. **Jordi Sunyer:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Payam Dadvand:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Elisa Llurba:** Writing – review & editing, Supervision, Resources, Methodology, Conceptualization.

Fundings

This work was conducted under contract to the Health Effects Institute (HEI), an organization jointly funded by the United States Environmental Protection Agency (EPA) (Assistance Award No. R-82811201) and certain motor vehicle and engine manufacturers. The contents of this article do not necessarily reflect the views of HEI, or its sponsors, nor do they necessarily reflect the views and policies of the EPA or motor vehicle and engine manufacturers. BiSC cohort was also supported by the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation program (785994 – AirNB project) and from the European Commission under the European Union's Horizon 2020 research and innovation program (874583 - ATHLETE project). We also acknowledge funding from the Primary Care Interventions to Prevent Maternal and Child Chronic Diseases of Perinatal and Developmental Origin Network (RICORS-SAMID, RD21/0012, Instituto de Salud Carlos III, Madrid, Spain), funded by the Recovery, Transformation and Resilience Plan 2017-2020, ISCIII, and by the European Union – Next Generation EU. Yana Luo received funding from China Scholarship Council (202308620109). We acknowledge support from the grant CEX2023-0001290-S funded by MCIN/AEI/10.13039/501100011033, and support from the Generalitat de Catalunya through the CERCA Program.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We would like to thank all the BiSC participants and their families for their generous collaboration. We are also very grateful to all the former and current BiSC team members (https://projectebisc.org/en/team/) for their tremendous contributions to this cohort. This work was carried out as part of doctorate studies in pediatrics, obstetrics, and gynecology at the Universitat Autònoma de Barcelona.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envpol.2026.129046.

Data availability

The authors do not have permission to share data.

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