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Prenatal air pollution exposure and placental biomarkers of oxidative stress and ageing: results from the BiSC cohort

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A B S T R A C T

Prenatal air pollution exposure has been associated with impaired fetal growth. However, the underlying biological mechanisms, potentially involving the placenta, remain poorly understood. This study aimed to investigate the effects of maternal air pollution exposure on placental biomarkers of oxidative stress and cellular ageing, and to determine whether these biomarkers contribute to the association between air pollution exposure and birth weight. The study included 499 participants from the Barcelona Life Study Cohort (BiSC), recruited between October 2018 and April 2021. Maternal exposure to nitrogen dioxide (NO_2), black carbon, and particulate matter ≤2.5 μm ($PM_{2.5}$) during pregnancy was estimated using hybrid Land Use Regression (LUR)-dispersion models. Placental relative mitochondrial DNA content (mtDNAcn) and telomere length (TL) were measured by qPCR, and associations between exposure and placental biomarkers were estimated using linear mixed-effects regression models adjusted for covariates. Increasing levels of NO_2 and $PM_{2.5}$ during the 1st and 3rd trimesters and across the entire pregnancy, as well as black carbon during the 3rd trimester, were significantly associated with an increase in placental mtDNAcn. No significant associations were observed between prenatal air pollution exposure and placental TL, nor between either placental biomarker and birth weight. In conclusion, prenatal air pollution exposure was associated with differences in placental mtDNAcn but not TL, and neither biomarker was significantly associated with birth weight.

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1. Introduction

There is currently substantial evidence associating exposure to air pollution with a wide range of adverse health outcomes. In recent years, special attention has been directed toward certain vulnerable populations, such as children and pregnant women, who might be more susceptible to the detrimental effects of exposure to air pollution (Sunyer and Dadvand, 2019).

Existing literature has consistently documented an association between maternal exposure to ambient air pollution during pregnancy and fetal growth (Nyadanu et al., 2022). Previous studies have also associated air pollution exposure during pregnancy to pregnant women's blood pressure, including an increased risk of gestational hypertension and preeclampsia (Bai et al., 2020). These maternal and fetal complications are suggested to be a result of abnormal placentation during the early stages of pregnancy, due to impaired trophoblast invasion and modification of spiral arteries. Additionally, air pollution particles (namely, black carbon) were recently observed to be present at both the maternal and fetal side of placental samples from pregnant women living in urban environments, demonstrating for the first time that air pollution can effectively reach both the placental tissue and the fetus (Bongaerts et al., 2022; Bové et al., 2019). This provides key evidence supporting the biological plausibility of the placenta's mediating role in the association between prenatal air pollution and birth outcomes.

An emerging body of evidence has also suggested that air pollution exposure might influence the placenta at the molecular level. For instance, prenatal air pollution exposure can induce oxidative stress and systemic inflammation in the placenta, which interferes with normal placental function and can lead to pregnancy complications (Sultana et al., 2018). Moreover, maternal air pollution exposure has been shown to affect the interplay between oxidative stress, epigenetics and the ageing phenotype (Saenen et al., 2019). In particular, oxidative stress caused by reactive oxygen species, along with mitochondrial dysfunction and telomere shortening, may induce cellular senescence in placental cells (Janssen et al., 2012; Sultana et al., 2018). These senescent cells undergo irreversible cell-cycle arrest and may contribute to accelerated placental cellular ageing (Martens et al., 2017).

Placental mitochondrial DNA content (mtDNAcn), a circular DNA essential for energy production, and telomere length (TL), repetitive non-coding DNA at chromosome ends that preserves genomic stability, are key indicators of placental oxidative stress and cellular ageing (Martens and Nawrot, 2016). Existing studies have demonstrated an association between prenatal air pollution exposure and altered placental mtDNAcn (Janssen et al., 2012). Placental mtDNAcn has also been found to mediate the association between first trimester air pollution exposure and infant length at 6 months (Clemente et al., 2017). Furthermore, exposure to air pollutants during pregnancy has been shown to be associated with placental TL decrease (Bijnens et al., 2015).

Considering that fetal development is a crucial window of susceptibility to the detrimental effects of ambient exposures and requires a proper functioning placenta, further research is needed to clarify the mechanisms linking environmental exposures to placental and fetal health (Singh et al., 2024). In the present study, we assessed the associations between prenatal air pollution exposure and both mitochondrial DNA and telomere length measurements in placental samples from the BiSC cohort. The BiSC study incorporates comprehensive exposure assessment methods, including microenvironment modeling, to enhance the accuracy of individual exposure estimates. In addition, we aimed to explore the contribution of these placental biomarkers on the negative effects of prenatal air pollution exposure on birth weight.

2. Materials and methods

2.1. Study population and setting

BiSC (Barcelona Life Study Cohort) is an ongoing population-based birth cohort in Barcelona, Spain. The detailed description of recruitment, follow-ups and data collection in BiSC has been detailed elsewhere (Dadvand et al., 2024). Briefly, 1080 pregnant women were recruited between 2018 and 2021 in three tertiary university hospitals including Hospital Sant Joan de Déu, Hospital Clínic-La Maternitat and Hospital de la Santa Creu i Sant Pau. Recruitment was conducted by midwives during the participants' first prenatal visit (between 8 and 14 weeks of gestation).

Eligibility criteria included: maternal age between 18 and 45 years old, singleton pregnancy, intending to give birth in one of the three recruiting hospitals and ability to effectively communicate in Catalan or Spanish. Exclusion criteria were: high-risk pregnancy, multiple pregnancy and fetus with congenital anomaly.

The BiSC study was proposed by principal investigator Dr. Jordi Sunyer (Universitat Pompeu Fabra) and approved by the Ethical Review Board of Parc de Salut Mar (CEIm - Parc de Salut Mar). Families were provided with information on the study aims and procedures, and gave their written informed consent prior to participation.

The present analysis includes N = 499 mother-child pairs for whom both exposure and clinical data were available, as well as placental biomarker measurements. Participant characteristics and key confounders are summarized in Table 1. The reporting of this study follows the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for cohort studies (von Elm et al., 2008).

2.2. Air pollution exposure assessment

We assessed maternal exposure to nitrogen dioxide (NO_2), black carbon and particulate matter $\leq$2.5 μm ($PM_{2.5}$) using hybrid land use regression (LUR)-dispersion models (See Supplementary Methods for further details). The hybrid model combined dispersion model estimates with the potential predictors from the LUR model together with routine air pollution monitoring data and meteorological data to estimate the levels of each pollutant at a weekly time resolution for the whole pregnancy period (Domínguez et al., 2024). Given the suboptimal model performance (R^2) for NO_2 and $PM_{2.5}$, it should be noted that these estimates serve as proxies for true personal exposure and may result in some degree of exposure measurement error.

Participants carried personal geolocation devices for one week during both the first and third trimesters of pregnancy to track their movements (ExpoApp - Smartphone app, Ateknea Solutions, Spain) and time-activity patterns (ActiGraph wGT3X-BT, ActiGraph Ltd, US). These data were used to estimate the time spent in different microenvironments such as home, workplace and commuting routes. Total exposure for each participant during each week of pregnancy was estimated by integrating pollutant concentrations in the different microenvironments, weighted by the time spent in each location.

We then calculated average concentrations of air pollutants during each trimester of pregnancy: namely, week 1 to 13 for the first trimester; week 14 to 27 for the second trimester, and week 28 to gestational age at birth for the third trimester. The final dataset comprised estimates of exposure to NO_2, black carbon and $PM_{2.5}$ for each trimester of pregnancy and for the overall pregnancy period.

2.3. Outcome assessment

2.3.1. Placental biomarkers: mitochondrial DNA content and telomere length

Placental biomarkers (namely, mtDNAcn and TL) were measured using a quantitative real-time polymerase chain reaction assay (qPCR) at the Centre for Environmental Sciences (CMK) at Hasselt University in

Belgium.

2.3.1.1. Sample selection. A total of 611 placental samples were collected from the BiSC cohort's 1032 births (out of $N_0 = 1080$ recruited pregnant women). Among them, 591 were selected for DNA extraction and 587 processed to obtain the placental biomarkers. The final sample size includes 499 mother-child pairs with exposure and placental biomarker measurements (more details can be found in the flowchart in Supplementary Fig. S1). Samples were randomized in laboratory batches (n = 8 samples per batch) and distribution of key variables (child sex and ethnicity, hospital of delivery, gestational age, birth weight, maternal smoking during pregnancy and COVID-19 pandemic birth status) was examined. Batches were manually adjusted to ensure an even representation of all variable categories and values.

2.3.1.2. Sample collection and DNA extraction. Trained gynecologists followed a standardized protocol to obtain placental biopsies of chorionic villi (See Supplementary Methods for further details). A 30-40 mg fragment of the upper chorionic villi preserved in RNAlater was used for genomic DNA extraction using the AllPrep®DNA/RNA/miRNA Universal Kit (Qiagen, CA, USA). DNA quality was assessed using a NanoDrop spectrophotometer (Thermo Fisher Scientific, MA, USA) and electrophoresis on 1% agarose gels. DNA concentration was quantified using the Invitrogen Qubit® Fluorometric Quantifier (Thermo Fisher). A final set of 96-well plates were generated at the desired DNA concentration and stored at −20°C for less than 10 days until further analyses were conducted.

In parallel DNA samples were also used to quantify DNA methylation using the Infinium MethylationEPIC BeadChip (Illumina, CA, USA) at the Human Genome facility (HUGE-F) in the Erasmus Medical Centre core facility following the manufacturer's protocol. DNA methylation was pre-processed as explained elsewhere (Vespalcova et al., 2025). Then, cell type proportions for six populations (trophoblasts, syncytiotrophoblasts, nucleated red blood cells (nRBCs), Hofbauer cells, endothelial cells and stromal cells) were estimated from DNA methylation via reference-based deconvolution using the placenta reference panel from the 3rd trimester (term) implemented in the *planet* R package (Yuan et al., 2021).

2.3.1.3. Placental mitochondrial DNA content measurements. Placental relative mtDNAcn was measured using a qPCR by determining the ratio of mitochondrial gene copy number (mitochondrial encoded NADH dehydrogenase subunit 1, or MT-ND1) to a nuclear single-copy reference gene (haemoglobin subunit gamma gene, HBG) as performed previously (Janssen et al., 2012) with some modifications (See Supplementary Methods). Final results are expressed as the ratio of mitochondrial DNA copy number to single-copy gene number (M/S) relative to the average M/S ratio of the entire sample set.

2.3.1.4. Placental telomere length measurements. Average relative telomere length was measured using a modified qPCR by determining the ratio of telomere native sequences copy number (using TelC and TelG primers) to a nuclear single-copy reference gene (haemoglobin subunit gamma gene, HBG) as performed previously (Martens et al., 2021) with some modifications (See Supplementary Methods). Final results are expressed as the ratio of telomere copy number to single-copy gene number (T/S) relative to the average T/S ratio of the entire sample set.

2.3.2. Clinical outcomes and covariates

Information on birth outcomes, such as birth weight and sex of the child, were abstracted from hospital records at each collaborating hospital. Gestational age at birth was based on crown–rump length measurement at the first trimester ultrasound and the date of delivery.

Participants of the BiSC cohort also attended supplementary visits during the 1st and 3rd trimesters of pregnancy, where a BiSC midwife intern collected additional clinically relevant variables including maternal weight (kg) and height (m). Maternal body mass index (BMI) was estimated as weight (kg) divided by height^2 (m^2) and then categorized above vs. below 25 kg/m^2, according to the World Health Organization (WHO) definition of overweight (World Health Organization, 2025). Other variables such as maternal age (years) and parity (nulliparous vs. multiparous) were extracted from clinical records at each hospital. Maternal age was categorized into two groups according to the standard American College of Obstetricians and Gynecologists definition of advanced maternal age: below 35 years and 35 years or older. Remaining lifestyle and sociodemographic variables were derived from questionnaires administered at pregnancy follow-up visits in the first, second and third trimesters: maternal smoking during pregnancy (no smoking vs. any smoking), educational level (university education vs. secondary or primary education, to ensure adequate sample size within categories), socioeconomic status (census tract-level average annual gross income per household, €) and parental ethnicity that was used to infer child ethnicity (European vs. Non-European). We created secondary variables including child ethnicity from the parental ethnicity (European vs. Non-European) and COVID-19 pandemic birth status (pre-COVID vs. post-COVID, using 11th March 2020 as the reference date based on the WHO pandemic declaration) (World Health Organization, 2026). We also created a variable to account for season of conception with two categories (warm season for spring and summer, and cold season for autumn and winter to simplify interpretation). Finally, cell type proportions were grouped into three categories: syncytiotrophoblasts, trophoblasts and other (including endothelial, stromal, Hofbauer and nRBC).

2.4. Statistical analysis

Linear mixed effects regression models were used to estimate the association between exposure to air pollutants from the hybrid LUR-dispersion model (one pollutant and exposure window at a time) and placental biomarkers (one at a time). All models were adjusted for child sex, child ethnicity, maternal age, parity, maternal educational level, smoking during pregnancy, gestational age at birth, pre-pregnancy maternal BMI, COVID-19 pandemic birth status, season of conception, hospital of birth and placental cell types as fixed effects and qPCR plate as random effect (all covariates were included in the analysis in the format defined in Section 2.3.2). More details on the model's adjustment can be found in Supplementary Methods.

Placental relative mtDNAcn was square-root transformed and TL was log2-transformed to better approximate a normal distribution of the model's residuals. Effect size is reported as difference in transformed variables of placental biomarkers by IQR increase of NO_2, black carbon and $PM_{2.5}$.

Several sensitivity analyses were conducted by: excluding minority ethnicities other than European (N = 340), excluding participants with a primary or secondary educational level (N = 333), excluding samples with less than 80% of syncythiotrophoblasts (N = 376), excluding individuals residing in census tracts above 90th percentile (N = 448) or below 10th percentile (N = 449) of average gross income per household, including only births after the onset of COVID-19 pandemic (N = 312) and including only male (N = 251) or female (N = 248) newborns. Additionally, we refitted the models without gestational age (to estimate the total effect of the exposure), adjusted for maternal age and BMI as continuous variables (instead of categorical), and used exposure estimates based on LUR models as an alternative set of exposures.

To assess the contribution of placental biomarkers to the association between prenatal air pollution exposure and birth weight, we applied both the standard Baron and Kenny mediation framework (Baron and Kenny, 1986) and a complementary change-in-estimate approach to evaluate the potential contribution to the exposure–outcome association (Mickey and Greenland, 1989). The latter consisted of examining changes in the regression coefficients from linear regression models

assessing the association between air pollution exposure and birth weight after adjustment for the placental biomarker, which allowed us to quantify its contribution on the outcome. The linear regression models implemented for these associations included the same exposure windows and were adjusted for the same covariates as the biomarker models (more details in Supplementary Methods and Supplementary Table S3).

All statistical analyses were performed using R Studio version 4.5.1.

3. Results

3.1. Characteristics of participants

Baseline characteristics of the study population are shown in Table 1. At 12 weeks of gestation, women's BMI was above 25 kg/m^2 in 33.9% of them, with a mean of 24.53 kg/m^2 (standard deviation [SD] 4.79). A total of 48.7% of them were over 35 years old, with a mean of 34.32 years (SD 4.49). Most women reported to have university education (66.7%). Maternal SES (average gross income per household) was €47216 (SD 12440). The proportion of women who smoked anytime during pregnancy was 7.0%. Season of conception was warm in 49.7% of participants. Women gave birth at Hospital Sant Joan de Déu (54.1%) or Hospital de la Santa Creu i Sant Pau (45.9%), and most of them were multiparous (56.1%). The gestational age varied from 30.71 to 42.86 gestational weeks with a mean of 39.68 gestational weeks (SD 1.49). Child sex was distributed as 50.3% male and 49.7% female. The majority of newborns were European (68.1%) and born after the outbreak of COVID-19 pandemic (62.5%). The birth weight ranged from 1400 to 4850 g, with a mean of 3280 g (SD 483). The aforementioned demographics did not substantially differ from those in the complete BiSC cohort (N = 1032 births). A comparison between study sample and BiSC cohort demographics is shown in Supplementary Table S1.

Table 1
Characteristics of the study population (N = 499).

Characteristics	Level or units	N (%) or Mean (SD)
Child sex	Male	251 (50.3)
	Female	248 (49.7)
Child ethnicity	European	340 (68.1)
	Non-European	159 (31.9)
Maternal age	<35 years	256 (51.3)
	≥35 years	243 (48.7)
Maternal parity	Nulliparous	219 (43.9)
	Multiparous	280 (56.1)
Maternal education	Secondary or primary education	166 (33.3)
	University education	333 (66.7)
Maternal BMI at 1st trimester	<25 kg/m^2	330 (66.1)
	≥25 kg/m^2	169 (33.9)
Hospital of birth	Hospital Sant Joan de Déu	270 (54.1)
	Hospital de la Santa Creu i Sant Pau	229 (45.9)
COVID-19 pandemic birth status	Pre-COVID-19	187 (37.5)
	Post-COVID-19	312 (62.5)
Season of conception	Warm (spring and summer)	248 (49.7)
	Cold (autumn and winter)	251 (50.3)
Birth weight	g	3280 (483)
Gestational age	Weeks	39.68 (1.49)
Maternal smoking	Any smoking during pregnancy	35 (7.0)
Census tract–level average gross income per household	€	47216 (12440)
NO_2 average exposure levels (hybrid)	μg/m^3	37.10 (6.81)
Black carbon average exposure levels (hybrid)	μg/m^3	1.19 (0.14)
$PM_{2.5}$ average exposure levels (hybrid)	μg/m^3	12.53 (1.04)
Syncytiotrophoblast ratio in placental sample	Cellular proportion	0.84 (0.10)
Trophoblast ratio in placental sample	Cellular proportion	0.07 (0.06)
Other cell ratio (endothelial, stromal, Hofbauer, nRBC)	Cellular proportion	0.08 (0.04)
Placental relative mitochondrial DNA content	Mitochondrial to single copy gene (M/S)	1.01 (0.33)
Placental relative telomere length	Telomere to single copy gene (T/S)	1.01 (0.23)

SD: standard deviation.

Air pollution exposure levels of BiSC participants substantially exceeded the World Health Organization recommendations (World Health Organization, 2021). Average pregnancy exposure was: 37.10 (SD 6.81) μg/m^3 for NO_2, 1.19 (SD 0.14) μg/m^3 for black carbon and 12.53 (SD 1.04) μg/m^3 for $PM_{2.5}$ estimated by hybrid models (Supplementary Table S2). Pearson correlation coefficients between pollutants, time windows and models are shown in Supplementary Fig. S2: correlations coefficients range from 0.06 (for $PM_{2.5}$ exposure between the 1st and 3rd trimesters based on LUR models) to 0.94 (for NO_2 exposure in the 1st trimester between the hybrid and LUR models), with a mean of 0.61 (SD 0.22).

Placental biomarker and cell type proportion measurements are summarized in Table 1. Syncytiotrophoblasts were the most abundant cell type in the placental biopsies, followed by trophoblasts, although some variation was observed between samples (Supplementary Fig. S3). The placental relative mtDNAcn was 1.01 (SD 0.33) and relative TL was 1.01 (SD 0.23) (data distribution of original values is shown in Supplementary Fig. S4). The placental relative mtDNAcn and relative TL had weak but positive correlation ($r = 0.162$, $p < 0.01$) (Supplementary Fig. S5). Placental biomarkers showed a weak relationship with cell type proportion: both trophoblast and endothelial cell levels displayed a slight positive relationship with mtDNcn and negative with TL; syncytiotrophoblast, nRBC and Hofbauer cell levels showed a slight negative relationship with mtDNcn and positive with TL (Supplementary Figs. S6 and S7). However, the data exhibit substantial variability for all cell types. The associations between placental biomarkers and main covariates (gestational age, pre-pregnancy BMI, socioeconomical status, maternal age, maternal educational level, child ethnicity, hospital of birth, maternal parity, sex and smoking during pregnancy) are shown in Supplementary Figs. S8 and S9. Among them, gestational age was the covariate showing the strongest association.

3.2. Association between prenatal air pollution exposure and placental biomarkers

We found statistically significant associations of prenatal air pollution exposure with placental mtDNAcn: increasing exposure to NO_2 and $PM_{2.5}$ during the 1st trimester, 3rd trimester and pregnancy periods, and increasing exposure to black carbon during the 3rd trimester, were associated with higher mtDNAcn (square root–transformed M/S ratio) (Fig. 1). Each IQR increase in NO_2, black carbon and $PM_{2.5}$ exposure (pregnancy average) was associated with an increase of 0.0184 (95% CI: 0.0018, 0.0369), 0.0100 (95% CI: −0.0063, 0.0263) and 0.0212 (95% CI: 0.0028, 0.0382) in mtDNAcn (square root–transformed M/S ratio), respectively.

We did not find statistically significant associations of prenatal air pollution exposure (NO_2, black carbon and $PM_{2.5}$) with placental TL measurements (log2-transformed T/S ratio) (Fig. 2).

3.3. The contribution of placental biomarkers in the air pollution–birth weight association

We found that higher levels of air pollution exposure were associated with lower birth weight in our sample of BiSC participants: 63.7 g decrease per IQR increase of NO_2 exposure during pregnancy (95% CI: −111.0, −16.4) and 50.5 g decrease per IQR increase of black carbon

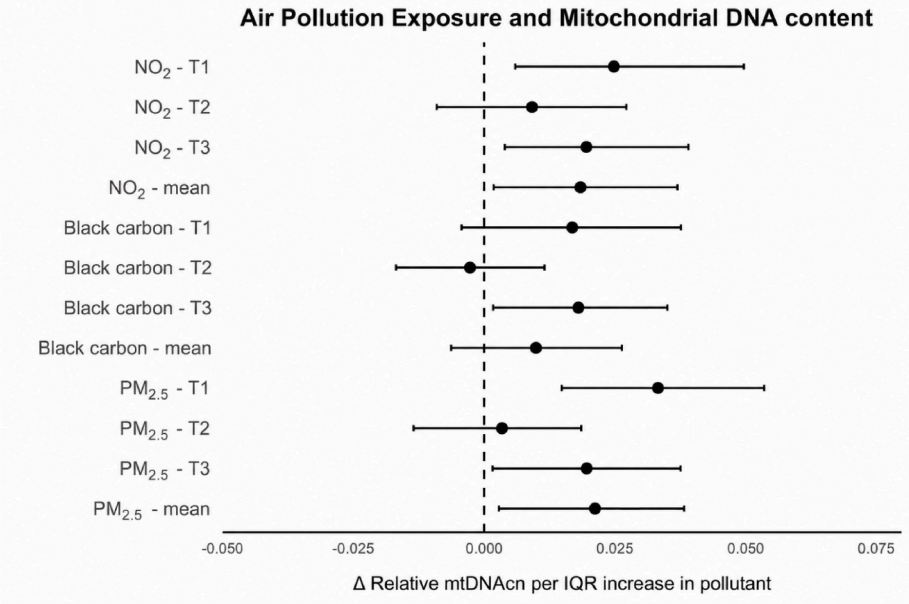

Fig. 1. Forest plot displaying coefficients and 95% confidence intervals for the relationship between air pollutants (NO_2, black carbon and $PM_{2.5}$ from hybrid models) and mitochondrial DNA content assessed by linear mixed effects models. Coefficients are expressed as differences in mitochondrial DNA to single copy gene (M/S) ratio (square-root-transformed) per IQR increase of pollutant (μg/m^3). T1, T2, and T3 indicate 1st, 2nd, and 3rd trimester, respectively. All models are adjusted for child sex, maternal age, parity, maternal education, ethnicity, smoking during pregnancy, gestational age at birth, pre-pregnancy maternal BMI, COVID-19 pandemic birth status, hospital of birth, season of conception and placental cell types as fixed effects, and qPCR plate as a random effect. The symbol Δ indicates differences in mtDNAcn measurements (square-root-transformed M/S ratio) per IQR increase of pollutant.

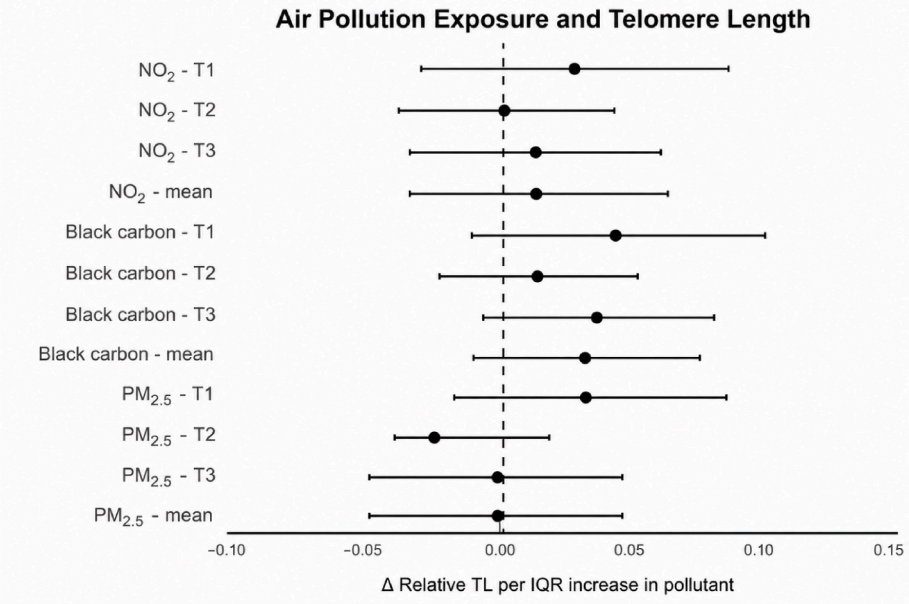

Fig. 2. Forest plot displaying coefficients and 95% confidence intervals for the relationship between air pollutants (NO_2, black carbon and $PM_{2.5}$ from hybrid models) and telomere length assessed by linear mixed effects models. Coefficients are expressed as differences in telomere to single copy gene (T/S) ratio (log2-transformed) per IQR increase of pollutant (μg/m^3). T1, T2, and T3 indicate 1st, 2nd, and 3rd trimester, respectively. All models are adjusted for child sex, maternal age, parity, maternal education, ethnicity, smoking during pregnancy, gestational age at birth, pre-pregnancy maternal BMI, COVID-19 pandemic birth status, hospital of birth, season of conception and placental cell types as fixed effects, and qPCR plate as a random effect. The symbol Δ indicates differences in TL measurements (log2-transformed T/S ratio) per IQR increase of pollutant.

exposure during pregnancy (95% CI: −94.0, −6.9) (Supplementary Table S3), while no significant results were found for $PM_{2.5}$ exposure (95% CI: −78.9, 16.7). Thus, we confirmed that our sample population showed associations in the same direction as those observed in the full BiSC cohort (Luo et al., 2026). Given the lack of statistically significant results for air pollution exposure and TL, we only analyzed the contribution of placental relative mtDNAcn in the previous association. However, mtDNAcn was not significantly associated with birth weight (−0.000011; 95% CI: −0.000047, 0.000025; p = 0.60). Therefore, although placental relative mtDNAcn was significantly associated with the exposure, a complete mediation analysis could not be performed as the mediator was not significantly associated with the outcome, a

required condition under the Baron and Kenny approach (Baron and Kenny, 1986). Thus, we evaluated the potential contribution of mtDNAcn by calculating the average reduction in the regression coefficients among pollutants and exposure windows after adjusting for mtDNAcn (Mickey and Greenland, 1989). This adjustment attenuated the significant associations between birth weight and air pollution exposures by an average of 39.04% (29.43% to 46.27%) (more details on the models can be found in Supplementary Table S3).

3.4. Sensitivity analyses

Across all sensitivity analyses (e.g., restricting to participants of European ethnicity, those with university education, samples with more than 80% of syncythiotrophoblasts, excluding families residing in census tracts above 90th or below 10th percentile of average gross income per household, births occurring after the onset of COVID-19 pandemic, analyses restricted to male or female newborns, use of LUR models for exposure assessment, excluding gestational age as covariate in the adjustment to estimate the total effect of the exposure, or adjusting for continuous maternal age and BMI) the effect estimates remained similar in magnitude and direction to the primary analyses, supporting the robustness of the findings. Detailed results are provided in Supplementary Tables S4 and S5.

4. Discussion

In this study, we hypothesized that air pollution might be influencing placental oxidative stress and cellular ageing, and that both could be mechanisms underlying the impact of air pollution on fetal growth. Our analyses showed that prenatal exposure to NO_2, black carbon and $PM_{2.5}$ were associated with increased mtDNAcn, but no relationship was found with TL. No significant associations were observed between birth weight and either mtDNAcn or TL.

Previous reviews suggest that air pollution exposure triggers oxidative stress pathways and therefore lead to a decrease in mtDNAcn (Saenen et al., 2019), however findings in the literature are mixed. While some studies have reported that air pollution exposure is associated with lower placental mtDNAcn (Clemente et al., 2017), others have found no association (Brunst et al., 2018). Studies in other tissues have found that mtDNAcn may exhibit a dynamic response to air pollution, depending on exposure levels and timing. For example, a cross-sectional study with healthy steel workers observed an increase in mtDNAcn in blood samples from workers exposed to higher levels of particulate matter (Hou et al., 2010). Moreover, it has been reported that short-term and moderate exposure (i.e., not high exposure) to air pollution could lead to an adaptive increase in mtDNAcn content in peripheral blood (Wang et al., 2020). Another explanation for these results is placental cellular heterogeneity: it is also possible that the response to air pollution varies by cell type and therefore depends on the biopsy location. Indeed, mitochondrial characteristics differ between syncytiotrophoblasts and trophoblasts (Jahan et al., 2023). Consistent with this, we observed that placental mtDNAcn increased with higher trophoblast cell proportion, while it decreased with higher syncytiotrophoblast proportion, whereas TL measurements showed the opposite pattern (Supplementary Figs. S6 and S7).

The complexity of this topic is further highlighted by multiple studies reporting associations between increased placental mtDNAcn and pregnancy complications. Specifically, significantly higher placental mtDNAcn has been observed in women with preeclampsia or intrauterine growth restriction compared to controls (Pandey et al., 2021; Vishnyakova et al., 2016). Additionally, preeclamptic women have been shown to have higher mtDNAcn in peripheral blood compared to controls (Mehzabin et al., 2025). These pregnancy complications usually compromise fetal growth, leading to lower birth weight (Nie et al., 2026). In our study, although the association between mtDNAcn and birth weight was not statistically significant, it was in the expected direction (increasing mtDNAcn associated with lower birth weight), supporting a potential contribution (see Supplementary Fig. S5). While cell type composition was adjusted for to account for potential technical artifacts and sampling noise inherent to placental biopsies, these cellular proportions may also lie on the causal pathway linking the studied placental biomarkers to birth weight. Consequently, adjustment for these variables could result in overadjustment and attenuation of biologically meaningful associations.

Furthermore, it must be noted that mtDNAcn is not an absolute marker of tissue oxidative stress, as mitochondrial toxicity can also develop due to other mechanisms such as alteration of mitochondrial membrane permeability and interference with the mitochondrial respiratory chain (Meyer et al., 2018). An *in vitro* study on the cellular response to air pollution exposure found that cultured trophoblasts exposed to collected urban (traffic-influenced) air samples showed no significant changes in measured mtDNAcn, but reported organelle swelling and vacuolated mitochondria (Nääv et al., 2020). Moreover, previous studies have reported that air pollution exposure is linked to changes in methylation in genes involved in cellular responses to oxidative stress and mitochondrial function, both in newborn cord blood and placenta tissue (Isaevska et al., 2021). Ultimately, these observations support the intricacy of how metabolically active tissues like the placenta can react to environmental insults such as different levels of air pollution exposure.

As for placental TL, we found no significant associations with prenatal air pollution exposure. Available evidence suggests that prenatal air pollution exposure, as well as other environmental insults, is associated with a decrease in TL in placenta as well as other tissues such as child blood (Gómez-Roig et al., 2021; Saenen et al., 2019). Air-pollution induced reactive oxygen species (ROS) are suggested to damage telomeres, leading to shortening and dysfunction. These alterations activate p53 signalling which suppresses the expression of key regulators of mitochondrial biogenesis and function (such as PGC-1α/β and Sirt1) resulting in decreased ATP production and increased ROS (Saenen et al., 2019). Together, these changes create a feedback loop between telomere dysfunction and mitochondrial impairment that promotes metabolic dysregulation and accelerates cellular ageing (Martens and Nawrot, 2016). This evidence points at a potential role of TL changes in placental pathways involved in oxidative stress, epigenetics, cellular ageing and energy metabolism. Thus, it seems unlikely that future studies demonstrate that TL is not a key component of the underlying mechanisms linking air pollution to adverse reproductive outcomes. However, our analysis could not contribute to this hypothesis. The lack of statistical associations in our study could be due to the small sample size as well as other limitations, as explained further below.

This study had several strengths. The main one is the detailed exposure assessment that is based on a combination of LUR and dispersion models, and includes the modelling of home, commuting and workplace environments, allowing a more accurate estimation of exposure. In addition, analyses were conducted including both hybrid and LUR models. Finally, the statistical models were adjusted for a wide range of potential confounders and covariates, such as the proportion of different placental cell types and season of conception to account for seasonal variations in birth weight and gene expression of the full-term placenta (Clarkson-Townsend et al., 2020), representing an important advancement compared with previous studies.

This study, however, had some limitations. First, the analyses were conducted in a subset of the total study population, which not only reduced the statistical power of the study, but could result in a selection bias. However, the fact that sociodemographic differences between the subset and the full sample were very small (as shown in Supplementary Table S1), and that the association between air pollution and birth weight in our subset is similar to that in the full BiSC population (Luo et al., 2026) suggest there is no such bias. Second, exposure measurement error could have affected the estimated associations; however, the consistency of the findings across the two exposure assessment models

provides some reassurance regarding their robustness. In addition, the implementation of single pollutant models may have introduced some bias, as they can be affected by residual confounding from correlated co-pollutants and cannot account for potential combined effects. Nevertheless, single-pollutant models were considered appropriate for evaluating pollutant-specific associations, given that correlations between pollutants were not consistently high. Of note, the results from each single-pollutant model cannot be interpreted as independent effects of the corresponding pollutant, as they do not account for co-pollutant confounding. Although exposure windows were investigated, more sophisticated models would be needed to disentangle window-specific effects. Third, a slightly higher proportion of BiSC participants (66.7%) had a university degree compared with the general population residing in Barcelona (46% in 2025) (Institut d'Estadística de Catalunya, 2025), which may limit the generalizability of our findings. Fourth, the data on smoking were collected by a self-administered questionnaire. It has been demonstrated that pregnant women tend to underreport their consumption of drugs during pregnancy (Gomez-Roig et al., 2018); therefore, our analysis might entail a misclassification of tobacco consumption levels as a covariate in the implemented models. Fifth, qPCR-based measurement of telomere length only provides a relative estimate and may show greater measurement variability compared with other methods, although it is considered adequate for large epidemiological studies due to its efficiency. Finally, although we adjusted for multiple potential confounders, the results cannot be interpreted as causal, and the potential contribution of mitochondrial DNA content to the association between air pollution and birth weight should be interpreted with caution.

5. Conclusion

In summary, prenatal exposure to ambient air pollutants was associated with increased placental mtDNAcn but not with placental TL. Neither placental biomarker fulfilled the assumptions required for mediation analysis. Further studies are needed to clarify the relationships between prenatal air pollution and placental molecular biomarkers.

Data availability

The data and code supporting the findings of this study are available from the corresponding author upon reasonable request.

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CRediT authorship contribution statement

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Conflict of interest

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijheh.2026.114865.

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