Environment International 204 (2025) 109801

Contents lists available at ScienceDirect

Environment International

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

Full length article

Unraveling the impact of prenatal air pollution for neonatal brain maturation

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ARTICLE INFO

Handling Editor: Adrian Covaci

Keywords:
Particulate matter
Neonates
Myelination
Brain development

ABSTRACT

Early brain development is highly sensitive to environmental influences. While prenatal exposure to airborne particulate matter ($PM_{2.5}$) has been broadly associated with harmful effects, $PM_{2.5}$ also contains trace elements such as iron, copper and zinc, which are essential for brain growth. This study examined both the overall impact of prenatal $PM_{2.5}$ exposure and the specific role of these trace elements on neonatal myelinated white matter—a key marker of brain maturation. This population-based study included 93 neonates recruited from three major hospitals in Barcelona (2018–2021). $PM_{2.5}$ exposure was estimated for the embryonic and late fetal periods using land-use regression models incorporating time-weighted maternal mobility data. MRI was performed at 29 days postnatally. Global myelinated white matter was manually segmented, and automated cortical myelination measures were obtained in 85 cases. Associations were examined using linear regression models with and without adjustment for potential confounders. Higher prenatal $PM_{2.5}$ exposure was associated with lower myelinated white matter content. Trace elements showed a similar pattern, but their associations became nonsignificant after adjusting for overall $PM_{2.5}$ exposure. The findings suggest that prenatal air pollution exposure may delay early myelination. Moreover, no specific associations were identified for iron, copper, or zinc. However, given the dynamic nature of white matter maturation, such delays may not necessarily be detrimental. This study underscores the impact of environmental factors on neonatal brain development and the

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https://doi.org/10.1016/j.envint.2025.109801
Received 5 May 2025; Received in revised form 4 September 2025; Accepted 15 September 2025
Available online 18 September 2025

importance of stringent air quality policies, while emphasizing the need for longitudinal research to assess long-term cognitive and behavioral outcomes.

1. Introduction

Understanding how environmental exposures shape early brain development is a pressing public health priority. Neurological and psychiatric disorders are among the leading causes of disability worldwide, and many originate in the prenatal and early postnatal periods (Rice and Barone, 2000). As the global burden of air pollution continues to rise, so does the urgency to uncover its potential impact on the developing brain. The prenatal period represents a uniquely vulnerable window during which environmental insults may exert lasting effects on brain structure, function, and ultimately, life-long health trajectories (Guxens et al., 2018; Lubczyńska et al., 2021). Identifying early biomarkers of environmental risk, such as altered myelination at the neonatal stage, may help guide targeted interventions and public health strategies to mitigate exposure-related neurodevelopmental harm.

Myelination, the formation of myelin sheaths around neuronal axons, begins prenatally and continues into late adulthood (Yakovlev and Lecours, 1967; de Faria et al., 2021; Paus, 2024). This process not only enables the rapid and efficient transmission of electrical impulses but also plays a key role in shaping neuronal circuits (de Faria et al., 2021; Paquola and Hong, 2023). Myelination follows a hierarchical sequence, progressing from basic to higher-order brain systems in alignment with behavioral milestones (Yakovlev and Lecours, 1967; Pujol et al., 2006; de Faria et al., 2021; Paquola and Hong, 2023). As such, myelination serves as a valuable indicator of brain maturation and functional competence.

Previous studies have indicated that prenatal exposure to air pollution is associated with alterations in myelin content and white matter integrity in childhood and preadolescence, potentially leading to long-term cognitive and behavioral consequences (Peterson et al., 2015; Guxens et al., 2018; Lubczyńska et al., 2021; Binter et al., 2024; Cotter et al., 2024; Yang et al., 2025). However, the specific effects of prenatal air pollution exposure on myelinated white matter have not yet been thoroughly evaluated in neonates (Morrel et al., 2025).

Among the different pollutant markers, particulate matter with a diameter of 2.5 μm or less ($PM_{2.5}$) is widely used as an indicator because it captures contributions from a variety of sources and contains diverse chemical components. As such, $PM_{2.5}$ can serve both as a global marker of overall pollution exposure and as a framework for disentangling the potential selective effects of individual constituents. $PM_{2.5}$ can be inhaled and penetrate physiological barriers, disrupting organ homeostasis at multiple levels (Block et al., 2012; Kim et al., 2015; Feng et al., 2016). In pregnant women, exposure to $PM_{2.5}$ has been shown to negatively affect gestation and fetal development (Yuan et al., 2019; Rodulfo-Cárdenas et al., 2023).

$PM_{2.5}$ consists of a diverse range of elements, many of which have been unequivocally shown to be harmful to the brain in various contexts (e.g., lead, mercury, arsenic). At the same time, it contains trace elements such as iron, copper and zinc, which are critical for brain development (Kim et al., 2015; Pan et al., 2022) and, importantly, play a key role in supporting white matter myelination during gestation (Brion et al., 2021; Georgieff, 2023; Chin-Chan et al., 2022).

Emerging work demonstrates that $PM_{2.5}$ −bound trace elements can cross the maternal-fetal barrier and affect offspring neurodevelopment (Johnson et al., 2021; Gude et al., 2004); moreover, maternal nutritional status may modulate their placental transfer and the neurodevelopmental impact of inhaled trace elements, potentially interacting with $PM_{2.5}$ mass to influence white matter maturation (Gude et al., 2004). Our group additionally reported that airborne copper exposure was associated with altered basal ganglia structure in school aged children, likely reflecting bypass of hepatic regulation and direct neurotoxic effects (Pujol et al., 2016). Importantly, these elements can have dual and opposing effects, as both deficiencies and excessive levels can lead to significant alterations in brain development (Pujol et al., 2016; Brion et al., 2021; Li et al., 2022; Cory-Slechta et al., 2023; Georgieff, 2023). This dual nature complicates the interpretation of $PM_{2.5}$'s effects, especially during gestation, a period of heightened maternal nutritional demand. For instance, maternal iron supplementation is widely used to prevent anemia and support fetal neurodevelopment (Georgieff, 2023), and zinc supplementation is increasingly recommended to optimize growth and neurodevelopment in at-risk infants (Brion et al., 2021; Alshaikh et al., 2022; Imdad et al., 2023).

Indeed, available imaging evidence suggests that the effects of prenatal air pollution on early brain morphology are neither simple nor unidirectional. Bos et al. (2023) reported opposing effects of in utero exposure to two key air pollution markers—particulate matter and nitrogen dioxide (NO_2). Specifically, higher gestational exposure to PM_{10} was strongly associated with larger relative ventricular and cerebellar volumes, while higher NO_2 exposure showed the opposite pattern. More modest, yet similarly inverse, associations were observed in other brain regions, where PM_{10} was linked to smaller cortical grey matter, amygdala, and hippocampus volumes, whereas NO_2 was associated with larger volumes in these areas. Interestingly, in our recent neurosonography study, we found that gestational exposure to $PM_{2.5}$ was associated with larger cerebellum dimensions (Gómez-Herrera et al., 2025).

Despite growing evidence that prenatal exposure to air pollution affects brain structure and function later in life, its impact during the neonatal period—a critical window when early brain changes may forecast long-term outcomes—remains poorly understood. Moreover, the biological complexity of $PM_{2.5}$ composition adds nuance to its potential effects. $PM_{2.5}$ contains essential trace elements like iron, copper, and zinc, which are crucial for neurodevelopment but may also be detrimental at abnormal levels. This complexity underscores the importance of examining not only overall $PM_{2.5}$ exposure but also the role of individual trace metals.

Therefore, this study aimed to investigate whether higher prenatal exposure to $PM_{2.5}$ is associated with alterations in global white matter myelination in neonates, using quantitative MRI. Because embryonic and late fetal stages involve distinct neurodevelopmental processes and vulnerabilities (Rice and Barone, 2000), we focused the analyses on exposures during the 1st and 3rd trimesters. Whole-brain myelinated white matter was segmented manually, and an automated image-processing pipeline was applied to specifically estimate cortical myelination. We hypothesized that greater $PM_{2.5}$ exposure during gestation would be associated with disrupted myelination in neonates. Additionally, we examined whether prenatal exposure to individual trace metals (iron, copper and zinc) would show distinct associations with neonatal myelin content, reflecting their biologically essential but potentially toxic roles in brain development.

2. Methods

2.1. Participants

This study was conducted as part of the European Research Council-funded project AirNB (ERC Advanced Grants 2018, Agreement 785994), which investigates the impact of prenatal environmental factors on brain development. AirNB was embedded within the population-based Barcelona Life Study Cohort (BiSC). A detailed description of the cohort profile, participant recruitment, and data collection process is provided in a previous report (Dadvand et al., 2024). The cohort

included 1,080 mother–child pairs recruited between October 2018 and March 2021 in Barcelona, Spain. Pregnant women between 18 to 45 years with singleton pregnancies were enrolled during their first-trimester routine hospital visit (around the 12th week of gestation) at three major university hospitals— Hospital Sant Joan de Déu, Hospital de la Santa Creu i Sant Pau, and Hospital Clínic de Barcelona— as well as their affiliated primary healthcare centers.

At the 32-week prenatal visit, all eligible participants from the general cohort were invited to join the MRI study and received a comprehensive explanation of its aims and procedures. Recruitment was consecutive and based on parental consent, with exclusion criteria including any potential risk and contraindication to MRI. A total of 132 neonates were enrolled, and high-quality anatomical MRI was successfully acquired in 93 cases, with a mean postmenstrual age of 44.0 weeks (SD = 1.2 weeks, range = 41.0–46.1 weeks), and mean postnatal age of 29.0 days (SD = 4.3 days, range = 23–45 days). Full demographic details are provided in Table 1.

All parents or legal guardians provided written informed consent for the study, which was approved by the Research Ethics Committee (No. 2018/8050/I) of Hospital del Mar, Barcelona. The study adhered to the principles of the Declaration of Helsinki. No compensation was provided to the parents of the assessed neonates.

2.2. Exposure assessment

$PM_{2.5}$ was used as an overall indicator of air quality. The measure includes fine inhalable particulate matter up to 2.5 μm in diameter, comprising chemical components emitted from diverse sources such as road traffic, industrial activities, land dust, and smokestacks (Kim et al., 2015). In addition, specific estimates were obtained for biologically essential trace elements, including iron, copper and zinc, which exist as suspended particles in the atmosphere and are also captured within the $PM_{2.5}$ measure. $PM_{2.5}$ was collected using 37 mm Teflon filters and BGI-400 pumps. Concentrations of trace elements were derived from the $PM_{2.5}$ fraction captured on these filters.

Land Use Regression (LUR) models were developed to estimate residential exposure to $PM_{2.5}$ and individual trace elements during pregnancy. These LUR models were developed following the guidelines of the European Study of Cohorts for Air Pollution Effects (ESCAPE) (Eeftens et al., 2012) and have been described in detail elsewhere (Domínguez et al., 2024), with a summary provided below.

Pollutant monitoring campaigns were conducted in 34 representative sites spread across the study area, each lasting an average of nine days. To account for seasonal variability, three monitoring campaigns were carried out in winter, summer and autumn. We first developed annual-average spatiotemporal LUR models using the 101 main predictors of air pollution concentrations (e.g., street type, greenness coverage, distance to major roads, population density, and traffic density) obtained as outlined in the ESCAPE guidelines. The adjusted coefficients of determination (R^2) for the LUR models were 47 % for $PM_{2.5}$, 91 % for $PM_{2.5}$ iron content, 90 % for $PM_{2.5}$ copper content, and 89 % for $PM_{2.5}$ zinc content.

We estimated exposure levels across three microenvironments: home, commuting and work. To determine total air pollutant exposure, we integrated the microenvironmental pollution levels with objective time-activity data reflecting the time spent in each setting. Using temporal data from a background station, we then adjusted the spatial estimates of the models following the ESCAPE ratio method, allowing for the calculation of hourly exposure levels throughout pregnancy for each participant (Eeftens et al., 2012). Finally, trimester-specific $PM_{2.5}$ measures were derived by averaging hourly concentrations.

Time-activity patterns of the participants were established using multiple complementary data sources: (i) Two one-week campaigns (one at the first and another at the third trimester) were conducted using GPS-enabled smartphones equipped with a validated geolocation application (ExpoApp, Ateknea Solutions, Spain) (Donaire-Gonzalez et al., 2019). (ii) Recoded commuting routes to and from the workplace using a GIS-based interface (QGIS software). (iii) Questionnaire and interview data were used to collect information on time spent at home, at work, and commuting, as well as residential and occupational addresses and preferred commuting modes at multiple time points during pregnancy. Further details about characterization of the time-activity patterns have been published elsewhere [https://www.sciencedirect.com/science/article/pii/S1353829225000024].

This study focused on data from the 1st and 3rd trimesters of gestation to differentially assess potential effects of embryonic versus late fetal exposure. The embryonic and fetal stages of brain development are qualitatively distinct in terms of key biological events and vulnerabilities (Rice and Barone, 2000). Organogenesis and the formation of early white matter tracts occur during the embryonic phase, making it highly susceptible to teratogenic disruption. In contrast, the fetal phase is characterized by rapid growth, synaptogenesis, gliogenesis, and the onset of myelination—processes that are more prone to subtle functional or connectivity-related perturbations (Rice and Barone, 2000; Dubois et al., 2014). Specifically, the embryonic period corresponds to a pre-myelinating state, when pre-oligodendroglial cells proliferate and settle along axons, while the fetal period is characterized by true myelination, with oligodendroglial processes ensheathing axons and progressive chemical maturation of the myelin sheath with increasing macromolecular content (Dubois et al., 2014; Jakovcevski et al., 2009).

2.3. MRI acquisition

MRI was acquired using a 3.0 Tesla Philips MRI scanner (Ingenia CX, Philips Healthcare, Best, The Netherlands) equipped with a 32-channel head-coil. Scans were performed during natural sleep, following feeding, without sedation. Infants were placed in an MRI-adapted foam cradle, fitted with hearing protectors, and monitored with a pediatric pulse oximeter to ensure a secure acquisition.

The MRI protocol has been previously described (Pujol et al., 2024). Two anatomical sequences were used in the present analysis. T1-weighted images were acquired using a high-resolution sagittal three-dimensional (3D) fast spoiled gradient inversion recovery-prepared (repetition time: 9.7 msec, echo time: 4.5 msec, flip angle: 8°, field of view: 180 × 180 × 120 mm, acquisition matrix: 180 × 180, voxel size: 1 mm^3). T2-weighted images were acquired using a fluid-attenuated inversion recovery (FLAIR) sequence (repetition time: 7,748 msec, echo time: 127 msec, inversion time: 2,100 msec, field of view: 180 × 180 × 129 mm, acquisition matrix: 120 × 120, in-plane voxel size: 1.5 × 1.5 mm, slice thickness: 3 mm).

Table 1
Characteristics of the study participants.

	Global myelination (n = 93)	Cortical myelination (n = 85)
Sex		
Boys	46.2 %	45.9 %
Girls	53.8 %	54.1 %
Postnatal age at MRI scan (days)	29.0 (4.3)	29.1 (4.2)
Postmenstrual age at MRI scan (weeks)	44.0 (1.2)	44.1 (1.1)
Maternal age at 1st trim. (years)	33.9 (4.2)	34.1 (4.1)
Maternal education		
University degree	74.2 %	74.1 %
No university degree	25.8 %	25.9 %
Family income, €/year	47,161 (10,715)	47,390 (10,819)
Ethnicity		
European	65.6 %	65.9 %
Other	34.4 %	34.1 %

Data are mean (standard deviation) or percentage (%).

2.4. MRI analysis

This study employed two complementary approaches to assess neonatal brain myelination. The global content of myelinated white matter was measured using manual segmentation, while cortical myelination was estimated through automated tools.

Manual segmentation: While image analysis in early developmental stages poses challenges, global myelinated white matter is easily identifiable in the neonatal brain due to its contrast with surrounding tissues (Fig. 1).

High-resolution 3D T1-weighted images were minimally preprocessed to prepare them for measurement. This included signal intensity normalization to optimize image uniformity and skull stripping to remove non-brain tissue. These steps were performed using Infant FreeSurfer pipelines, specifically tailored for neonatal brain MRI (Zöllei et al., 2020).

The Mango software (Research Imaging Institute, UTHSCSA) was used to display and manually segment myelinated white matter in the 3D brain volumes. An expert, extensively trained in neonatal neuroimaging, applied operational criteria to visually define the boundaries between myelinated white matter and other brain tissues.

First, signal intensity windows in Mango were adjusted by increasing the left (minimum) value and decreasing the right (maximum) value, ensuring that modifications did not exceed 20 % of the full range. The image histogram was then used to analyze voxel intensity distributions and determine the threshold that most accurately encompassed the myelinated white matter segment. The evaluator remained blinded to all demographic and exposure data throughout the process.

The measurement was repeated in a group of 50 randomly-selected cases to assess intra-rater reliability for the manual global myelination measure. The intra-class correlation coefficient (ICC) for single measures was 0.785 (Cronbach's alpha: 0.879), indicating good to excellent consistency of the measure (Cicchetti, 1994; Koo and Li, 2016).

Automated measurement. Cortical myelin content was estimated using the ratio of T1-weighted to T2-weighted images, which enhances the myelin contrast inherently present in both sequences (Glasser and Van Essen, 2011). High-quality images for both sequences were successfully acquired in 85 neonates, who exhibited demographic characteristics similar to those of the full 93-subject sample (Table 1).

Source images were processed using the Infant Brain Extraction and Analysis Toolbox (iBEAT v2.0 Cloud; http://www.ibeat.cloud), which includes pipelines specifically designed for infant MRI and fully described in the original report (Wang et al., 2023). Briefly, processing steps included reorientation and reslicing, intensity inhomogeneity correction, linear alignment of T1- and T2-weighted images, skull stripping, and tissue segmentation. The cortical surface was then reconstructed for each neonate in a vertex format to delineate the inner (gray-white matter) and outer (gray matter-CSF) cortical surface boundaries, defining a middle cortical surface as the geometric center between the two.

Separated from the previous steps, whole-brain T1-to-T2-weighted ratios were computed voxel-wise without intensity inhomogeneity correction from the source (T1 and T2) images. These voxel-wise ratios were then mapped onto the middle cortical surface so that each gray matter vertex corresponded a T1/T2-weighted myelination index. Finally, myelination values from all cortical vertices were averaged to obtain a single cortical myelination measure for each neonate.

2.5. Statistical analysis

Statistical analysis was performed using SPSS Version 23.0. Linear regression analyses were used to examine associations between age and both brain volume and myelination measures. Age is a general determinant of brain growth; therefore, these results served as a reference for interpreting the direction of associations related to air pollution exposure. Linear regression analyses were also conducted to assess the associations between early and late prenatal $PM_{2.5}$ exposure and myelination measures (both global and cortical), as the main analysis addressing the study's primary aim. Normality of outcome variables was assessed using the Kolmogorov–Smirnov test with Lilliefors correction, which showed $D = 0.049$, $p \geq 0.20$ ($n = 93$) for global myelination and $D = 0.093$, $p = 0.07$ ($n = 85$) for cortical myelination. The associations were further evaluated for selected trace elements (iron, copper and zinc), both in unadjusted models and models adjusted for $PM_{2.5}$, to assess the specificity of their potential associations with myelination. Correlations between $PM_{2.5}$ and trace elements yielded R^2 values ranging from 0.16 to 0.71.

As identified through a Directed Acyclic Graph (DAG) (Fig. A1), the linear regression analyses between $PM_{2.5}$ and myelination measures were repeated using potential confounders included as covariates. Results are presented for both unadjusted and adjusted models. We selected sex, postmenstrual age at MRI, ethnicity, maternal age, maternal education, and family income as potential confounders. This set of variables is commonly used in similar studies to reduce bias from confounding, as they broadly represent demographic and socioeconomic factors that may influence both prenatal air pollution exposure and early brain development.

Factors such as parity, season of delivery, vitamin supplementation, and breastfeeding may influence early brain maturation, also through effects on white matter development. While the overall cohort study was designed to investigate a broad range of early-life influences, the present imaging manuscript is specifically focused on examining the effects of prenatal air pollution exposure on myelination. In this context, exploratory analyses of the above factors did not reveal findings that would justify broadening the scope of the current report.

3. Results

Sociodemographic characteristics of participants are presented in Table 1. The MRI subsample did not differ significantly from the full cohort (N = 1,080) in any of these sociodemographic variables (Appendix Table A1). Descriptive statistics for $PM_{2.5}$, trace elements, and brain measures are presented in Table 2. Correlations between $PM_{2.5}$ and trace elements across developmental phases are presented in Appendix Table A2.

A statistically significant positive association was found between postmenstrual age at the time of MRI and both brain volume ($\beta = 18.5$, $r = 0.51$, $p = 2e\text{-}7$) and global myelination ($\beta = 1.37$, $r = 0.33$, $p = 0.001$), indicating that these brain measures were sensitive to detect developmental changes in neonates over a short period (Fig. 2). The association with postmenstrual age was stronger for brain volume, though brain volume and global myelination were highly correlated ($r = 0.55$, $p = 1e\text{-}8$). In contrast, no significant association was observed between postmenstrual age and cortical myelination index ($\beta = 0.005$, $r = 0.11$, $p = 0.330$).

Higher early gestation $PM_{2.5}$ exposure was significantly associated with lower cortical myelination ($\beta = -0.003$, $r = -0.31$, $p = 0.004$), whereas higher late gestation $PM_{2.5}$ exposure was significantly associated with lower global myelination ($\beta = -0.455$, $r = -0.29$, $p = 0.005$) (Fig. 3). Notably, $PM_{2.5}$ exposure was not associated with brain volume, neither for early ($\beta = -0.92$, $r = -0.10$, $p = 0.336$) nor late ($\beta = -1.69$, $r = -0.12$, $p = 0.243$) gestation $PM_{2.5}$.

Trace element exposure exhibited a relation pattern similar to that observed for $PM_{2.5}$ measures, regarding the direction of the associations. Overall, higher trace element exposure was associated with lower myelinated white matter. However, these associations were weaker, would not survive correction for multiple comparisons (e.g., Bonferroni or false discovery rate), and were further attenuated when models were adjusted for $PM_{2.5}$ exposure (Table 3).

Additional analyses were performed to evaluate whether the primary associations between pollutant exposure and myelination measures were influenced by potential confounders, including sex, postmenstrual

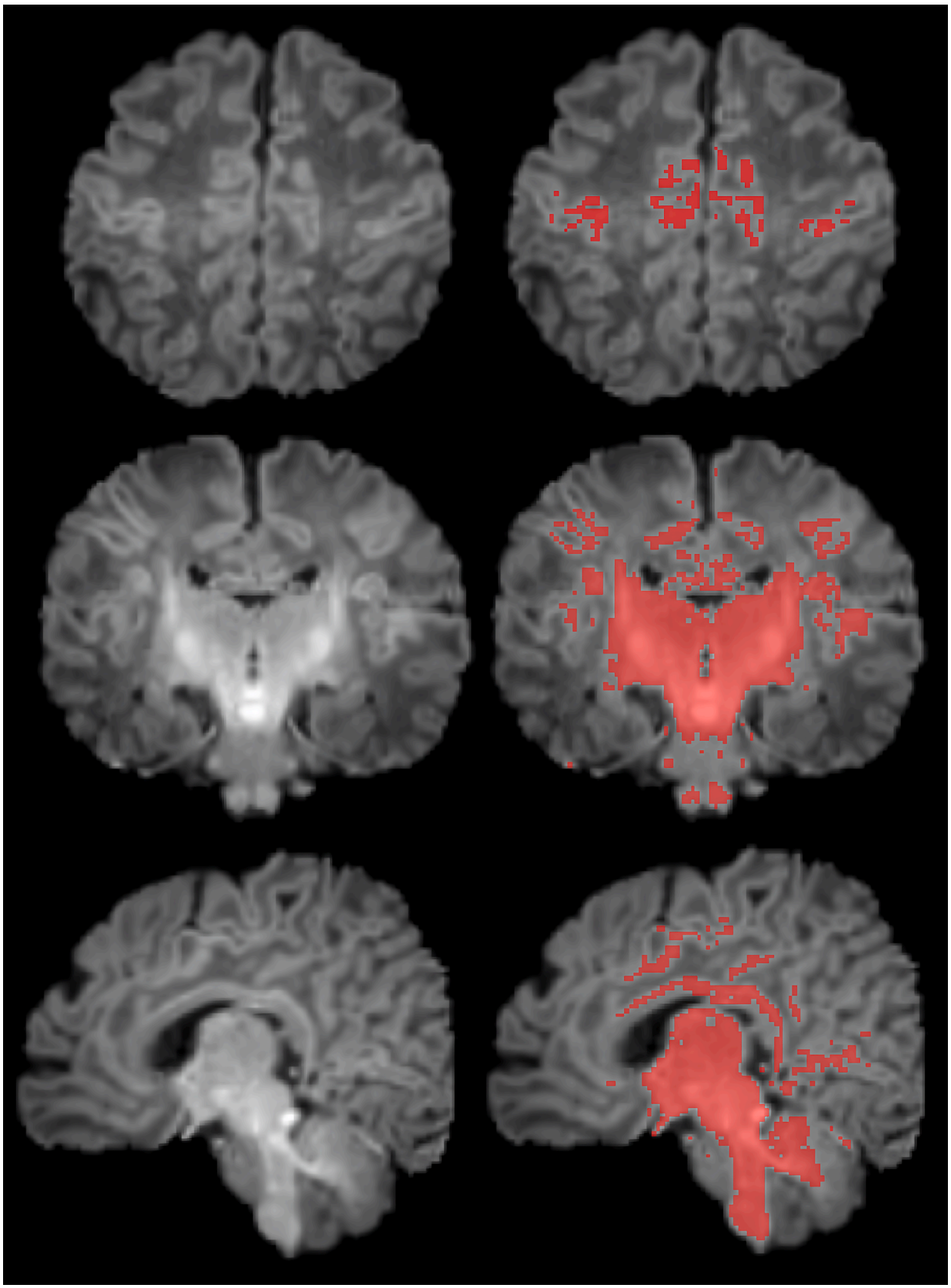

Fig. 1. High-resolution anatomical T1-weighted MRI illustrating the manual segmentation of myelinated white matter (shown in red). Note the clear contrast between myelinated white matter and surrounding brain tissues. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
$PM_{2.5}$, trace elements and brain measures.

	Mean	SD	Range
$PM_{2.5}$ (μg/m^3)			
$PM_{2.5}$ (embryonic)	17.0	4.6	11.0–29.6
$PM_{2.5}$ (late fetal)	16.2	3.0	10.1–22.0
Trace elements level			
Iron (embryonic) (μg/m^3)	0.22	0.07	0.10–0.59
Iron (late fetal) (μg/m^3)	0.21	0.07	0.10–0.44
Copper (embryonic) (ng/m^3)	6.1	2.2	2.9–13.1
Copper (late fetal) (ng/m^3)	5.7	1.6	3.1–9.7
Zinc (embryonic) (ng/m^3)	39.5	17.7	14.2–92.8
Zinc (late fetal) (ng/m^3)	37.8	17.1	18.1–87.2
Brain measures			
Global myelination (mL)	32.6	4.9	22.6–47.3
Cortical myelination (a.u.)	0.32	0.05	0.23–0.53
Brain Volume (mL)	468.3	42.2	352.5–566.4

a.u., arbitrary units.

age at MRI, ethnicity, maternal age, maternal education, and family income. Adjusting for these variables in regression analyses did not result in meaningful changes (Table 3).

4. Discussion

Maternal exposure to air pollution during gestation was significantly associated with white matter myelination in neonates. Higher $PM_{2.5}$ exposure in early gestation was related to lower cortical myelination, while higher exposure in late gestation was related to lower global myelination. The associations of iron, copper and zinc contents with myelinated white matter indexes followed the same pattern as $PM_{2.5}$, in terms of direction, although the correlations were weaker and became nonsignificant after adjusting for overall $PM_{2.5}$. Thus, no specific associations were identified for iron, copper, or zinc beyond the general implications.

Postmenstrual age at the time of the MRI examination was significantly associated with global myelination, supporting the accuracy of this measure. Myelination is a developmental process that progresses with age and the acquisition of new skills (Yakovlev and Lecours, 1967; Pujol et al., 2006; de Faria et al., 2021; Paquola and Hong, 2023), so a positive association between age and myelinated white matter content was expected. Notably, this association was significant despite the narrow postmenstrual age range of our neonatal sample (5 weeks), indicating that the global measure is sensitive to subtle changes in myelination. However, no significant association with age was observed for the cortical myelination index. Cortical myelination in neonates is still emerging and difficult to identify through visual inspection in

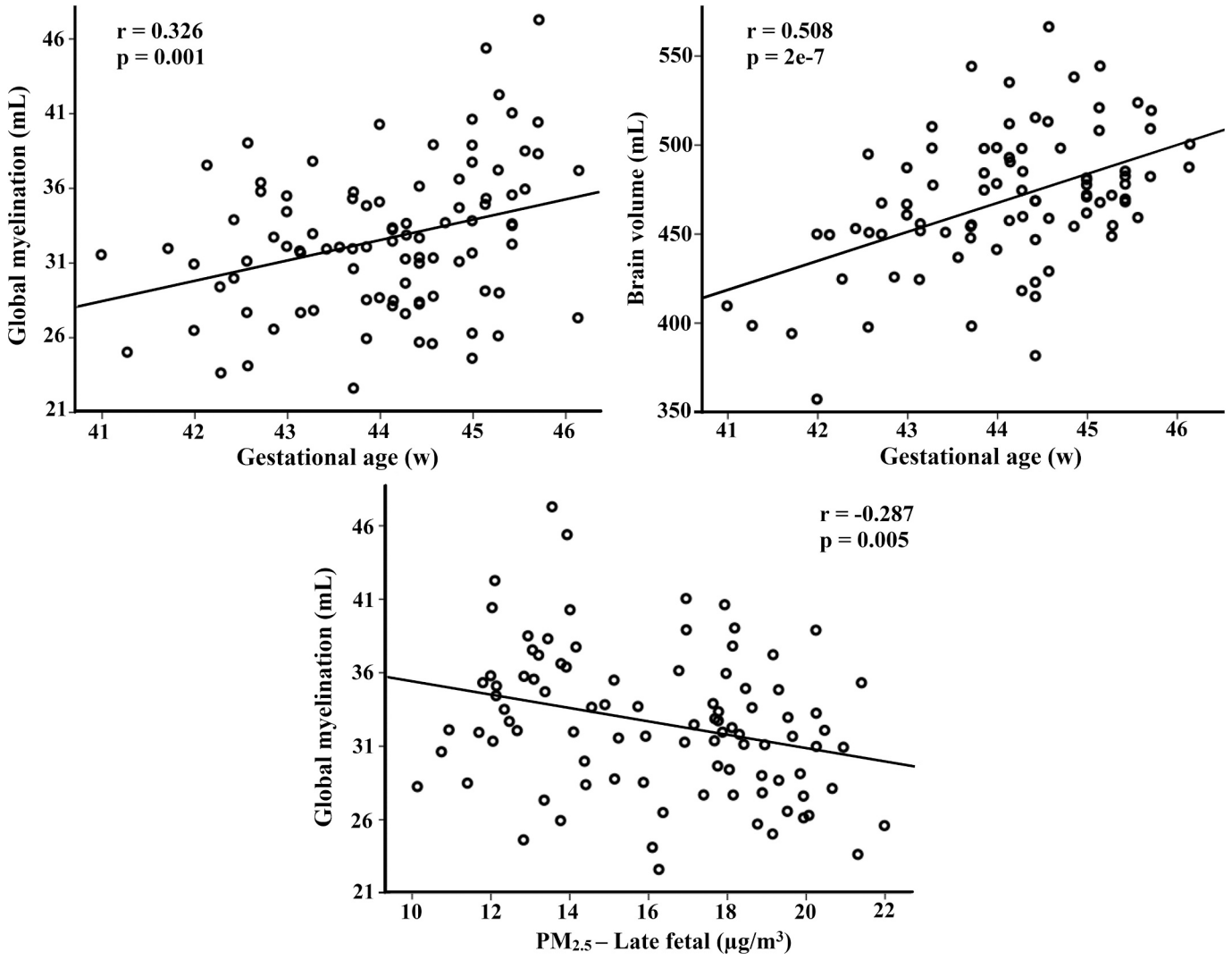

Fig. 2. Plots showing the correlations between postmenstrual age and both global myelination and brain volume, and between late gestation pollution exposure and global myelination.

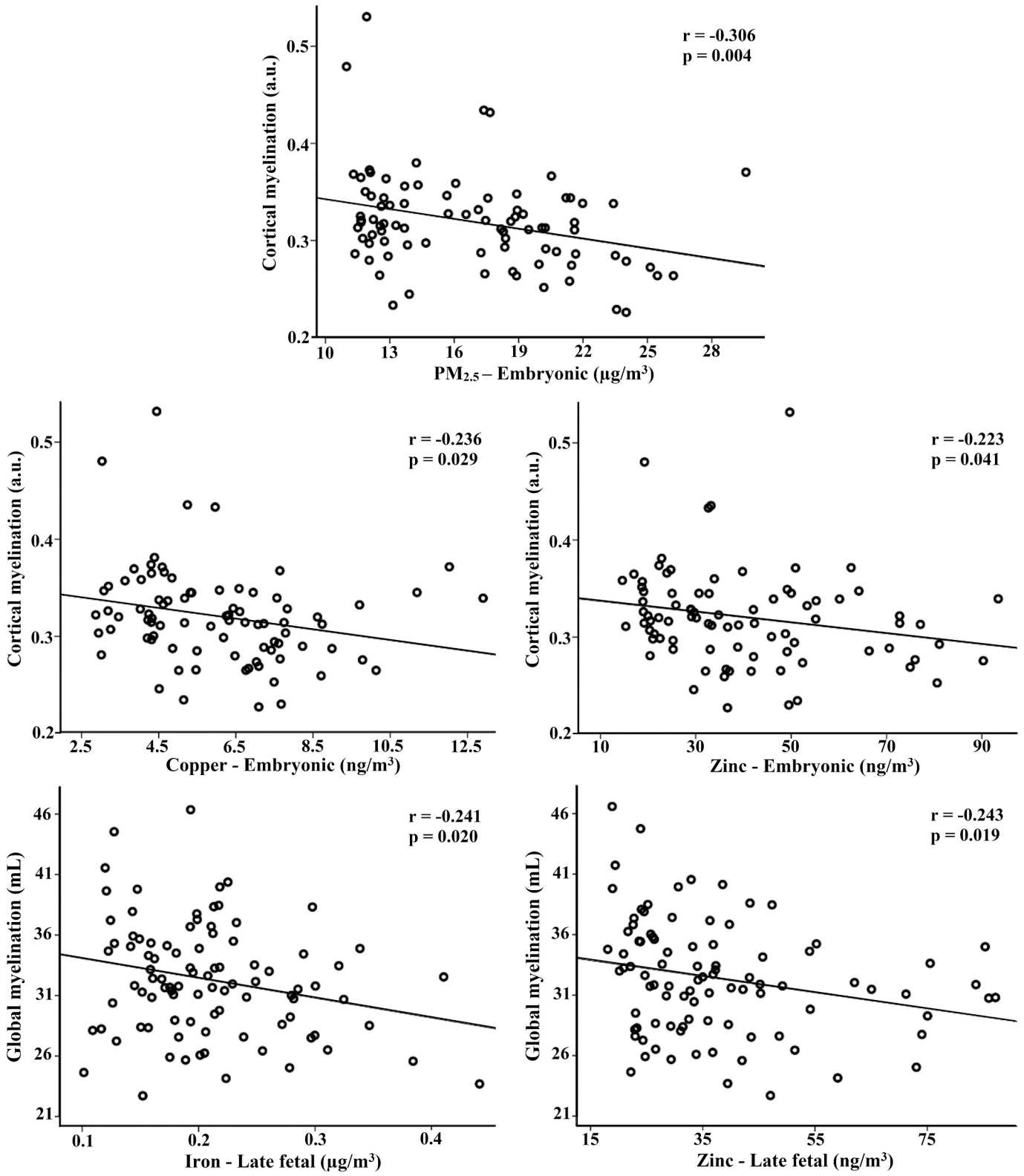

Fig. 3. Plots illustrating representative correlations between air pollution exposure and myelination measures.

neonatal MRI scans (Wang et al., 2023), making robust correlations with age less likely. Interestingly, $PM_{2.5}$ exposure was not associated with brain volume, neither for early nor late gestation, indicating a level of specificity in the influence of air pollution on distinct aspects of brain development.

Despite the low myelin content in the neonatal cortex, a significant negative association was observed between $PM_{2.5}$ exposure in early gestation and the cortical myelination index. This contrasts with global myelination, which was associated with $PM_{2.5}$ exposure in late gestation. The reasons for the discrepancy are not immediately clear. The cortex and deep white matter bundles may have different susceptibilities to chemical agents during the embryonic and fetal periods (Rakic and

Table 3
Linear regression analysis between air pollutants and myelination measures.

	Global myelination	Adjusted for $PM_{2.5}$	Cortical myelination	Adjusted for $PM_{2.5}$
	β (95 % CI)	β (95 % CI)	β (95 % CI)	β (95 % CI)
Pollutants				
$PM_{2.5}$ (embryonic)	−0.093 (−0.310, 0.124)		−0.003 (−0.006, −0.001)	
$PM_{2.5}$ (late fetal)	−0.455 (−0.771, −0.138)		4e-5 (−0.003, 0.004)	
Trace elements				
Iron (embryonic)	−5.021 (−15.92, 5.882)	−3.569 (21.82, 14.68)	−0.122 (−0.245, 0.001)	0.051 (−0.148, 0.251)
Iron (late fetal)	−17.058 (−31.39, −2.73)	−6.520 (−25.33, 12.29)	−0.027 (−0.191, 0.138)	−0.050 (−0.270, 0.171)
Copper (embryonic)	−0.062 (−0.516, 0.392)	0.351 (−0.492, 1.194)	−0.005 (−0.010, −0.001)	0.001 (−0.007, 0.010)
Copper (late fetal)	−0.540 (−1.158, 0.078)	−0.015 (−0.781, 0.752)	−0.0003 (−0.007, 0.007)	−0.001 (−0.009, 0.008)
Zinc (embryonic)	−0.048 (−0.104, 0.008)	−0.047 (−0.112, 0.017)	−0.001 (−0.001, −3e-5)	−0.0003 (−0.0009, −0.0004)
Zinc (late fetal)	−0.069 (−0.126, −0.012)	−0.043 (−0.104, 0.019)	−8e-5 (−0.001, 0.001)	−0.0001 (−0.001, 0.001)
Analysis adjusted for potential confounders				
Pollutants				
$PM_{2.5}$ (embryonic)	−0.105 (−0.316, 0.105)		−0.003 (−0.006, −0.001)	
$PM_{2.5}$ (late fetal)	−0.408 (−0.729, −0.086)		5e-4 (−0.003, 0.004)	
Trace elements				
Iron (embryonic)	−3.679 (−14.2, 6.84)	1.740 (−16.41, 19.89)	−0.130 (−0.256, −0.005)	0.044 (−0.165, 0.253)
Iron (late fetal)	−11.931 (−26.540, 2.678)	0.405 (−18.98, 19.79)	−0.027 (−0.201, 0.146)	−0.081 (−0.320, 0.158)
Copper (embryonic)	−0.061 (−0.495, 0.373)	0.444 (−0.377, 1.265)	−0.006 (−0.011, −0.001)	0.0004 (−0.009, 0.009)
Copper (late fetal)	−0.312 (−0.944, 0.320)	0.238 (−0.529, 1.006)	−0.0004 (−0.008, 0.007)	−0.002 (−0.011, 0.008)
Zinc (embryonic)	−0.031 (−0.91, 0.028)	−0.021 (−0.095, 0.053)	−0.001 (−0.001, 0.0002)	−0.0004 (−0.001, 0.0004)
Zinc (late fetal)	−0.055 (−0.120, 0.011)	−0.021 (−0.094, 0.052)	0.0002 (−0.001, 0.001)	−0.0003 (−0.001, 0.001)

β, beta regression coefficient (mL for Global Myelination and arbitrary units for Cortical Myelination). 95 % CI, 95 % confidence interval. Potential confounders: postmenstrual age, sex, maternal education, maternal age, ethnicity, annual family income (€).

Zecevic, 2000; Olney et al., 2002). Additionally, while the cortical myelination index – calculated as the ratio of T1- to T2-weighted MRI signal – is a robust marker of intracortical myelin density (Glasser and Van Essen, 2011; Parent et al., 2023), it may also reflect other tissue properties beyond myelin content (Parent et al., 2023; Sandrone et al., 2023), particularly in the immature neonatal cortex. Factors such as tissue composition and perfusion effects could further contribute to the cortical T1/T2 index (Sandrone et al., 2023). A more detailed investigation of the biological and methodological influences on this metric is needed to fully interpret these findings.

Our study's findings suggest that prenatal exposure to air pollution may interfere with early myelination, with the direction of the associations indicating a potential delay. A straightforward interpretation is that such exposure negatively impacts brain development, aligning with research on the long-term consequences of prenatal air pollution (e.g., Peterson et al., 2015; Guxens et al., 2018; Lubczyńska et al., 2021; Binter et al., 2024; Cotter et al., 2024; Yang et al., 2025). However, brain development is a complex and dynamic process. Strictly speaking, a delay in white matter myelination is not inherently detrimental, just as accelerated myelination is not necessarily beneficial.

Findings from the longitudinal study by Deoni et al. (2016) illustrated the dynamic nature of brain maturation. Their research showed that children with higher cognitive abilities exhibited a slower but more prolonged trajectory of white matter maturation. Specifically, higher cognitive ability was associated with slower initial myelination during the first year of life, followed by an extended period of rapid maturation between ages 1 and 2. Their study aligns with the consensus that white matter myelination parallels cognitive function while also emphasizing the significance of its temporal dynamics for optimal performance. Therefore, despite substantial evidence supporting the adverse effects of air pollution, further research considering the complexity and dynamism of brain development is needed.

As noted earlier in the introduction section, studies examining the associations between prenatal air pollution and brain morphology in fetuses and neonates have yielded paradoxical results (Bos et al., 2023; Gómez-Herrera et al., 2025). Depending on the air pollutant index considered, exposure has been linked to both increases and decreases in the volume of specific brain structures. All in all, the reported effects of maternal exposure to air pollution on the neonate appear heterogeneous. In contrast, brain imaging studies analyzing the direct effects during childhood have all consistently concluded that air pollution exposure adversely affects white matter development (reviewed in Morrel et al., 2025). Reported associations include smaller corpus callosum volumes (Lubczyńska et al., 2021), reduced striatal white matter (Pujol et al., 2016), and regional alterations in white matter morphology (Miller et al., 2022). Diffusion MRI studies further indicate disrupted myelination, reflected by lower fractional anisotropy or higher mean diffusivity (Lubczyńska et al., 2020; Binter et al., 2022; Kusters et al., 2024). Notably, some findings also show increased fractional anisotropy in areas of complex fiber crossing, a pattern consistent with less mature or less organized tissue (Pujol et al., 2016). Some studies observed heterogeneous effects depending on brain region and timing of exposure (Burnor et al., 2021; Cotter et al., 2024), reinforcing the view that white matter myelination is a complex and highly dynamic process.

A speculative explanation for dual effects in neonates is that the mother (and placenta) may act as a filter, preventing certain pollutants from reaching the fetus. This filtering process could selectively minimize the transfer of more harmful substances while allowing less harmful ones through—or even favoring the passage of essential elements for fetal development. It is well known that the fetus efficiently competes with the mother for oxygen and essential nutrients (Gude et al., 2004).

Limitations. Neuroimaging studies in neonates are challenging due to the need to obtain MRI scans without pharmacological sedation for ethical reasons. This constraint often results in a relatively high number of suboptimal exams due to motion artifacts. However, in neonates who remained asleep during the entire anatomical scan, MRI quality was

optimal, with minimal motion artifact. Additionally, complex image analyses tend to be less accurate in neonates than in adults because of factors such as smaller brain size and underdeveloped morphology (Gilmore et al., 2018; Fitzgibbon et al., 2020). However, our global measure of white matter myelination was obtained without the need for complex image transformations. The global index of myelinated white matter was directly estimated through manual segmentation with minimal preprocessing, taking advantage of the exquisite contrast between myelinated white matter and surrounding brain tissues.

Exposure misclassification is a concern. Although Land Use Regression (LUR) models are widely used to estimate air pollution exposure in epidemiological studies, they have inherent limitations. Specifically, LUR models are optimized for urban, traffic-related pollution and may not fully capture contributions from regional or natural sources. As a result, the prediction accuracy for $PM_{2.5}$ in our study was relatively low, but consistent with that of other $PM_{2.5}$ models previously developed for Barcelona (de Nazelle et al., 2013) and various locations across Europe (Eeftens et al., 2012).

Our imaging findings are based on a relatively small subsample of the overall cohort, which inevitably constrains statistical power and limits the scope for more detailed analyses of air pollution exposure. This restricted sample size may also introduce selection bias; however, as described in the Methods, the imaging subsample did not differ significantly from the full cohort with respect to key sociodemographic variables. Moreover, adjusted and unadjusted analyses yielded similar results, supporting the robustness of the findings. Finally, residual confounding is also a potential limitation, as not all early-life factors that may influence brain development could be comprehensively accounted for.

In conclusion, our findings suggest that prenatal air pollution exposure may interfere with early myelination, potentially delaying white matter maturation. No specific associations were identified for iron, copper, or zinc beyond their link to overall $PM_{2.5}$. Notably, myelination is a dynamic process, and delays are not inherently detrimental, as slower early myelination can be associated with prolonged maturation and higher cognitive abilities. While substantial evidence supports the adverse impact of air pollution, further research considering the complex nature of early brain development is needed.

CRediT authorship contribution statement

Jesus Pujol: Writing – review & editing, Writing – original draft, Validation, Supervision, Formal analysis, Conceptualization. **Gerard Martínez-Vilavella:** Writing – review & editing, Writing – original draft, Formal analysis. **Laura Gómez-Herrera:** Writing – review & editing, Investigation. **Ioar Rivas:** Writing – review & editing, Investigation. **Maria Dolors Gómez-Roig:** Writing – review & editing, Validation, Supervision, Investigation. **Elisa Llurba:** Writing – review & editing, Validation, Supervision, Investigation. **Laura Blanco-Hinojo:** Writing – review & editing, Validation, Supervision, Formal analysis. **Marta Cirach:** Writing – review & editing, Investigation. **Cecilia Persavento:** Writing – review & editing, Investigation. **Xavier Querol:** Writing – review & editing, Validation, Supervision, Methodology, Conceptualization. **Mireia Gascón:** Writing – review & editing, Investigation. **Maria Foraster:** Writing – review & editing, Investigation. **Juan Domingo Gispert:** Writing – review & editing, Supervision, Conceptualization. **Carles Falcón:** Writing – review & editing, Validation, Methodology. **Joan Deus:** Writing – review & editing, Visualization, Supervision, Methodology. **Payam Dadvand:** Writing – review & editing, Validation, Supervision, Conceptualization. **Jordi Sunyer:** Writing – review & editing, Validation, Supervision, Funding acquisition, Conceptualization.

Funding

The AirNB project has received funding from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme (AirNB projectERC- Advanced Grants 2018, agreement 785994).

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.

Acknowledgments

We would like to thank all the participants and their families for their generous collaboration. Thanks to all the researchers who work with the Mother-Child Barcelona Life Study Cohort- BiSC umbrella project. A full list of BiSC researchers can be found at https://projectebisc.org/en/team/. We extend our acknowledgment to the Health Effects Institute (4959-RFA17-1/18-1 – FRONTIER project); H2020 -EU.3.1.2. (874583 - ATHLETE project), H2020-EU.3.1.1. (GA964827 – AURORA project), the Marie Skłodowska-Curie grant agreement (886121); Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (2019/01/039 - HyPAXE project), AXA Research Fund (MOOD-COVID project), the Instituto de Salud Carlos III and the European Regional Development Fund - Maternal and Child Health and Development Network (RD16/0022/0014 and RD16/0022/0015), the AGAUR-Agència de Gestió d'Ajuts Universitaris de Recerca (2021 SGR 01570 - Population Neuroscience group), the Centro de Investigación Biomédica en Red de Epidemiología y Salud Pública (CB06/02/0041), and the Instituto de Salud Carlos III and the European Union Next Generation EU - Primary Care Interventions to Prevent Maternal and Child Chronic Diseases of Perinatal and Developmental Origin Network (RD21/0012/0001 and RD21/0012/0003) for funding the umbrella BiSC cohort. The authors thank the iBEAT V2.0 Cloud group at the University of North Carolina for their assistance with the analysis (DOIs: 10.1007/978-3-030-00931-1_47, 10.1016/j.neuroimage.2013.12.038, 10.1016/j.media.2015.04.005, 10.1016/j.neuroimage.2018.03.042). Gerard Martínez-Vilavella thanks the Department of Clinical and Health Psychology at the Autonomous University of Barcelona for its assistance during his PhD.

Appendix

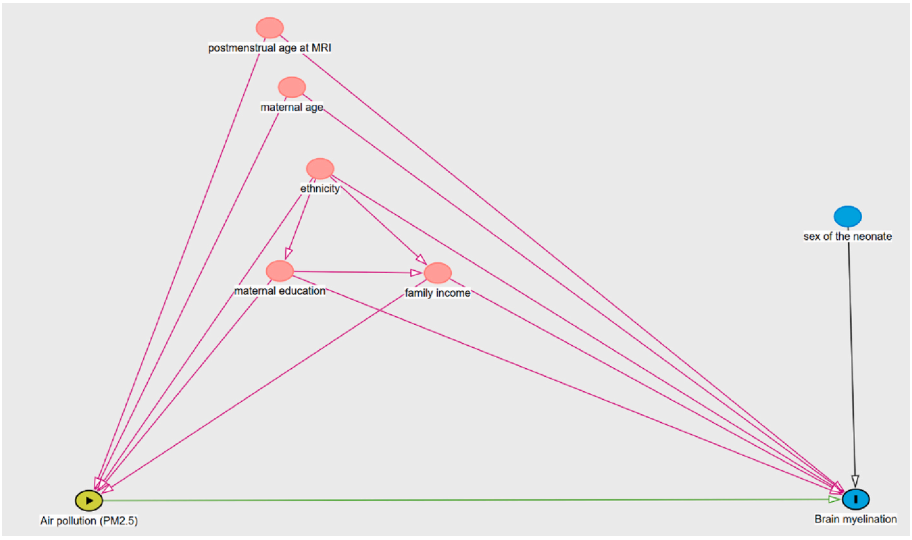

Fig. A1. Directed Acyclic Graph (DAG) showing the dependencies between air pollution (exposure), neonatal brain myelination (outcome) and other variables affecting the associations.

Table A1
Comparison between the MRI sample and the full cohort.

	MRI sample (n = 93)	Full cohort (n = 1,080)	X^2/t	p
Sex			0.627	0.428
Boys	46.2 %	50,7%		
Girls	53.8 %	49,3%		
Gestational age at birth (weeks)	39.9 (1.0)	39.7 (1.7)*	0.144	0.886
Maternal age at 1st trim. (years)	34.0 (4.2)	34.1 (4.7)	−0.313	0.754
Maternal education			0.745	0.388
University degree	74.2 %	69,2%		
No university degree	25.8 %	30,8%		
Family income, €/year	47,151 (10,669)	47,798 (12,241)	−0.533	0.594
Ethnicity			0.109	0.741
European	65.6 %	67,1 %		
Other	34.4 %	32,9 %		

Data are mean (standard deviation) or percentage (%). *Premature infants (<37 weeks) are not included in the comparison

Table A2
Correlations between $PM_{2.5}$ and trace elements across developmental phases.

Phase/pollutant	$PM_{2.5}$	Iron	Copper	Zinc
Embryonic phase				
$PM_{2.5}$	1	0.800	0.843	0.486
Iron		1	0.959	0.524
Copper			1	0.515
Zinc				1
Late fetal phase				
$PM_{2.5}$	1	0.656	0.613	0.406
Iron		1	0.874	0.468
Copper			1	0.369
Zinc				1
Cross-phase correlations (embryonic → late fetal)				
$PM_{2.5}$	−0.066	0.168	0.109	−0.140
Iron	−0.015	0.568	0.427	0.045
Copper	−0.090	0.450	0.387	−0.034
Zinc	−0.120	0.225	0.120	0.598

The correlations are expressed using the Pearson correlation coefficient (r).

Data availability

Data from the study will be available upon reasonable request to the senior authors.

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