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Modeling the effects of prenatal $PM_{2.5}$ exposure on development of school-aged children using functional regression

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ABSTRACT

Emerging evidence suggests that prenatal exposure to fine particulate matter ($PM_{2.5}$) may adversely affect child neurodevelopment. However, studies evaluating the multidimensional nature and timing of these effects remain limited. This study investigated the association between prenatal $PM_{2.5}$ exposure and child developmental outcomes in a cohort of Italian school-age children, with a focus on identifying critical exposure windows during gestation and recent WHO-recommended thresholds. Data were drawn from an observational study in Italy conducted between 2021–2022. Child development was assessed at school-age using the Developmental Profile 4 (DP-4), covering five key domains: physical, adaptive behavior, cognitive, social-emotional, and communication. Prenatal $PM_{2.5}$ exposure was estimated using the satellite reanalysis dataset, and penalized functional regression models were applied to evaluate time-varying associations across pregnancy. Models adjusted for a wide range of maternal, paternal, child, and family-related confounders. Higher exposure to $PM_{2.5}$ during pregnancy was significantly associated with lower total DP-4 scores. The strongest effects were observed in the cognitive and socio-emotional domains, and for exposure from the fifth month of pregnancy onward. With respect to the WHO-recommended threshold of 5 $\mu g/m^3$, children exhibited an average reduction of about 3 points in total developmental scores. Prenatal exposure to $PM_{2.5}$, particularly during mid-to-late pregnancy, is associated with deficits in key domains of child development. These findings underscore the importance of stringent air quality standards to protect fetal brain development, especially in highly polluted regions.

1. Introduction

Air pollution has become a constant element of daily life, with extensive evidence linking exposure to pollutants and detrimental health outcomes (Manisalidis et al., 2020). Among these pollutants, fine particulate matter ($PM_{2.5}$) has received increasing attention due to its substantial contribution to the global burden of non-communicable diseases (Southerland et al., 2022). While the respiratory and cardiovascular effects of air pollution are well established, data connecting exposure to $PM_{2.5}$ with neurobehavioral and cognitive development in children remains less clearly defined, with findings that are often mixed and inconsistent across studies (Guxens et al., 2014; Clifford et al., 2016; McGuinn et al., 2020; Ni et al., 2022).

Early-life exposure to environmental pollutants is of particular concern for child development, as the prenatal and early postnatal periods represent windows of heightened vulnerability. During these sensitive stages, even low levels of toxic substances can interfere with the complex processes involved in brain development, with long-term potential consequences for cognitive, behavioral, and emotional functioning (Grandjean and Landrigan, 2014; Landrigan et al., 2018). In particular, prenatal exposure to airborne pollutants has been shown to cross the placental barrier and induce systemic inflammation, oxidative stress, and epigenetic alterations, thereby disrupting essential neurodevelopmental processes (Bové et al., 2019).

A growing body of research has examined the association between early-life exposure to $PM_{2.5}$ and child developmental outcomes, reporting links with reduced cognitive performance, physical health, and socio-emotional difficulties (Johnson et al., 2021; Domínguez et al., 2024).

Evidence from large-scale cross-sectional studies conducted in the United States and Europe has shown associations between prenatal $PM_{2.5}$ and reductions in nonverbal IQ, deficits in fine motor skills, and memory performance in school-aged children (Harris et al., 2015; Lubczyńska et al., 2017). These findings have been supported by longitudinal and cohort-based studies (Kim et al., 2014; Sunyer et al., 2015;

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Forns et al., 2017; Gonzalez-Casanova et al., 2018). However, results vary considerably across geographical regions and study designs. Multi-site studies in the United States have reported substantial variability in both the magnitude and direction of associations between prenatal exposure to $PM_{2.5}$ and child developmental outcomes.

For instance, Chang et al. (2022) reported heterogeneous associations between third-trimester $PM_{2.5}$ exposure and childhood cognition across different US cohorts. Some sites showed stronger or weaker associations, and the effects appeared to be influenced by contextual and population-level factors, such as socio-demographic characteristics and urbanicity. In contrast, European cohort studies tend to report more consistent associations between prenatal exposure to air pollution and adverse developmental outcomes, including cognitive and behavioral impairments (e.g., Guxens et al., 2014). However, even within Europe, findings are not entirely consistent, as differences in study design, exposure assessment, and outcome measurement contribute to residual variability across studies.

Importantly, the heterogeneity observed across studies is not limited to variation in effect estimates, but also extends to the identification of critical windows of susceptibility. While several studies highlight mid-to-late pregnancy as a particularly sensitive period for $PM_{2.5}$ exposure (e.g., Harris et al., 2015; Liu et al., 2022; Zhang et al., 2022; Morgan et al., 2023), other evidence points to narrower early gestational windows as critical for later cognitive, behavioral, and motor outcomes (e.g., McGuinn et al., 2020; Bansal et al., 2021; Guilbert et al., 2023; Tokuda et al., 2023; Whitworth et al., 2024). Overall, these inconsistencies underscore the need for further research to better understand the timing and contexts in which prenatal exposure influences child development.

Despite the growing literature, important gaps remain. In particular, relatively few studies have examined these associations in regions characterized by persistently high levels of air pollution. Among them, the Po Valley in northern Italy stands out as one of the most polluted regions in Europe, frequently surpassing limits for $PM_{2.5}$, PM_{10}, and NO_2 (Beloconi and Vounatsou, 2023). This persistent air pollution burden provides a critical context in which to examine whether previously observed associations are detectable, and whether magnitude and timing differ in relation to compliance with established air quality standards (Block and Calderón-Garcidueñas, 2009; Peterson et al., 2015; Costa et al., 2020).

Over the past decades, several European regions have experienced persistently high levels of air pollution (Richardson et al., 2013). In response to accumulating evidence of health risks, particularly for children, the World Health Organization (WHO) revised its air quality guidelines in 2021, halving the recommended annual $PM_{2.5}$ limit from 10 $\mu g/m^3$ to 5 $\mu g/m^3$ and setting an interim daily average target at 15 $\mu g/m^3$ (World Health Organization, 2021). This revision reflects growing consensus that even low-level exposures are harmful (Guxens and Sunyer, 2012; Schraufnagel et al., 2019; World Health Organization, 2021). Despite regulatory efforts, many areas continue to report annual $PM_{2.5}$ concentrations exceeding the new WHO guideline. Therefore, investigating this context is critical to assess whether previously observed associations generalize to high-exposure settings and to better understand how sustained environmental burden may influence both the magnitude and timing of developmental effects.

Another key limitation of the existing literature lies in the widespread use of aggregated or trimester-based exposure metrics, which may obscure more refined temporal patterns of vulnerability. In the present study, to capture the dynamic nature of prenatal exposure, we employed functional regression models, a state-of-the-art analytical approach that allows for the assessment of time-varying effects of environmental exposures across the gestational period. Unlike traditional regression methods that assume static exposure-outcome relationships, functional regression enables the modeling of exposure trajectories as continuous functions over time, providing greater sensitivity in identifying critical windows of vulnerability during pregnancy (see e.g., Goldsmith et al., 2011; Morris, 2015). This approach is particularly suited for environmental epidemiology studies where exposure patterns may fluctuate substantially throughout gestation, thereby offering a more nuanced understanding of how specific timing of $PM_{2.5}$ exposure influences child developmental outcomes.

Last, child development is inherently shaped by a complex interplay of environmental, biological, and socio-contextual factors (e.g., Bronfenbrenner, 1979). Variables such as parental educational level (as a proxy for socioeconomic status), maternal age, parenting stress, and broader environmental conditions are well-established determinants of developmental outcomes. These factors may independently influence development, making it essential to account for them in empirical analyses. From a developmental perspective, isolating the specific contribution of air pollution requires careful consideration of these contextual influences, in order to disentangle pollution-related effects from broader environmental and familial conditions that are known to shape developmental trajectories.

2. Methods

2.1. Participants

As a part of a broader study, 1930 parents of a child residing in a large set of municipalities in Italy between May 2021 and December 2022 took part in the study. Each parent was interviewed once, and the study followed a cross-sectional design, with data collected at the time of recruitment. Out of 1930 participants we included in this study only those who met the inclusion criteria: 1) the presence of a valid address of residence; 2) to be resident in the same house during the pregnancy; 3) child age between 3 and 9 years old; 4) a link with the temporal window of the available air pollution data (2013–2023, for further details, see the next section); 5) absence of reported disability; 6) no missing data for the variables of interest (Table A.4).

The comparison between selected and non-selected children (Table A.5) shows that the main difference lies in the age distribution ($p < 0.001$), reflecting the selection criteria. Apart from age, the other variables display only modest differences, with largely similar socio-demographic and perinatal profiles across groups. Although some differences are statistically significant – such as slightly higher maternal education, a greater proportion of non-Italian mothers, longer breastfeeding duration, higher maternal smoking during pregnancy, lower PSI scores, more married or cohabiting parents, and more online interviews – their magnitude is small and likely partly driven by the underlying age structure.

The geographical distribution of the 624 children who met the inclusion criteria, based on their residential address, is presented in the Supplementary Material (Figure A.4). The study was carried out according to the Declaration of Helsinki. Informed consent was obtained from all participants and the study protocol was approved by the ethical committee of the University of Padua (Ethics Committee for Psychological Research; Protocol number 4216 on May 31st, 2021).

2.2. Interview and measures

Data were collected through interviews administered to a convenience sample of participants recruited on a voluntary basis. The interviews gathered socio-demographic information on the child (e.g. birth date, gender, nationality, and country of residence), the family (e.g. family structure, number and age of siblings, parental stress index), and the parents (e.g. occupation, educational attainment, and nationality), as well as a range of potential confounders such as smoking habits, years of residence, school location, and characteristics of the residential area. The majority of interviews (90%) were conducted with mothers. Overall, 86% of the interviews were administered online through secure videocall applications, while the remaining 14% were completed through face-to-face interviews. Each parent was interviewed once.

Data collection was conducted by multiple interviewers. Nineteen interviewers administered at least 10 interviews each; among these, the average number of interviews conducted was 31.5 (range: 10–90). There was no predefined minimum number of interviews per interviewer. Interviewers who conducted fewer than 10 interviews were grouped into a single "other" category, which comprised a total of 26 interviews. Importantly, all interviews followed the same standardized protocol, ensuring consistency across interviewers regardless of the number of interviews they administered.

2.3. Data and measures

2.3.1. Developmental Profile 4

The Developmental Profile 4 questionnaire (DP-4) (Alpern, 2020) was used to evaluate developmental domains. The DP-4 is a standardized instrument designed to assess development from birth to 21 years, and is therefore suitable for the age range considered in this study (3–9 years). It assesses child development across five domains – cognitive, communication, socio-emotional, adaptive, and physical – through parent reports of everyday behaviors. The instrument consists of 189 items describing developmental milestones observed in daily life. Parents are asked to indicate whether their child shows each behavior at a given frequency. The DP-4 follows standardized basal and ceiling rules, whereby items are administered along a hierarchical sequence of developmental milestones until a ceiling is reached, ensuring comparability of scores across different ages. Each domain can be evaluated and scored independently, providing domain-specific measures, as well as an overall General Development Score. In the present study, the DP-4 was administered as a semi-structured interview, conducted either online via a secure video call platform or in person. The distribution of DP-4 scores, both overall and by functional domain, is shown in Figure A.5. The empirical Cronbach coefficient α in all five subdomains was 0.915, indicating excellent internal consistency.

2.3.2. Parenting Stress Index - Short Form version

The Parenting Stress Index (PSI) is a widely used instrument for assessing parenting stress in both clinical and non-clinical populations. In this study, mothers were asked to complete the 36-item short form of PSI (Abidin et al., 2006), which is rated on a 5-point Likert scale. Items are organized into three subscales: Parental Distress, Parent-Child Dysfunctional Interaction, and Difficult Child, reflecting key dimensions of parenting stress. A total stress score is calculated by summing up the scores from all three subscales, providing an overall measure of perceived parenting stress. The PSI has been validated for use in the Italian population, demonstrating strong reliability and construct validity. We used the total raw stress score as an indicator of each mother's overall experience of parenting stress.

2.4. Data description

Table 1 summarizes the characteristics of the study population (N = 624). The median age of the children was 5.9 years (IQR = 4.3–7.1 years), and 53% were male. Mothers held a median age of 32.2 years at delivery (IQR = 28.6–35.7 years). Most mothers had a university degree (51%) and 93% of them were of Italian nationality. Regarding employment status, only 21% of mothers were unemployed. The majority of the children were born at term (median gestational age was 40 weeks). Breastfeeding for more than 12 months was reported in 32% of cases, while 10% of children were not breastfed. Maternal smoking during pregnancy was reported by 5.6% of mothers. Most of the children had no siblings (43%) or a sibling (45%). The median PSI score was 32 points (IQR = 28–38).

2.4.1. Satellite data

We used surface-level particulate matter ($PM_{2.5}$) concentration data provided by the Copernicus Atmosphere Monitoring Service (CAMS), specifically from the European Air Quality (EAQ) dataset (Inness et al., 2019; Copernicus Atmosphere Monitoring Service (CAMS), 2020). The dataset offers monthly mean $PM_{2.5}$ concentrations at a spatial resolution of $0.1\,^\circ \times 0.1^\circ$, corresponding to approximately 8.5–8.7 km at the latitudes of Italy. Satellite-derived data were available starting from January 2013 and were included in this analysis through December 2022. Each participant's residential address was geocoded using the Google Maps Geocoding API (Google, 2022) and spatially linked to the nearest grid cell of the air pollution data. For each participant, monthly average $PM_{2.5}$ concentrations were assigned for each of the nine months preceding birth, to assess exposure during pregnancy. The spatial distribution of average $PM_{2.5}$ concentrations during pregnancy is shown in Figure A.4, highlighting higher levels in Northern Italy, particularly in the Po Valley, and lower levels in southern regions and coastal areas. For the same residential addresses, we extracted daily temperature and relative humidity percentage values throughout the entire pregnancy period using the ERA5-Land reanalysis dataset. ERA5-Land provides high-resolution ($0.1\,^\circ \times 0.1^\circ$ spatial resolution), gridded meteorological data, allowing us to consistently estimate individual-level environmental exposures over time and space. These data were linked to each participant's residence to capture ambient conditions for each month of gestation.

2.5. Statistical methods

All continuous variables were summarized as medians and interquartile ranges (IQR: Q1–Q3), while categorical variables were reported as counts and percentages. Group comparisons were performed using the Wilcoxon rank-sum test for continuous variables and Pearson's chi-squared test for categorical variables. Initially, we assessed the association between DP-4 dimensions and exposure to prenatal $PM_{2.5}$ at the residential address using a generalized additive model (GAM) framework (Wood, 2012). In detail, we performed a regression model estimation for both the total DP-4 score and for each developmental domain (physical, adaptive behavior, socio-emotional, cognitive and communication). The GAM specification also included three random terms as random intercepts: the interviewer (19 interviewers with at least 10 responses plus one as "other interviewer" category collecting all interviewers with low frequencies), the interview modality (online vs. ace-to-face) and the parent interviewed (mother vs. father/other) to account for the hierarchical structure of data collection. This first GAM was specified to estimate the association between the exposure to trimester-specific average $PM_{2.5}$ concentration during pregnancy and DP-4 scores as follows:

$$Y_{iqcp} = \alpha + \sum_{k=1}^{3} \beta_k(t)\, X_{ki} + \sum_j \gamma_j Z_{ij} + \sum_l f_l(W_{il}) + \epsilon_{iqcp} \tag{1}$$

where the regression error is composed of four components:

$$\epsilon_{iqcp} = u_q + v_c + w_p + e_{iqcp}, \tag{2}$$

with

$$\begin{aligned} u_q &\sim \mathcal{N}(0, \sigma_q^2), \\ v_c &\sim \mathcal{N}(0, \sigma_c^2), \\ w_p &\sim \mathcal{N}(0, \sigma_p^2), \\ e_{iqcp} &\sim \mathcal{N}(0, \sigma^2). \end{aligned} \tag{3}$$

In Eq. (1), Y_{iqcp} is the scalar response for ith child (DP-4 dimension score or total score); β_1, β_2, and β_3 represent the effect associated with a 1-interquartile range (IQR) increase in the average $PM_{2.5}$ concentration in the first (X_{i1}), second (X_{i2}), and third trimester of pregnancy (X_{i3}), respectively. Z_{ij} denotes categorical confounders or covariates,

Table 1
Main characteristics overall, and by average prenatal $PM_{2.5}$ concentration cut-off.

Cross-sectional variables	Overall	Prenatal $PM_{2.5}$		p-value[b]
		≤ 15 μg/m³	>15 μg/m³	
	N = 624[a]	N = 390[a]	N = 234[a]	
Child - Age (years)	5.9 (4.3, 7.1)	6.2 (4.3, 7.3)	5.4 (4.4, 6.7)	0.007
Child - Gender [Male]	329 (53%)	211 (54%)	118 (50%)	0.4
Maternal Age (years)	32.2 (28.6, 35.7)	31.7 (28.3, 35.5)	32.8 (28.9, 36.0)	0.029
Mother – Educational level				0.15
Middle school or lower	43 (6.9%)	33 (8.5%)	10 (4.3%)	
High school	227 (36%)	146 (37%)	81 (35%)	
University	321 (51%)	192 (49%)	129 (55%)	
PhD or equivalent	33 (5.3%)	19 (4.9%)	14 (6.0%)	
Father – Educational level				0.8
Middle school or lower	106 (17%)	66 (17%)	40 (17%)	
High school	294 (47%)	181 (46%)	113 (48%)	
University	201 (32%)	130 (33%)	71 (30%)	
PhD or equivalent	23 (3.7%)	13 (3.3%)	10 (4.3%)	
Mother – Nationality				0.4
Italian	579 (93%)	359 (92%)	220 (94%)	
Non-Italian	45 (7.2%)	31 (7.9%)	14 (6.0%)	
Mother – Employment status				0.016
Part-time	186 (30%)	104 (27%)	82 (35%)	
Full-time	310 (50%)	194 (50%)	116 (50%)	
Unemployed	128 (21%)	92 (24%)	36 (15%)	
Gestational duration (weeks)	40 (38, 40)	40 (38, 40)	40 (38, 40)	0.3
Breastfeeding duration				0.2
No breastfeeding	65 (10%)	39 (10%)	26 (11%)	
1–6 months	193 (31%)	133 (34%)	60 (26%)	
6–12 months	169 (27%)	102 (26%)	67 (29%)	
> 12 months	197 (32%)	116 (30%)	81 (35%)	
Number of siblings				0.6
0	271 (43%)	164 (42%)	107 (46%)	
1	283 (45%)	179 (46%)	104 (44%)	
≥2	70 (11%)	47 (12%)	23 (9.8%)	
PSI score	32 (28, 38)	32 (27, 37)	34 (29, 41)	<0.001
Family Status [Divorced]	34 (5.4%)	21 (5.4%)	13 (5.6%)	>0.9
Interview modality [Online]	536 (86%)	325 (83%)	211 (90%)	0.018
Interviewed parent [Mother]	560 (90%)	354 (91%)	206 (88%)	0.3
During pregnancy variables				
Average THI	58.6 (55.3, 61.5)	60.0 (57.0, 62.5)	56.5 (53.3, 59.6)	<0.001
Maternal smoking [Yes]	35 (5.6%)	25 (6.4%)	10 (4.3%)	0.3
DP-4 scores				
Physical	32 (28, 35)	33 (29, 35)	32 (28, 35)	0.2
Adaptive behavior	30 (26, 34)	31 (26, 35)	29 (25, 32)	0.002
Socio-Emotional	28 (23, 31)	28 (24, 31)	27 (23, 30)	0.004
Cognitive	28 (23, 36)	30 (23, 37)	27 (23, 35)	0.040
Communicative	27 (25, 30)	28 (25, 30)	27 (24, 29)	<0.001
Total	146 (127, 164)	149 (129, 167)	143 (125, 157)	0.003

[a] Median (Q1, Q3); n (%);
[b] Wilcoxon rank sum test; Pearson's Chi-squared test.

included in the model through dummy variable along with the corresponding coefficients γ_j. W_{il} denotes continuous confounders or covariates, modeled using smooth functions $f_l(\cdot)$ specified as penalized regression splines. The GAM framework allows flexible adjustment for confounders and covariates by combining parametric terms for categorical variables and nonparametric smooth functions for continuous variables, thus avoiding the need to impose a priori assumptions on the functional form of continuous predictors. The error term ϵ_{iqcp} was specified to account for the hierarchical structure of the data collection process and was decomposed into four components corresponding to the three random effects (interviewer (q), data collection modality (c), and interviewed parent (p)) plus a residual term. The previous approach ensures comparability with older studies but it has some limitations, since we considered the average $PM_{2.5}$ by trimester of pregnancy instead of its effect over time. To overcome this limit, a penalized functional regression (PFR) model can be expressed as follows:

$$Y_{iqcp} = \alpha + \int_{t=1}^{9} \beta(t) X_i(t) dt + \sum_j \gamma_j Z_{ij} + \sum_l f_l(W_{il}) + \epsilon_{iqcp}, \quad (4)$$

where now $X_i(t)$ represents the functional predictor, i.e. the average monthly $PM_{2.5}$ concentration at the residential address during pregnancy the gestational time $t = 1, \ldots, 9$, and $\beta(t)$ is the functional coefficient function describing the time-varying association between the exposure $X_i(t)$ and outcome. Considering technical details, the PFR model is implemented as a wrapper around a Generalized Additive Model (GAM) using the mgcv package in R (Goldsmith et al., 2011; Wood, 2012).

The functional term $\beta(t)$ was estimated using a basis function expansion approach:

$$\beta(t) = \sum_{m=1}^{M} b_m B_m(t),$$

where $B_m(t)$ denote the B-spline basis functions (cubic splines with equally spaced knots) and b_m are the corresponding coefficients to be estimated. Given the limited number of time points (nine months), we employed a small number of basis functions ($m = 4$) to ensure model parsimony. To avoid overfitting, a roughness penalty was applied to the

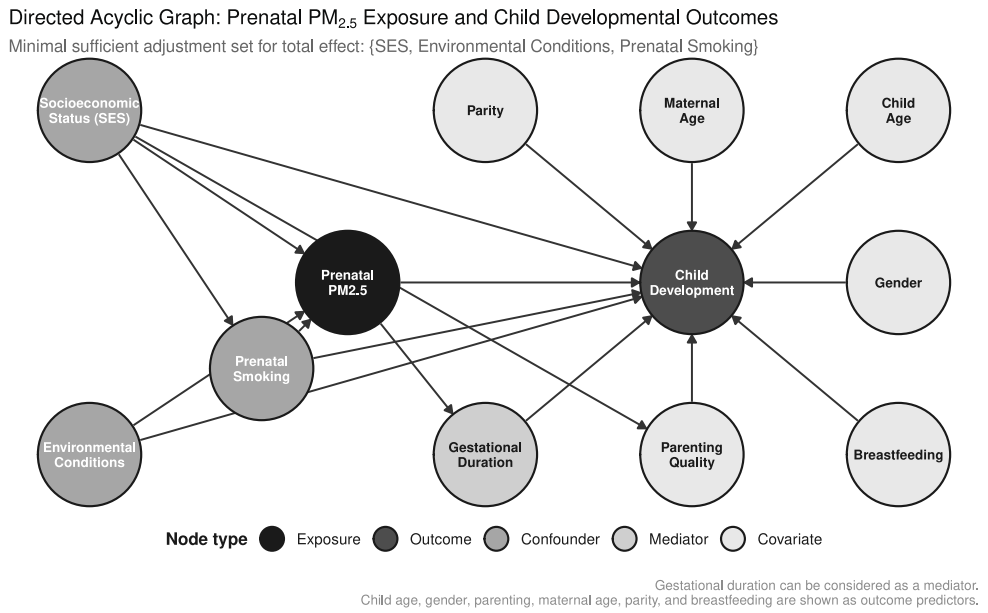

Fig. 1. Directed Acyclic Graph (DAG) of the causal pattern between prenatal $PM_{2.5}$ exposure and Child Development, considering confounders and covariates.

integrated squared second derivative of $\beta(t)$,

$$\min_{\beta(t),\gamma,\alpha} \left\{ \|Y - \alpha + \int_{t=1}^{9} \beta(t)X(t)\,dt + \sum_j \gamma_j Z_j + \sum_l f_l(W_l)\|^2 + \lambda \int [\beta''(t)]^2\,dt \right\}, \tag{5}$$

where λ is the smoothing parameter that controls the trade-off between model fit and smoothness of the functional estimate. The penalized estimation problem is reformulated as a mixed model, where the spline coefficients b_m are treated as random effects with variance inversely proportional to λ. This equivalence allows the smoothing parameter to be estimated directly from the data via Restricted Maximum Likelihood (REML), a method that typically provides more stable and unbiased estimates of smoothness compared to alternatives such as Generalized Cross-Validation (GCV). The REML optimization proceeds by maximizing the penalized log-likelihood over both fixed-effect parameters and variance components associated with the spline penalties.

This framework provides a flexible and statistically principled way to estimate the time-varying effects of the exposure to prenatal $PM_{2.5}$ while appropriately accounting for the nested data structure and uncertainty in smoothing. For a comprehensive technical discussion of penalized functional regression and REML estimation, see Crainiceanu et al. (2024) and Wood (2017).

We estimated six PFR models, one for each dimension of DP-4 and the total score. To control for multiple comparisons, p-values from each model examining the association between the focal predictor $PM_{2.5}$ and DP-4 outcomes were adjusted using the false discovery rate (FDR) approach of Benjamini and Hochberg (1995).

The specification of the GAMs and PFR models followed the directed acyclic graph (DAG) shown in Fig. 1, which represents the assumed relationships between exposure to prenatal $PM_{2.5}$ and child developmental outcomes. Variables identified by the DAG as confounders were included to estimate the total effect, whereas additional predictors of the outcome were incorporated to improve precision without being interpreted as confounders. According to this framework, the minimal sufficient adjustment set to estimate the total effect included socioeconomic status (SES), environmental stressors, and prenatal smoking. SES was operationalized through maternal education level, nationality, and occupational type, as well as paternal education level. Stressors concerning environmental conditions were considered calculating individual average temperature humidity index (THI; Howe et al., 2024) over the entire pregnancy period, while prenatal maternal smoking was modeled as a binary variable (yes/no). In addition to the minimal adjustment set, we included variables identified as predictors of the outcome. These included child-related factors (child age, gender, gestational age at birth, breastfeeding practices, and number of siblings), maternal age at delivery, and family-related characteristics (family status and parenting stress index). Although gestational duration may lie on the causal pathway between exposure and child outcomes, its inclusion in the main model can be justified when the aim is to estimate the direct effect independent of gestational age, given its strong influence on neonatal and developmental outcomes (Ananth and Brandt, 2022; Tan et al., 2025). Continuous covariates (child age, gestational age at birth, maternal age at delivery, parenting stress index, and gestational duration) were modeled using penalized regression splines with a basis dimension of 4 (corresponding to three internal knots equally spaced across the predictor distribution). The adequacy of the spline basis dimension was evaluated using standard diagnostic procedures implemented via the *gam.check()* function in R, which examines residual patterns and tests whether the chosen basis dimension is sufficient based on the estimated degrees of freedom and k-index. For infants born preterm (gestational age < 9 months), average $PM_{2.5}$ concentrations for the missing months of pregnancy were set to zero. A sensitivity analysis restricted to children with at least 38 weeks of gestation was also conducted (N = 565); in this case, gestational duration was excluded from the model, and no missing monthly $PM_{2.5}$ exposure values were present.

Finally, we quantified the effect of prenatal $PM_{2.5}$ exposure relative to the WHO guideline (5 $\mu g/m^3$) by contrasting predicted DP-4 scores based on the observed exposure trajectories with counterfactual predictions obtained by fixing $PM_{2.5}$ concentration at 5 $\mu g/m^3$.

The goodness of fit was evaluated by means of a quantile–quantile diagram. Statistical significance for all tests and model coefficients was set at 5%. All computations, tables, and graphical outputs were performed using R statistical software (Team, 2023).

3. Results

3.1. Descriptive statistics

Among the children included in the study, the median prenatal concentration of $PM_{2.5}$ was 13.4 $\mu g/m^3$ (range min–max, 6.5–29.5 $\mu g/m^3$, IQR = 5.3 $\mu g/m^3$) during the 9 months of pregnancy (Figure A.6). When

Table 2
Estimated adjusted[a] variation and 95% Confidence Interval (95% CI) for 1-IQR increase in $PM_{2.5}$ concentration (6.55 μg/m^3) for DP-4 total and by functioning areas.

Average	Physical			Adaptive behavior			Socio-Emotional		
$PM_{2.5}$	*β*	95% CI	p-value	*β*	95% CI	p-value	*β*	95% CI	p-value
1st trimester	−0.03	[−0.41, 0.35]	0.884	0.41	[−0.04, 0.87]	0.076	0.03	[−0.45, 0.52]	0.896
2nd trimester	−0.18	[−0.66, 0.30]	0.457	−0.54	[−1.12, 0.03]	0.064	−0.27	[−0.88, 0.35]	0.394
3rd trimester	−0.17	[−0.53, 0.20]	0.371	0.01	[−0.44, 0.45]	0.976	−0.60	[−1.07, −0.13]	**0.012**
R^2	0.641			0.638			0.528		
	Cognitive			Communicative			Total		
	β	95% CI	p-value	*β*	95% CI	p-value	*β*	95% CI	p-value
1st trimester	0.31	[−0.09, 0.71]	0.130	−0.07	[−0.38, 0.25]	0.673	0.57	[−0.96, 2.10]	0.462
2nd trimester	−0.03	[−0.53, 0.48]	0.915	0.11	[−0.29, 0.51]	0.588	−0.91	[−2.84, 1.02]	0.354
3rd trimester	−0.37	[−0.76, 0.02]	0.065	−0.37	[−0.67, −0.07]	**0.015**	−1.61	[−3.10, −0.12]	**0.034**
R^2	0.836			0.523			0.770		

[a] Models were adjusted for maternal and paternal education, maternal age at delivery, maternal smoking and average THI during pregnancy, number of siblings, child's gender and age, maternal nationality and employment status, PSI score, family status, gestational duration. Interview modality, interviewed parent and interviewer's name were included as random effects.

stratified by exposure to the average prenatal $PM_{2.5}$ concentrations (≤15 μg/m^3 vs. > 15 μg/m^3), several differences emerged mainly due to the different geographical distribution of exposure pattern (see A.4). As reported in Table 1, the children in the high exposure group were slightly younger (median 5.4 years vs. 6.2 years, p = 0.007) and had mothers who were older at delivery (32.8 vs. 31.7 years, p = 0.029). Differences in maternal employment status were also observed, unemployment being less common among mothers of children in the highest exposure group (p = 0.016). Environmental characteristics differed significantly between exposure groups: children in the high exposure group were more likely to report lower THI values (56.5 vs. 60, $p < 0.001$). The PSI score was significantly higher in the high exposure group (median 34 vs. 32, $p < 0.001$). A higher proportion of questionnaires were completed online among the high exposure group (p = 0.018). No significant differences were observed between the two exposure groups in child gender, maternal and paternal education levels, maternal nationality, breastfeeding duration, smoking during pregnancy, number of siblings, family status, or season of birth.

3.2. Impact of prenatal $PM_{2.5}$ exposure on developmental outcomes

Table 2 presents the adjusted associations between prenatal $PM_{2.5}$ exposure and developmental outcomes across functional domains. Overall, most trimester-specific estimates were small and not statistically significant. However, $PM_{2.5}$ exposure in the third trimester was associated with poorer socio-emotional outcomes ($\beta = -0.60$ for 1-IQR increase, 95% CI: −1.07, −0.13) and communicative abilities ($\beta = -0.37$ for 1-IQR increase, 95% CI: −0.67, −0.07), as well as a reduction in the total DP-4 score ($\beta = -1.61$ for 1-IQR increase, 95% CI: −3.10, −0.12).

The results obtained by the PFR models indicated that the total DP-4 score was significantly associated with $PM_{2.5}$ exposure during pregnancy ($p = 0.004$), with a detrimental effect emerging from approximately the fifth month of gestation (Fig. 2). This overall association was primarily driven by negative effects on the cognitive and socio-emotional domains (Fig. 2; $p = 0.002$ and $p = 0.002$, respectively; Tables A.6 and A.7). In contrast, the estimated functional coefficients for $PM_{2.5}$ in the physical, adaptive behavior, and communication domains were not statistically significant. After adjustment for multiple comparisons using the false discovery rate (FDR) procedure, associations remained statistically significant for the total DP-4 score ($p = 0.008$), as well as for the cognitive ($p = 0.006$), and socio-emotional ($p = 0.006$) domains.

The predicted contribution of $PM_{2.5}$ exposure relative to the WHO annual guideline of 5 μg/m^3 to the total DP-4 score is shown in Fig. 3. Exposure to high $PM_{2.5}$ concentration, particularly during the second and third trimesters, was associated with lower predicted scores, with an average decrease of 2.91 points ranging from −11.2 to 0.6 points. Using raw DP-4 scores, a reduction corresponds to fewer developmental skills attained, indicating a less advanced developmental level for age compared with peers.

3.3. Analysis of key confounding factors

The effect of $PM_{2.5}$ concentrations on the developmental domains under consideration was adjusted for several covariates (see Tables A.6 and A.7 for full details). As shown in Figure A.7, child age was strongly and approximately linearly associated with higher predicted DP-4 scores. In contrast, maternal age and gestational duration exhibited non-linear relationships, with predicted DP-4 scores peaking at intermediate predictor values and declining at higher ranges. The effect of the PSI score decreases, suggesting lower DP-4 scores for moderate-to-high stress levels, and levels off at extremely high PSI values. The average THI during pregnancy shows a modest, non-linear association with predicted DP-4 scores, decreasing slightly at higher levels.

3.4. Model assessment and sensitivity analysis

All models showed satisfactory explained variance, ranging from 56.3% to 84.9%, with 79% for the total DP-4 score. Residual diagnostics based on quantile–quantile plots indicated no major departures from normality (Figure A.6). Random effects are presented as quantile–quantile plots for the interviewer, type of interview, and the interviewed parent, indicating approximate normality of residuals and variability attributable to these grouping factors (Figure A.7). In the regression models, random effects were statistically significant, suggesting non-negligible between-group variance and supporting their inclusion in the mixed-effects model (Tables A.6 and A.7). The sensitivity analysis conducted on individuals with a gestational duration of at least 38 weeks confirmed the results obtained from the entire cohort (Tables A.8 and A.9, and Figure A.9).

4. Discussion

This study provides novel evidence that prenatal exposure to fine particulate matter ($PM_{2.5}$) is negatively associated with multiple domains of child development, particularly cognitive and socio-emotional functioning. Using penalized functional regression models (Crainiceanu et al., 2024), our findings indicate that the effects of prenatal exposure to $PM_{2.5}$ on child development are both domain-specific and timing-dependent.

While trimester-based models showed generally small and mostly non-significant associations, exposure during the third trimester emerged as particularly relevant, being significantly associated with lower

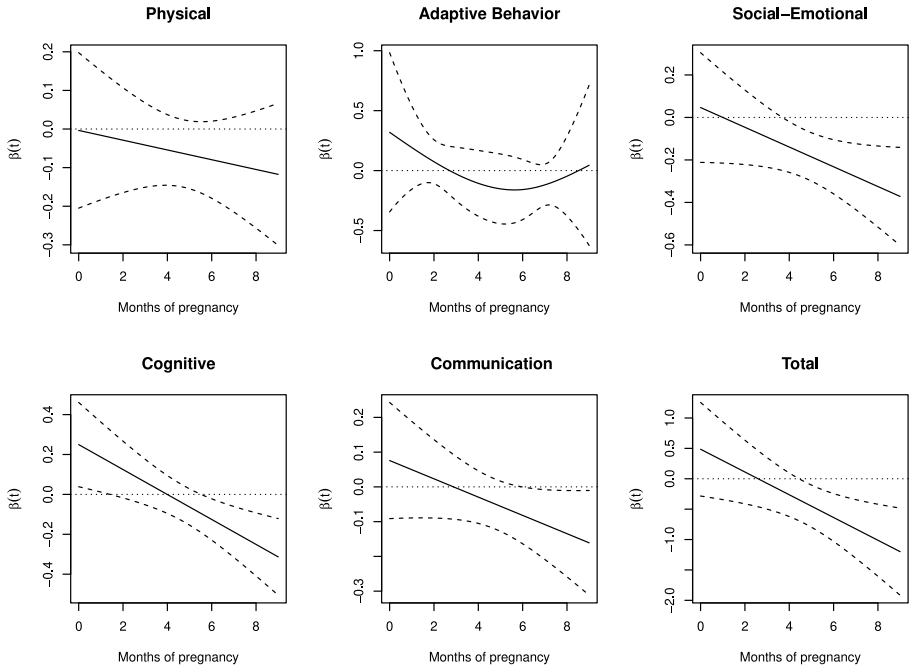

Fig. 2. Estimated adjusted functional effect of the $PM_{2.5}$ concentration for DP-4 total and by functioning areas, by month of pregnancy. 95% Pointwise Confidence Bands are reported with dashed lines. Full dataset (N = 624).

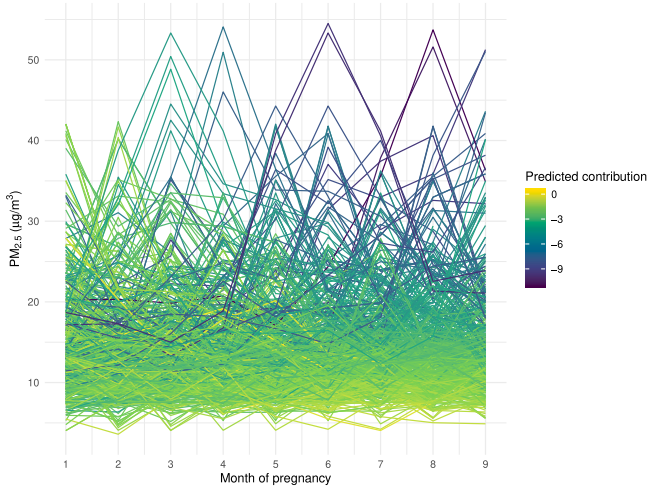

Fig. 3. Individual monthly $PM_{2.5}$ raw values during pregnancy and predicted difference in total DP-4 score relative to a $PM_{2.5}$ concentration of 5 µg/m^3.

socio-emotional functioning, communicative abilities, and overall developmental scores. Importantly, penalized functional regression models allowed a more refined characterization of exposure timing. These models revealed a detrimental effect of $PM_{2.5}$ starting from the fifth month of gestation onward. This effect was primarily driven by impairments in cognitive and socio-emotional domains, whereas no significant associations were observed for physical, adaptive, or communication domains when modeled continuously over gestation. These findings were highly consistent across model specifications, remained statistically significant after correction for multiple comparisons, and were further supported by sensitivity analyses. Moreover, exposure levels exceeding the revised World Health Organization (WHO) annual guideline of 5 µg/m^3 (World Health Organization, 2021) were associated with an average developmental reductions of three points in total DP-4 score, indicating that even moderate levels of air pollution can have substantial neurodevelopmental consequences. These results reinforce growing evidence that no safe exposure threshold exists for $PM_{2.5}$ (Schraufnagel et al., 2019; Payne-Sturges et al., 2019) and underscore the need for stringent air quality standards, particularly in regions with persistently high pollution such as the Po Valley (Beloconi and Vounatsou, 2023).

Additionally, several confounding factors were significantly associated with developmental outcomes, including child's age, parental educational level, parenting stress (PSI score), environmental conditions during pregnancy (THI score), and number of siblings. These findings highlight the multifactorial nature of child development, in which environmental, social, and family-level determinants interact. Moreover, the random effects associated with interviewer, interview type, and responding parent were statistically significant, indicating the presence of hierarchical variability in data collection and supporting the mixed-effects modeling approach.

From a mechanistic perspective, the observed associations in the third trimester are biologically plausible, given that this period represents a critical window in which key neurodevelopmental processes, including synaptogenesis, myelination, and cortical maturation (Becerra et al., 2012; Guxens et al., 2014; Sunyer et al., 2015), are particularly active. Fine particulate matter contains ultrafine components, such as black carbon, transition metals, and polycyclic aromatic hydrocarbons, that can cross the placental barrier and reach the fetal circulation (Bolton et al., 2012; Bové et al., 2019). These pollutants can induce oxidative stress, systemic inflammation, and placental dysfunction, disrupting oxygen and nutrient transfer to the fetus (Calderón-Garcidueñas et al., 2014; Costa et al., 2020). Experimental and epidemiological studies have linked prenatal $PM_{2.5}$ exposure to altered brain structure, reduced white matter integrity, and cognitive and emotional difficulties in childhood (Perera et al., 2013; Peterson et al., 2015; McGuinn et al., 2020; Wang et al., 2024). The specificity of the associations in the cognitive and socio-emotional domains in the present study is consistent with these mechanisms, as these neural networks mature during late gestation and are particularly sensitive to inflammatory and oxidative processes (Edwards et al., 2010; Guxens and Sunyer, 2012).

Consistent with our findings, several studies have reported adverse effects of prenatal exposure to particulate matter on cognitive

Table 3
Summary of included studies on prenatal air pollution exposure and neurodevelopmental outcomes.

Study (N)	Location/Age	Exposure/Outcome	Association
McGuinn et al. (2020) (N = 539)	Mexico City; 4–6y	$PM_{2.5}$; BASC-2	First-trimester $PM_{2.5}$↓ adaptive skills; stronger in males
Perera et al. (2024) (N = 470)	New York; 1–3y	$PM_{2.5}$, NO_2; Bayley-II	NO_2 (T1–T2)↓ Development; persistent at age 3
Tokuda et al. (2023) (N = 251[a])	Japan; 5–7y	$PM_{2.5}$; WISC-IV, CBCL	T2↓ working memory; T1↑ externalizing problems
Ni et al. (2022) (N = 1967)	USA; 5y	NO_2, $PM_{2.5}$; CBCL, IQ	NO_2 (T1–T2)↑ behavioral problems; no IQ effect
Zhang et al. (2022) (N = 348[b])	NY & Boston; 3–7y	$PM_{2.5}$; NIHTB-CB	T3↓ cognition; sex-specific effects
Liu et al. (2022) (N = 26,052)	China; 3.5y	Multiple; CPRS-48	T3 exposure↑ hyperactivity (peak month 9)
Bansal et al. (2021) (N = 320)	Mexico City; 9–10y	$PM_{2.5}$; Go/No-Go	All trimesters↑ poor performance, especially T2
Harris et al. (2015) (N = 1,046[c])	Massachusetts; 3y	$PM_{2.5}$; BRIEF, SDQ	Negative association in T3 attenuated after adjustment
Morgan et al. (2023) (N = 161)	California; 2y	NO_2, $PM_{2.5}$; Bayley-III	T3 exposure↓ motor and cognition
Peterson et al. (2022) (N = 330)	Manhattan; 6y	$PM_{2.5}$, PAH; multiple	No behavioral effects; brain structural changes
Whitworth et al. (2024) (N = 1303)	Spain (INMA); 5y	$PM_{2.5}$; MSCA	$PM_{2.5}$↓ cognitive/motor outcomes between 7–17 weeks
Cosemans et al. (2024) (N = 393)	Belgium (ENVIRONAGE); 4–6y	$PM_{2.5}$; SQD	T1↓ peer problems, T2↓ prosocial behaviour
Guilbert et al. (2023) (N = 1271)	France; school 5–6y	$PM_{2.5}$; WISC-IV	$PM_{2.5}$↓ cognitive; sensitive windows 5–11 weeks; sex-specific effects

[a] Recruited within a larger JECS sample.
[b] PRISM and First Thousand Days of Life studies.
[c] Black carbon data available for 1046 participants.

and behavioral development, particularly during mid-to-late gestation. Indeed, in line with our results, the third trimester emerges as a critical window of susceptibility during pregnancy, with multiple studies reporting associations between late pregnancy $PM_{2.5}$ exposure to reduced cognitive performance, increased hyperactivity, and poorer motor outcomes (Zhang et al., 2022; Liu et al., 2022; Morgan et al., 2023), although some associations attenuate after adjustment (Harris et al., 2015). Importantly, some studies suggest sex-specific effects, with stronger associations observed in males or differential vulnerability by sex. Nonetheless, these findings align with our study results and with previous research demonstrating heightened fetal susceptibility during this period, when neurogenesis, synaptogenesis, and myelination are most active (Becerra et al., 2012; Guxens et al., 2014; Sunyer et al., 2015).

However, findings across studies remain heterogeneous. For example, several cohorts highlight the first trimester as a sensitive period, with exposure linked to poorer adaptive functioning and increased externalizing behaviors (McGuinn et al., 2020; Tokuda et al., 2023) and early gestational windows (5–17 weeks) associated with reduced cognitive and motor performance (Guilbert et al., 2023; Whitworth et al., 2024). Evidence also supports a role for the second trimester, particularly in relation to cognitive domains such as working memory and later neurocognitive performance (Bansal et al., 2021; Tokuda et al., 2023). This variability across studies likely reflects important methodological and conceptual differences. In particular, developmental outcomes vary widely, ranging from global indices of development to specific cognitive, behavioral, or emotional domains, limiting direct comparability. Furthermore, the timing of outcome assessment spans from infancy to late childhood, a factor that may influence the detectability and expression of pollution-related effects. Differences in exposure characterization and modeling approaches also contribute to heterogeneity, with some studies focusing on specific trimesters, while others examine cumulative or postnatal exposure. Finally, variation in geographic context, exposure levels, socioeconomic characteristics, and covariate adjustment strategies may further account for inconsistencies in the literature (see Table 3 for a detailed summary of findings from studies examining prenatal air pollution exposure and child developmental outcomes).

This study has several strengths. Developmental data were obtained through structured interviews conducted by trained professionals, minimizing self-report bias. The application of penalized functional regression provided a flexible framework for modeling time-varying exposures and identifying sensitive gestational windows. Additionally, the extensive adjustment for demographic, socioeconomic, and environmental confounders enhances the validity of the findings. From a policy perspective, our findings highlight the urgent need for stricter air quality regulations and effective interventions to reduce prenatal exposure. Strategies such as clean air zones, traffic emission reductions, and urban green planning can contribute to lowering exposure levels. Public health initiatives promoting awareness and monitoring during pregnancy could mitigate risks in highly polluted regions.

Nonetheless, some limitations warrant consideration. The observational design precludes causal inference, and unmeasured confounding from factors such as indoor air pollution, maternal diet, or stress cannot be ruled out. $PM_{2.5}$ exposure estimates, although derived from high-resolution satellite data (Inness et al., 2019; Copernicus Atmosphere Monitoring Service (CAMS), 2020) do not fully capture personal exposure variability or time–activity patterns. Additionally, the sample size (N = 624), while adequate for explorative analyses, remains relatively limited and may reduce statistical power for detecting smaller effects or subgroup differences. Developmental outcomes were based on parental reports, which may introduce subjective bias, though the interviewer-administered format likely mitigated this effect. Finally, the cross-sectional design limits the ability to assess developmental trajectories or potential recovery over time. In addition, including gestational duration in the adjustment set may be debated, as it can lie on the causal pathway between prenatal $PM_{2.5}$ exposure and child development (Ananth and Brandt, 2022). However, its inclusion allows us to estimate the direct effect of exposure independent of gestational age, given its strong influence on developmental outcomes, particularly in relation to preterm birth (Wilcox et al., 2011). Consequently, our estimates should be interpreted as controlled direct effects rather than total effects. Notably, sensitivity analyses excluding gestational duration yielded consistent results, suggesting that its mediating role is limited in this study, likely due to the low prevalence of preterm birth and the small magnitude of the indirect effect.

Future research should employ longitudinal designs with repeated neurodevelopmental assessments and integrate neuroimaging, epigenetic, and inflammatory biomarkers to elucidate biological pathways linking prenatal pollution exposure to brain development. Multiexposure models incorporating co-pollutants such as NO_2, O_3, and black carbon (Ni et al., 2022; Domínguez et al., 2024) would improve understanding of cumulative effects. Exploring susceptibility by sex, socioeconomic status, and psychosocial resilience could identify vulnerable subgroups and inform targeted prevention. Finally, given the well-established role of contextual factors in shaping developmental outcomes, future research should explicitly examine whether they may buffer or exacerbate the effects of environmental exposures such as $PM_{2.5}$. Adopting an interaction-focused perspective would allow for a more nuanced understanding of how contextual factors jointly influence developmental outcomes. In particular, identifying factors that mitigate the negative impact of pollution could inform the design of targeted interventions aimed at compensating for adverse environmental conditions. Such an approach would be especially relevant

from a developmental standpoint, as it may help to promote resilience and support more favorable outcomes even in contexts of elevated environmental risk.

In conclusion, prenatal exposure to $PM_{2.5}$, particularly during mid-to-late gestation, was associated with reduced cognitive and socio-emotional development among Italian school-aged children. These results provide new evidence from a European context and support global efforts to enforce and strengthen WHO air quality guidelines to protect fetal and child neurodevelopment.

CRediT authorship contribution statement

Paolo Girardi: Writing – review & editing, Writing – original draft, Visualization, Supervision, Methodology, Investigation, Formal analysis, Conceptualization. **Libera Ylenia Mastromatteo:** Writing – review & editing, Writing – original draft, Visualization, Investigation, Conceptualization. **Silvia Lanfranchi:** Writing – review & editing, Visualization, Validation, Investigation, Data curation, Conceptualization. **Sara Scrimin:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Investigation, Conceptualization.

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.

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Appendix A. Supplementary data

Supplementary material related to this article can be found online at https://doi.org/10.1016/j.envpol.2026.128312.

Data availability

Data will be made available on request.

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