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Science of the Total Environment

Susceptible windows of prenatal and postnatal fine particulate matter exposures and attention-deficit hyperactivity disorder symptoms in early childhood

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HIGHLIGHTS

- Susceptible windows of pre- and post-natal PM$_{2.5}$ on ADHD symptoms were examined.
- Exposure in mid-gestation associated with hyperactivity symptoms ~age 5.
- Exposure in early toddlerhood associated with hyperactivity symptoms ~ages 5 and 7.

GRAPHICAL ABSTRACT
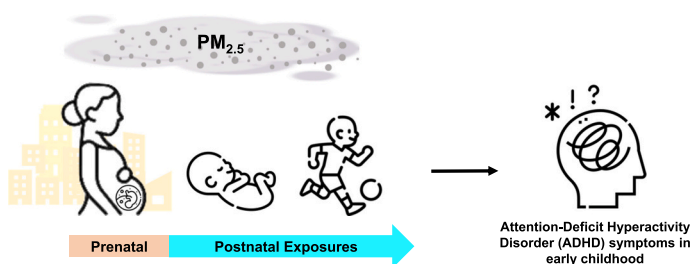
Distributed lag non-linear models were implemented to explore windows of susceptibility to PM$_{2.5}$ in both the prenatal and postnatal periods and ADHD symptoms at two-time points (~ages 5 and 7)

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ARTICLE INFO

ABSTRACT

Few prior studies have explored windows of susceptibility to fine particulate matter ($PM_{2.5}$) in both the prenatal and postnatal periods and children's attention-deficit/hyperactivity disorder (ADHD) symptoms.

We analyzed data from 1416 mother-child pairs from the Spanish INMA (INfancia y Medio Ambiente) Study (2003–2008). Around 5 years of age, teachers reported the number of ADHD symptoms (i.e., inattention, hyperactivity/impulsivity) using the ADHD Diagnostic and Statistical Manual of Mental Disorders. Around 7 years of age, parents completed the Conners' Parent Rating Scales, from which we evaluated the ADHD index, cognitive problems/inattention, hyperactivity, and oppositional subscales, reported as age- and sex-standardized T-scores. Daily residential $PM_{2.5}$ exposures were estimated using a two-stage random forest model with temporal back-extrapolation and averaged over 1-week periods in the prenatal period and 4-week periods in the postnatal period. We applied distributed lag non-linear models within the Bayesian hierarchical model framework to identify susceptible windows of prenatal or postnatal exposure to $PM_{2.5}$ (per 5-$\mu g/m^3$) for ADHD symptoms. Models were adjusted for relevant covariates, and cumulative effects were reported by aggregating risk ratios (RR_{cum}) or effect estimates (β_{cum}) across adjacent susceptible windows.

A similar susceptible period of exposure to $PM_{2.5}$ (1.2–2.9 and 0.9–2.7 years of age, respectively) was identified for hyperactivity/impulsivity symptoms assessed ~5 years (RR_{cum} = 2.72, 95% credible interval [CrI] = 1.98, 3.74) and increased hyperactivity subscale ~7 years (β_{cum} = 3.70, 95% CrI = 2.36, 5.03). We observed a susceptibility period to $PM_{2.5}$ on risk of hyperactivity/impulsivity symptoms ~5 years in gestational weeks 16–22 (RR_{cum} = 1.36, 95% CrI = 1.22, 1.52). No associations between $PM_{2.5}$ exposure and other ADHD symptoms were observed.

We report consistent evidence of toddlerhood as a susceptible window of $PM_{2.5}$ exposure for hyperactivity in young children. Although mid-pregnancy was identified as a susceptible period of exposure on hyperactivity symptoms in preschool-aged children, this association was not observed at the time children were school-aged.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the most prevalent childhood-onset neurodevelopmental disorders; it is characterized by a persistent pattern of impaired attention, motor hyperactivity, and impulsivity, which interfere with functioning or development and can continue into adolescence and adulthood (National Institute of Mental Health (NIMH), 2022; Thapar and Cooper, 2016). ADHD affects approximately 7.6% of children aged 3–12 years worldwide (Salari et al., 2023). In Europe, the estimated prevalence range of ADHD is from 3.2% to 7.5% (Aljadani et al., 2023), with a higher prevalence in high-income regions, including Western Europe (GBD 2019 Mental Disorders Collaborators, 2022). The impact of ADHD after childhood is not only associated with adverse social, economic, and occupational outcomes but is also a recognized risk factor for later substance use, psychiatric disorders, and mortality (Dalsgaard et al., 2015; Klein et al., 2012). While heritability is the strongest known risk factor for ADHD, numerous perinatal factors, such as use of illicit substances, obstetric complications, and prematurity, have also been associated with ADHD diagnosis (Thapar and Cooper, 2016). Exposure to environmental toxicants, including air pollution, specifically during periods of rapid brain development and neuroplasticity *in utero* and during early childhood, may be crucial to the development of ADHD (Grandjean and Landrigan, 2014; Ha, 2021; Thapar and Cooper, 2016).

Particulate matter (PM) is a heterogeneous mixture of ambient air pollutants of different particle sizes and chemical or biological components (Yang et al., 2020). PM with an aerodynamic diameter of < 2.5 μm ($PM_{2.5}$) is particularly concerning in terms of pathogenicity as it has a relatively greater surface area than larger particles, which may bind with toxic compounds; moreover, $PM_{2.5}$ accounts for most of the health burden of outdoor air pollution (Evangelopoulos et al., 2020; Yang et al., 2020). $PM_{2.5}$ can readily pass through the maternal bloodstream and cross the placental barrier during early gestation before the placenta has fully formed and late gestation when the placental wall is more vascularized (Adams et al., 2015; Feng et al., 2016). An impaired placenta may alter transplacental oxygenation and nutrient transport, adversely affecting fetal growth and brain development (Ha, 2021; Sunyer and Dadvand, 2019). In addition, of relevance to exposures experienced during early childhood, $PM_{2.5}$ can pass through the blood–brain barrier and trigger neurological impairments by inducing oxidative stress and

inflammatory mechanisms, given that the nasal epithelium, blood–brain barrier, and immune system are still immature in this vulnerable period (Ha, 2021). Although many studies have focused on the impact of air pollution exposure during the prenatal period on ADHD, while rapid myelination and neurotransmitter system maturation begin *in utero*, the impact continues into early childhood (de Graaf-Peters and Hadders-Algra, 2006; Thomason et al., 2018), pointing to the potential importance postnatal exposure as well.

Systematic reviews indicate that the overall evidence of adverse effects of both prenatal and postnatal $PM_{2.5}$ exposures on ADHD is still limited owing to heterogeneity in study design and geographic area, as well as assessments of outcome (e.g., different measuring tools for neurobehavioral problems) and exposure (e.g., variation in air pollution prediction models) (Aghaei et al., 2019; Bernardina Dalla et al., 2022; Donzelli et al., 2019; Health Effects Institute (HEI), 2022; Kaur et al., 2023; Zhang et al., 2022). The specific prenatal or postnatal periods when children may be most susceptible to the neurotoxic effects of $PM_{2.5}$ exposures remain unclear. To our knowledge, only three studies have evaluated associations of exposure to $PM_{2.5}$ in both periods on ADHD-related outcomes in early childhood (Chang et al., 2022; Liu et al., 2022; Ni et al., 2022). Chang et al. (2022) identified independent associations between $PM_{2.5}$ exposure during the first trimester of pregnancy and the first, second, and third years after birth with elevated risk of clinically diagnosed ADHD; they did not mutually adjust for exposure during different periods. Additionally, Ni et al. (2022) found that exposure to $PM_{2.5}$ during either the first trimester or from 2 to 4 years of age was independently associated with increased total problems score (including externalizing, internalizing, and attention problems) assessed by the Child Behavior Checklist, though these associations were attenuated and nonsignificant when included in the same model. Finally, Liu et al. (2022) fitted distributed lag non-linear models (DLNMs) to evaluate monthly air pollution estimates from conception to age 3 years on children's hyperactivity symptoms. They identified a period of susceptibility to $PM_{2.5}$ exposure that spanned the seventh month of pregnancy to the fourth month after birth on increased risk of hyperactivity.

To date, no study has simultaneously examined the susceptible windows to prenatal and postnatal $PM_{2.5}$ exposure on multiple ADHD symptoms. Identifying more refined windows of susceptibility to air pollution can provide insight into the biological mechanisms of neurotoxicity, particularly because specific neurodevelopmental disorders,

such as ADHD, may have different susceptible windows (Volk et al., 2021). In this study, we used data from the *INfancia y Medio Ambiente* (INMA) Study to evaluate the critical windows of susceptibility to prenatal and postnatal $PM_{2.5}$ exposures on ADHD symptoms. In addition, sex differences in physiology, neurochemistry, and neuroanatomy have been suggested (Andreano and Cahill, 2009) and both human and animal studies have demonstrated sex differences in neurobehavioral outcomes in response to air pollution, which may be due to differential neuroprotective effects in relation to sex hormones (Kern et al., 2017). However, the studies evaluating whether there are differences in susceptible periods of $PM_{2.5}$ exposures on ADHD symptoms according to child sex remain unclear. Thus, the sex-specific effects were additionally explored in our study.

2. Materials and methods

2.1. Study design and population

This analysis was based on data from INMA, a prospective population-based birth cohort study in which women were recruited from multiple regions in Spain (Guxens et al., 2012). Pregnant women who received their first prenatal clinic visit (10–13 weeks of gestation) from the main public hospital or health center in the regions of Gipuzkoa, Sabadell, and Valencia were recruited between November 2003 and February 2008. As described previously (Guxens et al., 2012), the women included in INMA were aged 16 years or older, had a singleton pregnancy, did not use assisted reproduction techniques to become pregnant, planned to deliver their child at the main hospital from their respective recruitment site, and had no communication issues. A total of 2150 women were initially recruited from the three INMA regions, and 2021 women with live births completed follow-up through the birth of their child (Fig. 1). Mothers and their children were followed through early childhood to assess ADHD symptoms. Written informed consent was obtained from parents once at enrollment during prenatal visits and again during the inclusion of their child in each follow-up assessment. Ethical approval was obtained from the Ethics Committee of the reference hospitals. The Institutional Review Board of Baylor College of Medicine approved the present study.
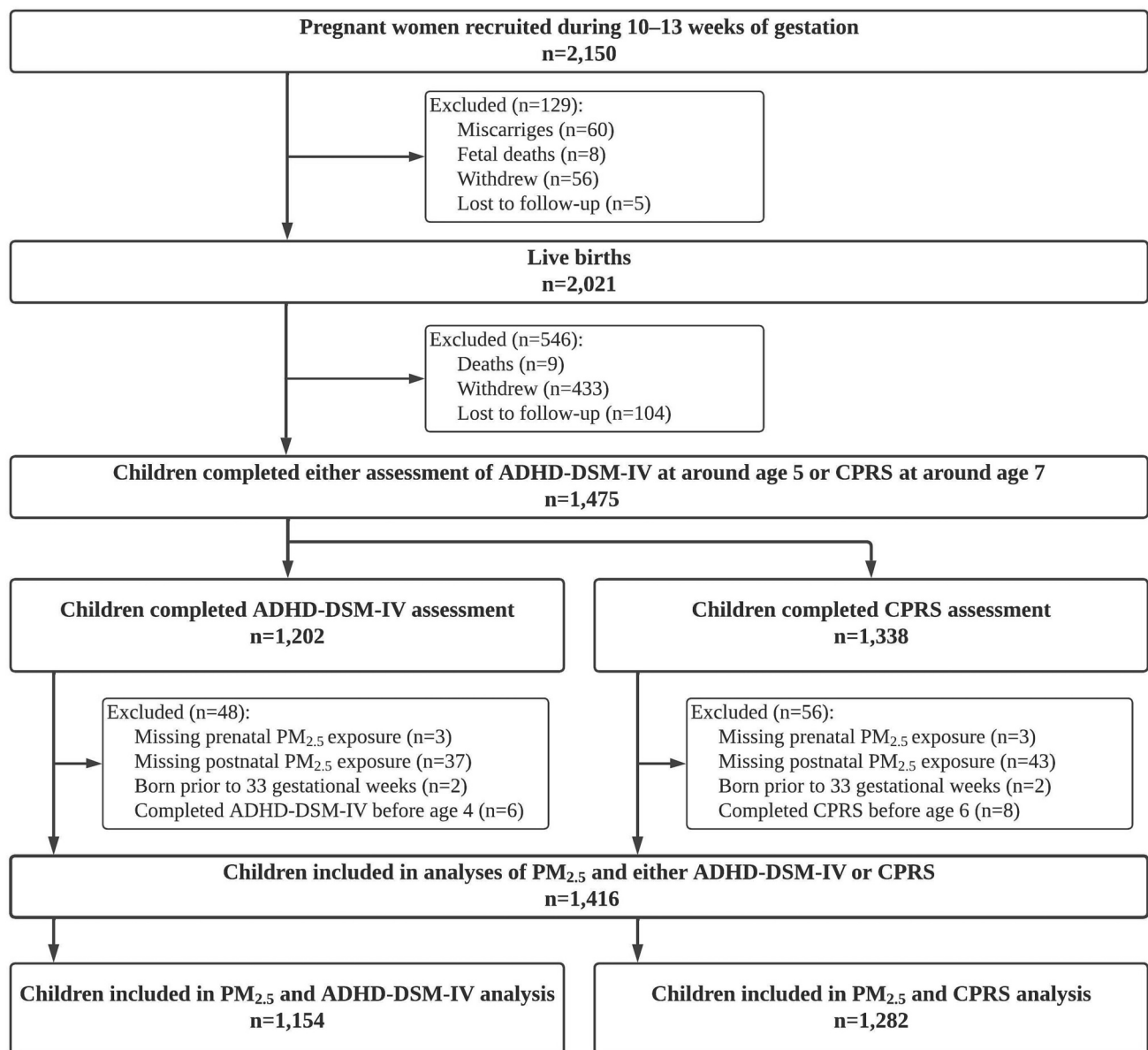

Fig. 1. Flowchart depicting inclusion of mothers and children for the analysis of $PM_{2.5}$ and ADHD symptoms from the INMA Study, 2003–2008. Abbreviation: ADHD-DSM-IV, ADHD Criteria of Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; CPRS: Conners' Parent Rating Scales.

2.2. Assessment of ADHD symptoms

We assessed ADHD symptoms at two-time points, using distinct assessments. First, around preschool-aged (~5 age), ADHD symptoms were assessed via teacher report using the ADHD Criteria of Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (ADHD-DSM-IV), which comprises 18 symptoms of either inattention or hyperactivity/impulsivity (American Psychiatric Association, 2000). In this assessment, teachers were asked to indicate the frequency with which children exhibited each symptom, and responses were dichotomized as 'Yes' if the child was assessed as 'Often' or 'Very often' showing the symptom or 'No' if the child was assessed as 'Sometimes' or 'Never or Rarely' showing the symptom (Avella-Garcia et al., 2016). These data were available for 1202 children (Fig. 1).

Additionally, during school-aged (~7 age), ADHD symptoms were reported by parents using the short form of Conners' Parent Rating Scales (CPRS). During this assessment, parents were asked whether each of 27 items on the CPRS was 'Not true at all' (scored 0), 'Just a little true' (scored 1), 'Petty much true' (scored 3), or 'Very much true' (scored 4) for their child. Scores were summed across four subscales (ADHD index, cognitive problems/inattention, hyperactivity, and oppositional) and converted into age- and sex-standardized T-scores (mean $\pm$ standard deviation (SD) = 50 $\pm$ 10) (Conners, 1997; Conners et al., 1998; Díaz-López et al., 2022). Higher T-scores represent more severe problematic behaviors. A total of 1338 children in the present study had data from the CPRS assessment (Fig. 1).

2.3. Assessment of PM$_{2.5}$ exposures

Residential PM$_{2.5}$ exposures were assessed from conception through early childhood using a two-stage mixed model framework. As described in our previous study (Chen et al., 2023), a spatiotemporal land-use random forest model that integrated ground-level air pollution and satellite-based measures of aerosol optical depth, land-use, meteorological, and traffic variables was developed to estimate daily PM$_{2.5}$ levels at a 1 km^2 resolution across Spain for 2009–2016. A second random forest model incorporating spatial variables (e.g., traffic, land use, population counts) was used to adjust PM$_{2.5}$ estimates to the residential address of the mother and/or child (based on address history assessed throughout the study period). Due to limited availability of PM$_{2.5}$ monitoring data prior to 2009, residential exposure estimates for the 2003–2008 period were estimated through temporal adjustment of the 2009 modeled annual average PM$_{2.5}$ concentrations based on the European Study of Cohorts for Air Pollution Effects (ESCAPE) protocol (Chen et al., 2023; Procedure for Back-Extrapolation: Manual by the ESCAPE project, 2012). For the present analysis, PM$_{2.5}$ exposure estimates were averaged for every one-week period in the prenatal period and for every four-week period (approximately monthly) during the postnatal period to approximate the time unit in which developmental milestones are often calculated and given that fetal development *in utero* is accelerated in comparison with that in early childhood.

2.4. Measurement of covariates

Questionnaires were administered to mothers during the first and third trimesters of pregnancy, at the time of their child's birth, and during each follow-up study visit. We developed a directed acyclic graph (DAG) for the association between air pollution exposures and children's ADHD symptoms to guide the selection of potentially confounding variables informed by prior knowledge (Supplementary Material, Fig. S1). We adjusted for the following confounders based on the minimally sufficient set of covariates: maternal education (primary, secondary, and university), social class (classified as low, middle, and high based on maternal and paternal occupation during pregnancy) (Domingo-Salvany et al., 2000), smoking during pregnancy (self-reported smoking at 12 and/or 32 weeks of gestation, yes/no), urbanicity of

residence during the first trimester (urban, semi-urban, and rural), and child's birth season. Birth season was classified as spring (March, April, and May), summer (June, July, and August), fall (September, October, and November), and winter (December, January, and February). We additionally adjusted the models for the following outcome predictors: maternal age (years) at last menstrual period, parity (0, 1, and $\geq$ 2), self-reported breastfeeding for the first six months of life (exclusive breast-feeding, mixed breastfeeding/formula feeding, and exclusive formula feeding), child sex, child's age (years) at the time of the outcome assessment, and maternal verbal intelligence quotient (IQ scores). The maternal IQ was estimated at the five-year follow-up visit using the Similarities subtest of the Wechsler Adult Intelligence Scales, Third Edition (WAIS-III) (Wechsler and Kaufman, 2001) and was standardized to mean $\pm$ SD of 50 $\pm$ 10.

2.5. Statistical analysis

We first conducted multiple imputation using the predictive mean matching method (van Buuren and Groothuis-Oudshoorn, 2011) to impute missing values among all INMA participants to reduce missingness in the covariate data. We obtained ten imputed datasets and performed analyses in all imputed datasets. As the number of children who completed the assessment of ADHD symptoms was fewer than the number of women initially enrolled, inverse probability weighting was applied in our analyses to account for potential selection bias due to attrition (Weisskopf et al., 2015). DLNMs, a flexible approach for estimating potentially non-linear variations in the dimensions of predictor intensity and lag, were applied to examine susceptible windows of exposure to PM$_{2.5}$ on ADHD symptoms. By specifying a bi-dimensional space of functions, i.e., a 'cross-basis', DLNMs simultaneously model the exposure-response relationships and the lag dimension that represents the change of the exposure-response relationship along lags (Gasparrini, 2011).

Considering biological differences in environmental exposures *in utero* and after birth (Ha, 2021), two distinct cross-basis functions were used to model PM$_{2.5}$ exposures for periods of prenatal (W_{pre}^T) and postnatal (W_{post}^T) in each model. We present the model equation below, which includes covariate matrix **u** with associated linear effects specified by λ.

$$Y = W_{pre}^T \alpha + W_{post}^T \gamma + u\lambda + \epsilon$$

The cross-basis representing exposure estimates in the prenatal period included 33 lags, representing average weekly PM$_{2.5}$ exposure from conception to 33 weeks of gestation. We did not consider exposure during later pregnancy periods (i.e., weeks of gestation between 34 and 37) because DLNMs require the same number of non-missing lags for all subjects and we wanted to include as many preterm births as possible given gestational age may be a mediator in the causal pathway between air pollution and behavioral outcomes (Neophytou et al., 2021). The cross-basis representing postnatal exposure included 53 4-week exposure periods for the analyses of AHDH-DSM-IV outcomes and 77 4-week exposure periods in our analyses of CPRS outcomes. Six children who completed ADHD-DSM-IV before the age of 4 and eight children who completed the CPRS before the age of 6 were excluded (Fig. 1).

A linear exposure-response was specified in each cross-basis and verified by residual analyses. We fitted a natural cubic spline in the lag dimension of the cross-basis of each model, allowing the association between exposures and each outcome to vary smoothly across lags. To determine the number and placement of knots in the splines, we evaluated the fit of multiple models with varying numbers of knots. Knot vectors were selected for the final models based on those that produced the lowest widely applicable information criterion (WAIC) (Gasparrini, 2014). We fitted DLNMs to each of the 10 imputed datasets using the Bayesian hierarchical model framework via the integrated nested Laplace approximation (Gómez-Rubio, 2020). In addition to adjusting for

covariates and accounting for inverse probability weights, models also included a random effect representing the INMA study region. A single set of estimates was produced after merging the effect estimates from the 10 imputed datasets. In our analyses of ADHD symptoms assessed via the ADHD-DSM-IV, where the outcomes were the number of teacher-reported hyperactivity or inattention symptoms, we fitted DLNM models using the negative binomial distribution with a log link to account for overdispersion of the data and present risk ratios (RR) and 95% credible intervals (CrIs) representing the risk of ADHD symptoms associated with a 5 $\mu g/m^3$ unit increase in $PM_{2.5}$ exposure. For the analysis of CPRS outcomes, which were operationalized as age and sex-standardized T-scores, DLNM models were fit with the Gaussian distribution with an identity link, and associations are represented by regression coefficients (β's) and 95% CrIs, representing the change in CPRS T-scores associated with a 5 $\mu g/m^3$ unit increase in $PM_{2.5}$. Susceptible windows of exposure were identified as those exposure periods for which 95% CrIs excluded the null. Cumulative effects (RR_{cum} or β_{cum}) were calculated by aggregating effects across lags when susceptible windows were identified in adjacent exposure periods.

We conducted several additional analyses. First, given that norms used to convert CPRS T-scores in the INMA study were based on U.S. children from the 1990s (Conners, 1997) and may not represent Spanish children in the 2000s, we conducted a sensitivity analysis using the raw scores from the CPRS. Second, to investigate the potential impact of multicollinearity of exposure on our results, we performed 'single-lag models' that examined the exposures at different time points separately (Basagaña and Barrera-Gómez, 2022). The effect estimates were visually compared between the single-lag models and DLNMs and potential multi-collinearity is indicated when the direction (i.e., positive vs. negative) of effects vary consistently between the two methods (Basagaña and Barrera-Gómez, 2022). Finally, we evaluated potential interactions between $PM_{2.5}$ exposure and child sex by including a cross-product term between each cross-basis and child sex and compared model fit between models with and without interaction terms. The statistical interaction between $PM_{2.5}$ exposures and child sex was indicated if the deviance information criterion (DIC) and WAIC for the interaction model were at least 2 and 7 units lower than the model without an interaction term, respectively (Duncan and Mengersen, 2020). We also conducted sex-specific models to visually compare the shapes of the DLNM curves for boys and girls.

Statistical analyses were conducted using R version 4.0.4 (R Core Team, Vienna, Austria) and SAS version 9.4 (SAS Institute, Cary, NC, USA).

3. Results

3.1. Participant characteristics

Maternal and child characteristics of the 1416 mother-child pairs who were included in analyses of $PM_{2.5}$ and ADHD symptoms (prior to imputing missing data) are shown in Table 1. The median age of mothers was 31 years [interquartile range (IQR): 28.0–33.0]. Additionally, 40.8% of the mothers had a secondary level of education, and 35.3% and 37.4% were classified in the low and high social class categories, respectively. Nearly one-third of women reported smoking during pregnancy (28.9%). Most women in the present study lived in urban areas (78.8%). More than half of the women reported giving their children formula in addition to breastfeeding during the first six months of life (58.8%). The characteristics of the 1154 and 1282 mother-child pairs included in the analysis of ADHD symptoms assessed at each time point (i.e., ~age 5 using the ADHD-DSM-IV and ~age 7 using the CPRS) were similar (Table 1). The median ages of children were 4.5 (IQR: 4.4–5.7) for ADHD-DSM-IV outcomes and 7.5 (7.0–7.7) years for CPRS outcomes. After multiple imputation, the distributions of demographic characteristics across the ten imputed datasets were similar (data not shown). The median (IQR) of the average weekly $PM_{2.5}$

Table 1

Maternal and child characteristics of mother-child pairs who were included in the analysis of $PM_{2.5}$ and ADHD symptoms.

Characteristics	Analytic sample for ADHD-DSM-IV or CPRS ($n = 1416$)	Analytic sample for ADHD-DSM-IV ($n = 1154$)	Analytic sample for CPRS ($n = 1282$)
Child age at ADHD symptoms assessment, years (median, IQR)	–	4.5 (4.4–5.7)	7.5 (7.0–7.7)
Maternal age, years (median, IQR)[a]	31.0 (28.0–33.0)	31.0 (28.0–34.0)	31.0 (28.0–33.0)
Maternal IQ score (median, IQR)[b]	10.1 (8.3–12.0)	10.5 (8.3–12.0)	10.5 (8.3–12.0)
Maternal education (n, %)			
Up to primary	303 (21.4)	246 (21.3)	270 (21.1)
Secondary	578 (40.8)	480 (41.6)	525 (40.9)
University	530 (37.4)	424 (36.7)	482 (37.6)
Missing	5 (0.4)	4 (0.4)	5 (0.4)
Social class (n, %)			
Low	499 (35.3)	408 (35.3)	452 (35.3)
Middle	387 (27.3)	323 (28.0)	349 (27.2)
High	530 (37.4)	423 (36.7)	481 (37.5)
Parity (n, %)			
0	800 (56.5)	652 (56.5)	724 (56.5)
1	528 (37.3)	429 (37.2)	483 (37.7)
≥ 2	86 (6.1)	71 (6.1)	73 (5.7)
Missing	2 (0.1)	2 (0.2)	2 (0.1)
Maternal smoking during pregnancy (n, %)			
No	988 (69.8)	799 (69.2)	897 (70.0)
Yes	410 (28.9)	340 (29.5)	370 (28.8)
Missing	18 (1.3)	15 (1.3)	15 (1.2)
Urbanicity of residence during first trimester (n, %)			
Urban	1116 (78.8)	936 (81.1)	1009 (78.7)
Semi-urban	230 (16.2)	166 (14.4)	211 (16.5)
Rural	69 (4.9)	51 (4.4)	61 (4.7)
Missing	1 (0.1)	1 (0.1)	1 (0.1)
Child sex (n, %)			
Girls	704 (49.7)	561 (48.6)	640 (49.9)
Boys	712 (50.3)	593 (51.4)	642 (50.1)
Birth season (n, %)			
Spring	370 (26.1)	291 (25.2)	344 (26.8)
Summer	328 (23.2)	275 (23.8)	294 (22.9)
Fall	374 (26.4)	312 (27.1)	330 (25.8)
Winter	344 (24.3)	276 (23.9)	314 (24.5)
Breastfeeding			
Exclusive breastfeeding	379 (26.8)	314 (27.2)	353 (27.5)
Mixed breastfeeding/ formula feeding	832 (58.8)	672 (58.3)	747 (58.3)
Exclusive formula feeding	180 (12.7)	155 (13.4)	158 (12.3)
Missing	25 (1.8)	13 (1.1)	24 (1.9)

[a] Maternal age was measured at the last menstrual period; 1 (< 1%) mother was missing data for age.
[b] 123 (8.7%) mothers were missing data for IQ scores.

exposure during the gestational weeks 1–33 was 14.6 (13.2–15.9) $\mu g/m^3$. For the postnatal period, the median (IQR) of the average 4-week $PM_{2.5}$ exposure from birth to age 6 years was 14.0 (11.0–15.9) $\mu g/m^3$.

3.2. Susceptible windows of $PM_{2.5}$ exposure on ADHD symptoms

In our study, the prevalence of positivity for teacher-reported ADHD symptoms assessed ~age 5 (using the ADHD-DSM-IV) was very low, with 79.3% and 77.6% of children having zero teacher-reported inattention or hyperactivity/impulsivity symptoms, respectively (data not shown). However, we identified that exposure to $PM_{2.5}$ during mid-pregnancy was associated with increased risk of hyperactivity/
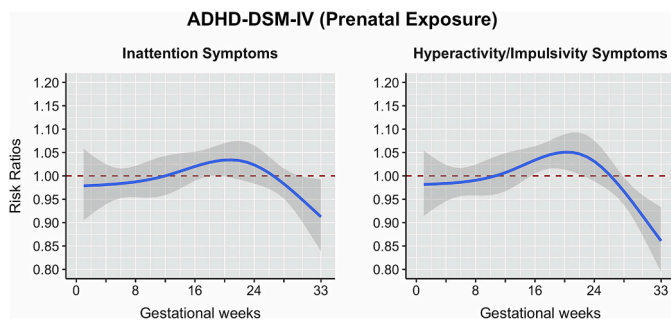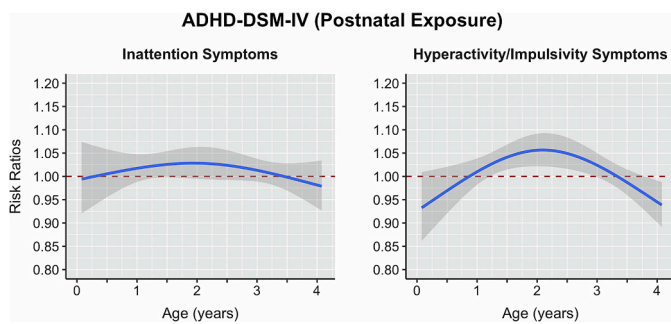
ADHD-DSM-IV (Prenatal Exposure)

Fig. 2. Associations between prenatal $PM_{2.5}$ exposure (per 5 μg/m^3 increase) and risk of ADHD symptoms (assessed by ADHD-DSM-IV) among preschool-aged children (~age 5). The blue line represents the estimated RR from the fitted distributed lag non-linear models, and the shaded areas represent 95% CrI around the estimate for each gestational week. The gestational weeks where the 95% CrI excludes the null value (dotted horizontal line) were identified as susceptible windows of exposure.

ADHD-DSM-IV (Postnatal Exposure)

Fig. 3. Associations between postnatal $PM_{2.5}$ exposure (per 5 μg/m^3 increase) and risk of ADHD symptoms (assessed by ADHD-DSM-IV) among preschool-aged children (~age 5). The blue line represents the estimated RR from the fitted distributed lag non-linear models, and the shaded areas represent 95% CrI around the estimate for each 4-week exposure period. The ages where the 95% CrI excludes the null value (dotted horizontal line) were identified as susceptible windows of exposure.

impulsivity symptoms in preschool-aged children (weeks 16–22, RR_{cum} = 1.36, 95% CrI = 1.22, 1.52) (Fig. 2). During the postnatal period, we identified a period of susceptibility to $PM_{2.5}$ on hyperactivity/impulsivity symptoms from age 1.2–2.9 years (RR_{cum} = 2.78, 95% CrI = 2.02, 3.82) (Fig. 3). We also identified several inverse associations with exposures occurring toward the end of the exposure periods, including between prenatal exposure in gestational weeks 31–33 and 28–33 with inattention (RR_{cum} = 0.80, 95% CrI = 0.71, 0.89) and hyperactivity/impulsivity (RR_{cum} = 0.58, 95% CrI = 0.50, 0.67) symptoms, respectively as well as between exposure from 3.8–4.1 years and hyperactivity/impulsivity symptoms (RR_{cum} = 0.81, 95% CrI = 0.74, 0.89).

Figs. 4 and 5 show the results of the DLNMs relating $PM_{2.5}$ exposures with ADHD symptoms assessed among children around school-aged (~age 7). Associations were not observed between prenatal $PM_{2.5}$ exposure and any of the CPRS subscales (Fig. 4). We identified a susceptible period of exposure to $PM_{2.5}$ from approximately 0.9–2.7 years of age on increased T-scores for the hyperactivity subscale (β_{cum} = 4.19, 95% CrI = 2.78, 5.61) (Fig. 5). No evidence of any specific susceptible windows of postnatal $PM_{2.5}$ exposure on T-scores of the ADHD index or the cognitive problems/inattention and oppositional subscales were observed. In our sensitivity analysis modeling raw CPRS scores, we found similar results with a nearly identical susceptible window of $PM_{2.5}$ exposure during the postnatal period (i.e., age 1.0–2.6 years) on hyperactivity symptoms (data not shown).

In our evaluation of the impact of potential multicollinearity, the effect estimates in the single-lag models and the DLNMs were in the same direction (data not shown), including the inverse associations observed in the late prenatal or postnatal periods on ADHD-DSM-IV outcomes. No evidence of sexually dimorphic impacts of prenatal or postnatal $PM_{2.5}$ on any of the CPRS subscales was observed based on the comparison of model fit between DLNMs with and without an interaction term (data not shown). Similarly, visual inspection of the DLNM curves did not reveal sex-specific patterns of association between prenatal exposure to $PM_{2.5}$ and CPRS subscales (Supplementary Material, Fig. S2). However, despite the fact that the model fit statistics do not support an interaction with sex, visual inspection of the sex-stratified DLNM curves suggests susceptible periods of postnatal exposure to
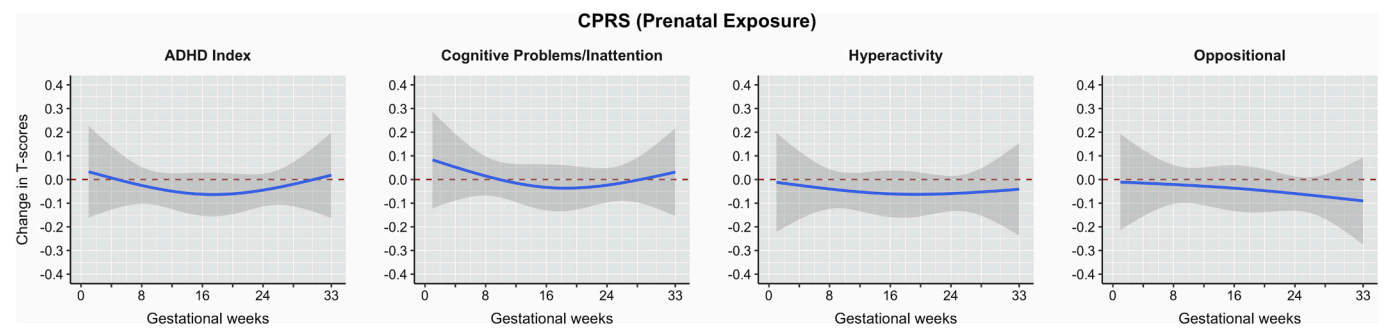
CPRS (Prenatal Exposure)

Fig. 4. Associations between prenatal $PM_{2.5}$ exposure (per 5 μg/m^3 increase) and change in CPRS T-scores among school-aged children (~age 7). The blue line represents the estimated β from the fitted distributed lag non-linear models, and the shaded areas represent 95% CrI around the estimate for each gestational week. The gestational weeks where the 95% CrI excludes the null value (dotted horizontal line) were identified as susceptible windows of exposure.
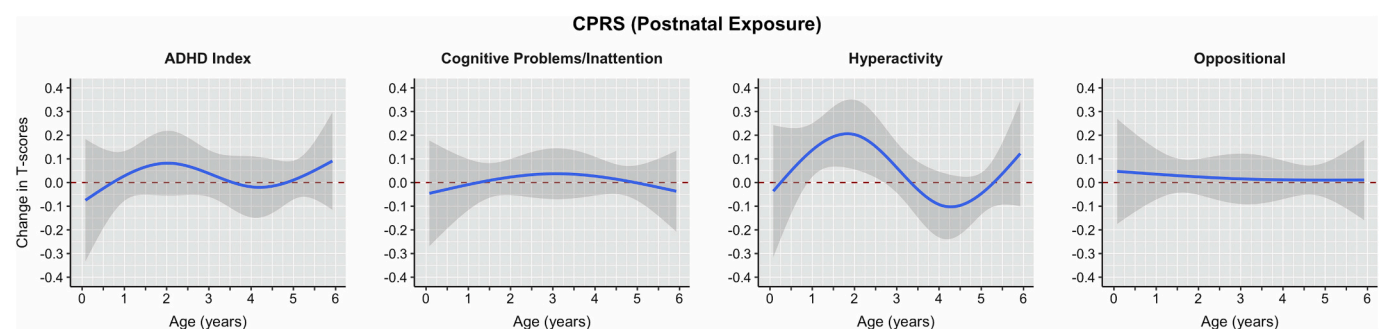
CPRS (Postnatal Exposure)

Fig. 5. Associations between postnatal $PM_{2.5}$ exposure (per 5 μg/m^3 increase) and change in CPRS T-scores among school-aged children (~age 7). The blue line represents the estimated β from the fitted distributed lag non-linear models, and the shaded areas represent 95% CrI around the estimate for each 4-week exposure period. The ages where the 95% CrI excludes the null value (dotted horizontal line) were identified as susceptible windows of exposure.

$PM_{2.5}$ on the CPRS ADHD index and cognitive problem/inattention among girls but not boys. (Supplementary Material, Fig. S3). Given the extremely low prevalence of ADHD symptomology ~5 years of age, interaction and sex-specific models were not constructed for ADHD-DSM-IV outcomes.

4. Discussion

We implemented DLNMs in a large prospective Spanish birth cohort to simultaneously examine temporally refined susceptible windows of exposure to $PM_{2.5}$ on ADHD symptoms. To the best of our knowledge, our study is the first to simultaneously evaluate the impact of prenatal and postnatal air pollution exposures on multiple ADHD symptoms in early childhood. Although we found a susceptible period of exposure during the second trimester on hyperactivity symptoms assessed when children were ~5 years of age, this finding was not observed in analyses evaluating outcomes assessed ~7 years of age. We found consistent evidence that toddlerhood (i.e., around the age range of 0.9–2.9 years) may be a particularly vulnerable period in relation to the adverse impacts of $PM_{2.5}$ exposure on hyperactivity symptoms in young children, regardless of the age at which children were assessed. We did not identify susceptible windows of $PM_{2.5}$ exposure on other ADHD symptoms.

Pregnant women exposed to air pollution, including $PM_{2.5}$, may experience increased systemic oxidative stress and inflammation, which may lead to impaired placental function and restrict fetal growth, followed by impaired brain function that may impact neurobehavioral development during childhood (Ha, 2021; Kannan et al., 2007; Sunyer and Dadvand, 2019). Effects of air pollution on fetal brain development are substantial during pregnancy as brain development is rapid in early to mid-gestation, and brain regional functional connectivity is critical during the latter half of pregnancy (Jakab et al., 2014; Salihagić Kadić and Predojević, 2012; Selevan et al., 2000). Imaging studies also provide evidence that prenatal exposure to $PM_{2.5}$ may alter fetal brain anatomy targeting corpus callosum and lateral ventricles, and reduce cortical blood flow affecting regions that regulate thought, emotion, and behavior in school-aged children (Mortamais et al., 2019; Peterson et al., 2022). On the other hand, postnatal $PM_{2.5}$ exposures experienced by children may cause neural impairments directly by passing through the blood-brain barrier or indirectly by oxidative stress and inflammation (Ha, 2021). Although brain architecture forms during pregnancy, the infant's brain continues to evolve rapidly during the first years of life, developing more synapses and becoming far more interconnected (Huttenlocher, 2002). An imaging study conducted in a Dutch birth cohort in which exposure to $PM_{2.5}$ from conception to the first four years of life was associated with changes in white matter microstructure in school-aged children (Binter et al., 2022), providing mechanistic evidence in support of the susceptibility of children's brains to air pollution exposures during the prenatal period and early childhood. Given that white matter damage is associated with brain damage relevant to disrupted fiber tracts and demyelination, exposure to air pollution during early childhood may underly dysregulated myelination and neuroplasticity that could be related to ADHD pathogenesis (Lebel and Deoni, 2018; Lesch, 2019).

Much of the previous epidemiologic literature regarding the impacts of $PM_{2.5}$ exposure on ADHD and related outcomes has focused on a single developmental period (i.e., either prenatal or postnatal exposures). Results from studies of prenatal $PM_{2.5}$ exposure and ADHD-related outcomes have largely been mixed with most studies examining exposures aggregated across the entire gestational period or within trimesters (Chang et al., 2022; Forns et al., 2018; McGuinn et al., 2020; Ni et al., 2022; Yorifuji et al., 2017). For example, both studies in Mexico (McGuinn et al., 2020) and the U.S. (Ni et al., 2022) observed that $PM_{2.5}$ exposure during the first trimester negatively impacted problematic behaviors assessed among 4–6 year old children. Similarly, Chang et al. (2022) followed Taiwanese children until 5 years of age and found that

first trimester $PM_{2.5}$ exposure was associated with increased risk of ADHD diagnosis. However, a meta-analysis of data from eight European birth cohorts (including INMA) reported no association between pregnancy-average $PM_{2.5}$ and ADHD symptoms in children with ages ranging from 3 to 10 years (Forns et al., 2018). Our study did not observe associations between prenatal exposures to $PM_{2.5}$ and ADHD symptoms based on our assessment of children ~7 years of age. However, in our analysis of ADHD symptoms ~5 years of age (based on the ADHD-DSM-IV), we identified a susceptible period of exposure to $PM_{2.5}$ on hyperactivity during second trimester (i.e., weeks 16–22). We are aware of only one previous study that has simultaneously modeled prenatal and postnatal exposures in relation to hyperactivity symptoms. In that study, Liu et al. (2022) report a susceptible period of exposure to $PM_{2.5}$ on hyperactivity (measured by Conners' Hyperactive Index) among 3-year-old children spanning the late prenatal period (gestational month seven) through early infancy (~four months of age); however, their exposure assessment relied on monthly mean data from stationary monitoring networks, and they did not evaluate for ADHD symptoms other than hyperactivity, and further, they restricted the study population to children who were born full term.

Additionally, we found a susceptible period of exposure to $PM_{2.5}$ during the first several years of life related to hyperactivity symptoms in early childhood, regardless of whether we evaluated ADHD symptoms ~age 5 or ADHD-related behaviors ~age 7. This finding is consistent with several previous epidemiologic studies (Chang et al., 2022; Thygesen et al., 2020; Yuchi et al., 2022), although these studies that evaluated exposure averaged across multiple postpartum years did not account for correlated exposures during the prenatal period. For example, Yuchi et al. (2022) and Thygesen et al. (2020) reported that the risk of ADHD during childhood was associated with $PM_{2.5}$ exposure averaged across the first 3 years or the first 5 years of life, respectively. Similarly, Chang et al. (2022) reported associations between annual $PM_{2.5}$ exposure during the first 3 years of life and increased risk of ADHD. Also, while Ni et al. (2022) reported a positive association between average $PM_{2.5}$ exposure during ages 2–4 years and higher total problems on the Child Behavior Checklist, this association was attenuated after adjusting for prenatal exposures as well as exposure during the first two years of life. However, the assessment of problem behaviors utilized in the Ni et al. (2022) via the Child Behavior Checklist may reflect children's emotional and behavioral problems broadly rather than informing ADHD symptoms specifically.

Although animal evidence has suggested that males may be more vulnerable to the neurotoxic effects of air pollution than females due to differential responses in inflammation and oxidative stress concerning sex hormones (Kern et al., 2017), the findings from epidemiological studies evaluating the sexually-dimorphic impacts of $PM_{2.5}$ exposures on ADHD-related outcomes remain inconsistent (Chang et al., 2022; Chiu et al., 2016; McGuinn et al., 2020; Ni et al., 2022). Although visual comparison of sex-stratified DLNMs implicated susceptible periods of $PM_{2.5}$ exposure during early childhood on increased T-scores for the ADHD index and cognitive problems/inattention subscale only among girls, evaluation of model fit did not support this finding. In contrast, Chiu et al. (2016) reported the association of exposure to $PM_{2.5}$ during mid- to late pregnancy with adverse attention performance among boys but not girls. Although Ni et al. (2022) found stronger associations between postnatal exposure to $PM_{2.5}$ and problem behaviors among females, there was no statistically significant interaction between exposure and child sex. Future studies utilizing large sample sizes from diverse populations and distinguishing subtypes of ADHD may provide insights into potential mechanisms through which sexually dimorphic impacts of susceptible windows for air pollution on ADHD development.

A major strength of our study was the application of DLNMs which allowed the exploration of more refined windows of susceptibility (i.e., weeks and months) compared with previous studies as the use of more broad windows (e.g., trimesters during pregnancy or yearly in the postnatal period) may mask the identification of true susceptible

windows (Wilson et al., 2017). DLNMs account for correlated lagged exposures across time by modeling the temporal and intensity components of exposure simultaneously on the cross-basis (Gasparrini et al., 2010; Gasparrini et al., 2017). Furthermore, specifying a spline function of time in the DLNMs will capture long-term trends in the time series data (Bhaskaran et al., 2013). However, because the number of observed exposures (i.e., lags) is required to be identical for all study subjects, we could not evaluate prenatal exposure across complete gestation without the exclusion of all preterm births, which could have led to collider stratification bias or resulted in shrinkage of the effect estimates toward the null due to overadjustment (Neophytou et al., 2021). Although two children born prior to 33 weeks were inevitably excluded from our analysis, we expect there is limited bias due to the loss of these two subjects. Our study included satellite-based measures of aerosol optical depth in the prediction modeling of air pollution assessment, which provides improved spatiotemporal resolution compared with methods using only monitoring data. Additionally, our exposure assessment accounted for residential mobility throughout the follow-up period, improving the accuracy of individual exposure estimation. However, we cannot rule out the impact of potential exposure misclassification due to the lack of information on indoor air pollution concentrations or individual time-activity patterns. It is also possible that some measurement error may have been introduced in our air pollution models by using the temporal adjustment for the exposure estimates for the 2003–2008 period due to the limited numbers of monitoring stations for $PM_{2.5}$ before 2009.

Several additional limitations need to be considered when interpreting our findings. The present study may be susceptible to potential live-birth bias because fetuses particularly susceptible to air pollution exposures were unobserved for neurobehavioral outcomes due to pregnancy loss (Raz et al., 2018). Although we applied inverse probability weighting to adjust for potential attrition bias, the possibility of selection bias cannot be ruled out. While we adjusted for several demographic and behavioral characteristics in the models, our results may still be influenced by the potential time-varying socioeconomic status as well as some unmeasured factors, such as the family history of neurodevelopmental problems or other factors related to the family and social environment (Thapar and Cooper, 2016). Although a confirmed clinical diagnosis of ADHD with standardized criteria by psychologists was not available in our study, reliance on the clinical diagnosis of ADHD may exclude some children with only mild to moderate symptoms. Given a wide range of subclinical neurodevelopmental deficits, the assessment of dimensional variation (i.e., change in scores) across different behaviors related to ADHD may be particularly appropriate to capture the subtle effect of air pollution on neurodevelopment (Rauh and Margolis, 2016). Our evaluation of outcomes ~5 years of age was limited by the low prevalence of ADHD symptomology. Although our investigation consistently pointed toward associations between postnatal $PM_{2.5}$ exposure and hyperactivity (and not other dimensions of ADHD-related symptoms), only the assessment of ADHD symptoms ~age 5 revealed susceptible periods of exposure in the prenatal period. In addition to the differences in instruments and respondents (i.e., teachers and parents) between our two ADHD assessments, ADHD symptoms may change over time due to children's growth or family and social environment (Díaz-López et al., 2022; Murray et al., 2021), outcome assessments conducted during different ages may possibly reveal different patterns of association and these findings should be followed up. Lastly, while the implementation of cross-basis in DLNMs generally reduces the impact of multicollinearity within exposures (Gasparrini et al., 2010), it is still possible for multicollinearity to cause unexpected results (Basagaña and Barrera-Gómez, 2022). Our sensitivity analyses using single-lag models did not reveal this issue in our analyses. While we observed unexpected inverse associations between $PM_{2.5}$ exposure in the late prenatal or postnatal periods and ADHD-DSM-IV-based outcomes, these associations are not supported by a biologically plausible mechanism and most likely have noncausal explanations.

5. Conclusion

In summary, our study provides evidence of a period of susceptibility to $PM_{2.5}$ exposure in toddlerhood on hyperactivity/impulsivity. Future research involving repeated measurements across childhood and early adolescence may provide further insights into associations of air pollution exposure on trajectories of ADHD-related outcomes.

CRediT authorship contribution statement

Wei-Jen Chen: Data curation, Formal analysis, Writing – original draft. **Alison M. Rector-Houze:** Data curation, Formal analysis, Writing – review & editing. **Mònica Guxens:** Funding acquisition, Methodology, Supervision, Writing – review & editing. **Carmen Iñiguez:** Formal analysis, Methodology, Writing – review & editing. **Michael D. Swartz:** Methodology, Supervision, Writing – review & editing. **Elaine Symanski:** Supervision, Writing – review & editing. **Jesús Ibarluzea:** Methodology, Writing – review & editing. **Antonia Valentin:** Data curation, Writing – review & editing. **Aitana Lertxundi:** Methodology, Writing – review & editing. **Llúcia González-Safont:** Writing – review & editing. **Jordi Sunyer:** Writing – review & editing. **Kristina W. Whitworth:** Conceptualization, Funding acquisition, Project administration, Supervision, Writing – review & editing.

Declaration of competing interest

All authors declare they have no actual or potential competing financial interest.

Data availability

Data are available upon reasonable request by contacting inma@proyectoinma.org. Information regarding the INMA

Collaboration Policy is available here: https://www.proyectoinma.org/en/inma-project/inma-collaboration-policy/.

Acknowledgments

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2023.168806.

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