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Relation of prenatal and postnatal $PM_{2.5}$ exposure with cognitive and motor function among preschool-aged children

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Declaration of competing interest

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

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijheh.2023.114317.

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Abstract

The literature informing susceptible periods of exposure on children's neurodevelopment is limited. We evaluated the impacts of pre- and postnatal fine particulate matter ($PM_{2.5}$) exposure on children's cognitive and motor function among 1303 mother-child pairs in the Spanish INMA (Environment and Childhood) Study. Random forest models with temporal back extrapolation were used to estimate daily residential $PM_{2.5}$ exposures that we averaged across 1-week lags during the prenatal period and 4-week lags during the postnatal period. The McCarthy Scales of Children's Abilities (MSCA) were administered around 5 years to assess general cognitive index (GCI) and several subscales (verbal, perceptual-performance, memory, fine motor, gross motor). We applied distributed lag nonlinear models within the Bayesian hierarchical framework to explore periods of susceptibility to $PM_{2.5}$ on each MSCA outcome. Effect estimates were calculated per 5 μg/m^3 increase in $PM_{2.5}$ and aggregated across adjacent statistically significant lags using cumulative β (β_{cum}) and 95% Credible Intervals (95%CrI). We evaluated interactions between $PM_{2.5}$ with fetal growth and child sex. We did not observe associations of $PM_{2.5}$ exposure with lower GCI scores. We found a period of susceptibility to $PM_{2.5}$ on fine motor scores in gestational weeks 1–9 (β_{cum} = −2.55, 95%CrI = −3.53,−1.56) and on gross motor scores in weeks 7–17 (β_{cum} = −2.27,95%CrI = −3.43,−1.11) though the individual lags for the latter were only borderline statistically significant. Exposure in gestational week 17 was weakly associated with verbal scores (β_{cum} = −0.17, 95%CrI = −0.26,−0.09). In the postnatal period (from age 0.5–1.2 years), we observed a window of susceptibility to $PM_{2.5}$ on lower perceptual-performance (β = −2.42, 95%CrI = −3.37,−1.46). Unexpected protective associations were observed for several outcomes with exposures in the later postnatal period. We observed no evidence of differences in susceptible periods by fetal growth or child sex. Preschool-aged children's motor function may be particularly susceptible to $PM_{2.5}$ exposures experienced *in utero* whereas the first year of life was identified as a period of susceptibility to $PM_{2.5}$ for children's perceptual-performance.

Keywords

Air pollution; $PM_{2.5}$; McCarthy scales of Children's abilities; Susceptible windows; Motor function; Cognitive function

1. Introduction

Given its protracted development, the human brain is influenced by environmental exposures (Grandjean and Landrigan, 2014; Landrigan et al., 2012; Paus, 2010), including air pollution, which has been deemed the most important environmental global threat (Lim et al., 2012). Exposure to particulate matter (PM), a heterogenous mix of chemical constituents, is a concern given that smaller particles, including PM with aerodynamic diameter less than 2.5 μm ($PM_{2.5}$), can readily pass through the upper and lower respiratory system, with the smallest particles entering the circulatory system and potentially, the brain (Forman and Finch, 2018). Animal studies have also demonstrated maternal-fetal translocation of airborne particles (Bongaerts et al., 2020, 2023).

Neural connectivity controlling myriad facets of neurodevelopment begins *in utero* and continues through early childhood, with the most rapid growth in the brain occurring before an infant is six months old (Thomason et al., 2018). Extensive myelination of the brain then occurs through the second year of life (Thomason et al., 2018), with neural development continuing through adolescence (Rice and Barone, 2000). Given the developmental potential of children (in addition to the fetus) and evidence that different areas of the brain develop at different time points during fetal and postnatal life (Bayer et al., 1993; Mendola et al., 2002), exposure timing is critical in identifying specific neurodevelopmental consequences of exposure. Further, the vulnerability of the placenta to endogenous chemicals crossing its boundaries may vary across gestation (e.g., in early gestation before the placenta has fully formed and in late gestation when the placental wall is more vascularized) (Woodward et al., 2015), providing further rationale for carefully examining critical windows of susceptibility to air pollution on child neurodevelopment during both the prenatal and postnatal periods.

Previous epidemiologic studies investigating associations of $PM_{2.5}$ exposure with children's cognitive and motor function have varied in their assessment of specific outcomes and have employed diverse exposure assessment methodologies, although many have had limited spatiotemporal specificity (Clifford et al., 2016). Further, several prior studies indicate adverse neurodevelopmental effects may be more profound with prenatal compared with postnatal air pollution exposures (Lam et al., 2016; Peterson et al., 2015; Raz et al., 2015), yet few have employed statistical methods to simultaneously assess exposure during refined periods of susceptibility during both periods. Chiu et al. (2016) identified several susceptible periods of weekly exposure during the prenatal period (adjusted for postnatal exposures) and deficits in both memory and attentional function. Ni et al. (2022) also examined prenatal and postnatal air pollution exposures and reported a negative association between average $PM_{2.5}$ exposures during ages 2–4 years on children's intelligence quotient (IQ). A recent investigation of combined prenatal and postnatal air pollution exposures on children's general, verbal, and non-verbal abilities at age 5–6 years identified susceptible periods of exposure to $PM_{2.5}$ among male children in mid-pregnancy and when the child was around 3–4 years of age (Guilbert et al., 2023). The literature regarding refined susceptible periods of exposure to air pollutants on early child neurodevelopment is limited, particularly among studies that have jointly investigated susceptible periods of pre- and postnatal exposure to $PM_{2.5}$ on specific domains of children's cognitive and motor function. Further, exposure during different developmental time points (spanning the prenatal and postnatal periods)

may result in different functional outcomes as could differences in timing or duration of exposure (Mendola et al., 2002).

The goal of the present study was to apply distributed lag non-linear models (DLNMs) within the Bayesian hierarchical model framework to data from a large prospective birth cohort, the INfancia y Medio Ambiente (INMA; English translation: Environment and Childhood) Study, to model $PM_{2.5}$ exposures during both the prenatal and postnatal periods in relation to a measure of children's general cognition as well as to explore impacts on specific domains of early childhood cognitive and motor function as measured by the McCarthy Scales of Children's Abilities (MSCA).

2. Materials and methods

2.1. Study design and study population

This study was conducted among mother-child pairs recruited in INMA, a population-based prospective birth cohort study in Spain. The present analysis includes mothers who were recruited during pregnancy from the Valencia, Sabadell, and Gipuzkoa regions between November 2003 and February 2008. Women were eligible for participation in this study if they were at least 16 years of age, resided in one of the study regions, attended the first prenatal visit between 10 and 13 gestation weeks, had a singleton pregnancy, had not followed any program of assisted reproduction, did not have communication problems, and planned to deliver at the recruitment hospital. Follow-up visits were conducted in each trimester during pregnancy and when the child was approximately 1–1.5, 2–2.5, and 4–5 years of age (Guxens et al., 2012). The INMA Study was approved by the Ethics Committee at the reference hospitals, and all women gave written informed consent prior to enrollment; the present analysis was also approved by the Institutional Review Board of Baylor College of Medicine.

2.2. Assessment of children's cognitive and motor function

To assess children's cognitive and motor function, the MSCA were administered to the children around the age of 5 years (MacCarthy, 1972) by trained neuropsychologists using the Spanish version in Sabadell and Valencia and also using the Basque version in Gipuzkoa (Andiarena et al., 2017). In Sabadell and Gipuzkoa, all tests were performed by a single psychologist and in Valencia, tests were performed by two psychologists. The MSCA evaluate children's cognitive and motor function through a series of independent subtests. For the current analysis, we focus on the general cognitive index (GCI), a summary measure, and we also explored global verbal function (processing verbal information), global perceptual-performance (related to nonverbal reasoning and visual-motor function), and global memory function (encompassing cognitive tasks related to temporary retention of verbal, visual, or numerical information) as well as fine (e.g., drawing), and gross (e.g., jumping, throwing a ball) motor skills. Raw scores for each scale were standardized to a mean of 100 and standard deviation of 15, with higher scores indicating better performance. Of 2020 mother-child pairs for whom data was available at birth, there were 604 (29.9%) mother-child pairs excluded due to deaths, because they withdrew from the study, were lost-to-follow up, or because the child did not undergo the MSCA (Fig. 1). Among 1416

children for whom the MSCA was administered, 74 (5.2%) were excluded from the present analysis for either incomplete MSCA data or data that were deemed not evaluable (Fig. 1).

2.3. Exposure assessment

Daily $PM_{2.5}$ levels were estimated for 2009–2016 for all Spain at a 1 square kilometer resolution using a spatio-temporal land-use random forest model. This model has been previously developed and applied in other countries and combines ground-level air pollution and satellite-based measures of aerosol optical depth, land-use, meteorological, and traffic variables (Stafoggia et al., 2019, 2020). Air pollution estimates were adjusted to the exact locations of woman's reported residence (or residences if the woman reported moving during the study period) using a second random forest model incorporating spatial variables such as traffic, land use, and population counts (Stafoggia et al., 2019). The model performance was evaluated by year using both out-of-bag sampling and 10-fold cross-validation, with R^2 values ranging from 0.68 to 0.78 and 0.46–0.58 for each method, respectively. To estimate exposures prior to 2009, we followed methodology for back extrapolation of the European Study of Cohorts for Air Pollution Effects (ESCAPE) project to temporally adjust the 2009 annual average concentration of $PM_{2.5}$ at each woman's residence using data from stationary ambient monitoring networks that operate continuously in each study area (Procedure for Back-Extrapolation: Manual by the ESCAPE project, 2012). In Gipuzkoa, the temporal adjustment was made by multiplying the 2009 annual $PM_{2.5}$ estimates at each woman's residence (obtained from the random forest model) by the ratio of daily to 2009 annual average $PM_{2.5}$ estimates from the stationary monitoring site. $PM_{2.5}$ concentrations from stationary monitoring networks during 2003–2008 were unavailable in Sabadell and Valencia. Thus, as recommended by the ESCAPE protocol, the temporal adjustment was made using PM_{10} concentrations followed by an additional adjustment for the median ratio of annual average PM_{10} to $PM_{2.5}$ concentrations from monitoring stations in which both pollutants were measured (Procedure for Back-Extrapolation: Manual by the ESCAPE project, 2012). Finally, daily predicted $PM_{2.5}$ concentrations at each mother-child pair's residence (accounting for residential mobility during pregnancy and early childhood) were averaged across each week of mothers' gestational periods and of the postnatal/early childhood period of her child. Three (<1%) children were excluded from the analysis due to missing prenatal exposure and 34 (2.5%) children were excluded due to missing postnatal exposure (Fig. 1).

2.4. Covariates

Sociodemographic and behavioral characteristics of women enrolled in INMA were assessed via interviewer-administered questionnaires during women's first and third trimesters of pregnancy. Inclusion of confounders and variables predicting child neurodevelopmental outcomes was guided by a directed acyclic graph (DAG; Supplemental Fig. 1). For consistency, we applied the same DAG to all MSCA outcomes. Based on our DAG, maternal education (primary, secondary, university), season of birth, and urbanicity (urban, semi-urban, rural) of women's residences in the first trimester of pregnancy were included in our models. Season of birth was categorized as: spring (March, April, May), summer (June, July, August), fall (September, October, November), or winter (December, January, February). In addition to these variables, we also adjusted for parental social class (high, middle, low)

during pregnancy, classified according to the highest of either the maternal or paternal social class assignment based on self-reported occupation (Domingo-Salvany et al., 2000). Finally, we adjusted the statistical models for the following predictors of the outcome: maternal age (years), maternal intelligence quotient (IQ; assessed at the five-year follow-up visit using the similarities subtest of the Wechsler Adult Intelligence Scales-third edition or WAIS-III (Psychological Corporation, 1999; Wechsler and Kaufman, 2001); standardized to a mean of 50 and standard deviation of 10 and modeled as a continuous score), parity (0, 1, or ≥2 previous pregnancies), smoking during pregnancy (self--reported smoking at 12 and/or 32 weeks of gestation; yes/no), self-reported breastfeeding during the first six months of the child's life (exclusively breastfed, mixed breastfeeding and formula feeding, exclusively formula feeding), child sex, and child's age at assessment of the MSCA. Psychologist was not included in the model given little to no variation in this variable. Finally, INMA study region (i.e., Sabadell, Gipuzkoa, Valencia) was included in models as a random effect.

2.5. Statistical analysis

We applied distributed lag nonlinear models (DLNMs) using the r package 'dlnm' version 2.4.5 in R version 4.0.2 (R Core Team, 2020). DLNMs model associations along the lagged occurrence of the exposure and outcome through the application of a cross-basis. The cross-basis is a bidimensional space of functions obtained from integrating two basis functions: one that represents the exposure ($PM_{2.5}$)-response relationship over the range of exposures and the other that represents the change of this exposure–response relationship over time (i.e., lags) (Gasparrini et al., 2010), thus accounting for temporal trends (Bhaskaran et al., 2013).

Due to the biological differences of *in utero* and postnatal exposures, prenatal and postnatal $PM_{2.5}$ exposures were modeled using two distinct cross-basis functions that were simultaneously modeled in a single DLNM. The prenatal cross-basis included weekly exposures during the first 33 weeks of gestation, resulting in the exclusion of 2 children born prior to 33 weeks. We did not consider exposure during later pregnancy periods because DLNMs do not allow variability in the number of observed exposure periods (lags) between subjects and doing so would have necessarily excluded most preterm births, raising concerns about collider stratification bias. The postnatal cross-basis included 53 four-week periods (i.e., from the first month of life through approximately the first month of the fourth year of the child's life). Our models assumed a linear exposure ($PM_{2.5}$) –response varying smoothly across exposure periods and this assumption was verified through residual analyses. We fit a natural cubic spline for the lag dimension of each cross-basis allowing the exposure-response to follow a different pattern at each lag. We selected knot placement in each cross-basis by evaluating the fit of multiple models and using a two-step selection process. For each MSCA outcome, models were constructed with either 1 or 2 evenly spaced knots in each of the prenatal and postnatal cross-bases. We first selected knot vectors that produced models with Widely Applicable Information Criterion (WAIC) within 2 units of the minimum WAIC value (Duncan and Mengersen, 2020). Then, among these knot vectors, the model with the lowest root mean squared error (RMSE) was selected for use in the final model.

To reduce missingness in the covariate data, multiple imputation using the mean matching method, using all covariates as predictors, and with 10 iterations was performed using the r package 'mice' 13.13.0 in version 4.0.4 (R Core Team, 2020). DLNM models were fit to each of the ten imputed data sets within the Bayesian hierarchical model framework via the integrated nested Laplace approximation using the r package 'INLA' (Gómez-Rubio, 2020). As mentioned, we specified INMA study region (i.e., Sabadell, Gipuzkoa, Valencia) as a random effect and we also applied inverse probability weights of attrition to account for potential selection bias. Effect estimates from each of the ten imputed data sets were merged to produce a single set of estimates, representing the change in MSCA scores associated with a 5 $\mu g/m^3$ increase in $PM_{2.5}$ exposure during each 1-week exposure period in the prenatal period or each 4-week exposure period in the postnatal period, which were visualized in figures. Individual susceptible periods of exposure within each period were identified if the 95% credible interval (CrI) for the individual lag excluded the null value. Here, we present the cumulative effect (β_{cum}) aggregated across adjacent susceptible windows and interpreted as the average expected change in the MSCA score assuming an average increase of 5 $\mu g/m^3$ $PM_{2.5}$ over the identified period.

We conducted a sensitivity analysis to investigate potential impact of multi-collinearity in exposure estimates on our results (Basagaña and Barrera-Gómez, 2022). Simple linear regression models were fit for each period of exposure (referred to as 'single-lag models'). We visually compared the effect estimates produced by the single-lag models with those from the DLNMs and identified potential multi-collinearity when the direction (i.e., positive vs. negative) of effects varied consistently between the two methods (Basagaña and Barrera-Gómez, 2022). Lastly, we evaluated interactions between $PM_{2.5}$ exposure and, separately, child sex and fetal growth, on MSCA outcomes. Interactions were evaluated through the addition of a cross-product term between the potential moderator and the cross-basis representing the exposure-lag-response surface for the desired exposure period. To characterize fetal growth, we used fetal growth trajectories previously described (Iñiguez et al., 2012) and briefly summarized here. We previously fit growth curves to data representing estimated fetal weight (EFW) at 12, 20, and 34 gestational weeks. *Z*-scores for EFW at 34 weeks, conditioned on EFW at 20 weeks, were calculated and represent deviations in actual growth of the fetus between 20 and 34 weeks compared with expected growth during this period. To evaluate fetal growth as a moderator of the $PM_{2.5}$-MSCA association, we dichotomized EFW z-scores at half a standard deviation below the mean. We focused on fetal growth during this period given previously observed associations with $PM_{2.5}$ exposure (Chen et al., 2022). For statistical assessment of interactions, two model fit statistics were compared between models with and without an interaction term: deviance information criteria (DIC) and the WAIC. Conservatively, we concluded that models including an interaction term provided better model fit if each of the following criterion were met: 1) the DIC was at least 2 units lower and 2) the WAIC was at least 7 units lower as compared with the no interaction model (Duncan and Mengersen, 2020).

3. Results

The distributions of sociodemographic characteristics of study subjects (prior to imputing missing data) are presented in Table 1. Of the 1303 mother-child pairs included in this

analysis, 77 were missing at least one covariate, although no single covariate was missing more than 3.3% of observations. The median age of mothers was 31 years (interquartile range (IQR): 28, 33). Most women lived in urban areas (79.4%), had secondary or university-level education (78.4%), and over one-third (37.0%) were classified in the highest social class category. There were some differences in the characteristics between participants recruited from different study regions (Supplemental Table 1). For example, in general, children in Valencia were assessed at older ages compared with children from Sabadell and Gipuzkoa. Additionally, women in Gipuzkoa typically had greater socioeconomic status, based on a larger proportion of women from this region with a university-level education and who were classified in the high social class category compared with women from the other two regions. The distributions of sociodemographic characteristics including the imputed values for subjects with missing data on covariates were similar (see Supplemental Table 2). The median (IQR) of the average weekly $PM_{2.5}$ exposure during the prenatal period was 14.6 (13.3, 16.0) $\mu g/m^3$. For the postnatal period, the median (IQR) of the average 4-week $PM_{2.5}$ exposure was 13.8 (11.8, 15.2) $\mu g/m^3$. The correlation between MSCA subscales is presented in Supplemental Fig. 2. The coefficients representing correlation between subscales ranged from 0.06 to 0.79; the highest correlations were between verbal and memory scores (r = 0.73) and between perceptual-performance and fine motor scores (r = 0.79).

No susceptible periods of exposure were identified for either pre- or postnatal $PM_{2.5}$ exposures on lower GCI scores, although we observed higher GCI scores associated with exposures in the late postnatal period, around age 3.5–4.1 years (β_{cum} = 2.56, 95% CrI = 1.53, 3.57) (Fig. 2). Fig. 3 presents the DLNM models for $PM_{2.5}$ exposures and the MSCA scores for several MSCA subscales related to cognitive function. We identified a susceptible period of exposure during gestational week 17 on lower verbal scores, though the magnitude of this effect was small (β_{cum} = −0.17, 95% CrI = −0.26, −0.09). During the postnatal period, $PM_{2.5}$ exposure during approximately 6–15 months of age (i.e., 0.6–1.2 years) was associated with moderately lower perceptual-performance scores (β_{cum} = −2.42, 95% CrI = −3.37, −1.47). We observed a tendency for the DLNM curves to trend upward at the end of the exposure periods with susceptible windows of exposure detected during gestational weeks 23–29 for higher perceptual-performance scores (β_{cum} = 1.30, 95% CrI = 0.77, 1.83) as well as in the late postnatal period for higher verbal (age 3.7–4.1 years: β_{cum} = 1.92, 95% CrI = 1.12, 2.72) and memory (age 2.9–3.4 years: β_{cum} = 1.07, 95% CrI = 0.59, 1.55) scores. Results for fine and gross motor function are shown in Fig. 4. A susceptible period of exposure during the first nine weeks of pregnancy was identified for lower fine motor scores (β_{cum} = −2.55, 95% CrI = −3.53, −1.56). $PM_{2.5}$ exposures during gestational weeks 8–17, which overlaps the first and second trimesters, were individually marginally associated with lower gross motor scores, although the cumulative effect during this period was statistically significant (β_{cum} = −2.27, 95% CrI = −3.43, −1.11). No associations were observed between postnatal $PM_{2.5}$ exposures and lower fine or gross motor function.

Overall, our evaluation of the impact of potential multi-collinearity of the exposure estimates (Basagaña and Barrera-Gómez, 2022) via single lag models (data not shown) revealed associations in the same direction as the DLNM results for most lags, including the few positive associations observed in the late prenatal and late postnatal periods. We observed

no evidence differential impacts of $PM_{2.5}$ on child cognitive and motor function by child sex (Supplemental Table 3) nor did we observe evidence of interactions between $PM_{2.5}$ exposures and fetal growth on MSCA outcomes (Supplemental Table 4).

4. Discussion

We used DLNMs to simultaneously model refined windows of pre- and postnatal $PM_{2.5}$ exposure in relation to cognitive and motor function among preschool-aged children and to explore specific windows of vulnerability to the neurotoxic effects of $PM_{2.5}$. Although we found no evidence that $PM_{2.5}$ during specific exposure windows in the pre- or postnatal periods adversely impacted children's general cognitive abilities (based on the MSCA GCI), our results suggest that children's motor function may be especially susceptible to $PM_{2.5}$ exposures in the prenatal period while lower global perceptual-performance was most susceptible to exposure during the first year and a half of life. Our models also revealed unexpected positive associations between $PM_{2.5}$ exposures in the late prenatal period with perceptual-performance scores and in the late postnatal period with verbal, memory, and GCI scores.

Previous studies have largely been mixed regarding the impacts of air pollution exposure on specific domains of children's cognitive function. For example, while the Health Effects Institute recently concluded moderate confidence in associations of traffic-related air pollutants (including $PM_{2.5}$) and cognitive outcomes in childhood, associations in reviewed studies were inconsistent across specific cognitive domains evaluated (HEI Panel on the Health Effects of Long-Term Exposure to Traffic-Related Air Polluton, 2022). Although we identified a weak association between lower MSCA global verbal scores and $PM_{2.5}$ exposures in a single week during the second trimester of pregnancy, this association was weak albeit consistent with our group's previous work evaluating impact of average pregnancy $PM_{2.5}$ exposures (based on a different exposure assessment model than employed in the current analysis) on cognitive outcomes in INMA (Lertxundi et al., 2019). We identified a period in early childhood (i.e., the from age 6 months to age 15 months) in which $PM_{2.5}$ exposures were associated with moderately lower perceptual-performance scores, a measure that encompasses children's nonverbal reasoning skills and visual-motor coordination. A recent study among children in the French EDEN and PELAGIE cohorts also identified a sensitive window of exposure to PM2.5 during childhood on children's non-verbal abilities, although they identified windows at a slightly older age than we did (around the time the child is 3–4 years) and only among male children (Guilbert et al., 2023). In contrast, neither Binter et al. (2022a), using data from four European Cohorts (including both INMA and EDEN), or Harris et al. (2015b) using data from the Project Viva Study in the United States, support a negative association between $PM_{2.5}$ exposure and children's non-verbal IQ. The prior literature regarding $PM_{2.5}$ exposure and preschool aged children's memory function have been mixed. Both Chiu et al. (2016) and Rivas et al. (2019) identified susceptible periods of $PM_{2.5}$ exposure on decreased memory function using DLNMs. However, the Chiu et al. (2016) study only evaluated susceptible periods during the prenatal period and while Rivas et al. (2019) evaluated both pre- and postnatal $PM_{2.5}$ exposure, they modeled prenatal exposure as a single lag comprising the entire gestational period. Also, the finding from Chiu et al. (2016) was restricted to girls while

the findings from Rivas et al. (2019) were restricted to boys. Additionally, while our group (Lertxundi et al., 2019) previously reported negative effects of average pregnancy $PM_{2.5}$ exposures on children's verbal function in INMA, our current analysis utilizing a more refined exposure assessment and considering both the pre- and postnatal periods did not identify specific periods during pregnancy associated with this outcome. Neither Kusters et al. (2022) nor Harris et al. (2015a) found associations between pre- or postnatal $PM_{2.5}$ exposures with memory function among children in the Netherlands or the U.S., respectively although second study in the U.S. (Chiu et al., 2016).

Our models also revealed moderate associations between prenatal $PM_{2.5}$ exposure and preschool-aged children's motor function, with indications that fine motor development may be sensitive to exposure during the earliest weeks of pregnancy. We found suggestive evidence of a susceptible period of exposure overlapping the first and second trimesters of pregnancy with gross motor function. However, while the cumulative impact of exposures during this period (gestational weeks 7–17) was statistically significantly associated with lower gross motor scores, effect estimates for individual exposure lags were only marginally associated with the outcome. We are unaware of previous studies that have evaluated specific susceptible periods of exposure to $PM_{2.5}$ (or other air pollutants) on children's motor function, but our results, particularly for fine motor function, are consistent with many previous studies evaluating average pregnancy exposures. For example, a meta-analysis of evidence from European cohort studies, including INMA, reported lower global psychomotor function associated with higher $PM_{2.5}$ exposure averaged across pregnancy, with similar results for fine and gross motor development (Guxens et al., 2014). Our group also reported a non-statistically significant negative association of total pregnancy exposure to $PM_{2.5}$ on fine (but not gross) motor skills (Lertxundi et al., 2019). Binter et al. (2022a) reported an association between prenatal $PM_{2.5}$ exposure and fine (but not gross) motor function with no association with postnatal exposures. On the other hand, a study among Italian children aged 5–8 and which employed a sophisticated spatio-temporal exposure model, did not report associations between average gestational or trimester specific $PM_{2.5}$ exposures and motor function among children aged 5–8 (Girardi et al., 2021).

Both human and animal studies have demonstrated sex differences in neurodevelopmental outcomes in response to air pollution, which may be due to differential neuroprotective of sex hormones (Kern et al., 2017). Air pollution impacts on child neurodevelopment may also be modified by *in utero* fetal growth as prenatal air pollution exposure is associated with fetal growth (Fu et al., 2019) and, in turn, poor fetal growth-related outcomes are related to poor cognitive development (Oudgenoeg-Paz et al., 2017). However, our analyses did not support differences in susceptible periods of exposure to $PM_{2.5}$ on children's cognitive or motor development by fetal sex or fetal growth. Though the evidence regarding sexually dimorphic neurotoxic effects of air pollutant exposures is mixed, when studies do report such differences, they tend to point to the vulnerability of males (HEI Panel on the Health Effects of Long-Term Exposure to Traffic-Related Air Polluton, 2022). We are aware of few previous studies that investigated sex differences in children's cognitive or motor function in relation to susceptible windows of exposure using DLNMs. Binter et al. (2022a) found no evidence of differences in susceptible periods of exposure to air pollution on 9–12-year-old children's white matter microstructure and brain volume. Chiu

et al. (2016) reported associations of prenatal exposure to $PM_{2.5}$ during 18–26 weeks with reduced visual memory and during 12–20 weeks with general memory among girls while Rivas et al. (2019) found associations of childhood exposure to $PM_{2.5}$ and working memory among boys. Additionally, Guilbert et al. (2023) identified both pre- and postnatal susceptible periods of exposure to $PM_{2.5}$ on male (but not female) children's general and non-verbal cognitive abilities. Also, despite evidence that children with reduced fetal growth have poorer neurodevelopmental outcomes in childhood (Miller et al., 2016), we did not find evidence of different windows of susceptibility to pre- or postnatal air pollution exposure on childhood cognitive and motor ability according to reduced fetal growth. We evaluated a dichotomous metric of fetal growth late in pregnancy based on our previous findings of an association between $PM_{2.5}$ exposure and this outcome (Chen et al., 2022) although it is possible that this metric does not adequately discriminate fetuses that are 'at risk' with regards to later detriments in neurodevelopment. It is also possible that fetal growth is a mediator of associations between prenatal air pollution exposure and child neurodevelopment, a hypothesis that was not within the scope of the present investigation.

$PM_{2.5}$ is a heterogenous mixture of different chemical constituents, including organic carbon (polycyclic aromatic hydrocarbons [PAHs], other organic compounds), elemental carbon, inorganic species, and trace elements. Exposure largely occurs through inhalation, with the smallest particles penetrating the lower respiratory tract and crossing into the circulatory system. Small particles may also be translocated to the brain either via the blood supply or through the olfactory nerves (Forman and Finch, 2018; Oberdörster et al., 2004; Qi et al., 2022) and result in neuroinflammation (Brockmeyer and D'Angiulli, 2016). During the prenatal period, $PM_{2.5}$ exposures experienced by the mother may impact the fetus through transfer to the placenta (Bongaerts et al., 2020, 2023), particularly during early pregnancy while the placenta is forming and later in pregnancy, during a period of intense vascularization (Burton et al., 2009). Though the exact mechanisms through which $PM_{2.5}$ affects specific functional alterations in children's cognition remain uncertain, $PM_{2.5}$ exposure impacts several neurotoxic mechanisms (e.g., oxidative stress, inflammation, mitochondrial dysfunction) each of which leads to white matter damage (Cory-Slechta et al., 2022). $PM_{2.5}$ exposure have also been directly associated with alterations in white matter microstructure in childhood (Binter et al., 2022b). White matter damage may provide a unifying mechanism through which $PM_{2.5}$ exposure can negatively impact a range of neurodevelopmental outcomes (Cory-Slechta et al., 2022). Further advances in statistical modeling to identify susceptible periods of exposure as well as studies utilizing functional MRI should help elucidate mechanisms linking air pollution exposures with specific domains of children's neurodevelopment (Sunyer and Dadvand, 2019).

Strengths of this study include its prospective nature and relatively large sample size. Additionally, the present study used estimated $PM_{2.5}$ concentrations for 2009–2012 derived from machine learning methods that provide flexibility in modeling relationships between spatial and spatiotemporal predictors of daily $PM_{2.5}$ estimates (Stafoggia et al., 2020). Unfortunately, a limitation of our study was that this methodology could not be applied to our entire study period due to limited numbers of stationary monitoring sites for $PM_{2.5}$ prior to 2009; however, we followed the ESCAPE methodology to temporally adjust 2009 annual estimates. Even so, we had to rely on PM_{10} rather than $PM_{2.5}$ to back-extrapolate estimates

in two study regions, which could lead to nondifferential misclassification. Additionally, our study did not account for exposure to other air pollutants such as nitrogen dioxide or ozone, which may potentially confound the observed associations. The use of the DLNMs allowed us to evaluate the impact of both prenatal and postnatal air pollution exposures in the same model using two cross-bases, which, to our knowledge, has not been evaluated with respect to specific domains of child cognitive and motor function. A limitation of DLNMs is the requirement that all subjects have observed exposure across all exposure lags. We did not consider prenatal exposures after 33 weeks to allow the inclusion of almost all the preterm infants as preterm birth may act as a mediator of the association between air pollution exposure and child neurodevelopment. Although examining exposures through 33 gestational weeks necessitated the exclusion of 2 children born prior to 33 weeks, we do not expect the loss of these subjects to bias our results. Unfortunately, this also impacted our ability to evaluate potential susceptible periods of exposure to $PM_{2.5}$ on children's cognitive and motor abilities during the last weeks of pregnancy. We also considered postnatal exposures through approximately 4 years, limiting our ability to assess exposures most proximal to the time of assessment although evidence points to the prenatal period and the early postnatal period (i.e., the first two years of life) as prime targets for environmental influences on brain development (Sunyer and Dadvand, 2019; Thomason et al., 2018). Even though DLNMs reduce the impact of multicollinearity of exposure through the implementation of the cross-basis (Gasparrini et al., 2010), there is still potential for multi-collinearity to cause unexpected results (Basagaña and Barrera-Gómez, 2022). Although sensitivity analyses exploring single-lag models did not provide evidence of this issue in our models, we observed unexpected positive associations between $PM_{2.5}$ exposure and several MSCA outcomes. As these protective findings are not biologically plausible, they are more likely due to a noncausal explanation such as uncontrolled confounding. Furthermore, since we used a hierarchical Bayesian framework for estimating our DNLM framework with bell shaped priors, our model is inherently robust to multiple comparisons through shrinkage towards the null (Gelman et al., 2013). Within a single DLNM model, effect estimates at each lag should also not be viewed as individual terms as they are estimated jointly within the cross-basis and do not contribute to multiple comparisons (Gasparrini and Armstrong, 2013; Gasparrini et al., 2010). Though we accounted for attrition using inverse probability weights in our models, it is still possible that some selection bias exists if we did not adequately capture all predictors of participation in our study.

5. Conclusions

Our study provides evidence of the susceptibility of children's motor function to prenatal air pollution exposures while children's perceptual-performance appears susceptible to $PM_{2.5}$ exposures during approximately the first year and a half of life. Our study is among the first to simultaneously investigate refined susceptible periods of exposure to both pre- and postnatal $PM_{2.5}$ exposures on specific domains of cognitive and motor function in early childhood and adds to this growing knowledge base.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data sharing

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/.

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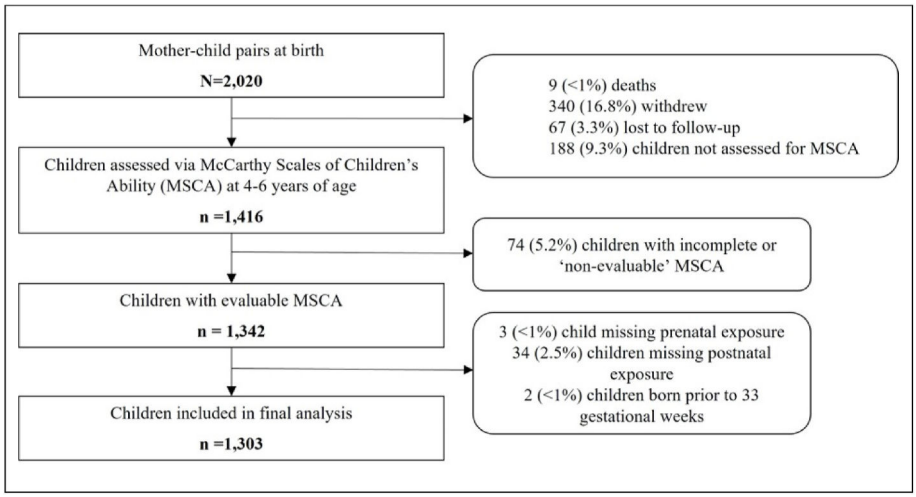

Fig. 1.

Flowchart depicting inclusion in the present analysis among mothers and children from the INMA Project, 2003–2008.

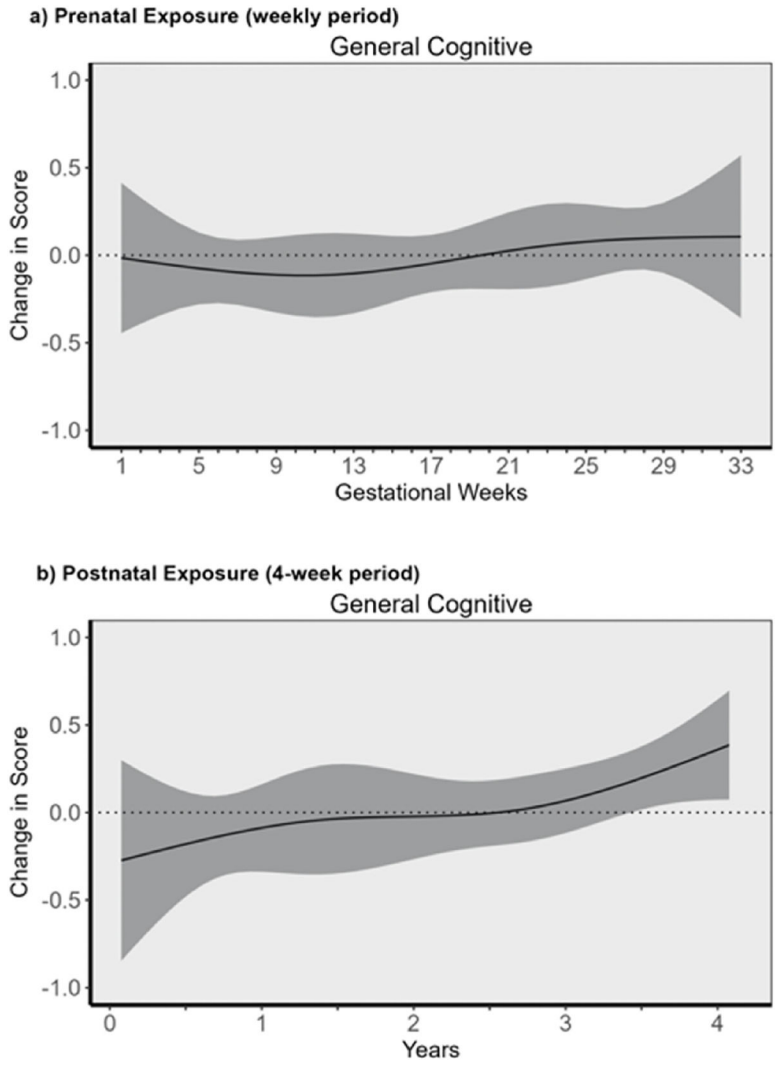

Fig. 2.

Associations between (a) prenatal and (b) postnatal $PM_{2.5}$ exposure (per 5 μg/m^3 increase) and the general cognitive index (GCI) from the McCarthy Scales of Children's Abilities (MSCA) among children in the INMA Project, 2003–2008. Models were adjusted for maternal age, maternal education, maternal IQ, child's season of birth, urbanicity of the residence in the first trimester of pregnancy, parental social class, parity, maternal smoking during pregnancy, breastfeeding, child sex, child age at the time of assessment, and study region (included as a random effect).

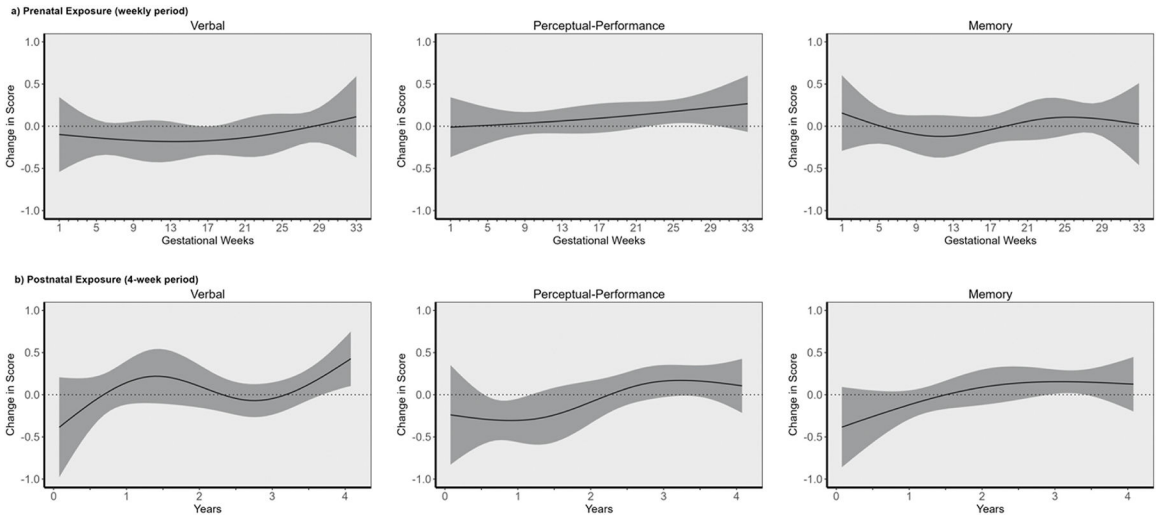

Fig. 3.

Associations between (a) prenatal and (b) postnatal $PM_{2.5}$ exposure (per 5 $\mu g/m^3$ increase) and verbal, perceptive, and memory scores from the McCarthy Scales of Children's Abilities (MSCA) among children in the INMA Project, 2003–2008. Models were adjusted for maternal age, maternal education, maternal IQ, child's season of birth, urbanicity of the residence in the first trimester of pregnancy, parental social class, parity, maternal smoking during pregnancy, breastfeeding, child sex, child age at the time of assessment, and study region (included as a random effect).

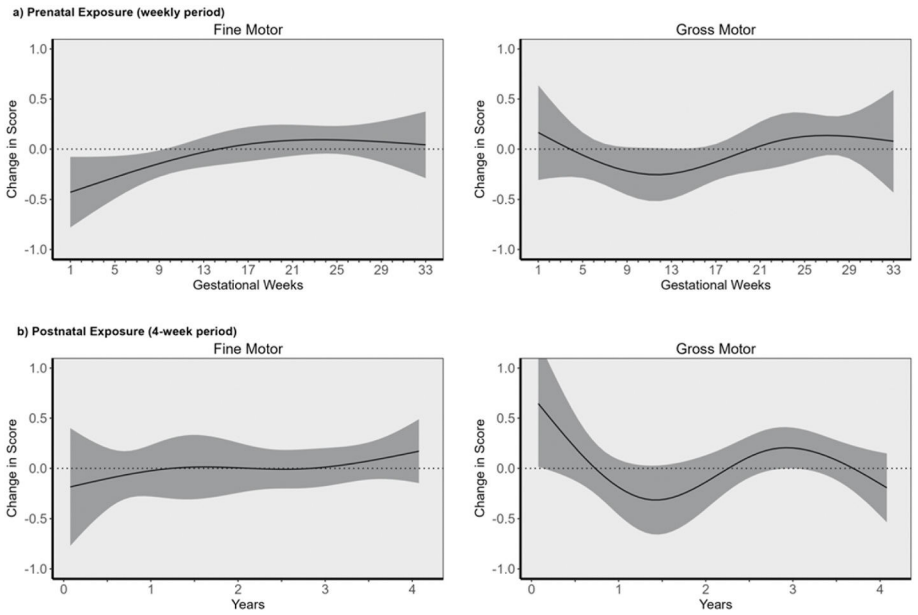

Fig. 4.

Associations between (a) prenatal and (b) postnatal $PM_{2.5}$ exposure (per 5 μg/m^3 increase) and fine and gross motors scores from the McCarthy Scales of Children's Abilities (MSCA) among children in the INMA Project, 2003–2008. Models were adjusted for maternal age, maternal education, maternal IQ, child's season of birth, urbanicity of the residence in the first trimester of pregnancy, parental social class, parity, maternal smoking during pregnancy, breastfeeding, child sex, child age at the time of assessment, and study region (included as a random effect).

Table 1

Sociodemographic characteristics of study subjects from the INMA Study (N = 1303).

Characteristics	
Child age at assessment, years (median, IQR)	4.5 (4.4, 5.7)
Maternal age, years (median, IQR)	31 (28, 33)
Maternal IQ (median, IQR)[a]	9.8 (8.3, 12)
Maternal education (n, %)	
Up to primary	279 (21.4)
Secondary	535 (41.1)
University	486 (37.3)
Missing	3 (0.2)
Social class (n, %)	
High	482 (37.0)
Middle	361 (27.7)
Low	460 (35.3)
Birth season (n, %)	
Spring	308 (23.6)
Summer	336 (25.8)
Fall	301 (23.1)
Winter	358 (27.5)
Urbanicity (n, %)	
Rural	59 (4.5)
Semiurban	210 (16.1)
Urban	1034 (79.4)
Breastfeeding in first 6 months of life (n, %)	
Exclusively breastfed	348 (26.7)
Both breastfed and formula fed	773 (59.3)
Exclusively formula fed	163 (12.5)
Missing	19 (1.5)
Parity (n, %)	
0	743 (57.0)
1	479 (36.8)
2+	79 (6.1)
Missing	2 (0.2)
Smoking during pregnancy (n, %)	
No	893 (68.5)
Yes	393 (30.2)
Missing	17 (1.3)
Prenatal $PM_{2.5}$ exposure, $\mu g/m^3$ (median, IQR)[b]	14.6 (13.3, 16.0)
Postnatal $PM_{2.5}$ exposure, $\mu g/m^3$ (median, IQR)[c]	13.8 (11.8, 15.2)

[a] 43 (3.3%) mothers were missing IQ.

[b] Average weekly $PM_{2.5}$ exposure during the gestational weeks 1–33.

[c] Average 4-week $PM_{2.5}$ exposure from birth to age 4 years.