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# Early life exposure to fine particulate matter and fine motor function, attentional function, and working memory among Spanish school-aged children

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**Background:** Evidence of the association between fine particulate matter ($PM_{2.5}$) exposure and child neuropsychological function is equivocal. We examined early life $PM_{2.5}$ exposure in relation to fine motor function, attention, and working memory in early childhood.
**Methods:** We used data from the Spanish INfancia y Medio Ambiente Project, 2003–2008. Exposure to $PM_{2.5}$ ($\mu g/m^3$) was assessed using spatiotemporal land-use random forest models and assigned based on residential address histories. Around age six, children completed the finger tapping test, attentional network test (ANT), and n-back task to evaluate fine motor speed, attention, and working memory, respectively. A total of 1,310 children had data from at least one neuropsychological assessment. General linear models were applied to assess associations between average prenatal and postnatal $PM_{2.5}$ with each outcome. Distributed lag nonlinear models were used to explore refined periods of susceptibility to $PM_{2.5}$. We reported $\beta$ estimates and 99% credible intervals (CrI) representing the change in each outcome per 5-$\mu g/m^3$ increase in $PM_{2.5}$.
**Results:** Prenatal $PM_{2.5}$ exposure was associated with decreased mean hit reaction time (HRT) ($\beta$ = –21.82; 99% CrI = –64.1, 20.4) and HRT-standard error ($\beta$ = –9.7; 99% CrI = –30.3, 10.9) on the ANT but estimates were imprecise. Postnatal $PM_{2.5}$ was associated with reduced mean HRT on the n-back task ($\beta$ = –39.4; 99% CrI = –115.1, 26.3). We observed sensitive periods of exposure in the postnatal period associated with both better and worse performance on the finger-tapping test and ANT.
**Conclusions:** We found limited evidence to support an association between $PM_{2.5}$ exposure and fine motor function, attentional function, or working memory in school-aged children.

**Keywords:** Air pollution; $PM_{2.5}$; Attention network test; Finger tapping test; n-back task; Susceptible windows; Fine motor function; Cognition; Executive function

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## Introduction

Globally, air pollution represents one of the biggest threats to human health,[1] accounting for approximately 16% of all deaths worldwide in 2015.[2] Fine particulate matter ($PM_{2.5}$), a heterogenous mixture of solid particles and liquid droplets less than 2.5 microns in diameter, has been well-studied for its adverse human health effects. $PM_{2.5}$ has been causally implicated in both pulmonary and cardiovascular diseases[2] and classified as a Group 1 Human Carcinogen by the International Agency for Research on Cancer.[3] Evidence is also emerging in support of $PM_{2.5}$ as a neurotoxicant, particularly among children who bear a high risk of air pollution-related disease and disability, even at relatively low exposure levels.[2,4] Children's

### What this study adds

Although there is a growing literature suggestive of the negative impact of early life exposure to fine particulate matter on children's neurodevelopment, studies are equivocal. Most previous studies have examined exposure during a single developmental period with little research examining susceptible periods of exposure, particularly in relation to specific neurocognitive domains. Our findings, using data from a large, well-characterized pregnancy cohort, and applying sophisticated exposure assessment methodology and validated computer-based neuropsychological assessments found only limited evidence to support an association between $PM_{2.5}$ exposure in early life and fine motor function, attentional function, or working memory in school-aged children.

brain development is characterized by a dynamic set of processes that occur throughout early life, beginning early in fetal development and continuing throughout childhood.[5,6] While the development of the cerebral cortex (i.e., the brain region involved in thought and action) largely occurs during the first 2 years of life, the prefrontal cortex (i.e., the brain region involved in executive functions such as inhibitory control, logical thinking, working memory, and attention) matures steadily during adolescence.[7] Although the mechanisms through which $PM_{2.5}$ influences children's cognitive outcomes are unknown, exposure during pregnancy may alter fetal brain development via chronic neuroinflammation, microglia activation, and neuronal migration damage.[8] Additionally, exposure to air pollution in the first several years of life may result in oxidative stress, first producing local inflammation in the airways,[9,10] progressing to systemic inflammation, and ultimately resulting in neuroinflammation.[11–13]

In a systematic review of studies published through September 2021, Castagna et al[14] indicated poorer executive function and attention associated with prenatal $PM_{2.5}$ exposure while studies evaluating postnatal exposure were equivocal. More recently published studies have been largely null. Kusters et al[15] found no evidence of an association between either pre- or postnatal $PM_{2.5}$ exposure and working memory among children in the Generation R cohort in the Netherlands. A US-based study analyzing data from several ECHO Cohorts also found no evidence of associations between postnatal $PM_{2.5}$ exposure (averaged from birth to age four) and a composite score of children's executive function (including working memory).[16] Only two studies evaluating associations of $PM_{2.5}$ with fine motor function were included in the review by Castagna et al[14] with mixed results. More recently, Domínguez et al[17] reported null associations between $PM_{2.5}$ exposure in different microenvironments averaged across the year before the neuropsychological assessment and both cognitive and fine motor function. Furthermore, relatively few studies have evaluated associations of $PM_{2.5}$ exposure in both the prenatal and postnatal periods with child neuropsychological function.[14] Rather, most previous studies have examined exposures during a single developmental period. Given the dynamic nature of cognitive development in children, there are likely periods of development when the brain is particularly susceptible to the impacts of air pollution exposure, and these periods may vary according to the cognitive domain.

Given the mixed findings of previous studies, the present study aimed to evaluate associations of both prenatal and postnatal exposure to $PM_{2.5}$ on working memory, attention, and fine motor function among school-aged children in a well-characterized cohort of Spanish children, and to explore potential susceptible periods of exposure to $PM_{2.5}$ for these outcomes.

## Methods

### *Study population*

This study was conducted using data from 2,020 mother–child pairs recruited in a prospective pregnancy cohort study in Spain, the INfancia y Medio Ambiente (INMA) Project. The present analysis includes data from mother-child pairs in which pregnant women were recruited from the main public hospital or health center in three INMA regions: Gipuzkoa, Sabadell, and Valencia. Pregnant women who resided in one of these study regions and who were aged at least 16 years, between 10 and 13 gestational weeks, and carrying a singleton pregnancy were recruited between November 2003 and February 2008. Additional inclusion criteria included not having a communication problem and planning to deliver at the recruitment hospital. Women recruited in the study were followed during each trimester of pregnancy and, once the child was born, study visits occurred around the time the child was 1–1.5, 2–2.5, 4–5, and 6–7 years of age. Among 2,020 mother–child pairs, 9 (<1%) infant deaths occurred, 433 (21.4%) participants withdrew from the study, and 102 (5.0%) participants were lost to follow-up (Figure 1). The INMA study was approved by the Ethics Committee at each reference hospital and all women provided written informed consent before enrollment and each follow-up visit. The current study was additionally approved by the Institutional Review Board of Baylor College of Medicine.

### *Children's Neurodevelopmental Assessment*

At the age of 6–7 years, a series of standardized computer-assisted tests were administered to children to assess fine motor and attentional function and working memory. A total of 1,310 children completed at least one of the assessments: the finger-tapping test, the attentional network test (ANT), or the n-back task. Additional details of each assessment are discussed below.

Children completed the finger-tapping test to assess fine motor speed. Here, children were asked to repeatedly press a key as fast as possible for 15 seconds with the dominant and nondominant hands. Children were asked to complete a total of four trials: two with their dominant hand and two with their nondominant hand. In the present analysis, we analyzed the average of the total number of taps from the trials for each hand. A lower number of taps indicates lower fine motor performance. One hundred and seventy children did not complete the finger-tapping test, resulting in 1,306 children with data available for analysis of this outcome.

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*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/. Computing code used to replicate the results can be obtained by contacting the corresponding author.*

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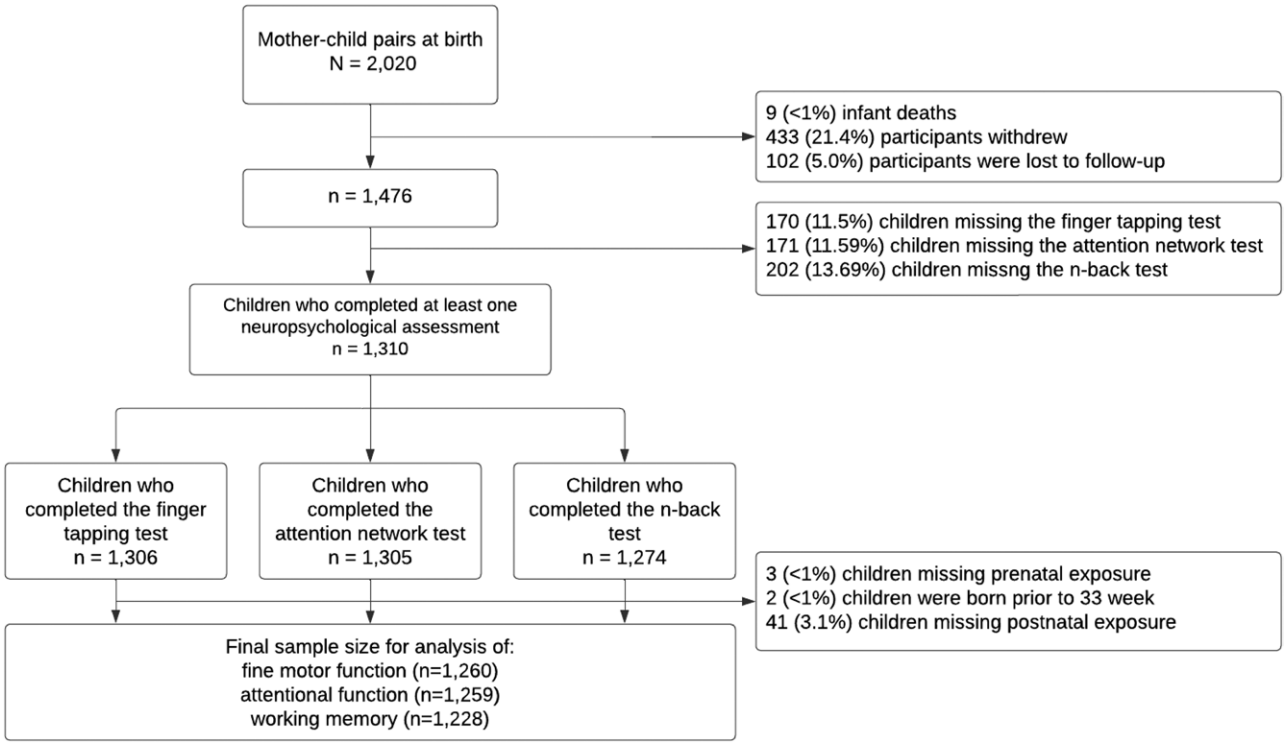


**Figure 1.** Flow diagram illustrating inclusion of mother–child pairs for the analysis of $PM_{2.5}$ and assessment of fine motor function, attentional function, and working memory among school-aged children in the INMA study (Spain).

To measure attentional function, children were administered the ANT. As part of this test, children were asked to indicate the direction (left or right) of a central fish that appeared on the computer screen by pressing the corresponding button on the computer mouse, while ignoring other flashing fish on the screen. As part of the present study, we analyzed the mean hit reaction time (HRT) in milliseconds (ms) for all correct responses (a measure of processing speed) and the standard error of the HRT (HRT-se) for all correct responses (a measure of consistency of responses). Higher HRT and HRTse are reflective of inattention. One hundred and seventy-one children did not complete the ANT, resulting in 1,305 children with available ANT data for the present study.

Working memory was assessed via the n-back task, a continuous recognition task in which children were asked to respond when a stimulus (e.g., a number or a color) presented on the computer screen matches the stimulus previously presented n-(i.e., 1, 2, or 3) trials back. Response accuracy and speed were recorded. For our study, we analyzed results from the 3-back test using numbers (i.e., results of tests in which children were asked to recognize whether a number matches the number that was presented three-trials previously). We analyzed both the mean HRT as well as d prime (d'), a measure of detection that subtracts the normalized false detection rate from the hit rate and reflects the ability of a child to discriminate stimuli presented n-trials back. Here, higher HRT on the n-back test indicates worse processing performance and lower d' indicates poorer working memory. A total of 202 children did not complete the n-back task, resulting in 1,274 children with available data for this measure.

### *Exposure assessment*

We assessed maternal exposure to ambient $PM_{2.5}$ during each woman's pregnancy and children's exposure to $PM_{2.5}$ during the first 6 years of life. $PM_{2.5}$ exposure assessment was based on a series of exposure models created for all of Spain and previously described.[18,19] Briefly, daily gridded estimates of $PM_{2.5}$ concentrations were estimated across Spain for the period 2009–2016, at a 1-km$^2$ resolution using a spatiotemporal land-use random forest model developed for application in other studies.[20,21] Gridded air pollution estimates were adjusted to the exact locations of all residences reported by INMA participants from 2009 to 2016 using a second random forest model incorporating spatial variables such as land use and population counts.[20] For $PM_{2.5}$ exposure estimates before 2009, temporal back extrapolation of the 2009 annual average $PM_{2.5}$ concentrations were applied, following the methodology of the European Study of Cohorts for Air Pollution Effects (ESCAPE) project.[22]

Several exposure metrics were created using the daily predicted $PM_{2.5}$ concentrations at each woman or child's residence. We evaluated mean prenatal exposures based on the entire pregnancy period and averaged exposure across the first 6 years of life to represent postnatal exposure. We also created exposure estimates representing mean $PM_{2.5}$ exposure during each trimester of pregnancy: trimester 1 (weeks 1–13), trimester 2 (weeks 14–27), and trimester 3 (weeks 28-birth). To assess more refined susceptible periods of exposure, we averaged $PM_{2.5}$ exposure across each week of the woman's pregnancy and each 4-week period of the child's first 6 years of life. Three mother–child pairs were excluded due to missing prenatal exposures, and 41 pairs were excluded due to missing postnatal exposures. An additional two mother–child pairs in which the child was born before 33 completed gestational weeks were also excluded from the analyses. This resulted in a final sample size of 1,260, 1,259, and 1,228 participants included in analyses of outcomes related to the finger-tapping test, ANT, and n-back task, respectively (see Figure 1).

### *Covariates*

We relied on a directed acyclic graph to specify covariates for inclusion on our statistical models (Supplementary Figure 1; https://links.lww.com/EE/A348). The minimally sufficient set

of variables included maternal education (up to primary, secondary, university), maternal smoking during pregnancy (self-reported at either 12- or 32-weeks of gestation, yes/no), parental social class, urbanicity (urban, semiurban, or rural) of women's residences during the first trimester, and birth season. We used the child's month of birth to classify the season of birth as spring (March, April, and May birth months), summer (June, July, and August birth months), fall (September, October, and November birth months), or winter (December, January, and February birth months). Parental social class was categorized as high, middle, or low, according to the highest of either the maternal or paternal social class assignment based on self-reported occupation during the prenatal period. In addition, we included in the models important predictors of the outcome, including maternal age, parity, breastfeeding, maternal IQ (assessed using the Similarities subtest of the Wechsler Adult Intelligence Scales, Third Edition [WAIS-III] at the 5-year follow-up), child's sex, and child's age at the time of the neurocognitive assessment. We did not include child's gestational age at birth given this variable may lie in the causal pathway between air pollution exposure and neurocognitive function.

### *Statistical analyses*

All statistical analyses were conducted using R version 4.3.1 (R Core Team, Vienna, Austria). We used descriptive statistics to summarize distributions of covariates and exposure variables. We summarized sociodemographic information on the study population using means, medians, and proportions, as appropriate. Additionally, we constructed boxplots for each weekly prenatal exposure period and each 4-week postnatal exposure period to explore the variability $PM_{2.5}$ exposure over the study period.

We applied multiple imputations to impute missing values for covariates using the R package "mice" (version 3.16.0),[23] generating 10 imputed data sets using predictive mean matching with 50 iterations. To assess the association between average prenatal and postnatal $PM_{2.5}$ exposure and each outcome, we first fit general linear models (GLM) to each imputed dataset through the integrated nested Laplace approximation (INLA) by using the R package "INLA" (version 23.08.18).[24] In each model, we mutually adjusted for prenatal and postnatal exposures. Models were also adjusted for covariates mentioned above and included study region (i.e., Sabadell, Gipuzkoa, or Valencia) as a random effect. To minimize selection bias resulting from attrition, we applied inverse probability weights (IPW) that were calculated within each of the 10 imputed data sets. We also explored trimester-specific associations in the GLM framework, building models for each outcome including all three trimester-specific exposure metrics. We reported β estimates and 99% CrIs representing the change in each outcome per 5 μg/m$^3$ increase in average $PM_{2.5}$ exposure over the specified exposure period. We conducted analyses using alpha = 0.01 given the relatively large number of comparisons and to reduce the chances of type 1 error.

In secondary analyses, to explore potential susceptible windows of exposure, we applied distributed lag nonlinear models (DLNMs) using the R package "dlnm" (version 2.4.7).[25] The DLNM framework grants flexibility to simultaneously model nonlinearity and distributed lag effects by utilizing the crossbasis—a bidimensional space of functions constructed from two basis functions—and allows the exploration of more "refined" sensitive windows of exposure than is feasible in GLMs. Because pre- and postnatal $PM_{2.5}$ exposures have distinct biological mechanisms through which they may affect child cognition (i.e., via maternal vs. child exposure),[26] we evaluated periods of susceptibility in these exposure periods using two distinct crossbases included as separate terms in a single model. In both the prenatal and the postnatal crossbasis we centered the exposure at 0 and assumed a linear exposure-outcome relationship. For the prenatal crossbasis, we modeled average weekly $PM_{2.5}$ exposure estimates during the first 33 gestational weeks. We did not model exposure during later gestational weeks because the DLNM model does not allow exposure periods with missing values. Further, we chose not to exclude preterm births from our analysis as gestational age may lie in the causal pathway between $PM_{2.5}$ exposure and children's neurodevelopment; thus, conditioning on gestational age may lead to overadjustment and introduce collider stratification bias.[27] The postnatal crossbasis included 77 4-week average $PM_{2.5}$ exposure periods, representing exposure from birth through the sixth year of the child's life. We implemented a flexible knot search procedure allowing a maximum of two internal knots in each crossbasis, with a minimum distance of three lags between neighboring knots. To determine the optimal knot placement in the crossbases, we implemented a two-stage selection procedure where we first identified the 10 models with the lowest Akaike information criterion values and, among these models, chose the model with the lowest root mean square error.[28]

Like the GLM models, DLNM models were fitted using the R package "INLA" (version 23.08.18) and were fitted within the 10 imputed datasets. DLNM models were adjusted for all covariates mentioned above, included a random effect for the study region, and were weighted for attrition using IPWs. Specific windows within either the prenatal or postnatal crossbasis were identified as susceptible periods of exposure if the 99% credible intervals (CrI) excluded the null value. As it is possible that the performance of the DLNM may be less optimal when modeling very long exposure periods, we also conducted a sensitivity analysis restricting the evaluation of susceptible periods of exposure in the postnatal period to the first 2 years of life. In these models, we additionally included a covariate representing the average $PM_{2.5}$ exposure during the remaining 4 years of life (i.e., from age 2 to 6).

## Results

Distributions of study characteristics are presented overall and by the INMA study region (Table 1). Overall, women were on average 30.8 years of age (SD = 3.93 years) and were relatively well educated, with more than one-third reporting a university-level education (38.4%). More than half of the women were classified in the middle (27.2%) or high (37.9%) social classes and had no live births before the index pregnancy (56.5%). The majority (79.4%) of women lived in urban areas and about one-quarter (27.6%) of women exclusively breastfed their infant in the first 6 months of life. In most cases, the distributions of characteristics were similar across INMA study regions, with a few exceptions. For example, the proportion of women whose residences were classified as urban varied considerably by INMA study region; all women recruited from INMA-Sabadell lived in urban areas, compared with 84.8% of women recruited from INMA-Valencia, and 48.3% of women from INMA-Gipuzkoa. Table 2 presents exposure distributions for average prenatal, trimester-specific, and postnatal $PM_{2.5}$ concentrations. Overall, mean prenatal exposures (14.68 μg/m$^3$) were slightly higher than postnatal exposures (13.63 μg/m$^3$) and mean concentration decreased from trimester 1 to 3. The distributions of prenatal weekly and postnatal 4-week average $PM_{2.5}$ concentrations are presented in Supplementary Figures 2 and 3; https://links.lww.com/EE/A348, respectively. The mean weekly prenatal $PM_{2.5}$ concentrations ranged from 14.27 to 15.04 μg/m$^3$ while the mean of the 4-week postnatal $PM_{2.5}$ concentrations ranged from 12.80 to 14.49 μg/m$^3$.

We observed little evidence of associations between $PM_{2.5}$ exposures averaged across the prenatal period or postnatal periods with fine motor function, attentional function, or working memory (Table 3). Evaluation of trimester-specific average $PM_{2.5}$ exposures with each of these outcomes was also null (Figure 2). In analyses utilizing DLNM models, we identified several

**Table 1.**

**Maternal and child characteristics (%) of mother–child pairs recruited in the INMA-Gipuzkoa, Sabadell, and Valencia cohorts, 2003–2008**

| | Gipuzkoa (n = 391) | Sabadell (n = 471) | Valencia (n = 448) | Overall (N = 1,310) |
|---|---|---|---|---|
| Maternal age | | | | |
| Mean (SD) | 31.4 (3.24) | 30.5 (4.20) | 30.5 (4.15) | 30.8 (3.94) |
| Median (Min, Max) | 31.0 (21.0, 43.0) | 30.0 (17.0, 42.0) | 30.0 (16.0, 42.0) | 31.0 (16.0, 43.0) |
| Maternal IQ | | | | |
| Mean (SD) | 10.0 (2.72) | 10.5 (2.89) | 9.96 (3.24) | 10.2 (2.99) |
| Median (Min, Max) | 9.76 (3.15, 18.6) | 10.5 (1.68, 19.3) | 9.76 (0, 20.0) | 10.5 (0, 20.0) |
| Missing | 73 (18.7%) | 20 (4.2%) | 21 (4.7%) | 114 (8.7%) |
| Maternal education | | | | |
| Up to primary | 39 (10.0%) | 112 (23.8%) | 118 (26.3%) | 269 (20.5%) |
| Secondary | 138 (35.3%) | 203 (43.1%) | 194 (43.3%) | 535 (40.8%) |
| University | 212 (54.2%) | 154 (32.7%) | 136 (30.4%) | 502 (38.3%) |
| Missing | 2 (0.5%) | 2 (0.4%) | 0 (0%) | 4 (0.3%) |
| Social class | | | | |
| High | 195 (49.9%) | 163 (34.6%) | 138 (30.8%) | 496 (37.9%) |
| Middle | 87 (22.3%) | 148 (31.4%) | 124 (27.7%) | 359 (27.4%) |
| Low | 109 (27.9%) | 160 (34.0%) | 186 (41.5%) | 455 (34.7%) |
| Parity (3 cat) | | | | |
| 0 | 222 (56.8%) | 267 (56.7%) | 251 (56.0%) | 740 (56.5%) |
| 1 | 149 (38.1%) | 176 (37.4%) | 170 (37.9%) | 495 (37.8%) |
| 2+ | 20 (5.1%) | 26 (5.5%) | 27 (6.0%) | 73 (5.6%) |
| Missing | 0 (0%) | 2 (0.4%) | 0 (0%) | 2 (0.2%) |
| Smoking during pregnancy | | | | |
| No | 295 (75.4%) | 338 (71.8%) | 283 (63.2%) | 916 (69.9%) |
| Yes | 85 (21.7%) | 127 (27.0%) | 165 (36.8%) | 377 (28.8%) |
| Missing | 11 (2.8%) | 6 (1.3%) | 0 (0%) | 17 (1.3%) |
| Urbanicity | | | | |
| Rural | 45 (11.5%) | 0 (0%) | 15 (3.3%) | 60 (4.6%) |
| Semiurban | 157 (40.2%) | 0 (0%) | 53 (11.8%) | 210 (16.0%) |
| Urban | 189 (48.3%) | 471 (100%) | 380 (84.8%) | 1,040 (79.4%) |
| Breastfeeding in first 6 months | | | | |
| Exclusively breastfed | 108 (27.6%) | 134 (28.5%) | 119 (26.6%) | 361 (27.6%) |
| Breastfed and formula-fed | 229 (58.6%) | 298 (63.3%) | 238 (53.1%) | 765 (58.4%) |
| Exclusively formula-fed | 31 (7.9%) | 38 (8.1%) | 91 (20.3%) | 160 (12.2%) |
| Missing | 23 (5.9%) | 1 (0.2%) | 0 (0%) | 24 (1.8%) |
| Child sex at birth | | | | |
| Female | 198 (50.6%) | 227 (48.2%) | 224 (50.0%) | 649 (49.5%) |
| Male | 193 (49.4%) | 244 (51.8%) | 224 (50.0%) | 661 (50.5%) |
| Birth season | | | | |
| Winter | 101 (25.8%) | 116 (24.6%) | 100 (22.3%) | 317 (24.2%) |
| Spring | 128 (32.7%) | 130 (27.6%) | 87 (19.4%) | 345 (26.3%) |
| Summer | 82 (21.0%) | 119 (25.3%) | 103 (23.0%) | 304 (23.2%) |
| Fall | 80 (20.5%) | 106 (22.5%) | 158 (35.3%) | 344 (26.3%) |

**Table 2.**

**Distribution of prenatal and postnatal $PM_{2.5}$ (μg/m³) concentrations from 1,310 mother–child pairs in the INMA study, 2003–2008**

| Exposure period | Mean (SD) | Median (25th, 75th) |
|---|---|---|
| Prenatal | 14.68 (2.04) | 14.60 (13.24, 15.88) |
| Trimester 1 | 14.83 (2.5) | 14.78 (13.07, 16.46) |
| Trimester 2 | 14.73 (2.45) | 14.57 (13.02, 16.26) |
| Trimester 3 | 14.49 (2.65) | 14.50 (12.52, 16.26) |
| Postnatal (birth to age 6) | 13.63 (2.27) | 14.0 (11.54, 15.48) |

**Table 3.**

**Effect estimates and 99% CrIs for associations of average prenatal and postnatal $PM_{2.5}$ exposure and measures of fine motor function, attentional function, and working memory among school-aged children in the INMA study, 2003–2008**

| | Average prenatal $PM_{2.5}$ exposure | | Average postnatal $PM_{2.5}$ exposure | |
|---|---|---|---|---|
| | β | 99% CrI | β | 99% CrI |
| Finger tapping test | | | | |
| Average number of taps | 0.45 | −3.33, 4.23 | 0.01 | −6.26, 6.28 |
| Attentional network test (ANT) | | | | |
| Mean HRT | −21.82 | −64.05, 20.42 | 22.99 | −38.41, 84.40 |
| HRT-se | −9.68 | −30.30, 10.93 | 0.59 | −28.19, 29.37 |
| n-Back task | | | | |
| D-prime | −0.25 | −0.56, 0.05 | 0.31 | −0.01, 0.63 |
| Mean HRT | 28.79 | −33.87, 91.45 | −39.4 | −115.11, 36.31 |

CrI indicates credible interval; HRT, hit reaction time; OR, odds ratio; se, standard error.

susceptible windows of exposure to $PM_{2.5}$ associated with fine motor function (Figure 3) or attentional function (Figure 4) among school-aged children, although few consistent patterns emerged and, in many cases, we observed periods of exposure associated with both positive and negative outcomes. For example, although no periods during the prenatal period were associated with fine motor function in school-aged children (assessed via the finger-tapping test), we identified two susceptible periods to $PM_{2.5}$ exposure during the postnatal period in relation to this outcome, although one was associated with fewer numbers of taps (ages 0.3–1.8 years; β = −11.53, 99% CrI = −13.68, −9.37) and another period was identified from ages 3.4 to 5.7 years

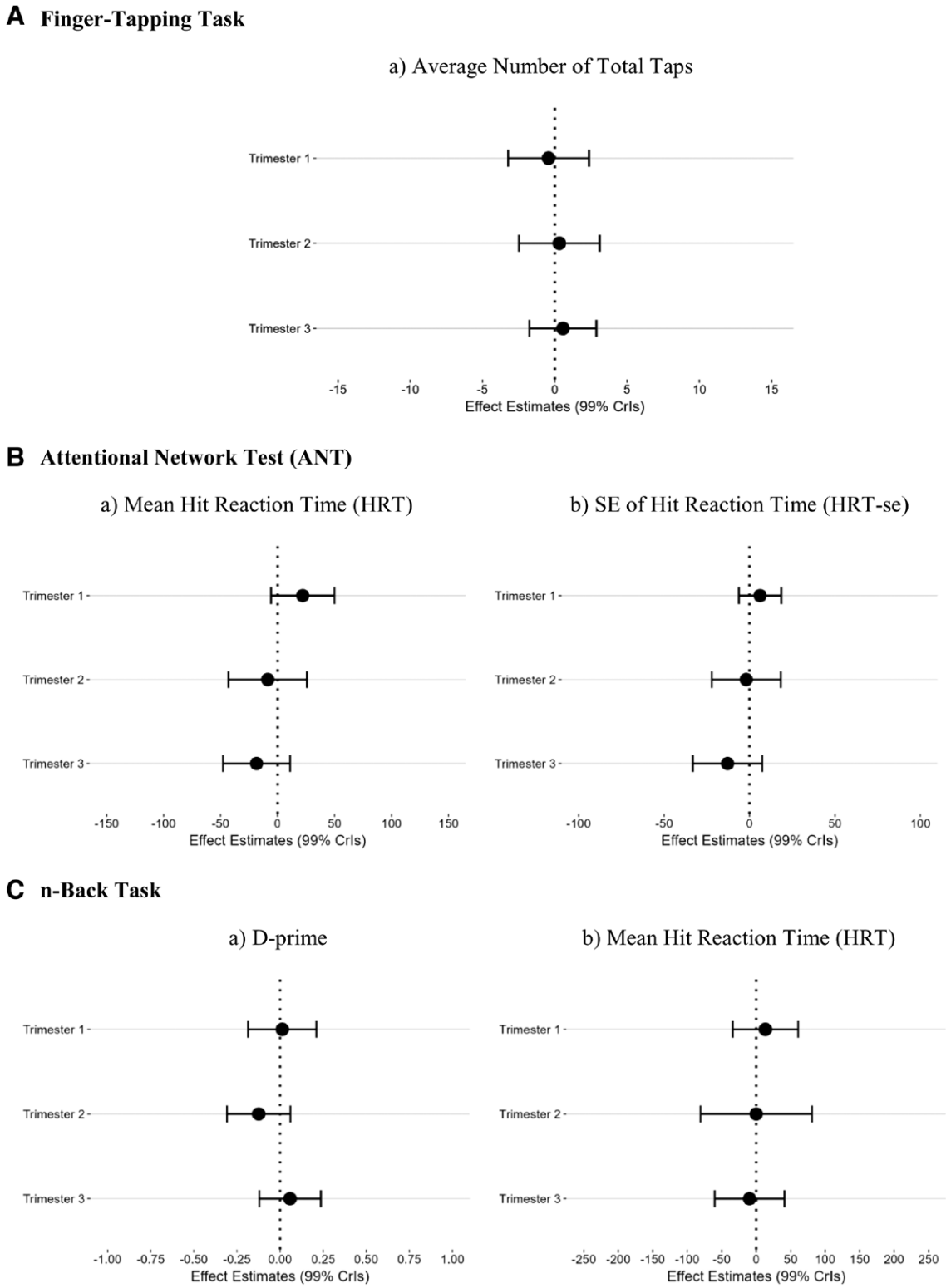


**Figure 2.** Effect estimates and 99% credible intervals (CrIs) for associations of trimester-specific $PM_{2.5}$ exposure and (A) fine motor function, based on the finger tapping test, (B) attentional function, based on the attentional network test (ANT), and (C) working memory, based on the n-back task, among school-aged children in the INMA study, 2003–2008.

and was associated with increased number of taps (β = 8.78, 99% CrI = 7.31, 10.24). Although a potentially sensitive period of exposure to $PM_{2.5}$ with regards to attentional function was identified from age 0.3 to 1.1 years for HRT (β = 68.45; 99% CrI = 48.72, 88.17) and from 0.4 to 1.5 years for HRT-se (β = 49.31, 99% CrI = 38.89, 59.73), several positive associations were also observed. No susceptible periods of exposure to $PM_{2.5}$ during either the prenatal or postnatal periods were identified in relation to working memory (Figure 5). Sensitivity analyses including only the first 2 years of exposure in the postnatal crossbasis produced similar results (Supplementary Figures 4–6; https://links.lww.com/EE/A348).

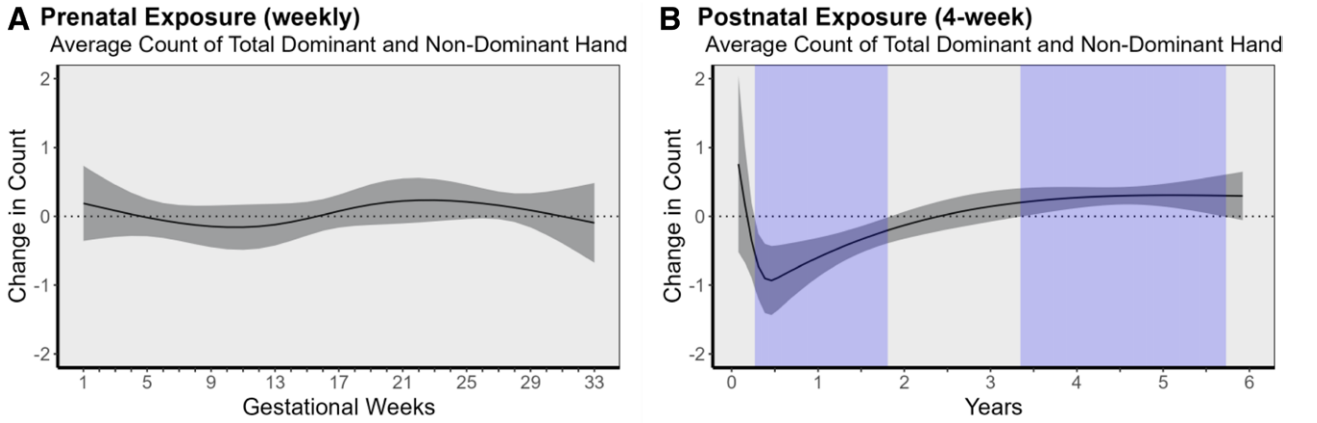


**Figure 3.** Evaluation of susceptible windows of exposure to $PM_{2.5}$ during the (A) prenatal and (B) postnatal periods and fine motor function based on the finger tapping test among school-aged children in the INMA study, 2003–2008.

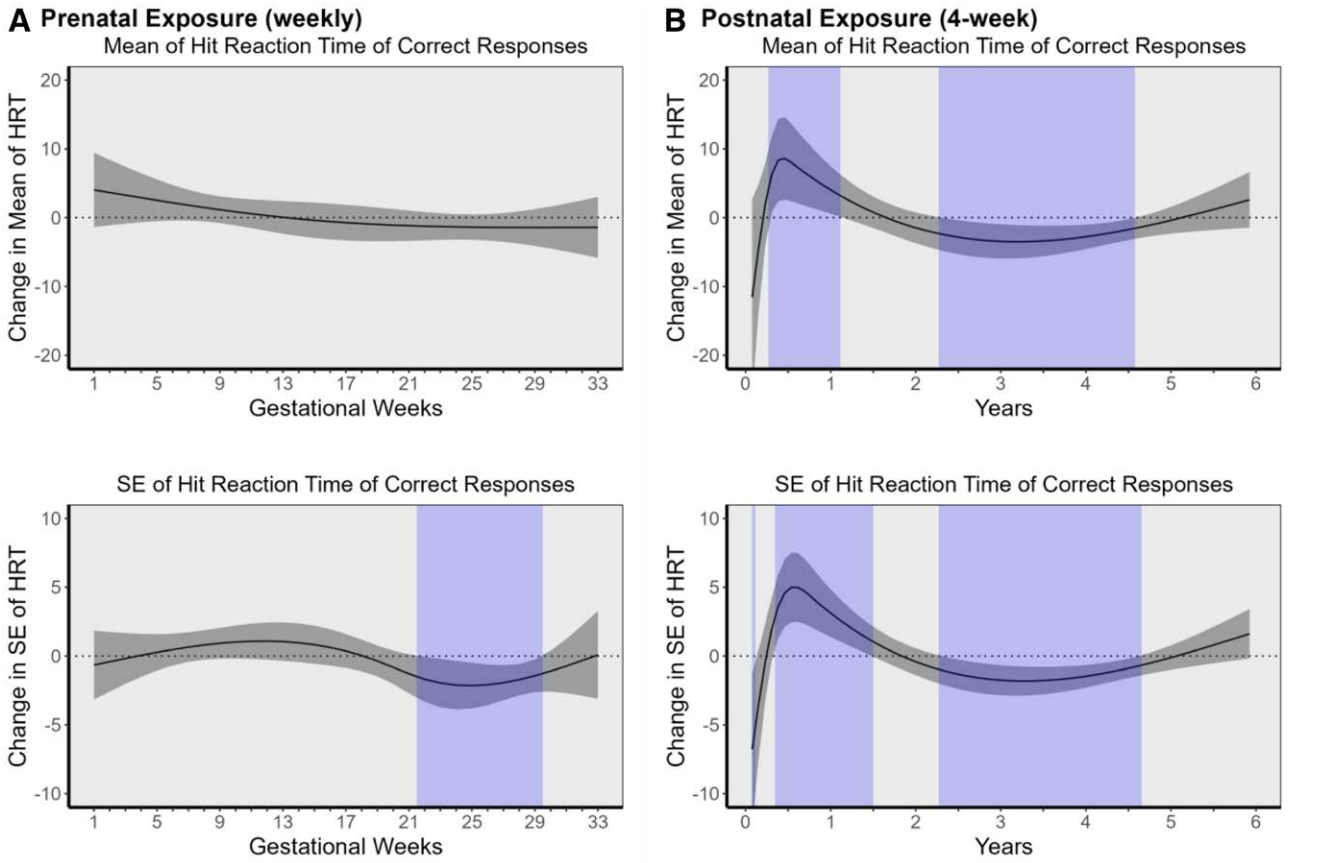


**Figure 4.** Evaluation of susceptible windows of exposure to $PM_{2.5}$ during the (A) prenatal and (B) postnatal periods and attentional function based on the attentional network test (ANT) among school-aged children in the INMA study, 2003–2008.

## Discussion

In this study, utilizing data from an established and well-characterized longitudinal birth cohort in Spain, we observed little evidence of associations between prenatal or postnatal $PM_{2.5}$ exposure and fine motor function, attentional function, or working memory among school-aged children. Analyses utilizing DLNM models revealed susceptible periods of exposure to $PM_{2.5}$ on both poorer motor performance and attention in the first 2 years of life. However, for both outcomes, we also observed unexpected associations between $PM_{2.5}$ exposure in late toddlerhood associated with better outcomes.

The developing brain is susceptible to environmental exposures, including exposure to $PM_{2.5}$, during sensitive periods *in utero* and in early life.[29,30] Important neurocognitive processes begin during fetal development and continue throughout early childhood, which set the stage for later life adjustment, physical health, and wellbeing. It is posited that the potential neurotoxicity of $PM_{2.5}$ may be due to its ability to cross the blood–brain barrier, directly access the central nervous system, increasing oxidative stress and inflammation.[31] There is a growing literature suggestive of the negative impact of early life $PM_{2.5}$ exposure during pregnancy and in early childhood on the

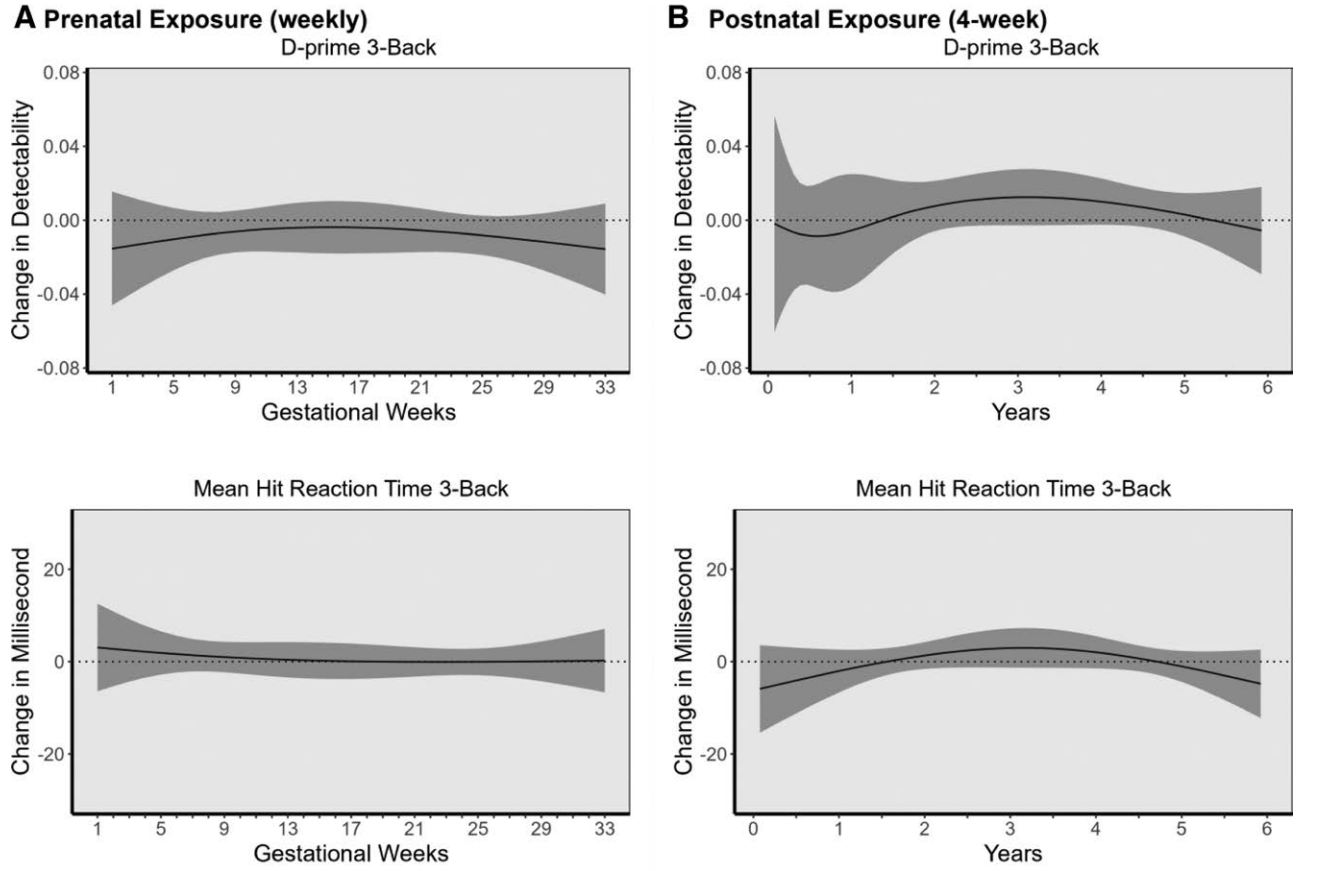


**Figure 5.** Evaluation of susceptible windows of exposure to $PM_{2.5}$ during the (A) prenatal and (B) postnatal periods and working memory based on the n-back task among school-aged children in the INMA study, 2003–2008.

neurocognitive performance of children.[14] Even so, results are not consistent and much heterogeneity between studies exists, particularly regarding the exposure assessment and timing, and specific instruments used to measure varied neurocognitive domains.

Attention and working memory are executive functions that emerge in toddlerhood and support the development of cognitive, early academic, and social-emotional skills.[32] In a review by Castagna et al,[14] attention and other executive functions were highlighted as domains most often impacted by prenatal air pollutant exposure (with more limited evidence for postnatal exposures), although the authors note that associations observed were often not of clinical relevance. Several studies not included in this review have since been published, with conflicting results. Two recent studies report negative associations between $PM_{2.5}$ exposure and working memory. Gui et al[33] found a cross-sectional association between increased average $PM_{2.5}$ exposures in the year before assessment (estimated using an inverse distance weighted average concentration from ambient monitoring stations near each participant's residence) and poorer working memory, assessed via the Corsi Block-tapping Task, in 6–12-year-old children in China. Notably, the average $PM_{2.5}$ concentrations in this study (39.06 $\mu g/m^3$ ± 1.12) were much higher than in other studies and nearly three times as high as observed in the present study. A study using data from the ABCD study in the United States[34] reported an association between 2-year average $PM_{2.5}$ concentrations (estimated at a resolution of 10 $km^2$ around each participants residence) and children's working memory assessed via change in children's performance in the n-back task over the same 2-year period ($\beta$ = −0.04, 95% confidence interval = −0.07, −0.02). On the other hand, three other recent studies have failed to corroborate these associations. A pooled analysis from six European cohorts in the HELIX project did not find an association between annual average $PM_{2.5}$ exposures in different microenvironments (school, home, and commuting), assessed in the year before the outcome assessment, and either attentional function (assessed via the HRTse on the ANT).[17] Kusters et al[15] reported no association between average $PM_{2.5}$ during pregnancy or during childhood (averaged from birth through the last follow-up, with a mean age of 10.1 years) and working memory, assessed using the Digit Span subtest of the Wechsler Intelligence Scale for Children, in a cohort of youth (13–16 years) from the Generation R study in the Netherlands. Similarly, a study in the United States,[16] relying on data from the ECHO-PATHWAYS consortium, found no association between residential $PM_{2.5}$ exposure in the first 4 years of life and working memory assessed around age 8–9 years, also using the Digit Span subtest.

As compared with attention and working memory, fewer studies have evaluated the impacts of $PM_{2.5}$ exposure on fine motor function. The impact of $PM_{2.5}$ exposure on motor function among children in INMA was reported in two previous studies, although both studies focused on outcomes among preschool-aged children and assessed motor function using McCarthy's Scales of Children's ability.[18,35] In contrast with the findings in the present study, both previous studies reported an association between prenatal exposure to $PM_{2.5}$ and decreased fine motor function including a susceptible period of exposure identified in the first 9 weeks of pregnancy by Whitworth et al[18] On the other hand, in the pooled analysis of data from HELIX cohorts, Domínguez et al[17] found no association between $PM_{2.5}$

exposures in different microenvironments and performance of school-aged children on the finger tapping test.

The strength of the current study was its relatively large sample size of mother–child pairs drawn from a well-characterized longitudinal birth cohort. Further, an assessment of children's neurocognitive function in several domains was conducted using a battery of validated computer-based neuropsychological assessments administered by trained neuropsychologists. Our study also benefited from a comprehensive assessment of air pollution exposure from conception through early childhood. Further, unlike many previous studies, our study simultaneously evaluated exposure to $PM_{2.5}$ during two different critical periods (prenatal and postnatal). And, in addition to operationalizing exposures during clinically relevant periods (i.e., trimesters), we applied statistical models that allowed a more agnostic approach to the evaluation of susceptible periods of exposure. Although we recognize that DLNMs can be sensitive to tuning parameters[36] such as the location and numbers of internal knots in the crossbases, we applied a systematic approach to fitting the DLNMs. Further, our statistical models accounted for potential selection bias through the implementation of IPW for attrition. While multiple comparisons should not be an issue within a single crossbasis of a DLNM, given our study utilized several GLM and DLNM models, we applied an alpha level of 0.01 to reduce the potential influence of type 1 error in interpreting our results. One additional limitation of our DLNMs, however, was our inability to evaluate potential susceptible periods of exposure beyond 33 weeks; as the DLNM requires nonmissing lag information for every participant, it was necessary to either restrict the exposure periods included in the prenatal crossbasis or to exclude preterm births. We chose not to do the latter given the potential for gestational age to lie in the causal pathway between air pollution exposure and child neurodevelopment.

In conclusion, this large study analyzing data from a well-characterized prospective birth cohort does not provide evidence of an association of $PM_{2.5}$ exposures during the prenatal period and several neuropsychological outcomes among school-aged children. We did find some evidence of the adverse impact of $PM_{2.5}$ exposure in the first years of life with motor function and attention although our analyses also produced some unexpected inverse associations; as we are not aware of any biologically plausible explanations for these results, they results should be interpreted cautiously. Future research should consider the potential impact of prenatal and postnatal $PM_{2.5}$ exposures on other domains of neuropsychological development and explore associations with neuropsychological development assessed among children and adolescents during different developmental stages.

## Conflicts of interest statement

The authors declare that they have no conflicts of interest with regard to the content of this report.

## Acknowledgments

None.

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