Association of developmental coordination disorder with early-life exposure to fine particulate matter in Chinese preschoolers

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GRAPHICAL ABSTRACT

PUBLIC SUMMARY
- A national study with over 109K preschoolers on PM$_{2.5}$-DCD in China
- Early life PM$_{2.5}$ exposure was associated with poorer motor performance and increased risk of DCD
- Significant associations were found on subscales of control during movement and general coordination function
- Children from rural areas and with NICU admission might be more susceptible
- Exclusive breastfeeding over 6 months may mitigate the effect of PM$_{2.5}$ on motor skills
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Although fine particulate matter (PM2.5) is a neurotoxicant, little is known about whether early-life PM2.5 exposure is associated with an increased risk of developmental coordination disorder (DCD). We conducted a cohort study of 109,731 children aged 3–5 years from 551 county-level cities in China between April 2018 and December 2019. Residential PM2.5 exposure was estimated using a hybrid satellite-based exposure model. Children’s motor performance was assessed using the Little DCD Questionnaire (LDCDQ). Linear mixed-effect models and generalized linear mixed models with a binomial distribution were used to examine the associations of PM2.5 exposure with LDCDQ scores and risk of DCD, respectively. Both prenatal and postnatal exposure to a higher level of PM2.5 was significantly associated with reduced total LDCDQ score, and the impacts were evident on subscales of control duration and results are mixed.25 For example, letxundi et al. found that prenatal exposure to PM2.5 was associated with a negative effect on motor development in 4– to 6-year-old children; however, none of the associations were statistically significant.28 On the contrary, Zhang et al. found that motor development in the first few weeks of life in preterm infants was particularly sensitive to pollution from major roads at birth.29 Nationally representative, large-scale studies are needed to confirm these findings.

In this study, we analyzed an established nationwide dataset including 551 county-level cities in China; we explored the quantitative relationships of prenatal and early childhood exposure to PM2.5 with motor development and the risk of DCD among preschoolers based on recent satellite-based measurements of PM2.5 concentrations. Additionally, we identified the subgroups in the study population that were more vulnerable to PM2.5 exposure.

RESULTS

A total of 109,731 children were included for analysis. The characteristics of the eligible children and their parents are shown in Table 1. The mean (±standard deviation) age of children was 4.40 (±0.80) years, 47.2% were girls, and 21.3% were from rural regions (Table S1). Over half of the children were vaginally delivered, 10.5% had been admitted to a neonatal intensive care unit (NICU), and 79.5% were breastfed over 6 months. The mean (±standard deviation) total score of the Little DCD Questionnaire (LDCDQ) was 67.9 (±8.8) (Table S2). Among all, 16,992 were screened as suspected DCD, accounting for 14.9%.

PM2.5 concentrations vary in different exposure windows and are summarized in Table 2. The mean (±standard deviation) of PM2.5 concentrations between birth and 36 months was 50 (±10) µg/m³ with an interquartile range (IQR) of 16 µg/m³. A wide range of PM2.5 concentrations in mainland China was observed (Figure S2), ranging from 13 to 113 µg/m³ from birth to 36 months. In general, there were moderate to high correlations among prenatal and postnatal exposure concentrations (Spearman’s r ≥ 0.65; Pearson’s r ≥ 0.64) (Table S3). PM2.5 concentrations were weakly to moderately correlated with gaseous air pollutants (Table S4).

Figure 1 presents changes in LDCDQ score per IQR of PM2.5 exposure during specific exposure time windows. We observed that increases in postnatal PM2.5 exposure were associated with decreases in the total scores and subscores of LDCDQ. For example, an IQR (16 µg/m³) increase in PM2.5 concentrations from birth to 36 months was associated with a decrement of 0.19 (95% confidence...
**Table 1.** Characteristics of the study participants (*N* = 109,731)

| Characteristic                      | Mean ± SD or number (%) |
|-------------------------------------|--------------------------|
| **Child**                           |                          |
| Age (years, mean ± SD)              | 4.40 ± 0.80              |
| Sex                                 |                          |
| Boys                                | 57,955 (52.8)            |
| Girls                               | 51,776 (47.2)            |
| Gestational age <37 weeks           | 13,583 (12.4)            |
| Delivery mode                       |                          |
| Vaginal delivery                    | 57,367 (52.3)            |
| Cesarean delivery                   | 52,364 (47.7)            |
| NICU admission                      |                          |
| No                                  | 98,264 (89.5)            |
| Yes                                 | 11,467 (10.5)            |
| Psychotropic medication             |                          |
| No                                  | 108,796 (99.1)           |
| Yes                                 | 935 (0.9)                |
| Breastfeeding                       |                          |
| Never breastfed or <6 months        | 22,460 (20.5)            |
| breastfeeding ≥ 6 months of breastfeeding | 87,271 (79.5)    |
| Region                              |                          |
| Urban                               | 86,333 (78.7)            |
| Rural                               | 23,398 (21.3)            |
| **Parents**                         |                          |
| Maternal age at conception (years)  | 27.76 ± 4.20             |
| (mean ± SD)                         |                          |
| Maternal education                  |                          |
| Middle school or below              | 21,708 (19.8)            |
| High school                         | 25,854 (23.6)            |
| College or above                    | 62,169 (56.7)            |
| Maternal employment                |                          |
| Employed (worker/businessman        | 69,248 (63.1)            |
| /administrator)                     |                          |
| Unemployed                          | 17,838 (16.3)            |
| Others                              | 22,645 (20.6)            |
| Gravidity                           |                          |
| Primigravida                        | 51,168 (46.6)            |
| Multigravida                        | 58,563 (53.4)            |
| **Pregnancy complications**         |                          |
| No                                  | 104,249 (95)             |
| Yes                                 | 5482 (5.0)               |
| **Maternal education**              |                          |
| Middle school or below              | 21,191 (19.3)            |
| High school                         | 27,798 (25.3)            |
| College or above                    | 60,742 (55.4)            |

SD, standard deviation; NICU, neonatal intensive care unit.

*Mother who had gestational hypertension and/or gestational diabetes mellitus.

**Table 2.** Description of PM$_{2.5}$ concentrations during specific exposure windows (µg/m$^3$)

| Exposure windows | Mean (SD) | Max | P75 | P50 | P25 | Min | IQR |
|------------------|-----------|-----|-----|-----|-----|-----|-----|
| 1st trimester    | 57 (19)   | 193 | 69  | 53  | 42  | 15  | 27  |
| 2nd trimester    | 56 (19)   | 184 | 68  | 53  | 42  | 15  | 26  |
| 3rd trimester    | 56 (19)   | 213 | 68  | 52  | 42  | 14  | 26  |
| Entire pregnancy | 56 (11)   | 152 | 63  | 56  | 49  | 15  | 14  |
| Birth to 18 months | 53 (11) | 130 | 60  | 52  | 44  | 14  | 16  |
| 18 to 36 months  | 48 (11)   | 109 | 55  | 46  | 39  | 12  | 16  |
| Birth to 36 months | 50 (10) | 113 | 58  | 50  | 42  | 13  | 16  |
| Birth to interview | 47 (10) | 104 | 54  | 45  | 39  | 12  | 15  |

PM$_{2.5}$, particulate matter with the aerodynamic diameter equal to or less than 2.5 µm; SD, standard deviation; P25, the 1st interquartile value of PM$_{2.5}$ concentration; P50, the median value of PM$_{2.5}$ concentration; P75, the 3rd interquartile value of PM$_{2.5}$ concentration; IQR, interquartile range; Max, maximum; Min, minimum.

PM$_{2.5}$ showed little changes (Table S5). For example, the associations of PM$_{2.5}$ exposure during the first trimester was associated with decrements of 0.35 (95% CI: 0.07, 0.62) and 0.52 (95% CI: 0.19, 0.86) in rural children, while the corresponding decreases were 0.24 (95% CI: 0.09, 0.41) and 0.21 (95% CI: 0.04, 0.38) in urban children. The total LDCDQ score decreased by 0.39 (95% CI: 0.09, 0.70) and 0.38 (95% CI: 0.07, 0.68) in rural children, respectively, while the corresponding decreases were 0.24 (95% CI: 0.07, 0.41) and 0.21 (95% CI: 0.04, 0.38) in urban children. The total LDCDQ score decreased by 0.24 (95% CI: 0.03, 0.44) and 0.28 (95% CI: 0.10, 0.47) in children who had over 6 months of exclusive breastfeeding, while the corresponding decreases were 0.35 (95% CI: 0.07, 0.62) and 0.52 (95% CI: 0.19, 0.86), respectively, in the group that never breastfed or exclusively breastfed for

**Figure 1.**

Figure 2 shows adjusted odds ratios (ORs) for DCD associated with an IQR increase in PM$_{2.5}$ concentrations during each exposure window. In general, both prenatal and postnatal PM$_{2.5}$ exposure was associated with elevated risks of DCD. Specifically, for each IQR increase in PM$_{2.5}$ concentrations during the first trimester, the risk increased by 6% (adjusted OR = 1.06, 95% CI: 1.01, 1.10). For each IQR in averaged PM$_{2.5}$ concentrations before the age of 3 and from birth to interview, the risks increased by 6% (adjusted OR = 1.06, 95% CI: 1.01, 1.13) and 8% (adjusted OR = 1.08, 95% CI: 1.03, 1.14) respectively.

We found that the associations of PM$_{2.5}$ exposure during specific exposure time windows with DCD and the total score of LDCDQ remained unchanged after additionally adjusting for gaseous air pollutants, while the effect estimates showed little changes (Table S5). For example, the associations of PM$_{2.5}$ exposure from birth to 36 months with risks of DCD remained statistically significant after being adjusted for sulfur dioxide (SO$_2$) and ozone (O$_3$), respectively, with less than 1% changes in magnitude, which spanned an OR of 1 when adjusted for nitrogen dioxide (NO$_2$) and carbon monoxide (CO).

**Table 3.** presents the results of the stratified analyses, which were overall consistent in various time windows of postnatal exposure. We found that associations between PM$_{2.5}$ and total score changes were relatively stronger in girls, those who were delivered through cesarean section, and those whose mothers received lower education compared with their counterparts. Particularly, region (urban or rural), breastfeeding condition (≥6 months or <6 months), and NICU admission (yes or no) appeared to modify the effect of PM$_{2.5}$ on the total score of LDCDQ, though the CIs of the two subgroups overlapped (possibly because of the unbalanced sample size between subgroups). For each IQR in averaged PM$_{2.5}$ concentrations before the age of 3 and between birth and interview, the total LDCDQ score decreased by 0.39 (95% CI: 0.09, 0.70) and 0.38 (95% CI: 0.07, 0.68) in rural children, respectively, while the corresponding decreases were 0.24 (95% CI: 0.07, 0.41) and 0.21 (95% CI: 0.04, 0.38) in urban children. The total LDCDQ score decreased by 0.24 (95% CI: 0.03, 0.44) and 0.28 (95% CI: 0.10, 0.47) in children who had over 6 months of exclusive breastfeeding, while the corresponding decreases were 0.35 (95% CI: 0.07, 0.62) and 0.52 (95% CI: 0.19, 0.86), respectively, in the group that never breastfed or exclusively breastfed for
less than 6 months. Also, larger effect estimates were found in children with history of NICU admission (0.38 [95% CI: 0.01, 0.75] during age 0–3; 0.41 [95% CI: 0.04, 0.78] between birth and interview) than their counterparts (0.19 [95% CI: 0.04, 0.34] during age 0–3; 0.16 [95% CI: 0.02, 0.31] between birth and interview).

**DISCUSSION**

In this study, we examined the effects of prenatal and early childhood exposure to PM$_{2.5}$ on motor development using a large-scale national study of 109,731 3- to 5-year-old children in China. We found significant associations between PM$_{2.5}$ exposure and decreased total score of LDCDQ, indicating poorer motor performance. And the impact was evident on subscales of control during movement and general coordination function but not of fine motor function. We also found that PM$_{2.5}$ exposure was associated with an increased risk of DCD. The associations remained when additionally controlling for gaseous air pollutants. Further, we observed the effects of PM$_{2.5}$ exposure were more prominent in children who were from rural areas, had NICU admission, were never breastfed, or had less than 6 months of exclusive breastfeeding than their counterparts.

Although the human brain continues to develop and change throughout life, the most rapid growth and highest plasticity are seen during pregnancy and the first few years of life.31 Very few studies have linked air pollutant exposure during pregnancy with poor motor skills and decreased total score of LDCDQ, indicating poorer motor performance. And the impact was evident on subscales of control during movement and general coordination function but not of fine motor function. We also found that PM$_{2.5}$ exposure was associated with an increased risk of DCD. The associations remained when additionally controlling for gaseous air pollutants. Further, we observed the effects of PM$_{2.5}$ exposure were more prominent in children who were from rural areas, had NICU admission, were never breastfed, or had less than 6 months of exclusive breastfeeding than their counterparts.

Our findings are biologically plausible. Previous studies have demonstrated that prenatal exposure to air pollutants could induce maternal immune activation and systemic inflammation during pregnancy.32 The released inflammatory cytokines and/or reactive oxygen species may enter the fetus by crossing the blood-placental barrier and further induce fetal immune dysregulation or may affect the placental function and further lead to deficiency in nutrient transport, and all these could consequently interfere with fetal neurodevelopment. In addition, evidence has shown that PM, especially nanoscale PM, could reach brain tissues at the early human developmental postconceptional week 8–15 stage, which may have detrimental effects on subsequent brain morphogenesis and function.
These observations may help explain our finding that the first trimester might be the most pivotal time window for the effects of prenatal PM2.5 exposure on children's neurobehavioral development. Compared with prenatal exposure, we found a greater effect of postnatal exposure, which may be due to the direct exposure to PM2.5 after birth. Inhaled PM2.5 can translocate from the child's nose up the olfactory nerve into their brain, leading to changes within the brain, such as microglial activation, neuroinflammation, neurovascular damage, and altered neurotransmitters, thereby directly causing neurotoxic effects on specific areas of the child's brain. Imaging studies have proved that the number of neural connections of the brain explode in the first years of life, while exposure to air pollution during this period may therefore alter the developmental trajectory of the child's brain.

This study also showed that children who were breastfed for less than 6 months might be more sensitive to postnatal PM2.5 exposure. One possible reason lies in that breastfeeding contains rich fatty acids (such as docosahexaenoic acid and arachidonic acid), which are key compounds to form the main structures of neuronal membranes. Additionally, breastfeeding is beneficial to children’s brain development, possibly by boosting the immunity of infants. We also observed larger effects of PM2.5 exposure in children living in rural areas and who had a history of NICU admission compared with their counterparts. Rural children are more likely to have lower socioeconomic status and to be exposed to different compositions of PM. Children in rural areas might have higher outdoor PM exposure to biomass burning, more frequent use of wood stoves, and less protective measures (such as masks and air purifiers). Besides, NICU admission may reflect a poor condition of gestation, such as gestational diabetes and hypertension, premature rupture of the membrane, and preterm birth; consequently, these children could be more vulnerable to air pollution exposure. These findings highlight the potentially vulnerable subgroups and indicate that breastfeeding might protect against the neurotoxic effects of PM2.5.

This study has several strengths. First, to our best knowledge, this is the first nationwide study to examine the associations between early-life PM2.5 exposure and DCD. By focusing on pediatric populations in China, our findings provide evidence from those who suffer from the most serious air pollution in the world. Second, ground-based observations of particulate matter compositions are scarce in much of the developing world, which makes the quantification of dose-response functions challenging. This study took advantage of satellite-based measurements with a high spatial resolution (1 km), which allowed us to include rural areas. Lastly, our study population was widely distributed across China and covered a wide range of geographic PM2.5 levels, offering a unique opportunity to identify the relationship between PM2.5 and neurobehavioral development within the full range of global variations.

Several limitations of this study should be noted. First, although we used a satellite-based comprehensive model and assigned exposures according to the home addresses, exposure misclassification was still possible. Data on microenvironmental PM2.5 exposure (eg, indoor, outdoor, or commute related) or activity patterns were not collected in our study, which may have contributed to exposure misclassification. Second, we used the LDCDQ to measure motor development and to define motor impairment in the current study. Although the LDCDQ was specifically designed to identify preschoolers at risk of DCD and previous studies have shown that the LDCDQ has high sensitivity and specificity in identifying DCD, there are potential limitations as it is a short questionnaire. Possible report bias may also exist because the assessments of children’s motor performance were reported by parents. Besides, the participants included in our study might not represent the population with a particularly low level of cognition and socioeconomic status (eg, having difficulty understanding the questions), though the proportion of this group was very low. Third, although the study cohort included representative samples from 551 cities in China, the majority of enrolled participants were from urban areas with higher parental education levels. Therefore, this may limit the applicability of our findings to populations with lower education levels or from rural areas. Finally, although we adjusted for several key covariates, we did not have information on other potential confounders such as secondhand smoking, environmental noise exposure, etc. Future studies should consider measuring these additional covariates.

**Conclusions**

In the present study, we identified a modifiable environmental risk factor (ie, PM2.5) for neurodevelopmental disorders. We found that prenatal and postnatal exposure to PM2.5 were associated with decreased LDCDQ scores and a higher risk of DCD, suggesting a link between higher PM2.5 exposure and impaired neurobehavioral development in preschoolers. These findings may have important implications for public health interventions and environmental policies. More studies are warranted to explore the impact of the potential interaction of genetic and environmental risk factors on short- and long-term neurological outcomes.

**METHODS**

**Study design and participants**

This study was based on the Chinese National Cohort of Motor Development, which was originally designed to explore neurobehavioral development in Chinese preschool children. Details on the study design have been previously described. Briefly, to ensure a nationally representative sample, the Chinese National Cohort of Motor Development used a stratified cluster sampling strategy to select preschool children aged 3-5 years in mainland China. Local kindergartens were invited to participate in this study through the government-supported kindergarten counseling and health care center. Preschoolers without physical disabilities or intellectual impairment assessed during the kindergarten entrance physical examinations were enrolled.

Given the regular practice of communication between parents and kindergartens via smart devices in China, an electronic version of the motor function measure was filled out by participating parents through smart devices with guidance attached. Additionally, information on demographic characteristics, individual medical history, and risk factors for neurobehavioral development was collected using online questionnaires. The questionnaires have built-in pop-up instructions and an automatic error-checking system to ensure data quality. Data management, maintenance, and quality controls were conducted by a data coordination center.

Between April 2018 and December 2019, a total of 188,814 preschoolers were recruited from 2403 public kindergartens in 551 county-level cities in China. A high completion rate was achieved, and only a small proportion of parents (N = 561; 0.3%) chose not to participate.
or disregarded the questionnaire before completion (Figure S1). For data analyses, we restricted to children aged 3–5 years of age having a full set of key information, resulting in 109,731 children. The details of the exclusion criteria can be found in Figure S1.

The study was approved by the Ethics Committee of Shanghai First Maternity and Infant Hospital (KSI18156). All information acquired was kept confidential and was used for research purposes only.

### Outcome assessment

We applied the LDCDQ to assess children’s motor performance. The LDCDQ is a low-cost measure to screen for motor coordination difficulties in children aged 3 and 4 years, and it has also been extended for use with children as old as 5 years. It has been validated against the Movement Assessment Battery for Children-2, as a gold standard to diagnose motor impairment, in groups of South African and Chinese preschoolers. LDCDQ is a parent-reported questionnaire with a total of 15 items under three main components: control during execution, fine motor execution, and overall coordination. Parents were asked to compare the motor performance of their child with that of the child’s peers, providing a measure of the child’s coordination in everyday functional activities. The total score of LDCDQ ranges from 15 to 75, with a higher score indicating a higher level of motor proficiency. The Chinese version of LDCDQ has demonstrated high internal consistency (Cronbach’s alpha coefficient of all items was >0.9), good split-half reliability (the Guttman coefficient was 0.934), and fair factor construct validity (factor loadings exceeded 0.6 for each item based on exploratory factor analysis).

We followed Wilson et al.’s recommendations and used the age- and sex-specific norms of the LDCDQ. Cutoff scores were provided, based on a national sample in China, to indicate suspected impairments of motor coordination. We defined “DCD” as LDCDQ ≤15th percentile and “not DCD” as LDCDQ >15th percentile.

### Exposure assessment

We estimated early-life exposure to PM$_{2.5}$ using a hybrid satellite-based exposure model. Random forest algorithms were used to develop an aerosol optical depth gap-filling approach by linking ground-level PM$_{2.5}$ measurements to predictors, including MAIAC aerosol optical depth product, MODIS-2 simulation, meteorological parameters, land use, population density, and visibility data. Then, we used this model to predict ambient daily PM$_{2.5}$ concentrations at 1 km spatial resolution in China. The cross-validation R$^2$ between predictions and measurements of daily PM$_{2.5}$ in 2017–2018 was 0.81, with a root–mean–square error of 18.5 μg/m$^3$, suggesting a high accuracy of the model in predicting historical PM$_{2.5}$ levels. Further details on this model, including methods and performance, can be found elsewhere.

The 1 km exposure grid was linked to each participant based on their residential address. Average levels of daily PM$_{2.5}$ were calculated for the pregnancy (i.e., prenatal) and the time period after birth (i.e., postnatal). For prenatal exposure, we calculated PM$_{2.5}$ means for the entire pregnancy (week 1 to delivery) and each trimester of pregnancy (1st trimester: 1–13 weeks, 2nd trimester: 14–26 weeks, and 3rd trimester: 27 weeks–delivery). For postnatal exposure, we calculated mean PM$_{2.5}$ concentrations from the date of delivery through follow-up assessment. We also calculated mean PM$_{2.5}$ concentrations from birth to 36 months to examine the effect of the first 3 years of exposure on motor performance. Previous studies have found that by about 18 months was an important time window for neurodevelopment. It is around this time that children begin to demonstrate a range of social–cognitive and motor skills. Therefore, from birth to 18 months and from 18 to 36 months were also selected as the exposure time windows of interest.

To adjust for the potential confounding effects of other air pollutants, we obtained daily averages of gaseous pollutants, including SO$_2$, NO$_2$, CO, and O$_3$ collected at ambient monitoring stations (http://www.cnemc.cn/). Data from the nearest station to a residential address were assigned to the corresponding participant. We also obtained daily averages of ambient temperature at the city level from the China Meteorological Data Sharing Service System (http://data.cma.cn/).

### Statistical analyses

Associations between PM$_{2.5}$ exposure and LDCDQ scores were assessed using linear mixed-effect models. Associations between PM$_{2.5}$ exposure and DCD were examined using generalized linear mixed models (GLMMs) with a binomial distribution. In both linear mixed-effect models and GLMMs with a binomial distribution, we included a random intercept of founders, including the child’s age and sex, body mass index, gestational age, preterm birth (yes or no), mode of delivery, breastfeeding (“≥6 months of exclusive breastfeeding” or “never breastfed or <6 months of exclusive breastfeeding”), NICU admission (yes or no), psychiatric medication (yes or no), maternal age at conception, gravidity, maternal complications during pregnancy and at delivery (defined according to the International Classification of Diseases, Revision 10, yes or no), maternal and paternal education (“low,” indicating high school or below, or “high,” indicating college or above), maternal employment (employed, unemployed, or others), region (urban or rural), provincial-level gross domestic product, and mean temperature and humidity during the corresponding exposure time windows. We also included the survey calendar year to adjust for any longitudinal trend of unmeasured time-varying covariates.

We also conducted sensitivity analyses to assess the robustness of our results. We fitted two-pollutant models by additionally controlling for concentrations of O$_3$, CO, NO$_2$, and SO$_2$, respectively. Furthermore, we did stratified analyses to explore the potential effect modification of sex, exclusive breastfeeding, mode of delivery, maternal education, NICU admission, and region on the associations of PM$_{2.5}$ with the total score of LDCDQ.

All statistical analyses were performed using R software (v.3.4.0, R Foundation for Statistical Computing, Vienna, Austria). All tests were two-sided, and a p value <0.05 was considered statistically significant. Results of the linear mixed-effect models were presented as mean differences and their 95% CIs in total score and subscore per IQR increase in PM$_{2.5}$ concentrations. Results of the GLMMs with a binomial distribution were presented as ORs and their 95% CIs for DCD per IQR increase in PM$_{2.5}$ concentrations.

### Table 3. Changes in the total score of LDCDQ per interquartile range increase of PM$_{2.5}$ exposure during specific exposure time windows stratified by child’s sex, delivery mode, maternal education, breastfeeding condition, NICU admission, and region

| Exposure windows            | Birth to 18 months | 18 to 36 months | Birth to 36 months | Birth to interview |
|-----------------------------|--------------------|-----------------|--------------------|-------------------|
| Sex                         |                    |                 |                    |                   |
| boy (N = 57 955)            | −0.12 (−0.29, 0.05)| −0.28 (−0.45, −0.11)| −0.16 (−0.35, 0.03)| −0.17 (−0.35, 0.01)|
| girl (N = 51 776)           | −0.21 (−0.38, −0.04)| −0.33 (−0.49, −0.17)| −0.29 (−0.48, −0.10)| −0.26 (−0.44, −0.08)|
| Delivery mode               |                    |                 |                    |                   |
| vaginal (N = 57 367)        | −0.12 (−0.31, 0.06)| −0.24 (−0.43, −0.06)| −0.20 (−0.45, 0.05)| −0.31 (−0.53, −0.09)|
| cesarean (N = 52 364)       | −0.14 (−0.33, 0.05)| −0.27 (−0.46, −0.09)| −0.30 (−0.56, −0.04)| −0.36 (−0.59, −0.13)|
| Maternal education          |                    |                 |                    |                   |
| low (N = 47 562)            | −0.12 (−0.34, 0.10)| −0.30 (−0.53, −0.07)| −0.35 (−0.66, −0.05)| −0.36 (−0.63, −0.09)|
| high (N = 62 169)           | −0.13 (−0.29, 0.03)| −0.24 (−0.40, −0.09)| −0.16 (−0.37, 0.06)| −0.36 (−0.55, −0.16)|
| Breastfeeding ≥6 months     |                    |                 |                    |                   |
| yes (N = 87 271)            | −0.12 (−0.27, 0.03)| −0.25 (−0.41, −0.10)| −0.24 (−0.44, −0.03)| −0.28 (−0.47, −0.10)|
| no (N=22 460)               | −0.24 (−0.51, 0.04)| −0.31 (−0.59, −0.03)| −0.35 (−0.62, −0.07)| −0.52 (−0.86, −0.19)|
| NICU admission              |                    |                 |                    |                   |
| yes (N = 11 467)            | −0.29 (−0.64, 0.05)| −0.35 (−0.69, −0.002)| −0.38 (−0.75, −0.01)| −0.41 (−0.78, −0.04)|
| no (N = 98 264)             | −0.14 (−0.27, 0.00)| −0.29 (−0.42, −0.16)| −0.19 (−0.34, −0.04)| −0.16 (−0.31, −0.02)|
| Region                      |                    |                 |                    |                   |
| urban (N = 86 333)          | −0.18 (−0.34, −0.02)| −0.31 (−0.46, −0.16)| −0.24 (−0.41, −0.07)| −0.21 (−0.38, −0.04)|
| rural (N = 23 398)          | −0.31 (−0.60, −0.03)| −0.44 (−0.73, −0.15)| −0.39 (−0.70, −0.09)| −0.38 (−0.68, −0.07)|

LDCDQ, Little Developmental Coordination Disorder Questionnaire; PM$_{2.5}$, particulate matter with the aerodynamic diameter equal to or less than 2.5 μm; NICU, neonatal intensive care unit.
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AUTHOR CONTRIBUTIONS
J.C., Y.Z., H.K., and J.H. initiated the study. J.C. and Y.S. analyzed the data and drafted the manuscript. Y.Z. and H.K. contributed to data analyses. Y.S., X.M., and G.Q. collected the data. Y.Z., W.D., A.L.B., and G.J. thoroughly helped improved the sentence structure and word choice of this manuscript. All authors contributed to the interpretation of results and critically revised the draft.

DECLARATION OF INTERESTS
The authors declare no competing interests.

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