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

Jing Cai,[1,7] Yang Shen,[1,7] Xia Meng,[1] Yan Zhao,[2] Yue Niu,[1] Renjie Chen,[1] Wenchong Du,[3] Guangbin Quan,[1] Anna L. Barnett,[4] Gary Jones,[5] Haidong Kan,[1,6,*] and Jing Hua[2,*]

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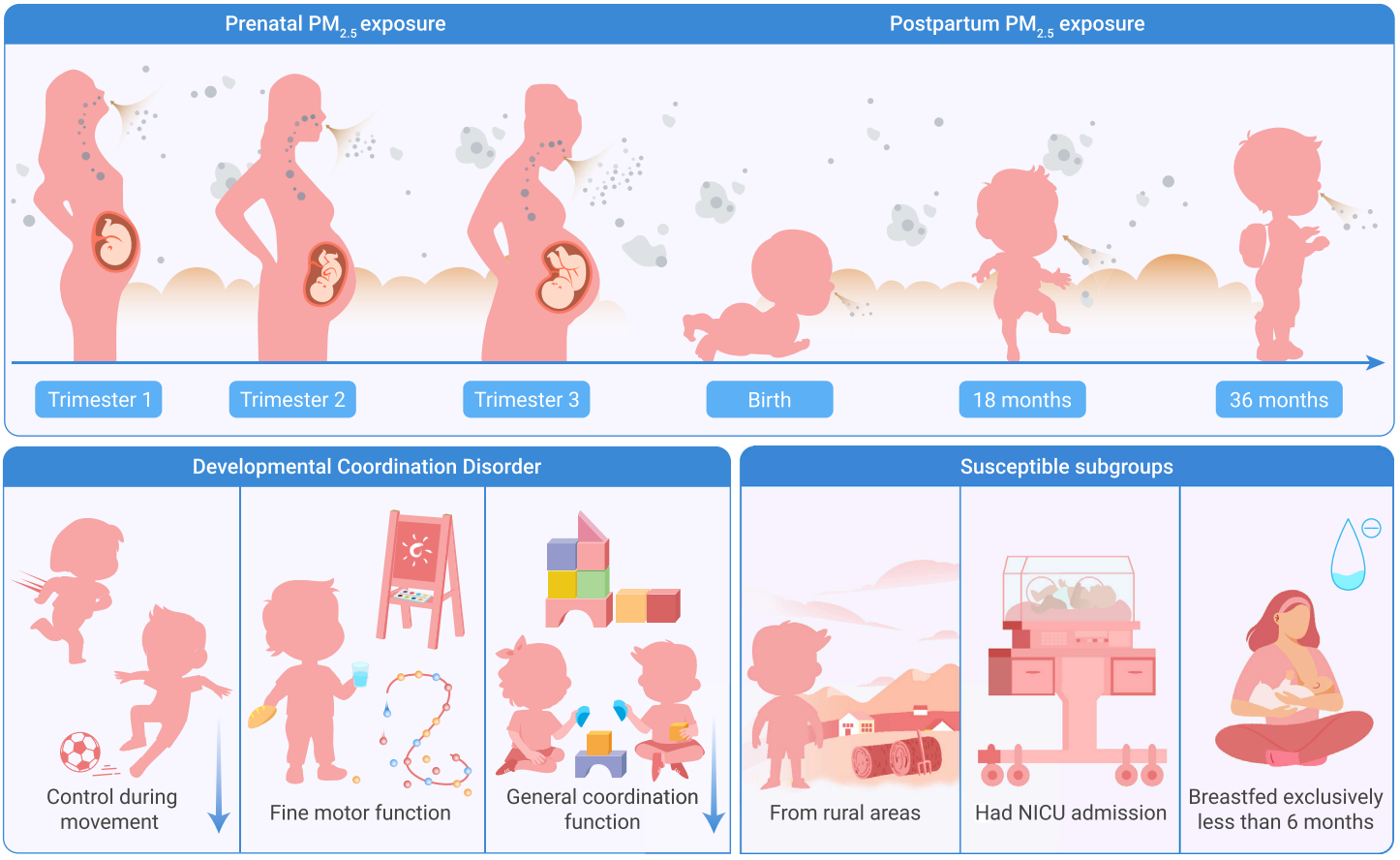
GRAPHICAL ABSTRACT



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

Report

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

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Although fine particulate matter ($PM_{2.5}$) is a neurotoxicant, little is known about whether early-life $PM_{2.5}$ 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 $PM_{2.5}$ 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 $PM_{2.5}$ exposure with LDCDQ scores and risk of DCD, respectively. Both prenatal and postnatal exposure to a higher level of $PM_{2.5}$ was significantly associated with reduced total LDCDQ score, and the impacts were evident on subscales of control during movement and general coordination function but not fine motor function. For example, an interquartile range increase in $PM_{2.5}$ exposure in ages 0–3 was associated with a 0.19 (95% confidence interval [CI]: 0.05, 0.33) decrement in the total score. Additionally, higher $PM_{2.5}$ exposure was associated with increased risk of DCD, and the adjusted odds ratios were 1.06 (95% CI: 1.01, 1.10) and 1.06 (95% CI: 1.01, 1.13) for each interquartile range increase in $PM_{2.5}$ exposure during the first trimester and the first 3 years, respectively. Children who were from rural areas, had neonatal intensive care unit admission, or were exclusively breastfed for less than 6 months appeared to be more susceptible to $PM_{2.5}$ exposure than their counterparts. Our findings provide robust evidence that early-life $PM_{2.5}$ exposure contributes to an elevated risk of DCD.

INTRODUCTION

Eight percent of children worldwide, approximately 53 million, suffer from some form of neurodevelopmental disorder.[1] Although conceptualized as a childhood disability, neurodevelopmental disorders have increasingly been recognized as life-long neurological conditions that could significantly impact functioning and the quality of life in adulthood.[2] Developmental coordination disorder (DCD) is a neurodevelopmental disorder that affects children's ability to execute coordinated motor actions, resulting in slow, clumsy, or inaccurate motor performances,[3] with a prevalence ranging between 5% and 6% among children aged 5–11 years.[4] DCD commonly results in persistent and significant difficulties in performing daily activities involving balance or manual dexterity.[5] DCD has also been associated with mental health problems,[6,7] learning difficulties, problems with psychosocial adjustment,[8] and lower cognitive function.[9] DCD persists into adulthood for 30%–70% of individuals, with direct consequences in the academic realm and even beyond,[10,11] and may result in secondary associations with self-esteem[12] and poor physical health.[13,14]

Neurodevelopmental disorders could be the result of shared causes that involve genetic and nongenetic environmental factors occurring during development, especially those critical windows such as the prenatal period and early childhood.[15] Air pollution has been shown as an important environmental contributor to neurodevelopmental disorders.[16–18] Several studies using MRI-based brain imaging techniques reported that childhood exposure to air pollutants, especially particles with 2.5 μm or less in diameter (fine particulate matter [$PM_{2.5}$]), was associated with significant structural brain alterations in children.[19,20] Experimental studies have shown that $PM_{2.5}$ can induce neurological impairments by causing systemic inflammation after respiratory uptake[21,22] and/or being directly translocated to the brain through the nasal pathway involving the olfactory bulb.[21,23]

Despite the abundance of evidence on the adverse health outcomes of $PM_{2.5}$ exposure,[24] little is known regarding the impacts of early-life (including prenatal and postnatal) $PM_{2.5}$ exposure on neurodevelopmental disorders, especially DCD. Only a few studies with small sample sizes have linked $PM_{2.5}$ exposure (ranging from 9.0 to 22.3 $\mu g/m^3$) with DCD or motor function among children, and results are mixed.[25–30] For example, Lertxundi et al. found that prenatal exposure to $PM_{2.5}$ 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, with an established nationwide dataset including 551 county-level cities in China, we explored the quantitative relationships of prenatal and early childhood exposure to $PM_{2.5}$ with motor development and the risk of DCD among preschoolers based on recent satellite-based measurements of $PM_{2.5}$ concentrations. Additionally, we identified the subgroups in the study population that were more vulnerable to $PM_{2.5}$ 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, 16 392 were screened as suspected DCD, accounting for 14.9%.

$PM_{2.5}$ concentrations during different exposure windows are summarized in Table 2. The mean (±standard deviation) of $PM_{2.5}$ concentrations between birth and 36 months was 50 (±10) $\mu g/m^3$, with an interquartile range (IQR) of 16 $\mu g/m^3$. A wide range of $PM_{2.5}$ concentrations in mainland China was observed (Figure S2), ranging from 13 to 113 $\mu g/m^3$ from birth to 36 months. In general, there were moderate to high correlations among prenatal and postnatal exposure concentrations (Spearman's $r \geq 0.65$; Pearson's $r \geq 0.64$) (Table S3). $PM_{2.5}$ concentrations were weakly to moderately correlated with gaseous air pollutants (Table S4).

Figure 1 presents changes in LDCDQ score per IQR of $PM_{2.5}$ exposure during specific exposure time windows. We observed that increases in postnatal $PM_{2.5}$ exposure were associated with decreases in the total scores and subscores of LDCDQ. For example, an IQR (16 $\mu g/m^3$) increase in $PM_{2.5}$ 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 of breastfeeding	22 460 (20.5)
≥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, mean ± SD)	27.76 ± 4.20
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 /administrator)	69 248 (63.1)
Unemployed	17 838 (16.3)
Others	22 645 (20.6)
Gravidity	
Primigravida	51 168 (46.6)
Multigravida	58 563 (53.4)
Pregnancy complications[a]	
No	104 249 (95)
Yes	5482 (5.0)
Paternal 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.
[a]Mother who had gestational hypertension and/or gestational diabetes mellitus.

Table 2. Description of $PM_{2.5}$ concentrations during specific exposure windows ($\mu g/m^3$)

Exposure windows	Mean (SD)	Max	Percentile			Min	IQR
			P75	P50	P25		
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.

interval [CI]: 0.05, 0.33) in the total score. These associations were consistently significant for two of the three LDCDQ subscores: general coordination (−0.09 [95% CI: −0.14, −0.04]) and control during movement (−0.08 [95% CI: −0.13, −0.03]). For the subscore of fine motor skills, most associations were suggestive or null.

Significant associations were also found for prenatal $PM_{2.5}$ exposure and LDCDQ scores, though the effect estimates were relatively smaller than those with postnatal exposure. Each IQR increase in $PM_{2.5}$ concentrations during the entire pregnancy and during the first trimester was associated with decrements of 0.14 (95% CI: 0.04, 0.24) and 0.18 (95% CI: 0.04, 0.32) in the total LDCDQ score, respectively. Similarly, these associations were consistently significant for general coordination and control during movement but not for fine motor skills (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

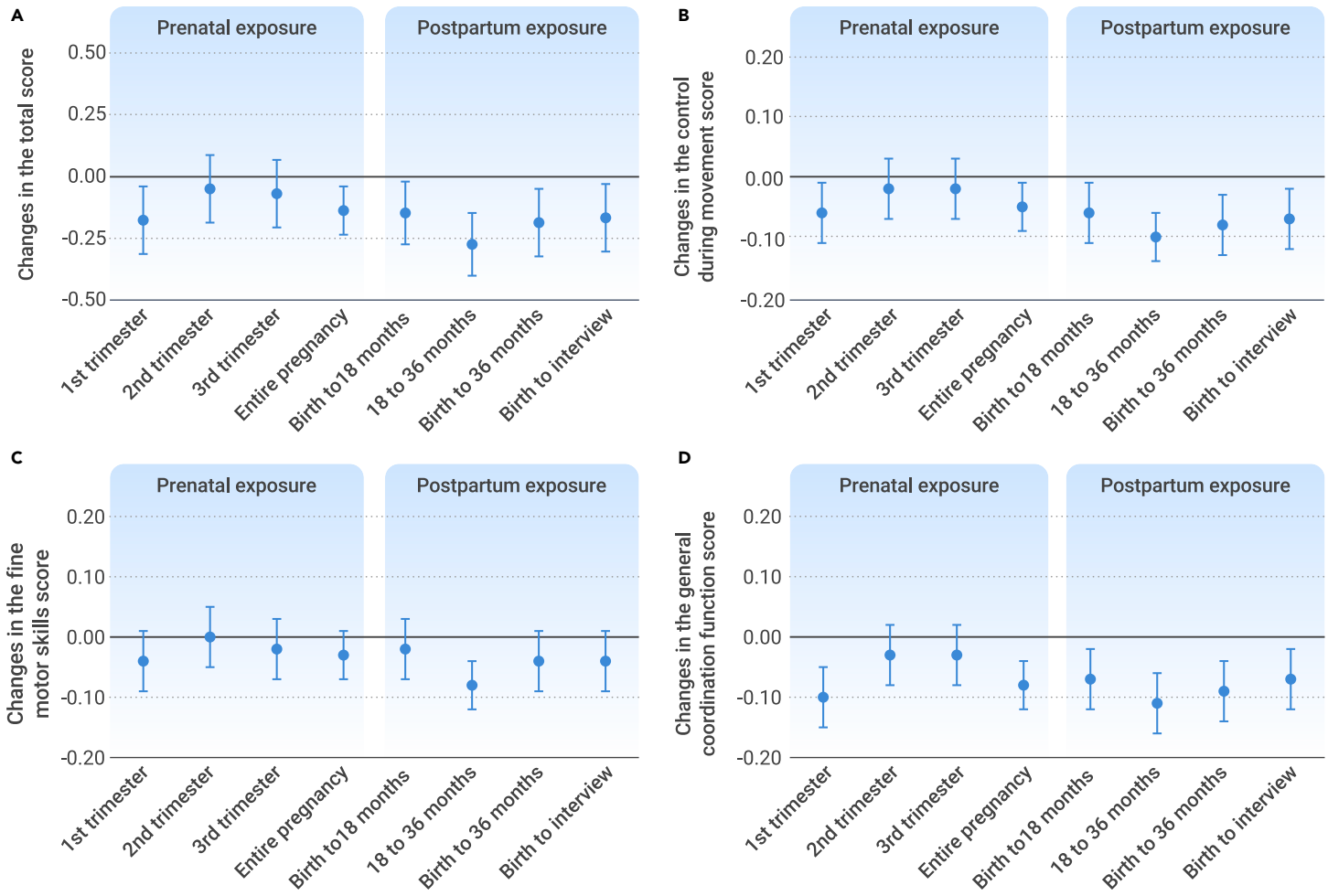

Figure 1. Changes and 95% CIs in the scores of LDCDQ with per interquartile range increase of $PM_{2.5}$ exposure during specific exposure time windows Adjusted for child sex, child age, and body mass index at testing, psychotropic medication, gestational days, preterm birth, delivery mode, NICU admission, breastfeeding, region, maternal age at conception, maternal gravidity, medical conditions during pregnancy, maternal and paternal education, maternal employment, year of test, gross domestic product at province level, temperature and relative humidity, and the random contribution of kindergarten.

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,[26–28,32] and mixed results were found. Two European cohort studies reported no significant association of prenatal exposure to $PM_{2.5}$ with any scale of motor skills at 1–6[26] and 4–6 years of age,[28] whereas significant associations were found in a group of 4- to 6-year-old Mexican children.[32] In line with our results, they also observed that the impact of $PM_{2.5}$ could occur as early as the first trimester of pregnancy, when the cerebellum (responsible for motor control) starts to develop. Heterogeneous findings between studies may be ascribed to different age groups, sample sizes, and measures of motor skill and exposure assessment. Using a large nationwide sample, our findings add robust evidence on the effects of prenatal exposure to $PM_{2.5}$ on neurobehavioral development.

The effects of early childhood exposure to $PM_{2.5}$ on motor development were less studied previously, especially for regions with a high level of air pollution. Existing studies were only available in Europe[25,26] and North America,[33] where the annual concentrations rarely exceeded 35 $\mu g/m^3$, and reported positive or no associations between $PM_{2.5}$ exposure and motor performance among children with 8–36 months and 1–6 years of age. On the contrary, our study shows that exposure to $PM_{2.5}$ during the first 3 years was associated with lower LDCDQ scores and elevated risk of neurodevelopmental disorders at 3–5 years of age. Our study adds value to the literature by studying the impact of $PM_{2.5}$ exposure on the neurodevelopment of children in Asia. Also, our study population were exposed to a much wider range of $PM_{2.5}$ levels (as much as 10-fold compared with previous studies), which facilitated the exploration of the exposure-response relationship of $PM_{2.5}$ and neurodevelopmental outcomes.

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.[34] 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.[35] In addition, evidence has shown that PM, especially nanoscale PM, could reach brain tissues at the early human developmental postconceptional week 8–15 stage,[18] which may have detrimental effects on subsequent brain morphogenesis and

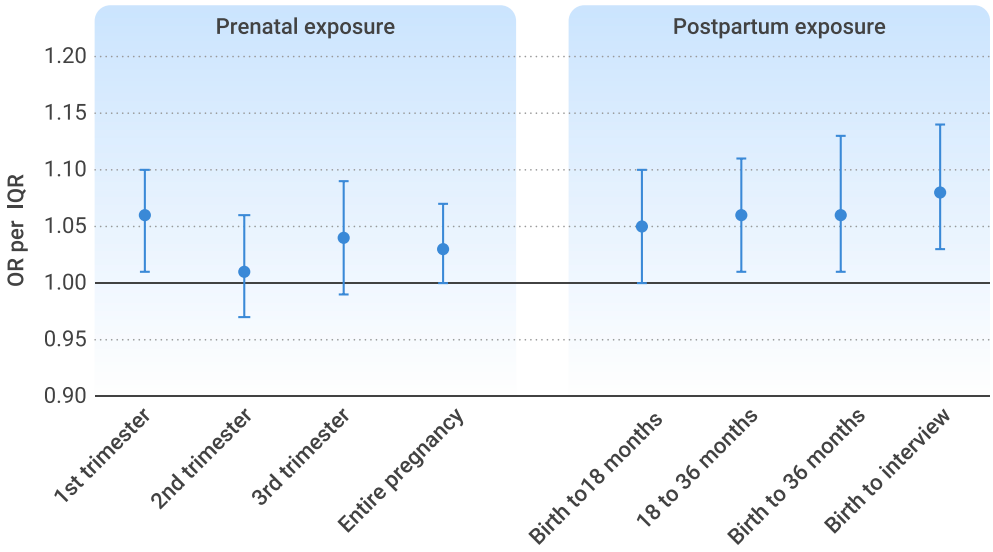

Figure 2. Adjusted ORs and 95% CIs for developmental coordination disorder associated with an IQR increase in $PM_{2.5}$ concentration during specific exposure windows Adjusted for child sex, child age, and body mass index at testing, psychotropic medication, gestational days, preterm birth, delivery mode, NICU admission, breastfeeding, region, maternal age at conception, maternal gravidity, medical conditions during pregnancy, maternal and paternal education, maternal employment, year of test, gross domestic product at province level, temperature and relative humidity, and the random contribution of kindergarten.

microvasculature development.[36] These observations may help explain our finding that the first trimester might be the most pivotal time window for the effects of prenatal $PM_{2.5}$ 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 $PM_{2.5}$ after birth. Inhaled $PM_{2.5}$ can translocate from the child's nose up the olfactory nerve into their brain,[21] 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.[19,37] Imaging studies have proved that the number of neural connections of the brain explode in the first years of life,[38] 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 $PM_{2.5}$ 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.[39,40] Additionally, breastfeeding is beneficial to children's brain development, possibly by boosting the immunity of infants.[41,42] We also observed larger effects of $PM_{2.5}$ 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 socio-economic 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.[43] These findings highlight the potentially vulnerable subgroups and indicate that breastfeeding might protect against the neurotoxic effects of $PM_{2.5}$.

This study has several strengths. First, to our best knowledge, this is the first nationwide study to examine the associations between early-life $PM_{2.5}$ 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.[44] This study took advantage of satellite-based measurements with a high spatial resolution (1 × 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 $PM_{2.5}$ levels, offering a unique opportunity to investigate the relationship between $PM_{2.5}$ 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 micro-environmental $PM_{2.5}$ 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,[45,46] 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 low 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, $PM_{2.5}$) for neurodevelopmental disorders. We found that prenatal and postnatal exposure to $PM_{2.5}$ were associated with decreased LDCDQ scores and a higher risk of DCD, suggesting a link between higher $PM_{2.5}$ 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.[47] 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 years in mainland China. Local kindergartens were invited to participate in this study through the government-supported maternity and children's healthcare 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 nurseries 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

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.

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 (KS18156). 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,[45] and it has also been extended for use with children as old as 5 years[46] 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.[48,49] 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).[48] We followed Wilson et al.'s recommendations[46,50] 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, MERRA-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 $\mu g/m^3$, 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.[51] 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 (ie, prenatal) and the time period after birth (ie, 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.[52] It is around this time that children begin to demonstrate a range of social–cognitive[53] and motor skills.[54,55] 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 kindergarten as it was the primary sampling unit. Additionally, we adjusted for potential confounders, 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, SO_2, and NO_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.

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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.

SUPPLEMENTAL INFORMATION

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