Early life exposure to $PM_{2.5}$ and sleep disturbances in preschoolers from 551 cities of China

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At a Glance Commentary

Scientific Knowledge on the Subject

Sleep problems can affect children's health and development, resulting in long-term adverse health outcomes in later childhood and adulthood. Exposure to ambient air pollutants, including fine particulate matter ($PM_{2.5}$), has been linked with increased risk of sleep disturbance in adults, but the association in children remained unclear. In addition, the possible critical exposure windows for $PM_{2.5}$ exposure and sleep health in children have not been examined. To our knowledge, no national-scale studies have been conducted.

What This Study Adds to the Field

In this nationwide study of 115,023 children aged 3-7 years in China, we found early life $PM_{2.5}$ exposure was associated with lower sleep quality and higher risk of sleep disturbances among preschoolers. Sleep-disordered breathing and daytime sleepiness were two major symptoms associated with $PM_{2.5}$. Postnatal exposure, especially in the first 18 months after birth, may be a critical exposure time window. Children who had NICU admission may be more sensitive to $PM_{2.5}$ exposure and breastfeeding for more than 6 months may mitigate the adverse effect of $PM_{2.5}$ on sleep health. Our findings suggest exposure to air pollution was associated with impaired sleep quality and higher risk of sleep disturbance in early childhood.

Abstract

Rationale: Air pollution has been linked with sleep disturbance in adults, but the association in children remains unclear.

Objectives: To examine the associations of prenatal and postnatal exposure to fine particulate matter ($PM_{2.5}$) with sleep quality and sleep disturbances among children in 551 Chinese cities.

Methods: A total of 115,023 children aged 3–7 years from the Chinese National Cohort of Motor Development were included. Sleep quality was measured using the Children's Sleep Habits Questionnaire (CSHQ). $PM_{2.5}$ exposure was estimated using a satellite-based model. Generalized additive mixed models with Gaussian and binomial distributions were used to examine the associations of $PM_{2.5}$ exposure with CSHQ scores and risk of sleep disturbance, respectively, adjusting for demographic characteristics and temporal trends.

Measurements and Main Results: Early life $PM_{2.5}$ exposure was associated with higher total CSHQ score, and the association was stronger for exposure in age 0–3 years (change of CSHQ score per interquartile range increase of $PM_{2.5}$=0.46, 95% CI: 0.29, 0.63) than during pregnancy (0.22, 95% CI: 0.12, 0.32). The associations were more evident on sleep-disordered breathing and daytime sleepiness. Postnatal $PM_{2.5}$ exposure was associated with increased risk of sleep disturbance (adjusted odds ratios for per interquartile range increase of $PM_{2.5}$ exposure in age 0–3=1.10, 95% CI: 1.04, 1.15), but no associations were found for prenatal exposure. Children who were breastfed for less than 6 months and had NICU admission may be more vulnerable to sleep disturbance related to $PM_{2.5}$ exposure.

Conclusions: $PM_{2.5}$ exposure can impair sleep quality in preschool children.

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Key words: fine particulate matter; sleep disturbance; preschool children; prenatal; postnatal; early life

1. Introduction

Sleep is important for children's health and development(1). Poor sleep quality can affect children's physical growth(2), emotion(3), cognitive function(4), and attention(5), and can persist until later childhood and adulthood(6). Unhealthy sleep patterns and sleep disturbances were common across different populations(7-12). In western countries, 20%–30% of children aged 1 to 5 years experienced sleep problems(6, 13-15). In China, the prevalence of sleep problems among school-age children was nearly 40% over the past two decades and is still increasing(12).

Air pollution has been recognized as a major public health concern, particularly in developing countries. In China, the annual mean of fine particulate matter ($PM_{2.5}$) between 2016 and 2020 was more than 6–9 times higher than the air quality guidelines of World Health Organization (5 $\mu g/m^3$)(16-18). Children has been suggested to be one of the most vulnerable populations of air pollution exposure(19).

Epidemiological studies have suggested that long-term $PM_{2.5}$ exposure could cause sleep disturbances in adults(20-23), but evidence is still scarce for children. Only limited studies have examined the association of prenatal or postnatal exposure to $PM_{2.5}$ with sleep health in pediatric population(24, 25). However, these studies had small sample size and limited geographic coverage, and only considered exposure during pregnancy or after birth. Therefore, it is not clear which exposure time window is more critical. Additionally, the associations of $PM_{2.5}$ with specific symptoms of sleep disturbance have rarely been examined(24). Whereas, this information could be crucial for developing tailored efficient intervention strategies to better protect children's health.

Using data from a nationwide cohort of pre-school age children in China, we examined the associations of early life (including both prenatal and postnatal periods) exposure to $PM_{2.5}$ with sleep quality, sleep disorder symptoms, and sleep disturbance in preschoolers. Further, we sought to identify critical exposure windows for impact of $PM_{2.5}$ on sleep health and susceptible subgroups in the study population.

2. Methods

2.1. Study population and study design

Our study population was from the Chinese National Cohort of Motor Development (CNCMD). The primary goal of this cohort is to explore factors affecting neurobehavioral development and sleep status among Chinese young children. Participants were recruited from 551 county-level cities using a stratified cluster sampling approach based on age, sex, geographic region, and socioeconomic status from the 2018 and 2019 National Census. Recruitment was conducted between April 1, 2018, and December 31, 2019, during which government-supported maternity and children's health centers in the 551 cities invited children in local kindergartens to participate in this study. After enrollment, parents of the child participant were requested to fill out surveys on demographic characteristics, pregnancy history, and sleep quality in an online questionnaire system. More details on the survey and dataset have been described and published elsewhere(26). For this analysis, we included CNCMD participants who were singleton, aged 3–7 at enrollment, and whose maternal conception age was above 18 into the study.

Parents of the child participant had given written consent to participate in the study at

enrollment. This study was approved by the Institutional Review Board of Shanghai First Maternity and Infant Hospital (KS18156).

2.2. Determination of sleep disturbances

Sleep behaviors and disturbances were evaluated using the Children's Sleep Habits Questionnaire (CSHQ), which was completed by the participant's parents. This questionnaire is a sleep disturbance screening instrument originally designed for children aged between 4 to 10 years(27) but later has been shown to be feasible for children younger than 4 years old(28). In this study, we used a Chinese version of the questionnaire, which had been validated previously(29). More details on the CSHQ have been described and published elsewhere(27).

The CSHQ measures eight domains of sleep quality, including bedtime resistance, sleep onset delay, sleep duration, sleep anxiety, night waking, parasomnias, sleep-disordered breathing, and daytime sleepiness, using 33 items of sleep-related behaviors or symptoms. Each item is rated by frequency as "usually" (5–7 times/week), "sometimes" (2–4 times/week), or "rarely" (0–1 time/week). A sub-score for each domain is calculated by summing up scores of all items under that domain. The total score of the questionnaire, which reflects overall sleep quality, is the sum of all eight sub-scores. A higher score indicates higher likelihood of having sleep disturbance, and a total score above 41 was used to identify sleep disturbance in our participants as recommended by a previous study(27).

2.3. Exposure assessment

We collected home addresses during pregnancy and after birth and measured prenatal and

postnatal $PM_{2.5}$ exposure at each location, respectively. Daily $PM_{2.5}$ concentrations during the study period were measured using a satellite-based geospatial predicting model with a spatial resolution of 1 km × 1 km. Detailed methodology has been described previously(30) and Text E1 in Supplement.

For each participant, we averaged the daily $PM_{2.5}$ exposure over four prenatal exposure windows, including the first (gestational weeks 1–13), second (weeks 14–26), and third trimester (weeks 27 to delivery), and the entire pregnancy. Similarly, postnatal $PM_{2.5}$ exposures were estimated over three postnatal exposure windows, including 0 to 18 months, 18 to 36 months, and 0 to 36 months.

To adjust for potential confounding of other air pollutants, we obtained daily concentration of sulfur dioxide (SO_2), nitrogen dioxide (NO_2), carbon monoxide (CO), ozone (O_3), and particle with aerodynamic diameter of 10 μm or less (PM_{10}) from fixed monitoring stations (http://www.cnemc.cn/). Data of the nearest station to the residential address were assigned to the corresponding participant. We also obtained daily ambient temperature and relative humidity from China Meteorological Data Service Center (http://data.cma.cn/).

2.4. Covariates

Based on substantive knowledge from existing literature(12, 24, 31) and the results of statistical tests (t-test and chi-square test) on the differences between participants with and without sleep disturbance (Table 1), we selected covariates on child factors, including child's sex, age, body mass index-for-sex/age z-score (BMIz) at the time of survey(32) (compared to BMI, which allows for better measurement of child growth by sex and month of age), birth

weight, preterm birth (PTB, yes or no), delivery mode (vaginal or cesarean), neonatal intensive care unit (NICU) admission (yes or no), and being breastfed ≥ 6 months (yes or no), as well as parental factors, including maternal age at conception, maternal gravidity (primigravida or multigravida), gestational hypertension and/or gestational diabetes mellitus (yes or no), maternal and paternal education (middle school or below, high school, or college or above), maternal employment (employed, unemployed, or others), and marital status (first marriage or others). We also considered variables reflecting living conditions and area-level socioeconomic status, including family structure (nuclear household, consisting either of a married couple or a divorced/widowed parent and their children; lineal household, consisting of grandparents, parents, and their children; or the joint household, consisting of grandparents, parents and their children, as well as married or unmarried siblings of the parents)(33) and annual gross domestic product (GDP) per capita at the provincial level.

2.5 Statistical analyses

We applied generalized additive mixed models with Gaussian (for the continuous CSHQ scores) or binomial (for the binary outcome of sleep disturbance) distributions to examine the associations of $PM_{2.5}$ in each exposure window with sleep outcomes. This model can incorporate splines for potential non-linear relationships between meteorological conditions and the outcomes. We fitted 4 sets of models. In Model 1 we controlled for sex, age, and BMIz at the time of survey of the child and a random intercept by kindergarten to account for within-kindergarten correlation. In Model 2 we further adjusted for other child characteristics that could affect sleep health, including birth weight, PTB, delivery mode, NICU admission, and

being breastfed for ≥ 6 months. In Model 3 we added parental characteristics, including maternal age at conception, gravidity, pregnancy complications, and socioeconomic status (maternal and paternal education, maternal employment, marital status, family structure, and GDP per capita). Finally, in Model 4 we further controlled for ambient temperature and relative humidity (in natural cubic splines with 3 df) and survey year for long-term time trends. We also examined possible non-linear exposure-response relationships by using quartiles of $PM_{2.5}$ levels in the model.

Several sensitivity analyses were conducted to examine the robustness of our results. First, we fitted two-pollutant models by adding SO_2, NO_2, CO, O_3, and coarse particulate matter ($PM_{2.5-10}$), respectively, into the model with $PM_{2.5}$ to examine possible confounding by co-exposure to other air pollutants. $PM_{2.5-10}$ was calculated by subtracting $PM_{2.5}$ concentrations from PM_{10}. We additionally adjusted for residential distance to the major roads (including major highways, national-level and provincial-level roads) at residential address as a proxy of traffic-related exposure (e.g., noise) in the model. Lastly, to examine possible confounding of prenatal $PM_{2.5}$ exposure on the associations of postnatal exposure, we introduced $PM_{2.5}$ concentrations during the entire pregnancy into the models for postnatal $PM_{2.5}$.

Further, we considered possible effect modification by child's sex, breastfeeding, NICU admission, and maternal education by adding a multiplicative interaction term with $PM_{2.5}$ into the model, respectively. Associations of $PM_{2.5}$ with the outcomes within each stratum of these modifiers were estimated in separate models. We also considered the relative excess risk due to interaction (RERI) to evaluate possible additive effect modification by these factors(34).

All statistical analyses were performed in R (version 4.0.5) with "gamm4" package for

generalized additive mixed models. All statistical tests were two-sided and a p-value < .05 was considered statistically significance. Results of the CSHQ scores were presented as the differences and 95% confidence intervals (CIs) of the scores per interquartile range (IQR) increases of $PM_{2.5}$ exposure. Results for sleep disturbance were presented as the odds ratios (ORs) and 95% CIs of sleep disturbance per IQR increases of $PM_{2.5}$ exposure or comparing $PM_{2.5}$ exposure in the other quartiles with the lowest one.

3. Results

Participant characteristics

A total of 166,520 children aged 3 to 7 years from 2,403 kindergartens in 551 Chinese cities were initially included. We further excluded records according to exclusion criteria, which are illustrated in Figure E1. Eventually, 115,023 children were eligible for this study.

Table 1 summarizes the characteristics of the study population. The mean (±standard deviation, SD) of children's age and BMIz were 4.5 (±0.9) years old and 0.4 (±2.2) SDs, respectively. Approximately 53.0% of the children were boys, 47.8% were delivered by cesarean section, 10.2% had NICU admission, and 79.5% were breastfed for at least 6 months. The mean maternal age at conception was 27.7 (±4.2) years old and 4.8% of the mothers had pregnancy complications. The mean (±SD) of total CSHQ score was 46.6 (±7.6) (Table 2). The prevalence of sleep disturbance in our study population was 76.3%, which was comparable to previous studies among Chinese children using the same assessment tool and cutoff(8, 10, 35).

$PM_{2.5}$ exposure levels

As shown in Table E1 in the Supplement, the median levels of $PM_{2.5}$ during the entire pregnancy and the first three years after birth were 55 (IQR: 49-63) μg/m^3 and 50 (IQR: 42-58) μg/m^3, respectively. A moderate correlation (Spearman correlation coefficient=0.73) was observed between $PM_{2.5}$ exposures during pregnancy and in age 0-3.

Associations of $PM_{2.5}$ exposure with CSHQ scores

Table 3 presents the associations between $PM_{2.5}$ exposure and total CSHQ score. Overall, results of the 4 models were similar. We found both prenatal and postnatal exposure to $PM_{2.5}$ was associated with lower sleep quality, as indicated by higher CSHQ scores, and the associations were stronger for postnatal exposure. For example, after adjusting for all covariates, the total CSHQ score was 0.46 (95% CI: 0.29, 0.63) higher per IQR (16 μg/m^3) increase of $PM_{2.5}$ exposure from birth to 36 months, and was 0.22 (95% CI: 0.12, 0.32) higher per IQR (14 μg/m^3) increase of $PM_{2.5}$ exposure during the entire pregnancy. Larger effect estimates were found on the first trimester (0.26, 95% CI: 0.13, 0.39) during pregnancy, and the first 18 months after birth (0.39, 95% CI: 0.26, 0.52). As for the associations of $PM_{2.5}$ and CSHQ sub-scores, we found the $PM_{2.5}$ was associated with higher scores for sleep-disordered breathing and daytime sleepiness; while the associations with other symptoms were null (Table 4).

Associations of $PM_{2.5}$ exposure with risk of sleep disturbance

The associations between $PM_{2.5}$ exposure and the risk of sleep disturbance are shown in Figure 1. We observed $PM_{2.5}$ exposure after birth was associated with higher odds of sleep

disturbance. For example, an IQR increase of $PM_{2.5}$ concentrations in age 0-3 was associated with a 10% (adjusted OR=1.10, 95% CI: 1.04, 1.15) higher odds of sleep disturbance. However, no associations were observed for prenatal exposure and risk of sleep disturbance.

We further compared the risk of sleep disturbance by quartiles of $PM_{2.5}$ exposure. As shown in Figure 2, the risks of sleep disturbance increased monotonically across quartiles of $PM_{2.5}$ exposure levels. Compared with the lowest quartile, children whose $PM_{2.5}$ exposure during pregnancy in the highest quartile (> 62.7 $\mu g/m^3$) had 8% (OR=1.08, 95% CI: 1.01, 1.15) higher odds of sleep disturbance at age of 3–7. The estimate was higher (OR=1.13, 95% CI: 1.04, 1.23) for the first three years exposure after birth in the highest quartile (> 58.3 $\mu g/m^3$).

Sensitivity analyses

Results from the two-pollutant models showed similar estimates with single-pollutant models (Table E2). When controlling for the distance to the major roads, the effect of $PM_{2.5}$ with sleep disturbances remained statistically significant but attenuated slightly (Table E3). After adjusting for the exposure during pregnancy, the estimates for $PM_{2.5}$ during birth to 36 months remained almost unchanged for total score of CSHQ, and became larger for sleep disturbance (Table E4).

Child and maternal characteristics, $PM_{2.5}$ exposure and sleep health

Our stratified analyses showed stronger associations of $PM_{2.5}$ exposure in age 0-3 with total CSHQ score among children who were breastfed for less than 6 months (β=0.60, 95% CI: 0.25, 0.96) compared to those who were breastfed for more than 6 months (β=0.43, 95% CI:

0.24, 0.62). In addition, children who had a history of NICU admission (Yes: β=0.92, 95% CI: 0.46, 1.38 vs. No: β=0.41, 95% CI: 0.23, 0.59) and who had lower maternal education (high school or below: β=0.60, 95% CI: 0.35, 0.84 vs. college or above: β=0.32, 95% CI: 0.09, 0.55) had stronger associations of postnatal $PM_{2.5}$ exposure with CSHQ score (Table 5). However, the statistical significances of most multiplicative interaction terms were large ($p_{\text{interaction}}$ = .34 –.87) except for the breastfeeding ($p_{\text{interaction}}$ = .13).

As presented in Table 6, we found that sleep disturbance risk related to $PM_{2.5}$ exposure after birth was much lower among children who were breastfed for at least 6 months (OR=1.09, 95% CI: 1.03, 1.15), compared to those who were not (OR=1.15, 95% CI: 1.02, 1.29). Additionally, there was a significantly negative interaction on the additive scale (RERI= -0.06, 95% CI: -0.11, -0.01), which means that the risk of sleep disturbance in children breastfed for at least 6 months is 0.06 less with each IQR increase in $PM_{2.5}$ concentrations than if there was no interaction. We also observed higher $PM_{2.5}$-related sleep disturbance risk among children had NICU admission (OR=1.32, 95% CI: 1.13, 1.54) compared to the others (OR=1.07, 95% CI: 1.02, 1.14). There was a significantly positive interaction on the additive scale (RERI=0.05, 95% CI: 0.004, 0.10), which means that the risk of sleep disturbance in children admitted to NICU is 0.05 more with each IQR increase in $PM_{2.5}$ concentrations than if there was no interaction.

4. Discussion

This study estimated the associations between early life $PM_{2.5}$ exposure and sleep health among 115,023 Chinese preschoolers. We found both prenatal and postnatal exposure to $PM_{2.5}$

was associated with lower sleep quality and the associations were stronger for postnatal exposure, especially for exposure during the first 18 months after birth. More specifically, $PM_{2.5}$ exposure was mainly associated with increased scores of sleep-disordered breathing and daytime sleepiness. We also found that $PM_{2.5}$ exposure after birth was associated with increased risk of sleep disturbance. Children who were breastfed for less than 6 months and had been admitted to NICU might have higher risk of sleep disturbance with $PM_{2.5}$. To our knowledge, this is the first nationwide study to examine the association between $PM_{2.5}$ exposure and sleep health among pre-school children in China.

Sleep plays an important role in neurobehavioral functioning since infancy, and some sleep characteristics have been found to reflect neural plasticity, which is critical for supporting learning, memory consolidation, motor functioning, and cognitive abilities(36). However, evidence on the impact of long-term $PM_{2.5}$ exposure on children's sleep health is very limited(24, 25). Lawrence et al., reported that $PM_{2.5}$ exposure after birth was positively associated with score of sleep disorder among children and adolescents aged 2–17 years in 7 Chinese northeastern cities(24). Bose et al., also observed significant associations between prenatal $PM_{2.5}$ exposure and sleep disruption among 397 children aged 4–5 years old in Mexico City(25). Our study provides new evidence for the adverse effect of $PM_{2.5}$ exposure on sleep health in young children from a large, nationwide population sample. In addition, our analysis on exposure-response relationships suggested a greater risk of sleep disturbance found in more polluted areas (i.e., with $PM_{2.5}$ concentrations over 58.3 $\mu g/m^3$) may inform future research studies and targeted environmental policies.

Our results suggested that although both prenatal and postnatal $PM_{2.5}$ exposure were

associated with poorer sleep health, exposure in the first three years after birth had stronger associations with the outcomes. In addition, the associations for postnatal exposure persisted after adjusting for prenatal exposure. To our knowledge, this is the first study to explore the possible critical exposure window for the adverse effects of $PM_{2.5}$ on sleep health. Across the exposure time windows after birth, the first 18 months appeared to be important, which has been recognized as a critical time window for brain development(37), and is also found to be the period when the first peak of sleep problems occurrence(6). Our finding is biologically plausible. Although a few studies suggested a possibility that $PM_{2.5}$ may cross the blood-placental barrier, the adverse impact is most likely to be weakened by the blood-placental barrier(38). After birth, infants are directly exposed to $PM_{2.5}$ and it has been documented that $PM_{2.5}$ exposure may interrupt sleep by affecting the airways and central nervous system(39, 40). The respiratory system of young children is particularly vulnerable to air pollutants because of underdeveloped lung defenses and a higher ratio of breathing rate to body size than adults(19, 41). Previous studies showed that inhaled $PM_{2.5}$ can cause upper airway cell damage(42, 43). Airway cell injury may trigger inflammation and/or edema of mucosa, which can lead to airway restriction and obstruction, and result in compromised sleep quality and sleep disorders related to breathing(22, 44, 45). In particular, cellular proliferation in tonsils and upper airway inflammation have been consistently found in children with sleep-disordered breathing(46). Evidence also suggested that exposure to air pollution may promote inflammatory changes in lymph-adenoid tissue and exacerbate adenotonsillar proliferation and hypertrophy(47, 48). In addition, inhaled $PM_{2.5}$ may enter the central nervous system by blood circulation (49-51) or being directly transported from the nose to the brain via the olfactory

nerve (39, 52), resulting disrupted biochemical and/or physiological activity of the central nervous system and impaired sleep regulation(44).

Our study showed that $PM_{2.5}$ exposure was mainly associated with two specific symptoms: sleep-disordered breathing and daytime sleepiness. Daytime sleepiness is one of the most common symptoms of sleep disturbance(7, 53) and previous studies have found strong association of ambient $PM_{2.5}$ and traffic-related exposure with daytime sleepiness in adults(54-56). Another study demonstrated the incidence of daytime sleepiness in children reduced substantially (from 21.1% to 1.8%) with improved air quality(57). Daytime sleepiness might be related to sleep-disordered breathing at night, which typically leads to broken/lighter nocturnal sleep, resulting in sleep deprivation(58). A few studies have examined the associations of air pollution and sleep-disordered breathing in children, but the results were inconsistent(24, 40, 59, 60). Consistent with our findings, the study by Lawrence et al., in 7 Chinese cities found that 4-year average $PM_{2.5}$ exposure after birth was associated with increased risk of sleep-breathing disorders(24).

We further found that breastfeeding may mitigate the adverse impact of $PM_{2.5}$ exposure on sleep disturbance. Beneficial effects of breastfeeding on childhood neurodevelopment have been widely observed(61, 62), and long-term protection from breastfeeding against the incidence of snoring and sleep-disordered breathing in children have also been documented(63-65). Fatty acids in breast milk, such as docosahexaenoic acid and arachidonic acid, are essential for neuronal membranes formation and neurodevelopment(66, 67). Breastfeeding may also contribute to immune maturation and secure a proper immunological response(68). This protection could sustain even after breastfeeding termination(69), which may, partially at least,

attenuate the inflammation and oxidative stress caused by air pollution. Our results also suggested that children admitted to NICU appeared to be more sensitive to $PM_{2.5}$ exposure. Maternal conditions such as gestational diabetes, hypertension, and premature rupture of the membrane and adverse neonatal outcomes such as preterm birth and low birth weight are the main reasons for NICU admission. Therefore, NICU admission may be a predictor of poor overall health in children, who could be more susceptible adverse environmental exposures(70-72).

This study has several strengths. First, our findings provide evidence of early-life $PM_{2.5}$ exposure and impaired sleep quality in preschool aged children from a large, nationwide population. In addition, we firstly explored the critical exposure windows for the adverse effects of $PM_{2.5}$ on sleep health, which could have important implications for targeted intervention. Second, we used satellite-based model to measure $PM_{2.5}$ exposures with high spatial-temporal resolution, which allowed us to achieve better spatial coverage and included those areas disproportionally excluded from previous studies due to lack of $PM_{2.5}$ measurement data. Lastly, our study population had sufficient variation in $PM_{2.5}$ exposure, which allowed us to investigate the exposure-response relationship of $PM_{2.5}$ and sleep health in a large exposure range.

There are also several notable limitations. First, although CSHQ has previously been validated, potential recall bias is possible because the assessments of children's sleep quality were reported by parents. Second, information on indoor air pollution exposure and time spent at the residential addresses was not collected. Therefore, exposure measurement error is possible. Finally, we did not adjust for factors such as second-hand smoking, bedroom light

use, nighttime noise, and had very limited information on living condition. Therefore, residual confounding is possible.

5. Conclusions

In this study, we found both prenatal and postnatal exposures to $PM_{2.5}$ were associated with lower sleep quality in a large, nationwide cohort of pre-school aged children. Postnatal exposure, especially the time period of first 18 months, might be an important time window for intervention. We further found that breastfeeding over 6 months may mitigate the impact of $PM_{2.5}$ exposure on sleep quality. Our findings add new evidence on $PM_{2.5}$ associated effect of sleep health among children and highlight the importance of reducing air pollution for children's health.

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Table 1 Summary characteristics of study population.

Characteristics	**Total**	**Sleep disturbance ***	**Not sleep disturbance**	**P value †**
N (%) / mean ± SD	**(N=115023)**	**(N=87734)**	**(N=27289)**	
Children				
Age (years)	4.5 ± 0.9	4.5 ± 0.9	4.6 ± 0.9	< .001
Birth weight (g)	3325.2 ± 470.5	3322.2 ± 470.5	3334.8 ± 470.3	< .001
Gestational age <37wk	14133 (12.3)	11151(12.7)	2982(10.9)	< .001
Sex				.018
Male	60929 (53.0)	46303(52.8)	14626(53.6)	
female	54094 (47.0)	41431(47.2)	12663(46.4)	
BMIz (SDs)	0.4 ± 2.2	0.5 ± 2.3	0.4 ± 2.1	< .001
Delivery mode				< .001
Vaginal delivery	60035 (52.2)	46156(52.6)	13879(50.9)	
Cesarean delivery	54988 (47.8)	41578(47.4)	13410(49.1)	
NICU admission				< .001
No	103246 (89.8)	78462(89.4)	24784(90.8)	

Yes	11777 (10.2)	9272(10.6)	2505(9.2)	
Exclusive breastfeeding for 6 months				.001
No	23541 (20.5)	18157(20.7)	5384(19.7)	
Yes	91482 (79.5)	69577(79.3)	21905(80.3)	
Parents				
Maternal age at conception (years)	27.7 ± 4.2	27.6 ± 4.2	28.0 ± 4.3	< .001
Maternal gravidity				< .001
Primigravida	53557 (46.6)	41169(46.9)	12388(45.4)	
Multigravida	61466 (53.4)	46565(53.1)	14901(54.6)	
Pregnancy complications ‡				< .001
No	109465 (95.2)	83287(94.9)	26178(95.9)	
Yes	5558 (4.8)	4447(5.1)	1111(4.1)	
Maternal education				< .001
Middle school or below	23080 (20.1)	17988(20.5)	5092(18.7)	
High school	27299 (23.7)	20722(23.7)	6527(23.9)	
College or above	64644 (56.2)	48974(55.8)	15670(57.4)	

Maternal employment				< .001
Employed (Worker/businessman/administrator)	72324 (62.9)	55472(63.2)	16852(61.8)	
Unemployed	18908 (16.4)	14403(16.4)	4505(16.5)	
Others	23791 (20.7)	17859(20.4)	5932(21.7)	
Paternal education				< .001
Middle school or below	22583 (19.6)	17540(20.0)	5043(18.5)	
High school	29289 (25.5)	22437(25.6)	6852(25.1)	
College or above	63151 (54.9)	47757(54.4)	15394(56.4)	
Marital status				.027
First marriage	107618 (93.6)	82007(93.5)	25611(93.9)	
Others	7405 (6.4)	5727(6.5)	1678(6.1)	
Family structure				< .001
Nuclear household	73287 (63.7)	55267 (63.0)	18020 (66.0)	
Lineal household	37366 (32.5)	28999 (33.1)	8367 (30.7)	
Joint household	4370 (3.8)	3468 (4.0)	902 (3.3)	

* A total score of > 41 has been defined as the cut-off for overall sleep disturbance.

† Chi-square test was applied to compare the differences in categorical variables between groups with and without sleep disturbance; t-test was applied to compare the differences in continuous variables between groups with and without sleep disturbance.

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

Abbreviation: SD, standard deviation; BMIz, body mass index-for-sex/age z-score; NICU, neonatal intensive care unit.

Table 2 Descriptive statistics of the total score and sub-scores of CSHQ in study children.

Outcome variables	**Total (N=115023)**	**Sleep disturbance (N=87734)**	**Not sleep disturbance (N=27289)**
Total score	46.6 ± 7.6	49.1 ± 6.9	38.7 ± 2.2
Bedtime resistance	11.1 ± 2.3	11.8 ± 2.0	9.0 ± 1.9
Sleep onset delay	1.6 ± 0.7	1.8 ± 0.7	1.3 ± 0.5
Sleep duration	4.8 ± 1.5	5.1 ± 1.5	3.9 ± 1.2
Sleep anxiety	7.2 ± 2.0	7.7 ± 1.9	5.8 ± 1.4
Night waking	3.6 ± 1.1	3.7 ± 1.2	3.2 ± 0.5
Parasomnias	8.6 ± 2.3	8.9 ± 2.4	7.4 ± 0.8
Sleep-disordered breathing	3.4 ± 0.9	3.5 ± 1.1	3.1 ± 0.3
Daytime sleepiness	10.7 ± 2.7	11.4 ± 2.6	8.6 ± 1.6

Abbreviation: CSHQ, Children's Sleep Habits Questionnaire.

Table 3 Estimates and 95% CI for the total score of CSHQ associated with IQR increases in $PM_{2.5}$ exposure during different exposure windows.

Outcome variables	Exposure windows	Model 1 *	Model 2 †	Model 3 ‡	Model 4 §
Total score	**Prenatal exposure**				
	1st trimester	**0.22 (0.10, 0.35)**	**0.23 (0.10, 0.35)**	**0.26 (0.13, 0.38)**	**0.26 (0.13, 0.39)**
	2nd trimester	**0.13 (0.01, 0.26)**	**0.15 (0.02, 0.28)**	**0.17 (0.04, 0.30)**	**0.18 (0.05, 0.30)**
	3rd trimester	**0.14 (0.01, 0.27)**	**0.15 (0.02, 0.28)**	**0.17 (0.04, 0.30)**	**0.17 (0.04, 0.30)**
	Entire pregnancy	**0.20 (0.10, 0.29)**	**0.19 (0.09, 0.28)**	**0.21 (0.12, 0.31)**	**0.22 (0.12, 0.32)**
	Postnatal exposure				
	Birth-18 months	**0.34 (0.21, 0.47)**	**0.35 (0.22, 0.48)**	**0.38 (0.25, 0.51)**	**0.39 (0.26, 0.52)**
	18-36 months	**0.21 (0.06, 0.36)**	**0.22 (0.07, 0.37)**	**0.25 (0.10, 0.39)**	**0.26 (0.11, 0.41)**
	Birth-36 months	**0.42 (0.25, 0.59)**	**0.42 (0.26, 0.59)**	**0.44 (0.28, 0.61)**	**0.46 (0.29, 0.63)**

* Adjusted for child sex, child age and BMIz at the time of survey, and the random contribution of kindergarten.

† Further adjusted for birth weight, PTB, delivery mode, NICU admission, and exclusive breastfeeding for 6 months based on Model 1.

‡ Further adjusted for maternal age at conception, maternal gravidity, medical conditions during pregnancy, maternal and paternal education, maternal employment, marital status, family structure, and GDP based on Model 2.

§ Further adjusted for survey year, ambient temperature, and relative humidity based on Model 3.

Bold indicates p-value < .05.

Table 4 Estimates and 95% CI for the sub-scores of CSHQ associated with per IQR increase in $PM_{2.5}$ exposure during prenatal and postnatal exposure windows *.

Outcome variables	Exposure windows	β coefficients (95%CI)
Bedtime resistance	**Prenatal exposure**	
	1st trimester	0.03 (-0.01, 0.07)
	2nd trimester	0.01 (-0.03, 0.05)
	3rd trimester	-0.01 (-0.05, 0.03)
	Entire pregnancy	0.01 (-0.01, 0.04)
	Postnatal exposure	
	Birth-18 months	0.02 (-0.02, 0.06)
	18-36 months	0.00 (-0.04, 0.04)
	Birth-36 months	0.04 (-0.01, 0.09)
Sleep onset delay	**Prenatal exposure**	
	1st trimester	0.01 (-0.00, 0.02)
	2nd trimester	0.01 (-0.00, 0.02)
	3rd trimester	0.01 (-0.00, 0.02)
	Entire pregnancy	0.01 (-0.00, 0.02)
	Postnatal exposure	
	Birth-18 months	0.01 (-0.00, 0.02)
	18-36 months	-0.01 (-0.02, 0.01)
	Birth-36 months	0.01 (-0.01, 0.02)
Sleep duration	**Prenatal exposure**	
	1st trimester	0.02 (-0.01, 0.04)
	2nd trimester	**0.03 (0.002, 0.05)**

	3rd trimester	0.02 (-0.01, 0.05)
	Entire pregnancy	0.02 (-0.00, 0.04)
	Postnatal exposure	
	Birth-18 months	**0.03 (0.002, 0.06)**
	18-36 months	0.02 (-0.01, 0.05)
	Birth-36 months	**0.04 (0.01, 0.08)**
Sleep anxiety	**Prenatal exposure**	
	1st trimester	0.03 (-0.00, 0.07)
	2nd trimester	0.02 (-0.01, 0.06)
	3rd trimester	-0.00 (-0.04, 0.03)
	Entire pregnancy	0.02 (-0.00, 0.05)
	Postnatal exposure	
	Birth-18 months	**0.04(0.01, 0.07)**
	18-36 months	0.02 (-0.02, 0.06)
	Birth-36 months	0.04 (-0.00, 0.09)
Night waking	**Prenatal exposure**	
	1st trimester	0.00(-0.02, 0.02)
	2nd trimester	-0.00 (-0.02, 0.01)
	3rd trimester	0.02 (-0.00, 0.04)
	Entire pregnancy	0.00 (-0.01, 0.02)
	Postnatal exposure	
	Birth-18 months	0.02 (-0.00, 0.04)
	18-36 months	0.00 (-0.02, 0.02)
	Birth-36 months	0.01 (-0.01, 0.04)
Parasomnias	**Prenatal exposure**	

	1st trimester	0.01 (-0.02, 0.05)
	2nd trimester	0.01 (-0.03, 0.05)
	3rd trimester	0.01 (-0.03, 0.05)
	Entire pregnancy	0.01 (-0.02, 0.04)
	Postnatal exposure	
	Birth-18 months	**0.05 (0.01, 0.09)**
	18-36 months	0.03 (-0.02, 0.07)
	Birth-36 months	0.04 (-0.01, 0.09)
Sleep-disordered breathing	**Prenatal exposure**	
	1st trimester	**0.02 (0.01, 0.04)**
	2nd trimester	0.01 (-0.00, 0.03)
	3rd trimester	0.01 (-0.01, 0.03)
	Entire pregnancy	**0.02 (0.01, 0.03)**
	Postnatal exposure	
	Birth-18 months	**0.03 (0.01, 0.05)**
	18-36 months	**0.02 (0.003, 0.04)**
	Birth-36 months	**0.03 (0.01, 0.05)**
Daytime sleepiness	**Prenatal exposure**	
	1st trimester	**0.14 (0.10, 0.19)**
	2nd trimester	**0.09 (0.04, 0.13)**
	3rd trimester	**0.09 (0.05, 0.14)**
	Entire pregnancy	**0.13 (0.10, 0.17)**
	Postnatal exposure	
	Birth-18 months	**0.19 (0.14, 0.24)**
	18-36 months	**0.17 (0.12, 0.23)**

	Birth-36 months	**0.25 (0.19, 0.32)**

* Adjusted for child sex, child age and BMIz at the time of survey, birth weight, PTB, delivery mode, NICU admission, exclusive breastfeeding for 6 months, maternal age at conception, maternal gravidity, medical conditions during pregnancy, maternal and paternal education, maternal employment, marital status, family structure, GDP, survey year, ambient temperature, relative humidity, and the random contribution of kindergarten.

Bold indicates p-value < .05.

Table 5 Mean differences for the total CSHQ score in association with per interquartile range increase in $PM_{2.5}$ concentrations stratified by child's sex, breastfeeding, NICU admission, and maternal education, and interactions between $PM_{2.5}$ concentrations and each variable.

Subgroups	β coefficients * (95%CI)		P_i †
Child's sex	Male	Female	
	(N=60929)	(N=54094)	
Entire pregnancy	**0.23 (0.10, 0.37)**	**0.24 (0.10, 0.38)**	0.87
Birth-36 months	**0.51 (0.28, 0.75)**	**0.44 (0.21, 0.68)**	0.63
Maternal education	High school or below	College or above	
	(N=50379)	(N=64644)	
Entire pregnancy	**0.23 (0.09, 0.38)**	**0.20 (0.07, 0.33)**	0.38
Birth-36 months	**0.60 (0.35, 0.84)**	**0.32 (0.09, 0.55)**	0.34
Exclusive breastfeeding	Yes	No	
	(N=91482)	(N=23541)	
Entire pregnancy	/	/	/
Birth-36 months	**0.43 (0.24, 0.62)**	**0.60 (0.25, 0.96)**	0.13
NICU admission	Yes	No	
	(N=11777)	(N=103246)	
Entire pregnancy	/	/	/
Birth-36 months	**0.92 (0.46, 1.38)**	**0.41 (0.23, 0.59)**	0.35

* Model 4 excepted stratified-variables.

† Interaction p-value of models additionally adjusting for a multiplicative interaction term between $PM_{2.5}$ exposure and each stratified-variable based on Model 4.

Bold indicates p-value < .05.

Abbreviation: NICU: neonatal intensive care unit.

Table 6 Adjusted odd ratios for sleep disturbances in association with per interquartile range increase in $PM_{2.5}$ concentrations stratified by child's sex, breastfeeding, NICU admission, and maternal education, and interactions between $PM_{2.5}$ concentrations and each variable.

Subgroups	Exposure window	OR * (95% CI)		P_i †	RERI (G1 vs. G0) ‡
Child's sex		Female (G1)	Male (G0)		
		(*N*=54094)	(*N*=60929)		
	Entire pregnancy	1.03 (0.99, 1.08)	1.03 (0.99, 1.08)	0.59	0.01 (-0.02, 0.04)
	Birth-36 months	**1.10 (1.02, 1.18)**	**1.10 (1.03, 1.19)**	0.61	0.01 (-0.02, 0.05)
Maternal education		College or above (G1)	High school or below (G0)		
		(N=64644)	(N=50379)		
	Entire pregnancy	1.02 (0.98, 1.06)	1.03 (0.99, 1.08)	0.10	0.03 (0.00, 0.06)
	Birth-36 months	**1.11 (1.03, 1.19)**	**1.08 (1.00, 1.16)**	0.03	0.04 (0.01, 0.07)
Exclusive breastfeeding		Yes (G1)	No (G0)		
		(*N*=91482)	(*N*=23541)		

	Entire pregnancy	/	/	/	/
	Birth-36 months	**1.09 (1.03, 1.15)**	**1.15 (1.02, 1.29)**	0.02	-0.06 (-0.11, -0.01)
NICU admission		Yes (G1) (N=11777)	No (G0) (N=103246)		
	Entire pregnancy	/	/	/	/
	Birth-36 months	**1.32 (1.13, 1.54)**	**1.07 (1.02, 1.14)**	0.14	0.05 (0.004, 0.10)

* Model 4 excepted stratified-variables.

† Interaction p-value of models additionally adjusting for a multiplicative interaction term between $PM_{2.5}$ exposure and each stratified-variable based on Model 4.

‡ Additive joint effects.

Bold indicates p-value < .05.

Abbreviation: NICU: neonatal intensive care unit, RERI: relative excess risk due to interaction.

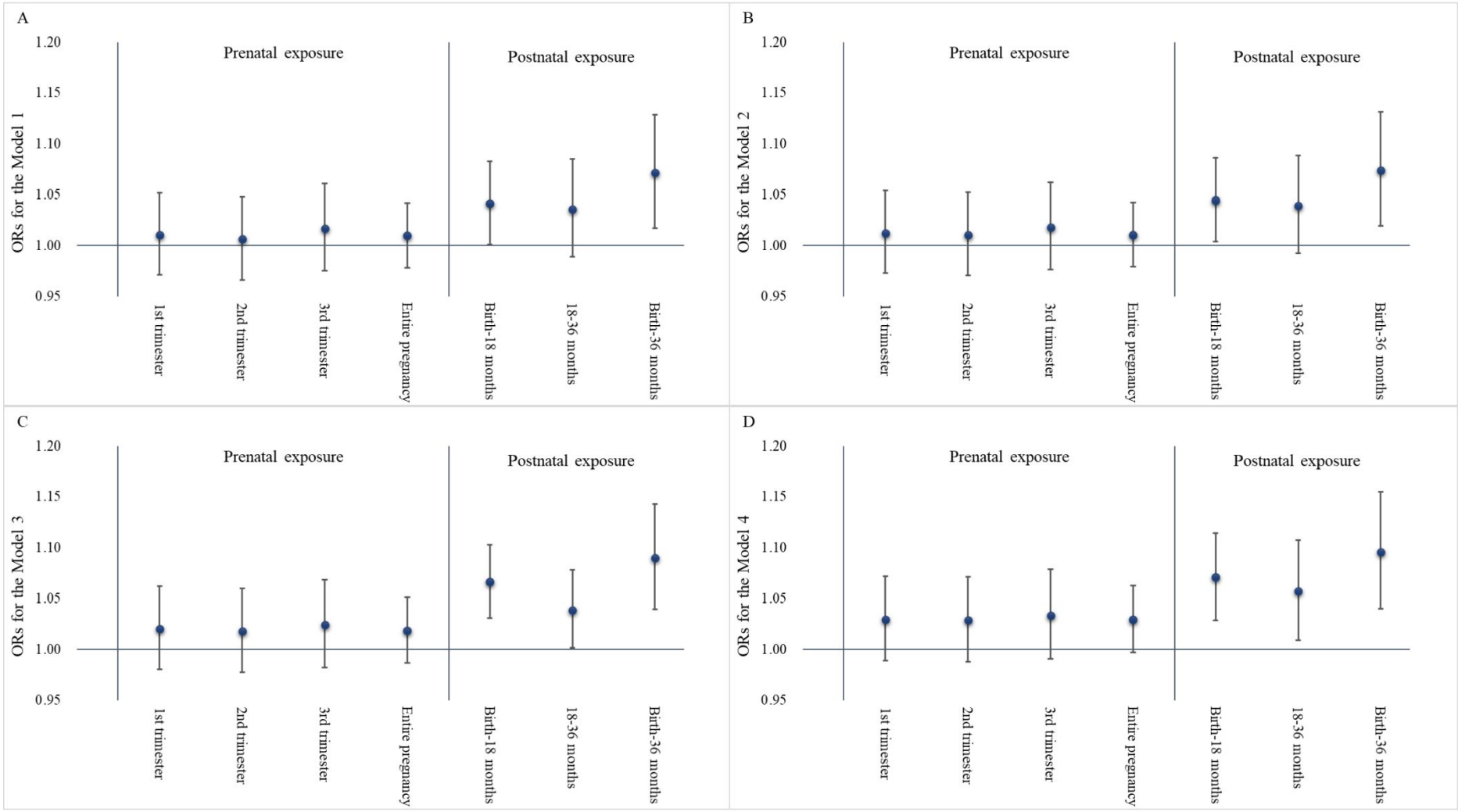

Figure 1 Adjusted odd ratios and 95% confidence interval for sleep disturbances associated with per interquartile range increase in $PM_{2.5}$ concentrations during specific exposure windows.

A: Adjusted for child sex, child age and BMIz at the time of survey, and the random contribution of kindergarten.

B: Further adjusted for birth weight, PTB, delivery mode, NICU admission, and exclusive breastfeeding for 6 months based on Model 1.

C: Further adjusted for maternal age at conception, maternal gravidity, medical conditions during pregnancy, maternal and paternal education, maternal employment, marital status, family structure, and GDP based on Model 2.

D: Further adjusted for survey year, ambient temperature, and relative humidity based on Model 3.

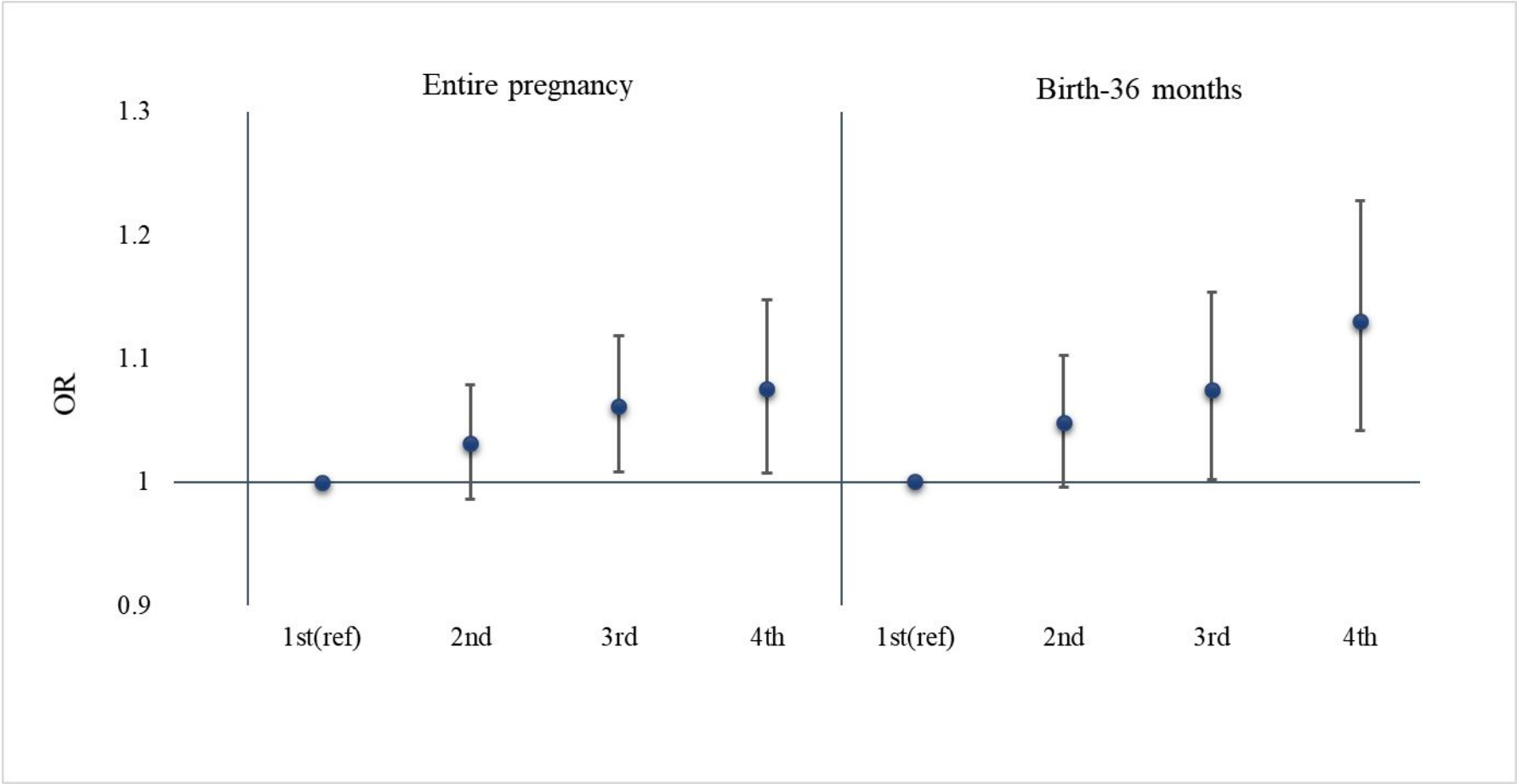

Figure 2 Adjusted odd ratios and 95% CI for sleep disturbances associated with the categorized $PM_{2.5}$ exposure levels during the entire pregnancy and birth to 36 months *. During the entire pregnancy, the $PM_{2.5}$ concentrations of the 1st, 2nd, 3rd, and 4th groups are < 48.6 μg/m^3, 48.6-55.3 μg/m^3, 55.3-62.7 μg/m^3, and > 62.7 μg/m^3, respectively. During birth to 36 months, the $PM_{2.5}$ concentrations of the 1st, 2nd, 3rd, and 4th groups

are < 42.4 μg/m^3, 42.4-50.2 μg/m^3, 50.2-58.3 μg/m^3, and > 58.3 μg/m^3, respectively.

* Adjusted for child sex, child age and BMIz at the time of survey, birth weight, PTB, delivery mode, NICU admission, exclusive breastfeeding for 6 months, maternal age at conception, maternal gravidity, medical conditions during pregnancy, maternal and paternal education, maternal employment, marital status, family structure, GDP, survey year, ambient temperature, relative humidity, and the random contribution of kindergarten.