



# Association of air pollution exposure during pregnancy and early childhood with children's cognitive performance and behavior at age six

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## ABSTRACT

**Background:** The impact of air pollution on neurodevelopment in children has attracted much attention in recent times. We aim to clarify the association between prenatal and postnatal air pollutant exposure and children's cognitive performance and behavior at age six.

**Methods:** This study was conducted based on a birth cohort study in Japan. Children's intelligence quotient (IQ) was assessed using the Wechsler Intelligence Scale for Children and a score <85 was deemed as low intelligence. A score ≥60 on the Child Behavior Checklist indicated behavioral problems. Exposure to outdoor fine particulate matter (PM<sub>2.5</sub>) during pregnancy and early childhood was estimated using a spatiotemporal model, while indoor concentrations of air pollutants inside subjects' homes were measured for a week when the child was of ages 1.5 and 3. The associations of exposure to air pollution during pregnancy and after childbirth with cognitive performance and behavior were analyzed using logistic regression models.

**Results:** The estimated exposure to outdoor PM<sub>2.5</sub> during pregnancy and early childhood was not associated with decreased cognitive performance. However, exposure during the first trimester, 0–1 and 3–5 years of age was associated with children's externalizing problems (odds ratios (ORs) were 2.77 [95% confidence interval (CI): 1.05–7.29], 1.66 [95%CI: 1.05–2.62], and 1.80 [95%CI: 1.19–2.74] per interquartile range (IQR) increase, respectively). Exposure to indoor PM<sub>2.5</sub> and coarse particles after childbirth was associated with lower full scale IQ (ORs were 1.46 [95%CI: 1.03–2.08] and 1.85 [95%CI: 1.12–3.07] per IQR increase, respectively). However, some inverse associations were also observed.

**Conclusions:** These results suggest associations between prenatal and postnatal exposure to outdoor air pollution and behavioral problems, and between indoor air pollution after childbirth and cognitive performance at age six. However, the effects of exposure to outdoor PM<sub>2.5</sub> during pregnancy on cognitive performance were not observed.

## 1. Introduction

With the increasing incidence of developmental disorders in children in recent years, several studies have begun to focus on the effects of exposure to air pollutants during pregnancy and early childbirth (Casatagna et al., 2022; Lin et al., 2022; Thompson et al., 2023). According to

the World Health Organization (WHO), air pollution can affect almost every organ in the body, and exposure to it increases the risk of cognitive impairment and neurological diseases (World Health Organization, 2021). Many epidemiological studies have examined how exposure to air pollutants during pregnancy and after childbirth affect children's cognitive performance. Notably, air pollutants such as particulate

**Abbreviations:** PM<sub>2.5</sub>, particulate matter with a diameter of 2.5 μm or less; PM<sub>10-2.5</sub>, particulate matter with a diameter between 2.5 and 10 μm; NO<sub>2</sub>, nitrogen dioxide; O<sub>3</sub>, ozone. Data are shown as odds ratios and 95% confidence intervals (CIs) for low intelligence (WISC-IV scores <85) or behavioral problems (CBCL scores ≥60), associated with interquartile range increases in each concentration; adjusted for the children's sex, mother's age; gestational age, birth weight; annual household income, mother's educational background; mother's smoking history, mother's drinking history; mother's autistic tendencies, older siblings of the child; child's history of passive smoking at 18 months of age, and child's birth season.

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matter with a diameter of 2.5  $\mu\text{m}$  or less ( $\text{PM}_{2.5}$ ) and nitrogen dioxide ( $\text{NO}_2$ ) can negatively impact children's neurodevelopmental skills (Castagna et al., 2022).

Although many studies have demonstrated the effects of air pollutant exposure during pregnancy and after childbirth on child development, its time-varying effects have been inconsistent (Chun et al., 2020). The CANDLE cohort in the United Kingdom reported that exposure to particulate matter with a diameter of 10  $\mu\text{m}$  or less ( $\text{PM}_{10}$ ) during pregnancy is associated with low intelligence quotient (IQ) in children between ages 4 and 6 (Loftus et al., 2019). A study in Iran found that children aged between 6 and 8 years living in areas with high levels of air pollution have low IQ (Seifi et al., 2022). Likewise, a birth cohort study conducted in Spain reported that exposure to outdoor  $\text{NO}_2$  during pregnancy and after childbirth impaired attention function in children aged between 4 and 5 years (Sentís et al., 2017). Prenatal and postnatal ozone ( $\text{O}_3$ ) exposure was also reported to be associated with developmental delay (Ha et al., 2019). Further, exposure to  $\text{PM}_{2.5}$  during pregnancy has been found to disrupt children's brain development between ages 6 and 14 through one or more common molecular pathways (Peterson et al., 2022). A study in the United States showed that exposure to  $\text{PM}_{2.5}$  during pregnancy is associated with behavioral problems in children between ages 4 and 6 (Ni et al., 2022). Exposure to  $\text{NO}_2$  during pregnancy was also reported to increase externalizing problems at age four (Loftus et al., 2020). Nevertheless, the association between the indoor environment and children's neurodevelopment has not been fully evaluated, although children spend a lot of time indoors (Midouhas et al., 2018).

In Japan, the association between early life exposure to indoor air pollutants and neurodevelopmental delays in 3-year-old children was studied using a questionnaire on children who participated in a nationwide birth cohort study, Japan Environment and Children's Study (JECS) (Madaniyazi et al., 2022). The findings suggested the associations of neurodevelopmental delays in 3-year-old children with exposure to indoor *m,p*-xylene and *o*-xylene; however, the associations with other indoor pollutants, including  $\text{PM}_{2.5}$ ,  $\text{NO}_2$ , and  $\text{O}_3$ , were not observed. Moreover, the associations between exposure to outdoor air pollution and children's neurodevelopment have not been evaluated in Japan. In this study, therefore, we aimed to clarify the effects of exposure to outdoor  $\text{PM}_{2.5}$  during pregnancy and early childhood on children's cognitive performance and behavioral problems at age six based on the JECS. Concentrations of outdoor  $\text{PM}_{2.5}$  from conception to when the child turned five were estimated by time period using a validated spatiotemporal model. We also explored the effects of exposure to indoor air pollutants after childbirth.

## 2. Method

This was an Adjunct Study of the JECS. The protocol of the JECS and the JECS Sub-Cohort Study and the baseline profiles of the participants have been described in other studies (Kawamoto et al., 2014; Michikawa et al., 2018; Sekiyama et al., 2022). Briefly, the JECS is an ongoing nationwide birth cohort study that recruited approximately 100,000 pregnant women across 15 regions in Japan between January 2011 and March 2014. The JECS Sub-Cohort Study was conducted with 5017 randomly selected participants who met the eligibility criteria and consented to participate in a face-to-face assessment of neuropsychiatric development, a pediatrician's examination, and clinical testing. The main eligibility criteria is that all the questionnaire data and medical records of children and their mothers were collected until they were 6 months of age. The characteristics of the participants in the JECS main cohort were confirmed to be similar to those from the general Japanese population (Michikawa et al., 2018). Additionally, the baseline profiles of the participants in the Sub-Cohort Study did not substantially differ from those of the main cohort (Sekiyama et al., 2022). The Hyogo Regional Center in Amagasaki City, Hyogo Prefecture, covers approximately 5000 participants of the main study and 251 participants of the

sub-cohort study. Amagasaki is an industrial city located in an urban district in west Japan. As of 2022, its land area is 50.7  $\text{km}^2$ , and the population is approximately 460,000.

We approached the 251 participants of the JECS Sub-Cohort Study that were covered by the Hyogo Regional Center to collect data on children's cognitive performance and behavior for our Adjunct Study. We targeted children aged between 5 years and 11 months and 6 years and 11 months between April 2019 and February 2021.

The study protocol was reviewed and approved by the Ethics Review Board of the Hyogo Medical University (approval number: 2999). Moreover, written informed consent was obtained from all caregivers.

### 2.1. Children's cognitive performance

Children's cognitive performance was assessed using the Japanese version of the Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV) (Ueno et al., 2010; Wechsler, 2003). To measure intelligence, we used the Full-Scale Intelligence Quotient (FSIQ) that comprises four indices: the Verbal Comprehension Index (VCI), Perceptual Reasoning Index (PRI), Working Memory Index (WMI), and Processing Speed Index (PSI). Deviation IQ was used for the absolute measurement of cognitive ability in an IQ test (Cohen and Swerdlik, 2018). The scores are considered to be normally distributed for all five categories, with a mean of 100 and a typical standard deviation of 15 (McGrath, 2011). As the scores were approximately normally distributed in this study, a score less than 85 (a standard deviation below the mean) was deemed as "low intelligence."

The WISC-IV was administered by two qualified Japanese clinical psychologists who had attended a workshop held by Nihon Bunka Kagakusha, the owner of the Japanese copyright to WISC-IV. They had received a certificate of completion indicating that they were proficient in the techniques required for administering the scale. Moreover, they administered the WISC-IV to several volunteer children before the main survey, and their techniques were confirmed to be similar. During the survey, the administrators examined each other's techniques one by one multiple times to minimize the effect of different administration techniques, if any, on subjects' responses.

### 2.2. Children's behavior

Children's behavior was assessed using the Child Behavior Checklist for ages 6–18 (CBCL/6–18) (Achenbach and Rescorla, 2001; Funabiki and Murai, 2017) that is administered to children and adolescents aged between 6 and 18 years. It involves caregivers reporting a wide range of emotional and behavioral problems in their children and is broadly used in both research and clinical settings. Caregivers rate 113 items on their child's behavior over the past six months with either Not True (0), Somewhat or Sometimes True (1), or Very True or Often True (2). The 113 items reflect nine behavioral problems: anxious/depressed, withdrawn/depressed, somatic complaints, social problems, thought problems, attention problems, rule breaking behavior, aggressive behavior, and other problems. Moreover, the checklist has three sub-scales: the internalizing scale (anxiety/depression, withdrawal/depression, and somatic complaints), the externalizing scale (rule breaking behavior and aggressive behavior), and the total problems scale (all nine behavioral problems). A score lower than 60, between 60 and 63, and 64 or more are defined as normal, borderline, and clinical scores, respectively, for all three scales (Funabiki and Murai, 2017). In this study, the scores were almost normally distributed, and a score of 60 or more indicated possible behavioral problems (borderline and clinical scores taken together) (Nolan et al., 1996). The validity and reliability of the cut-off score are documented to identify normal from deviant scores (Achenbach and Rescorla, 2001).

### 2.3. Exposure to outdoor and indoor pollutants

We calculated exposure to outdoor PM<sub>2.5</sub> during pregnancy and the first five years after childbirth with a machine learning-based spatio-temporal model developed based on various environmental factors including co-existing pollutant concentrations and meteorological parameters, as well as land use and traffic related variables. A random forest algorithm was employed to model the association between the daily PM<sub>2.5</sub> concentrations and various predictors. The model accurately predicted daily concentrations of PM<sub>2.5</sub> at a spatial resolution of 1 km × 1 km grid cells. The model exhibited high R<sup>2</sup> values of 0.91 and 0.92 for spatial and temporal cross-validation, respectively. Root mean squared errors were 2.3 and 2.2 µg/m<sup>3</sup>, respectively (Araki et al., 2022). To address any situation of a possible address change, we collected the residential addresses of the subjects from the time of the child's conception to it turning five years of age by the day, and geocoded them at 1 km × 1 km grid cells. Using the daily estimates of PM<sub>2.5</sub> concentration in each grid, we calculated the average concentrations of outdoor PM<sub>2.5</sub> for each trimester, the entire pregnancy, and 0–1, 1–3, and 3–5 years after childbirth.

To quantify the exposure to indoor air pollutants, we measured the concentrations of PM<sub>2.5</sub>, coarse particulate matter with a diameter between 2.5 and 10 µm (PM<sub>10-2.5</sub>), NO<sub>2</sub>, and O<sub>3</sub> in subjects' homes twice, when the child was 1.5 and 3 years old. The methods of their measurement have been described previously (Jung et al., 2021; Nishihama et al., 2021). In brief, each sampling period lasted approximately seven days, and particulate matter and gaseous pollutants were collected using active samplers (MP-Σ300NIIT, Sibata Scientific Technology, Soka, Japan) and diffusion passive samplers (DSD-TEA and DSD-BPE/DNPH, Sigma-Aldrich, Tokyo, Japan), respectively. In our analysis, we used the geometric mean concentrations at both ages.

### 2.4. Control variables

Based on the findings of previous studies that investigated air pollution and neurodevelopment (Castagna et al., 2022; Chun et al., 2020; Lin et al., 2022), we determined the control variables. The mother's age, child's sex, gestational age, and birth weight were included as control variables. Considering reports of the association between birth season or conception and children's development (Hebert et al., 2010; Lee et al., 2019), and the seasonal variations in the concentrations of air pollutants, such as PM<sub>2.5</sub> and O<sub>3</sub>, birth month was considered as a covariate. Data on these were obtained from the medical information recorded at the time of delivery. We also included the annual household income, mother's educational background, mother's smoking history, mother's drinking history, mother's autistic tendencies, older siblings of the child, and child's history of passive smoking at 18 months of age as the control variables. Mother's autistic tendency was measured by a Japanese version of the 10-item Autism-Spectrum Quotient (AQ-10-J) (Kurita et al., 2005) in the second or third trimester during pregnancy. Data on them were sourced from the J ECS dataset, "jecs-ta-20190,930-ver006," released in October 2019.

### 2.5. Statistical analysis

The demographic characteristics of children who had "low intelligence (WISC-IV scores less than 85)" and "behavioral problems (CBCL scores equal to or more than 60)" at age six were compared to that of other children. We controlled for the mother's age, mother's educational background, mother's smoking history, mother's drinking history, mother's autistic tendencies, gestational age, birth month, birth weight, annual household income, older siblings of the child, child's sex, and child's history of passive smoking at 18 months. We applied a multiple imputation with predictive mean matching for the missing values of potential confounders for all subjects with available data on the

exposures and outcomes. Then, logistic regression analyses were utilized to investigate the association of children's low intelligence and behavioral problems at age six with exposure to estimated concentrations of outdoor PM<sub>2.5</sub> during pregnancy and after childbirth. The results were presented as the odds ratios (ORs) and 95% confidence intervals (CIs) of the risk of having low intelligence or behavioral problems for an inter-quartile range (IQR) increase in estimated outdoor PM<sub>2.5</sub> concentration during each trimester, the entire pregnancy, and 0–1, 1–3, and 3–5 years after childbirth. In a similar manner, we analyzed the impact of exposure to indoor air pollutants after childbirth. The results were presented as the ORs and 95% CIs of the risk of having low intelligence or behavioral problems for an IQR increase in indoor particulate matter and gaseous pollutants (NO<sub>2</sub> and O<sub>3</sub>), respectively. For sensitivity analyses to evaluate the robustness of the results, we investigated the associations between air pollution exposure and outcomes using the models in which mother's autistic tendencies, gestational age, birth weight, and passive smoking were excluded from the covariates. Furthermore, sex-by-pollutants interactions were also considered to evaluate differences in the effects of air pollution by sex of the child. All statistical analyses were performed using the SPSS software version 27 (IBM Corp., Armonk, NY, USA) and a p-value <0.05 was considered significant.

## 3. Results

We received 195 (77.7%) and 201 (80.1%) valid responses on the WISC-IV and the CBCL, respectively. Table 1 presents the characteristics of the participants. Most mothers (73.1%) were 30 years old or older at the time of giving birth, and the gestational age of most (96%) was 37 weeks or more. In most cases (91%), the child weighed 2500 g or more at the time of birth.

Table 2 shows the average scores on the WISC-IV and CBCL and the percentage of children who crossed the cut-off score. The percentage of children with FSIQ score less than 85 was 14.9% (males 19.3% and females 8.6%). The percentages of lower scores in the categories other

**Table 1**  
Characteristics of the study participants (n = 201).

Characteristic	n (%)
Child's sex	
Male	118 (58.7)
Female	83 (41.3)
Mother's age	
<30	54 (26.9)
≥30	147 (73.1)
Gestational age	
<37 weeks	8 (4.0)
≥37 weeks	193 (96.0)
Birth weight	
<2500 g	18 (9.0)
≥2500 g	183 (91.0)
Annual household income	
<JPY 4,000,000	57 (28.4)
≥JPY 4,000,000	136 (67.7)
Missing	8 (4.0)
Mother's educational background, years	
<13	56 (27.9)
≥13	145 (72.1)
Mother's smoking history	
Nonsmoker	132 (65.7)
Ex-smoker/Smoker	65 (32.3)
Missing	4 (2.0)
Mother's drinking history	
No	62 (30.8)
Yes	137 (68.2)
Missing	2 (1.0)
Mother's autistic tendencies	
No	195 (97.0)
Yes	6 (3.0)
Older children living together	
No	88 (43.8)
Yes	113 (56.2)
Child's history of passive smoking at 18 months	
No	148 (73.6)
Yes	51 (25.4)
Missing	2 (1.0)
Birth month	
April–June	66 (32.8)
July–September	63 (31.3)
October–December	42 (20.9)
January–March	30 (14.9)

Mother's autistic tendencies were measured by a Japanese version of the 10-item Autism-Spectrum Quotient (AQ-10-J).

**Table 2**

Scores for cognitive performance and behavior at age six.

<b>a. Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV)</b>						
Category	Total (n=195)		Males (n=114)		Females (n=81)	
	Mean (SD)	<85, n (%)	Mean (SD)	<85, n (%)	Mean (SD)	<85, n (%)
Full Scale Intelligence Quotient (FSIQ)	96.3 (13.8)	29 (14.9)	93.9 (13.8)	22 (19.3)	99.6 (13.0)	7 (8.6)
Verbal Comprehension Index (VCI)	98.3 (13.4)	32 (16.4)	95.7 (13.3)	25 (21.9)	101.9 (12.9)	7 (8.6)
Perceptual Reasoning Index (PRI)	101.5 (15.1)	18 (9.2)	102.2 (15.1)	8 (7.0)	100.5 (15.1)	10 (12.3)
Working Memory Index (WMI)	88.4 (15.7)	65 (33.3)	86.3 (16.5)	43 (37.7)	91.3 (14.0)	22 (27.2)
Processing Speed Index (PSI)	96.4 (14.2)	38 (19.5)	92.6 (13.8)	30 (26.3)	101.6 (13.1)	8 (9.9)
<b>b. Child Behavior Checklist (CBCL)</b>						
Category	Total (n=201)		Males (n=118)		Females (n=83)	
	Mean (SD)	≥60, n (%)	Mean (SD)	≥60, n (%)	Mean (SD)	≥60, n (%)
Total problems	55.8 (8.7)	68 (33.8)	54.2 (9.3)	36 (30.5)	55.3 (7.8)	32 (38.6)
Internalizing	54.7 (8.7)	55 (27.4)	54.8 (9.1)	28 (23.7)	56.4 (9.4)	27 (32.5)
Externalizing	55.4 (9.3)	71 (35.3)	55.4 (8.7)	41 (34.7)	56.4 (8.7)	30 (36.1)

than the PRI in the WISC-IV were higher in males than in females. As to the CBCL, the percentages of children who scored 60 or more in all categories were higher in females (38.6%) than in males (7.8%).

Table 3 presents the estimated concentrations of outdoor PM<sub>2.5</sub> during pregnancy and early childhood and the geometric mean concentrations of indoor air pollutants at ages 1.5 and 3 after childbirth. On average, the estimated concentration of outdoor PM<sub>2.5</sub> during entire pregnancy was 15.1 µg/m<sup>3</sup>. Meanwhile, the geometric mean concentration of indoor PM<sub>2.5</sub> at 1.5 and 3 years was 15.3 µg/m<sup>3</sup>. The correlation coefficients among the estimated concentrations of outdoor PM<sub>2.5</sub> and the geometric mean concentrations of indoor air pollutants are as shown in Table S1. PM<sub>2.5</sub> concentrations were found to be highly correlated for each period in early childhood. Although the concentrations during entire pregnancy were correlated with those during the first and second trimesters, there were less correlated among different

trimesters of pregnancy.

Table 4 shows the results of the logistic regression analysis on the association between the estimated exposure to outdoor PM<sub>2.5</sub> during pregnancy and early childhood and children's cognitive performance and behavior at age six. In the second trimester, the risk of a lower WMI decreased in association with the estimated exposure to PM<sub>2.5</sub> (OR: 0.34 [95%CI: 0.15–0.76] per IQR increase). Except for this, no significant association was found between the estimated exposure and the five indices of the WISC-IV. Regarding children's behavioral problems, the risks of total problems decreased in association with the estimated exposure during the entire pregnancy and the third trimester (OR: 0.51 [95%CI: 0.27–0.95] and OR: 0.26 [95%CI: 0.10–0.68] per IQR increase, respectively). Risks of externalizing problems increased in association with the estimated exposure during the first trimester and 0–1 and 3–5 years after childbirth (OR: 2.77 [95%CI: 1.05–7.29], OR: 1.66 [95%CI: 1.05–2.62], and OR: 1.80 [95%CI: 1.19–2.74] per IQR increase, respectively). Internalizing problems were not significantly associated with the estimated exposure during pregnancy or after childbirth.

Table 5 shows the results of logistic regression analysis on the association between exposure to indoor air pollutants after childbirth and children's cognitive performance and behavior at age six. Exposure to high concentrations of indoor PM<sub>2.5</sub> and PM<sub>10-2.5</sub> significantly increased risks of low FSIQ (OR: 1.46 [95%CI: 1.03–2.08] and OR: 1.85 [95%CI: 1.12–3.07] per IQR increase, respectively). Indoor concentration of PM<sub>10-2.5</sub> was also associated with low VCI (OR: 1.88 [95%CI: 1.13–3.11]). Moreover, high indoor concentration of NO<sub>2</sub> increased the risk of lower PRI, but decreased the risk of lower PSI (OR: 1.40 [95%CI: 1.02–1.91] and OR: 0.93 [95%CI: 0.64–0.98] per IQR increase, respectively). In contrast, high concentration of indoor NO<sub>2</sub> decreased the risk of internalizing problems of the CBCL (OR: 0.70 [95%CI: 0.50–0.98]).

These results were almost the same in the sensitivity analyses wherein covariates were limited (Tables S2 and S3). Although the estimated exposures to PM<sub>2.5</sub> in early childhood were prominently associated with externalizing problems in females, there were no significant interactions. There were only significant interactions with sex for the estimated PM<sub>2.5</sub> in the second and third trimesters on externalizing problems and low PSI, respectively (Table S4). The associations between exposure to indoor air pollutants after childbirth and lower scores in some categories in the WISC-IV were observed in both males and females. Only an interaction with sex was significant for indoor O<sub>3</sub> and low VCI (Table S5).

**Table 3**Distributions of the estimated concentrations of outdoor PM<sub>2.5</sub> during pregnancy and early childhood and the geometric mean concentrations of indoor air pollutants at 1.5 and 3 years of age.

	n	Mean (SD)	Minimum	25th percentile	50th percentile	75th percentile	Maximum	IQR
Estimated concentrations of outdoor PM <sub>2.5</sub> (µg/m <sup>3</sup> )								
During pregnancy								
Entire pregnancy	199	15.1 (1.0)	12.8	14.4	15.1	15.8	17.5	1.4
The first trimester	199	14.3 (2.5)	10.2	12.1	14.0	16.7	19.4	4.6
The second trimester	199	15.5 (2.1)	11.2	13.8	16.0	17.1	20.3	3.3
The third trimester	199	15.6 (2.5)	9.8	13.3	15.9	17.7	20.5	4.4
In early childhood								
0–1 year	199	14.5 (0.9)	12.2	13.9	14.5	15.2	16.7	1.3
1–3 years	197	13.2 (0.7)	11.9	12.8	13.1	13.6	15.1	0.8
3–5 years	197	12.6 (0.6)	11.3	12.2	12.5	12.9	14.2	0.7
Geometric mean concentrations of indoor air pollutants at 1.5 and 3 years of age								
PM <sub>2.5</sub> (µg/m <sup>3</sup> )	194	15.3 (7.2)	5.2	11.3	13.9	16.9	60.6	5.6
PM <sub>10-2.5</sub> (µg/m <sup>3</sup> )	196	9.2 (3.1)	2.6	7.2	8.8	10.7	21.4	3.5
NO <sub>2</sub> (ppb)	196	18.5 (13.4)	5.4	10.7	14.6	20.9	124.1	10.2
O <sub>3</sub> (ppb)	195	2.8 (1.6)	0.8	1.6	2.5	3.5	13.3	1.9

Abbreviations: IQR, interquartile range; PM<sub>2.5</sub>, particulate matter with a diameter of 2.5 µm or less; PM<sub>10-2.5</sub>, particulate matter with a diameter between 2.5 and 10 µm; NO<sub>2</sub>, nitrogen dioxide; O<sub>3</sub>, ozone.

**Table 4**Association of estimated concentrations of outdoor PM<sub>2.5</sub> during pregnancy and early childhood with cognitive performance and behavior at age six.

<b>a. Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV)</b>					
	Full Scale Intelligence Quotient (FSIQ)	Verbal Comprehension Index (VCI)	Perceptual Reasoning Index (PRI)	Working Memory Index (WMI)	Processing Speed Index (PSI)
	Odds ratios (95%CI)	Odds ratios (95%CI)	Odds ratios (95%CI)	Odds ratios (95%CI)	Odds ratios (95%CI)
During pregnancy					
Entire pregnancy	0.66 (0.30–1.45)	0.91 (0.43–1.95)	0.42 (0.14–1.22)	0.75 (0.42–1.35)	0.96 (0.47–1.96)
The first trimester	0.62 (0.16–2.38)	0.36 (0.09–1.42)	0.20 (0.03–1.36)	1.31 (0.47–3.62)	0.49 (0.13–1.80)
The second trimester	0.57 (0.19–1.74)	1.06 (0.40–2.78)	1.40 (0.40–4.88)	0.34 (0.15–0.76)	1.44 (0.52–4.01)
The third trimester	1.11 (0.33–3.71)	2.37 (0.70–8.03)	0.36 (0.07–1.95)	1.35 (0.55–3.28)	1.21 (0.38–3.80)
In early childhood					
0–1 year	1.00 (0.54–1.82)	1.17 (0.66–2.08)	1.09 (0.48–2.49)	0.98 (0.61–1.58)	1.52 (0.86–2.69)
1–3 years	1.02 (0.61–1.72)	1.24 (0.76–2.02)	1.08 (0.58–2.02)	0.86 (0.58–1.28)	1.36 (0.84–2.22)
3–5 years	0.79 (0.44–1.43)	1.10 (0.63–1.91)	0.90 (0.43–1.86)	0.74 (0.48–1.15)	0.86 (0.49–1.51)
<b>b. Child Behavior Checklist (CBCL)</b>					
	Total problems	Internalizing	Externalizing		
	Odds ratios (95%CI)	Odds ratios (95%CI)	Odds ratios (95%CI)		
During pregnancy					
Entire pregnancy	0.51 (0.27–0.95)	0.65 (0.35–1.21)	0.98 (0.57–1.71)		
The first trimester	1.21 (0.43–3.42)	1.00 (0.35–2.88)	2.77 (1.05–7.29)		
The second trimester	0.58 (0.25–1.31)	0.69 (0.30–1.57)	0.86 (0.41–1.82)		
The third trimester	0.26 (0.10–0.68)	0.48 (0.19–1.24)	0.42 (0.18–1.02)		
In early childhood					
0–1 year	1.28 (0.80–2.05)	1.34 (0.83–2.18)	1.66 (1.05–2.62)		
1–3 years	0.98 (0.65–1.46)	0.94 (0.62–1.41)	1.44 (0.99–2.11)		
3–5 years	1.11 (0.72–1.70)	1.02 (0.60–1.59)	1.80 (1.19–2.74)		

Data are shown as odds ratios and 95% confidence intervals (CIs) for low intelligence (WISC-IV scores <85) or behavioral problems (CBCL scores ≥60), associated with interquartile range increases in each concentration, adjusted for the children's sex, mother's age, gestational age, birth weight, annual household income, mother's educational background, mother's smoking history, mother's drinking history, mother's autistic tendencies, older siblings of the child, child's history of passive smoking at 18 months of age, and child's birth season.

Mother's autistic tendencies were measured by a Japanese version of the 10-item Autism-Spectrum Quotient (AQ-10-J).

**Table 5**

Association of geometric mean concentrations of indoor air pollutants at 1.5 and 3 years of age with cognitive performance and behavior at age six.

<b>a. Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV)</b>					
	Full Scale Intelligence Quotient (FSIQ)	Verbal Comprehension Index (VCI)	Perceptual Reasoning Index (PRI)	Working Memory Index (WMI)	Processing Speed Index (PSI)
	Odds ratios (95%CI)	Odds ratios (95%CI)	Odds ratios (95%CI)	Odds ratios (95%CI)	Odds ratios (95%CI)
PM <sub>2.5</sub>	1.46 (1.03–2.08)	1.17 (0.84–1.63)	1.31 (0.88–1.94)	1.09 (0.83–1.42)	1.04 (0.70–1.54)
PM <sub>10–2.5</sub>	1.85 (1.12–3.07)	1.88 (1.13–3.11)	1.56 (0.84–2.88)	1.15 (0.77–1.71)	1.46 (0.87–2.43)
NO <sub>2</sub>	1.19 (0.89–1.59)	1.00 (0.69–1.45)	1.40 (1.02–1.91)	1.06 (0.83–1.35)	0.93 (0.64–0.98)
O <sub>3</sub>	1.10 (0.63–1.91)	1.58 (0.98–2.55)	1.03 (0.55–1.91)	1.05 (0.71–1.55)	0.99 (0.58–1.42)
<b>b. Child Behavior Checklist (CBCL)</b>					
	Total problems	Internalizing	Externalizing		
	Odds ratios (95%CI)	Odds ratios (95%CI)	Odds ratios (95%CI)		
PM <sub>2.5</sub>	0.84 (0.62–1.14)	0.75 (0.53–1.04)	0.76 (0.55–1.03)		
PM <sub>10–2.5</sub>	1.34 (0.90–1.99)	1.18 (0.80–1.75)	1.05 (0.72–1.52)		
NO <sub>2</sub>	0.83 (0.64–1.07)	0.70 (0.50–0.98)	0.87 (0.68–1.13)		
O <sub>3</sub>	1.25 (0.85–1.85)	0.93 (0.61–1.42)	1.21 (0.84–1.74)		

Abbreviations PM<sub>2.5</sub>, particulate matter with a diameter of 2.5 μm or less; PM<sub>10–2.5</sub>, particulate matter with a diameter between 2.5 and 10 μm; NO<sub>2</sub>, nitrogen dioxide; O<sub>3</sub>, ozone.

Data are shown as odds ratios and 95% confidence intervals (CIs) for low intelligence (WISC-IV scores <85) or behavioral problems (CBCL scores ≥60), associated with interquartile range increases in each concentration, adjusted for the children's sex, mother's age, gestational age, birth weight, annual household income, mother's educational background, mother's smoking history, mother's drinking history, mother's autistic tendencies, older siblings of the child, child's history of passive smoking at 18 months of age, and child's birth season.

Mother's autistic tendencies were measured by a Japanese version of the 10-item Autism-Spectrum Quotient (AQ-10-J).

#### 4. Discussion

We investigated the association of exposure to air pollutants by time period during pregnancy and early childhood with children's cognitive performance and behavior at age six, based on a birth cohort study. We

found no association between estimated exposure to outdoor PM<sub>2.5</sub> during pregnancy and after childbirth and low intelligence, except for the negative association between outdoor PM<sub>2.5</sub> in the second trimester and low WMI. As for children's behavioral problems, estimated exposures to outdoor PM<sub>2.5</sub> in some periods during pregnancy and after

childbirth were associated with externalizing problems. In contrast, higher exposure to indoor PM<sub>2.5</sub> after childbirth was associated with low FSIQ. Further, the associations between exposure to indoor PM<sub>10-2.5</sub> and FSIQ and VCI were also observed. Exposure to indoor NO<sub>2</sub> was positively associated with low PRI, but negatively associated with low PSI and internalizing problems. Thus, association between exposure to air pollutants and cognitive or behavior abilities was inconsistent.

Many studies have reported that prenatal and postnatal exposure to air pollutants, including PM<sub>2.5</sub>, causes neurodevelopmental delays in children. For instance, a birth cohort study in China revealed that exposure to PM<sub>2.5</sub> during preconception and the first trimester is associated with neurodevelopmental delay in offspring at 24 months of age (Li et al., 2021). Cohort studies in other countries have also shown that exposure to air pollutants, including PM<sub>2.5</sub>, PM<sub>10</sub>, and NO<sub>2</sub>, during pregnancy causes neurodevelopmental delays in early childhood (Ha et al., 2019; Hurtado-Díaz et al., 2021; Kim et al., 2014). While Ni et al. (2022) reported that high exposure to PM<sub>2.5</sub> after childbirth is associated with low IQ between ages 4 and 6, they found no significant association between exposure to PM<sub>2.5</sub> during pregnancy and children's cognitive performance. A British study found that outdoor and indoor air quality in early childhood is associated with children's cognitive abilities (Midouhas et al., 2018). A recent birth cohort study in the Netherlands observed no association between exposure to air pollution during childhood and lower cognitive function or behavioral problems (Kusters et al., 2022). In the present study, we found that exposure to outdoor PM<sub>2.5</sub> during pregnancy or after childbirth was not associated with low cognitive performance in children at age six, consistent with Kusters et al. (2022). However, our finding on the association between outdoor PM<sub>2.5</sub> and the risk of externalizing problems seemed inconsistent.

Studies have shown that children's behavioral problems are associated with exposure to air pollutants during pregnancy or after childbirth. Ni et al. (2022) found that prenatal and postnatal exposure to PM<sub>2.5</sub> and NO<sub>2</sub> is associated with children's behavioral problems between ages 4 and 6. Exposure to high levels of NO<sub>2</sub> during pregnancy has also been reported to increase externalizing problems at age four (Loftus et al., 2020). Six European cohort studies reported an association between exposure to pollutants caused by heavy traffic during pregnancy and behavioral problems in children (Maitre et al., 2021). Studies in other countries have also shown that exposure to PM<sub>2.5</sub> during pregnancy or early childhood is associated with behavioral problems in children (Bansal et al., 2021; Rivas et al., 2019). In our study, exposure to the estimated concentrations of outdoor PM<sub>2.5</sub> in the first trimester and after childbirth was found to be associated with externalizing problems. This result is in line with findings from previous studies (Ni et al., 2022; Bansal et al., 2021; Rivas et al., 2019). In contrast, the meta-analysis of eight European birth cohort studies suggested that overall prenatal and postnatal exposure to PM<sub>2.5</sub> is not associated with behavioral problems in children, but a higher odds ratio for aggressive symptoms was observed in only one region of the studies (Jorcano et al., 2019). Thus, no consistent association has been reported between prenatal and postnatal exposure to air pollution and behavioral problems in children. This inconsistency may be due to differences in exposure assessments and lifestyle characteristics.

Aggressive behavior, an externalizing problem in the CBCL, and erratic behaviors are associated with the defiance induced by untreated attention deficit hyperactivity disorder (ADHD) (Biederman et al., 2021). Many studies have suggested a link between exposure to air pollutants, such as PM<sub>2.5</sub>, and ADHD (Aghaei et al., 2019). A cohort study that used brain magnetic resonance imaging (MRI) showed that exposure to PM<sub>2.5</sub> during pregnancy decreases the white matter surface area in the brain of children aged between 6 and 14, suggesting that the exposure leads to lower processing speed and behavioral disorders (Peterson et al., 2015). Similarly, a birth cohort in Netherlands, in which children aged between 6 and 10 years underwent MRI, showed that prenatal exposure to PM<sub>2.5</sub> alters brain structure and causes a decline in

cognitive function through inhibitory regulation (Lubczyńska et al., 2021). Thus, exposure to PM<sub>2.5</sub> may affect the brain area responsible for extroverted functions, such as aggressive and irregular behavior in children.

Several studies have shown the association between indoor air pollution after childbirth and neurodevelopment in children. However, most of them evaluated exposure to indoor air pollution using questionnaires, for instance, on passive smoking and air purifier use (Brabhukumr et al., 2020; Midouhas et al., 2018). Only a few have objectively measured the concentrations of indoor air pollutants. A European birth cohort study measured indoor PM<sub>2.5</sub> for 24 h over two seasons and showed that exposure to PM<sub>2.5</sub> and passive smoking is associated with cognitive function decline in children aged between ages 6 and 11 (Julvez et al., 2021). In this study, we measured the concentrations of indoor air pollutants, such as PM<sub>2.5</sub>, PM<sub>10</sub>, and NO<sub>2</sub>, in the subjects' homes at ages 1.5 and 3 of the children and on examining their associations with children's cognitive performance and behavior, found that these indoor air pollutants were associated with the former, that is, children's cognitive performance. These results suggest improving the indoor environment for the neurodevelopment of children who spend a lot of time indoors.

The main strength of this study is that it estimates exposure to outdoor PM<sub>2.5</sub> from conception to the time the child turns five using the daily PM<sub>2.5</sub> concentration at each subject's home address and examines its long-term effect on children's cognitive performance and behavior at age six. In Japan, airborne PM<sub>2.5</sub> concentrations vary by the season, high in winter and spring and relatively low in summer and fall, and the degree of exposure to PM<sub>2.5</sub> during pregnancy may differ depending on the time of conception or birth. Additionally, the association between birth season and children's development has also been reported (Hebert et al., 2010; Lee et al., 2019). Therefore, we examined the association between the estimated exposure to PM<sub>2.5</sub> and children's cognitive performance and behavior after adjusting for the birth season. This study also measured the concentration of indoor air pollutants during early childhood. Even though children spend a lot of time indoors, few studies have investigated the association between the indoor environment and children's neurodevelopment by measuring the concentrations of indoor air pollutants (Midouhas et al., 2018). Therefore, our study is significant in that we could identify an association between the indoor environment and children's cognitive performance based on the concentrations of indoor air pollutants measured in the children's homes.

However, this study has some limitations. First, most of the subjects lived in one city since we targeted only those participants of the JECS Sub-Cohort who were covered by the Hyogo Regional Center. Since the sample size was small, it may lead to insufficient statistical detection power. Although the concentrations of outdoor PM<sub>2.5</sub> vary depending on the season and region, the difference in their concentrations was small. For some associations between outdoor PM<sub>2.5</sub> during pregnancy and risks of cognitive performance and behavior, very low ORs were observed which may be due to a possible small sample bias. Moreover, we estimated the concentration of only PM<sub>2.5</sub> as an outdoor air pollutant. Other major air pollutants should also be considered; however, the concentrations of outdoor NO<sub>2</sub> and sulfur dioxide (SO<sub>2</sub>) were very low in the study area, as seen from the results of air monitoring (Ministry of the Environment Japan, 2020). Since O<sub>3</sub> is a broad-area pollutant, little difference was observed in its concentration in the study area, although the concentrations show seasonal variation. In this study, we measured indoor O<sub>3</sub> concentrations to evaluate the effects of using certain electronic equipment including air purifiers (Yoda et al., 2020), but the concentrations were very low. In a future study, we plan to conduct tests on the cognitive performance of the JECS participants from 15 areas across Japan. Since the concentrations of air pollutants will vary based on the area, we will be able to investigate the association between exposure to air pollution and children's cognitive performance and behavior more effectively. Second, we measured the concentrations of indoor air pollutants for only a week when the child was 1.5 and 3

years old. Since these measurements were conducted in different seasons, we used the mean values in the two periods to minimize the effect of seasonal differences. Third, we did not measure the concentrations of indoor air pollutants during pregnancy, because the subjects of the JECS Sub-Cohort Study were recruited after childbirth from the participants of the Main Study. Since pregnant women spend considerable time indoors, indoor air pollution during pregnancy may affect children's development. A recent study reported that prenatal indoor air pollution adversely affects neurodevelopment and behavior (Gonzalez-Casanova et al., 2018; Christensen et al., 2022). A study conducted in Mongolia found that decreasing PM<sub>2.5</sub> by using an air purifier during pregnancy improves children's cognitive performance (Ulziikhuu et al., 2022). Therefore, it is necessary to examine the association between exposure to indoor air pollutants during pregnancy and children's neurodevelopment. Fourth, we estimated exposure to outdoor PM<sub>2.5</sub> in many periods during pregnancy and early childhood and analyzed the association with many scores in cognitive performance and behavior, raising the possibility of multiple testing. We did not counter the potential problem, but the results should be considered important in accordance with the precautionary principle. Finally, paternal characteristics were not considered in this study. Studies have reported the association of paternal age with neurodevelopment and behavioral impairment (Zweifel and Woodward, 2022). However, fathers' detailed information was available for only less than half of the participants in the JECS. Future studies should consider paternal characteristics, including their age and educational level.

## 5. Conclusion

This study shows the association between exposure to air pollution during pregnancy and after childbirth and children's cognitive performance and behavior at age six. No association was found between outdoor exposure to PM<sub>2.5</sub> during pregnancy or after childbirth and children's cognitive performance. However, exposure to indoor concentrations of PM<sub>2.5</sub>, PM<sub>10-2.5</sub>, and NO<sub>2</sub> after childbirth was found to be associated with decreased cognitive performance in children. Furthermore, exposure to the estimated concentrations of outdoor PM<sub>2.5</sub> during the first trimester, first year, and three to five years after childbirth was associated with externalizing problems in children; however, some inverse associations with other scores have also been observed. These results suggest that it is necessary to improve not only the outdoor air environment but also the indoor air environment for healthy neurodevelopment in children.

## Credit author statement

Narumi Tokuda: Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Writing – original draft. Rina Ishikawa: Methodology, Investigation, Data curation. Yoshiko Yoda: Methodology, Investigation, Data curation, Visualization. Shin Araki: Methodology, Software, Investigation, Data curation. Hikari Shimadera: Methodology, Software, Investigation, Supervision, Funding acquisition. Masayuki Shima: Conceptualization, Methodology, Supervision, Project administration, Writing- Reviewing and Editing, Funding acquisition. All authors read and approved the final manuscript.

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## Institutional review board statement

This study design was approved by the Ethics Review Board of the Hyogo Medical University (Approval number: 2999). Written informed consent was obtained from all caregivers.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

Data will be made available on request.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envres.2023.116733>.

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