

Prenatal Exposure to Traffic-related Air Pollution and Child Behavioral Development Milestone Delays in Japan

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Background: Recent studies suggest that prenatal exposure to outdoor air pollution is associated with unfavorable neurodevelopment in children. We examined associations between prenatal exposure to traffic-related air pollution and child behavioral development milestone delays, using data from a nationwide population-based longitudinal survey in Japan, where the participants were recruited in 2001 and followed.

Methods: Particulate matter, nitrogen dioxide, and sulfur dioxide concentrations during the 9 months before birth were obtained at the municipality level and assigned to the participants who were born in the corresponding municipality. We analyzed data from singleton births with linked pollution data available ($N = 33,911$ at the maximum). We used responses to survey questions about age-appropriate behaviors at ages 2.5 and 5.5 years as indicators of behavioral development. We conducted multilevel logistic regression analysis, adjusting for individual and municipality-level variables.

Results: Air pollution exposure during gestation was positively associated with the risk of some developmental milestone delays at both ages. Specifically, air pollution was associated with verbal and fine motor development at age 2.5 years, and with behaviors related to inhibition and impulsivity at 5.5 years. In the fully-adjusted models,

odds ratios following one-interquartile-range increase in nitrogen dioxide and suspended particulate matter were 1.24 (95% confidence interval: 1.07, 1.43) for inability to compose a two-phrase sentence at ages 2.5 and 1.10 (1.05, 1.16) for inability to express emotions at age 5.5 years, respectively.

Conclusions: Prenatal exposure to traffic-related air pollution was associated with behavioral development milestone delays of children in a nationally representative sample in Japan.

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Systematic reviews consistently suggest that prenatal exposure to ambient air pollution is associated with adverse birth outcomes.^{1–3} Recently, further evidence has been accumulating on the associations between prenatal exposure to ambient air pollution and neurodevelopmental outcome.^{4,5} This is plausible considering that the developing human brain is vulnerable to toxic chemical exposure, in particular in utero.⁶

Several epidemiologic studies have shown associations of prenatal ambient air pollution exposure with neurodevelopmental outcomes. Five studies have suggested negative associations between prenatal polycyclic aromatic hydrocarbon (PAH) exposure and several cognitive functions (e.g., motor, verbal, and mental development).^{7–11} One study from Spain has shown that prenatal exposure to nitrogen dioxide (NO_2) or benzene was associated with increased risk of unfavorable mental development only among infants whose mothers reported low intakes of fruits/vegetables during pregnancy.¹² An international collaborative study from Europe has shown negative associations of prenatal exposure to NO_2 with psychomotor development, but not on general cognition or language development.¹³ One study in Korea also suggested the potential negative associations between exposure to particulate matter (PM) and NO_2 and mental or psychomotor development at 6 months, but not at 12 or 24 months.¹⁴ Because associations between prenatal exposure to ambient air pollution and child neurodevelopment are not consistent, air pollution exposure still remains categorized as a “suspected” developmental neurotoxicant, according to a recent review.⁶

To provide further evidence regarding this issue, we examined the association of prenatal exposure to traffic-related

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air pollution with child behavioral development milestone delays, using data from a nationwide population-based longitudinal survey in Japan, where the participants were recruited in 2001 and followed. Previous studies have included a relatively small sample and were conducted in geographically distinct areas. The large and geographically representative sample in this study will provide further insight into this topic.

METHODS

Participants

The Japanese Ministry of Health, Labour, and Welfare has implemented a nationally representative longitudinal survey to follow babies born between January 10 and 17 or July 10 and 17, 2001, throughout the country. Roughly one-twentieth of babies born in 2001 in Japan are enrolled in the survey. The survey is known as the Longitudinal Survey of Babies in the 21st century and is described elsewhere in detail.^{15,16} When surveyed newborns were 6 months old, baseline questionnaires were sent to all families. Of the 53,575 questionnaires mailed, 47,015 were completed and returned (88% response rate). Every year (at 18, 30, 42, 54, 66 months, and so on), follow-up questionnaires are sent to all participants who initially responded. Currently, the 13th survey (in 2014) has been completed. Birth record data from Japanese vital statistics are linked to each child in this survey. Birth record data include weight, gestational age, singleton or twin or other multiple births, sex, parity, and parental age.

Among the 47,015 participants in the nationwide survey, we restricted participants in this study to singleton births. This led to exclusion of 976 children, leaving 46,039 participants in the analysis.

Air Pollution Data

In this study, we focused on municipality-level traffic-related air pollution during pregnancy as the main exposure variable.¹⁷ We considered exposure of pregnant mothers to air pollution during the 9 months before giving birth as prenatal exposure to air pollution. Because participants were born between January 10 and 17 or July 10 and 17, 2001, we considered prenatal air pollution exposure to be relevant between April 2000 and December 2000 for participants born in January 2001 and between October 2000 and June 2001 for participants born in July 2001.

With respect to traffic-related air pollution data,¹⁸ we first obtained monthly concentrations of suspended PM, NO₂, sulfur dioxide (SO₂), and carbon monoxide (CO) measured at all general monitoring stations throughout Japan during the study period, from the environmental database managed by the National Institute for Environmental Studies in Japan. In Japan, suspended PM is measured for PM and accounts for PM with aerodynamic diameter less than 7 µm (PM₇). We have two types of monitoring stations throughout Japan based on Air Pollution Control Act: general and roadside stations. General stations should be located at places where they are

not affected by specific sources of air pollutants, such as elementary schools, municipal offices, and community centers, whereas roadside stations should be located next to or close to roads in places where people live. We considered that air pollution concentrations measured at the general stations were relevant.

We then calculated municipality-representative monthly average concentrations of each air pollutant from monthly concentrations at each monitoring station in each municipality. Subsequently, we calculated average concentrations of each air pollutant during gestation of study participants for each municipality. We used only those sampling stations at which each air pollutant was measured throughout the entire 9 months of each exposure period. There were 3,368 municipalities throughout Japan according to the 2000 national census, and we were able to obtain air pollution information from more than 700 municipalities for suspended PM, NO₂, and SO₂ (Table 1). Most municipalities from which we were unable to obtain air pollutant information were small towns or villages. Because CO is measured mainly at roadside stations (not at general stations) in many municipalities, and the number of municipalities where CO information was available was considerably small compared with other pollutants (e.g., only 118 municipalities had CO data available from April 2000 to December 2000), we did not further consider exposure to CO in this study. The median size of municipalities with available data for the remaining three pollutants ranged from 65.9 to 69.6 km². Mean air pollution concentrations in total or separated by municipalities are shown in Table 1 or in the eFigure 1 (<http://links.lww.com/EDE/A954>). We also show number of monitoring stations per municipality as well as correlations between size of municipalities and number of the stations. The number of monitoring stations tended to increase depending on the size of the municipality. During both exposure periods, suspended PM was moderately correlated with NO₂ and SO₂.

Finally, we assigned air pollution exposure (suspended PM, NO₂, and SO₂) in each municipality to participants who were born in the corresponding municipality. The municipality at birth for each participant was obtained from the birth record. Among the 46,039 eligible infants, we could assign suspended PM exposure to 33,911 participants, NO₂ exposure to 33,890 infants, and SO₂ exposure to 31,679 infants.

Behavioral Development Milestone Delays

For behavioral development milestone delays, we included answers to questions from the nationwide survey asking whether children were behaving age-appropriately at ages 2.5 and 5.5 years. The parents answered these questions by a “yes” or “no” category.

At 2.5 years old, the following questions were asked: (1) Can your child walk? (2) Can your child run? (3) Can your child climb stairs? (4) Can your child say things that make sense? (5) Can your child compose two-phrase sentences? (6) Can your child say his or her own name? (7) Can your

TABLE 1. Number of Municipalities Monitored, Municipality Size, and Air Pollution Exposure Information in Each Municipality (Mean Values, Number of Monitoring Stations, and Estimated Pearson Correlation Coefficients)

	No of Municipalities Monitored	Size of Municipalities (km ²)	Mean Concentrations Per Municipality ± SD	Mean (Min, Max) Monitoring Stations Per Municipality	Pearson Correlation Coefficients Between Size of Municipality and Number of Monitoring Stations	Pearson Correlation Coefficients of Pollutants		
		Median (Min, Max)				Suspended PM	NO ₂	SO ₂
Exposure during pregnancy for newborns born in January 2001 (April 2000–December 2000)								
Suspended PM ^a (μg/m ³)	812	65.9 (4.6, 1,231.1)	32±8.6	2.0 (1, 15)	0.33	1		
NO ₂ (ppb)	811	65.2 (4.6, 1,231.1)	16±7.4	1.9 (1, 13)	0.37	0.65	1	
SO ₂ (ppb)	758	69.6 (4.6, 1,231.1)	4.7±1.9	2.1 (1, 19)	0.41	0.47	0.55	1
Exposure during pregnancy for newborns born in July 2001 (October 2000–June 2001)								
Suspended PM ^a (μg/m ³)	803	66.4 (4.6, 1,231.1)	30±8.2	2.0 (1, 15)	0.33	1		
NO ₂ (ppb)	806	65.9 (4.6, 1,231.1)	18±8.0	1.9 (1, 13)	0.37	0.69	1	
SO ₂ (ppb)	750	69.6 (4.6, 1,231.1)	4.8±1.9	2.1 (1, 19)	0.41	0.51	0.57	1

^aSuspended PM accounts for PM with aerodynamic diameter less than 7 μm (PM₇).
SD indicates standard deviation.

child use a spoon to eat? These items are related to motor and verbal developments. The Ministry of Health, Labor, and Welfare extracted these items from the Maternal and Child Health Handbook. The Handbook (“boshi kenkou techyou”) is a record of health and child development given to every pregnant mother in Japan under Maternal and Child Health Act. We did not include survey questions addressing behaviors that seemed heavily dependent upon parenting practices.

At age 5.5 years, the following questions were asked on the nationwide survey: (1) Can your child listen without fidgeting? (2) Can your child focus on one task? (3) Does your child remain patient? (4) Can your child express emotions appropriately? (5) Can your child get along with others in a group setting? (6) Can your child keep promises? These items are related to behaviors like attention, self-regulation, and socially appropriate behavior. According to the Ministry of Health, Labor, and Welfare, these survey questions were developed to capture early signs of behavioral and developmental problems.

Although we could not confirm whether these questions (at both ages) have been validated or selected from an established scale, these items were used in previous studies, which suggested associations of shorter gestational age or shorter breastfeeding duration with milestone delays.^{16,19}

Statistical Analysis

In all analyses, we conducted multilevel logistic regression analysis to evaluate the relationships between prenatal air pollution exposure and behavioral development milestone delays, considering that participants were nested in each municipality. We used pollutant exposure data as continuous variables, based on previous studies^{13,14} and estimated the adjusted odds ratios (ORs) for an interquartile range (IQR) increase in each air pollutant during the study periods. Because distributions of each exposure did not deviate from

normality, we did not transform the exposure variables in the analyses. We adjusted for both individual and municipality-level variables. We selected these covariates based on previous original studies.^{13,14} We excluded cases with missing data from our analysis.

Individual characteristics that were considered in our analysis included sex (dichotomous variable), birth month (January or June 2001, dichotomous), parity (0 or more than 1, dichotomous), maternal age at delivery (continuous variable), maternal smoking habits (dichotomous), maternal educational level (categorical variable), and paternal income during the year in which the child was born (continuous). Maternal age was entered as a linear and quadratic term into the models because a U-shaped association was expected between maternal age and development. Data of infant sex, birth month, parity, and maternal age at delivery were obtained from the birth record. Maternal smoking status and paternal income were ascertained at the first survey (i.e., at infant age 6 months). Maternal level of educational attainment was obtained from the second survey (at child age 18 months). We classified the original eight categories of education level into four, as follows: junior high school or other; high school; junior college (2 years) or vocational school; and university (4 years) or higher. Because we were unable to obtain information about maternal smoking status during pregnancy, we used maternal smoking status after birth as a proxy for smoking status during pregnancy. In addition, as maternal educational level before or at the time of delivery was not obtained, we substituted maternal educational level obtained during the second survey; however, this lag is unlikely to cause substantial misclassification because maternal educational level is relatively stable by the ages at delivery in the survey.

The municipality-level variables considered included the type of municipality in which participants were born

(ward, city, town or village; categorical), per capita taxable income (continuous), and population density (continuous) of each municipality. The municipality type and population density were obtained from the 2000 national census. Per capita income was derived from dividing total tax revenue in 2000 from each municipality by the number of taxpayers in the municipality in 2000. These data were obtained from the Statistics Bureau of Japan.²⁰

With respect to sensitivity analysis, to reduce exposure misclassification, we restricted participants to children who were born in those municipalities with an area less than 400 km² (square of 20 km). Moreover, at the first survey, parents were asked whether they had moved or built an extension to their residence during the period 1 year before the birth of their child up to the child's age of 6 months. We thus restricted the analysis to children whose parents had not moved or built a home extension, and we repeated the analysis. We could not separate information on moving and building an extension because they were queried in the same item.

In addition, to examine possible residual confounding, we entered air pollutant concentrations 9 months before pregnancy as a negative control^{21–23} and mutually adjusted for air pollution before pregnancy and during pregnancy in the fully adjusted model.

Finally, we checked the linearity assumption between air pollution exposure and outcomes by replacing the continuous exposure variables by quartile exposure categories for each air pollutant.

All confidence intervals (CI) were calculated at the 95% level. Stata statistical software (Stata SE version 13; StataCorp., College Station, TX) was used for all analyses. The function “xtmelogit” was used for the multilevel analysis. This study was approved by the Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences Institutional Review Board (Nos. 486 and 881).

RESULTS

Table 2 shows the demographic characteristics of children eligible for our study, children to whom suspended PM exposure could be assigned, and children included in the analysis and lost to follow-up at both ages. As expected, children assigned tended to live in wards or cities, which would explain higher maternal education, paternal income, and per capita tax income among those assigned. Children who were lost to follow-up at age 2.5 years were more likely than children included in the analysis to have younger mothers, mothers who smoked, mothers with lower educational attainment, and lower paternal income. However, air pollution concentrations were not different. The same tendency was observed at age 5.5 years.

We also show demographic characteristics of 33,911 children to whom suspended PM exposure could be assigned, separated by quartile exposure categories (Table 3). Children to whom higher exposure was assigned were more likely to

be born in January, to have mothers with higher academic attainment, higher paternal income, and higher per capita tax income.

In Table 4, we present number of cases of children who exhibited behavioral development delays, and adjusted ORs for the association between exposure and these behavioral delays at age 2.5 years. Each air pollutant was associated with increased risk of behavioral development delays, in particular verbal and fine motor development: adjusted ORs following a one-IQR increase in NO₂ exposure were 1.24 (95% CI: 1.07, 1.43) for the inability to compose a two-phrase sentence, 1.14 (95% CI: 1.04, 1.25) for the inability to say own name, and 1.24 (95% CI: 1.00, 1.54) for the inability to use a spoon to eat.

We also observed negative associations of each air pollutant with age-appropriate behaviors at 5.5 years old (Table 5). Elevated ORs were consistently observed for suspended PM: adjusted ORs following a one-IQR increase in suspended PM exposure were 1.10 (95% CI: 1.04, 1.17) for the inability to listen without fidgeting, 1.06 (95% CI: 1.00, 1.13) for the inability to focus on one task, 1.10 (95% CI: 1.05, 1.16) for the inability to express emotions, and 1.08 (95% CI: 1.02, 1.14) for the inability to keep promises.

In sensitivity analyses, when analysis were restricted to children born in municipalities with area less than 400 km² (n = 31,986 for suspended PM), the results did not change substantially (eTable 1; <http://links.lww.com/EDE/A954>). When we included only children whose parents said that they had not moved or built an extension to their home from 1 year before pregnancy to age 6 months of their child (n = 23,596 for suspended PM), the effect estimates were slightly attenuated but they remained elevated (eTable 2; <http://links.lww.com/EDE/A954>).

Air pollution exposure before and during pregnancy were strongly correlated ($r = 0.82$ for suspended PM, 0.94 for NO₂, and 0.84 for SO₂). After mutually adjustment, effect estimates for exposure during pregnancy were equivocal for suspended PM and NO₂, but still elevated for SO₂ at age 2.5 years (eTable 3; <http://links.lww.com/EDE/A954>). The results were more robust at age 5.5 years (eTable 4; <http://links.lww.com/EDE/A954>); even after adjusting for exposure before pregnancy in the same model, effect estimates for exposure during pregnancy were still elevated and higher than those for exposure before pregnancy. For example, adjusted ORs for the inability to express emotions following a one-IQR increase were 1.16 (95% CI: 1.06, 1.27) for suspended PM, 1.31 (95% CI: 1.08, 1.59) for NO₂, and 1.11 (95% CI: 1.02, 1.20) for SO₂.

Finally, even if we replaced the continuous exposure variables by quartile exposure categories, although there were some fluctuations, the association between air pollutants and outcomes did not substantially deviate from linearity, in particular for the outcomes we observed negative associations with (data not shown).

TABLE 2. Demographic Characteristics of Eligible Children, Children to Whom Suspended PM Exposure Could Be Assigned, and Children Included and Lost to Follow-up at Both Ages

	Eligible Children	Suspended PM Exposure ^a		Age 2.5 Years ^b		Age 5.5 Years ^b	
		Available	Not Available	Included	Lost to Follow-up	Included	Lost to Follow-up
		(n = 46,039)	(n = 33,911)	(n = 12,128)	(n = 30,752)	(n = 3,159)	(n = 27,527)
Characteristics of children							
Sex, n (%) ^c							
Boys	23,903 (52)	17,619 (52)	6,284 (52)	15,969 (52)	1,650 (52)	14,283 (52)	3,336 (52)
Girls	22,136 (48)	16,292 (48)	5,844 (48)	14,783 (48)	1,509 (48)	13,244 (48)	3,048 (48)
Birth month, n (%) ^c							
January	22,939 (50)	17,039 (50)	5,900 (49)	15,467 (50)	1,572 (50)	13,771 (50)	3,268 (51)
July	23,100 (50)	16,872 (50)	6,228 (51)	15,285 (50)	1,587 (50)	13,756 (50)	3,116 (49)
Parental characteristics							
Mean maternal age at delivery, years (SD) ^c	30±4.5	30±4.5	30±4.6	30±4.4	28±5.0	30±4.3	29±4.9
Parity, n (%) ^c							
0	22,699 (49)	16,874 (50)	5,825 (48)	15,311 (50)	1,563 (49)	13,623 (49)	3,251 (51)
≥1	23,340 (51)	17,037 (50)	6,303 (52)	15,441 (50)	1,596 (51)	13,904 (51)	3,133 (49)
Maternal smoking status, n (%) ^d							
Nonsmoker	37,725 (82)	27,905 (82)	9,820 (81)	25,874 (84)	2,031 (64)	23,492 (85)	4,413 (69)
Smoker	8,038 (17)	5,813 (17)	2,225 (18)	4,729 (15)	1,084 (34)	3,911 (14)	1,902 (30)
Missing	276 (0.6)	193 (0.6)	83 (0.7)	149 (0.5)	44 (1.4)	124 (0.5)	69 (1.1)
Maternal educational attainment, n (%) ^e							
University or higher	5,909 (13)	4,695 (14)	1,214 (10)	4,532 (15)	163 (5.2)	4,283 (16)	412 (6.5)
Junior college	17,644 (38)	13,242 (39)	4,402 (36)	12,648 (41)	594 (19)	11,643 (42)	1,599 (25)
High school	16,799 (36)	11,844 (35)	4,955 (41)	11,078 (36)	766 (24)	9,803 (36)	2,041 (32)
Junior high school or others	2,431 (5.3)	1,783 (5.3)	648 (5.3)	1,539 (5.0)	244 (7.7)	1,236 (4.5)	547 (8.6)
Missing	3,256 (7.1)	2,347 (6.9)	909 (7.5)	955 (3.1)	1,392 (44)	562 (2.0)	1,785 (28)
Mean paternal income, million yen (SD) ^d	4.4±2.8	4.6±2.8	4.1±2.9	4.7±2.8	3.7±2.8	4.7±2.8	3.9±2.5
Municipality-level variables							
Residential area, n (%)							
Wards	10,080 (22)	8,562 (25)	1,518 (13)	7,778 (25)	784 (25)	6,972 (25)	1,590 (25)
Cities	27,125 (59)	23,922 (71)	3,203 (26)	21,678 (70)	2,244 (71)	19,406 (71)	4,516 (71)
Towns or villages	8,834 (19)	1,427 (4.2)	7,407 (61)	1,296 (4.2)	131 (4.2)	1,149 (4.2)	278 (4.4)
Mean per capita tax income, million yen (SD)	3.6±0.5	3.7±0.5	3.3±0.5	3.7±0.5	3.7±0.5	3.7±0.5	3.7±0.5
Mean population density, person per km ² (SD)	3,568±4,163	4,085±4,140	2,086±3,862	4,086±4,134	4,078±4,200	4,098±4,136	4,031±4,156
Mean suspended PM ^a (μg/m ³) (SD)	-	33±0.8	-	33±0.8	33±0.8	33±0.8	33±0.8

There were 2,412 cases missing paternal income data, 383 cases missing per capita tax income data, and 275 cases missing population density data among eligible children (n = 46,039).

^aSuspended PM accounts for PM with aerodynamic diameter less than 7 μm (PM₇).

^bAmong 33,911 children to whom suspended PM exposure could be assigned.

^cObtained from the birth record.

^dObtained from the first survey (at age 6 months).

^eObtained from the second survey (at age 18 months).

SD indicates standard deviation.

DISCUSSION

In this study, we examined the association of prenatal exposure to traffic-related air pollution with behavioral developmental delays in children, using data from a nationwide population-based longitudinal survey in Japan. We found that

air pollution exposure during gestation was associated with unfavorable subsequent child verbal and fine motor development at age 2.5 years and social behaviors at 5.5 years. The findings at 5.5 years were more robust than those at age 2.5 years, which became equivocal in sensitivity analysis.

TABLE 3. Demographic Characteristics of 33,911 Children to Whom Suspended PM Exposure Could Be Assigned, Separated by Quartile Air Pollution Exposure

	Suspended PM ($\mu\text{g}/\text{m}^3$) ^a			
	Q1 (≤ 27.8) (n = 8,493)	Q2 (27.9–33.56) (n = 8,516)	Q3 (33.57–38.9) (n = 8,640)	Q4 (≥ 39.0) (n = 8,262)
Characteristics of children				
Sex, n (%) ^b				
Boys	4,443 (52)	4,401 (52)	4,525 (52)	4,250 (51)
Girls	4,050 (48)	4,115 (48)	4,115 (48)	4,012 (49)
Birth month, n (%) ^b				
January	3,212 (38)	4,340 (51)	4,140 (48)	5,347 (65)
July	5,281 (62)	4,176 (49)	4,500 (52)	2,915 (35)
Parental characteristics				
Mean maternal age at delivery, years (SD) ^b	30 $\pm$ 4.5	30 $\pm$ 4.4	30 $\pm$ 4.5	30 $\pm$ 4.4
Parity, n (%) ^c				
0	4,135 (49)	4,131 (49)	4,375 (51)	4,233 (51)
≥ 1	4,358 (51)	4,385 (51)	4,265 (49)	4,029 (49)
Maternal smoking status, n (%) ^c				
Nonsmoker	6,871 (81)	7,147 (84)	7,146 (83)	6,741 (82)
Smoker	1,569 (18)	1,315 (15)	1,453 (17)	1,476 (18)
Missing	53 (0.6)	54 (0.6)	41 (0.5)	45 (0.5)
Maternal educational attainment, n (%) ^d				
University or higher	947 (11)	1,135 (13)	1,373 (16)	1,240 (15)
Junior college	3,177 (37)	3,364 (40)	3,426 (40)	3,275 (40)
High school	3,332 (39)	3,008 (35)	2,810 (33)	2,694 (33)
Junior high school or others	463 (5.5)	412 (4.8)	435 (5.0)	473 (5.7)
Missing	574 (6.8)	597 (7.0)	596 (6.9)	580 (7.0)
Mean paternal income, million yen (SD) ^e	4.2 $\pm$ 2.3	4.4 $\pm$ 2.7	4.8 $\pm$ 3.1	4.9 $\pm$ 3
Municipality-level variables				
Residential area, n (%)				
Wards	1,231 (14)	1,669 (20)	2,740 (32)	2,922 (35)
Cities	6,675 (79)	6,539 (77)	5,675 (66)	5,033 (61)
Towns or villages	587 (6.9)	308 (3.6)	225 (2.6)	307 (3.7)
Per capita tax income, million yen (SD)	3.4 $\pm$ 0.4	3.7 $\pm$ 0.4	3.9 $\pm$ 0.5	4.0 $\pm$ 0.4
Population density, person per km ² (SD)	1,430 $\pm$ 1,749	2,920 $\pm$ 2,942	5,615 $\pm$ 4,553	6,417 $\pm$ 4,480

There were 1,719 cases missing paternal income data and 232 cases missing per capita income data.

^aSuspended PM indicates exposure to PM with aerodynamic diameter less than 7 μm ($\text{PM}_{2.5}$).

^bObtained from the birth record.

^cObtained from the first survey (at age 6 months).

^dObtained from the second survey (at age 18 months).

SD indicates standard deviation.

At age 2.5 years, we observed that prenatal exposure to air pollution, particularly NO_2 , was associated with increased risk of verbal and fine motor developmental delays, although the findings became equivocal after we adjusted for exposure before pregnancy as a negative control. Some previous studies suggested negative associations of prenatal exposure to air pollution with verbal and motor development, but the findings are not consistent across studies. Several studies measured PAH as an air pollution exposure biomarker and evaluated the association with several cognitive functions.^{7–11} For example, Tang et al.¹¹ demonstrated an association of PAH-DNA

adducts in umbilical cord blood with decreased motor and language development measured by the Gesell Developmental Schedules at age 2 years in China. Other studies have evaluated the associations of gaseous pollutants or PM with neurodevelopment. Guxens et al.¹³ combined six European birth cohorts and showed that prenatal air pollution exposure, in particular NO_2 , was associated with reduced psychomotor development, but not with general cognition or language development, assessed between 1 and 6 years of age. Kim et al.¹⁴ also demonstrated negative associations of prenatal exposure to PM and NO_2 with mental development (e.g., language

TABLE 4. Associations Between Prenatal Traffic-related Outdoor Air Pollution and Behavioral Development Milestone Delays at Age 2.5 Years

	Cases with Behavioral Delays	Adjusted ORs (95% CIs) Per an Interquartile Range Increase ^a		
	No. Cases/Total No. ^b	Suspended PM ^c	NO ₂	SO ₂
Unable to walk	91/30,752	1.01 (0.71, 1.43)	1.34 (0.79, 2.27)	1.07 (0.81, 1.41)
Unable to run	173/30,749	1.08 (0.83, 1.40)	1.48 (0.99, 2.21)	1.18 (0.96, 1.46)
Unable to climb stairs	588/30,727	1.05 (0.91, 1.22)	1.09 (0.87, 1.36)	1.09 (0.96, 1.23)
Unable to say meaningful words	199/30,743	1.08 (0.85, 1.38)	1.31 (0.91, 1.89)	1.20 (0.99, 1.45)
Unable to compose a two-phrase sentence	1,267/30,728	1.07 (0.97, 1.18)	1.24 (1.07, 1.43)	1.08 (0.99, 1.17)
Unable to say his or her own name	3,568/30,690	1.06 (0.99, 1.12)	1.14 (1.04, 1.25)	1.06 (1.01, 1.11)
Unable to use a spoon to eat	602/30,735	0.97 (0.84, 1.11)	1.24 (1.00, 1.54)	1.07 (0.95, 1.20)

^aAdjusted for individual characteristics (sex, birth month, maternal age at delivery, parity, maternal smoking status, maternal educational level, and paternal income) and municipality-level variables (residential area, per capita income, and population density). Interquartile ranges are 11.0 µg/m³ for suspended PM, 10.9 ppb for NO₂, and 2.3 ppb for SO₂.

^bAmong 33,911 children to whom suspended PM exposure could be assigned. Total no. represents total number of children whose development was assessed by questionnaire at age 2.5 years.

^cSuspended PM accounts for PM with aerodynamic diameter less than 7 µm (PM₇).

TABLE 5. Associations Between Prenatal Traffic-related Outdoor Air Pollution and Behavioral Development Milestone Delays at Age 5.5 Years

	Cases with Behavioral Delays	Adjusted ORs (95% CIs) Per an Interquartile Range Increase ^a		
	No. Cases/Total No. ^b	Suspended PM ^c	NO ₂	SO ₂
Unable to listen without fidgeting	4,787/27,487	1.10 (1.04, 1.17)	1.07 (0.98, 1.17)	1.06 (1.01, 1.11)
Unable to focus on one task	3,531/27,527	1.06 (1.00, 1.13)	1.10 (1.01, 1.21)	1.01 (0.96, 1.06)
Unable to remain patient	6,693/27,397	1.04 (0.99, 1.09)	0.95 (0.88, 1.02)	1.01 (0.97, 1.05)
Unable to express emotions	6,332/27,368	1.10 (1.05, 1.16)	1.17 (1.09, 1.26)	1.07 (1.03, 1.12)
Unable to get along with others in a group	1,725/27,501	1.07 (0.99, 1.17)	1.14 (1.00, 1.30)	1.05 (0.98, 1.13)
Unable to keep promises	5,234/27,260	1.08 (1.02, 1.14)	1.01 (0.93, 1.09)	1.01 (0.97, 1.06)

^aAdjusted for individual characteristics (sex, birth month, maternal age at delivery, parity, maternal smoking status, maternal educational level, and paternal income) and municipality-level variables (residential area, per capita taxable income, and population density). Interquartile ranges are 11.0 µg/m³ for suspended PM, 10.9 ppb for NO₂, and 2.3 ppb for SO₂.

^bAmong 33,911 children to whom suspended PM exposure could be assigned. Total n represents total number of children whose development was assessed by questionnaire at age 5.5 years.

^cSuspended PM accounts for PM with aerodynamic diameter less than 7 µm (PM₇).

and cognitive functions) and psychomotor development only at age 6 months (but not at 12 or 24 months), measured by the Korean version Bayley Scale of Infant Development-II.

We also observed positive associations between prenatal exposure to traffic-related air pollution exposure, in particular suspended PM, and behavioral developmental delays at age 5.5 years. Survey items assessed at this age are related to behaviors like attention, self-regulation, and socially appropriate behavior, i.e., behaviors that can be said to be related to inhibition and impulsivity.²⁴ Decreased self-inhibitory control and poor impulsive control are behaviors that often coexist with the most common neurobehavioral disorder of childhood, attention-deficit/hyperactivity disorder (ADHD).²⁵ Previous epidemiological studies have evaluated the association between outdoor air pollution and ADHD or behaviors that coexist with ADHD. A cross-sectional study from India suggested a positive association between living in polluted areas and a prevalence of ADHD,²⁶ and a birth cohort study in the

United States suggested an association with traffic-related air pollution in the first year of life with behavioral scores, particularly hyperactivity scores, at age 7 years.²⁷

Moreover, given the observed possible negative associations with verbal development at age 2.5 years and with social behaviors (e.g., expressing emotions, acting cooperatively in a group) at age 5.5 years, we can say that prenatal exposure to air pollution may be associated with not only behaviors that often coexist with ADHD but also those that coexist with other neurodevelopmental disorders (such as communication disorders and autism spectrum disorder).²⁵ For example, several previous studies have suggested a possible role of prenatal air pollution exposure in autism spectrum disorder.^{23,28–30} Although we did not use specific diagnoses as health outcomes and thus our study cannot provide direct insight into these associations, these findings may support possible negative roles of prenatal exposure to outdoor air pollution on neurodevelopmental disorders in general.

The observed associations of prenatal exposure to air pollution with behavioral developmental delays are biologically plausible. Prenatal exposure to ambient air pollution is positively associated with maternal systemic inflammation,³¹ which may affect fetal brain development via several pathways involving placental transfer of maternal inflammation to the fetus or fetal inflammation.³² Alternatively, PM or PM constituents transmitted to maternal blood can pass through the placenta from mother to fetus, which may invoke brain inflammation, blood–brain barrier breakdown, or neuronal and glial damage.³³ For example, poor inhibitory control and impulsive behaviors, which were associated with air pollution exposure in the analysis of children at age 5.5 years in this study, are related to the prefrontal cortex.^{34,35} Indeed, Calderon-Garciduenas et al.³⁶ used magnetic resonance imaging and found more frequent prefrontal white matter hyperintense lesions among both healthy children and young dogs from Mexico City compared with those from a city with low pollution levels. A pathological finding of these exposed dogs showed neuroinflammation in prefrontal lesions. Although it is unclear when participants in the Mexican study were exposed to air pollution (prenatally, postnatally, or both), this finding supports the biological plausibility of these results.

The strength of our study is that we have a large, nationally representative sample. To the best of our knowledge, this is the largest study to date examining the association between air pollution and neurodevelopment. Roughly one-twentieth of the children born in 2001 in Japan are included in this survey. In addition, the high response rate at baseline (88%) and high follow-up rates (e.g., more than about 80%, even at age 5.5 years among children to whom prenatal exposure could be assigned) strengthen the validity of our findings. We were also able to collect individual covariates, such as maternal education level and paternal income.

However, the study has several limitations. First, we could not use several validated cognitive function tests used in previous studies (e.g., the Bayley Scales of Infant Development-II). In addition, we could not confirm whether the questions we used (at both ages) have been validated or selected from an established scale. The uncertainty regarding external validation of survey questions used to assess behavioral outcomes poses a threat to the validity of our findings. However, the developmental delays assessed by these questions were related to shorter gestational age in an anticipated direction in our previous study.¹⁶ In addition, we cannot exclude the possibility of misclassification of behavioral outcomes because of the subjective nature of these questions. However, any misclassification would be nondifferential, moving the effect estimates toward the null.

We assigned municipality-level air pollution exposure to each participant and did not estimate individual-level air pollution exposure using land-use regression models or geostatistical models used in other recent studies.^{12–14} Thus, there is a possibility of measurement error, which may underestimate

the effect estimates.³⁷ However, in the sensitivity analysis, which aimed to reduce possible measurement error by including only children born in municipalities with area less than 400 km², we still obtained elevated effect estimates.

Maternal relocation during pregnancy can also induce measurement error. Again, we did a sensitivity analysis restricting children to those whose parents did not move or build a home extension from 1 year before birth to 6 months of age, and still obtained slightly attenuated but elevated effect estimates. Theoretically, the effect estimates should have been stronger, but the reason of the attenuation may be related with the fact that we could not separate information on moving and building an extension because they were queried in the same item.

There is a possibility of residual confounding. Information about maternal smoking habits and maternal educational levels not listed in the birth records was collected after birth; thus, these data may not reflect maternal status before delivery. Moreover, we do not have covariates related to the level of maternal intelligence. In our additional analysis using exposure to air pollution before pregnancy as a negative control, the associations between air pollutants and developmental delays became equivocal at age 2.5 years but still remained elevated at age 5.5 years. Thus, residual confounding may explain the elevated effect estimates at age 2.5 years to some extent, whereas elevated effect estimates at age 5.5 years could not be explained by any factor that is not differently related to air pollution exposure during pregnancy versus before pregnancy.²³

We could not assign air pollution exposure to one fourth of the eligible children (Table 2), which may affect generalizability of the findings. We also had considerable children lost to follow-up at both ages. However, exposure distributions were not different between children included in the analysis and those lost to follow-up. We calculated standardized inverse probability weights (IPW)³⁸ to account for those who answered the baseline questionnaire with exposure information, but not the later child development assessments (e.g., $n = 3,159$ at age 2.5 years for suspended PM in Table 2). Although we were only able to use the weights for simple logistic regression, the results did not change substantially between the analysis without IPW and the analysis with IPW (eTable 5; <http://links.lww.com/EDE/A954>). Therefore, selection bias due to the loss may not be large.

Finally, we did not evaluate the association of postnatal exposure to air pollution with behavioral development, thus we could not definitively determine whether prenatal or postnatal exposures were more relevant to behavioral development in childhood.

CONCLUSIONS

Prenatal exposure to traffic-related air pollution was associated with increased risk of some child behavioral developmental delays, particularly social behaviors, in a nationally representative sample in Japan.

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