ORIGINAL RESEARCH

Exposure to $PM_{2.5}$ and Lung Function Growth in Pre- and Early-Adolescent Schoolchildren

A Longitudinal Study Involving Repeated Lung Function Measurements in Japan

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Abstract

Rationale: Epidemiological evidence indicates that ambient exposure to particulate matter ⩽2.5 μm in aerodynamic diameter ($PM_{2.5}$) has adverse effects on lung function growth in children, but it is not actually clear whether exposure to low-level $PM_{2.5}$ results in long-term decrements in lung function growth in pre- to early-adolescent schoolchildren.

Objectives: To examine long-term effects of $PM_{2.5}$ within the 4-year average concentration range of 10–19 μg/m^3 on lung function growth with repeated measurements of lung function tests.

Methods: Longitudinal analysis of 6,233 lung function measurements in 1,466 participants aged 8–12 years from 16 school communities in 10 cities around Japan, covering a broad area of the country to represent concentration ranges of $PM_{2.5}$, was done with a multilevel linear regression model. Forced expiratory volume in 1 second, forced vital capacity (FVC), and maximal expiratory flow at 50% of FVC were used as lung function indicators to examine the effects of 10-μg/m^3 increases in the $PM_{2.5}$ concentration on relative growth per each 10-cm increase in height.

Results: The overall annual mean $PM_{2.5}$ level was 13.5 μg/m^3 (range, 10.4–19.0 μg/m^3). We found no association between any of the lung function growth indicators and increases in $PM_{2.5}$ levels in children of either sex, even after controlling for potential confounders. Analysis with two-pollutant models with O_3 or NO_2 did not change the null results.

Conclusions: This nationwide longitudinal study suggests that concurrent, long-term exposure to $PM_{2.5}$ at concentrations ranging from 10.4 to 19.0 μg/m^3 has little effect on lung function growth in preadolescent boys or pre- to early-adolescent girls.

Keywords: $PM_{2.5}$; lung function growth; pre- and early-adolescent; schoolchildren; longitudinal study

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A growing body of epidemiological evidence has been accumulated regarding the effects of exposure to particulate matter ⩽2.5 μm in aerodynamic diameter ($PM_{2.5}$) on lung health in children (1–19), and studies employing a longitudinal design with repeated measurements of lung function have been particularly useful in improving our understanding of the effects of $PM_{2.5}$ exposure on lung function growth (5–11, 17–19). Evaluating the impact of air pollution exposure on lung function development in school-aged and adolescent children is essential because lung function growth is closely linked with the adolescent growth spurt that occurs at about 10 years of age in girls and 12 years of age in boys (20). Recent longitudinal studies demonstrated that lung health during preadolescence and young adulthood is important to predict middle-aged lung function or the occurrence of respiratory disorders in later life.

Trajectories of forced expiratory volume in 1 second (FEV_1) from 7 to 53 years of age in the Tasmanian Longitudinal Health Study identified six distinct trajectories and showed that not only those with "persistently low" trajectories but also those with "below average" trajectories had an increased risk of developing chronic obstructive pulmonary disease (COPD) by middle age (21). In the same cohort, respiratory risk profiles at age 7, such as parental smoking or frequent asthma, bronchitis, and allergy, were associated with future decline in FEV_1 and forced vital capacity (FVC) at age 53, as well as with increased risk of COPD at age 53 (22). In the study from UK cohorts, 44 cytosine–phosphate–guanine dinucleotide sites of DNA methylation measured in peripheral blood at the age of 10 years were associated with lung function trajectories from the age of 10 years to the age of 26 years, also indicating the importance of environmental insults during the preadolescent period for lung health (23).

Key evidence with a wider range of $PM_{2.5}$ levels has been reported from the University of Southern California CHS (Children's Health Study), and the latest results of the CHS showed that improvements in air quality resulted in improvements in the 4-year growth of FEV_1 and FVC in children between the ages of 11 and 15 years across the three cohorts. In fact, the 3-year mean $PM_{2.5}$ levels improved significantly from cohort to cohort: in the 1994 cohort, the levels ranged from 21.3 to 31.5 $\mu g/m^3$; in the 1997 cohort, they ranged from 19.9 to 27.6 $\mu g/m^3$; and in the 2007 cohort, they ranged from 11.9 to 17.8 $\mu g/m^3$ (10).

The preceding epidemiological evidence suggests that reductions in lung function growth could be observed in adolescents aged 10 years and over when $PM_{2.5}$ levels exceed 20 $\mu g/m^3$. However, information is quite limited regarding the long-term effects of exposure to $PM_{2.5}$ within the range of 10–19 $\mu g/m^3$ on lung function growth as measured with repeated lung function tests in preadolescents and adolescents. Therefore, we performed repeated lung functions tests in a longitudinal study of pre- and early-adolescent schoolchildren living in Japanese communities where annual $PM_{2.5}$ levels ranged from 10 to 19 $\mu g/m^3$, and we report herein on the association between exposure to $PM_{2.5}$ and lung function growth in these children.

Methods

Study Design and Participants

We initiated a prospective study of third-grade elementary school children aged 8–9 years, who were recruited from nine public elementary schools of six cities in 2011 and seven public elementary schools of four cities in 2012. In total, this study included 16 school communities in 10 cities from 2011–2012, covering a broad area of the country to represent wide concentration ranges of $PM_{2.5}$ in Japan to maximize the geographical variability of the $PM_{2.5}$ concentration across Japan (Figure 1). Before the recruitment process, we evaluated the feasibility of conducting a longitudinal study that would maximize statistical power to increase the probability of detecting the effects on the annual average of FEV_1 growth comparable with those in the CHS 1993 cohort (4) under the $PM_{2.5}$ concentration distributions from April 2001 to March 2005 in Japan (24), indicating that the expected number of enrolled communities would be 10, with 100–150 participants being included per community. At one school, the study was postponed from 2011 to 2012 after obtaining informed consent from third-grade children in 2011 because of the 2011 Great East Japan Earthquake, and we decided to enroll both third- and fourth-grade children in 2012. Follow-up was planned to occur annually until the children were in the fifth grade (aged 10–11 yr) and to occur twice when they were in the sixth grade (aged 12 yr).

To enroll as many children as possible, details of the study were given to parents at parent meetings and through information materials distributed at every school. Written informed consent was obtained from the parents of all participants. Out of 1,381 children, 1,307 participated from the start of the year, and then 51 were enrolled in later years, whereas 131 were moved out to different school districts during the study period. An additional 108 children entered the study schools and participated thereafter (*see* Figure E1 in the online supplement). About 80% ($N = 86$) of the 108 children participated in the first half of the study and attended the lung function testing three times or more.

The study was centrally approved by the Ethical Committee of the Ministry of the Environment of Japan (approval number 11021001) and was also approved at each regional study center.

Exposure Measurement to Selected Air Pollutants

Ambient $PM_{2.5}$, ozone (O_3), and nitrogen dioxide (NO_2) were measured continuously over the study period at or near each school. The place to set the measuring equipment was decided so that the measurement data avoided the direct exhaust gases of heavy traffic. Note that the measurement regarding schools O and P was performed near the schools (within 2 km) because of difficulty in setting up the equipment at the schools. $PM_{2.5}$ was measured by using the β-ray attenuation method and a PM-712 monitor (Kimoto Electric Co. Ltd.). O_3 and NO_2

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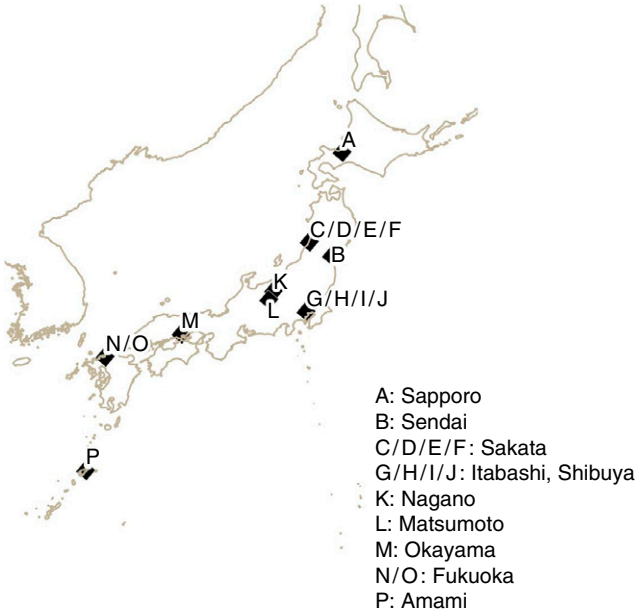

Figure 1. Study sites.

concentrations were measured by using the ultraviolet absorption and chemiluminescence methods and OA-781 and NA-721 monitors (Kimoto Electric Co. Ltd.), respectively. The automated measurement of these air pollutants, including quality assurance of the measured data, was in accordance with the *Manual for Continuous Monitoring of Air Pollution* prepared by the Ministry of the Environment, Japan (25).

Annual level of suspended particulate matter (SPM), O_3, and NO_2 before the study period—when the study pupils were under 8 years old—and during the study period were calculated as 5-year means and a range of yearly means on the basis of data obtained from the National Institute of Environmental Studies' environmental values database. SPM in Japan is classified as particulates whose aerodynamic diameter is less than 10 μm with a 100% cutoff level. Concentrations in the database were measured in accordance with the methods given in the *Manual for Continuous Monitoring of Air Pollution* (25), and the monitoring stations whose data were used were those closest to each elementary school.

Lung Function Tests and Questionnaire on Asthma and Allergies

Lung function testing of the children in the third to sixth grades was scheduled in the morning hours during the same season every year to minimize seasonal effects such as temperature and pollution levels; the same spirometers with Lilly-type pneumotach sensors (Chest HI801, CHEST M.I., Inc.) were used for testing at all locations. Except in two schools, pupils in the sixth grade were given an additional lung function test in February or March (i.e., a month before they moved on to junior high school); after having their height and weight measured, they were asked to perform a maximum forced expiratory maneuver. The tests were conducted by trained technicians who followed the testing protocol of the American Thoracic Society standards (26). As these standards were modified for school-aged children, no more than six blows are attempted in each test. The FEV_1, FVC, and maximal expiratory flow rate at 50% of FVC ($\dot{V}50$) were determined from three satisfactory blows delivered under the guidance of two pediatric pulmonologists.

A baseline questionnaire on asthmatic and allergic symptoms, as classified in the Japanese version of the ISAAC (International Study of Asthma and Allergies in Childhood) questionnaire (27), was distributed to the participants' parents and returned on the day of the lung function testing. The questionnaire also contained questions on medical history, food allergies, exercise habits, exposure to environmental tobacco smoke (ETS), the types of heating appliances used, and pet ownership in each household. A follow-up questionnaire was administered every time lung function testing was done.

Statistical Analysis

The proxy measure of long-term exposure to $PM_{2.5}$ was defined as the arithmetic mean of the annual average of daily $PM_{2.5}$ concentrations over the study period at each school site. Most of the pupils lived within a 10-km radius of their school. Because O_3 and NO_2 are short-lived pollutants, their proxy measures were defined as the arithmetic mean of the annual average of hourly concentrations over the study period.

Of the participants, 834 underwent lung function testing five times, 358 were tested four times, 134 were tested three times, 89 were tested two times, and 51 were tested one time; all available data were used to construct a statistical model. It is known that this method is valid under the missing-at-random assumption (28). Lung function indicators were log-transformed in the following models because they were more linearly associated with height in both boys and girls in our preliminary analysis.

To assess the association between $PM_{2.5}$ concentrations and FVC, FEV_1, and $\dot{V}50$, the following multilevel linear regression model (29) was used for each sex:

$$\log Y_{cih} = a_{ci} + b_{ci}h + \gamma^T z_{ci} + e_{cih} \quad (1)$$

$$b_{ci} = B_c + e'_{ci} \quad (2)$$

$$B_c = \beta_0 + \beta_1 x_c + e''_c \quad (3)$$

where c denotes the school community, i denotes the individual, h denotes the height, Y_{cih} denotes the value of each lung function test, z_{ci} denotes confounding factors, x_c denotes the $PM_{2.5}$ concentration, and e_{cih}, e'_{ci}, and e''_c denote the independent random-error terms after normal distributions. We note that unlike the model used in CHS (29), our model used height instead of age in the first-stage model (Equation 1).

The first-stage model (Equation 1) was a linear regression that included the results of each lung function test (values were log-transformed) and height and adjusted for confounders to assess the community-specific associations between height and lung function in both sexes. We assumed the association was linear after using fractional polynomials with 1 degree of freedom to check model fitting (30). We used the following confounders determined *a priori* in the main analysis: wheezing (yes/no), defined as the presence of wheezing or whistling in

Table 1. Participant characteristics at the time of the first survey

School	City	Prefecture	Number of Participants at Baseline	Male [*n* (%)]	Age (*yr*) [*mean (SD)*]	Height (*cm*) [*mean (SD)*]	Rohrer Index [*mean (SD)*]	ETS at Home [*n* (%)]	Pets* [*n* (%)]	Wheezing† [*n* (%)]	Sneezing† [*n* (%)]	Itchy Rash† [*n* (%)]	Exercise‡ [*n* (%)]
A	Sapporo	Hokkaido	138	74 (53.6)	9.15 (0.61)	132.0 (6.2)	121.8 (14.9)	21 (15.2)	20 (14.5)	20 (14.5)	75 (54.3)	35 (25.4)	20 (14.5)
B§	Sendai	Miyagi	109	50 (45.9)	8.95 (0.58)	131.2 (6.5)	122.6 (14.7)	12 (11.0)	8 (7.3)	14 (12.8)	59 (54.1)	28 (25.7)	17 (15.6)
B′			92	49 (53.3)	9.96 (0.60)	137.4 (7.4)	121.8 (14.2)	8 (8.7)	6 (6.5)	11 (12.0)	51 (55.4)	20 (21.7)	11 (12.0)
C	Sakata	Yamagata	42	21 (50.0)	9.12 (0.54)	131.8 (5.8)	128.6 (20.1)	9 (21.4)	5 (11.9)	4 (9.5)	17 (40.5)	7 (16.7)	10 (23.8)
D			37	23 (62.2)	9.01 (0.46)	130.2 (6.4)	127.8 (17.0)	6 (16.2)	0 (0)	3 (8.1)	14 (37.8)	3 (8.1)	12 (32.4)
E			58	33 (56.9)	9.10 (0.42)	132.1 (6.3)	125.6 (15.6)	16 (27.6)	9 (15.5)	3 (5.2)	22 (37.9)	6 (10.3)	21 (36.2)
F			14	8 (57.1)	9.07 (0.39)	134.3 (6.0)	121.8 (14.2)	3 (21.4)	3 (21.4)	0 (0)	8 (57.1)	5 (35.7)	6 (42.9)
G	Itabashi	Tokyo	91	52 (57.1)	9.01 (0.67)	129.1 (5.8)	123.4 (14.5)	27 (29.7)	10 (11.0)	6 (6.6)	46 (50.5)	23 (25.3)	17 (18.7)
H	Shibuya		35	17 (48.6)	8.92 (0.66)	129.8 (8.1)	126.0 (14.4)	8 (22.9)	7 (20.0)	6 (17.1)	19 (54.3)	11 (31.4)	5 (14.3)
I			37	17 (45.9)	9.05 (0.89)	131.7 (7.3)	122.4 (14.9)	3 (8.1)	6 (16.2)	3 (8.1)	22 (59.5)	6 (16.2)	4 (10.8)
J			56	26 (46.4)	9.14 (0.68)	132.1 (6.0)	119.4 (14.7)	12 (21.4)	7 (12.5)	8 (14.3)	30 (53.6)	13 (23.2)	8 (14.3)
K	Nagano	Nagano	81	45 (55.6)	9.22 (0.62)	131.5 (7.0)	123.7 (16.7)	9 (11.1)	10 (12.3)	10 (12.3)	42 (51.9)	20 (24.7)	14 (17.3)
L	Matsumoto		78	29 (37.2)	9.36 (0.69)	132.4 (6.8)	120.4 (13.3)	13 (16.7)	12 (15.4)	5 (6.4)	36 (46.2)	18 (23.1)	12 (15.4)
M	Okayama	Okayama	101	50 (49.5)	8.61 (0.36)	128.3 (5.4)	124.9 (12.7)	8 (7.9)	17 (16.8)	7 (6.9)	36 (35.6)	11 (10.9)	9 (8.9)
N	Fukuoka	Fukuoka	82	35 (42.7)	8.98 (0.66)	131.2 (6.9)	120.5 (14.5)	21 (25.6)	11 (13.4)	8 (9.8)	40 (48.8)	20 (24.4)	7 (8.5)
O			144	75 (52.1)	9.04 (0.76)	129.8 (7.3)	125.6 (16.3)	39 (27.1)	19 (13.2)	12 (8.3)	69 (47.9)	30 (20.8)	15 (10.4)
P	Amami	Kagoshima	112	63 (56.3)	9.17 (0.80)	130.5 (7.3)	129.0 (17.1)	37 (33.0)	13 (11.6)	23 (20.5)	52 (46.4)	19 (17.0)	12 (10.7)

Definition of abbreviations: ETS = exposure to environmental tobacco smoke; ISAAC = International Study of Asthma and Allergies in Childhood; SD = standard deviation.
*"Pets" was defined as household pet ownership over the previous 12 months.
†"Wheezing," "sneezing," and "itchy rash" were defined according to the Japanese version of the ISAAC questionnaire (27).
‡"Exercise" was defined as habitual exercise three times a week or more.
§"B" indicates third-grade students and "B′" indicates fourth-grade students, as both third- and fourth-grade children were enrolled in 2012.

the chest more than once in the previous 12 months; sneezing (yes/no); itchy rash (yes/no), defined as having had at least one rash in the previous 6 months; exposure to ETS at home (yes/no), defined as either parent smoking in the same room as the child; household pet ownership (yes/no), defined as having had a dog or a cat over the previous 12 months; habitual exercise (none/once or twice a week/more than twice a week), defined as doing vigorous exercise; and the Rohrer index (weight in kilograms divided by the height in meters cubed multiplied by 10) as used as an anthropometric index ($\geqslant$115 / $<$115).

The second-stage model (Equation 2) was a linear regression of community- and individual-specific estimates of lung function growth per each 1-unit increase of height on communities. The third-stage model (Equation 3) was a linear regression of community-specific average growth on the $PM_{2.5}$ concentrations.

The main parameter of interest in the above model was the effect of 10-μg/m^3 increases in $PM_{2.5}$ on the relative growth of lung function per each 10-cm increase in height: $\exp(\beta_1 \times 10^2)$. We calculated estimates and 95% confidence intervals (CIs) as well as the *P* values of $\exp(\beta_1 \times 10^2)$

As sensitivity/additional analyses, we also fitted the following models: *1*) a two-pollutant model with O_3 or NO_2 in addition to $PM_{2.5}$ in the third-stage model; *2*) a model with additional covariates as potential confounders, namely ETS, household pet ownership, and the indoor heating modality; *3*) a subgroup (stratified) analysis to assess the effect modification by asthma and ETS; and *4*) models excluding children with obesity with a Rohrer index greater than 160, as extreme obesity could affect lung function testing. Furthermore, to ensure that inclusion of later-stage participants did not distort the study results, additional analysis was done by excluding those who participated in the latter half of the study ($N = 20$).

Results

Table 1 shows the baseline characteristics of the participants in the first-year survey ($N = 1,307$). The mean age and height of the third-grade children were 9.05 years and 130.83 cm, and the mean age and height of the fourth-grade children were 9.96 years and 137.4 cm.

Table 2. Four-year average concentrations of $PM_{2.5}$ (left), ozone (center), and NO_2 (right) during the study period

City	School	Four-Year Average Concentration		
		$PM_{2.5}$ ($\mu g/m^3$)	Ozone (*ppb*)	NO_2 (*ppb*)
Sapporo	A	10.4	30	11
Sendai	B*	10.8	32	11
	B′	10.8	32	11
Sakata	C	11	36	3
	D	10.5	38	5
	E	11.4	38	3
	F	10.6	36	3
Itabashi	G	16.4	27	21
Shibuya	H	16.5	26	20
	I	15.4	29	20
	J	16.2	26	23
Nagano	K	12.9	29	9
Matsumoto	L	11.4	30	9
Okayama	M	16.4	32	11
Fukuoka	N	19	31	15
	O	16.5	33	10
Amami	P	12.5	35	3

Definition of abbreviations: $PM_{2.5}$ = particulate matter ≤2.5 μm in aerodynamic diameter; ppb = parts per billion.
*"B" indicates third-grade students and "B′" indicates fourth-grade students, as both third- and fourth-grade children were enrolled in 2012.

Exposure estimates for the major pollutants are shown in Table 2, Figure 2, and Table E1. The overall annual mean concentration of $PM_{2.5}$ over the study period was 13.5 $\mu g/m^3$ (range, 10.4–19.0 $\mu g/m^3$). Annual mean $PM_{2.5}$ concentrations at eight schools with 568 participants were below 12 $\mu g/m^3$, whereas those at seven schools with 546 participants were above 15 $\mu g/m^3$.

In the boys, the relative effects of a 10-$\mu g/m^3$ increase in $PM_{2.5}$ on the relative growth of lung function per each 10-cm increase in height for FEV_1, FVC, and $\dot{V}50$ were 1.00054 (95% CI, 0.99969–1.00139), 1.00038 (95% CI, 0.99958–1.00118), and 1.00071 (95% CI, 0.99900–1.00242); in the girls, they were 1.00012 (95% CI, 0.99916–1.00109), 1.00004 (95% CI, 0.99899–1.00108), and 0.99989 (95% CI, 0.99813–1.00165). These results indicate no associations for either sex between $PM_{2.5}$ exposure and relative growth in lung function, even after controlling for potential confounders (Table 3 and Figure 3). Analysis using two-pollutant models that included O_3 or NO_2 did not affect these null results (Table 3), nor did using sensitivity analyses (including fully adjusted modeling for ETS, household pet ownership, use of indoor heating appliances, and sneezing), using stratified analyses for participants with asthma and participants without asthma, or using stratified analyses that included or did not include ETS or that excluded participants with extreme obesity or participants who entered at a later stage (data not shown).

Discussion

This longitudinal analysis of the effects of $PM_{2.5}$ on lung function growth in preadolescent boys and pre- to early-adolescent girls aged 8–12 years involved 6,233 measurements in 1,466 participants but did not support clear evidence of an association between $PM_{2.5}$ and the relative growth of lung function as measured by using FEV_1, FVC, and $\dot{V}50$ for each 10-cm height growth in both preadolescent male participants and pre- to early-adolescent female participants. Mean $PM_{2.5}$ levels over the study period ranged from 10 $\mu g/m^3$ to 19 $\mu g/m^3$ in the school communities studied. Our results were consistent even after control for the major co-pollutants NO_2 or O_3 and for additional potential confounders at the individual level. Nor were any effect modifications observed in association with the participants' asthmatic status or ETS at home.

Previous reports from the CHS have indicated significant associations between $PM_{2.5}$ and lung function growth, but the results were based on $PM_{2.5}$ concentrations as high as around 30 $\mu g/m^3$. In the fourth-grade participants of the 1993 cohort (10 yr of age), no significant reductions in lung function were observed in association with $PM_{2.5}$ levels during a 4-year follow-up (4), but an extended follow-up until the participants were 18 years old indicated a significant difference in average growth as measured by FEV_1 over the 8-year period between those from the most and least polluted communities (which had average annual $PM_{2.5}$ levels of 30 $\mu g/m^3$ and 5 $\mu g/m^3$, respectively) (6). Further CHS data show improving 4-year growth in lung function as measured by FEV_1 and FVC (ages 11–15 years), in line with improving $PM_{2.5}$ levels across the three cohorts: the 3-year mean of $PM_{2.5}$ in the five participating communities ranged from 21.3 to 31.5 $\mu g/m^3$ in the 1994–1998 cohort, 19.9 to 27.6 $\mu g/m^3$ in the 1997–2001 cohort, and 11.9 to 17.8 $\mu g/m^3$ in the 2007–2011 cohort (10). This strongly suggests that exposure to $PM_{2.5}$ at annual average concentrations exceeding 20 $\mu g/m^3$ reduces lung function growth in children between the ages of 10 and 18 years. However, it remains unclear from the CHS whether long-term exposure to $PM_{2.5}$ at levels below 20 $\mu g/m^3$ causes reduced lung function growth in preadolescent children.

Birth cohort studies have provided useful data on lung function growth, as they included participants of preadolescent age living in places with relatively low annual $PM_{2.5}$ levels. The PIAMA (Prevention and Incidence of Asthma and Mite Allergy) birth cohort study, for example, provided a longitudinal analysis of lung function tests performed on 555 participants at the ages of 8 years and 12 years, which indicated no significant association between growth in FEV_1 and FVC and the $PM_{2.5}$ concentration at birth or during follow-up (31). This supported our results, but further analysis of 915 participants who attended at least two lung function tests at ages 8, 12, and 16 years indicated that exposure to $PM_{2.5}$ at ages 0–4 years resulted in reduced FEV_1 growth from ages 8–16 years, with an adjusted difference of −0.26% per each 1.2-$\mu g/m^3$ increase in $PM_{2.5}$ being demonstrated. However, the only exposure variable was $PM_{2.5}$ concentrations near the time of the participants' birth, and no analysis using exposure levels at the age of 4 years or using later or concurrent exposure from ages 8–16 years was reported (18). $PM_{2.5}$ concentrations in the PIAMA study were estimated from a land-use regression model

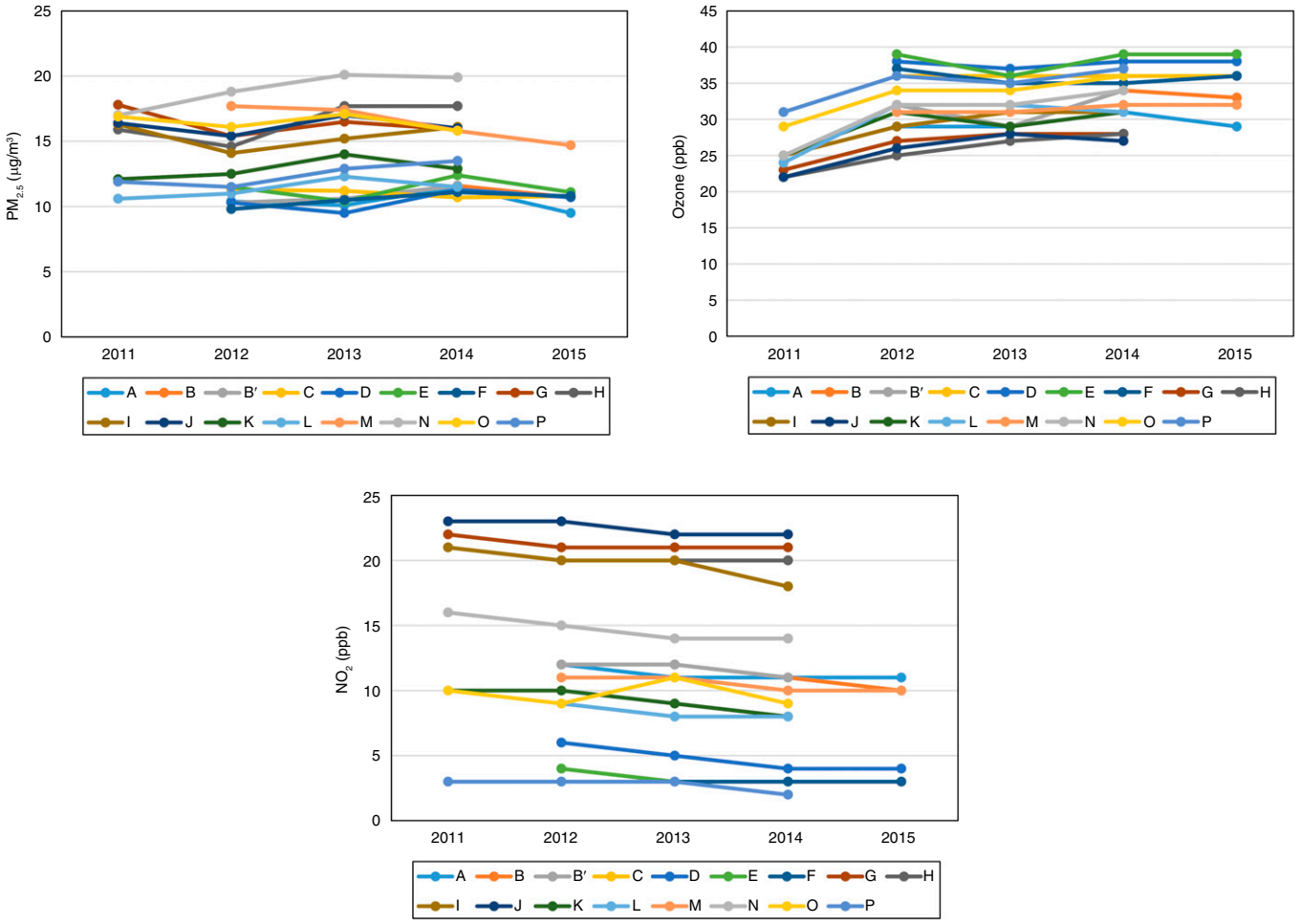

Figure 2. Annual average concentrations of $PM_{2.5}$ in $\mu g/m^3$ (upper left), ozone in parts per billion (upper right), and NO_2 in parts per billion (bottom center) by year during the study period. The letters A, B, C–F, G–J, K, L, M, N–O, and P indicate schools in Sapporo, Sendai, Sakata, Itabashi and Shibuya, Nagano, Matsumoto, Okayama, Fukuoka, and Amami, respectively. $PM_{2.5}$ = particulate matter ⩽2.5 μm in aerodynamic diameter; ppb = parts per billion.

extrapolated back from monitoring data collected between 2008 and 2010; the medians (ranges) of $PM_{2.5}$ used in the further analysis were 16.4 (15.2–19.4) $\mu g/m^3$ for participants in the 0- to 4-year age range, 16.4 (14.9–19.4) $\mu g/m^3$ for those aged 5–12 years, and 16.4 (14.9–18.6) $\mu g/m^3$ for those aged 13–16 years. In the BAMSE birth cohort study, no association was observed in 2,278 participants between the longitudinal changes in FEV_1 and FVC from ages 8–16 years and the exposure to particulate matter ⩽10 μm in aerodynamic diameter and nitrogen oxides at the ages of 0–1 year, 1–8 years, or 8–16 years (17). Thus, the results are mixed when it comes to the effects of long-term exposure to $PM_{2.5}$ in the 10–19 $\mu g/m^3$ range on lung function growth in preadolescence to early adolescence.

A mechanistic understanding of what amount of $PM_{2.5}$ during childhood may or may not influence lung growth trajectories and other lung health outcomes is also of value and could be expounded through pathophysiological or molecular approaches. Although their roles remain speculative, airway dysanapsis, a physiological incongruence between the growth of the lung parenchyma and the caliber of the airways (32–34), or epigenetic modification as assessed through DNA methylation (23, 35, 36) may mediate the effects of $PM_{2.5}$ on lung growth during the preadolescent and adolescent period.

One important question is whether a phase of lung function development during an adolescent growth spurt is a critical time period that is vulnerable to air pollution exposure. Longitudinal analysis in a population-based British birth cohort study indicated that pubertal age as defined by the median (interquartile range) age at the peak velocity of height growth was 13.5 (13.0–13.9) years for males and 11.7 (11.2–12.1) years for females, respectively (37). The study also showed that the effect of pubertal growth was manifested by an increase in both FEV_1 and FVC, indicating the importance of lung function growth in the preadolescent to adolescent age ranges. Extended follow-up of our cohort until adolescent age is expected to add to the epidemiological evidence of a nonlinear growth period of height and lung function at relatively low levels of annual $PM_{2.5}$. In the ESCAPE (European Study of Cohorts for Air Pollution Effects) project, a random-effect meta-analysis combining lung function data on five European birth cohorts at the ages of

Table 3. Effect of 10-μg/m^3 increase in $PM_{2.5}$ on relative growth of lung function indicators per 10-cm growth in height: stratified analysis by sex

Outcome by Model and Sex	Adjusted Estimate of $\exp(\beta_1 \times 10^2)$*	95% CI	*P* Value
Single-pollutant model			
Male			
FVC	1.00038	0.99958–1.00118	0.351
FEV_1	1.00054	0.99969–1.00139	0.211
$\dot{V}50$	1.00071	0.99900–1.00242	0.417
Female			
FVC	1.00004	0.99899–1.00108	0.944
FEV_1	1.00012	0.99916–1.00109	0.803
$\dot{V}50$	0.99989	0.99813–1.00165	0.905
Two-pollutant model (+O_3)			
Male			
FVC	1.00005	0.99997–1.00014	0.230
FEV_1	1.00007	0.99997–1.00016	0.166
$\dot{V}50$	1.00006	0.99986–1.00025	0.570
Female			
FVC	1.00005	0.99995–1.00015	0.364
FEV_1	1.00004	0.99994–1.00014	0.432
$\dot{V}50$	1.00000	0.99980–1.00020	0.997
Two-pollutant Model (+NO_2)			
Male			
FVC	1.00004	0.99994–1.00014	0.392
FEV_1	1.00006	0.99995–1.00017	0.279
$\dot{V}50$	1.00006	0.99984–1.00027	0.604
Female			
FVC	1.00008	0.99997–1.00019	0.162
FEV_1	1.00007	0.99996–1.00018	0.207
$\dot{V}50$	1.00003	0.99981–1.00026	0.765

Definition of abbreviations: CI = confidence interval; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; $PM_{2.5}$ = particulate matter ≤2.5 μm in aerodynamic diameter; $\dot{V}50$ = maximal expiratory flow rate at 50% of FVC.
*Adjusted for Rohrer index, allergic symptoms (wheezing, itchy rash), habitual exercise, and exposure to environmental tobacco smoke at home.

6 and 8 years showed a small but statistically significant decrease in FEV_1 per each 5-μg/m^3 increase in the estimated $PM_{2.5}$ level in a participant's local area ($PM_{2.5}$ range, 7.4–17.3 μg/m^3), but no association was observed when the $PM_{2.5}$ level at birth was applied (14). In a U.S. birth cohort study, a 2-μg/m^3 increase in $PM_{2.5}$ 1 year before lung function testing at age 7 was also shown to result in a significant decrease in FEV_1 ($PM_{2.5}$ range, 4.08–16.23 μg/m^3). However, neither $PM_{2.5}$ levels when participants were aged 0–1 year nor the average $PM_{2.5}$ levels throughout their lifetime were associated with reductions in FEV_1 (16). In contrast, the PIAMA birth cohort study indicated that exposure to $PM_{2.5}$ in early life (from birth to the age of 4 yr) resulted in reduced FEV_1 growth from ages 8–16 years (median $PM_{2.5}$, 16.4 μg/m^3) (18). In addition, in the Oslo Birth Cohort Study, peak expiratory flow and forced expiratory flow at 25% and 50% of FVC measured in participants aged 9–10 years were significantly associated with exposure to $PM_{2.5}$, particulate matter ≤10 μm in aerodynamic diameter, and NO_2 in the first year of life or throughout the lifetime (mean $PM_{2.5}$, 16.4 μg/m^3 at age 0–1 yr and 14.5 μg/m^3 for the lifetime), although no associations were observed for FEV_1 or FVC (13). Relatively high levels of $PM_{2.5}$ in early life might relate to such an effect. In our cohort setting, air-pollutant levels before the study period were not directly measured, but historical data on SPM, O_3, and NO_2 levels were collected from the monitoring station closest to each study school. These showed steadily decreasing levels of SPM and NO_2 and increasing levels of O_3 over the years, although the degree of change varied from area to area (Table E2). For $PM_{2.5}$, annual $PM_{2.5}$ levels in Japan have undergone a downward trend since the introduction of the national air quality standard in 2009, and the concentration was reported as 20–25 μg/m^3 in large metropolitan areas such as Tokyo and Fukuoka in 2005 in the survey data collected by the Ministry of the Environment (24).

On the multilevel regression model used in this study, we used height rather than age as a factor to describe children's overall growth. We believe this is reasonable because lung function is expected to grow with the child's height. In fact, in our preliminary data analysis, height was more strongly associated with the results of each lung function test than age (data not shown). Furthermore, we also conducted an additional unplanned analysis by using age instead of height in Equation 1. The results were essentially the same as in our main analysis (Table E3).

Strengths and Limitations

There are several strengths and limitations to this study. First, we secured a representative sample of the Japanese population with a wide range of $PM_{2.5}$ levels by closely following up with the participants and maintaining a high participation rate. More than 95% of the participants underwent lung function tests at least twice, and 81.3% were tested four or five times. Only 3.5% of the participants were moved out after a single test. The relatively large sample size (6,233 measurements in 1,466 participants) reduced the risk of random errors. Use of pollutant concentrations monitored at each school site during the whole study period is another strength, although using the school-based, community-level concentration instead of using the individua-level concentration could lead to an increased chance of getting null results because of random misclassification of exposure. Lack of at-home or indoor measurement could also contribute to random misclassification of exposure. Lung function testing is not easy to perform on children, especially young ones, but all testing was performed by trained technicians following a standardized protocol. The tests were strictly scheduled throughout the study in the morning hours during the same season every year, and they were all performed with the same spirometers equipped with

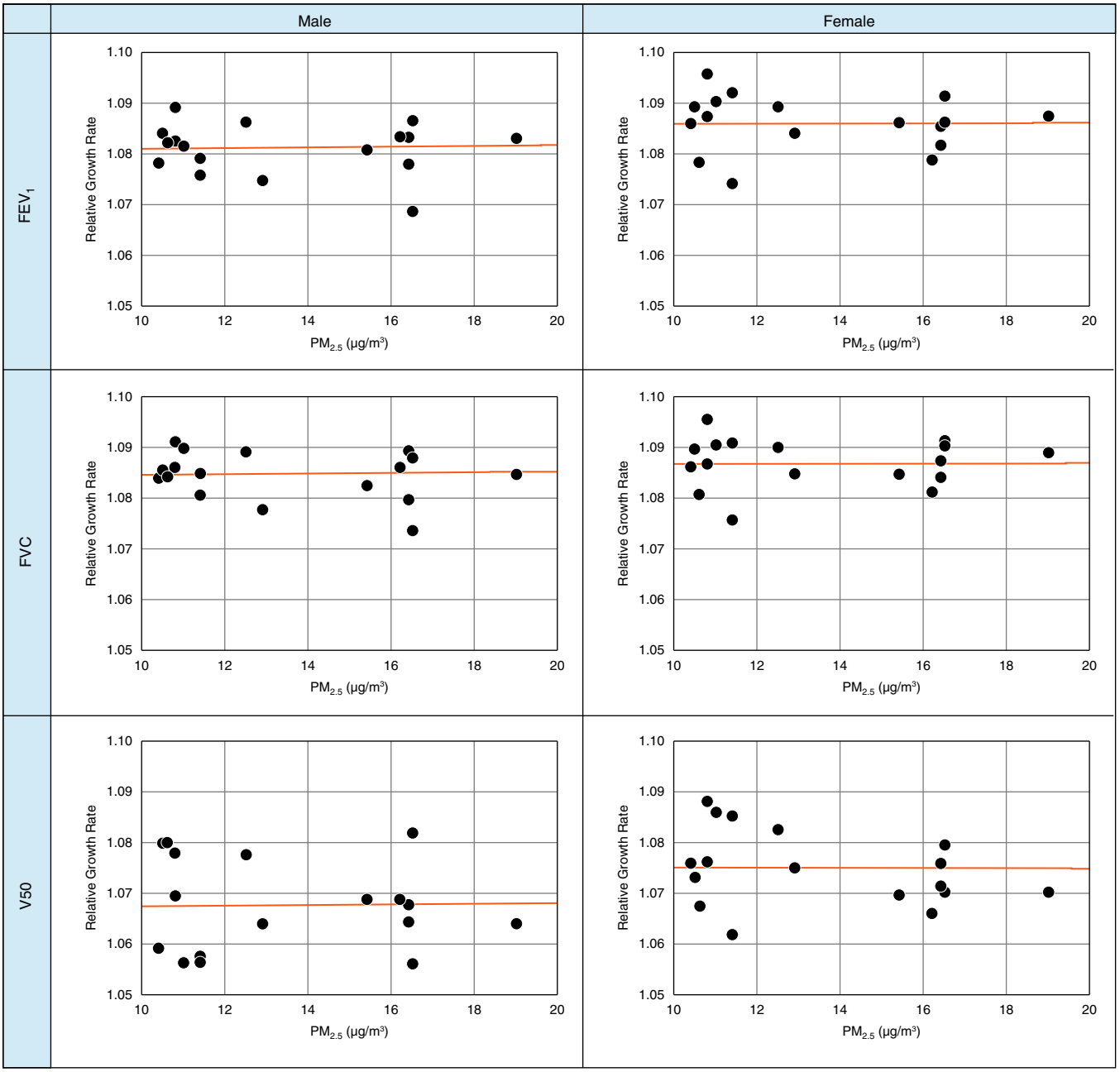

Figure 3. Relative growth of lung function indicators (FEV_1, FVC, and $\dot{V}50$) per each 10 cm of growth in height by sex. FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; $PM_{2.5}$ = particulate matter ⩽2.5 μm in aerodynamic diameter; $\dot{V}50$ = maximal expiratory flow rate at 50% of FVC.

Lilly-type pneumotach sensors to reduce the possibility of measurement errors. Unmeasured confounding factors may distort the study results naturally, although known, major confounding factors were already considered in the analysis. The result of this study could be implicative of a need to examine the adequacy of the air quality standard of $PM_{2.5}$, although the generalizability issue must be taken into account when applying our study results to a different population because of differences in ethnicity or $PM_{2.5}$ composition. The range of exposure in this study is equivalent to the annual air quality standard levels of various countries, including the United States (12 $\mu g/m^3$) (38), Japan (15 $\mu g/m^3$) (39), and the European Union (20 $\mu g/m^3$ per the 3-yr Average Exposure Indicator goals) (40).

Conclusions

In conclusion, our large, nationwide longitudinal cohort study of

preadolescent males and pre- to early-adolescent females in Japan with repeated measurements of lung function suggests that concurrent exposure to $PM_{2.5}$ in the range of 10.4–19.0 μg/m^3 during the preadolescent and early-adolescent period has little effect on lung function growth. Further studies with extended follow-up of this population until pubertal age are needed to expound the effects of $PM_{2.5}$ exposure on lung function growth. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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References

1 Peters JM, Avol E, Gauderman WJ, Linn WS, Navidi W, London SJ, *et al.* A study of twelve Southern California communities with differing levels and types of air pollution. II. Effects on pulmonary function. *Am J Respir Crit Care Med* 1999;159:768–775.
2 Lee YL, Wang WH, Lu CW, Lin YH, Hwang BF. Effects of ambient air pollution on pulmonary function among schoolchildren. *Int J Hyg Environ Health* 2011;214:369–375.
3 Chen CH, Chan CC, Chen BY, Cheng TJ, Guo YL. Effects of particulate air pollution and ozone on lung function in non-asthmatic children. *Environ Res* 2015;137:40–48.
4 Gauderman WJ, McConnell R, Gilliland F, London S, Thomas D, Avol E, *et al.* Association between air pollution and lung function growth in Southern California children. *Am J Respir Crit Care Med* 2000;162: 1383–1390.
5 Gauderman WJ, Gilliland GF, Vora H, Avol E, Stram D, McConnell R, *et al.* Association between air pollution and lung function growth in Southern California children: results from a second cohort. *Am J Respir Crit Care Med* 2002;166:76–84.
6 Gauderman WJ, Avol E, Gilliland F, Vora H, Thomas D, Berhane K, *et al.* The effect of air pollution on lung development from 10 to 18 years of age. *N Engl J Med* 2004;351:1057–1067.
7 Gauderman WJ, Vora H, McConnell R, Berhane K, Gilliland F, Thomas D, *et al.* Effect of exposure to traffic on lung development from 10 to 18 years of age: a cohort study. *Lancet* 2007;369:571–577.
8 Roy A, Hu W, Wei F, Korn L, Chapman RS, Zhang JJ. Ambient particulate matter and lung function growth in Chinese children. *Epidemiology* 2012;23:464–472.
9 Hwang BF, Chen YH, Lin YT, Wu XT, Lee YL. Relationship between exposure to fine particulates and ozone and reduced lung function in children. *Environ Res* 2015;137:382–390.
10 Gauderman WJ, Urman R, Avol E, Berhane K, McConnell R, Rappaport E, *et al.* Association of improved air quality with lung development in children. *N Engl J Med* 2015;372:905–913.
11 Chen BY, Chen CH, Chuang YC, Wu YH, Pan SC, Guo YL. Changes in the relationship between ambient fine particle concentrations and childhood lung function over 5 years. *Environ Res* 2019;179:108809.
12 Guo C, Hoek G, Chang LY, Bo Y, Lin C, Huang B, *et al.* Long-term exposure to ambient fine particulate matter ($PM_{2.5}$) and lung function in children, adolescents, and young adults: a longitudinal cohort study. *Environ Health Perspect* 2019;127:127008.
13 Oftedal B, Brunekreef B, Nystad W, Madsen C, Walker SE, Nafstad P. Residential outdoor air pollution and lung function in schoolchildren. *Epidemiology* 2008;19:129–137.
14 Gehring U, Gruzieva O, Agius RM, Beelen R, Custovic A, Cyrys J, *et al.* Air pollution exposure and lung function in children: the ESCAPE project. *Environ Health Perspect* 2013;121:1357–1364.
15 Fuertes E, Bracher J, Flexeder C, Markevych I, Klümper C, Hoffmann B, *et al.* Long-term air pollution exposure and lung function in 15 year-old adolescents living in an urban and rural area in Germany: the GINIplus and LISAplus cohorts. *Int J Hyg Environ Health* 2015;218:656–665.
16 Rice MB, Rifas-Shiman SL, Litonjua AA, Oken E, Gillman MW, Kloog I, *et al.* Lifetime exposure to ambient pollution and lung function in children. *Am J Respir Crit Care Med* 2016;193:881–888.
17 Schultz ES, Hallberg J, Bellander T, Bergström A, Bottai M, Chiesa F, *et al.* Early-life exposure to traffic-related air pollution and lung function in adolescence. *Am J Respir Crit Care Med* 2016;193: 171–177.
18 Milanzi EB, Koppelman GH, Smit HA, Wijga AH, Oldenwening M, Vonk JM, *et al.* Air pollution exposure and lung function until age 16 years: the PIAMA birth cohort study. *Eur Respir J* 2018;52: 1800218.
19 Majewska R, Pac A, Mróz E, Spengler J, Camann D, Mrozek-Budzyn D, *et al.* Lung function growth trajectories in non-asthmatic children aged 4–9 in relation to prenatal exposure to airborne particulate matter and polycyclic aromatic hydrocarbons—Krakow birth cohort study. *Environ Res* 2018;166:150–157.
20 Wang X, Dockery DW, Wypij D, Fay ME, Ferris BG Jr. Pulmonary function between 6 and 18 years of age. *Pediatr Pulmonol* 1993;15: 75–88.
21 Bui DS, Lodge CJ, Burgess JA, Lowe AJ, Perret J, Bui MQ, *et al.* Childhood predictors of lung function trajectories and future COPD risk: a prospective cohort study from the first to the sixth decade of life. *Lancet Respir Med* 2018;6:535–544.
22 Bui DS, Walters HE, Burgess JA, Perret JL, Bui MQ, Bowatte G, *et al.* Childhood respiratory risk factor profiles and middle-age lung function: a prospective cohort study from the first to sixth decade. *Ann Am Thorac Soc* 2018;15:1057–1066.
23 Sunny SK, Zhang H, Mzayek F, Relton CL, Ring S, Henderson AJ, *et al.* Pre-adolescence DNA methylation is associated with lung function trajectories from pre-adolescence to adulthood. *Clin Epigenetics* 2021; 13:5.
24 Ministry of the Environment. Report on assessment of the exposure and health effects of fine particulate matter on public health [in Japanese]. Tokyo, Japan: Government of Japan; 2007 [accessed 2021 Jul 14]. Available from: https://www.env.go.jp/air/report/h19-03/.
25 Ministry of the Environment. Sixth manual for continuous monitoring of air pollution 2010 [in Japanese]. Tokyo, Japan: Government of Japan; 2010 [accessed 2021 Jul 14]. Available from: https://www.env.go.jp/air/osen/manual_6th/.
26 Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, *et al.*; ATS/ERS Task Force. Standardisation of spirometry. *Eur Respir J* 2005;26:319–338.
27 Nishima S, Odajima H. Prevalence of childhood allergic disease using International Study of Asthma and Allergies in Childhood (ISAAC) in phase I trials [in Japanese]. *Jpn J Pediatr Allergy Clin Immunol* 2002; 16:207–220.
28 Little RJA, Rubin DB. Statistical analysis with missing data, 2nd ed. Hoboken, NJ: Wiley; 2002.
29 Peters JM. Epidemiologic investigation to identify chronic effects of ambient air pollutants in Southern California. Sacramento, CA: California Air Resources Board; 2004 [created 2004 May; accessed 2021 Jan 4]. Available from: https://www.arb.ca.gov/research/single-project.php?row_id=60245.
30 Royston P, Altman DG. Regression using fractional polynomials of continuous covariates: parsimonious parametric modelling. *J R Stat Soc Ser C Appl Stat* 1994;43:429–467.
31 Gehring U, Beelen R, Eeftens M, Hoek G, de Hoogh K, de Jongste JC, *et al.* Particulate matter composition and respiratory health: the PIAMA birth cohort study. *Epidemiology* 2015;26:300–309.
32 Green M, Mead J, Turner JM. Variability of maximum expiratory flow-volume curves. *J Appl Physiol* 1974;37:67–74.

33 Forno E, Weiner DJ, Mullen J, Sawicki G, Kurland G, Han YY, *et al.* Obesity and airway dysanapsis in children with and without asthma. *Am J Respir Crit Care Med* 2017;195:314–323.
34 Smith BM, Kirby M, Hoffman EA, Kronmal RA, Aaron SD, Allen NB, *et al.*; MESA Lung, CanCOLD, and SPIROMICS Investigators. Association of dysanapsis with chronic obstructive pulmonary disease among older adults. *JAMA* 2020;323:2268–2280.
35 Sunny SK, Zhang H, Relton CL, Ring S, Kadalayil L, Mzayek F, *et al.* Sex-specific longitudinal association of DNA methylation with lung function. *ERJ Open Res* 2021;7:0127–2021.
36 Han L, Zhang H, Kaushal A, Rezwan FI, Kadalayil L, Karmaus W, *et al.* Changes in DNA methylation from pre- to post-adolescence are associated with pubertal exposures. *Clin Epigenetics* 2019; 11:176.
37 Mahmoud O, Granell R, Tilling K, Minelli C, Garcia-Aymerich J, Holloway JW, *et al.* Association of height growth in puberty with lung function: a longitudinal study. *Am J Respir Crit Care Med* 2018;198:1539–1548.
38 United States Environmental Protection Agency. National Ambient Air Quality Standards (NAAQS) for PM. Washington, D.C.; 2021 [accessed 2021 Jul 14]. Available from: https://www.epa.gov/pm-pollution/national-ambient-air-quality-standards-naaqs-pm.
39 Ministry of the Environment. Information on particulate matter (PM2.5) [in Japanese]. Tokyo, Japan: Government of Japan; 2021 [accessed 2021 Jul 14]. Available from: http://www.env.go.jp/air/osen/pm/info.html#STANDARD.
40 European Commission. Air quality standards. 2021 [accessed 2021 Jul 14]. Available from: Available from: https://ec.europa.eu/environment/air/quality/standards.htm.