


## ORIGINAL ARTICLE

# Sex Differences in the Prevalence and Severity of Exercise-Induced Bronchoconstriction in Kindergarteners in Japan

Miwa Shinohara MD, PhD<sup>1,2</sup>  | Sigeto Ogawa<sup>3</sup> | Takahiro Nakaya MD<sup>4,2</sup> | Ryouji Niino MD<sup>5,2</sup> | Masanori Ito MD, PhD<sup>4,2</sup> | Kaoru Haro MD<sup>6,2</sup> | Eiichi Ishii MD, PhD<sup>7</sup>

<sup>1</sup>Department of Pediatrics, Juntendo University, Tokyo, Japan

<sup>2</sup>Department of Pediatrics, Ehime University Hospital, Toon, Japan

<sup>3</sup>Faculty of Medicine, Ehime University Graduate School of Medicine, Toon, Japan

<sup>4</sup>Department of Pediatrics, Yawatahama City General Hospital, Yawatahama, Japan

<sup>5</sup>Department of Pediatrics, Ehime Prefectural Central Hospital, Matsuyama, Japan

<sup>6</sup>Department of Pediatrics, University of Occupational and Environmental Health, Kitakyushu, Japan

<sup>7</sup>Department of Pediatrics, Ehime University Graduate School of Medicine, Toon, Japan

## Correspondence

Miwa Shinohara, Department of Pediatrics, Juntendo University, Tokyo, Japan.  
Email: mi-shinohara@juntendo.ac.jp

## Abstract

**Background:** Exercise-induced bronchoconstriction (EIB), a strong positive predictor of asthma, becomes progressively less frequent with age. Although asthma tends to become less common only in boys during adolescence, sex differences in EIB, especially in preschoolers, remain unclear. To find EIB for early diagnosis and intervention asthma, mass-screening tests considering sex differences in preschoolers are needed. In this study, we investigated whether sex differences influence the prevalence and severity of EIB in prepubertal children aged 5–6 years.

**Methods:** Fifty-one children aged 5–6 years who were attending a kindergarten in Matsuyama City, Ehime, Japan, were enrolled in this cross-sectional study. The children underwent a 6-minute free-running test in 2015. The peak expiratory flow rate (PEFR) was measured before exercise and 0, 3, 10, and 20 minutes after exercise. The severity of EIB was classified according to the reduction in PEFR, measured as the difference between the postexercise PEFR and the highest pre-exercise PEFR.

**Results:** Of the 51 children (23 boys and 28 girls) enrolled, the prevalence of EIB defined as three criteria: a  $\geq 15\%$ ,  $\geq 20\%$ , or  $\geq 25\%$  decrease was 54.9% (28/51), 41.2% (21/51), and 25.5% (13/51), respectively. The prevalence of EIB defined as  $\geq 25\%$  decrease was significantly higher in girls than in boys (39.3% vs 8.7%,  $P = .013$ ). In girls, the mean percentage change in PEFR was significantly higher 20 minutes than 10 minutes postexercise ( $P = .043$ ).

**Conclusions:** Sex difference in the prevalence and severity of EIB should be considered when evaluating EIB, even in young, prepubertal children.

## KEYWORDS

asthma, children, exercise-induced bronchoconstriction, peak expiratory flow rate, sex differences

## 1 | INTRODUCTION

Exercise-induced bronchoconstriction (EIB) is characterized by transient airway narrowing occurring during and after exercise. It can occur in individuals with and without asthma<sup>1</sup>. Estimates of the prevalence of EIB

range from 10% to 20% in school-aged children<sup>2</sup>, from 40% to 90% in those with asthma<sup>3</sup>, and from 30% to 70% in Olympic or elite-level athletes. EIB is more common in young children, and the prevalence of EIB progressively decreases with age<sup>4</sup>. However, the reported prevalence of EIB is varied, depending on the populations, regions, and methods<sup>1</sup>.

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Exercise-induced bronchoconstriction in childhood is a positive predictor of asthma, an important component of asthma, and an early sign of bronchial hyper-responsiveness<sup>5,6</sup>. On the other hand, asthma-related death is major in sport-related death that is a cause of death during or after sporting activity, especially in adolescent among boys<sup>7</sup>. Feasible, simple, and effective mass-screening tests to find EIB in general young children may be helpful to detect subclinical asthma and be able to prevent subsequent asthma-related deaths in association with sporting activities.

In childhood, wheezing disorders/asthma represent a heterogeneous group of conditions characterized by increased responsiveness to methacholine and increased peak flow variability according to age<sup>8</sup>. Thus, the timing to perform is an important issue for a mass-screening test to find EIB in young children with subclinical asthma. Although recurrent cough and wheeze commonly develop in 2–6-year-old children<sup>9</sup>, at least three different wheezing phenotypes associated with different risk factors co-exist during the first 11 years of life<sup>8</sup>. “Transient early wheezers” limited to the first 3 years of life and unrelated to increased airway lability; however, part of “nontopic wheezers” and “IgE-associated wheezers/asthma” at 4–6 years will continue to have asthma that persists into adult life<sup>8</sup>. Our aim was to establish an effective mass screening to find EIB in general young children with subclinical asthma; thus, we chose 5- to 6-year-old children who might subsequently onset persistent asthma in the near future.

However, the answer to the question “Which test should be used to diagnose EIB in the preschool age group, especially mass survey?” is inconclusive<sup>9</sup>. Almost preschool-aged children have difficulties in performing the forced expiratory maneuvers required for spirometry, because they can either blow “hard” or “long,” but frequently cannot blow both hard and long<sup>9</sup>. On the contrary, the PEFr can be measured by a simple instrument—peak expiratory flow meter. The standard ranges of PEFr in normal healthy children are reported in Japanese aged 6 to 18 years and in other races aged more than 4 years<sup>10</sup>. Thus, 5–6-year-old children can perform peak expiratory flow meter enough. However, in Japanese, the regression equations for PEFr in children aged less than 5 years and a kindergarten-based general population survey to detect EIB have not been investigated.

For a pulmonary function test in the mass screening, “preschool-aged child-friendly” is the utmost importance. These young children must be made to feel comfortable in the survey environment if they are to perform the measurements accurately. Operators to participate in the test have a significant impact on the comfort level of the child, because the children need to be engaged and encouraged by them during the tests. Additionally, safety precautions and hygiene requirements are necessary for preschoolers<sup>9</sup>. Thus, for the EIB survey, we chose the 6-minute free-running test (6MFRT) with using PEFr meter, because the free-running in their familial place; a kindergarten makes 5- to 6-year-old children fun, joyful, and comfortable like playing.

The prevalence of wheezing is stable from birth to adolescence in boys; however, it rapidly decreases from birth to the preschool years and increases from childhood to adolescence in girls<sup>11</sup>. Sex

hormones appear to exert regulatory effects on human lung development from the neonatal period<sup>12</sup>. Moreover, sex- and age-specific differences in lung function and wheezing disorders and associated risk factors have been reported<sup>13,14</sup>. However, sex differences related to the prevalence of EIB in childhood are controversial<sup>4,15–18</sup>. Furthermore, sex differences in EIB among preschool children are unclear because such young children are usually unable to perform standard spirometry<sup>9</sup>. Sex- and age-specific early screening methods for EIB in young children may allow for timely interventions and a more personalized approach to the treatment of EIB and asthma<sup>11,19</sup>.

To establish an effective mass-screening test for early findings of EIB in general young children with subclinical asthma, we performed the first kindergarten-based preliminary survey for EIB in a general 5–6-year-old Japanese children using the 6MFRT. In this survey, we hypothesized that sex differences in EIB exist even since prepubertal children. In this study, we investigated airway reactivity to exercise using peak flow meter measurement in the children and evaluated differences in the prevalence of EIB between boys and girls based on EIB defined as three criteria: a  $\geq 15\%$ ,  $\geq 20\%$ , or  $\geq 25\%$  decrease in postexercise PEFr.

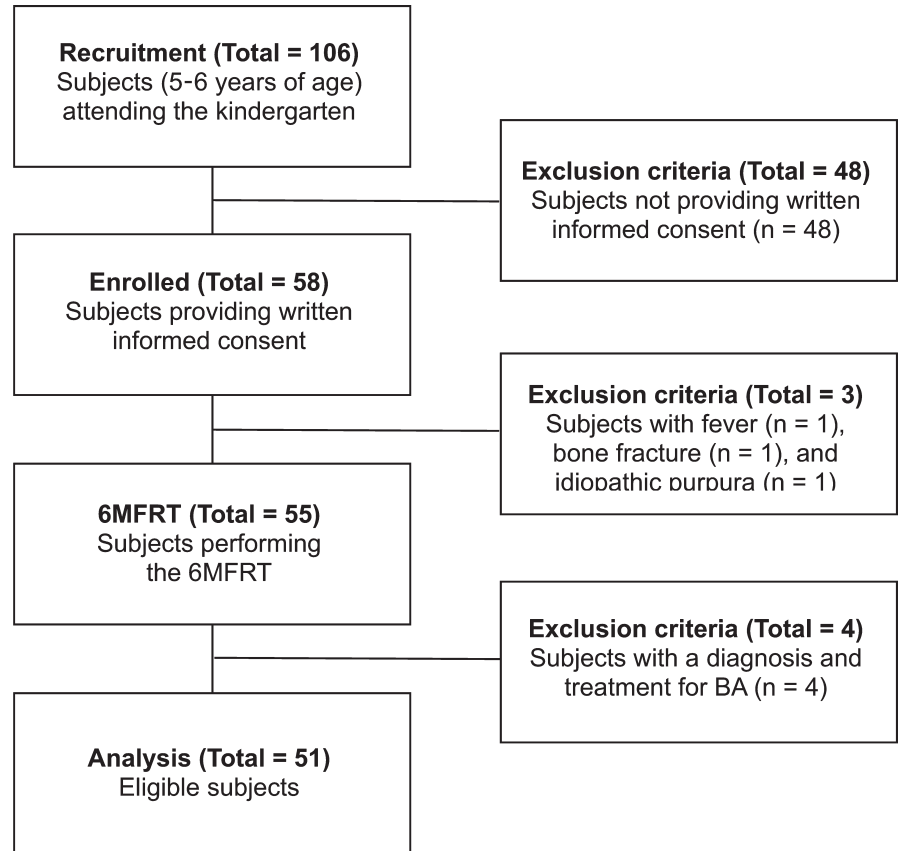
## 2 | MATERIALS AND METHODS

### 2.1 | Study design and patients

This epidemiological cross-sectional study was performed during June 2015 in Matsuyama City, Ehime, Japan. In May 2015, the guardians of 106 children aged 5–6 years, who attended Aiko Kindergarten, were asked permission for their children to perform the 6MFRT and to be included in the study after obtaining written informed consent. Overall, 54.7% (58/106) of the children were enrolled. Children with a fever ( $n = 1$ ), bone fracture ( $n = 1$ ), and idiopathic purpura ( $n = 1$ ) were excluded. Fifty-five children underwent physical examinations that revealed no evidence of wheezing—they performed the 6MFRT and underwent peak expiratory flow rate (PEFr) measurement. This is the first preliminary mass survey to find EIB in a general kindergarten-based. Some of the children are supposed to be subclinical asthma or have undiagnosed asthma. In Japan, test for EIB is not commonly performed in children, even in with BA. Because of participating in the 6MFRT is an incentive for children, we performed 6MFRT for all kindergarteners whose guardians allowed the informed consent. Then, four children were subsequently excluded because they either had a diagnosis of asthma or used medication to treat asthma, including inhaled steroids, antihistamines, allergy medications, antibiotics, antitussive drugs, or expectorant drugs. Finally, the data of children were eligible for analysis (Figure 1).

Age, sex, height, and weight were recorded for all children. Standing heights were measured without shoes or traction. Body mass index (BMI) was calculated as weight (kg) divided by the square of the height ( $m^2$ ), rounded to one decimal place. BMI (World Health Organization) z-scores were calculated. The normality was defined as the z-score between  $-3$  and  $3$ <sup>20</sup>.

**FIGURE 1** Flow diagram showing the study's recruitment, eligibility, and exclusion process. 6MFRT, 6-minute free-running test; BA, bronchial asthma



The study was approved by the Institutional Review Board at Ehime University in May 2015 (No. 1506014) and was performed according to the tenets of the Helsinki Declaration of 1975, revised in 2008. 106.

## 2.2 | Outcomes

The primary outcome was the sex difference in the prevalence of EIB, defined as three criteria: a  $\geq 15\%$ ,  $\geq 20\%$ , or  $\geq 25\%$  decrease in postexercise PEFR. The secondary outcomes were sex differences in the mean PEFR and the response of the mean PEFR percentage to exercise.

## 2.3 | The 6-minute free-running test

The 6MFRT was performed in the kindergarten corridors under the supervision of pediatricians and with the assistance of medical students, as previously described<sup>21,22</sup>. The research team constructed by 3–4 pediatrician and 3–5 medical students wearing casual clothes always made the children feel to relax and joy to participate in the 6MFRT like one of the joyful plays in the kindergarten. The children and we had an ice-breaking time to ask each other about humorous questions about asthma, EIB, and us, because the comfort level of the child has a significant impact on the accuracy of pulmonary tests<sup>9</sup>. First, we performed PEFR meter in front of the children, and then, the children practiced the PEFR with us like a play before the 6MFRT. The children performed a 6-minute free run without a warm-up period between 10:00 and 11:00AM in June 2015. They were asked to run freely back and forth in the 55-m-long kindergarten

corridor. The mean relative humidity in the corridor was 46%–71%, and the temperature was 24.2–35.4°C. Several adults (pediatricians and medical students) ran with the children to encourage continued running. A portable mobile pulse oximeter monitor (myBeat; Union Tool A, Inc.) measured the heart rate and oxygen saturation continuously throughout the run. The results of the 6MFRT were considered acceptable because exercise was encouraged until the heart rate reached at least 80%–90% of the predicted maximum (calculated as  $220 - \text{age in years}$ )<sup>23</sup>. We categorized the running speed of the children by common running tests in the kindergarten: slow, middle, and fast groups. Then, a child was selected from each categorized group, and a total of three children were measured by the myBeat. The heart rate of the children reached over the target range during the 6MFRT. Coughing, auscultatory wheeze, heart rate, and oxygen saturation, monitored by a portable mobile pulse oximeter monitor (PULSOX-Lite; Konica Minolta, Inc.), were recorded before exercise and 0, 3, 10, and 20 minutes after exercise. We also prepared administration of an inhaled  $\beta_2$  agonist using a nebulizer, if the children occur wheezing.

## 2.4 | Peak expiratory flow rate measurements

The PEFR was measured before exercise and 0, 3, 10, and 20 minutes after exercise using a Mini-Wright peak flow meter (Clement Clarke International, Ltd.). For the accuracy and hygiene aspects of PEFR meters, we used new PEFR meters for the study. Before exercise, the children were taught how to exhale into the peak flow meter. The tests were performed standing in a position in which the neck could

not be flexed. Maximal expiration (as hard as possible) was performed immediately after full inspiration. The highest PEFR of three correctly performed expirations was recorded and defined as the best PEFR<sup>24</sup>. If the values of the highest two of the three acceptable expirations were not within 40 L/min or 5%, one additional expiration was performed to obtain consistent measurements; if this was not achieved, failure to do so was recorded along with the highest reading. Regarding the standard PEFR using Mini-Wright flow meter, the estimated regression equations in 2614 healthy Japanese aged 6–18 years (1241boysand1,373girls) using Mini-Wright flow meter are below: boys (L/min) =  $64.53 \times \text{Ht (m)}^3 + 0.4795 \times \text{Age (y)}^2 + 77.0$  and girls (L/min) =  $310.4 \times \text{Ht (m)} + 6.463 \times \text{Age (y)} - 209.0$ <sup>10</sup>.

## 2.5 | Exercise-induced bronchoconstriction criteria

Exercise-induced changes were quantitated from the PEFR measurements; the following formula was used: EIB = (best pre-exercise PEFR minus postexercise PEFR/best pre-exercise PEFR)  $\times 100$ <sup>17,25</sup>. The severity of EIB was classified according to the magnitude of the reduction in PEFR, as follows:  $\geq 15\%$ ,  $\geq 20\%$ , or  $\geq 25\%$  decrease in postexercise PEFR. The selection of a 15% cutoff for EIB was based

on previous studies<sup>16,21,22</sup>, and the selection of a  $\geq 20\%$  cutoff was based on the Japanese Guideline for Childhood Asthma<sup>25</sup>. Previous studies used different normal ranges for the percentage decrease in postexercise PEFR, such as 10%–15%<sup>21</sup>, and even  $< 25\%$ <sup>1,26–28</sup>.

## 2.6 | Statistical analysis

To identify significant differences between girls and boys, the Mann-Whitney *U* test was used to analyze differences in age, height, body weight, BMI, heart rate, best PEFR, the mean best PEFR, and the mean percentage change in PEFR. The chi-square test or Fisher's exact test was used, as appropriate, to assess differences between boys and girls regarding the number of children with EIB defined as three criteria: a  $\geq 15\%$ ,  $\geq 20\%$ , or  $\geq 25\%$  decrease in PEFR after the 6MFR.

All statistical analyses were performed using STATA software (Stata/SE 13.1; Stata Corp.). *P*-values  $< .05$  were considered significant.

We also calculated sample sizes by two-sample comparison of proportions (power 80%) using STATA software.

**TABLE 1** Characteristics of the 51 participants

Characteristics	Total	Boys	Girls	<i>P</i> value*
	(n = 51)	(n = 23)	(n = 28)	
	Median (range)	Median (range)	Median (range)	
	Mean (SD)	Mean (SD)	Mean (SD)	
Age (y)	5.8 (5.1–6.2)	5.7 (5.1–6.2)	5.9 (5.4–6.2)	.162
	5.8 (0.3)	5.7 (0.3)	5.9 (0.3)	
Height (cm)	110.7 (101–123)	110.5 (101–123)	111.0 (102.5–118.7)	.571
	110.7 (4.3)	110.5 (4.9)	111.0 (3.7)	
Body weight (kg)	18.8 (15.5–24.5)	18.9 (15.5–24.0)	18.7 (16.0–24.5)	.992
	18.8 (2.0)	18.9 (2.2)	18.7 (1.8)	
BMI (kg/m <sup>2</sup> )	15.3 (13.3–17.6)	15.4 (13.9–16.9)	15.2 (13.3–17.6)	.333
	15.3 (1.0)	15.4 (0.9)	15.2 (1.0)	
WHO z-scores	-0.03 (-1.42–1.26)	0.07 (-1.12–1.15)	-0.11 (-1.42– 1.26)	.384
(BMI-for-age in kg/m <sup>2</sup> )	-0.03 (0.66)	0.07 (0.71)	-0.11 (0.61)	
Pre-exercise heart rate (/min)	91.4 (57–130)	90.7 (57–120)	91.9 (71–130)	.985
	91.4 (12.4)	90.7 (12.5)	91.9 (12.6)	
Postexercise heart rate (/min)	118.9 (71–170)	118.7 (85–140)	119.0 (71–170)	.865
	118.9 (18.8)	118.7 (13.8)	119.0 (22.3)	
Pre-exercise SpO <sub>2</sub> (%)	97.6 (94–100)	97.8 (95–99)	97.5 (94–100)	.337
	97.6 (1.2)	97.8 (1.1)	97.5 (1.3)	
Postexercise SpO <sub>2</sub> (%)	97.3 (91–99)	97.4 (92–99)	97.2 (91–99)	.738
	97.3 (1.6)	97.4 (1.6)	97.2 (1.7)	
Best PEFR (L/min)	144.4 (90–250)	160.0 (100–250)	131.6 (90–190)	.003
	144.4 (33.5)	160.0 (35.1)	131.6 (26.5)	

Note: Data expressed as number, the median (range), or the mean (SD).

Abbreviations: BMI, body mass index; PEFR, peak expiratory flow rate; WHO, World Health Organization.

\*Mann-Whitney *U* test.

**TABLE 2** Associated variables with the regression equation of PEFR in Japanese children in the 51 participants separated by age

Variables	Total		P value <sup>†</sup>	Boys		P value <sup>†</sup>	Girls		P value <sup>†</sup>	P value <sup>‡</sup>
	Median	(range)		Median	(range)		Median	(range)		
	Mean	(SD)		Mean	(SD)		Mean	(SD)		
Height (cm)										
5-year-old children	(n = 33)		.007	(n = 18)		.195	(n = 15)		.019	
	109.8	(101–123)		109.8	(101–123)		109.7	(103–119)		.940
	109.8	(4.5)		109.8	(5.1)		109.7	(4.0)		
6-year-old children	(n = 18)			(n = 5)			(n = 13)			
	112.5	(106–118)		112.6	(106–118)		112.4	(106–118)		.657
	112.5	(3.2)		112.6	(4.3)		112.4	(2.9)		
Best PEFR (L/min)										
5-year-old children	(n = 33)		.149	(n = 18)		.793	(n = 15)		.004	
	141.5	(90–250)		161.4	(100–250)		117.7	(90–150)		.0005
	141.5	(38.0)		161.4	(39.3)		117.7	(17.5)		
6-year-old children	(n = 18)			(n = 5)			(n = 13)			
	149.7	(100–190)		155.0	(145–175)		147.7	(100–190)		.654
	149.7	(23.4)		155.0	(12.7)		147.7	(26.5)		

Note: Data expressed as number, the median (range), or the mean (SD).

Abbreviation: PEFR, peak expiratory flow rate.

<sup>†</sup>Statistical difference between 5- and 6-year-old children by Mann-Whitney *U* test.

<sup>‡</sup>Statistical difference between boys and girls by Mann-Whitney *U* test.

### 3 | RESULTS

#### 3.1 | Characteristics of the participants

We enrolled 23 boys and 28 girls in this study. All children completed the 6MFRT, and none exhibited an asthma attack or audible wheezing after exercise. Their mean age ( $\pm$ standard deviation) was  $5.8 \pm 0.3$  years: range, 5.1–6.2 years. The mean PEFR before exercise was significantly lower in girls than in boys ( $P = .003$ ) (Table 1).

Associations between the age of the children and variables, such as height and PEFR, related to the standard regression equation of PEFR in Japanese children<sup>10</sup> are shown in Table 2. The ranges of PEFR 6-year-old in boys and girls in our study were almost within the estimated range in Japanese. Notably, both associated variables with the standard regression equation of PEFR, such as height and PEFR, were significantly different between the 5-year-old and 6-year-old girls ( $P = .019$  and  $P = .004$ , respectively), except boys (Table 2). In total children, a significant difference between the 5-year-old and 6-year-old children was found only in their height ( $P = .007$ ), except the best PEFR.

#### 3.2 | Mean PEFR and changes in the mean percentage PEFR

The nadir time of the mean percentage change in postexercise PEFR was 10 minutes in girls and 3 minutes in boys. At any time point, there were no significant differences in the mean percentage change in PEFR in all children (Figure 2A) and between boys and

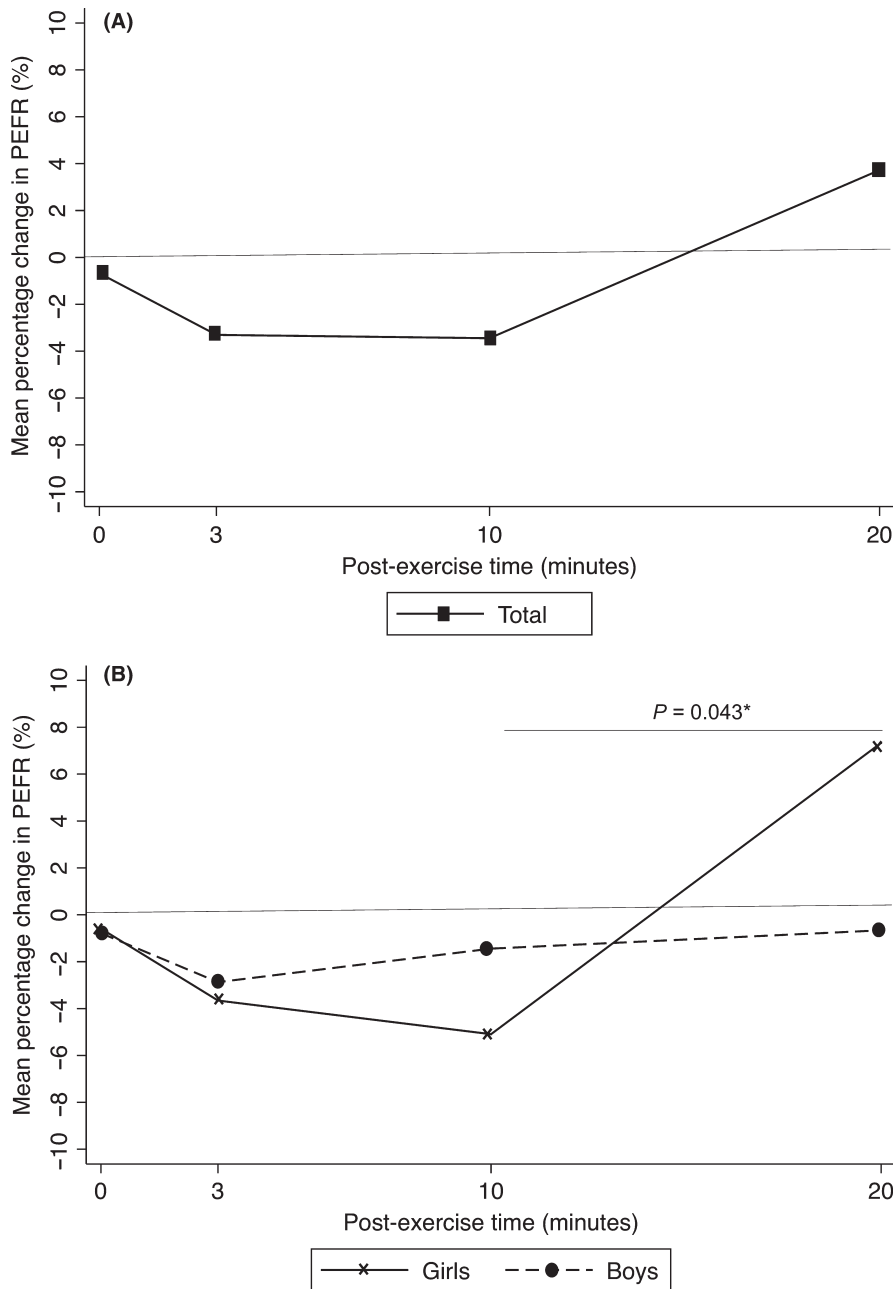
girls (Figure 2B). The recovery to best PEFR appeared to occur more quickly in girls than in boys at 20 minutes. In girls, the mean percentage change in PEFR was significantly higher at 20 minutes than at 10 minutes after exercise ( $P = .043$ ) (Figure 2B).

#### 3.3 | Sex differences in prevalence of EIB

Overall, the prevalence of EIB defined as a  $\geq 15\%$  and  $\geq 20\%$  decrease in postexercise PEFR was not significantly different between boys and girls, respectively, at any time point (47.8% vs 60.7%,  $P = .357$  and 30.4% vs 50.0%,  $P = .158$ , respectively; Figure 3A). However, the prevalence of EIB defined as  $\geq 25\%$  decrease in postexercise PEFR was significantly higher in girls than in boys (39.3% [11/51] vs 8.7% [2/23],  $P = .013$ ; Figure 3A). For all children and for girls, respectively, the prevalence of EIB defined as a  $\geq 15\%$  and  $\geq 20\%$  decrease in postexercise PEFR peaked 10 minutes after exercise (25.5% [13/51] vs 35.7% [10/28] and 19.6% [10/51] vs 25.0% [7/28], respectively; Figure 3B). The prevalence of EIB defined as  $\geq 25\%$  decrease in postexercise PEFR peaked immediately (0 minutes) after exercise in all children (11.8% [6/51]), boys (4.4% [1/23]), and girls (17.9% [5/28]), as shown in Figure 3B.

### 4 | DISCUSSION

In this study, sex differences in the prevalence of EIB and in the pattern of response to exercise were clarified in prepubertal children.



**FIGURE 2** Mean percentage change in PEFR at 0–3, 10, and 20 min postexercise in all participants (A) and stratified by sex (B). Data are shown as mean values. *P*-values were calculated using the Mann-Whitney *U* test. The *P*-values for the mean percentage changes in PEFR in girls vs those in boys at 0, 3, 10, and 20 min postexercise were 0.432, 0.924, 0.378, and 0.099, respectively. PEFR, peak expiratory flow rate

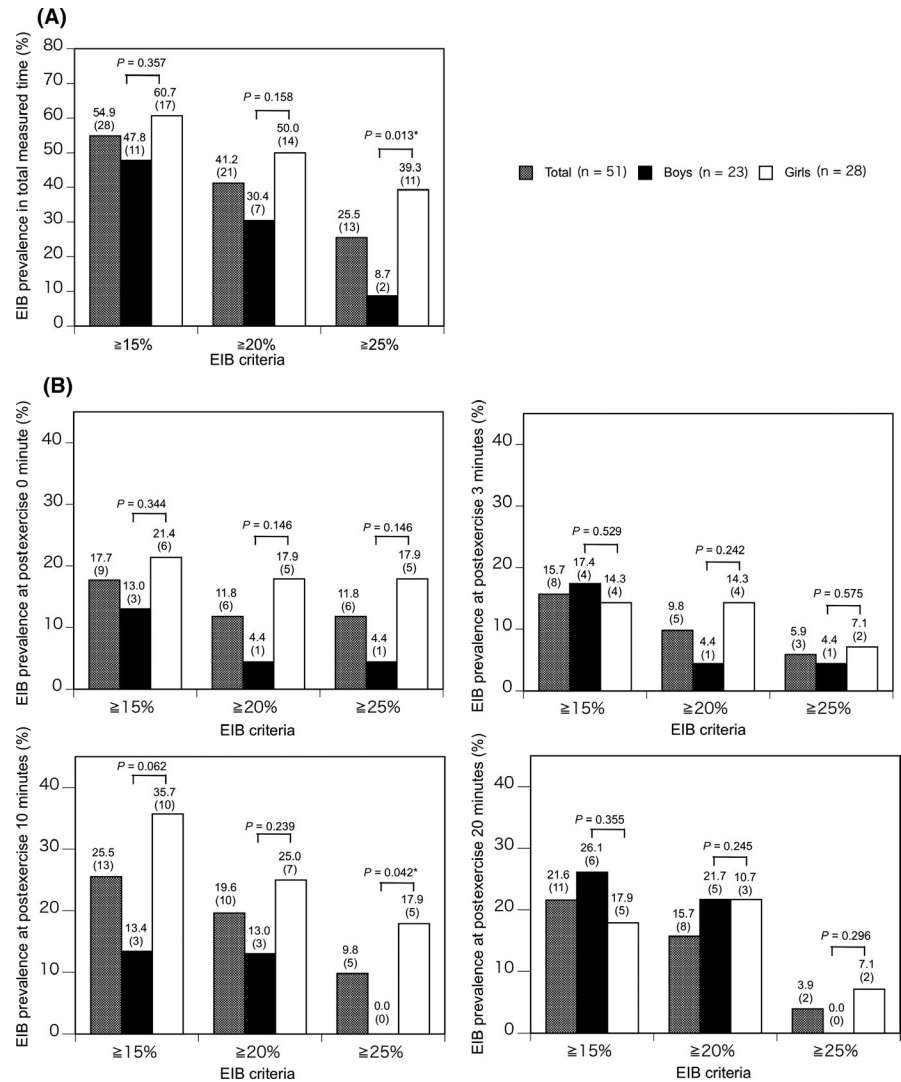
The prevalence of EIB ( $\geq 25$  decrease in postexercise PEFR) was higher in girls than in boys. Additionally, the time to maximal bronchoconstriction was slower and the pattern of recovery after exercise was faster in girls than in boys. Regardless of the severity of EIB, its prevalence was higher in our participants than in those included in previous studies conducted in other countries<sup>2,14,23,28–30</sup>. The younger age<sup>29</sup> and Asian race of the subjects<sup>30</sup>, as well as the use of a high-intensity running test<sup>31</sup>, may have contributed to the high prevalence of EIB in our study. Additionally, the policy of the kindergarten recommends physical fitness, and daily exercise might make the physical fitness in children like athletes' level.

In this study, girls had a lower PEFR than boys (Table 1), and the time to maximal bronchoconstriction was slower and the pattern of recovery after exercise was faster in girls than in boys (Figure 2B).

Only in the girls, but not in boys, the significant differences in the standard regression equation of PEFR<sup>10</sup>-related variables, height and PEFR, might reflect the sex difference in lung function and growth. For example, in 6-year-old children, the standard estimated PEFR is 158.8–205.8 L/min (range 47.0 L/min) in boys (height 1.00–1.20 m) and 124.7–217.8 L/min (range 93.1 L/min) in girls (height 0.95–1.25 m). The range of the estimated PEFR is wider in girls than in boys. In line with the result, interestingly, a recent paper shows that the significant interaction between high peak flow variability and age was significant in females, but not in males, and the diurnal peak flow variability is considered an important measurement of airway lability in the screening and diagnosis of asthma in population-based studies<sup>32</sup>.

On the contrary, in clinical practice using spirometry by preschoolers, forced expiratory volumes at 0.75 second (FEV<sub>0.75</sub>) or at

**FIGURE 3** Prevalence of EIB defined as a  $\geq 15\%$ ,  $\geq 20\%$ , or  $\geq 25\%$  decrease in PEFR, respectively, in all participants and stratified by sex, during the total measured time (A) and at 0–3, 10, and 20 min after exercise (B). *P*-values were calculated using the Chi-square test or Fisher's exact test, as appropriate. EIB, exercise-induced bronchoconstriction; 6MFRT, 6-minute free-running test; CI, confidence interval; PEFR, peak expiratory flow rate



0.5 second ( $FEV_{0.5}$ ) have not been adopted, because children in the preschool age group will not have the chest wall muscle strength to maintain flow limitation to lung volumes as low as 90% of exhaled vital capacity<sup>9</sup>. Additionally, morphometry has demonstrated that the lungs of females are generally smaller than those of males throughout the human lifespan<sup>12,33</sup>. Furthermore, airway caliber is thought to be smaller (in proportion to total lung volume) in boys than in girls, predisposing boys to airway obstruction and wheezing in young children<sup>13,34,35</sup>. The sex differences in the recovery of EIB may be explained by sex differences in airway resistance, airway caliber, and lung function; female lungs have lower specific airway resistance than male lungs<sup>13</sup>, and females have larger airways in relation to lung size<sup>36</sup> and higher forced expiratory flow rates controlling for FVC than males do<sup>13</sup>. These sex differences in peak flow variability, lung function, and morphometry might cause the sex differences in the recovery of EIB.

In this study, the prevalence of EIB was higher in girls than in boys only when EIB was defined as a  $\geq 25\%$  decrease in postexercise PEFR. When EIB was defined as a  $\geq 15\%$  decrease in postexercise PEFR using a free-running test in children aged 10–15 years, the prevalence of

EIB was higher in girls than in boys in school-based studies in the USA<sup>16</sup> and Spain<sup>15</sup>, whereas the prevalence did not differ in a study from Algeria<sup>17</sup>. The discrepancies in study findings may partly be due to different criteria and/or exercise tests used, different methods of measuring postexercise PEFR, and the different ethnic groups examined.

Sex differences in the morphology, maturation, and physiology of the airways begin during gestation<sup>13</sup>. Sex hormones appear to exert regulatory effects on fetal lung development and maturation before birth throughout the human lifespan<sup>8,14,37,38</sup>. Moreover, most immune cells—including eosinophils, mast cells, and macrophages—express estrogen receptors to varying degrees and can respond to sex hormones<sup>38</sup>. Furthermore, a recent study found that testosterone blocks the production of a type of immune cell (group 2 innate lymphoid cell) that triggers allergic asthma<sup>39</sup>. These results suggest that sex hormone-related differences in age, together with sex differences in lung size and function and other unknown factors, may contribute to the prevalence and severity of EIB in children.

Our study has both strengths and limitations. First, the main strength of this study was the selection of children. The preschoolers were recruited from a general population in a restricted region; thus,

environmental factors such as air pollution, weather, and epidemic infections were similar among the subjects. Second, 6MFRT was performed during a single month in the early summer, which is not the pollen season of the Japanese cedar and cypress trees, and the subjects' lung function was unlikely to have been influenced by pollen. Third, the BMI of all subjects fell within the normal standardized range; thus, obesity had no influence on individual variability of lung function. A limitation of this study was that the temperature and humidity varied during the test period. However, previous studies were also performed outside on different days or during different seasons<sup>16,21,22,25</sup>. Second, lung function was measured using only a peak flow meter because during a survey, however, even school-aged children have difficulty to perform the physiological maneuvers to measure pulmonary function<sup>1,9,23,35,40</sup>. Although previous studies also used free-running tests in which children performed sustained maximum running for specified, measured periods of time<sup>2,16,21,22</sup>, the intensity of 6MFRT might have varied among individual children. Third, the sample size was small; thus, the significant difference in the prevalence of EIB defined as <25% is true. However, the conclusions of the difference in the prevalence of EIB defined as <15% and <20% need further studies in larger sample size. Finally, the results were from Matsuyama City only and cannot be generalized to the whole of Japan or to other countries.

In conclusion, among prepubertal children, the prevalence of EIB defined as a  $\geq 25\%$  decrease in the postexercise PEFR was higher in girls than in boys, and bronchoconstriction recovers more quickly (within 20 minutes) after exercise in girls. The nadir time is within 10 minutes in girls and within 3 minutes in boys. Therefore, even in prepubertal preschool children, the influence of sex should be considered when evaluating the prevalence and severity of EIB in kindergarten-based surveys to detect EIB using the 6MFRT. To establish more effective and accurate mass-screening tests for the early finding of EIB in general kindergarten-based children, further studies are needed.

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## CONFLICT OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

## ORCID

Miwa Shinohara  <https://orcid.org/0000-0002-6965-2061>

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