

# Exercise-Induced Wheezing among Japanese Pre-School Children and Pupils

Yoko Murakami<sup>1</sup>, Satoshi Honjo<sup>1</sup>, Hiroshi Odajima<sup>1</sup>, Yuichi Adachi<sup>2</sup>, Koichi Yoshida<sup>3</sup>, Yukihiro Ohya<sup>4</sup> and Akira Akasawa<sup>3</sup>

## ABSTRACT

**Background:** Exercise-induced wheezing (EIW) may be a symptom of asthma and is a predictor of exercise-induced bronchoconstriction, transient narrowing of the lower airway following exercise in the presence or absence of diagnosed asthma. Population-based studies with a large sample of EIW in relation to age, sex, current asthma severity and medication usage have been sparse.

**Methods:** International Study of Asthma and Allergies in Childhood questionnaires were distributed at 885 nurseries, 535 primary schools, 321 junior high schools and 190 high schools, respectively, across Japan, and the corresponding data on 46,597, 41,216, 45,960 and 51,104 children were analyzed.

**Results:** Prevalence of EIW was 4.8, 4.7, 17.9 and 15.4% for each of the four educational facility types, respectively. Among 24,103 current asthmatics, 20.9, 28.7, 76.1 and 73.6% of subjects for the 4 educational facility groups reported to have experienced EIW, respectively. Severity of current asthma was associated with the risk of EIW; odds ratio (95% confidence interval) of children with asthma attack every day for having EIW once a week or more, using intermittent asthmatics as reference group, were 24.48 (19.33 to 31.01) adjusted for other covariates. Among current asthmatic kindergartners, increase in risk for EIW due to ascending severity of current asthma was mitigated by daily use of leukotriene receptor antagonist ( $p$  for interaction = 0.071).

**Conclusions:** EIW was not rare among current asthmatic children. An increased risk for EIW was in accordance with increasing severity of current asthma and this relation was mitigated with leukotriene receptor antagonist daily use among kindergartners.

## KEY WORDS

bronchial asthma, childhood asthma, inhaled steroid, leukotriene receptor antagonist, wheeze

## ABBREVIATIONS

EIW, Exercise-induced wheezing; EIB, Exercise-induced bronchoconstriction; ISAAC, International Study of Asthma and Allergies in Childhood.

## INTRODUCTION

Exercise is a trigger of bronchial asthma attack<sup>1</sup> in some cases and exercise-induced asthma might be defined as one of early childhood onset phenotypes.<sup>2</sup> Meanwhile, diagnosis of asthma can be initiated with a report of wheezing during and/or after exercise, exercise-induced wheezing (EIW); and asthma attack

triggered by exercise may have a rapid exacerbation and possibly contribute to urgent medical visit.<sup>3</sup> Report of EIW is a clinical expression of diseases other than bronchial asthma in some cases and it has been stated self-reported EIW alone should not be used to define exercise-induced bronchoconstriction (EIB) exactly in the absence of indirect and/or direct challenge tests.<sup>4</sup> An aim of the present study was to de-

<sup>1</sup>Department of Paediatrics, National Hospital Organization Fukuoka National Hospital, Fukuoka, <sup>2</sup>Department of Paediatrics, Faculty of Medicine, Graduate School of Medicine and Pharmaceutical Science for Education, Toyama University, Toyama, <sup>3</sup>Division of Allergy, Tokyo Metropolitan Children's Medical Centre and <sup>4</sup>Division of Allergy, National Centre for Child Health and Development, Tokyo, Japan.

Conflict of interest: No potential conflict of interest was disclosed.

Correspondence: Satoshi Honjo, Department of Paediatrics, National Hospital Organization Fukuoka National Hospital, 4-39-1 Yakatabaru, Minami-ku, Fukuoka 811-1394, Japan.

Email: [satoshihonjo@hotmail.com](mailto:satoshihonjo@hotmail.com)

Received 14 October 2013. Accepted for publication 24 December 2013.

©2014 Japanese Society of Allergology

lineate a prevalence of EIW among more than 180,000 children aged 3 to 18 in relation to age, sex, severity of asthma and medication usage in a nationwide cross-sectional survey conducted in 2008<sup>5-7</sup> in order to provide an insight for clinician and public health physician seeing asthmatic patients and those patient populations. Although a study with the concomitant use of provocation challenge test is ideal to correlate EIW with bronchial asthma rigorously, large-sized population-based studies with challenge tests are unlikely to execute and such tests are likely unfeasible for small children. Ponsonby and colleagues found the exercise challenge had sensitivity and specificity estimates for exercise-induced wheeze based on the ISSAC question of 0.60 and 0.77 for 7-year old or older children, respectively, using a 12% or greater fall in FEV1 post-exercise as a positive test response.<sup>8</sup> Although an Italian group reported the prevalence of wheeze with exercise based on the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire were 2.2 and 1.2% for 9,674 boys and 9,062 girls aged 6 to 7, respectively,<sup>9</sup> findings on EIW based on large samples from general populations are sparse.

## METHODS

### STUDY SUBJECTS

The present analysis was based on the nation-wide cross-sectional survey of asthma and other allergic diseases in Japan a part of which survey was mentioned elsewhere<sup>5-7</sup> and relevant details were briefly described here. The study subjects were recruited as follows. Firstly 1,109 nurseries, 672 primary schools, 396 junior high schools and 219 high schools were selected and asked for participation in this survey by each of the 47 prefectural boards of education in response to our request to secure 1,000 or more participants in each prefecture without any other intention. Among those nurseries and schools 885 (79.8%), 535 (79.6), 321 (81.1) and 190 (86.8) agreed to the requests by prefectural boards of education, respectively. Secondly a Japanese version of the ISAAC questionnaire<sup>10</sup> was distributed from April to July 2008 to parents of 47,915 pupils aged 6 - 8 in the first and second grades of the primary schools, 63,359 pupils aged 13 - 15 in the first and second grades of the junior high schools and 67,944 aged 16 - 18 in the first and second grades of the high schools located in all 47 prefectures of Japan. A questionnaire based on the ISAAC one with additional enquiries regarding diagnosis for ever having asthma in kindergartners was also sent to parents of 50,959 kindergartners aged 3 - 6 years. Forty-seven thousand, two hundred and ninety-one parents of the kindergartens responded to our survey (response rate = 92.8%) while 92.1% of parents of the pupils attending primary schools, 78.8 and 81.6% of the pupils at junior high school and high school answered, respectively. A response was de-

defined as invalid 1) if the child's age was not in agreement with the grade of nursery or schools, or 2) a) the responder did not answer to a question, "Have you (or your child) ever had wheezing or whistling in the chest at any time in the past?", or b) the responder answered "yes" to the above question but did not answer to another question, "Have you (or your child) had wheezing or whistling in the chest in the past 12 months?" The invalid response numbered 279, 327, 1,452 and 1,498 for kindergartners, primary school pupils, junior high school and high school pupils, respectively; and those with the invalid response were excluded from the study subjects. We further excluded 423 subjects with unknown sex; and then 8,323 undetermined for presence of EIW as defined in the following section were omitted. Thus, 46,597 kindergartners, 41,216 pupils, 45,960 junior high school pupils and 51,104 high school pupils were used for the present study.

### DEFINITION OF ASTHMA, EIW AND MEDICATION USAGE

We defined having current asthma if a child or a parent answered "Yes" to both of two questions, "Have you (or your child) ever had wheezing or whistling in the chest at any time in the past?" and "Have you (or your child) had wheezing or whistling in the chest in the past 12 months?" Severity of asthma (intermittent, mild, moderate, or severe) was assigned for current asthmatic children according to reported frequency of wheezing in the past 4 weeks: none, monthly or more but not weekly, weekly or more but not every day and every day. Having EIW was defined if a child or a parent answered "Yes" to a question, "In the past 12 months, has your (or your child's) chest sounded wheezy during or after exercise?" regardless of the answer to the question in regards to having current asthma as mentioned above. Severe EIW was defined if reported frequency of wheezing during or after exercise was weekly or more in the past 4 weeks. Among kindergartners whose parents answered "No" to the above question regarding EIW in the past 12 month, 231 kindergartners were reported to have such wheezing once or more during or after exercise in the past 4 weeks. Similarly 1,475 pupils reported by themselves or by parents (for primary school pupils) to have wheezing with the same frequency as that for kindergarten in spite of the fact that they reported no wheezy episodes during or after exercise in the past 12 months. Those 1,706 children were re-classified as having EIW in the present analysis.

Age and sex were specified as they were answered in the completed questionnaires. Inhaled medication daily use was defined if the subject or subject's guardian answered Flutide<sup>®</sup> (fluticasone propionate), Qvar<sup>®</sup> (beclometasone dipropionate), Pulmicort<sup>®</sup> (budesonide), or other inhaled medication was used

daily; the last one was not applicable for kindergartners, however. Daily use of leukotriene-receptor antagonist (LTRA) was defined if the subject or subject's guardian answered Onon<sup>®</sup> or Pranlukast<sup>®</sup> (pranlukast hydrate), Singulair<sup>®</sup> (montelukast sodium), or Kipres<sup>®</sup> (montelukast sodium) was used daily.

### STATISTICAL ANALYSIS

Most of analyses were conducted separately for each of 4 types of educational facility because we assumed physique and other factors including sport activity and sleeping time were not adequately adjusted for by statistical methods. All statistical analyses were performed with STATA statistical software.<sup>11</sup>

### Age, Severity of Current Asthma and EIW

We calculated prevalence of EIW among study subjects regardless of presence of current asthma by age group and examined a risk for having EIW calculating odds ratios (ORs) with the largest age group within each of four types of educational facilities ranging from nursery to high school as reference. Then we examined a trend of severity of EIW with increasing age within each type of educational facilities by a nonparametric test for trend across ordered groups developed by Cuzick which is an extension of the Wilcoxon rank-sum test.<sup>12</sup> We also obtained prevalence of EIW among current asthmatics by age and examined the risk for having EIW similarly as mentioned above. We examined in addition the risk for having EIW according to severity of asthma using subjects with intermittent asthmatic attack as reference.

### Medication Use and EIW

The risk for having EIW due to leukotriene-receptor antagonist daily use and inhaled medication daily use was examined with mutual adjustment using multiple logistic regression analysis. The similar analyses were repeated only among current asthmatics allowing for severity of current asthma additionally.

### Possible Interactions Regarding Medication Use

Because both effects of LTRA daily use and inhaled medication daily use were deemed to differ according to four educational facility types as shown below, each of possible interaction was statistically examined with log-likelihood ratio test.<sup>13</sup> Finally possible interaction between the severity of current asthma and daily medication usage was also investigated using log-likelihood ratio test.

This study was approved by the independent review board of the National Centre for Child Health and Development.

## RESULTS

### AGE, SEVERITY OF CURRENT ASTHMA AND EIW

Among 23,600 boys and 22,997 girls attending kindergartens, 5.7 and 3.8% reported to have EIW, respectively ( $p$  for difference between boys and girls <0.01) (Table 1). The predominance of boys was observed also for primary school pupils while a predominance of girls was seen for junior high school pupils. Distribution of the severity of EIW among children with EIW was not much differed across the four educational facility types and no measurable association between the severity of EIW and age was observed for children in each of the four educational facility types (described in detail in Supplementary Table 1).

EIW was more reported among kindergartners who reported having current asthma: 1,955 subjects with EIW among 9,343 current asthmatics (20.92%) vs. 278 subjects with EIW among 37,212 without current asthma (0.75%). Corresponding figures were 28.65 vs. 0.74%, 76.12 vs. 11.55% and 73.61 vs. 9.97% for primary school pupils, junior high school pupils and high school pupils, respectively. An OR for having EIW due to having current asthma was 35.16 (95% confidence interval (CI) = 30.93 - 39.96) for kindergartners. The increased ORs for EIW due to being current asthmatic for primary school pupils, junior high school pupils and high school pupils were 53.63 (46.91 - 61.31), 24.42 (22.66 - 26.31) and 25.20 (23.41 - 27.13), respectively. Prevalence of EIW among current asthmatics were 22.0% for boys and 19.3 for girls in kindergartners ( $p$  for difference between boys and girls <0.01), 29.2 and 27.9 in primary school pupils in the first and second grades (0.30), 74.6 and 77.7 in junior high school pupils in the second and third grades (0.02) and 74.8 and 72.3 in high school pupils in the second and third grades (0.05), respectively. The highest prevalence among current asthmatics was observed for the aged 16 high school asthmatics for boys (76.6%) and for the aged 15 junior high school asthmatics for girls (78.1%), respectively.

Severity of current asthma was related to the risk of having EIW; 4 to 6-fold increase in the risk for having EIW was observed for severe asthmatics as compared to those with intermittent asthma attack in the past 4 weeks, and those severe asthmatic children had an OR of 24.48 (19.33 to 31.01) for having EIW once a week or more (described in more detail in Supplementary Table 2).

### MEDICATION USE AND EIW

Both daily use of LTRA and that of inhaled medication were associated with having EIW and severe EIW, respectively (Table 2). Among 3,805 school children with reported daily use of inhaled medication, 581 children or child's parents answered those children used inhaled medication other than fluticasone

**Table 1** Prevalence of exercise-induced wheezing (EIW) by age and sex, a nation-wide survey in Japan

Age (years)	Total (n)	All						Boys							
		EIW (-)		EIW (+)		Odds ratio	95% confidence interval		P value	EIW (-)		EIW (+)		Odds ratio	
		n	%	n	%		Lower limit	Upper limit		n	%	n	%		
<b>Kindergartners</b>															
3	6,557	6,317	96.3%	240	3.7%	0.66	0.57	0.76	<0.01	3,317	3,170	95.6%	147	4.4%	0.67
4	16,106	15,385	95.5%	721	4.5%	0.81	0.74	0.89	<0.01	8,163	7,722	94.6%	441	5.4%	0.82
5	20,795	19,662	94.6%	1,133	5.4%	1.00		Reference		10,504	9,820	93.5%	684	6.5%	1.00
6	3,139	3,000	95.6%	139	4.4%	0.80	0.67	0.96	0.02	1,616	1,538	95.2%	78	4.8%	0.73
Total	46,597	44,364	95.2%	2,233	4.8%		P for trend of odds		<0.01	23,600	22,250	94.3%	1,350	5.7%	
<b>Primary school pupils in the 1st and 2nd grades</b>															
6	17,491	16,667	95.3%	824	4.7%	1.00	0.91	1.10	0.99	8,926	8,419	94.3%	507	5.7%	1.07
7	20,223	19,270	95.3%	953	4.7%	1.00		Reference		10,345	9,796	94.7%	549	5.3%	1.00
8	3,502	3,344	95.5%	158	4.5%	0.96	0.80	1.14	0.60	1,786	1,693	94.8%	93	5.2%	0.98
Total	41,216	39,281	95.3%	1,935	4.7%		P for trend of odds		0.73	21,057	19,908	94.5%	1,149	5.5%	
<b>Junior high school pupils in the 1st and 2nd grades</b>															
13	19,229	15,785	82.1%	3,444	17.9%	0.99	0.94	1.04	0.76	9,355	7,703	82.3%	1,652	17.7%	1.02
14	22,563	18,496	82.0%	4,067	18.0%	1.00		Reference		11,061	9,144	82.7%	1,917	17.3%	1.00
15	4,168	3,437	82.5%	731	17.5%	0.97	0.89	1.05	0.45	2,186	1,813	82.9%	373	17.1%	0.98
Total	45,960	37,718	82.1%	8,242	17.9%		P for trend of odds		0.82	22,602	18,660	82.6%	3,942	17.4%	
<b>High school pupils in the 1st and 2nd grades</b>															
16	21,567	18,028	83.6%	3,539	16.4%	1.12	1.07	1.18	<0.01	11,094	9,238	83.3%	1,856	16.7%	1.13
17	25,166	21,418	85.1%	3,748	14.9%	1.00		Reference		12,938	10,990	84.9%	1,948	15.1%	1.00
18	4,371	3,776	86.4%	595	13.6%	0.90	0.82	0.99	0.03	2,331	2,013	86.4%	318	13.6%	0.89
Total	51,104	43,222	84.6%	7,882	15.4%		P for trend of odds		<0.01	26,363	22,241	84.4%	4,122	15.6%	

Continued to the next page.

propionate, beclometasone dipropionate, or budesonide, daily. When excluding those 581 children from the analysis, the OR due to daily use of inhaled medication for having EIW changed from 5.09 (Table 2) to 5.19 (4.80 - 5.61) with the OR due to LTRA daily use changing from 6.39 (Table 2) to 6.50 (5.99 - 7.04).

### POSSIBLE INTERACTIONS REGARDING MEDICATION USE

ORs were larger for LTRA daily use than for inhaled medication use among kindergartners and primary school pupils while the reverse was observed for junior high school and high school pupils (described in more detail in Supplementary Table 3); the relations of the LTRA daily use to EIW and to severe EIW were both significantly modified by educational facility type ( $p$  for interaction <0.01 and <0.01, respectively) and the relations between the daily inhaled medication use and EIW and severe EIW were also significantly altered by educational facility type ( $p$  < 0.01 and < 0.01, respectively).

The LTRA daily use and inhaled medication daily use among current asthmatics were also related to

having EIW with ORs around 1.5 to 2.0 across the four educational facility types (described in detail in Supplementary Table 4). The interaction between the inhaled medication daily use and educational facility type on the OR for EIW was not observed among current asthmatics ( $p$  = 0.172) while the significant interaction was observed for the LTRA daily use ( $p$  < 0.01). The effect modification by educational facility type on the relation between the LTRA daily use and having severe EIW among current asthmatics was suggested ( $p$  = 0.067) while the significant interaction was observed for the daily use of inhaled medication ( $p$  = 0.019).

Only among kindergartners the effect modification by the LTRA use was suggested on the relation between the severity of current asthma and having EIW ( $p$  = 0.071) and on that between the current asthma severity and having severe EIW ( $p$  = 0.037), respectively, and the ORs due to the severity of current asthma were shown by status of the LTRA daily use (no daily use vs. daily use) for EIW and for severe EIW in Table 3, respectively.

Only for junior high school pupils the association

## EIW among Pre-School Children and Pupils

			Girls									P for difference between boys and girls
95% confidence interval		P value	Total (n)	EIW (-)		EIW (+)		Odds ratio	95% confidence interval		P value	
Lower limit	Upper limit			n	%	n	%		Lower limit	Upper limit		
0.55	0.80	<0.01	3,240	3,147	97.1%	93	2.9%	0.65	0.52	0.81	<0.01	
0.72	0.93	<0.01	7,943	7,663	96.5%	280	3.5%	0.80	0.69	0.93	<0.01	
Reference			10,291	9,842	95.6%	449	4.4%	1.00	Reference			
0.57	0.93	<0.01	1,523	1,462	96.0%	61	4.0%	0.91	0.70	1.20	0.52	
P for trend of odds		<0.01	22,997	22,114	96.2%	883	3.8%		P for trend of odds		<0.01	
0.95	1.22	0.26	8,565	8,248	96.3%	317	3.7%	0.90	0.78	1.05	0.17	
Reference			9,878	9,474	95.9%	404	4.1%	1.00	Reference			
0.78	1.23	0.86	1,716	1,651	96.2%	65	3.8%	0.92	0.71	1.21	0.56	
P for trend of odds		0.24	20,159	19,373	96.1%	786	3.9%		P for trend of odds		0.38	
0.95	1.10	0.54	9,874	8,082	81.9%	1,792	18.1%	0.96	0.90	1.03	0.31	
Reference			11,502	9,352	81.3%	2,150	18.7%	1.00	Reference			
0.87	1.11	0.76	1,982	1,624	81.9%	358	18.1%	0.96	0.85	1.09	0.51	
P for trend of odds		0.43	23,358	19,058	81.6%	4,300	18.4%		P for trend of odds		0.61	
1.06	1.21	<0.01	10,473	8,790	83.9%	1,683	16.1%	1.11	1.03	1.19	<0.01	
Reference			12,228	10,428	85.3%	1,800	14.7%	1.00	Reference			
0.78	1.01	0.08	2,040	1,763	86.4%	277	13.6%	0.91	0.79	1.04	0.18	
P for trend of odds		<0.01	24,741	20,981	84.8%	3,760	15.2%		P for trend of odds		<0.01	

Continued from the previous page.

between the severity of current asthma and having EIW was modified by the daily use of inhaled medication ( $p < 0.01$ ) while the association between the severity and having severe EIW was not ( $p = 0.246$ ). The increment in ORs for having EIW according to the ascending asthmatic severity was augmented by the inhaled medication daily use; ORs were 1.00, 2.39, 3.66 and 3.07, respectively ( $p$  for trend  $< 0.01$ ), among children without daily use of inhaled medication while corresponding ORs were 1.00, 5.62, 7.49 and 14.79, respectively ( $p$  for trend  $< 0.01$ ), among children with the daily use, according to the current asthma severity including intermittent, mild, moderate and severe. When 241 junior high school pupils with reported daily use of inhaled medication other than fluticasone propionate, beclometasone dipropionate, or budesonide, were excluded in the analysis, the ORs due to increasing severity of current asthma were 1.00, 2.42, 18.16 and 19.27, respectively ( $p$  for trend  $< 0.01$ ), among children without daily use of inhaled steroid including the three above-mentioned prescriptions while the corresponding figures were 1.00, 2.35, 21.88 and 43.44, respectively ( $p$

for trend  $< 0.01$ ), among those with the daily use of inhaled steroid although the interaction was not statistically significant ( $p = 0.389$ ).

### DISCUSSION

It should be difficult to judge promptly whether questionnaire-based EIW is phenotypic exercise-induced asthma or non-asthmatic symptom in each case. However, it should not be unreasonable to assume that the EIW observed by clinician in an asthmatic patient is asthmatic symptom, EIB, in most cases. Practically studying EIW encompassing asthmatic symptom and other clinical entities should be worth doing for daily clinical work and research on exercise-induced asthma.

The present study is, to our knowledge, the largest one so far describing current figures of EIW among general childhood population. The sample size made precise examination of prevalence of EIW in relation to sex, age, medication usage and severity of current asthma and produced stable ORs for those relations with relatively narrow 95% confidence intervals if the association was significant.

**Table 2** Relation between exercise-induced wheezing (EIW) and sex, age, daily use of leukotriene receptor antagonist and daily use of inhaled medication, a nation-wide survey in Japan: multivariate analysis

Variables	Total <sup>†</sup> (n)	EIW (n)	%	Severe EIW (n) <sup>‡</sup>	%	EIW			Severe EIW				
						Adjusted odds ratio <sup>†</sup>	95% confidence interval Lower limit	Upper limit	P value	Adjusted odds ratio <sup>§</sup>	95% confidence interval Lower limit	Upper limit	P value
Sex													
Boy	93,622	10,563	11.3%	3,173	3.4%	1.00	Reference	Reference	1.00	Reference	Reference	Reference	<0.01
Girl	91,255	9,729	10.7%	2,625	2.9%	0.99	0.96	1.02	0.89	0.84	0.94	0.94	<0.01
Educational facility type													
Kindergartners	46,597	2,233	4.8%	494	1.1%	1.00	Reference	Reference	1.00	Reference	Reference	Reference	0.026
Primary school pupils in the 1st and 2nd grades	41,216	1,935	4.7%	381	0.9%	0.98	0.91	1.04	0.86	0.75	0.98	0.98	<0.01
Junior high school pupils in the 1st and 2nd grades	45,960	8,242	17.9%	2,660	5.8%	5.59	5.30	5.89	6.66	6.03	7.36	7.36	<0.01
High school pupils in the 1st and 2nd grades	51,104	7,882	15.4%	2,263	4.4%	4.75	4.51	5.01	5.14	4.65	5.69	5.69	<0.01
Daily use of leukotriene receptor antagonist													<0.01
No	179,614	18,060	10.1%	5,098	2.8%	1.00	Reference	Reference	1.00	Reference	Reference	Reference	<0.01
Yes	5,263	2,232	42.4%	700	13.3%	6.39	5.90	6.91	3.85	3.40	4.37	4.37	<0.01
Daily use of inhaled medication													<0.01
No	179,940	17,772	9.9%	4,919	2.7%	1.00	Reference	Reference	1.00	Reference	Reference	Reference	<0.01
Yes	4,937	2,520	51.0%	879	17.8%	5.09	4.73	5.47	4.25	3.81	4.74	4.74	<0.01

<sup>†</sup>Excluded were subjects with a missing value for severity of current asthma. <sup>‡</sup>Defined if EIW occurred  $\geq 1$ /week. <sup>§</sup>Adjusted for other variables in Table and prefecture [Northern (20 prefectures) and Southern (27) Japan].



**Table 3** Relation between exercise-induced wheezing (EIW) and severity of asthma among kindergartners with current asthma referring to daily use of leukotriene receptor antagonist, a nation-wide survey in Japan: multivariate analysis

Severity of asthma	EIW				Severe EIW <sup>†</sup>			
	Adjusted odds ratio <sup>‡</sup>	95% confidence interval		P value	Adjusted odds ratio <sup>‡</sup>	95% confidence interval		P value
		Lower limit	Upper limit			Lower limit	Upper limit	
	<i>P</i> for interaction with daily use of leukotriene receptor antagonist: 0.071				<i>P</i> for interaction with daily use of leukotriene receptor antagonist: 0.037			
	No daily use of leukotriene receptor antagonist							
Intermittent	1.00			Reference	1.00			Reference
Mild	2.85	2.47	3.29	<0.01	2.50	1.69	3.69	<0.01
Moderate	4.88	3.99	5.98	<0.01	14.81	10.34	21.21	<0.01
Severe	7.81	4.72	12.93	<0.01	32.31	17.40	59.98	<0.01
		<i>P</i> for trend of odds		<0.01		<i>P</i> for trend of odds		<0.01
	Daily use of leukotriene receptor antagonist							
Intermittent	1.00			Reference	1.00			Reference
Mild	2.28	1.83	2.84	<0.01	3.96	1.88	8.32	<0.01
Moderate	4.15	3.17	5.43	<0.01	33.24	16.55	66.76	<0.01
Severe	2.88	1.55	5.34	<0.01	23.97	9.09	63.19	<0.01
		<i>P</i> for trend of odds		<0.01		<i>P</i> for trend of odds		<0.01

Excluded were subjects with a missing value for severity of current asthma. <sup>†</sup> Defined if EIW occurred  $\geq 1$ /week. <sup>‡</sup> Adjusted for sex, age, daily use of inhaled medication and prefecture [Northern (20 prefectures) and Southern (27) Japan].

Proportion of children with reported EIW in the present study did not seem high although directly comparable data for general population were sparse while circa 10 to 50% among various populations of athletes was reported to have EIB as tabulated in the report by Weiler *et al.*<sup>4</sup> For primary school children aged 6 - 8, the proportion of those with EIW was larger than that reported for Italian children aged 6 - 7,<sup>9</sup> however. The difference in proportion between the two studies may be partly attributed to different study time, place and ethnicity, or by chance. Because exercise-associated symptoms other than wheeze were not captured in the present study, the prevalence of exercise-related asthma symptoms, some part of which was EIW, may have been underestimated in the present study.

It is well known the fact that prevalence of asthma is greater among boys than among girls before age of 13 - 14 years with a greater incidence for female among adolescent and young adulthood.<sup>14</sup> De Baets *et al.* assessed 15,241 primary school pupils using a 6-minute run and a decrease of 15% for peak flow as an indicator of EIB and found girls (8.5%) were more likely than boys (6.4%) to have a positive challenge result.<sup>15</sup> Not reported EIW but reported wheeze was more prevalent in boys than in girls aged 11 but the opposite finding was shown for adolescents aged 12 to 16 in a study conducted in England.<sup>16</sup> Report of asthma or wheeze in past 12 month was more common in boys than in girls at age of 7, 11 and 16 years, respectively, with the OR of 1.35 for incident asthma or wheezy bronchitis among boys aged 8 to 11 years

and that of 1.45 among boys aged 12 to 16 years using girls as reference group while the marked reversal with the OR of 0.55 was found for those aged 17 to 23 years in a study of British 1958 birth cohort.<sup>17</sup> The present findings of male preponderance among pupils aged 3 to 8 years and opposite findings of female preponderance among junior high school pupils roughly accorded with those of previous studies shown above. These relationships between gender and risk of having EIW were unchanged across the four educational facility types adjusted for other covariates in the present study. Gender difference in risk for severe EIW was observed only among high school pupils. Not well understood but similar mechanism may operate in relation to gender for asthma and for EIW both.

Burr and colleagues reported in 817 12-year-old schoolchildren living in two areas of Wales the ratio of two measures of peak expiratory flow rates before and after 6 minutes of running was lower for current asthmatics, current wheezers, ex-wheezers and those with atopic history as compared to other children without family history of asthma.<sup>18</sup> Concordantly EIW was more prevalent among current asthmatics than subjects without reported current asthma in the present study. In a cross-sectional study in Barcelona, school children aged 13 to 14 years with a positive result of a fall in peak expiratory flow rate  $\geq 15\%$  after exercise showed an OR for 2.82 of affirmative answer to the question in relation to exercise-induced asthma as compared to children with negative answer.<sup>19</sup> As limits to our study, distinction between exercise-induced asthma attack and exercised-unrelated one

was not made. Thus the strong and consistent relation between the severity of current asthma and having EIW and having severe EIW in the present study can be theoretically interpreted partially as follows; higher frequency of EIW may be counted as higher frequency of asthma attack in general. Allowing for the fact that substantial proportion of the study subjects without current asthma also reported to have EIW especially among pupils aged 13 years or older, it was reasoned at least some participants did not assume EIW as asthma attack. When seeing patients in this age range with suspected asthma, possible presence of EIW should be asked. Better control of asthma is essential to control EIW that may decrease school activities including sports and may contribute to emergency visit to hospital.<sup>3</sup> Better control of EIW may, alternatively, initiate better control of asthma especially among asthmatics who are not enough aware of the presence of EIB.

We should refer to limitation of the present study. The fact EIW was defined based on questionnaire but not on challenge test with no validation study was weakness of the present investigation, and other clinical entities showing EIW may be present in children with reported wheezing and/or cough after exercise.<sup>20</sup>

Although we were unable to determine the causal relationship between medication usage and risk of having EIW due to cross-sectional nature of the present study, positive relations between two medication usages and having EIW consistently observed over the 4 educational facility types were in accordance with current treatment for EIB with LTRA and inhaled corticosteroid use.<sup>4</sup> The mitigated association of the severity of current asthma with having EIW and severe EIW by the LTRA daily use among kindergartners may be due to protective effect of the LTRA on occurrence of EIB.<sup>4</sup> Among asthmatic children with LTRA use, the ORs for EIW and severe EIW both were higher for moderate asthmatics than for severe asthmatics. This reversal may be differentiated effect of LTRA use for current asthmatic children with the different degree of severity or due to chance. In the meanwhile, the apparent augmentation of the relation between the current asthma severity and having EIW by the daily use of inhaled medication among junior high school pupils may be related to a possible real situation where severe asthmatic pupils failed to protect EIB in spite of the inhaled corticosteroid daily use. Possible alternative partial interpretation may be some of current asthmatic children with frequent EIW had recourse to daily use of beta stimulant for symptomatic relief instead of inhaled steroid daily use.

It is concluded that EIW was not rare among current asthmatic children, and the increasing severity of current asthma was associated with the heightened risk of having EIW; children with asthma attack every

day for having EIW once a week or more had more than 24-fold risk as compared to current asthmatic children with no attack in the past 4 weeks. Relation between the severity of current asthma and the risk of EIW was partly modified with medication use although causal relationship should not be verified in this cross-sectional study. EIW can be practically employed for clinical work and research on exercise-induced asthma.

## ACKNOWLEDGEMENTS

We are grateful to the study participants and the 47 prefectural boards of education for their cooperation. This study was supported by a grant from Japanese Ministry of Health, Labour and Welfare for Japanese Asthma Survey Group.

## SUPPLEMENTARY MATERIALS

Supplementary Table 1-4 are available online.

## REFERENCES

1. Liu AH, Covar RA, Leung DYM. Childhood asthma. In: Kliegman RM, Behrman RE, Jenson HB, Stanton BF (eds). *Nelson Textbook of Pediatrics*, 19th edn. Philadelphia: Saunders Elsevier, 2007;953-70.
2. Wenzel SE. Asthma: defining of the persistent adult phenotypes. *Lancet* 2006;**368**:804-13.
3. Mainardi TR, Mellins RB, Miller RL *et al.* Exercise-induced wheeze, urgent medical visits, and neighborhood asthma prevalence. *Pediatrics* 2013;**131**:e127-35.
4. Weiler JM, Anderson SD, Randolph C *et al.* Pathogenesis, prevalence, diagnosis, and management of exercise-induced bronchoconstriction: a practice parameter. *Ann Allergy Asthma Immunol* 2010;**105**:S1-47.
5. Okabe Y, Adachi Y, Itazawa T *et al.* Association between obesity and asthma in Japanese preschool children. *Pediatr Allergy Immunol* 2012;**23**:550-5.
6. Higuchi O, Adachi Y, Itazawa T *et al.* Relationship between rhinitis and nocturnal cough in school children. *Pediatr Allergy Immunol* 2012;**23**:562-6.
7. Okabe Y, Itazawa T, Adachi Y *et al.* Association of overweight with asthma symptoms in Japanese school children. *Pediatr Int* 2011;**53**:192-8.
8. Ponsonby A, Couper D, Dwyer T, Carmichael A, Wood-Baker R. Exercise-induced bronchial hyperresponsiveness and parental ISAAC questionnaire responses. *Eur Respir J* 1996;**9**:1356-62.
9. Asthma and respiratory symptoms in 6-7 yr old Italian children: gender, latitude, urbanization and socioeconomic factors. SIDRIA (Italian Studies on Respiratory Disorders in Childhood and the Environment). *Eur Respir J* 1997;**10**:1780-6.
10. Asher M, Montefort S, Bjorksten B *et al.* Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet* 2006;**368**:733-43.
11. Stata Statistical Software. Release 11.1 ed. College Station, TX: Stata Corporation, 2009.
12. Cuzick J. A Wilcoxon-type test for trend. *Stat Med* 1985;**4**: 87-90.
13. Breslow NE, Day NE. Statistical Methods in Cancer Research, Vol. I: *The Analysis of Case-Control Studies*. Lyon:



- International Agency for Research on Cancer, 1980.
14. Subbarao P, Mandhane PJ, Sears MR. Asthma: epidemiology, etiology and risk factors. *CMAJ* 2009;**181**:E181-90.
  15. De Baets F, Bodart E, Dramaix-Wilmet M *et al.* Exercise-induced respiratory symptoms are poor predictors of bronchoconstriction. *Pediatr Pulmonol* 2005;**39**:301-5.
  16. Venn A, Lewis S, Cooper M, Hill J, Britton J. Questionnaire study of effect of sex and age on the prevalence of wheeze and asthma in adolescence. *BMJ* 1998;**316**:1945-6.
  17. Anderson HR, Pottier AC, Strachan DP. Asthma from birth to age 23: incidence and relation to prior and concurrent atopic disease. *Thorax* 1992;**47**:537-42.
  18. Burr M, Eldridge B, Borysiewicz L. Peak expiratory flow rates before and after exercise in schoolchildren. *Arch Dis Child* 1974;**49**:923-6.
  19. Busquets R, Anto J, Sunyer J, Sancho N, Vall O. Prevalence of asthma-related symptoms and bronchial responsiveness to exercise in children aged 13-14 yrs in Barcelona, Spain. *Eur Respir J* 1996;**9**:2094-8.
  20. Weiss P, Rundell KW. Imitators of exercise-induced bronchoconstriction. *Allergy Asthma Clin Immunol* 2009;**5**:7.