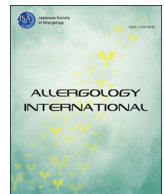




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Original Article

An independent relation of atopic dermatitis to exercise-induced wheezing in asthmatic children

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AD	Atopic dermatitis
AR	Allergic rhinitis
EIA	Exercise-induced asthma
EIW	Exercise-induced wheezing
ISSAC	International Study of Asthma and Allergies in Childhood

ABSTRACT

Background: Atopic dermatitis (AD) and exercise-induced asthma (EIA) are common in asthmatic children, and exercise is the most common trigger other than infection for acute onset asthma attack in children. We examined whether AD is related to exercise-induced wheezing (EIW), some proxy for EIA. **Methods:** Japanese version of the International Study of Asthma and Allergies in Childhood questionnaires were used. For 12,405 asthmatic school children, AD was defined as itchy rash coming and going for at least 6 months at any time in the last 12 months with affecting places of flexural parts of body, and severity of AD was rated according to frequency of being kept awake at night with the itch as follows: never in the past 12 months, less than one night per week and one or more nights per week.

Results: Adjusted for frequency of asthma attack, odds ratios (OR) of children with current AD as compared to those without AD for having EIW were 1.32 (95% confidence interval = 1.15–1.52), 1.35 (1.14–1.68) and 1.10 (0.92–1.31) for primary school, junior high school and high school children, respectively. EIW was more likely observed in accordance with increasing severity of AD in the primary school children with ORs of 1.12, 1.59 and 1.54 (p for trend < 0.01), and in the junior high school ones with ORs of 1.18, 1.31, 2.03 (<0.01), respectively.

Conclusions: AD may be possibly related to EIW. Further studies investigating effect of AD treatment on EIW may be required.

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Introduction

Exercise-induced asthma (EIA) is one of asthma phenotypes,^{1,2} and may not be rare although the true prevalence has been poorly defined.^{3,4} In a recent nation-wide survey across Japan in 2008^{5,6}, the prevalence of wheezing during and/or after exercise, then called as exercise-induced wheezing (EIW), were 4.8, 4.7, 17.9 and 15.4% for kindergartners, school children aged 6–8, aged 13–15 and aged 16–18, respectively; and 20.9, 28.7, 76.1 and 73.6% for the current asthmatic children belonging to the corresponding age categories, respectively. 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.³ Although the concomitant use of provocation challenge test is ideal in order to correlate EIW with EIA, large-sized population-based studies with such a challenge test are unlikely to execute. Ponsonby and colleagues found the exercise challenge had sensitivity of 0.60 and specificity of 0.77 for EIW based on the International Study of Asthma and Allergies in Childhood (ISSAC) questionnaire for 7-year or older children, respectively, using a 12% or greater fall in FEV1 post-exercise as a positive test response.^{4,7,8}

Physical activity is the second leading trigger of airway constriction,⁴ and EIW may contribute to an increased risk of urgent medical visit for asthmatic children.⁸ Determinants and predisposing factors for EIW have been little investigated, however. Atopic dermatitis (AD) is a chronic relapsing inflammatory skin

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disorder, characterized by severe pruritus, a characteristic spread of eczematous skin lesions and often a personal or family history of atopic conditions.⁹ Because AD frequently precede asthma on the way to the atopic march,^{10,11} it would be worth enquiring into possible association between AD and a risk for having EIA independently from an effect of current asthma severity. Allergic rhinitis (AR) is also common in asthmatics, and vice versa. This relation may be in line with the 'one airway - one disease' concept.¹² From another point of view, the nose is involved in humidifying and warming inspired air and the damaged nasal airway in subjects with AR may increase occurrence of asthma and also EIB by changing a degree of airway cooling and dehydration. In the present study, AR was thus always adjusted for in the analyses of the relation between AD and EIW.

Methods

Study subjects

The subjects were from the nation-wide survey of asthma and other allergic morbidities of children in Japan^{13,14} and pertinent details were mentioned here. The subjects were recruited as follows and shown in Fig. 1. The 47 prefectural boards of education selected and asked educational institutions across Japan for participation in response to our request to secure 1000 or more participants in each prefecture without any other intention. The selection of educational institutions was thus not totally at random, and unmeasured particularity of selected institutions cannot be utterly eliminated, while it did not presuppose an introduction of a bias in estimation of the relation between AD and EIW. In the second place, a Japanese version of the ISAAC questionnaire¹⁵ was distributed from April to July 2008 to guardians of pupils aged 6–8 in the first and second grades of the primary schools, pupils aged 13–15 in the second and third grades of the junior high schools and those aged 16–18 in the second and third grades of the high schools (Fig. 1), while a modified questionnaire based on the ISAAC questionnaire but dispensing with enquiries regarding eczema and

rhinitis was distributed to guardians of kindergartners and only reported history of doctor-diagnosed AD and doctor-diagnosed AR were available for this youngest group. The kindergartners were thus omitted for the present analysis. Junior high school and high school pupils were advised to take the questionnaire to home for filling it in by themselves consulting with their guardians. A response was defined as invalid 1) if the child's age was not in agreement with the grade of schools, or 2) 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?" The inapposite responses as well as those with unknown sex were excluded, and 41,216 primary school pupils, 45,960 junior high school pupils and 51,104 high school pupils remained to be analysed further.

Definition of current asthma and EIW

We defined having current asthma if a child or a guardian 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 was rated 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 guardian 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. Having EIW was also defined for children reporting by themselves or by guardians to have wheezing with the frequency of once or more during or after exercise in the past 4 weeks even when they reported no wheezy episodes during or after exercise in the past 12 months.

Definition of AD and AR

Having current AD was defined if a child or a guardian answered "Yes" to all of three questions, "Have you ever had an itchy rash

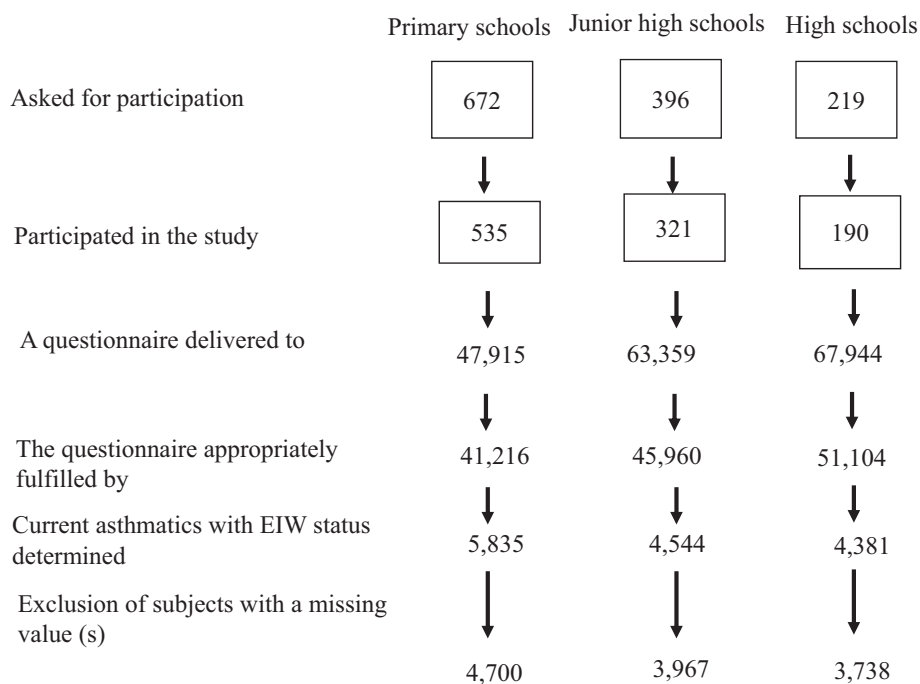


Fig. 1. Study subjects from the participants in the nation-wide survey of asthma and other allergic morbidities of children in Japan.

which was coming and going for at least six months?”, “Have you had this itchy rash at any time in the past 12 months” and “Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears or eyes?” Persistency of the AD was dichotomized according to an answer to a question, “Has this rash cleared completely at any time during the past 12 months?” Degree of itching due to AD was categorized to three levels among children with current AD in accordance with a response to a question, “In the past 12 months, how often, on average, have you been kept awake at night by this itchy rash?: never in the past 12 months, less than one night per week, or one or more nights per week, while use of topical corticosteroids, antihistamines, and other medication for AD was not available. Age at onset of AD was determined in conformity with a response to a question, “At what age did this itchy rash first occur: under 2 years, age 2–4 years, or age 5 or more?”

Having current AR was defined if a child or a guardian answered “Yes” to a question, “In the past 12 months, have you had a problem with sneezing, or a runny, or blocked nose when you DID NOT have a cold or the flu?”

Statistical analysis

Relation between AD and risk of having EIW was examined calculating an odd ratio (OR) of children with current AD for having EIW using children without this skin lesion as reference. Because AD is an established risk factor for developing asthma and the risk for having EIW was consistently related to the increasing severity of current asthma in our study subjects,¹³ the relationship between AD and EIW were thus examined among current asthmatic children

exclusively in the present study adjusted for the current asthma severity rated according to the reported frequency of wheezing in the past 4 weeks. The OR was obtained by use of a multiple logistic regression model¹⁶; sex, age, current AR, severity of current asthma, daily use of leukotriene receptor antagonist, daily use of inhaled medication and place of residence as defined in our previous report¹³ were always adjusted for. In the analyses of the possible association between the degree of itching due to AD and a risk for having EIW, the OR was calculated for each of three children groups of different degrees of itching while keeping children without AD as reference group. When examining a trend of the risk for having EIW due to the increasing severity of itching, ordinary scores from 0 to 3 were assigned to each of the reference and the three groups with AD, respectively. The similar procedures were made when examining the possible relationship of the persistency of and the age at onset of AD to the risk for having EIW. Possible interaction between the school type and AD was investigated using log-likelihood ratio test when applicable.¹⁷ All statistical analyses were performed with STATA statistical software¹⁸ and *p* value < 0.05 was deemed statistically significant otherwise specified. Subjects with any missing values for variables used in the analyses were excluded (Fig. 1).

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

Results

School children with the current AD had a moderately increased risk for having EIW adjusted for the current asthma severity (Table 1). The OR for high school pupils was not significant (Supplementary Table 1) and apparently smaller than those for the

Table 1

Relation between current atopic dermatitis (AD), current allergic rhinitis (AR) and risk of exercise-induced wheezing (EIW) among current asthmatic school children.

Clinical characteristics	EIW				Adjusted odds ratio [†]	95% confidence interval		p value
	No		Yes			Lower limit	Upper limit	
	n	%	n	%				
All school children, aged 6–8, 13–15, and 16–18								
Current AD								
No	3788	42.3%	5176	57.7%	1.00		Reference	
Yes	1340	38.9%	2101	61.1%	1.26	1.14	1.38	<0.001
Current AR								
No	793	49.9%	796	50.1%	1.00		Reference	
Yes	4335	40.1%	6481	59.9%	1.22	1.07	1.38	0.002
Reported frequency of wheezing in the past 4 weeks								
None	3743	51.8%	3487	48.2%	1.00		Reference	
Monthly or more but not weekly	1076	30.7%	2433	69.3%	2.38	2.16	2.63	<0.001
Weekly or more but not every day	270	19.1%	1140	80.9%	3.96	3.38	4.62	<0.001
Every day	39	15.2%	217	84.8%	4.68	3.21	6.80	<0.001
						p for trend <0.001		
School								
Primary school pupils aged 6-8	3275	69.7%	1425	30.3%	1.00		Reference	
Junior high school pupils aged 13–15	915	23.1%	3052	76.9%	8.72	7.85	9.69	<0.001
High school pupils aged 16–18	938	25.1%	2800	74.9%	8.12	7.30	9.03	<0.001
Sex								
Boy	2894	42.8%	3865	57.2%	1.00		Reference	
Girl	2234	39.6%	3412	60.4%	1.02	0.93	1.10	0.724
Daily use of leukotriene receptor antagonist								
No	4475	41.9%	6214	58.1%	1.00		Reference	
Yes	653	38.1%	1063	61.9%	1.49	1.29	1.72	<0.001
Daily use of inhaled medication								
No	4558	44.1%	5767	55.9%	1.00		Reference	
Yes	570	27.4%	1510	72.6%	1.81	1.58	2.07	<0.001
Place of residence								
Southern 27 prefectures	2813	40.8%	4088	59.2%	1.00		Reference	
Northern 20 prefectures	2315	42.1%	3189	57.9%	0.95	0.87	1.03	0.226

[†] Mutually adjusted for current AD, current AR, severity of current asthma, sex, age category (school type), daily use of leukotriene receptor antagonist, daily use of inhaled medication and place of residence.

two younger age groups (p for interaction = 0.118). As shown in Table 2, as compared to pupils without current AD, the children with AD having cleared in the past 12 months and those with AD not having cleared in the past year had an increased risk for EIW in a dose–response manner for the two younger groups only (Supplementary Table 2) (p for interaction = 0.198). Subsequently we examined the relation between having AD and having EIW referring to the age at onset of the skin lesion (Table 3). For primary school and junior high school children, children with current AD had an increased risk for having EIW regardless of the age at onset although the increased OR for junior high school pupils with AD of the onset before age of 2 was not statistically significant (Supplementary Table 3). In contrast to that finding, for high school children, only pupils with current AD of the onset at the age of 5 or older had an increased risk for having EIW (Supplementary Table 3) (p for interaction = 0.038). In relation to the itching due to AD (Table 4), children with more frequently having been kept awake at night by the itching had increasing ORs in a dose–response relationship for primary school and junior high school pupils while such correlation was not observed for high school pupils (Supplementary Table 4) (p for interaction = 0.062).

As to a relation between AR and EIW, children with current AR had an increased risk for having EIW with an OR of 1.22 for all school children combined disregarding use of different indicators of AD (Tables 1–4) although numerical values of 4 or greater decimal places were not the exactly same to each other (data not shown). The positive association between current AR and EIW was, however, mostly concentrated on primary school children regardless of the AD indicator (Supplementary Tables 1–4).

Relation of increasing severity of current asthma and EIW in a dose–response manner was consistently observed for all school children combined (Tables 1–4) and for each of school type (Supplementary Tables 1–4) as shown in our previous report.¹³ As reported also in our preceding paper,¹³ both daily uses of leukotriene receptor antagonist and of inhaled medication were positively associated with EIW (Tables 1–4).

Discussion

The present study produced an association between AD and risk for EIW among current asthmatics after the adjustment for the current asthma severity was made. Although possible residual confounding both from the association between AD and having asthma and from the relation of the severity of current asthma to the risk for EIW may not be totally eliminated even after statistical adjustments and the observed increment in risk for EIW due to AD and/or its characteristics were generally moderate, it is possible that AD and EIW interrelate to each other through shared factors as discussed below.

The cysteinyl leukotrienes (LTC₄, LTD₄ and LTE₄) that alter airway tone directly have been discussed in relation to pathogenesis of EIA with inconsistent findings,⁴ while elevated urinary LTE₄ in children with AD was reported¹⁹ and cysteinyl LTs by eosinophil derived LTC₄ synthase was shown to promote skin fibrosis in a mouse model of AD.²⁰ Nitric oxide (NO) is another potentially important inflammatory compound linking AD with the risk for EIW; NO has a critical effect on bronchial calibre and vasomotor tone in pathogenesis of the EIA,⁴ and AD was positively associated with fractional exhaled

Table 2
Relation between persistency of the atopic dermatitis (AD) during the past 12 months, current allergic rhinitis (AR) and risk of exercise-induced wheezing (EIW) among current asthmatic school children.

Clinical characteristics	EIW				Adjusted odds [†]	95% confidence interval		p value
	No		Yes			Lower limit	Upper limit	
	n	%	n	%				
All school children, aged 6–8, 13–15, and 16–18								
No current AD	3788	42.3%	5176	57.7%	1.00		Reference	
Current AD								
Having cleared completely	606	40.0%	908	60.0%	1.24	1.09	1.41	0.001
Not having cleared completely	734	38.1%	1193	61.9%	1.28	1.13	1.44	<0.001
						p for trend <0.001		
Current AR								
No	793	49.9%	796	50.1%	1.00		Reference	
Yes	4335	40.1%	6481	59.9%	1.22	1.07	1.38	0.002
Reported frequency of wheezing in the past 4 weeks								
None	3743	51.8%	3487	48.2%	1.00		Reference	
Monthly or more but not weekly	1076	30.7%	2433	69.3%	2.38	2.16	2.63	<0.001
Weekly or more but not every day	270	19.1%	1140	80.9%	3.95	3.38	4.62	<0.001
Every day	39	15.2%	217	84.8%	4.67	3.21	6.80	<0.001
						p for trend <0.001		
School								
Primary school pupils aged 6-8	3275	69.7%	1425	30.3%	1.00		Reference	
Junior high school pupils aged 13–15	915	23.1%	3052	76.9%	8.72	7.85	9.69	<0.001
High school pupils aged 16–18	938	25.1%	2800	74.9%	8.12	7.30	9.03	<0.001
Sex								
Boy	2894	42.8%	3865	57.2%	1.00		Reference	
Girl	2234	39.6%	3412	60.4%	1.02	0.93	1.11	0.717
Daily use of leukotriene receptor antagonist								
No	4475	41.9%	6214	58.1%	1.00		Reference	
Yes	653	38.1%	1063	61.9%	1.49	1.29	1.72	0.224
Daily use of inhaled medication								
No	4558	44.1%	5767	55.9%	1.00		Reference	
Yes	570	27.4%	1510	72.6%	1.81	1.58	2.07	<0.001
Place of residence								
Southern 27 prefectures	2813	40.8%	4088	59.2%	1.00		Reference	
Northern 20 prefectures	2315	42.1%	3189	57.9%	0.95	0.87	1.03	0.224

[†] Mutually adjusted for persistency of AD, current AR, severity of current asthma, sex, age category (school type), daily use of leukotriene receptor antagonist, daily use of inhaled medication and place of residence.

Table 3

Relation between age at onset of atopic dermatitis (AD), current allergic rhinitis (AR) and risk of exercise-induced wheezing (EIW) among current asthmatic school children.

Clinical characteristics	EIW				Adjusted odds ratio [†]	95% confidence interval		p value
	No		Yes			Lower limit	Upper limit	
	n	%	n	%				
All								
No current AD	3788	42.3%	5176	57.7%	1.00	Reference		
Age at onset of current AD								
Under 2 years	704	46.1%	822	53.9%	1.21	1.06	1.38	0.004
Age 2–4 years	369	42.1%	508	57.9%	1.18	1.00	1.40	0.045
Age 5 or more	267	25.7%	771	74.3%	1.41	1.20	1.66	<0.001
					p for trend <0.001			
Current AR								
No	793	49.9%	796	50.1%	1.00	Reference		
Yes	4335	40.1%	6481	59.9%	1.22	1.07	1.38	0.002
Reported frequency of wheezing in the past 4 weeks								
None	3743	51.8%	3487	48.2%	1.00	Reference		
Monthly or more but not weekly	1076	30.7%	2433	69.3%	2.38	2.16	2.63	<0.001
Weekly or more but not every day	270	19.1%	1140	80.9%	3.96	3.39	4.63	<0.001
Every day	39	15.2%	217	84.8%	4.68	3.22	6.81	<0.001
					p for trend <0.001			
School								
Primary school pupils aged 6–8	3275	69.7%	1425	30.3%	1.00	Reference		
Junior high school pupils aged 13–15	915	23.1%	3052	76.9%	8.60	7.73	9.57	<0.001
High school pupils aged 16–18	938	25.1%	2800	74.9%	8.01	7.19	8.91	<0.001
Sex								
Boy	2894	42.8%	3865	57.2%	1.00	Reference		
Girl	2234	39.6%	3412	60.4%	1.01	0.93	1.10	0.741
Daily use of leukotriene receptor antagonist								
No	4475	41.9%	6214	58.1%	1.00	Reference		
Yes	653	38.1%	1063	61.9%	1.49	1.29	1.72	<0.001
Daily use of inhaled medication								
No	4558	44.1%	5767	55.9%	1.00	Reference		
Yes	570	27.4%	1510	72.6%	1.81	1.58	2.07	<0.001
Place of residence								
Southern 27 prefectures	2813	40.8%	4088	59.2%	1.00	Reference		
Northern 20 prefectures	2315	42.1%	3189	57.9%	0.95	0.87	1.03	0.224

[†] Mutually adjusted for age at onset of AD, current AR, severity of current asthma, sex, age category (school type), daily use of leukotriene receptor antagonist, daily use of inhaled medication and place of residence.

Table 4

Relation between severity of itching due to atopic dermatitis (AD), current allergic rhinitis (AR) and risk of exercise-induced wheezing (EIW) among current asthmatic school children.

Clinical characteristics		EIW				Adjusted odds ratio [†]	95% confidence interval		p value
		No		Yes			Lower limit	Upper limit	
		n	%	n	%				
All									
No current AD		3788	42.3%	5176	57.7%	1.00		Reference	
Current AD									
Frequency of having been kept awake at night by the itchy rash									
Never in the past 12 months		727	43.9%	930	56.1%	1.13	1.00	1.28	0.059
Less than one night per week		392	36.6%	679	63.4%	1.36	1.17	1.59	<0.001
One or more nights per week		221	31.0%	492	69.0%	1.46	1.21	1.76	<0.001
							p for trend <0.001		
Current AR									
No		793	49.9%	796	50.1%	1.00		Reference	
Yes		4335	40.1%	6481	59.9%	1.22	1.07	1.38	0.002
Reported frequency of wheezing in the past 4 weeks									
None		3743	51.8%	3487	48.2%	1.00		Reference	
Monthly or more but not weekly		1076	30.7%	2433	69.3%	2.38	2.16	2.62	<0.001
Weekly or more but not every day		270	19.1%	1140	80.9%	3.93	3.36	4.60	<0.001
Every day		39	15.2%	217	84.8%	4.64	3.19	6.75	<0.001
							p for trend <0.001		
School									
Primary school pupils aged 6–8		3275	69.7%	1425	30.3%	1.00		Reference	
Junior high school pupils aged 13–15		915	23.1%	3052	76.9%	8.70	7.83	9.67	<0.001
High school pupils aged 16–18		938	25.1%	2800	74.9%	8.07	7.25	8.97	<0.001
Sex									
Boy		2894	42.8%	3865	57.2%	1.00		Reference	
Girl		2234	39.6%	3412	60.4%	1.01	0.93	1.10	0.739

(continued on next page)

Table 4 (continued)

Clinical characteristics	EIW				Adjusted odds ratio [†]	95% confidence interval		p value
	No		Yes			Lower limit	Upper limit	
	n	%	n	%				
Daily use of leukotriene receptor antagonist								
No	4475	41.9%	6214	58.1%	1.00		Reference	
Yes	653	38.1%	1063	61.9%	1.81	1.58	2.07	<0.001
Daily use of inhaled medication								
No	4558	44.1%	5767	55.9%	1.00		Reference	
Yes	570	27.4%	1510	72.6%	1.81	1.58	2.07	<0.001
Place of residence								
Southern 27 prefectures	2813	40.8%	4088	59.2%	1.00		Reference	
Northern 20 prefectures	2315	42.1%	3189	57.9%	0.95	0.87	1.03	0.232

[†] Mutually adjusted for severity of itching due to AD, current AR, severity of current asthma, sex, age category (school type), daily use of leukotriene receptor antagonist, daily use of inhaled medication and place of residence.

nitric oxide (FeNO) among children with suspected asthma²¹ although such a positive association was not always observed.²² Later age at onset of the AD was associated with an increasing risk of having EIW in the present study. Magnitude of effects of risk factors for AD are varied according to age at onset of AD^{11,23} and such variations may be possibly related to the risk for having EIW.

Another allergic disease, AR, was also related to a moderate increased risk for EIW in the present study subjects adjusted for the current asthma severity and AD. It is possible that the presence of AR is related to the risk for having EIW, as the nose is associated with respiratory heat change that is linked to hyperventilation due to exercise.

The EIW, a proxy for EIA, AD and AR were defined in the present study using a ISAAC questionnaire that was originally developed to examine global variation in the prevalence of asthma and other allergic diseases²⁴ and its time trends.¹⁵ Apart from the descriptive studies, the ISAAC questionnaire have been used in analytical studies: exploring an association between rhinitis and nocturnal cough,⁶ a relation of obesity to asthma,⁵ enquiring into an urgent medical visit in relation to EIW,⁸ or researching health-related quality of life in association with EIA.²⁵ Misclassification of EIW and AD may be expected at least to some extent. However, the observed association in the present study was assumed to have been diluted as far as the misclassification of AD was unrelated to the misclassification of EIW.

Because the present study was based on the cross-sectional data, causal inference resorting only to the current findings should be avoided, and a possible reverse relation that well-controlled asthmatics have better adherence of atopic dermatitis than that of uncontrolled cannot be ruled out. Although we were also unable to determine the causal relationship between medication usage and risk of having EIW, positive relations between two medication usages and having EIW consistently observed over the 4 different age groups were in accordance with current treatment for EIB with LTRA and inhaled corticosteroid use.³ Further studies, especially, investigating effect of AD treatment on occurrence of EIW may be interesting and contributing to advancement of care for asthmatic children.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.alit.2018.04.013>.

Conflict of interest

The authors have no conflict of interest to declare.

Authors' contributions

SH conceptualized and designed the study, performed the final analyses, draughted the initial manuscript, and reviewed and revised the manuscript. YM conceptualized and designed the study, performed the preliminary analyses, reviewed the manuscript.

HO conceptualized and designed the study, reviewed the manuscript, and coordinated and supervised data collection. YA designed the study, reviewed and revised the manuscript, and coordinated and supervised data collection. KY designed the study, reviewed and revised the manuscript, and coordinated and supervised data collection.

YO designed the study, reviewed the manuscript, and coordinated and supervised data collection. AA designed the study, reviewed the manuscript, and coordinated and supervised data collection, and secured the study fund. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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