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Associated Factors for Asthma Severity in Korean Children: A Korean Childhood Asthma Study

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ABSTRACT

Purpose: Childhood asthma has a considerable social impact and economic burden, especially in severe asthma. This study aimed to identify the proportion of childhood asthma severity and to evaluate associated factors for greater asthma severity.
Methods: This study was performed on 667 children aged 5–15 years with asthma from the nationwide 19 hospitals in the Korean childhood Asthma Study (KAS). Asthma was classified as mild intermittent, mild persistent, and moderate/severe persistent groups according to the National Asthma Education and Prevention Program recommendations. Multinomial logistic regression models were used to identify the associated factors for greater asthma severity.
Results: Mild persistent asthma was most prevalent (39.0%), followed by mild intermittent (37.6%), moderate persistent (22.8%), and severe persistent asthma (0.6%). Onset later

than 6 years of age (adjusted odds ratio [aOR], 1.69 for mild persistent asthma; aOR, 1.92 for moderate/severe persistent asthma) tended to increase asthma severity. Exposure to environmental tobacco smoke (aOR, 1.53 for mild persistent asthma; aOR, 1.85 for moderate/severe persistent asthma), and current dog ownership with sensitization to dog dander (aOR, 5.86 for mild persistent asthma; aOR, 6.90 for moderate/severe persistent asthma) showed increasing trends with greater asthma severity. Lower maternal education levels (aOR, 2.32) and no usage of an air purifier in exposure to high levels of outdoor air pollution (aOR, 1.76) were associated with moderate/severe persistent asthma.

Conclusions: Modification of identified environmental factors associated with greater asthma severity might help better control childhood asthma, thereby reducing the disease burden due to childhood asthma.

Keywords: Child; asthma; severity; risk factor; environmental exposure; smoke; dogs; education status; air pollution

INTRODUCTION

Asthma is a chronic inflammatory airway disease with a considerable social impact and economic burden.[1,2] Asthma is not a single disease, but a large group of heterogeneous diseases with diverse phenotypes.[3] With the aim of designing targeted therapies for individualized care, much effort has been made to identify factors associated with and the underlying mechanisms of the diverse asthma phenotypes.[4-8]

Recent information on the prevalence of each asthma group classified by severity is lacking. A previous study identified the distribution of asthma severity in children aged 5–12 years by using the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire and the Global Initiative for Asthma (GINA) classification in an urban area of Brazil,[9] but its limitation was that it did not reflect the general population. Another study identified the asthma control status by using telephonic interviews based on the GINA guideline in children younger than 15 years old,[10] but this study was limited by the lack of objective assessment of asthma.

The interactions between environmental factors and host factors contribute to asthma severity,[11,12] but studies on factors associated with greater asthma severity in children are relatively scarce.[13] In a case-control study, low paternal education and household income were associated with persistent asthma.[14] In a causal network analysis, the allergy pathway, including allergic inflammation and pulmonary physiology, and the environmental tobacco smoke (ETS) exposure pathway showed significant effects on asthma severity.[12] The identified pulmonary function and sensitization might be unmodifiable outcomes rather than the causes of greater asthma severity. Therefore, identifying modifiable factors that can affect asthma severity could be one of the unmet needs, and application of these factors in real life can help decrease the asthma severity and thereby better control asthma.

The aim of the present study was to identify the proportion of each asthma group classified according to the National Asthma Education and Prevention Program (NAEPP) recommendations. In addition, we attempted to evaluate factors associated with greater asthma severity in children with asthma.

MATERIALS AND METHODS

Study population

This study included 667 children (age, 5–15 years) enrolled from a nationwide prospective cohort study as a part of the Korean childhood Asthma Study (KAS).[15] The children with asthma were enrolled from 19 regional tertiary hospitals between August 2016 and December 2018. Asthma was diagnosed on the basis of symptoms (wheezing or cough), a significant bronchodilator response of forced expiratory volume in 1 second (FEV1) greater than 12% improvement from baseline on a pulmonary function test, and/or the provocative concentration resulting in a 20% fall in FEV1 (PC20) ≤ 16 mg/mL on methacholine bronchial provocation tests.[16-18] Children with bronchiolitis obliterance or bronchopulmonary dysplasia were excluded. Asthma severity was classified as mild intermittent, mild persistent, moderate persistent, or severe persistent according to the NAEPP recommendations (**Table 1**).[19] Since the number of children with severe persistent asthma was small (n = 4), we classified 3 asthma groups as follows: mild intermittent, mild persistent, and moderate/severe persistent. At the time of enrollment, current status of asthma medication used in the participants is summarized in **Supplementary Table S1**. The Institutional Review Boards of each of the participating institutions approved the study protocol (IRB No. 2016-0914).[15]

Questionnaire

At the time of enrollment in the KAS, the patients or their caregivers were asked to complete a questionnaire.[20] The questionnaire was derived from that used in the cohort of growth and development[20] and included the following questions: 1) general characteristics, including birth weight, gestational age, delivery mode, current height and weight, maternal educational level, and family history of allergic diseases, including allergic rhinitis (AR), atopic dermatitis (AD), and asthma; 2) exposure to environmental factors, such as the usage of an indoor air purifier on days with high levels of outdoor air pollution, current ownership of indoor pets including dogs, and current exposure to ETS; 3) physician-diagnosed allergic diseases, including AD, AR, asthma, and food allergy (FA), in their life; and 4) asthma-related factors, including the onset age of asthma and exacerbating triggers.

Table 1. Classification of asthma severity according to NAEPP recommendation*

Components of severity	Mild intermittent	Mild persistent	Moderate persistent	Severe persistent
Impairment				
Days with symptoms	≤ 2 days/week	> 2 days/week, but not daily	Daily	Throughout the day
Nighttime awakenings	≤ 2 times/month	3–4 times/month	> 1 times/week, but not nightly	Often 7 times/week
Short-acting beta2-agonist use for symptom control	≤ 2 days/week	> 2 days/week, but not daily†	Daily	Several times per day
Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
Lung function				
- FEV1 (predicted) or peak flow (personal best)	Normal FEV1 between exacerbations > 80%	> 80%	60%–80%	< 60%
- FEV1/FVC	> 85%	> 80% (≥ 85% in children ≥ 12 years of age)	75%–80% (FEV1/FVC reduced 5% in children ≥ 12 years of age)	< 75% (FEV1/FVC reduced > 5% in children ≥ 12 years of age)
Risk				
Exacerbations requiring oral systemic corticosteroids (consider severity and interval since last exacerbation)	0–1 /year	≥ 2 times/year	-	-

FEV1, forced expiratory volume in 1 second; NAEPP, National Asthma Education and Prevention Program.
*2007 NAEPP Expert Panel Report 3; †In children ≥ 12 years of age, > 2 days/week, but not daily, and more than 1 times on any day.

Parents were asked the following questions about their child's ETS exposure at home: "Has your child ever been currently exposed to smoke from tobacco at home?" and "Are there any active smokers among your family members who live together?" The usage of an air purifier during exposure to high levels of outdoor air pollution was identified using the question: "Do you use an indoor air purifier during exposure to high levels of outdoor air pollution based on the forecast of fine dust?" The children's parents or guardians were asked about mold exposure as follows: "Were visible molds seen in your home during the preceding 12 months?" and "Are visible molds seen in your home at present?" The children's parents or guardians were asked about current pet ownership using the questions: "Do you currently keep any dog at home?" and "Do you currently keep any cat at home?" The status of asthma control was evaluated using the Childhood Asthma Control Test (ACT) for children aged 5–11 years old and the ACT for those aged 12 years and older.[21,22]

Physician's assessment of allergic diseases

Pediatric allergists assessed the presence of asthma symptoms, AR, AD, and FA at the time of enrollment. AR was diagnosed on the basis of individual symptoms and nasal examination findings satisfying the criteria of AR, such as pale appearance, mucosal swelling, and thin secretions.[23] Current AR was defined as physician-diagnosed AR at any point in the child's lifetime and having nasal symptoms at any time during the preceding 12 months. AD was diagnosed on the basis of the Hanifin and Rajka criteria.[24] Current AD was defined as physician-diagnosed AD at any point in the child's lifetime and having eczema in the preceding 12 months. FA was diagnosed by pediatric allergists based on the clinical symptoms and results of skin prick tests (SPTs) or specific immunoglobulin E (IgE) levels.[25] Current FA was defined as physician-diagnosed FA at any point in the child's lifetime and having symptoms of FA in the preceding 12 months with confirmed results on SPTs or specific IgE levels.

Pulmonary function test and methacholine bronchial provocation test

Pulmonary function and methacholine bronchial provocation tests were performed when the study subjects had no history of upper or lower respiratory tract infection during the 4 weeks prior to the tests and they avoided bronchodilator treatment for at least 8–24 hours.[17] Spirometry was performed according to the European Respiratory Society and American Thoracic Society (ATS) guidelines.[18,26] The forced vital capacity (FVC), FEV1, and maximal mid-expiratory flow (MMEF) were measured before and 15 minutes after inhaling 2 puffs of salbutamol. For the methacholine bronchial provocation test, fresh solutions of methacholine were serially diluted in buffered saline solution at concentrations of 0, 0.0625, 0.25, 1, 4, and 16 mg/mL.[17] We used a modified 5-breath dosimeter method in accordance with the ATS guideline.[17]

SPTs

SPTs were performed for 18 inhalant allergens including *Dermatophagnoides pteronyssinus*, *Dermatophagoides farinae*, *Alternaria* spp., *Aspergillus* spp., *Cladosporium* spp., dog dander, cat epithelium, cockroach, and 10 pollen allergens (oak, alder, hazel, beech, birch, rye grass, ragweed, hop, timothy, and mugwort). Normal saline was used as a negative control and histamine (10 mg/mL) was used as the positive control. Atopy was defined as at least 1 positive SPT response, in which the wheal size exceeding 3 mm and exceeding that of the positive control.[27]

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Statistical analysis

The data are presented as means ± standard deviations or number (%). The Kruskall-Wallis test or χ^2 test was appropriately used to compare the prevalence of the associated factors among the groups classified according to asthma severity. For comparisons of mean values, analysis of variance test was used for variables with a normal distribution and Kruskall-Wallis test was used for those with non-normal distribution. Multiple comparisons between 2 groups were counteracted using Bonferroni correction. To identify the associations between related factors and asthma severity, multinomial logistic regression analysis was used after adjusting for age, sex, and a family history of allergic diseases. Data were analyzed using SPSS Statistics, Version 24 (SPSS Inc., Chicago, IL, USA). A *P* value of 0.05 or less was considered significant.

RESULTS

Study population

The demographics of the participants are described in **Table 2**. The mean age of the study population was 8.90 years, and the proportion of boys was higher (66.7%). Mild persistent asthma was most prevalent (39.0%), followed by mild intermittent (37.6%), moderate persistent (22.8%), and severe persistent asthma (0.6%).

Comparisons of baseline characteristics among childhood asthma severity groups

Later onset age of asthma was associated with greater asthma severity (*P* for trend < 0.001) (**Table 3**). The prevalence of a history of bronchiolitis in infancy showed a significantly decreasing trend with greater asthma severity (*P* for trend = 0.001). Lower maternal education levels and lower ACT scores showed a significant trend with higher asthma severity (*P* for trend < 0.001). Age at the time of enrollment showed significantly increasing trends with more severe asthma, as the body mass index showed an increasing trend in more severe asthma with statistical significance in its trend. No significant differences were observed in the prevalence of a family history of allergic diseases and a parental history of asthma according to asthma severity. No significant trend was observed in the prevalence of FA, AD, and AR as well as atopy and multi-sensitization according to asthma severity.

Table 2. Demographics of the study population

Variables	Values
Number	667
Age (yr)	8.90 ± 2.59
Sex (male)	445/667 (66.7)
Height (cm)	136.15 ± 15.69
Weight (kg)	35.81 ± 14.34
Body mass index (kg/m^2)	18.56 ± 3.58
Asthma severity	
Mild intermittent	251/667 (37.6)
Mild persistent	260/667 (39.0)
Moderate persistent	152/667 (22.8)
Severe persistent	4/667 (0.6)
Positive bronchodilator responses of FEV1 (≥ 12%)	140/442 (31.7)
Methacholine PC20 (< 16 mg/mL)	498/498 (100.0)

Values are presented as mean ± standard deviation or number (%).
FEV1, forced expiratory volume in 1 second; PC20, cumulative methacholine dose that caused a 20% reduction in FEV1.

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Table 3. Comparisons of baseline characteristics according to the severity of asthma in children

NAEPP classification	Mild intermittent	Mild persistent	Moderate/severe persistent	Total	P value*	Trend P value†
No. of patients (%)	251/667 (37.6)	260/667 (39.0)	156/667 (23.4)	667 (100.0)		
Age (yr)	8.9 ± 2.5	8.7 ± 2.5	9.5 ± 2.8	9.47 ± 4.23	0.005	0.002
Sex (male)	176/251 (70.1)	159/260 (61.2)	107/156 (68.6)	442/667 (66.3)	0.079	NA
Gestational age (wk)	38.6 ± 2.4	38.5 ± 2.5	38.9 ± 2.2	38.6 ± 2.4	0.407	0.258
Body mass index (kg/m²)	18.4 ± 3.6	18.4 ± 3.6	19.1 ± 3.5	18.6 ± 3.6	0.078	0.042
Asthma onset age (yr)					0.011	< 0.001
< 3	50/246 (20.3)	39/254 (15.4)	19/152 (12.5)	108/652 (16.6)		
3 ≤ age < 6	99/246 (40.2)	80/254 (31.5)	43/152 (28.3)	222/652 (34.0)		
6 ≤ age < 9	55/246 (22.4)	76/254 (29.9)	49/152 (32.2)	180/652 (27.6)		
9 ≤ age < 12	32/246 (13.0)	42/254 (16.5)	25/152 (16.4)	99/652 (15.2)		
≥ 12	10/246 (4.1)	17/254 (6.7)	16/152 (10.5)	43/652 (6.6)		
Family history of allergic diseases	170/246 (69.1)	183/253 (72.3)	113/153 (73.9)	466/652 (28.5)	0.550	0.286
Parental history of asthma	37/246 (15.0)	47/248 (19.0)	30/153 (19.6)	114/647 (17.6)	0.397	0.210
C-section delivery	35/105 (33.3)	46/120 (38.3)	21/47 (44.7)	102/272 (37.5)	0.397	0.176
History of bronchiolitis	98/243 (40.3)	88/250 (35.2)	36/151 (23.8)	222/644 (34.5)	0.004	0.001
Maternal education level					< 0.001	< 0.001
≤ High school	43/242 (17.8)	65/253 (25.7)	58/150 (38.7)	166/645 (25.7)		
College	165/242 (68.2)	168/253 (66.4)	76/150 (50.7)	409/645 (63.4)		
Graduate school	34/242 (14.0)	20/253 (7.9)	16/150 (10.7)	70/645 (10.9)		
Atopy	192/219 (87.7)	182/232 (78.4)	125/139 (89.9)	499/590 (84.6)	0.003	0.922
Multi-sensitization (≥ 2 allergens)	178/219 (81.3)	164/232 (70.7)	115/139 (82.7)	457/590 (77.5)	0.006	0.894
ACT score	22.65 ± 3.22	20.76 ± 4.37	19.07 ± 4.84	21.10 ± 4.31	< 0.001	< 0.001
Current FA	36/249 (14.5)	24/236 (9.2)	19/154 (11.9)	79/663 (11.9)	0.188	0.375
Current AD	71/246 (28.9)	52/252 (20.6)	45/152 (29.6)	168/650 (25.8)	0.053	0.843
Current AR	188/246 (76.4)	198/254 (78.0)	112/152 (73.7)	498/652 (76.4)	0.619	0.614
FA diagnosis ever	64/247 (25.9)	50/253 (19.8)	50/154 (32.5)	164/654 (25.1)	0.015	0.275
AD diagnosis ever	110/247 (44.5)	85/254 (33.5)	64/154 (41.6)	259/655 (39.5)	0.034	0.338
AR diagnosis ever	206/247 (83.4)	200/260 (76.9)	117/155 (75.5)	523/662 (79.0)	0.095	0.042

Values are presented as mean ± standard deviation or number (%).
NAEPP, National Asthma Education and Prevention Program; NA, not applicable; ACT, Asthma Control Test; FA, food allergy; AD, atopic dermatitis; AR, allergic rhinitis.
*χ^2 test; †Linear-by-linear association.

Comparisons of environmental factors among childhood asthma severity groups

The prevalence of exposure to current ETS showed an increasing trend with greater asthma severity (*P* for trend < 0.001), even though no significant difference was observed in the prevalence of any current smoker at home (**Table 4**). The prevalence of current dog ownership (*P* for trend = 0.015) and current dog ownership with sensitization to dog dander (*P* for trend = 0.001) increased with greater asthma severity. However, no significant difference was observed in the proportion of current cat ownership according to asthma severity. The usage of an air purifier during exposure to high levels of outdoor air pollution showed a decreasing trend with greater asthma severity (*P* for trend < 0.001). No significant differences were observed in the proportion of current mold exposure as well as mold exposure in the previous 12 months.

Comparison of pulmonary function according to asthma severity

The levels of FEV1, FVC, and MMEF percent predicted, as well as those after bronchodilator inhalation showed a significantly decreasing trend with greater asthma severity (**Table 5**). These significant differences were more prominent between children in the moderate/severe persistent asthma group and the other 2 groups. The levels of fractional exhaled nitric oxide (FeNO) showed a significantly increasing trend with greater asthma severity, but those of log-transformed methacholine PC20 did not show consistently decreasing trends according to asthma severity, even though a statistical significance.

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Table 4. Comparison of environmental factors according to the severity of asthma in children

NAEPP classification	Mild intermittent	Mild persistent	Moderate/severe persistent	Total	*P* value*	Trend *P* value†
Current exposure to ETS at home	57/246 (23.2)	86/250 (34.4)	61/153 (39.9)	204/649 (31.4)	0.001	< 0.001
Presence of any smoker at home	97/246 (39.4)	108/251 (43.0)	72/153 (47.1)	277/650 (42.6)	0.321	0.132
Usage of air purifier in exposure to high levels of outdoor PM	132/245 (53.9)	141/251 (56.2)	63/153 (41.2)	336/649 (51.8)	0.010	0.029
Mold exposure in the previous 12 months	63/244 (25.8)	74/251 (29.5)	52/153 (34.0)	189/648 (29.2)	0.217	0.081
Current mold exposure	43/244 (17.6)	46/251 (18.3)	41/153 (26.8)	130/648 (20.1)	0.058	0.039
Current cat ownership	8/246 (3.3)	12/251 (4.8)	9/153 (5.9)	29/350 (4.5)	0.443	0.204
Current dog ownership	21/246 (8.5)	38/251 (15.1)	25/153 (16.3)	84/650 (12.9)	0.032	0.015
Current dog ownership with sensitization to dog	2/244 (0.8)	13/254 (5.1)	11/151 (7.3)	26/649 (4.0)	0.003	0.001
Current mold exposure with sensitization to mold (*Aspergillus*, *Alternaria* or *Cladosporium*)	7/214 (3.3)	6/226 (2.7)	10/138 (7.2)	23/578 (4.0)	0.075	0.096

NAEPP, National Asthma Education and Prevention Program; ETS, environmental tobacco smoke; PM, particulate matter
*χ^2 test; †Linear by linear association.

Table 5. Comparisons of pulmonary function tests according to severity of asthma in children

NAEPP classification	Mild intermittent	Mild persistent	Moderate/severe persistent	Overall *P* value*	Trend *P* value
FEV1, % predicted					
Prebronchodilator	91.52 (79.21–105.75)	91.59 (77.57–108.15)	79.61 (57.86–109.53)	< 0.001	< 0.001
Postbronchodilator	97.54 (85.08–111.83)	97.06 (83.90–112.30)	82.01 (60.13–111.86)	< 0.001	< 0.001
FVC, % predicted					
Prebronchodilator	97.65 (85.34–111.74)	98.00 (83.88–114.49)	89.81 (71.16–113.35)	< 0.001	< 0.001
Postbronchodilator	99.21 (86.9–113.28)	98.96 (85.19–114.97)	89.68 (71.29–112.81)	< 0.001	< 0.001
FEV1/FVC (%)					
Prebronchodilator	93.72 (84.85–103.52)	93.37 (84.09–103.69)	88.62 (74.43–105.53)	< 0.001	< 0.001
Postbronchodilator	98.31 (89.31–108.23)	98.08 (90.38–106.44)	91.45 (76.91–108.74)	< 0.001	< 0.001
MMEF, % predicted					
Prebronchodilator	78.14 (56.89–107.32)	77.14 (55.67–106.87)	64.38 (37.47–110.60)	0.001	< 0.001
Postbronchodilator	101.81 (74.96–138.28)	95.79 (70.10–130.89)	72.32 (43.46–120.34)	< 0.001	< 0.001
DFEV1 (L)	0.196 (0.002–19.522)	0.1827 (0.003–12.775)	0.254 (0.003–20.671)	< 0.001	< 0.001
DFEV1, % predicted	6.16 (2.59–14.67)	6.27 (2.61–15.07)	8.22 (3.36–20.09)	0.002	< 0.001
FeNO (ppb)	25.15 (12.47–50.73)	25.77 (12.4–53.53)	32.44 (15.3–68.76)	0.010	0.003
Methacholine PC20 (mg/mL)	2.10 (0.59–7.48)	2.49 (0.67–9.29)	1.04 (0.20–5.53)	< 0.001	< 0.001

Values are presented as geomean ± one standard deviation.
NAEPP, National Asthma Education and Prevention Program; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; MMEF, maximal mid-expiratory flow; FeNO, fractional exhaled nitric oxide; ppb, parts per billion; PC20, cumulative methacholine dose that caused a 20% reduction in FEV1.
*Kruskall-Wallis test.

Main effect analysis on asthma severity using multinomial logistic regression

In the final model, we took into account the significant environmental factors except for symptom severity reflected in the ACT score and the levels of pulmonary function to identify the effect of modifiable factors on childhood asthma severity (**Table 6**). In the multinomial logistic analysis, asthma onset later than 6 years of age (adjusted odds ratio [aOR], 1.69 and 95% confidence interval [CI], 1.13–2.52 for mild persistent asthma; aOR, 1.92 and 95% CI, 1.20–3.08 for moderate/severe persistent asthma when mild intermittent asthma was considered as a reference) was associated with greater asthma severity. Exposure to ETS (aOR, 1.53 and 95% CI, 1.01–2.32 for mild persistent asthma; aOR, 1.85 and 95% CI, 1.14–2.98 for moderate/severe persistent asthma, when mild intermittent asthma was considered as a reference), and current dog ownership with sensitization to dog dander (aOR, 5.86 and 95% CI, 1.30–26.41 for mild persistent asthma; aOR, 6.90 and 95% CI, 1.41–33.76 for moderate/severe persistent asthma when mild intermittent asthma was considered as a reference) tended to increase asthma severity. Lower maternal education levels (aOR, 2.32 and 95% CI, 1.40–3.86) and no usage of an air purifier in exposure to high levels of outdoor air pollution (aOR, 1.76, 95% CI, 1.11–2.77) were associated with moderate/severe asthma, when mild intermittent asthma was considered as a reference.

Table 6. Main effects analysis on asthma severity using multinomial logistic regression

Factors	Mild intermittent (ref) *vs.* mild persistent		Mild intermittent (ref) *vs.* moderate/severe persistent	
	aOR (95% CI)	*P* value	aOR (95% CI)	*P* value
Asthma onset age ≥ 6 years	1.69 (1.13–2.52)	0.010	1.92 (1.20–3.08)	0.007
Current exposure to ETS	1.53 (1.01–2.32)	0.046	1.85 (1.14–2.98)	0.012
Maternal education level, ≤ High school	1.47 (0.92–2.35)	0.106	2.32 (1.40–3.86)	0.001
No usage of air purifier in exposure to high levels of outside PM	0.97 (0.67–1.43)	0.897	1.76 (1.11–2.77)	0.016
History of physician-diagnosed bronchiolitis in infancy	0.88 (0.59–1.31)	0.523	0.53 (0.32–0.88)	0.014
Current dog ownership with sensitization to dog dander	5.86 (1.30–26.41)	0.012	6.90 (1.41–33.76)	0.017

Nagelkerke R^2 = 0 .123, χ^2 = 70.978 (P < 0.001). Values are presented as aOR (95% CI) from multinomial logistic regression models, related to mild intermittent asthma. Adjusted by age, sex, and a family history of allergic diseases.
aOR, adjusted odds ratio; CI, confidence interval; ETS, environmental tobacco smoke; PM, particulate matter.

DISCUSSION

We identified the proportion of each asthma severity group and modifiable factors associated with greater asthma severity in Korean children in a nationwide asthma cohort study. The prevalence of mild persistent asthma was highest, followed by mild intermittent asthma and moderate/severe persistent asthma. Current exposure to ETS and current dog ownership with sensitization to dog dander tended to be associated with greater asthma severity. A history of bronchiolitis in infancy was inversely associated with greater asthma severity. No usage of an air purifier during exposure to high levels of outdoor air pollution showed a decreasing trend according to asthma severity and was associated with moderate/severe persistent asthma. The application of the modifiable factors identified in the present study may contribute to better control of childhood asthma and thereby decrease the disease burden.

According to the results of the present study, the proportion of children with mild persistent asthma as well as moderate/severe persistent asthma is considerably high, and the proportion of children with mild persistent asthma is higher than that of those with mild intermittent asthma. In a previous study on the distribution of childhood asthma severity in children aged 5–12 years old, a similar finding was observed as mild persistent asthma (40.3%) was the most common type, followed by mild intermittent (36.0%), moderate persistent (12.8%), and severe persistent asthma (10.8%).[9] These findings might suggest the need for more active steps to better controlling and decreasing asthma severity, considering the high proportion of persistent asthma. Identification and actual application of the modifiable environmental factors, which significantly affect the control status of childhood asthma, in daily life are inevitable for better control of asthma. These steps could be practical measures for better management of childhood asthma.

One of the significant factors affecting greater asthma severity was current exposure to ETS. The positive association between greater asthma severity in children and current exposure to ETS was identified in a previous study performed only in one state in the USA.[28] The consistent results in the present nationwide study provide stronger evidence for the need of reducing exposure to ETS to better control asthma. Both our study and the previous study assessed exposure to ETS by using a questionnaire,[28] and the assessment of ETS by using a questionnaire was identified to yield results similar to those obtained using biomarkers of exposure to ETS, such as cotinine levels.[29]

Interestingly, we identified that no usage of an indoor air purifier during exposure to high levels of outdoor air pollution was associated with moderate/severe asthma when

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mild intermittent asthma was considered as a reference. Air pollution is known to affect respiratory health, including asthma, with increases in hospitalization.[30] In a previous study, the use of high-efficiency particulate air (HEPA) filters decreased the frequency of unscheduled clinic visits due to asthma exacerbation in children.[31] Although our questionnaire did not enquire about the inclusion of HEPA filters in the air purifiers used by the patients, we identified that the use of indoor air purifiers can help control moderate/severe asthma. The results of the present study are promising in that they have suggested practical strategies to reduce asthma severity in the era of worsening air pollution and lack of protective strategies to decrease the disease burden due to asthma. A lower socioeconomic status, reflected in the household income levels or maternal education levels, may be associated with the severity of asthma[32-34] as shown in the present study. The underlying mechanisms are not well identified, but the increased exposure to the associated factors in lower socioeconomic groups and among those with less access to medication can be considered as the underlying causes of these associations.

A history of bronchiolitis in infancy was negatively associated with moderate/severe persistent asthma when mild intermittent asthma was considered as a reference. This finding is interesting in that the cumulative evidence suggested that bronchiolitis in early life is a major risk factor of asthma, given the lack of information on the association between a history of bronchiolitis and asthma severity.[35,36] Diverse factors, such as severity of bronchiolitis, sex, and viruses, can affect the association between a history of bronchiolitis in infancy and asthma in later life,[37-40] through interactions between antiviral and atopic inflammatory pathways.[35,41] Since we did not evaluate causative respiratory viruses, frequency of bronchiolitis, and severity of bronchiolitis in infancy in the present study, we could not identify the associations between diverse factors and development and severity of asthma. Nevertheless, the negative association between a history of bronchiolitis in infancy and childhood asthma severity was significant without differences in the possible important confounding factors, such as the sensitization rate, a family history of allergic diseases, among the 3 groups classified according to asthma severity. In a previous study, lower respiratory tract illnesses due to respiratory syncytial virus in early life increased the risk of subsequent development of wheezing up to 11 years of age, but not at 13 years of age.[42] Taken together, bronchiolitis in early life might be associated with early life wheezing, but the effect does not persist until later life. Further large-scale studies are warranted to confirm the results of the present study and to identify mechanisms underlying these associations.

The present study has identified that later onset of childhood asthma was associated with greater asthma severity. Asthma severity was positively associated with onset age in adult patients with asthma, but studies on these associations in childhood asthma are lacking.[43,44] The associations between onset age and asthma severity might be partially modified by differences in comorbidities or environmental factors, such as socioeconomic status.[33,44] In the present study, the proportions of combined AR (onset age of asthma < 6 years of age vs onset age of asthma ≥ 6 years of age, 75.3% vs. 82.5%; $P = 0.024$) and maternal education level less than high school (39.5% vs. 60.5%; $P = 0.001$) were higher in children with later onset of asthma than in those of children with early onset asthma. Further studies are needed in the future to identify the associations and its underlying mechanisms.

In the present study, no significant differences were observed in the prevalence of atopy, even including that of multiple sensitizations, across the 3 groups. Sensitization to dog dander in itself was not associated with greater asthma severity (data not shown). However, sensitization to dog dander in children currently keeping dogs at home was associated with moderate/severe asthma. This was not applicable in the case of cats. The results suggest that sensitized allergens combined with other factors, but not sensitization in itself, are responsible for greater asthma severity.[45] The positive association between current dog ownership with sensitization to dog dander and greater asthma severity suggests the importance of environmental management for asthma control in susceptible patients with asthma.[46]

In a previous study, asthma in children can be clinically classified according to symptom frequency and medication use rather than pulmonary function, since asthma severity may not be correlated with pulmonary function.[47] However, the present study showed that pulmonary function indices were lowest in children with moderate/severe persistent asthma, and the differences in the levels of pulmonary function indices were prominent between children with moderate/severe persistent asthma and those with mild intermittent asthma or mild persistent asthma. The remarkable decreases in pulmonary function in children with moderate/severe persistent asthma suggest the need for more active steps to better controlling asthma in children with moderate/severe asthma. The application of the modifiable factors, identified in the present study, might help control greater asthma severity in children.

This study has some limitations. First, a questionnaire was used to evaluate environmental factors. However, diverse epidemiologic studies on allergic diseases have also used questionnaires to identify factors associated with allergic diseases. In addition, the questionnaire lacked qualitative and quantitative assessments of some environmental factors, such as the frequency of ETS exposure or the use of air purifiers with HEPA filters. There might be some bias regarding onset age of asthma and asthma severity. Children with greater asthma severity might have had a greater probability of being enrolled in the present cohort study and therefore the results of the present study may not represent findings from Korean children with asthma. Since this study is a cross-sectional study, which enables comparisons among many different variables at the same time, limitations in providing definite information on cause-and-effect relationships.

In conclusion, we identified that later onset age of asthma, current exposure to ETS, and current dog ownership with sensitization to dog dander in children with asthma tended to be associated with greater asthma severity. A lower maternal educational level and no usage of an indoor air purifier during exposure to high levels of outdoor air pollution were associated with greater asthma severity in children. Modification of the associated factors for greater asthma severity might help control asthma severity in children and thereby reduce the disease burden due to childhood asthma and future respiratory health even in adults.

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SUPPLEMENTARY MATERIAL

Supplementary Table S1

Current status of usage of asthma controller medication at the time of enrollment

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