Asian Pacific Journal of Allergy and Immunology

ORIGINAL ARTICLE

Atmospheric environment and persistence of pediatric asthma: A population-based cohort study

Hwan Soo Kim,[1,†] Kyunghoon Kim,[2,†] Eun Hee Rhee,[3,4] Woo Kyung Kim,[5] Dae Jin Song,[6] Ji Soo Park,[2] Dong In Suh,[2] Jisun Yoon,[7] Eun Lee,[8] Seung Won Lee,[9] Jin Tack Kim,[1] Dae Hyun Lim,[10] Hey Sung Baek,[11] Meeyong Shin,[3] Ji Won Kwon,[2] Gwang Cheon Jang,[12] Ju Hee Seo,[13] Sung Il Woo,[14] Hyung Young Kim,[15] Ju Suk Lee,[16] Jinho Yu,[17] Hyeon-Jong Yang,[3,4,‡] Young Yoo[6,‡]

Abstract

Background: Asthma is a heterogeneous disease with different outcomes. For children with asthma at the age of 7 years, 67–75% are symptom-free as adults. Data on the important link between childhood and adult asthma are sparse.

Objective: We aimed to investigate factors associated with persistence of childhood asthma over three years of follow-up by linking data between Korea childhood Asthma Study (KAS) and their matched claims data from Health Insurance Review and Assessment Service (HIRA).

Methods: We analyzed data from 450 preadolescent children aged 7 to 10 years and classified them into remission or persistence groups. Baseline clinical characteristics and exposure to air pollution materials including PM2.5 and PM10 during three years of follow-up were compared. The main outcome was asthma persistence which was defined as the presence of asthma episodes with healthcare utilization and prescription of asthma medications within three years after KAS enrollment.

Results: At the third year of follow-up, after stepwise regression analysis, lower age at enrollment (adjusted odds ratio (aOR): 0.79; 95% confidence interval (CI): 0.64–0.96), male sex (aOR: 1.66; 95%CI: 1.05–2.63), proximity from an air-polluting facility (aOR: 2.4; 95%CI: 1.34–4.29), higher level outdoor PM2.5 (aOR: 1.1; 95%CI: 1.02–1.20), and higher rate of doctor-diagnosed food allergy (FA) (aOR: 2.33; 95%CI: 1.06–5.12) were significantly associated with persistence.

Conclusion: We discovered various independent risk factors for the persistence of childhood asthma. By linking HIRA claims data, we could clarify risk factors for persistence in a well-defined study population.

Key words: Asthma, Children, Persistence, Air pollution, National Claims Data

Citation:
Kim, H. S., Kim, K., Rhee, E. H., Kim, W. K., Song, D. J., Park, J. S., Suh, D. I., Yoon, J., Lee, E., Lee, S. W., Kim, J. T., Lim, D. H., Baek, H. S., Shin, M., Kwon, J. W., Jang, G. C., Seo, J. H., Woo, S. I., Kim, H. Y., Lee, J. S., Yu, J., Yang, H. J., Yoo, Y. (0000). Atmospheric environment and persistence of pediatric asthma: A population-based cohort study. *Asian Pac J Allergy Immunol*, 00(0), 000-000. https://doi.org/10.12932/ap-170623-1635

Affiliations:
[1] Department of Pediatrics, College of Medicine, The Catholic University of Korea, Seoul, Korea
[2] Department of Pediatrics, Seoul National University College of Medicine, Seoul, Korea
[3] Department of Pediatrics, Pediatric Allergy and Respiratory Center, Soonchunhyang University School of Medicine, Korea
[4] SCH Biomedical Informatics Research Unit, Soonchunhyang University Seoul Hospital, Seoul, Republic of Korea
[5] Department of Pediatrics, Inje University Seoul Paik Hospital, Seoul, Korea
[6] Department of Pediatrics, Korea University College of Medicine, Seoul, Korea
[7] Department of Pediatrics, Chung-Ang University Gwang-Myeong Hospital, Chung-Ang University College of Medicine, Seoul, Korea
[8] Department of Pediatrics, Chonnam National University Hospital, Chonnam National University Medical School, Gwangju, Korea
[9] Department of Precision Medicine, Sungkyunkwan University School of Medicine, Suwon, Republic of Korea
[10] Department of Pediatrics, College of Medicine, Inha University, Incheon, Korea
[11] Department of Pediatrics, Hallym University Kangdong Sacred Heart Hospital, Seoul, Korea

Affiliations (Continued):
[12] Department of Pediatrics, National Health Insurance Service Ilsan Hospital, Ilsan, Korea
[13] Department of Pediatrics, Dankook University Hospital, Cheonan, Korea
[14] Department of Pediatrics, College of Medicine, Chungbuk National University, Cheongju, Korea
[15] Department of Pediatrics, Pusan National University Yangsan Hospital, Yangsan, Korea
[16] Department of Pediatrics, Samsung Changwon Hospital, Sungkyunkwan University School of Medicine, Changwon, Korea
[17] Department of Pediatrics, Childhood Asthma Atopy Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

[†]These authors contributed equally to this work as co-first authors
[‡]These authors contributed equally to this work as co-corresponding authors.

Corresponding author:
1. Hyeon-Jong Yang
Department of Pediatrics, Pediatric Allergy and Respiratory Center, Soonchunhyang University School of Medicine, 59 Daesagwan-ro, Yongsan-gu, Seoul 04401, Korea
E-mail: ilove902@hanmail.net
2. Young Yoo
Department of Pediatrics, Korea University College of Medicine, Seoul, 73 Goryeodae-ro, Seongbuk-gu, Seoul 02841, Korea
E-mail: yoolina@korea.ac.kr

Introduction

Asthma is a heterogeneous disease, with different underlying disease processes including chronic airway inflammation.[1] Because of this heterogeneity, children with asthma may show different outcomes.[2] Patients may show persistence, relapse, and remission.[2] For children with asthma at the age of 7 years, 67–75% are symptom-free as adults.[3,4] Data on the important link between childhood and adult asthma are sparse. Despite some prospective studies spanning age ranges, a substantial knowledge gap exists regarding the transition of asthma from childhood to adulthood.[4]

Asthma remission can be defined as clinical remission comprised of 12 or more months with (1) absence of significant symptoms by validated instrument, (2) lung function optimization/stabilization, (3) patient/provider agreement regarding remission, and (4) no use of systemic corticosteroids.[5] Remission off treatment requires no asthma treatment for 12 or more months.[5]

However, a population-based cohort study in Canada has revealed that while the majority of individuals with asthma might have persistent asthma, some have experienced a gap of two or more years during which their asthma symptoms were in remission.[6] In adults, factors associated with remission include mild asthma, better lung function, better asthma control, younger age, early-onset asthma, shorter duration of asthma, milder bronchial hyperresponsiveness, fewer comorbidities, and smoking cessation or never smoking.[7] In a study from Danish birth cohort, the cumulative occurrence rate of asthma in children aged 3-14 years was 13.3% and the remission rate was 44.1%.[8] Being female had a lower risk of asthma and a higher remission rate of asthma.[8] A different retrospective study demonstrated that 87.2% of patients with asthma had early-onset (≤ 3 years) asthma and 12.8% had late-onset (4-6 years) asthma.[9] Over 10 years of follow-up, the rate of asthma remission was 37 per 100 person-years. Early-onset asthma, being female, and living in a rural and medium urban location were positively associated with remission.[9] Patients with chronic respiratory allergic diseases such as pediatric asthma have difficulty visiting hospitals regularly. Follow-up loss is a critical limitation in hospital-based asthma cohort studies.

In this study, we investigated independent risk factors associated with the persistence of childhood asthma over three years of follow-up by linking data between the Korea childhood Asthma Study (KAS) cohort and their matched claims data from the Health Insurance Review and Assessment Service (HIRA) to overcome follow-up loss and to reflect the real-world situation.

Methods

KAS and HIRA data

KAS is a nationwide prospective cohort of 917 children aged 5–15 years diagnosed with asthma, enrolled from 19 regional tertiary hospitals between August 2016 and December 2018. Methods of the cohort have previously been described.[10] Children who experienced typical asthma symptoms (wheezing, dyspnea, and chronic cough) within the past 12 months with variable expiratory airflow limitation confirmed by either positive bronchodilator response (BDR) or bronchial hyper-responsiveness (BHR) were included.[11] Children returned every six months for a total of six visits for questionnaires, spirometry, and physician evaluation. In this study, we analyzed data of preadolescent children aged 7 to 10 years[12] who were enrolled in KAS. Among children aged 7 to 10 years at the time of enrollment in KAS, 450 children's data were used for analysis, excluding data of children having any missing information. Written informed consent was obtained from all parents and guardians of all patients after a detailed explanation of the study. IRB approval of each center is listed in the supplement.

HIRA is an involuntary government-operated organization to build review and quality assessments for the National Health Insurance program in Korea. The National Health Insurance program is the only health insurance provider in Korea. In South Korea, HIRA manages health insurance and medical claims data for 96.6% of the population and facilitates nationwide quality assessments.[13] HIRA database includes patient diagnosis, treatment, procedures, surgical history, and prescription drugs, serving as a valuable resource for healthcare service research.

Data linkage methods

Written informed consent for data linkage was obtained from patients at the time of enrollment in KAS. We linked KAS subjects and their matched HIRA data (from birth to August 2020) using unique identification numbers of claim billing statements as a joint key (i.e, year, number of medical institution, and serial number of billing statements).

Operational definition of asthma status at follow-up

We used the HIRA database to identify asthma persistence. Persistence of asthma, the primary outcome, was defined as the presence of asthma episodes within three years after KAS enrollment. Asthma episodes were defined as healthcare utilization with asthma codes (J45 and J46 according to the 10th International Statistical Classification of Diseases and Related Health Problems [ICD-10]) and being prescribed asthma medications. Remission of asthma was defined as those with no asthma episodes without prescription of asthma medications within three years after KAS enrollment.

Asthma medications were defined as inhaled corticosteroids (ICSs), ICS combined with inhaled long-acting *β2*-agonists (ICS/LABAs), inhaled short-acting *β2*-agonists (SABAs), LABAs, oral leukotriene receptor antagonists (LTRAs), xanthine derivatives, and systemic corticosteroids.

Operational definitions of covariates

We obtained information on several covariates at baseline and follow-up from KAS database and assessed their relationships with asthma outcomes. Covariates of interest included were demographics, asthma onset, associated allergic diseases (i.e, doctor diagnosed food allergy (FA) or allergic rhinitis (AR)), presence of pets, and exposure to tobacco smoke or mold. Results from skin prick test determined sensitization to house dust mite, mold, tree, pet, and weed. 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 one positive skin prick test response, in which the wheal size exceeding 3 mm compared with negative control and exceeding that of the positive control. Asthma onset was determined by "When did your child's asthma symptoms start?", associated allergic diseases were determined by "Was your child ever diagnosed by a physician with FA or AR?", proximity from an air-polluting factory, waste incineration plant, or landfills was determined by "Is your place of residence close to an air-polluting factory, waste incineration plant, or landfills?", presence of pets was determined by "Do you have any furry pets at home?", exposure to smoking and mold was determined by "Does anyone smoke tobacco in your household?" and "Is there visible mold in your household?" from questionnaires completed by the parents. The questionnaire regarding allergy was modified from the Korean version of the International Study of Asthma and Allergies in Childhood, and the questionnaire regarding environment was modified from the Mothers and Children's Environmental Health study.[14,15]

Operational definition of exposure to air pollution

We obtained data on air pollutants from the website of the Korea Environment Corporation and the Korean Ministry of Environment (www.airkorea.or.kr/web). Exposure to sulfur dioxide (SO_2), nitrogen dioxide (NO_2), ozone (O_3), particulate matter (PM)10, and PM2.5 at residential addresses was estimated by land-use regression models using a previously described standardized method.[16] Concentrations of ambient air pollutants in various areas at various time points were compiled using air quality monitoring data routinely recorded by monitoring stations. Each monitoring station measures air pollutants hourly. Centrally and locally available geographic variables were used as potential predictors. Predictor variables, such as traffic indicators, surrounding-land usage, topography, and spatial trends, were computed at each location using ArcGIS version 9.3 (ESRI, Redlands, WA, USA). Multiple linear regression models were built using a supervised forward stepwise procedure. Predictor variables used in the final land-use regression model for air pollution included lengths of all roads, traffic intensity on nearest roads, total heavy-duty traffic loads of all roads, and a variable representing spatial trends. Each participant was assigned an average air pollutant exposure level for years after the time of enrollment in KAS cohort to August 2020, based on the predicted value at the participant's address of residence.

Statistical analysis

Baseline characteristics, lung function, and laboratory findings at enrollment were used to compare group differences. For categorical variables, numbers and percentages were calculated and chi-square test or Fisher's exact test was used as a between-group difference test. For all continuous variables, mean and standard deviations were derived. To compare continuous variables by groups, T-test was used for parametric continuous variables and Kruskal-Wallis rank test, one type of non-parametric statistical analysis, was used for nonparametric continuous variables. To select variables to be included in the multivariate logistic model, a univariate logistic model was performed, and then we constructed a multivariate logistic regression model by including variables with P-values < 0.05. Finally, we obtained the final model with the lowest Akaike information criterion by applying the stepwise algorithm. In order to determine factors affecting the persistence of asthma in children, we used univariate regression analysis to determine significant variables. Even variables significant after univariate regression might show multicollinearity in multivariate regression model. In order to control for multicollinearity, we used stepwise selection after multivariate regression model. In this process, we used Akaike information criterion to choose the ideal combination of variables.

Data management and statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA), and R version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria). All reported P values were two-sided; $P < 0.05$ was considered statistically significant.

Results

Differences in subject characteristics

Baseline subject characteristics are summarized in **Table 1**. We examined the differences in baseline subject characteristics at enrollment of those who showed persistence or remission at the third year of follow-up. At the third year of follow-up, male sex, lower age at enrollment, earlier onset of asthma, proximity from an air-polluting factory, waste incineration plant, or landfills, and higher levels of outdoor PM10 and PM2.5 were observed in those who showed asthma persistence (**Table 2**).

Table 1. Baseline subject characteristics.

	n = 450
Sex, male	309 (68.67%)
Age, year	8.46 ± 1.09
Asthma onset, year	
< 3	70 (15.56%)
3 to less than 6	130 (28.89%)
6 to less than 9	166 (36.89%)
9 to less than 12	84 (18.67%)
FEV_1, % pred	91.75 ± 16.17
FVC, % pred	96.00 ± 14.82
FEV_1/FVC, %	82.22 ± 8.80
Asthma severity	
Mild intermittent	170 (37.78%)
Mild persistent	178 (39.56%)
Moderate persistent	126 (28.00%)
Severe persistent	4 (0.89%)
Baseline asthma treatment	
Intermittent	103 (22.89%)
Montelukast monotherapy	52 (11.56%)
ICS monotherapy	96 (21.33%)
ICS plus Montelukast	67 (14.89%)
ICS plus LABA	45 (10.00%)
ICS plus Montelukast and LABA	84 (18.67%)
Doctor diagnosed FA	44 (9.78%)
Doctor diagnosed AR	353 (78.44%)
Presence of pets	57 (12.67%)
Presence of mold	97 (21.56%)
Environmental tobacco exposure	204 (45.33%)
Atopy	356 (79.11%)
HDM sensitization	269 (59.78%)
Mold sensitization	53 (11.78%)
Tree sensitization	115 (25.56%)
Pet sensitization	117 (26.00%)
Weed sensitization	100 (22.22%)
Proximity from an air-polluting factory, waste incineration plant, or landfills	90 (20.00%)
Level of air pollutants	
SO_2, μg/m^3	0.00 ± 0.00
NO_2, μg/m^3	0.02 ± 0.01
O_3, μg/m^3	0.03 ± 0.00
PM10, μg/m^3	41.77 ± 4.20
PM2.5, μg/m^3	23.00 ± 2.52

Data expressed as n (%) or mean ± SD
Abbreviations: FEV_1, forced expiratory volume at 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroid; LABA, long acting beta agonist; FA, food allergy; AR, allergic rhinitis; HDM, house dust mite; SO_2, sulfur dioxide; NO_2, nitrogen dioxide; O_3, ozone; PM, particulate matter

Table 2. Differences in baseline subject characteristics of those who showed persistence or remission at the third year of follow up.

	Asthma remission (n = 187)	Asthma persistence (n = 263)	*P*-value
Sex, male	116 (62.03%)	193 (73.38%)	0.014
Age, year	8.60 ± 1.09	8.32 ± 1.10	0.008
Asthma onset, year			< 0.001
< 3	26 (13.90%)	44 (16.73%)	
3 to less than 6	40 (21.39%)	90 (34.22%)	
6 to less than 9	72 (38.50%)	94 (35.74%)	
9 to less than 12	49 (26.20%)	35 (13.31%)	

Table 2. (Continued)

	Asthma remission (n = 187)	Asthma persistence (n = 263)	*P*-value
FEV_1, % pred	90.49 ± 16.42	93.01 ± 16.05	0.105
FVC, % pred	97.27 ± 15.16	99.72 ± 14.64	0.113
FEV_1/FVC, %	82.17 ± 9.28	82.26 ± 8.49	0.638
Asthma severity			0.849
Mild intermittent	73 (39.04%)	97 (36.88%)	
Mild persistent	70 (37.43%)	108 (41.06%)	
Moderate persistent	70 (37.43%)	56 (21.29%)	
Severe persistent	2 (1.07%)	2 (0.76%)	
Baseline asthma treatment			0.893
Intermittent	42 (22.46%)	61 (23.19%)	
Montelukast monotherapy	24 (12.83%)	28 (10.65%)	
ICS monotherapy	37 (19.79%)	59 (22.43%)	
ICS plus Montelukast	31 (16.58%)	36 (13.69%)	
ICS plus LABA	18 (9.63%)	27 (10.27%)	
ICS plus Montelukast and LABA	33 (17.65%)	51 (19.39%)	
Doctor diagnosed FA	12 (6.42%)	32 (12.17%)	0.063
Doctor diagnosed AR	139 (74.33%)	214 (81.37%)	0.094
Presence of pets	20 (10.70%)	37 (14.07%)	0.359
Presence of mold	40 (21.39%)	57 (21.67%)	1.000
Environmental tobacco exposure	75 (40.11%)	129 (49.05%)	0.075
Atopy	149 (79.68%)	207 (78.71%)	0.895
HDM sensitization	113 (60.43%)	156 (59.32%)	0.889
Mold sensitization	21 (11.23%)	32 (12.17%)	0.876
Tree sensitization	49 (26.20%)	66 (25.10%)	0.876
Pet sensitization	45 (24.06%)	72 (27.38%)	0.496
Weed sensitization	41 (21.93%)	59 (22.43%)	0.990
Proximity from an air-polluting factory, waste incineration plant, or landfills	25 (13.37%)	65 (24.71%)	0.004
Level of air pollutants			
SO_2, μg/m^3	0.00 ± 0.00	0.00 ± 0.00	0.858
NO_2, μg/m^3	0.02 ± 0.01	0.02 ± 0.01	0.133
O_3, μg/m^3	0.03 ± 0.00	0.03 ± 0.00	0.081
PM10, μg/m^3	41.35 ± 4.43	42.19 ± 4.06	0.012
PM2.5, μg/m^3	22.71 ± 2.44	23.28 ± 2.59	0.002

Data expressed as n (%) or mean ± SD

Abbreviations: FEV_1, forced expiratory volume at 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroid; LABA, long acting beta agonist; FA, food allergy; AR, allergic rhinitis; HDM, house dust mite; SO_2, sulfur dioxide; NO_2, nitrogen dioxide; O_3, ozone; PM, particulate matter

Univariate regression analysis

Univariate regression analysis showed that at the third year of follow-up, male sex, lower age at enrollment and at diagnosis, when grouped in three-year intervals, doctor-diagnosed FA, and proximity from an air-polluting factory, waste incineration plant, or landfills, were associated with asthma persistence. Regarding air pollution, 1 μg/m^3 higher levels of outdoor PM10 or PM2.5 resulted in a 5% or 9% increased chance of asthma persistence, respectively (**Table 3**).

Stepwise logistic regression analysis

After stepwise logistic regression analysis, male sex, age at enrollment, level of outdoor PM2.5, doctor-diagnosed FA, proximity from an air-polluting factory, waste incineration plant, or landfills, and were significantly associated with persistence at the third year (**Table 4**).

Table 3. Univariate Regression Analysis for Third-Year Persistence.

	Odds Ratio	95%CI	*P*-value
Sex, male	1.69	(1.13 – 2.52)	0.011
Age, year[a]	0.79	(0.67 - 0.94)	0.008
Asthma onset, year			
< 3	Ref		0.001
3 to less than 6	1.33	(0.72 - 2.45)	
6 to less than 9	0.77	(0.43 - 1.37)	
9 to less than 12	0.42	(0.22 - 0.81)	
FEV_1, % pred	1.01	(1.00 - 1.02)	0.105
FVC, % pred	1.01	(1.00 - 1.02)	0.086
FEV_1/FVC, %	1.00	(0.98 - 1.02)	0.918
Asthma severity			
Mild intermittent	Ref		0.877
Mild persistent	1.16	(0.76 - 1.78)	
Moderate persistent	1.00	(0.61 - 1.66)	
Severe persistent	0.75	(0.10 - 5.47)	
Doctor diagnosed FA	2.02	(1.04 - 4.19)	0.046
Doctor diagnosed AR	1.51	(0.96 - 2.37)	0.075
Presence of pets	1.37	(0.77 - 2.48)	0.290
Presence of mold	1.02	(0.65 - 1.61)	0.943
Environmental tobacco exposure	1.44	(0.98 - 2.11)	0.061
Atopy	0.94	(0.59 - 1.49)	0.803
HDM sensitization	0.95	(0.65 - 1.4)	0.813
Mold sensitization	1.10	(0.61 - 1.99)	0.761
Tree sensitization	0.94	(0.62 - 1.45)	0.791
Pet sensitization	1.19	(0.78 - 1.84)	0.430
Weed sensitization	1.03	(0.66 - 1.62)	0.898
Proximity from an air-polluting factory, waste incineration plant, or landfills[b]	2.13	(1.30 - 3.58)	0.003

Table 3. (Continued)

	Odds Ratio	95% CI	*P*-value
Level of air pollutants			
SO_2, μg/m^3	0.00	(0.00 - Inf)	0.848
NO_2, μg/m^3	Inf	(0.00 - Inf)	0.156
O_3, μg/m^3	0.00	(0.00 - Inf)	0.254
PM10, μg/m^3	1.05	(1.00 - 1.10)	0.040
PM2.5, μg/m^3	1.09	(1.01 - 1.18)	0.021

Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume at 1 second; FVC, forced vital capacity; FA, food allergy; AR, allergic rhinitis; HDM, house dust mite; SO_2, sulfur dioxide; NO_2, nitrogen dioxide; O_3, ozone; PM, particulate matter; Inf, infinite
[a]per 1 year increase
[b]per 1 μg/m^3 increase

Table 4. Stepwise Logistic Regression Analysis for Third Year Persistence (N = 450)

Variable	Estimate	Adj OR	95%CI	*P* value
Age, year[a]	-0.242	0.79	(0.64–0.96)	0.017
Sex, male	0.507	1.66	(1.05–2.63)	0.031
Doctor diagnosed FA	0.846	2.33	(1.06–5.12)	0.035
Proximity from an air-polluting factory, waste incineration plant, or landfills	0.875	2.4	(1.34–4.29)	0.003
PM2.5, μg/m^3 [b]	0.099	1.1	(1.02–1.20)	0.021
AIC = 514.37				

Abbreviations: OR, odds ratio; CI, confidence interval; FA, food allergy; PM, particulate matter; AIC, Akaike information criterion
[a]per 1 year increase
[b]per 1 μg/m^3 increase

Discussion

In this study, we aimed to identify the baseline characteristics at the time of study entry, personal factors, and early life characteristics that might be associated with the persistence of asthma in children. After stepwise regression analysis, at the third year of follow-up, lower age at enrollment, male sex, higher level outdoor PM2.5, and a higher rate of doctor-diagnosed FA were significantly associated with persistence.

We found that lower age at enrollment was associated with persistence at the third year of follow-up. There have been no studies that specifically showed that lower age at enrollment was a risk factor for persistence. However, there has been a previous study that found that wheezing phenotypes identified at an early age were an independent risk factor for asthma persistence in adolescence.[17] Further study would be needed to clarify whether age at diagnosis or enrollment are significant factors associated with asthma persistence.

We found that in our preadolescent patients, the third-year asthma persistence was associated with the male sex. Several studies also found that being male was associated with persistence.[8,9] However, other studies have shown that males were more likely to show asthma remission. For example, in the Tucson Children's Respiratory Study, remittance of asthma signs by age 22 years was higher in men than in women.[18] Before adolescence, male sex was associated with wheezing phenotypes and school-age asthma in another study.[19] However, as puberty progresses, asthma prevalence and severity increase in the female population while the opposite is seen in males.[20,21] In a Swedish population-based cohort followed from mid-childhood until the age of 19 years, male sex predicted asthma remission in children with physician-diagnosed asthma.[22] This is in contrast to recent findings from the Childhood Asthma Management Program study in BHR-positive children with moderate-to-severe asthma showing that sex was not a predictor of asthma remission.[23] Because our study population consisted of preadolescents, we can assume that male sex is a risk factor for persistence before adolescence. The course of asthma is associated with puberty and sex, likely because sex hormones can affect airway homeostasis and development.[20]

We found that doctor-diagnosed FA was associated with persistence, while AR failed to reach statistical significance. The relationship between FA and asthma persistence remains unclear. It is known that eczema, FA, and AR have significant associations with cumulative asthma.[24] Follow-up of the Tasmanian Asthma Study cohort to age 44 years identified that childhood AR was not only associated with a 2- to 7-fold increased risk of incident asthma in preadolescence, adolescence, or adult life, but also associated with a 3-fold increased risk of childhood asthma persisting rather than remitting by middle age.[25] Clinical remission rates of asthma and AR were 46.4% and 31.8%, respectively, and subjects reporting AR were less likely to have asthma remission.[26] Late and early persistent coughs without a cold are positively associated with atopic respiratory diseases and FA.[27] The mechanism between FA and asthma may be related to when FA is present in various phenotypes of atopic dermatitis in early life, it might be associated with gut Wnt signaling and later development of asthma ('Wnt/β-catenin signaling').[28] Relative abundance of Wnt6 mRNA was positively correlated with food-specific IgE levels at 1 and 3 years.[28]

We found that proximity to an air-polluting factory, waste incineration plant, or landfill was associated with asthma persistence. A previous study has found that proximity to any air-polluting factories or heavy-vehicle traffic had a significant association with the prevalence of cumulative asthma.[24]

Regarding air pollution, we found that exposure to higher levels of outdoor PM2.5 was a significant factor for persistence at the third year of follow-up. Air pollution has been associated with the development of asthma. Especially, PM2.5, a ubiquitous air pollutant, can deposit in the small airways that play a vital role in asthma.[29] However, how each different air pollution material affects the development and persistence remains controversial. Prenatal NO_2 is associated with increased persistence of wheeze and increased prevalence and onset of rhinitis.[30] Prenatal exposure to PM2.5 is associated with an increased prevalence of wheeze.[30] Postnatal exposure to NO_2 and PM10 is associated with increased prevalence and lower remission of wheeze and rhinitis.[30] Annual changes in the prevalence of asthma are related to changes in air concentrations of NO, NO_2 suspended particulate matter, and smoking rate in boys, but not in girls.[31] A different study found no association between annual average exposure to ultra-fine particles and allergic sensitization in children up to 16 years of age while NO_2, PM2.5, PM2.5 absorbance, and PM10 were associated with sensitization to food allergens.[32] However, a different study has found no relationship between remission of asthma and any pollutants.[31] Further study will be needed to clarify the effect of exposure to air pollution on the persistence of asthma.

Interestingly, we found that atopy, sensitization to common allergens, and lung function were not significant factors affecting asthma persistence. This is different from previous studies.[4,7] However, due to our novel method of linking KAS data with HIRA data, we will be able to determine if these factors play a significant role in asthma persistence in the following years.

To our best knowledge, this is the first study to link a childhood asthma cohort and their matched healthcare claim data. Therefore, our study could overcome an inherent limitation of longitudinal study consisting of mild to moderate childhood asthma, which tends to naturally remit. Data linkage study would be a reliable alternative to reflect the real world. In addition, by linking HIRA data, it will be possible to determine risk factors for asthma remission or persistence each year in succession. Lastly, KAS data include lung function and pattern of sensitization that we can analyze to determine factors for remission occurring after the third year of follow-up. However, our study was limited by the fact that most of the study population consisted of patients with mild or moderate persistent asthma. This study was also limited by the fact that the cohort consisted of Eastern Asian ethnicity. Ethnicity/race is known to affect the remission of asthma.[33]

Conclusion

In conclusion, we found that male sex, lower age at enrollment, doctor-diagnosed FA, proximity to an air-polluting factory, waste incineration plant, or landfills, and exposure to higher levels of outdoor PM2.5 were independent risk factors for persistence of asthma in preadolescent Korean children. Using results from this paper, we want to further drive clinical prediction of asthma trajectories, enabling pediatricians to forecast future asthma remission and persistence and initiate prevention strategies. By linking HIRA claims data, we could clarify risk factors for persistence in a well-defined study population.

Conflict of Interest Disclosures

Authors report no conflict of interest.

Funding/Support

This research was supported by the "National Institute of Health" research project (2016-ER6703, 2019-ER6701, and 2022-ER1201-00) and by the Soonchunhyang University Research Fund.

References

1. Cloutier MM, Dixon AE, Krishnan JA, Lemanske RF, Jr., Pace W, Schatz M. Managing Asthma in Adolescents and Adults: 2020 Asthma Guideline Update From the National Asthma Education and Prevention Program. JAMA. 2020;324:2301-17.
2. Sears MR. Predicting asthma outcomes. J Allergy Clin Immunol. 2015; 136:829-36; quiz 37.
3. Strachan DP, Butland BK, Anderson HR. Incidence and prognosis of asthma and wheezing illness from early childhood to age 33 in a national British cohort. BMJ. 1996;312:1195-9.
4. Fuchs O, Bahmer T, Rabe KF, von Mutius E. Asthma transition from childhood into adulthood. Lancet Respir Med. 2017;5:224-34.
5. Menzies-Gow A, Bafadhel M, Busse WW, Casale TB, Kocks JWH, Pavord ID, et al. An expert consensus framework for asthma remission as a treatment goal. J Allergy Clin Immunol. 2020;145:757-65.
6. Gershon A, Guan J, Victor JC, Wang C, To T. The course of asthma activity: a population study. J Allergy Clin Immunol. 2012;129:679-86.
7. Thomas D, McDonald VM, Pavord ID, Gibson PG. Asthma remission: what is it and how can it be achieved? Eur Respir J. 2022;60:2102583

8. Chen Q, Chen J, Zhou Y, Huang L, Tang Y, Li J, et al. Natural history and associated early life factors of childhood asthma: a population registry-based cohort study in Denmark. BMJ Open. 2021;11:e045728.
9. Oluwole O, Rennie DC, Goodridge D, Blackburn D, Litzenberger T, Penz E, et al. The course of asthma: A population-based 10-year study examining asthma remission in children diagnosed with asthma in preschool. Pediatr Pulmonol. 2020;55:1924-35.
10. In Suh D, Song DJ, Baek HS, Shin M, Yoo Y, Kwon JW, et al. Korean childhood asthma study (KAS): a prospective, observational cohort of Korean asthmatic children. BMC Pulm Med. 2019;19:64.
11. National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007. J Allergy Clin Immunol. 2007;120: S94-138.
12. Sitarik AR, Wegienka G, Johnson CC, Joseph CLM. Impact of Spirometry Race-Correction on Preadolescent Black and White Children. J Allergy Clin Immunol Pract. 2023; S2213-2198(23)00644-X.
13. Kim SH, Cho BL, Shin DW, Hwang SS, Lee H, Ahn EM, et al. The Effect of Asthma Clinical Guideline for Adults on Inhaled Corticosteroids PrescriptionTrend: A Quasi-Experimental Study. J Korean Med Sci. 2015;30:1048-54.
14. Park YM, Lee SY, Kim WK, Han MY, Kim J, Chae Y, et al. Risk factors of atopic dermatitis in Korean schoolchildren: 2010 international study of asthma and allergies in childhood. Asian Pac J Allergy Immunol. 2016;34:65-72.
15. Kim BM, Ha M, Park HS, Lee BE, Kim YJ, Hong YC, et al. The Mothers and Children's Environmental Health (MOCEH) study. Eur J Epidemiol. 2009;24:573-83.
16. Lee JY, Leem JH, Kim HC, Hwang SS, Jung D, Park M, et al. Land use regression model for assessing exposure and impacts of air pollutants in school children. J Korean Soc Atmos Environ. 2012;28:571-80.
17. Pité H, Gaspar Â, Morais-Almeida M. Preschool-age wheezing phenotypes and asthma persistence in adolescents. Allergy Asthma Proc. 2016;37:231-41.
18. Stern DA, Morgan WJ, Halonen M, Wright AL, Martinez FD. Wheezing and bronchial hyper-responsiveness in early childhood as predictors of newly diagnosed asthma in early adulthood: a longitudinal birth-cohort study. Lancet. 2008;372:1058-64.
19. Granell R, Henderson AJ, Sterne JA. Associations of wheezing phenotypes with late asthma outcomes in the Avon Longitudinal Study of Parents and Children: A population-based birth cohort. J Allergy Clin Immunol. 2016;138:1060-70.
20. Fu L, Freishtat RJ, Gordish-Dressman H, Teach SJ, Resca L, Hoffman EP, et al. Natural progression of childhood asthma symptoms and strong influence of sex and puberty. Ann Am Thorac Soc. 2014;11:939-44.
21. Trivedi M, Denton E. Asthma in Children and Adults-What Are the Differences and What Can They Tell us About Asthma? Front Pediatr. 2019;7:256.
22. Andersson M, Hedman L, Bjerg A, Forsberg B, Lundback B, Ronmark E. Remission and persistence of asthma followed from 7 to 19 years of age. Pediatrics. 2013;132:e435-42.
23. Wang AL, Datta S, Weiss ST, Tantisira KG. Remission of persistent childhood asthma: Early predictors of adult outcomes. J Allergy Clin Immunol. 2019;143:1752-9.
24. Molnar D, Galffy G, Horvath A, Tomisa G, Katona G, Hirschberg A, et al. Prevalence of Asthma and Its Associating Environmental Factors among 6-12-Year-Old Schoolchildren in a Metropolitan Environment-A Cross-Sectional, Questionnaire-Based Study. Int J Environ Res Public Health. 2021;18:13403.
25. Martin PE, Matheson MC, Gurrin L, Burgess JA, Osborne N, Lowe AJ, et al. Childhood eczema and rhinitis predict atopic but not nonatopic adult asthma: a prospective cohort study over 4 decades. J Allergy Clin Immunol. 2011;127:1473-9.
26. Heldin J, Malinovschi A, Johannessen A, Alving K, Holm M, Franklin KA, et al. Clinical Remission of Asthma and Allergic Rhinitis - in a Longitudinal Population Study. J Asthma Allergy. 2022;15: 1569-78.
27. Divaret-Chauveau A, Mauny F, Hose A, Depner M, Dalphin ML, Kaulek V, et al. Trajectories of cough without a cold in early childhood and associations with atopic diseases. Clin Exp Allergy. 2022;53:429-42.
28. Lee SY, Kim S, Kang MJ, Song KB, Choi EJ, Jung S, et al. Phenotype of Atopic Dermatitis With Food Allergy Predicts Development of Childhood Asthma via Gut Wnt Signaling. Allergy Asthma Immunol Res. 2022;14:674-86.
29. Sompornrattanaphan M, Thongngarm T, Ratanawatkul P, Wongsa C, Swigris JJ. The contribution of particulate matter to respiratory allergy. Asian Pac J Allergy Immunol. 2020;38:19-28.
30. Norback D, Lu C, Zhang Y, Li B, Zhao Z, Huang C, et al. Onset and remission of childhood wheeze and rhinitis across China - Associations with early life indoor and outdoor air pollution. Environ Int. 2019;123: 61-9.
31. Odajima H, Kawano T, Wakatsuki M, Akaminea Y, Okabe K, Oki T, et al. Annual changes in the prevalence of asthma may be related to air pollution in Fukuoka: 29 years of observation. ERJ Open Res. 2020; 6:00166-2020.
32. Bouma F, Hoek G, Koppelman GH, Vonk JM, Kerckhoffs J, Vermeulen R, et al. Exposure to ambient ultrafine particles and allergic sensitization in children up to 16 years. Environ Res. 2023;219:115102.
33. Curry CW, Felt D, Kan K, Ruprecht M, Wang X, Phillips G, 2nd, et al. Asthma Remission Disparities Among US Youth by Sexual Identity and Race/Ethnicity, 2009-2017. J Allergy Clin Immunol Pract. 2021;9: 3396-406.

Supplements

IRB approval

The study was approved by

- the Institutional Review Boards (IRBs) of Asan Medical Center (IRB No. 2016-0914)
- Seoul National University Hospital (IRB No. 1607-165-779)
- Pusan National University Yangsan Hospital (IRB No. 05-2016-121)
- Inha University Hospital (IRB No. 2016-07-016-008)
- Seoul National University Bundang Hospital (IRB No. 10-2017-036),
- Chonnam National University Hospital (IRB No. 2017-201),
- Korea University Anam Hospital (IRB No. 2015 AN 0310)
- Soonchunhyang University Hospital in Seoul (IRB No. 2017-01-011-002)
- Bucheon St. Mary's Hospital (IRB No. HC16SNMI0056)
- Sungkyunkwan University Samsung Changwon Hospital (IRB No. 2017-02-006-001)
- Kangdong Sacred Heart Hospital (IRB No. 2016-12-007-001)
- The Catholic University of Korea, Uijeongbu St. Mary's Hospital (IRB No. UC16ONMI0113)
- Chungbuk National University Hospital (IRB No. 2016-09-003)
- Dankook University Hospital (IRB No. 2017-02-013)
- Korea University Guro Hospital (IRB No. 2016GR0336)
- Inje University Seoul Paik Hospital (IRB No. 2016-314)
- CHA Gangnam Medical Center (IRB No. GCI-16-37),
- National Health Insurance Service Ilsan Hospital (IRB No. NHIMC 2017-02-008)
- Soonchunhyang University School of Medicine in Bucheon (IRB No 2016-08-007-009).