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Original Article

Atopic Dermatitis With Coexisting Food Allergy in Early Life Is Associated With Childhood Asthma

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ABSTRACT

Purpose: Atopic dermatitis (AD) and food allergy (FA) are associated with respiratory comorbidities, in the concept of 'atopic march.' However, children with AD and a coexisting FA have various disease courses, and the mechanism of atopic march remains unclear. In this study, we investigated whether the phenotype of AD with coexisting FA in early life affected asthma or allergic rhinitis (AR) in school children.
Methods: A total of 1,579 children from the Panel Study on Korean Children (PSKC) cohort were followed-up in 2013. The participants diagnosed with AD in this cohort were classified by the age of AD onset and persistence as well as FA history. We compared the presence of comorbidities—asthma and rhinitis—among different AD phenotypes.
Results: Asthma and AR with current symptoms within 12 months at age 6–8 years were associated with early-onset persistent AD phenotype, regardless of coexisting FA. AD with FA conferred a higher risk of recent wheezing at 8 years of age than AD without FA (adjusted odds ratio, 8.09; 95% confidence interval, 2.54–25.76). Children with early-onset persistent AD with FA manifested a distinctive trajectory with a higher prevalence of wheezing and AR at age 5–8 years than those without AD.
Conclusions: AD with FA in early life is strongly associated with asthma and AR in school children, and the early-onset persistent AD with FA had a strong additive effect on the risk of asthma at school age. Classifying AD phenotypes regarding FA in early life will help predict and prevent asthma and AR in school children.

Keywords: Atopic dermatitis; food allergy; asthma; children; phenotype; atopic march

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Disclosure

There are no financial or other issues that might lead to a conflict of interest.

INTRODUCTION

Atopic dermatitis (AD) generally begins within the first 2 years of life.[1,2] Most cases resolve naturally.[3] Moreover, AD has various disease courses and is the first step in atopic march linked with respiratory comorbidities.[4,5] Although 2 prior population-based birth cohort studies using machine learning methods showed that only a small proportion of affected children develop the atopic march,[6] other studies have found that early-onset eczema, persistent eczema, a severe phenotype, multiple sensitizations and filaggrin mutation are risk factors leading to the development of asthma and atopic march in AD.[2,7,12]

Most food allergy (FA) cases develop in early childhood and have various disease courses.[13,17] Several studies have revealed that FA or sensitization to food allergens in early childhood increases the risk of subsequent respiratory allergies,[18-20] suggesting that they may also be responsible for atopic march along with AD. Indeed, children with AD and food sensitization or FA increased the risk of developing subsequent asthma.[10,21,22] Most of the prior studies, however, have focused on wheezing in preschool children and not asthma in school-aged children.[19,21] Moreover, very few studies have investigated allergic rhinitis (AR) in school-aged children.[22] Further, the endotype and phenotype of AD in Asian populations, who have higher TH_{17} activation and a strong TH_2 component, may differ from Europeans and Americans.[23,24] Furthermore, common food allergens in Western countries differ from those in Asia. For example, peanut allergy predominates in children less than 5 years of age in the UK, US, and Australia,[25] but is less common in Asia.[26] These findings suggest that the clinical phenotypes of AD associated with FA in early life may be affected by race and ethnicity. Some birth cohort studies including Asian population have investigated the AD phenotype in children.[27,28] However, it is still unclear whether the risk of respiratory allergic diseases differs according to the AD phenotypes classified by FA in Asian populations.

Therefore, we aimed to investigate the association of clinical phenotypes of AD with FA and respiratory comorbidities, namely, asthma and AR, in school children in a birth cohort study.

MATERIALS AND METHODS

Study participants

The Panel Study of Korean Children (PSKC) is a nationwide general population-based birth cohort that we previously established to provide longitudinal data on childhood development.[29] This cohort recruited 2,078 mother-baby dyads using a 2-step stratified random sampling across Korea in 2008, and has been collecting longitudinal data on allergic diseases in children annually since 2013.[30,31] A total of 1,579 subjects were followed in 2013, 1,448 subjects in 2014, 1,565 subjects in 2015, 1,450 subjects in 2016, and an allergy questionnaire for AD phenotypes was completed. Among the children followed up in 2015, 594 children aged 7 years visited a regional hospital and underwent laboratory testing for allergic diseases, including skin prick tests, blood tests, and standard spirometry. We analyzed the data collected until 2016. A flowchart for the current study series is shown in **Supplementary Fig. S1**. **Supplementary Table S1** presents the patient characteristics of those who visited the regional study hospitals compared to those who did not. The history of environmental tobacco smoke was higher in the hospital-visiting subjects, but no other baseline characteristics were significantly different between these 2 groups.

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The Institutional Review Board (IRB) of Asan Medical Center reviewed and approved the current study protocol (IRB No. 2015-0907). Written consent forms were obtained from all parents and guardians following a detailed explanation of the study.

Definition of AD, FA, current asthma, current AR, and AD phenotypes

Confirmed cases of AD or FA were defined as those children whose diagnoses were confirmed by a physician using parental responses to a questionnaire when the child was 5 years of age. Current asthma was defined as a wheezy episode during the prior 12 months by a questionnaire at the age of 6 to 8 years in children whose diagnoses of asthma were confirmed by a physician. Moreover, current AR was defined as a rhinitis episode during the prior 12 months by a questionnaire at the age of 6 to 8 years in children whose diagnoses of AR were confirmed by a physician at any age.

Among the AD phenotypes, we defined early-onset AD as the manifestation of AD at less than 2 years of age. Late-onset AD was defined as the development of AD at 2 years of age and older. The persistence of AD was defined as persistent eczema at the age of 6 to 8 years, as confirmed in the questionnaire. Hence, an early-onset persistent phenotype was defined by a combination of early-onset AD and persistent eczema at the age of 6 to 8 years. An early-onset remitting phenotype was defined as early-onset AD combined with no more eczema symptoms at the age of 6 to 8 years. We classified AD phenotypes into the early-onset persistent, early-onset remitting and late-onset phenotypes, and then compared the respiratory comorbidities among these AD phenotypes with and without FA.

Skin prick test

Skin prick tests were conducted using a standardized method.[32] A total of 18 allergens were tested, including histamine and saline, as a positive and negative control, respectively. Inhalants and food allergens (Allergopharma GmbH & Co. KG, Darmstadt, Germany) included 2 kinds of house dust mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*); dog and cat epithelia; cockroaches; 2 fungal strains (*Alternaria alternate*, *Aspergillus fumigatus*); outdoor inhalation antigens such as pollen from grass, ragweed, mugwort, alder, oak, Japanese hops, birch and hazel; and food allergens (egg white, milk, peanuts). When the positive control response exceeded 3 mm and the wheal size for the tested allergen was greater than the wheal size of the positive control, we defined the subject as being sensitized to this allergen. Drugs such as antihistamines, which can affect the results of skin prick tests, were withdrawn for 2 weeks prior to testing.

Statistical analysis

Statistical analyses were conducted using SPSS version 23 (SPSS, Chicago, IL, USA). χ^2 tests were performed to compare the subjects who had visited a regional hospital with those who did not. Logistic regression analyses were conducted to investigate the risk factors for the AD phenotypes, and the odds ratio (OR) and 95% confidence interval (CI) values were calculated with adjustment for the following confounders: sex, maternal education levels, history of second-hand smoking, residential area and economic status.

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RESULTS

Prevalence of AD phenotypes in the PSKC cohort

The proportion of 5-year-old Korean children diagnosed with AD by a physician (as ascertained by parental responses to a questionnaire at 5 years of age) in our cohort was 26.0%. Compared with the late-onset phenotype, the early-onset phenotype showed higher prevalence in the study population (12.0% vs. 18.9%). Among the cases of the early-onset phenotype, early-onset remitting phenotypes without FA showed the highest prevalence at 11.1%, followed by early-onset remitting with FA at 0.9%, early-onset persistent without FA at 5.6%, and early-onset persistent with FA at 1.3%. The prevalence of the late-onset phenotype was 7.2%, late-onset without FA at 6.7% and late-onset with FA at 0.4%. In addition, the prevalence of no AD with FA was 2.5%. Neither AD nor FA was found at 71.4% (**Table 1**).

Asthma according to the AD phenotype at school age

We investigated whether asthma was comorbid at school age according to the AD phenotype. When we stratified the participants with AD as early-onset persistent, early-onset remitting, and late-onset phenotypes, the early-onset persistent (adjusted odds ratio [aOR], 4.96; 95% CI, 1.89–13.07) and late-onset (aOR, 3.55; 95% CI, 1.22–10.34) phenotypes showed an association with current asthma (**Supplementary Table S2**). When we stratified the AD phenotypes by FA, no phenotype was associated with a bronchiolitis history. However, early-onset persistent AD with FA phenotype (aOR, 13.60; 95% CI, 3.18–58.14), early-onset persistent AD without FA phenotype (aOR, 3.30; 95% CI, 1.02–10.73), early-onset remitting AD with FA phenotype (aOR, 21.30; 95% CI, 3.26–139.24), and late-onset AD without an FA phenotype (aOR, 3.75; 95% CI, 1.28–11.01) showed an association with current asthma (**Table 2**).

We investigated recent wheezing episodes within 12 months of each year from 5 to 8 years of age. **Fig. 1** illustrates the wheezing trajectories that were observed according to the AD phenotype. When we compared wheezing episodes between the AD phenotypes, no significant difference in bronchiolitis history was found. However, children with early-onset persistent AD with FA phenotype showed higher recent wheezing episodes from 5 to 8 years of age than those without AD. The groups of early-onset persistent AD without FA and late-onset AD without FA phenotypes showed higher recent wheezing episodes at 7 years of age than those without. In addition, children with the early-onset remitting AD with FA phenotype showed more episodes of recent wheezing at 6 and 8 years of age than those without AD (**Fig. 1**, **Supplementary Table S3**).

Table 1. Prevalence of the AD phenotypes among the Panel Study on Korean Children subjects

Variable	No./Total No. (%)
No AD	1,168/1,579 (74.0)
With FA	40/1,579 (2.5)
Without FA	1,128/1,579 (71.4)
Early-onset AD	298/1,579 (18.9)
Early-onset, persistent AD	109/1,579 (6.9)
With FA	20/1,579 (1.3)
Without FA	89/1,579 (5.6)
Early-onset, remitting AD	189/1,579 (12.0)
With FA	14/1,579 (0.9)
Without FA	175/1,579 (11.1)
Late-onset AD	113/1,579 (7.2)
With FA	7/1,579 (0.4)
Without FA	106/1,579 (6.7)

AD, atopic dermatitis; FA, food allergy.

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Table 2. Current asthma according to the AD phenotypes with or without coexisting FA

Variable	No./Total No. (%)	OR (95% CI)	aOR* (95% CI)
Bronchiolitis history before 3 yr of age	309/1,456 (21.2)		
No AD	216/1,073 (20.1)	1 (Reference)	1 (Reference)
Early-onset persistent with FA	3/19 (15.8)	0.74 (0.22–2.58)	0.62 (0.18–2.17)
Early-onset persistent without FA	23/88 (26.1)	1.40 (0.85–2.31)	1.41 (0.84–2.34)
Early-onset remitting with FA	2/12 (16.7)	0.79 (0.17–3.65)	0.76 (0.16–3.57)
Early-onset remitting without FA	39/158 (24.7)	1.30 (0.88–1.92)	1.28 (0.86–1.91)
Late-onset with FA	2/7 (28.6)	1.59 (0.31–8.24)	1.92 (0.36–10.35)
Late-onset without FA	24/99 (24.2)	1.27 (0.78–2.06)	1.20 (0.73–1.98)
Current asthma	33/1,222 (2.7)		
No AD	16/899 (1.8)	1 (Reference)	1 (Reference)
Early-onset persistent with FA	3/16 (18.8)	12.74 (3.30–49.09)‡	13.60 (3.18–58.14)‡
Early-onset persistent without FA	4/76 (5.3)	3.07 (1.00–9.41)†	3.30 (1.02–10.73)†
Early-onset remitting with FA	2/9 (22.2)	15.77 (3.04–81.89)‡	21.30 (3.26–139.24)‡
Early-onset remitting without FA	3/132 (2.3)	1.28 (0.37–4.47)	1.19 (0.33–4.33)
Late-onset onset with FA	0/5 (0.0)	-	-
Late-onset without FA	5/85 (5.9)	3.45 (1.23–9.66)†	3.75 (1.28–11.01)†

Current asthma was defined as physician-diagnosed asthma-ever and a wheezy episode during the prior 12 months from 6 to 8 years of age confirmed by questionnaire.
AD, atopic dermatitis; FA, food allergy; Sx, symptoms; Dx, diagnosis; OR, odds ratio; CI, confidence interval; aOR, adjusted odds ratio.
*Adjusted by sex, maternal education levels, parental allergy history, history of second-hand smoking, residential area, and economic status.
†$P < 0.05$; ‡$P < 0.01$.

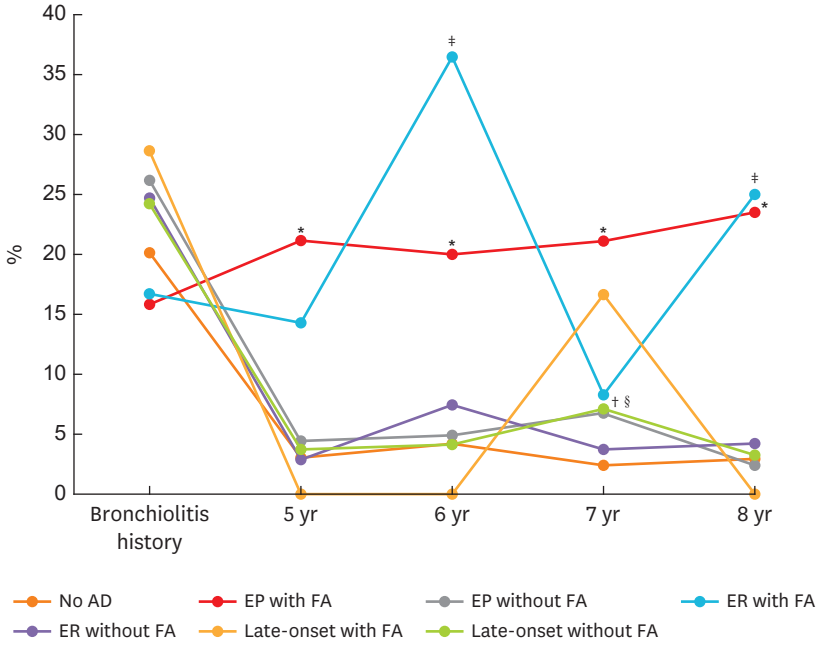

Fig. 1. Comparison of trajectories of wheezing episodes in children with AD among the different phenotypes. χ^2 tests were used for comparisons between groups.
AD, atopic dermatitis; FA, food allergy; EP, early-onset persistent; ER, early-onset remitting.
$P < 0.05$: *No AD vs. EP with FA; †No AD vs. EP without FA; ‡No AD vs. ER with FA; §No AD vs. Late-onset without FA.

When we compared the recent wheezing episodes between the AD with and without FA phenotypes, AD patients with FA (aOR, 8.09; 95% CI, 2.54–25.76) showed a higher risk of wheezing at 8 years of age than those without FA. In children with the early-onset persistent AD phenotype, in particular, the presence of FA had an additive effect on the risk of a wheezing episode at 8 years of age (aOR, 52.49; 95% CI, 1.71–1,612.82; **Table 3**). In children with the early-onset remitting AD phenotype, only those with FA was associated with a

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Table 3. Interactive effects of FA and the AD phenotype on wheezing episodes in school-aged children

Variable	FA (−)		FA (+)		OR for wheezing episode within strata of AD
	No./Total No. (%)	aOR* (95% CI)	No./Total No. (%)	aOR* (95% CI)	
Wheezing episode at 7 yr of age					
No AD	24/1,035 (2.3)	1 (Reference)	3/35 (8.6)	4.81 (1.30–17.62)‡	4.81 (1.30–17.62)‡
AD	19/344 (5.5)	2.45 (1.30–4.61)‡	6/37 (16.2)	7.81 (2.84–21.47)‡	2.77 (0.96–7.97)
Early-onset persistent	6/88 (6.7)	3.25 (1.24–8.51)†	4/19 (21.1)	10.52 (2.95–37.57)‡	4.54 (0.67–30.75)
Early-onset remitting	6/157 (3.8)	1.70 (0.66–4.33)	1/12 (8.3)	3.56 (0.41–31.09)	1.49 (0.06–34.34)
Late-onset	7/99 (7.1)	3.25 (1.34–7.89)‡	1/6 (16.7)	8.86 (0.78–101.01)	2.45 (0.14–42.05)
Wheezing episode at 8 yr of age					
No AD	26/980 (2.7)	1 (Reference)	4/28 (14.3)	5.03 (1.49–16.94)‡	5.03 (1.49–16.94)‡
AD	11/316 (3.5)	1.35 (0.64–2.83)	7/36 (19.4)	10.13 (3.80–26.99)‡	8.09 (2.54–25.76)‡
Early-onset persistent	2/82 (2.4)	0.86 (0.19–3.82)	4/17 (23.5)	12.99 (3.50–48.23)‡	52.49 (1.71–1,612.82)‡
Early-onset remitting	6/143 (4.2)	1.66 (0.65–4.25)	3/12 (25.0)	12.84 (2.94–56.02)‡	9.74 (0.59–159.90)
Late-onset	3/91 (3.3)	1.46 (0.42–5.04)	0/7 (0.0)	-	-

AD, atopic dermatitis; FA, food allergy; OR, odds ratio; CI, confidence interval; aOR, adjusted odds ratio.
*Adjusted by sex, maternal education levels, parental allergy history, history of second-hand smoking, residential area, and economic status.
†$P < 0.05$; ‡$P < 0.01$.

wheezing episode at 8 years of age (aOR, 12.84; 95% CI, 2.94–56.02), unlike patients without FA. Additionally, FA without AD cases showed a higher risk of developing wheezing at 7 (aOR, 4.81; 95% CI, 1.30–17.62) and 8 years of age (aOR, 5.03; 95% CI, 1.49–16.94; **Table 3**), respectively, than those with neither AD nor FA.

AR according to the AD phenotypes at school age

We investigated whether AR coexist at school age according to the AD phenotype. When we stratified our subjects with AD by early-onset persistent, early-onset remitting or late-onset phenotype, early-onset persistent phenotype (aOR, 2.23; 95% CI, 1.39–3.58), early-onset remitting phenotype (aOR, 1.53; 95% CI, 1.05–2.24) and late-onset phenotype (aOR, 1.77; 95% CI, 1.11–2.81) were all associated with current AR (**Supplementary Table S2**). When we classified the AD phenotypes by FA, the early-onset persistent AD with (aOR, 4.82; 95% CI, 1.29–17.93) and without an FA phenotype (aOR, 1.97; 95% CI, 1.18–3.27), both showed an association with current AR. In addition, the early-onset remitting AD without FA phenotype (aOR, 1.53; 95% CI, 1.04–2.26), and late-onset AD without FA phenotype (aOR, 1.76; 95% CI, 1.02–2.66) were associated with current AR (**Table 4**).

We investigated recent AR episodes that occurred within 12 months of each year, from 5 to 8 years of age. **Fig. 2** illustrates the AR trajectories according to the AD phenotype. When we

Table 4. Current AR according to the AD phenotype with or without coexisting FA

Variable	No./Total No. (%)	OR (95% CI)	aOR* (95% CI)
Current AR	508/1,229 (41.3)		
No AD	328/906 (36.2)	1 (Reference)	1 (Reference)
Early-onset persistent with FA	12/15 (80.0)	7.05 (1.98–25.16)‡	4.81 (1.29–17.93)‡
Early-onset persistent without FA	41/75 (54.7)	2.13 (1.32–3.42)‡	1.97 (1.18–3.27)†
Early-onset remitting with FA	4/8 (50.0)	1.76 (0.44–7.09)	1.63 (0.36–7.33)
Early-onset remitting without FA	66/134 (49.3)	1.71 (1.19–2.46)‡	1.53 (1.04–2.26)‡
Late-onset with FA	4/6 (66.7)	3.52 (0.64–19.35)	5.08 (0.78–33.22)
Late-onset without FA	43/85 (50.6)	1.80 (1.16–2.82)	1.65 (1.02–2.66)‡

Current AR was defined as physician-diagnosed AR-ever and an AR episode during the prior 12 months from 6 to 8 years of age confirmed by questionnaire.
AR, allergic rhinitis; AD, atopic dermatitis; FA, food allergy; Sx, symptoms; Dx, diagnosis; OR, odds ratio; CI, confidence interval; aOR, adjusted odds ratio.
*Adjusted by sex, maternal education levels, parental allergy history, history of second-hand smoking, residential area, and economic status.
†$P < 0.05$; ‡$P < 0.01$.

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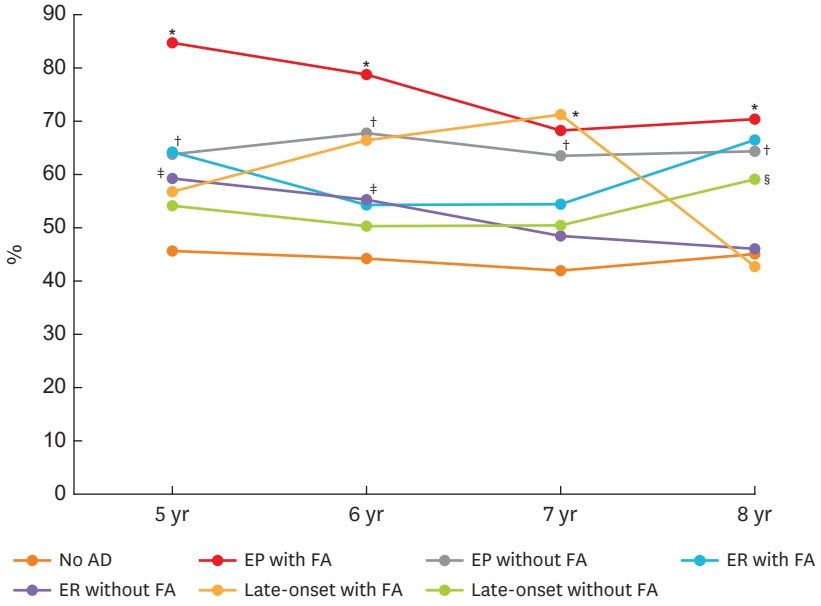

Fig. 2. Comparison of trajectories of AR episodes in children with AD among the different phenotypes. χ^2 tests were used for comparisons between groups.
AD, atopic dermatitis; FA, food allergy; EP, early-onset persistent; ER, early-onset remitting.
$P < 0.05$: *No AD vs. EP with FA; †No AD vs. EP without FA; ‡No AD vs. ER without FA; §No AD vs. Late-onset without FA.

compared the recent AR episodes, both phenotypes of early-onset persistent AD with and without FA showed a higher recent AR episode from 5 to 8 years of age than children without AD. The early-onset remitting AD without FA phenotype showed more episodes of recent AR at 5 and 6 years of age than those without AD, and recent AR episode in this phenotype showed a decreasing pattern from 7 to 8 years of age. However, recent AR episode showed an increasing pattern from 7 to 8 years of age in the early-onset remitting AD with FA phenotype, although this was not statistically significant (6 years of age, 54.5%, *P* value = 0.553; 7 years of age, 54.6%, *P* value = 0.542; 8 years of age, 66.7%, *P* value = 0.139). The late-onset AD without FA phenotype showed a higher incidence of recent AR at 8 years of age than the group without AD (**Fig. 2**, **Supplementary Table S4**). When we compared recent AR symptomatic episodes between the AD with FA and without FA phenotypes, AD and FA did not have positive correlations with the risk of AR symptomatic episodes among the school-aged children in our cohort (**Table 5**).

Table 5. Interactive effects of FA and the AD phenotype on AR episodes in school-aged children

Variable	FA (−)		FA (+)		OR for AR episode within strata of AD
	No./Total No. (%)	aOR* (95% CI)	No./Total No. (%)	aOR* (95% CI)	
AR episode at 7 yr of age					
No AD	426/1,036 (41.1)	1 (Reference)	23/34 (67.6)	2.91 (1.36–6.23)‡	2.91 (1.36–6.23)‡
AD	183/345 (53.0)	1.48 (1.14–1.92)‡	24/37 (64.9)	2.15 (1.05–4.40)†	1.43 (0.68–3.04)
Early-onset persistent	56/88 (63.6)	2.19 (1.37–3.41)‡	13/19 (68.4)	2.08 (0.77–5.65)	0.79 (0.24–2.63)
Early-onset remitting	77/158 (48.7)	1.22 (0.85–1.74)	6/11 (54.5)	1.62 (0.46–5.71)	1.81 (0.43–7.67)
Late-onset	50/99 (50.6)	1.45 (0.94–2.24)	5/7 (71.4)	3.97 (0.68–23.13)	3.66 (0.39–34.61)
AR episode at 8 yr of age					
No AD	442/981 (45.1)	1 (Reference)	15/28 (53.6)	1.40 (0.64–3.09)	1.40 (0.64–3.09)
AD	173/316 (54.7)	1.41 (1.08–1.85)†	23/36 (63.9)	1.70 (0.82–3.53)	1.15 (0.53–2.48)
Early-onset persistent	53/82 (64.6)	2.06 (1.26–3.37)‡	12/17 (70.6)	1.78 (0.60–5.30)	0.80 (0.20–3.27)
Early-onset remitting	66/143 (46.2)	0.97 (0.67–1.41)	8/12 (66.7)	2.20 (0.62–7.82)	2.49 (0.59–10.45)
Late-onset	54/91 (59.3)	1.76 (1.12–2.82)†	3/7 (42.9)	1.03 (0.21–5.12)	0.55 (0.09–3.32)

AR, allergic rhinitis; AD, atopic dermatitis; FA, food allergy; OR, odds ratio; CI, confidence interval; aOR, adjusted odds ratio.
*Adjusted by sex, maternal education levels, parental allergy history, history of second-hand smoking, residential area, and economic status.
†$P < 0.05$; ‡$P < 0.01$.

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Total immunoglobulin E (IgE), eosinophils and skin prick testing among the AD phenotypes

We compared the total IgE and eosinophil levels among the AD phenotypes at 7 years of age. The total IgE level was higher in the early-onset persistent AD than in the group without AD. Moreover, the eosinophil (%) was higher in the early-onset persistent AD (5.2% ± 3.5%) and late-onset AD (5.5% ± 5.6%) than in those without AD (3.8% ± 2.9%) (**Supplementary Table S5**). We assessed the association of a positive skin prick test result between the AD phenotypes and found that the early-onset persistent AD was associated with sensitization to tree pollens (aOR, 2.56; 95% CI, 1.01–6.48), grass pollens (aOR, 4.44; 95% CI, 1.40–14.05), and animal danders (aOR, 2.75; 95% CI, 1.17–8.43), and marginally with sensitization to house dust mites (aOR, 1.76; 95% CI, 0.95–3.24) (**Supplementary Table S6**).

Risk factors for AD phenotypes during the prenatal and postnatal periods

We investigated the risk factors for AD phenotypes during the prenatal and postnatal periods. When we stratified the AD subjects by phenotypes, the frequent use of antibiotics during infancy (aOR, 1.98; 95% CI, 1.36–2.90) was associated with early-onset remitting AD, and house remodeling during pregnancy (aOR, 2.55; 95% CI, 1.17–5.56) showed an association with late-onset AD. In addition, mold exposure during pregnancy to infancy showed a marginal association with early-onset persistent AD (aOR, 1.47; 95% CI, 0.97–2.21) (**Supplementary Table S7**). When we further stratified the data by FA, the frequent use of antibiotics during infancy was associated with early-onset remitting AD without FA (aOR, 2.02; 95% CI, 1.36–2.98). For other environmental exposures, house remodeling during pregnancy showed an association with the phenotype of late-onset AD without FA (aOR, 2.75; 95% CI, 1.25–6.01). Regarding a family history, maternal FA was associated with the phenotype of early-onset persistent with FA (aOR, 6.98; 95% CI, 1.81–26.87) (**Table 6**).

DISCUSSION

Our present analyses using a nationwide and general population-based birth cohort database showed that the AD with FA phenotype in early life was associated with asthma and AR in school-aged children. Further, an early-onset persistent AD phenotype is associated

Table 6. Risk factors for different AD phenotypes

Variable	No./Total No. (%)	OR (95% CI)	aOR* (95% CI)
Use of antibiotics during pregnancy	25/1,411 (1.8)		
No AD	20/1,032 (1.9)	1 (Reference)	1 (Reference)
Early-onset persistent with FA	0/20 (0.0)	-	-
Early-onset persistent without FA	2/81 (2.5)	1.28 (0.29–5.58)	1.04 (0.23–4.69)
Early-onset remitting with FA	1/12 (8.3)	4.60 (0.57–37.36)	5.81 (0.64–53.20)
Early-onset remitting without FA	1/162 (0.6)	0.31 (0.04–2.36)	0.29 (0.04–2.27)
Late-onset with FA	0/6 (0.0)	-	-
Late-onset without FA	1/98 (1.0)	0.52 (0.07–3.93)	0.50 (0.07–3.86)
Frequent use of antibiotics during infancy (≥ 3 days and ≥ 3 times)	272/1,461 (18.6)		
No AD	184/1,077 (17.1)	1 (Reference)	1 (Reference)
Early-onset persistent with FA	2/19 (10.5)	0.57 (0.13–2.49)	0.47 (0.11–2.09)
Early-onset persistent without FA	13/88 (14.8)	0.84 (0.46–1.55)	0.83 (0.45–1.54)
Early-onset remitting with FA	3/12 (25.0)	1.62 (0.43–6.03)	1.64 (0.43–6.22)
Early-onset remitting without FA	48/159 (30.2)	2.10 (1.44–3.05)§	2.02 (1.36–2.98)§
Late-onset with FA	3/7 (42.9)	3.64 (0.81–16.40)	3.70 (0.78–17.59)
Late-onset without FA	19/99 (19.2)	1.15 (0.68–1.95)	1.22 (0.71–2.09)

(continued to the next page)

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Table 6. (Continued) Risk factors for different AD phenotypes

Variable	No./Total No. (%)	OR (95% CI)	aOR* (95% CI)
Exclusive breast milk feeding until 6 mon of age	668/1,420 (47.0)		
No AD	493/1,040 (47.4)	1 (Reference)	1 (Reference)
With FA	10/20 (50.0)	1.11 (0.46–2.69)	1.19 (0.47–3.01)
Early-onset persistent without FA	41/82 (50.0)	1.11 (0.71–1.74)	1.02 (0.64–1.61)
Early-onset remitting with FA	5/12 (41.7)	0.79 (0.25–2.51)	0.72 (0.21–2.53)
Early-onset remitting without FA	73/162 (45.1)	0.91 (0.65–1.27)	0.87 (0.62–1.24)
Late-onset with FA	4/6 (66.7)	2.22 (0.41–12.17)	2.03 (0.36–11.63)
Late-onset without FA	42/98 (42.9)	0.83 (0.55–1.26)	0.78 (0.51–1.19)
Second-hand smoking exposure during pregnancy	552/915 (60.3)		
No AD	383/656 (58.4)	1 (Reference)	1 (Reference)
Early-onset persistent with FA	7/14 (50.0)	0.71 (0.25–2.06)	0.87 (0.28–2.75)
Early-onset persistent without FA	35/49 (71.4)	1.78 (0.94–3.38)	1.82 (0.93–3.56)
Early-onset remitting with FA	6/9 (66.7)	1.43 (0.35–5.75)	1.22 (0.27–5.57)
Early-onset remitting without FA	64/106 (60.4)	1.09 (0.71–1.65)	0.91 (0.57–1.44)
Late-onset with FA	4/6 (66.7)	1.43 (0.26–7.84)	1.20 (0.19–7.50)
Late-onset without FA	53/75 (70.7)	1.72 (1.02–2.89)‡	1.65 (0.95–2.89)
Maternal direct smoking during pregnancy	11/913 (1.2)		
No AD	6/657 (0.9)	1 (Reference)	1 (Reference)
Early-onset persistent with FA	0/14 (0.0)	-	-
Early-onset persistent without FA	0/48 (0.0)	-	-
Early-onset remitting with FA	0/9 (0.0)	-	-
Early-onset remitting without FA	3/105 (2.9)	3.19 (0.79–12.96)	4.24 (0.92–19.60)
Late-onset with FA	0/7 (0.0)	-	-
Late-onset without FA	2/73 (2.7)	3.05 (0.61–15.43)	3.47 (0.63–19.17)
House remodeling during pregnancy	60/1,423 (4.2)		
No AD	36/1,042 (3.5)	1 (Reference)	1 (Reference)
Early-onset persistent with FA	1/20 (5.0)	1.47 (0.19–11.29)	-
Early-onset persistent without FA	5/82 (6.1)	1.82 (0.69–4.76)	1.68 (0.63–4.51)
Early-onset remitting with FA	0/12 (0.0)	-	-
Early-onset remitting without FA	9/163 (5.5)	1.63 (0.77–3.46)	1.73 (0.80–3.73)
Late-onset with FA	0/7 (0.0)	-	-
Late-onset without FA	9/98 (9.2)	2.83 (1.32–6.05)§	2.75 (1.25–6.01)‡
Mold exposure from pregnancy to infancy	550/1,574 (34.9)		
No AD	385/1,163 (33.1)	1 (Reference)	1 (Reference)
Early-onset persistent with FA	8/20 (40.0)	1.35 (0.55–3.32)	1.32 (0.52–3.36)
Early-onset persistent without FA	40/89 (44.9)	1.65 (1.07–2.55)‡	1.50 (0.96–2.34)
Early-onset remitting with FA	4/14 (28.6)	0.81 (0.25–2.59)	1.02 (0.31–3.36)
Early-onset remitting without FA	69/175 (39.4)	1.32 (0.95–1.82)	1.24 (0.88–1.76)
Late-onset with FA	2/7 (28.6)	0.81 (0.16–4.19)	0.62 (0.12–3.29)
Late-onset without FA	42/106 (39.6)	1.33 (0.88–1.99)	1.23 (0.80–1.87)
Pet owner from pregnancy to infancy	75/1,579 (4.7)		
No AD	59/1,168 (5.1)	1 (Reference)	1 (Reference)
Early-onset persistent with FA	0/20 (0.0)	-	-
Early-onset persistent without FA	1/89 (1.1)	0.21 (0.03–1.56)	0.23 (0.03–1.70)
Early-onset remitting with FA	0/14 (0.0)	-	-
Early-onset remitting without FA	9/175 (5.1)	1.02 (0.50–2.09)	0.92 (0.41–2.07)
Late-onset with FA	1/7 (14.3)	3.13 (0.37–26.45)	4.09 (0.46–36.11)
Late-onset without FA	5/106 (4.7)	0.93 (0.37–2.37)	0.94 (0.37–2.42)
Maternal FA	55/1,384 (4.0)		
No AD	35/1,027 (3.4)	1 (Reference)	1 (Reference)
Early-onset persistent with FA	3/15 (20.0)	7.09 (1.91–26.24)§	6.98 (1.81–26.87)†§
Early-onset persistent without FA	4/81 (4.9)	1.47 (0.51–4.25)	1.37 (0.47–4.02)†
Early-onset remitting with FA	1/12 (8.3)	2.58 (0.32–20.52)	2.24 (0.27–18.57)†
Early-onset remitting without FA	9/146 (6.2)	1.86 (0.88–3.96)	1.76 (0.82–3.78)†
Late-onset with FA	0/6 (0.0)	-	-
Late-onset without FA	3/97 (3.1)	0.91 (0.27–3.00)	0.91 (0.27–3.03)†

AD, atopic dermatitis; FA, food allergy; OR, odds ratio; CI, confidence interval; aOR, adjusted odds ratio.
*Adjusted by sex, maternal education levels, parental allergy history, history of second-hand smoking, residential area, and economic status.
†Adjusted by sex, maternal education levels, history of second-hand smoking, residential area, and economic status, excluding parental allergy history.
‡$P < 0.05$; §$P < 0.01$.

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with asthma and AR at school age. In particular, FA showed a strong positive effect in this phenotype on the risk of recent wheezing episodes at 8 years of age. Children with an early-onset persistent AD with FA phenotype showed a higher incidence of recent wheezing and AR episodes from 5 to 8 years of age than those without AD. Furthermore, this phenotype was associated with maternal FA. Predicting respiratory comorbidities in the AD phenotype is crucial for the management and prevention of respiratory allergic diseases. Our current findings suggest that careful attention must be paid to children with concomitant AD and FA in early life, since timely prediction may assist in preventing asthma and AR at school age.

Several population-based birth cohort studies have shown AD phenotypes and their association with asthma. The Avon Longitudinal Study of Parents and Children study reported that a persistent AD phenotype is highly associated with asthma in school children.[33] The Protection Against Allergy Study in Rural Environments (PASTURE) study also showed that an early-onset AD phenotype was highly associated with asthma by 6 years of age. Our current findings are consistent with the results of these earlier studies.[22]

Several reports have also demonstrated the risk of subsequent asthma in children with AD coexisting with food sensitization. The Canadian Healthy Infant Longitudinal Development study showed that food sensitization and AD had a significant positive interaction with the risk of asthma at the age of 3 years.[21] The Observatory of Risks linked with Cutaneous Atopy study of early-onset AD (<12 months), indicated that initial multiple food sensitizations increased the development of asthma up to 6 years of age.[10] However, it is necessary to analyze food sensitization and FA separately, since many studies have reported them to be different conditions.[10,34]

Few studies have reported an association between AD with FA and respiratory allergies at school age. A prior birth cohort study of 1,218 children from the Isle of Wight found that an egg allergy history was associated with rhinitis and asthma at 4 years of age, especially when eczema coexisted.[19] However, that study did not evaluate asthma in school-aged children. The PASTURE cohort study indicated that children with both early-onset AD and FA had the highest risks of developing asthma and AR at 6 years of age,[22] which is consistent with our current findings. However, that study evaluated the effect of only early-onset AD and FA on asthma and AR, and did not include early-onset remitting, early-onset persistent or late-onset AD. In our current study, early-onset remitting AD phenotype was associated with a wheezing episode at 8 years of age, only when FA coexisted. However, FA cases were associated with wheezing episodes at 7 and 8 years of age, regardless of coexisting AD. This finding suggests that FA plays a more important role in the risk of school-age asthma than AD in early-onset remitting AD phenotype. In addition, an appreciable difference between wheezing in preschool-aged children and asthma in school-aged children has been established.[35-37] To our knowledge, there have not been any previous studies on the combined effects of AD and FA on asthma or AR in children older than 7 years of age. Our current study revealed the trajectory of wheezing and AR at 7 and 8 years of age. We found that FA had a strong positive effect on the risk of wheezing episodes at 8 years of age.

AR is another consequence of the 'atopic march,' along with asthma. In our present analyses, the early-onset persistent AD phenotype was associated with a higher rate of AR from 5 to 8 years. A previous high-risk cohort study also demonstrated that children with an early-onset persistent AD phenotype had a significantly greater risk of AR by 7 years of age.[7] Likewise, we confirmed this significance in our current general population-based birth cohort study.

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The PASTURE birth cohort study reported that children with the early-onset persistent AD phenotype had an increased risk of developing AR at 6 years of age,[22] wherein AR was defined by AR symptoms or a physician diagnosis at 6 years of age. In contrast, we defined current AR as physician-diagnosed AR at any age and AR symptoms from 6 to 8 years of age. We also investigated the trajectory of the AR episodes. To date, there has not been a study on trajectories of AR based on the AD phenotypes. Hence, one of the strengths of our present study was that the longitudinal AR trajectory assessments helped us to interpret the association between AR and the different AD phenotypes coexisting with FA.

Aeroallergen sensitization in children plays a critical role in the onset of respiratory allergic diseases at school age. Its relationship with the AD phenotype has been well investigated. The PASTURE study reported that the early-onset persistent AD phenotype identified by latent class analysis was associated with inhalant sensitization at 6 years of age.[22] Another high-risk cohort study of AD also found that the early-onset persistent AD phenotype was significantly associated with inhalant sensitization at 7 years,[7] which concurred with our current study results. Our current analyses have indicated that an early-onset persistent AD phenotype is associated with sensitization to house dust mites, tree pollens, grass pollens, and animal dander, at 7 years of age. In other words, early-onset persistent AD may be associated with respiratory allergic diseases at school age by means of inhalant allergen sensitization.

We observed that the early-onset persistent AD with FA phenotype is associated with maternal FA, which suggested that it may involve genetic susceptibility. Knowing the history of maternal FA may be helpful in predicting an atopic march phenotype. We also found that the frequent use of antibiotics during infancy was associated with the early-onset remitting without FA phenotype and that house remodeling during pregnancy was associated with late-onset AD without FA phenotype. Environmental factors may, therefore, influence the natural course of AD, regardless of genetic susceptibility. Previous studies have found that the perinatal environment plays an important role in AD development.[38-41] Moreover, antibiotic use may lead to atopic disorders via dysregulation of gastrointestinal microbiota as proposed by the "microflora hypothesis."[42,43] Furthermore, the Cohort for Childhood Origin of Asthma and allergic diseases, another prospective birth cohort study in Korea, revealed that antibiotic exposure within the first 6 months of life was associated with early-onset persistent AD.[44] Further studies are needed to clarify how indoor environments and antibiotic use interact with the AD phenotypes, especially in relation to atopic march.

Our current study revealed that late-onset AD may be associated with current asthma and AR. Several studies have reported that both late- and early-onset AD increased the risks of respiratory allergic diseases and aeroallergen sensitizations in schoolchildren.[22,27,45] Furthermore, both AD phenotypes may be linked to respiratory allergies through a Th2-skewed immune system.[46] A prior systematic review concluded that the risk of asthma in those with early-onset AD was slightly higher than that in subjects with late-onset AD.[47] However, further clarification of the different mechanisms of late and early-onset AD, with regard to the development of respiratory allergic disorders, is warranted. A prospective study of an at-risk mother-child cohort indicated that aeroallergen sensitization at school age was associated with the severity of early-onset AD, but not late-onset AD.[48] A case-control study has reported that filaggrin gene mutations are associated with only early-onset AD.[49] In our current study, the late-onset AD phenotype was associated with house remodeling during pregnancy, but not aeroallergen sensitizations at 7 years of age. Further studies on the association between late-onset AD and respiratory allergic diseases and the underlying

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mechanisms are needed in the future. Advances in molecular genetics are facilitating the investigation of AD pathogenesis.[50] Multi-omics studies, including transcriptome, short-chain fatty acid, and microbiome analyses, may also help to further elucidate the mechanisms underlying the AD phenotypes.

The key strength of our present study is the use of a nationwide population-based birth cohort, which included results for both allergic laboratory testing and the skin prick test. There are also several limitations. First, the information about allergic diseases was obtained by questionnaire. FA was not confirmed using a food challenge test, which is the gold standard for diagnosing FA. Our FA definition was limited to cases diagnosed by a physician and not based on symptoms. However, our data did provide useful information for identifying the AD phenotypes with a high risk of asthma and AR at school age. Second, only 594 children in our series underwent hospital laboratory tests. Hence, the PSKC birth cohort subjects, who attended their regional hospital, may have had more pronounced medical conditions than those who did not. We also could not investigate the association between inhalant sensitizations and the AD with FA phenotypes, because the skin prick tests were performed in regional hospitals. However, the baseline characteristics were not different between the hospital-visiting and non-hospital visiting subjects without a history of environmental tobacco smoke (**Supplementary Table S1**). The Middle East Respiratory Syndrome outbreak in Korea in 2015 prevented many of our subjects from visiting a clinic, despite the efforts of the regional hospitals. Third, the effects of upper respiratory infection and sinusitis can be misinterpreted as AR in preschool-aged children. Finally, CIs were wide due to the relatively small study sample of patients with allergic diseases. To verify our results, it is necessary to confirm the results in large-scale prospective cohort studies in the future.

Our results confirmed that AD with FA phenotype in early life was strongly associated with asthma and AR at school age. Moreover, AD and FA have a significant positive relationship with asthma at school age. In particular, the early-onset persistent AD with FA phenotype had a strong additive effect on the risk of asthma at school age. The early-onset persistent AD with FA phenotype was found to be associated with maternal FA. Classifying the AD phenotype in relation to a coexisting FA in early life will help to predict and prevent asthma and AR in school-aged children. It will be necessary to elucidate the precise mechanisms underlying this particular AD phenotype in future multi-omics studies.

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SUPPLEMENTARY MATERIALS

Supplementary Table S1
Characteristics of the whole Panel Study on Korean Children cohort stratified by attendance at a hospital for allergic testing

Click here to view

Supplementary Table S2
Current asthma and AR according to AD phenotype

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Supplementary Table S3
Comparison of trajectories of wheezing episodes in children with AD among the different phenotypes

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Supplementary Table S4
Comparison of trajectories of AR episodes in children with AD among the different phenotypes

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Supplementary Table S5
Total IgE and eosinophil levels in the peripheral blood from children with different AD phenotypes

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Supplementary Table S6
Association of sensitization with the different AD phenotypes

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Supplementary Table S7
Risk factors for the different AD phenotypes in early childhood

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Supplementary Fig. S1
Study flowchart.

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