Longitudinal atopic dermatitis control and persistence vary with timing of disease onset in children: A cohort study

Joy Wan, MD, MSCE,[a,b] Nandita Mitra, PhD,[c,d] Ole J. Hoffstad, MA,[c] Albert C. Yan, MD,[b] and David J. Margolis, MD, PhD[a,c,d]
Philadelphia, Pennsylvania

Background: Wide variation exists in the timing of atopic dermatitis (AD) disease onset among children. Distinct trajectories of early-onset, mid-onset, and late-onset AD have been previously described.

Objective: To evaluate longitudinal disease control and persistence with respect to age at onset of AD.

Methods: A cohort study was performed using the Pediatric Eczema Elective Registry, a prospective observational cohort of subjects with childhood-onset AD. AD control and persistence were assessed biannually for up to 10 years.

Results: A total of 8015 subjects with 41,934 person-years of follow-up were included. In longitudinal analyses using generalized linear latent and mixed modeling, older age at onset of AD was associated with better disease control and less-persistent AD. For each additional year of age at onset of AD, the adjusted odds ratios for poorer AD control and for persistent AD were 0.93 (95% confidence interval, 0.91-0.94) and 0.84 (95% confidence interval, 0.80-0.88), respectively. Differences in AD control and persistence among subjects with early-, mid-, and late-onset AD were most pronounced from early adolescence onward.

Limitations: Misclassification bias may arise from using self-reported data on age at onset. Attrition and missing data in longitudinal studies may introduce bias.

Conclusion: Early-, mid-, and late-onset pediatric AD appear to be clinically distinct subtypes of the disease. (J Am Acad Dermatol 2019;81:1292-9.)

Key words: atopic dermatitis; disease control; disease persistence; early onset; eczema; epidemiology; late onset; prognosis.

Atopic dermatitis (AD) affects up to 20% of children and waxes and wanes in its severity.[1,2] Traditionally, most children were thought to "outgrow" the disease, but evidence suggests that AD often persists into adulthood.[3-5] Although AD most commonly begins in infancy, it may not arise until later in childhood or adolescence.[3,6] This wide variation in timing of disease

From the Department of Dermatology,[a] Department of Biostatistics, Epidemiology and Informatics,[c] and Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania Perelman School of Medicine, Philadelphia,[d] and Section of Pediatric Dermatology, Children's Hospital of Philadelphia.[b]

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Correspondence to: Joy Wan, MD, MSCE, 3400 Civic Center Blvd, PCAM South Tower, 7th Floor, Office 775, Philadelphia, PA 19104. E-mail: joywan@pennmedicine.upenn.edu.

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onset has led to a distinction between early-onset and late-onset AD.[5,7,8] Our previous work has shown that later-onset AD is associated with a lower risk of asthma and seasonal allergies compared with infantile-onset AD.[9] Several phenotypes of AD, as distinguished by their temporal disease trajectories, have also recently been identified in European birth cohorts.[10,11] Early-onset, mid-onset, and late-onset AD appear to differ in the presence of active disease over time; however, whether these groups also differ in terms of the severity of AD is unknown. The objective of our study was to evaluate the impact of age at onset of AD on both longitudinal disease control and persistence in a US cohort.

CAPSULE SUMMARY

- The disease course of pediatric atopic dermatitis varies significantly by the timing of its onset, with earlier onset being associated with more longstanding and poorly controlled disease.
- Age of disease onset is a useful parameter for risk-stratifying and counseling patients with atopic dermatitis.

METHODS

We conducted a cohort study using the Pediatric Eczema Elective Registry (PEER), a prospective pediatric AD cohort in the United States. PEER was designed as a postmarketing safety evaluation of malignancy risk associated with pimecrolimus, a topical calcineurin inhibitor for treating mild-to-moderate AD. Details of PEER have been previously reported.[12] All subjects were 2 to 17 years old at time of registry enrollment and had a physician-confirmed diagnosis of AD. All had used pimecrolimus for at least 6 weeks in the 6-month period preceding enrollment; however, subjects were not required to continue pimecrolimus, and many did not.[13] Informed written consent was obtained from subjects upon registry enrollment. The current study was granted exempt status by the University of Pennsylvania Institutional Review Board.

Subjects enrolled in PEER between November 2004 and September 2018 were included. At the time of enrollment (ie, baseline), subjects or their caregivers provided information on demographics and AD history and treatment, including age at onset of AD. At baseline and every 6 months thereafter, subjects were surveyed about their AD disease control and treatment use in the preceding 6-month period. Subjects in PEER are followed for up to 10 years.

Age at onset of AD was reported by the subject or caregiver as 0 to 6 months, 6 to 12 months, or the exact age in years if greater than 12 months. In the primary analysis, age at onset of AD was considered as a continuous variable, with 0 to 6 months and 6 to 12 months being treated as 3 and 9 months, respectively. In secondary analyses, age at onset was categorized as less than 2, 3 to 7, or 8 to 17 years (ie, early-onset, mid-onset, and late-onset AD, respectively). Early-onset AD has traditionally been defined as that beginning before the age of 2 years.[3,5,14-16] Although no uniform definitions exist for mid- or late-onset AD, we used an age cutoff of 8 years based on a prior study showing that this age best differentiated between patients with and without filaggrin gene (*FLG*) mutations, which are a known genetic risk factor for AD, suggesting that this age may separate different subgroups of individuals with AD.[17] Our age definitions for early-, mid-, and late-onset AD also align with those recently described by Paternoster et al.[10]

The primary outcomes were AD disease control and persistence. Disease control was assessed by using the survey question "During the last 6 months, would you say that your child's skin disease has shown complete disease control, good disease control, limited disease control, or uncontrolled disease?" This type of patient global assessment has commonly been used in research and has been shown to correlate with the Patient-Oriented Eczema Measure, which is a robust patient-reported severity measure.[18] AD was defined as persistent if the subject reported less than complete control and/or any AD medication use or as nonpersistent if complete control *and* no medication use were reported.

To evaluate the relationship between age at onset of AD and disease control or persistence, we used generalized linear latent and mixed models with random intercepts to estimate subject-specific odds ratios for persistent AD (binary outcome) and worse disease control (categorized ordinally as complete, good, limited, and uncontrolled) while accounting for repeated measures in each subject. Analyses were adjusted for potential confounders specified a priori, including sex, race/ethnicity, household income, age at enrollment, atopic comorbidities, family history of atopy, baseline AD control, and duration of follow-up. We also examined data missingness to assess the assumption of random missingness required for our models. Sensitivity analyses were performed to evaluate the impact of missing data, variable duration of follow-up, and enrollment timing on results.

Abbreviations used:

aOR: adjusted odds ratio
AD: atopic dermatitis
CI: confidence interval
IQR: interquartile range
PEER: Pediatric Eczema Elective Registry

Local polynomial smoothed plots using the Epanechnikov kernel function were plotted for control and persistence by year of age and timing of onset of AD; plots were constructed for ages up to 25 years because of sparse data on older subjects. Data analysis was performed by using Stata software (version 14.1, StataCorp, College Station, TX).

RESULTS

In total, 8015 subjects (4273 female [53.3%]) were included in the study. They completed 70,841 follow-up surveys (mean surveys per subject, 8.8; standard deviation, 7.4), comprising 41,934 person-years of follow-up. Subject characteristics are presented in Table I. The median age of subjects upon enrollment was 6.6 years (interquartile range [IQR], 3.9-10.4). The median age at onset of AD was 0.75 year (IQR, 0.25-3.0), with 5770 children (72.0%) having early-onset AD, 1492 (18.6%) having mid-onset AD, and 712 (8.9%) having late-onset AD. Children with mid- or late-onset AD were more likely to be female but less likely to have asthma, seasonal allergies, or a family history of atopy (Table I). The early-onset group had slightly longer follow-up (median, 5.5 years [IQR 1.1-9.9]) than did the mid-onset or late-onset groups (5.1 [IQR, 1.0-9.6] and 4.6 [IQR, 0.7-9.1] years, respectively). At baseline, subjects with mid- and late-onset AD were more likely to report good or complete control whereas subjects with early-onset AD were more likely to report limited control or uncontrolled disease (Table I).

Complete AD control was reported on 16.0% of all surveys, good control on 50.2%, limited control on 28.6%, and uncontrolled disease on 5.2%. In longitudinal analyses, older age at onset of AD was

Table I. Baseline characteristics of the study participants

Characteristic	Overall cohort N = 8015	Participants with early-onset AD n = 5770	Participants with mid-onset AD n = 1492	Participants with late-onset AD n = 712	*P* value*
Median age at enrollment, y (IQR)	6.6 (3.9-10.4)	5.2 (3.3-8.6)	8.3 (6.4-10.9)	13.1 (11.2-15.1)	<.001*
Female sex, n (%)	4273 (53.3%)	2996 (51.9%)	826 (55.4%)	427 (60.0%)	<.001
Race/ethnicity, n (%)†					
White	2576 (32.1%)	1895 (32.8%)	429 (28.8%)	242 (34.0%)	<.001
Hispanic	851 (10.6%)	554 (9.6%)	210 (14.1%)	77 (10.8%)	
Black	4079 (50.9%)	2966 (51.4%)	734 (49.2%)	362 (50.8%)	
Asian/Pacific Islander	254 (3.2%)	161 (2.8%)	74 (5.0%)	18 (2.5%)	
American Indian/Alaskan	49 (0.6%)	33 (0.6%)	11 (0.7%)	5 (0.7%)	
Multiracial	204 (2.6%)	159 (2.8%)	34 (2.3%)	8 (1.1%)	
Annual household income, n (%)					
$0-$49,999	4544 (56.8%)	3317 (57.6%)	820 (55.1%)	380 (53.5%)	<.001
$50,000-$99,999	889 (11.1%)	680 (11.8%)	142 (9.5%)	63 (8.9%)	
≥$100,000	410 (5.1%)	320 (5.6%)	58 (3.9%)	28 (3.9%)	
Prefer not to answer	2161 (27.0%)	1446 (25.1%)	469 (31.5%)	240 (33.8%)	
Median duration of registry follow-up, y (IQR)	5.3 (1.1-9.9)	5.5 (1.1-9.9)	5.1 (1.0-9.6)	4.6 (0.7-9.1)	<.001*
AD control at baseline, n (%)					
Complete	406 (5.1%)	255 (4.4%)	83 (5.6%)	61 (8.6%)	<.001
Good	3797 (47.5%)	2628 (45.6%)	789 (53.0%)	366 (51.5%)	
Limited	3036 (38.0%)	2305 (40.0%)	495 (33.2%)	226 (31.8%)	
Uncontrolled	762 (9.5%)	575 (10.0%)	122 (8.2%)	58 (8.2%)	
Median duration of AD at enrollment, y (IQR)	4.0 (2.3-7.1)	4.5 (2.6-7.8)	3.6 (1.9-6.3)	2.1 (1.2-3.7)	<.001
Asthma, n (%)	3671 (45.9%)	2777 (48.2%)	598 (40.2%)	281 (39.5%)	<.001
Seasonal allergies, n (%)	5608 (70.1%)	4110 (71.3%)	998 (66.9%)	477 (67.1%)	.001
Family history of atopy, n (%)	6243 (77.9%)	4567 (79.2%)	1112 (74.5%)	536 (75.3%)	<.001

AD, Atopic dermatitis; *IQR*, interquartile range.
*Fisher's exact or Kruskal-Wallis test, as appropriate.
†Non-Hispanic unless otherwise specified or multiracial.

Table II. Multivariable models for worse AD control and persistence of AD, with respect to timing of onset of AD

	Adjusted OR (95% CI)*			
	Worse AD control†		Persistent AD	
Variable	Model 1	Model 2	Model 1	Model 2
Timing of onset of AD				
Age at onset of AD, per year‡	0.93 (0.91-0.94)	—	0.84 (0.80-0.88)	—
Early-onset (≤2 y)	—	Reference	—	Reference
Mid-onset (3-7 y)	—	0.71 (0.64-0.80)	—	0.45 (0.34-0.60)
Late-onset (8-17 y)	—	0.51 (0.43-0.60)	—	0.19 (0.12-0.30)
Female sex	1.20 (1.11-1.30)	1.20 (1.11-1.30)	1.77 (1.44-2.18)	1.76 (1.43-2.16)
Race/ethnicity§				
White	Reference	Reference	Reference	Reference
Black	2.27 (2.06-2.50)	2.28 (2.07-2.51)	7.01 (5.45-9.02)	7.09 (5.51-9.12)
Other	1.60 (1.41-1.81)	1.62 (1.43-1.83)	3.36 (2.47-4.58)	3.50 (2.57-4.78)
Annual household income				
$0-$49,999	Reference	Reference	Reference	Reference
$50,000-$99,999	0.72 (0.64-0.83)	0.73 (0.64-0.83)	0.53 (0.39-0.73)	0.53 (0.39-0.73)
≥$100,000	0.62 (0.52-0.75)	0.62 (0.52-0.75)	0.51 (0.33-0.77)	0.51 (0.33-0.77)
Prefer not to answer	0.82 (0.75-0.91)	0.82 (0.75-0.91)	0.70 (0.55-0.91)	0.70 (0.54-0.90)
Age at registry enrollment, y	1.03 (1.02-1.04)	1.03 (1.02-1.04)	1.06 (1.03-1.10)	1.06 (1.03-1.09)
Duration of registry follow-up, y	0.98 (0.97-0.99)	0.98 (0.97-0.99)	1.00 (0.96-1.04)	1.00 (0.97-1.04)
AD control at baseline				
Complete	Reference	Reference	Reference	Reference
Good	4.30 (3.55-5.21)	4.33 (3.57-5.25)	2.60 (1.71-3.95)	2.64 (1.74-4.01)
Limited	19.77 (16.25-24.05)	19.96 (16.40-24.28)	7.61 (4.92-11.77)	7.76 (5.02-12.00)
Uncontrolled	75.65 (60.26-94.98)	76.36 (60.83-95.85)	15.92 (9.07-27.94)	16.26 (9.27-28.53)
History of asthma	1.12 (1.03-1.22)	1.13 (1.03-1.23)	1.31 (1.05-1.64)	1.32 (1.06-1.65)
History of seasonal allergies	1.19 (1.08-1.31)	1.20 (1.09-1.32)	1.46 (1.14-1.86)	1.47 (1.15-1.88)
Family history of atopy	1.15 (1.04-1.27)	1.16 (1.05-1.28)	1.19 (0.92-1.54)	1.21 (0.93-1.57)

Timing of onset of AD is measured as a continuous variable in model 1 and as a categoric variable in model 2.
AD, Atopic dermatitis; *CI*, confidence interval; *OR*, odds ratio.
*Multivariable generalized linear mixed models also adjusted for repeated surveys and interaction term between survey number and age at onset.
†Ordinally defined as complete control, good control, limited control, and uncontrolled.
‡Age measured as continuous variable in years.
§Non-Hispanic white and black; other includes Hispanic, Asian, Pacific Islander, American Indian/Native Alaskan, and multiracial.

associated with better control and less persistence (Table II). For each additional year of age at onset of AD, the adjusted odds ratio (aOR) for poorer control was 0.93 (95% confidence interval [CI], 0.91-0.94); thus, a child whose AD began at the age of 10 years had 44% lower odds of worse control over time than did a child whose AD began at the of age 2 years. Similarly, when AD was categorized as early-, mid-, or late-onset, the aORs for worse control were 0.71 (95% CI, 0.64-0.80) and 0.51 (95% CI, 0.43-0.60) in the mid- and late-onset groups, respectively, compared with in the early-onset group (Table II). Plotting AD control by age, we visualized differences across the 3 onset age groups (Fig 1, *A*). Although all groups increasingly reported complete control with increasing age, the late-onset group was more likely to report complete control than were the mid-onset and early-onset groups across all ages, and differences among the 3 groups were most distinct in the second and third decades of life.

Persistent AD was reported on 90% of all surveys. In longitudinal analyses, the odds of persistent AD were significantly lower for each additional year of age at onset of AD (aOR, 0.84 [95% CI, 0.80-0.88]) (Table II). A child whose AD began at age 10 thus had 75% lower odds of persistent disease over time compared with a child whose AD began at age 2. When age at onset was analyzed categorically, the odds of persistent AD were also lower for mid-onset (aOR 0.45 [95% CI 0.34-0.60]) and late-onset (aOR 0.19 [95% CI 0.12-0.30]) AD relative to early-onset AD (Table II). In all 3 groups, the proportion of subjects reporting persistent AD generally declined with older age, and the differences among the 3 onset age groups were most pronounced from early adolescence onward (Fig 1, *B*).

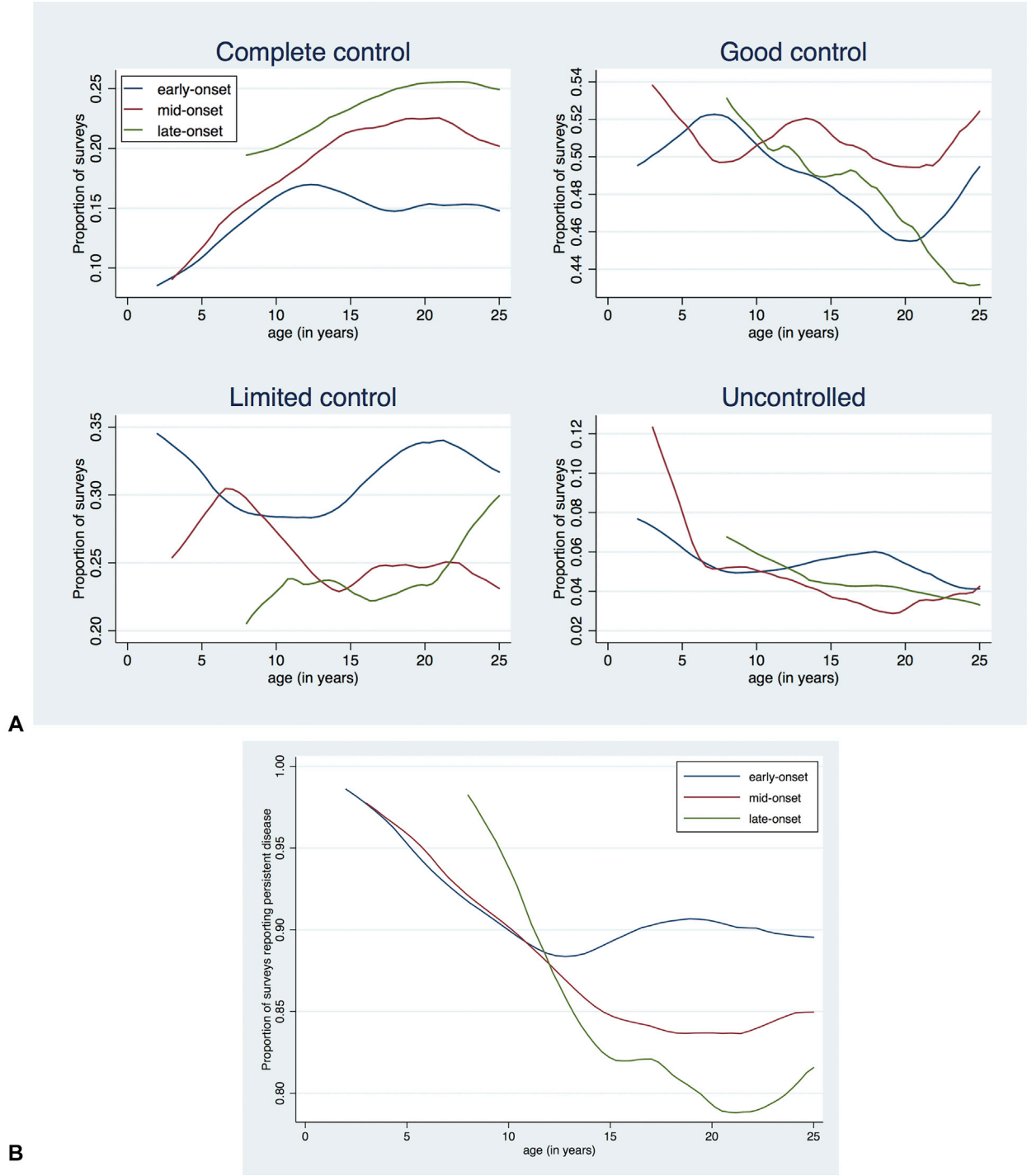

Fig 1. Atopic dermatitis (AD) disease control and persistence by age (in years) and timing of disease onset. Local polynomial smoothed plots are shown for early-, mid-, and late-onset AD. The *y* axis represents the proportion of surveys reporting the specified level of disease control (**A**) or persistent AD (**B**) at each age. The *x* axis represents age in years.

In multivariable models, other statistically significant predictors of worse AD control and persistence were female sex, nonwhite race, lower income, history of asthma or seasonal allergies, and family history of atopy (Table II).

Response rates to the follow-up surveys were 55% to 70% per survey. The proportion of subjects who did not complete any follow-up surveys was 18.0%; 47.3% of subjects returned no more than 50% of their follow-up surveys, whereas 20.8% of subjects

Table III. Sensitivity analyses

Model	Adjusted OR (95% CI)					
	Worse AD control*			Persistent AD		
	Age at onset of AD, per year†	Mid-onset‡	Late-onset‡	Age at onset of AD, per year†	Mid-onset‡	Late-onset‡
Primary model	0.93 (0.91-0.94)	0.71 (0.64-0.80)	0.51 (0.43-0.60)	0.84 (0.80-0.88)	0.45 (0.34-0.60)	0.19 (0.12-0.30)
Subjects with ≥80% of surveys completed	0.91 (0.89-0.94)	0.66 (0.56-0.78)	0.41 (0.31-0.54)	0.80 (0.76-0.85)	0.33 (0.22-0.48)	0.13 (0.07-0.23)
Subjects with 100% of surveys completed	0.90 (0.87-0.94)	0.63 (0.50-0.80)	0.40 (0.27-0.60)	0.80 (0.73-0.87)	0.38 (0.22-0.66)	0.15 (0.06-0.36)
Subjects with ≥6 years of registry follow-up	0.91 (0.89-0.93)	0.68 (0.58-0.80)	0.39 (0.30-0.50)	0.78 (0.74-0.82)	0.36 (0.25-0.52)	0.09 (0.05-0.16)
Subjects with 10 years of registry follow-up	0.90 (0.86-0.93)	0.72 (0.55-0.93)	0.34 (0.23-0.50)	0.72 (0.66-0.79)	0.35 (0.19-0.65)	0.04 (0.02-0.10)
Subjects with ≥80% of surveys completed *and* ≥6 years of registry follow-up	0.90 (0.88-0.93)	0.67 (0.56-0.81)	0.36 (0.26-0.49)	0.77 (0.72-0.83)	0.34 (0.23-0.52)	0.08 (0.04-0.15)
Subjects who enrolled in PEER ≤2 years after onset of AD	0.72 (0.60-0.87)	0.52 (0.38-0.71)	0.22 (0.11-0.43)	0.52 (0.33-0.82)	0.15 (0.07-0.32)	0.03 (0.01-0.13)

AD, Atopic dermatitis; *CI*, confidence interval; *OR*, odds ratio; *PEER*, Pediatric Eczema Elective Registry.
*Ordinally defined as: complete control, good control, limited control, and uncontrolled.
†Age measured as continuous variable in years.
‡Reference group is early-onset AD.

completed all surveys. However, the distributions of missing surveys among the early-, mid-, and late-onset groups were similar, supporting the assumption that missingness is independent of the exposure (data not shown). Subjects missing up to 50% of their scheduled follow-up surveys and those missing more than 50% were generally similar in their baseline characteristics (data not shown). Sensitivity analyses of only subjects with a survey completion rate of at least 80% or 100% found results similar to those of the primary analysis (Table III). Effect estimates were only further strengthened in analyses limited to subjects with at least 6 years of follow-up, 10 years of follow-up, or a survey completion rate of at least 80% *and* at least 6 years of follow-up (Table III).

DISCUSSION

In this study of 8015 children with AD followed into young adulthood, earlier-onset AD was associated with worse disease control and greater persistence over time, independent of sociodemographic characteristics and atopic comorbidities. Our findings suggest that age at onset of AD differentiates clinically distinct forms of the disease. AD subtypes that are partly distinguished by the timing of disease onset have been identified in previous cross-sectional studies using cluster or latent class analysis.[19,20] Two longitudinal studies have described distinct trajectories of AD also defined in part by the age of disease onset. Using data from British and Dutch cohorts, Paternoster et al identified 6 latent classes of AD from birth to age 16: early-onset, persistent; early-onset, late-resolving; early-onset, early-resolving; mid-onset, resolving; late-onset, resolving; and unaffected/transient.[10] Similarly, Roduit et al defined 4 classes of AD by using a rural European birth cohort followed until age 6: early-onset, transient; early-onset, persistent; late-onset (after age 2); and never/infrequent.[11]

Our findings in a US cohort are consistent with the aforementioned previous observations in European children. We did not further separate early-onset AD into resolving and persistent subtypes, as our objective was to compare the disease course, on average, among patients with early-, mid-, and late-onset AD. We recognize that a subset of patients with early-onset AD experience disease resolution, which our data also support. In our early-onset group, a continuous decline in reports of persistent AD occurred in early childhood and reached the nadir at age 13, likely reflecting those individuals whose AD resolved; however, the proportion of patients with persistent AD remained fairly stable thereafter, representing those with active AD into adulthood

(Fig 1, *B*). In contrast to previous birth cohort studies, our study followed children into their 20s, providing insight into older ages. Notably, rates of persistence in early-, mid-, and late-onset AD most clearly separated after age 13 (Fig 1, *B*), suggesting that these groups differ more strikingly during adolescence and early adulthood. Additionally, whereas previous studies only measured *any* AD activity, we evaluated the level of disease control and found that earlier-onset AD also portended worse longitudinal control. Finally, our study was strengthened by the frequency of outcome assessments, thus better capturing the variations inherent to a waxing and waning disorder such as AD.

The identification of distinct AD phenotypes and endotypes is a major focus of ongoing research.[5,21] Variations in the longitudinal course of early-, mid-, and late-onset pediatric AD support the concept that they are distinct subtypes. Previous studies in PEER and other cohorts have also shown that earlier-onset AD is associated with a greater risk of asthma, allergic rhinitis, and food allergies and the presence of genetic risk variants for AD.[9-11,17,19,22-24] Together, these suggest that the timing of onset of AD is driven in part by genetics and is associated not only with AD severity and persistence but also with atopic burden overall. However, additional research is needed to understand whether and how early-, mid-, and late-onset AD differ molecularly or immunologically, and whether they respond differentially to treatment.

There are several potential limitations to note. First, all subjects in PEER were required to have used pimecrolimus, potentially biasing our cohort toward children with more persistent or active disease requiring pharmacologic therapy. It is also possible that subjects with milder or transient AD were less likely to respond to follow-up surveys, thereby also contributing to this potential bias. Nevertheless, pimecrolimus is commonly used for mild-to-moderate AD, and its utilization would not be expected to vary by age at onset of AD. Second, as with all longitudinal studies, attrition and missing data may introduce bias. However, sensitivity analyses limited to subjects with longer follow-up and/or fewer missing data showed similar results, and subjects with more than 50% versus no more than 50% missing surveys were fairly similar at baseline. Third, as children could enroll in PEER at any time after AD diagnosis, we do not have information on disease activity between onset of AD and registry enrollment, which amounted to 4 years on average. It is unlikely that children with any particular timing of onset of AD were differentially included in PEER on the basis of disease activity before registry entry, because subjects and enrolling physicians were unaware of the current study hypothesis. However, it is possible that some children with early-onset, early-resolving AD are under-represented in PEER, as they may have had AD resolution before 2 years of age or been less likely to use pimecrolimus because of age or milder disease, for example. Therefore, our early-onset group is probably more representative of children whose AD remained active after age 2. Similarly, as some children with mid-onset or late-onset AD did not enroll in PEER until a few years after onset of their disease, it is possible that children with later-onset but transient or quickly resolving AD were also less likely to be included in PEER. Nevertheless, the results of a sensitivity analysis limited to subjects who enrolled within 2 years after onset of AD were similar to the primary findings (Table III). Finally, ages of onset of AD were self-reported, which may have led to misclassification bias. However, analyses that broadly categorized age at onset of AD into early-, mid-, and late-onset AD were consistent with those evaluating age as a continuous variable. Despite these potential limitations, our study is strengthened by the use of a large and diverse cohort of subjects with AD with frequent disease assessments and relatively long follow-up.

From a clinical perspective, age at onset of AD may be helpful for risk-stratifying and counseling patients about their expected disease course. Although more precise subtypes of AD may be identified by combining clinical, genetic, and biomarker data, a simple approach to AD subclassification remains clinically useful. The timing of disease onset is normally assessed as part of the clinical history for patients with AD, and genetic and laboratory tests are not routinely performed. By considering the framework of early-onset or late-onset disease, we can identify those patients who are at greater risk of persistent or poorly controlled AD and who may benefit from more intensive treatment or monitoring.

CONCLUSION

The disease course of AD in children varies significantly by the timing of its onset. AD that begins early in life is associated with more longstanding and poorly controlled disease. Our findings suggest that early-, mid-, and late-onset pediatric AD are clinically distinct disease subtypes, thus making age at onset a useful parameter for risk-stratifying and counseling patients.

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