

Letter to the Editor

Patterns and predictors of atopic dermatitis disease control past childhood: An observational cohort study

To the Editor:

Atopic dermatitis ([AD], synonymous with eczema or atopic eczema) is a common and burdensome condition occurring in patients of all ages. Most research has focused on pediatric disease because symptoms often present early in life, and little is known about disease course past childhood.¹ We report on the results of a longitudinal cohort study using the Pediatric Eczema Elective Registry (PEER), which follows individuals for up to 10 years during the transition to early adulthood. Our objectives were to define patterns of AD disease control by age and to examine whether patient characteristics are predictive of these patterns.

We studied 6720 patients with mild-to-moderate AD who had used pimecrolimus for >6 weeks. They were enrolled by physicians from across the United States and subsequently followed via biannual mail surveys. The primary outcome used to define patterns of disease control was complete control without treatment (yes/no) for each 6-month period. This was derived from 2 repeating questions about disease control and treatment use.

Latent class analysis was used to identify patterns of disease control. We included age at survey as a predictor of the outcome,

and we controlled for age at cohort enrollment. As predictors of the latent class, we included all the covariates available at baseline hypothesized *a priori* to explain variation in persistence: sex, race, baseline family income, history of atopy, and age at disease onset.

After performing the latent class analysis, we compared the proportion of individuals in each subgroup with filaggrin and filaggrin-2 null mutations. These were not used as predictors in the model because they were only available for a subset of the population who sent biosamples. In addition, we compared history of treatment use, history of allergies, and history of smoke exposure at baseline between the subgroups from the model. Additional details regarding the methods are available in this article's Online Repository at www.jacionline.org.

A total of 65,237 surveys (mean, 10.4) were returned by 6,270 racially diverse participants ages 2 to 26 years, comprising 33,074 person-years of follow-up (Table I). The primary outcome, complete control without treatment, was reported on 9% of all surveys.

Latent class analysis suggested there were 2 subgroups with clinically distinct patterns of disease control: a group more likely to report periods of complete control without treatment as they aged (termed "resolving") and a group more likely to report "persistently active" disease past childhood (Fig 1).

History of atopy, female sex, family income under \$50,000/year at enrollment, nonwhite race, and younger age at eczema onset were significant predictors of membership in the

TABLE I. Demographic characteristics of cohort and results of latent class analysis

	Overall N = 6270	Class 1	Class 2	OR (95% CI)*
		Resolving n = 702	Persistently active n = 3905	
Patient characteristics included in the model	n (%)	%	%	
Female sex	6270 (53)	43	55	1.63 (1.35-1.95)
Income <\$50,000/y	4639 (75)	57	78	1.69 (1.37-2.08)
Nonwhite race	6269 (65)	47	73	2.38 (1.94-2.91)
History of atopy	4682 (75)	72	75	1.36 (1.10-1.67)
Age at eczema onset (y), mean $\pm$ SD	n = 6239, 2.3 $\pm$ 3.0	2.9 $\pm$ 2.5	2.0 $\pm$ 2.9	0.91 (0.88-0.93)
Additional patient characteristics compared by model classification				P value†
Genetics				
Any filaggrin null mutation	829 (17)	18	16	.596
Any filaggrin-2 null mutation	337 (45)	36	46	.294
Mean proportion of visits with frequent treatment use before age 8				
Topical calcineurin inhibitor	4010 (80)	57	85	.000
Topical steroids	4000 (54)	37	56	.000
Any prescription med for eczema	4010 (91)	69	96	.000
History of allergies at enrollment				
Animals	6262 (22)	18	23	.003
Foods	6265 (24)	18	25	.000
Meds	6264 (12)	13	11	.135
Smoker in the home at enrollment				
Yes	6213 (16)	11	15	.001

OR, Odds ratio.

*Odds of membership in the "persistently active" class from the 2-class model that included age at survey and age at enrollment as predictors of outcome and all of the listed patient characteristics as predictors of class.

†Pearson chi-square or *t*-test.

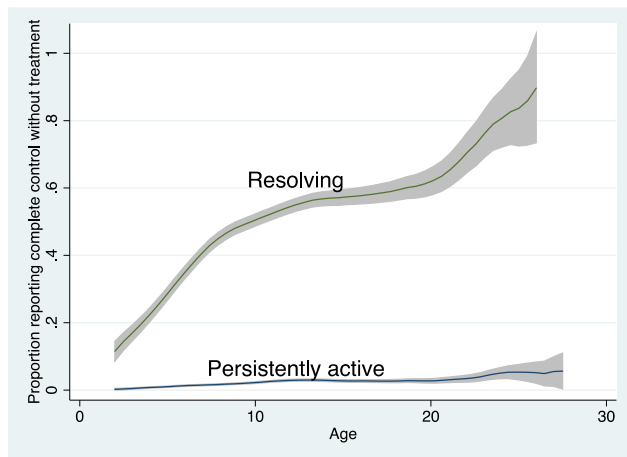


FIG 1. Proportion of cohort reporting complete control without treatment by age and disease class. We plotted the proportion of individuals reporting complete control without treatment at each age for each of the 2 subgroups resulting from the latent class model using Epanechnikov kernel-weighted local polynomial smoothed plots with 95% CIs in gray. Note this graph represents actual data and not predicted probabilities from the models.

“persistently active” subgroup (Table I). Blacks made up nearly half of the cohort, and the results of sensitivity analyses using alternate categorizations of race (eg, black vs white) resulted in even higher odds of membership in the “persistently active” subgroup (odds ratio, 3.23, 95% CI, 2.54–4.10) (see Table E2 in this article’s Online Repository at www.jacionline.org). Income data was limited to self-reported family income at enrollment and was not adjusted for family size. To address this potential source of measurement error, we conducted a sensitivity analysis without income and found similar results (Table E2).

When comparing the classes produced by the model, we found no significant differences in the proportion of patients with filaggrin or filaggrin-2 null mutations. Patients classified into the “persistently active” class were significantly more likely to have reported frequent use of eczema medications at younger ages. Results are presented for treatment before age 8 years; additional comparisons varying the age cut point and found similar results (data not shown). Finally, we found that those in the “persistently active” group were significantly more likely to report a history of animal allergies, food allergies, or presence of a smoker in the home.

Using a latent class analysis, which is well suited to identify trajectories of heterogeneous patterns of discrete outcomes, we demonstrate the existence of subgroups of patients with clinically distinct disease courses and found that standard patient characteristics are highly predictive of persistently active disease. These are helpful for clinicians to consider when counseling patients and identifying who may benefit from more intensive follow-up and intervention. This article builds on a prior publication that found similar factors are associated with symptom-free periods at any age, but that publication did not address disease course or answer the crucial and more clinically relevant question of which children are most likely to have persistent disease.²

Our findings that female sex and history of allergies are associated with more persistent disease corroborate those from other studies with limited follow-up.^{3–5} We also report a number of novel findings. Notably, we found that income and race were

strongly associated with AD persistence. In multivariate models, the magnitude of association with income <\$50,000/year and black race was larger than the association with history of atopy, previously thought to be among the strongest predictors of AD persistence.⁶ Our results differ from many studies that have found that higher income is associated with higher AD incidence or prevalence.⁷ We hypothesize that drivers of disease onset may be different from drivers of disease persistence; additional research is needed to test this hypothesis and to examine how changes in income or socioeconomic status over time relate to eczema disease control.

The strengths of our study include a large and diverse cohort with repeated measures of disease control and treatment use. The primary limitation relates to the generalizability of the findings. Because patients were required to use pimecrolimus for ≥ 6 weeks prior to enrollment, the PEER cohort is likely biased toward more persistent disease (because those who had early clearance would be less likely to have required pimecrolimus at later ages). Therefore the proportion of individuals in each disease class may not be representative of the general AD population. The goal of our study was not to describe how many individuals are likely to have each disease control pattern. Rather, our focus was to identify predictors of each subgroup, which are more likely to be generalizable to AD population seeking treatment. It is also possible that use of pimecrolimus, corticosteroids, or other topical treatments could alter the skin barrier and predispose to more persistent disease, but sensitivity analyses stratifying by history of treatment use during follow-up did not reveal any differences in our results.

An additional limitation, common to nearly all large longitudinal studies, is attrition; 35% of individuals were lost to follow-up. There was only a median of 0 missing surveys in sequence (interquartile range, 0–1), and although sensitivity analyses do not exclude the possibility of bias, they did not reveal any difference in the results when we included only individuals with longer-term or full follow-up (Table E2).

Our results highlight the importance of characterizing AD as a chronic condition and the necessity of longitudinal studies that permit the analysis of disease control over time. Future research should examine mechanisms for these differences.

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METHODS

Study setting and participants

PEER began enrollment in 2004 and follows a diverse sample of US children and young adults with physician-diagnosed AD (based on the UK Working Party Criteria^{E1}) for up to 10 years. Participants return surveys that include information on self-reported disease control and medication use at 6-month intervals. Subjects were enrolled by >1000 pediatricians, allergists, or dermatologists, and represent all major ethnic groups and geographic areas in the United States. The cohort was designed to test whether there is an increased risk of malignancy associated with the use of pimecrolimus, a topical calcineurin inhibitor, and all participants used 1% topical pimecrolimus cream for at least 42 of the 180 days prior to enrollment. After enrollment, data collection continued via mail surveys and was independent of physician visits and treatment decisions. Subjects were not required to continue to see the enrolling provider or continue using pimecrolimus, and in fact, use declined to a minority of participants over time.^{E2} Participants were excluded if, at baseline, they had a history of lymphoproliferative disease, systemic malignancy, skin malignancy, or had used oral immunosuppressive medications such as cyclosporine, tacrolimus, or methotrexate. For this analysis, we included data from all subjects with ≥ 1 returned survey after the baseline questionnaire through December 2015. The sample size is larger than in prior publications because PEER is an ongoing study.

All study procedures were approved by the institutional review board at the University of Pennsylvania (no. 706073). All participating patients (or their guardians) signed an informed consent form.

Variables measured

The primary outcome we used to define patterns of disease control was a repeated composite variable: complete control without treatment (yes/no) for each 6-month period. It was derived from 2 survey questions: "During the last 6 months, would you say your (or your child's) skin disease has shown: complete disease control, good disease control, limited disease control, or uncontrolled disease?" and "Have you used a prescription cream or ointment to treat this child's eczema during the last 6 months?" These questions were chosen because they are easily interpretable, patient-centered, and comprehensive. The level of disease control question has been used in randomized controlled trials and has been shown to correlate with a well-validated objective severity measure, the Eczema Area Severity Index (Spearman correlation coefficient at 6 months, 0.794).^{E3,E4} Examples of individual participant response patterns are shown in Fig E1.

Covariates included sex, race, income, history of atopy, and age of disease onset. Race was reported as ≥ 1 of the following: American Indian, Asian, black or African American, Hawaiian or other Pacific Islander, or white; and for the primary analysis it was modeled as a binary variable: white only (yes/no). Family income at baseline was reported in 6 categories, and for the primary analysis was modeled as $> \$50,000/\text{year}$ or $\leq \$50,000/\text{year}$ based on the distribution of responses. Data on income at disease onset and household size were not collected. Self-reported age at disease onset was modeled as a numeric variable. History of atopy was defined as a personal history of asthma or seasonal allergies if ≥ 4 years of age, or a family history of asthma, seasonal allergies, or AD in a parent or sibling if age < 4 years. For a subset of the population who sent biosamples, filaggrin (R501X, 2282del4, R2447X, and S3247X) and filaggrin-2 null mutations (rs1256874 and rs1683397) were genotyped using custom-made TaqMan allelic discrimination assays (Applied Biosystems, Foster City, Calif).^{E5,E6} Duration of follow-up was calculated from the date of enrollment to the last available survey date. Loss to follow-up was defined as an 18-month period without a returned survey.

Statistical analysis

Using the generalized linear latent and mixed model framework, we performed a repeated measures latent class analysis to identify subgroups of

individuals within the cohort who had different patterns of disease control over time.^{E7} Each latent class is associated with a characteristic vector of responses. We chose this method because it accommodates change that is discrete or discontinuous (as is the case with an episodic condition like AD) and allows for heterogeneity in patterns among subgroups.^{E8} It also has the capacity to accommodate differential missingness and covariate-dependent missingness at random.

We fit latent class models with 2 to 5 classes. To determine the optimal number of classes, we examined model fit statistics including the log likelihood and Bayesian information criterion and considered the homogeneity, separation, and size of classes.^{E9} As we added more classes to the model, the statistical fit improved and we found that a 4-class model had the lowest Bayesian information criterion. Specifying models with larger numbers of classes created intermediate groupings between the "persistently active" and "resolving" groups, but these represented a small proportion of the total population (3% to 14%) (see Table E1 and Fig E2). Therefore, we present detailed results for the 2-class model because it is the most parsimonious and clinically meaningful.

We explored various options for modeling time, including whether there were any inflection points in the disease course, and we found that a simple linear variable using the age at survey (rounded to the nearest half-year) allowed for good model fit and interpretability. We included age at survey as a predictor of the outcome in our model and controlled for age at cohort enrollment. As predictors of the latent class, we included all the covariates available at baseline hypothesized *a priori* to explain variation in persistence: sex, race, baseline family income, history of atopy, and age at disease onset. We ran binary logistic latent class models using repeated measures for a 2-level measure of disease control (complete control without treatment vs all other levels of control) and ordinal logistic latent class models using a repeated measure with all 5 levels of disease control (poor, limited, good, complete control with treatment, and complete control without treatment) and found similar results. The binary logistic models were chosen for presentation because they are more easily interpretable. We indicated the number of missing variables in Table 1 and performed sensitivity analyses using subsets of the cohort without missing data and alternative categorizations of race.

After performing the latent class analysis, we compared the proportion of individuals in each subgroup with filaggrin or filaggrin-2 mutations. Genetic data were not used as predictors in the model because they were only available for a subset of the data. Instead, using the model results, we compared the proportions of individuals with null mutations in each class/subgroup of individuals. In addition, we compared history of treatment use, history of allergies, and history of smoke exposure at baseline between the subgroups from the model. All analyses were performed with Stata software (version 14.1, StatCorp, College Station, Tex), and we followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting of observational studies.^{E10}

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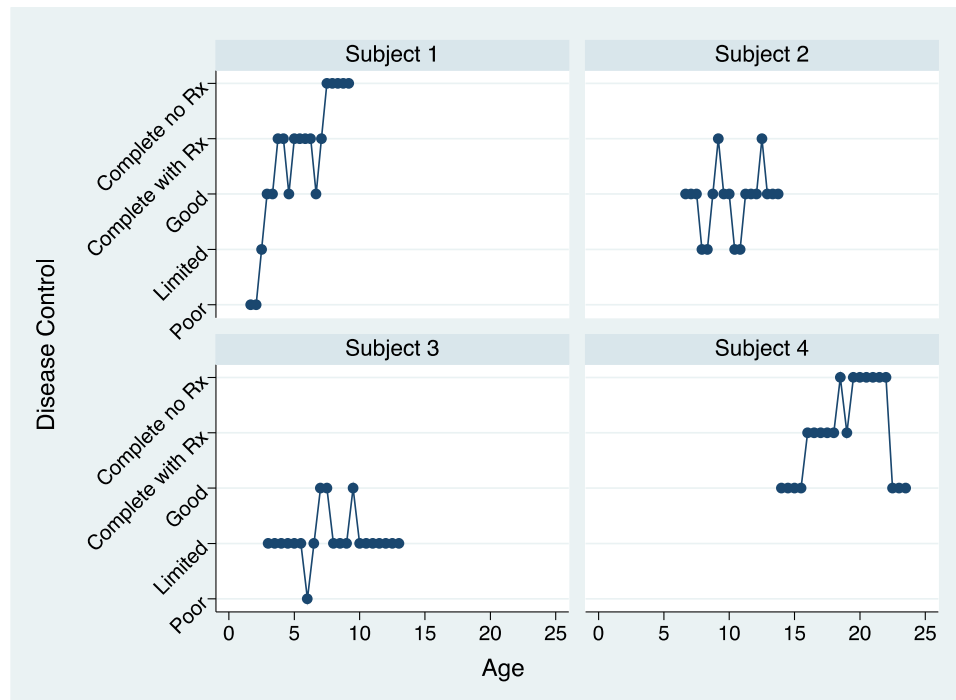


FIG E1. Example of 4 individuals' response patterns of disease control by age. To illustrate how disease control varies over time, the response to the primary outcome measure, self-reported disease control with or without treatment, is shown on the y-axis, plotted against the age in years for 4 selected subjects. Rx, Prescription.

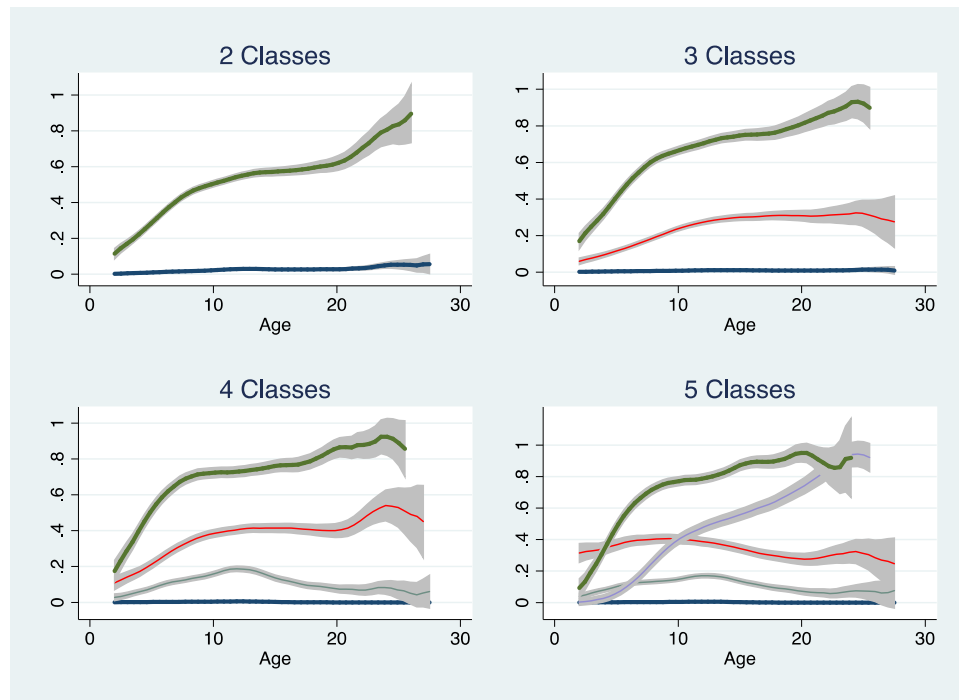


FIG E2. Graphical comparison of results from 2 to 5 class models. Epanechnikov kernel-weighted local polynomial smoothed plots with 95% CIs in gray. The x-axis represents age in years, and y-axis represents the proportion of the cohort reporting complete control without treatment at each age. As more classes were added to the model, the “resolving” and “persistently active” subgroups, which included over 75% of the population, remained similar.

TABLE E1. Results of 2 to 5 class models from latent class analysis

	2-Class model	3-Class model	4-Class model	5-Class model
Model fit statistics				
Log likelihood	−10,875	−10,279	−10,148	−10,108
Degrees of freedom	11	19	27	35
BIC	21,869	20,764	20,589	20,595
Distribution of individuals among subgroups				
	n (%)	n (%)	n (%)	n (%)
Persistently active class	3,905 (85)	3,622 (79)	3,344 (73)	3,343 (73)
Intermediate class A	N/A	592 (13)	615 (13)	629 (14)
Intermediate class B	N/A	N/A	377 (8)	276 (6)
Intermediate class C	N/A	N/A	N/A	151 (3)
Resolving class	702 (15)	393 (9)	271 (6)	208 (5)
Odds of subgroup membership by patient factor				
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
“Persistently active” vs “Resolving” class				
Female	1.63 (1.35-1.95)	1.73 (1.36-2.19)	1.68 (1.24-2.27)	1.91 (1.30-2.79)
Income <\$50,000/y	1.69 (1.37-2.08)	1.68 (1.28-2.21)	1.74 (1.23-2.45)	1.55 (1.03-2.34)
History of atopy	1.36 (1.10-1.67)	1.55 (1.19-2.02)	1.76 (1.27-2.46)	2.07 (1.40-3.07)
Nonwhite race	2.38 (1.94-2.91)	2.94 (2.25-3.84)	3.57 (2.54-5.01)	4.24 (2.80-6.42)
Age of onset (y)	0.91 (0.88-0.93)	0.88 (0.85-0.91)	0.79 (0.75-0.85)	0.81 (0.75-0.88)
“Intermediate class A” vs “Resolving” class				
Female		1.19 (0.88-1.62)	1.47 (1.04-2.07)	1.63 (1.08-2.46)
Income <\$50,000/y		0.78 (0.55-1.10)	0.97 (0.66-1.42)	0.90 (0.57-1.43)
History of atopy		1.19 (0.85-1.66)	1.28 (0.88-1.85)	1.45 (0.93-2.24)
Nonwhite race		1.62 (1.14-2.28)	1.67 (1.14-2.45)	1.99 (1.26-3.14)
Age of onset (y)		0.97 (0.93-1.01)	0.96 (0.91-1.01)	0.98 (0.92-1.04)
“Intermediate class B” vs “Resolving” class				
Female			0.92 (0.61-1.39)	1.24 (0.70-2.20)
Income <\$50,000/y			0.77 (0.48-1.22)	0.84 (0.45-1.55)
History of atopy			1.20 (0.77-1.89)	1.21 (0.68-2.15)
Nonwhite race			1.71 (1.08-2.71)	2.18 (1.18-4.04)
Age of onset (y)			0.97 (0.92-1.03)	1.04 (0.97-1.11)
“Intermediate class C” vs “Resolving” class				
Female				1.03 (0.57-1.85)
Income <\$50,000/y				0.45 (0.23-0.89)
History of atopy				2.42 (1.18-4.98)
Nonwhite race				1.73 (0.87-3.44)
Age of onset (y)				1.00 (0.92-1.09)

BIC, Bayesian information criterion; N/A, not applicable.

TABLE E2. Results of sensitivity analyses for 2-class latent class analysis

	Sensitivity analyses exploring race categorization		
	Class 1 “resolving”	Class 2 “persistently active”	OR (95% CI)*
Race modeled as any black vs any white (including Hispanic and mixed)			
No. in each subgroup	n = 629	n = 3628	
Female sex	45	55	1.51 (1.25-1.84)
Income <\$50,000/y	58	78	1.52 (1.22-1.89)
History of atopy	74	75	1.19 (0.95-1.48)
Any black	35	65	2.83 (2.27-3.53)
Age at eczema onset (y), mean	2.9	2.0	0.90 (0.87-0.92)
Race modeled as black only vs white only			
No. in each subgroup	n = 573	n = 3268	
Female sex	44	55	1.53 (1.25-1.88)
Income <\$50,000/y	56	78	1.44 (1.14-1.83)
History of atopy	76	76	1.11 (0.88-1.41)
Black only	34	67	3.23 (2.54-4.10)
Age at eczema onset (y), mean	2.9	2.0	0.90 (0.87-0.93)
Sensitivity analyses exploring missing and limited variables			
Modeled without income variable (because only available at enrollment, not adjusted for family size, and 26% had preferred not to answer)			
No. in each subgroup	n = 1015	n = 5215	
Female sex	45	55	1.47 (1.25-1.71)
History of atopy	40	70	1.26 (1.05-1.51)
Nonwhite race	74	75	3.50 (2.99-4.09)
Age at eczema onset (y), mean	3.1	2.1	0.90 (0.88-0.92)
Including only those not lost to follow-up (ie, survey within the last 18 mo)			
No. in each subgroup	n = 562	n = 2413	
Female sex	44	55	1.55 (1.26-1.90)
Income <\$50,000/y	55	76	1.75 (1.39-2.21)
History of atopy	45	71	1.31 (1.04-1.65)
Nonwhite race	72	76	2.27 (1.8-2.85)
Age at eczema onset (y), mean	2.8	2.0	0.90 (0.87-0.93)
Including only those with follow-up over 5 y			
No. in each subgroup	n = 522	n = 2130	
Female sex	43	55	1.62 (1.32-2.01)
Income <\$50,000/y	49	70	1.79 (1.42-2.26)
History of atopy	41	67	1.41 (1.12-1.78)
Nonwhite race	71	76	2.29 (1.82-2.89)
Age at eczema onset (y), mean	2.7	1.9	0.91 (0.88-0.94)

Values are percentages unless otherwise indicated.

*Odds of membership in the “persistently active” class from a 2-class model that included age at survey and age at enrollment as predictors of outcome and all of the listed patient characteristics as predictors of class.