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Younger pubertal age is associated with allergy and other atopic conditions in girls

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Abstract

Background—Early menarche is linked to higher incidence of adult asthma, suggesting that earlier puberty may influence type 2 immune response characteristics of allergic diseases. We examined the hypothesis that timing of breast and pubic hair development, which precede menarche, is associated with increased childhood atopic conditions.

Methods—Girls were enrolled at 6–8 yr of age (2004–2007) in the Breast Cancer and the Environment Research Program Puberty Study and were followed through 2011. Pubertal stages were assessed and atopic conditions were queried annually. Associations of age at pubertal stage 2 for breast or pubic hair development with atopic conditions were assessed using prevalence ratios (PR) or odds ratios (OR) and 95% confidence intervals (CI) from log-binomial regression and generalized estimating equation models, controlling for body mass index and other covariates. A total of 1055 girls with medical and pubertal stage data were included.

Results—Asthma (ever vs. never) was associated with younger pubarche (10 vs. >10 yr, PR = 1.15, CI: 1.04–1.28 adjusted for race/ethnicity and site; PR = 1.13, CI: 1.01–1.25 further adjusted for BMI), but not thelarche. In longitudinal models, risk of developing allergies increased with younger age at pubarche (adjusted OR = 1.60, CI: 1.10–2.34; 10 vs. >10 yr). Risks were highest

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Supporting Information

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among black girls with earlier pubarche (n = 248/326); for allergies, their fully adjusted OR was 2.35, CI: 1.06–5.19 for pubarche 10 vs. >10 yr.

Conclusions—Atopic conditions during childhood are associated with younger age at pubarche, independent of obesity, and these relationships may vary by racial/ethnic groups.

Keywords

allergies; asthma; breast development; early puberty; girls; pubic hair development

Early pubertal onset, characterized by development of secondary sexual characteristics and menarche, has been linked with a number of adverse health outcomes including increased breast cancer risk (1). Reasons for the secular trend toward earlier age at pubertal onset (2, 3) are largely unknown, although obesity is consistently associated with early menses (2, 3) and younger puberty stage 2 (any development) (4). Black girls, who are more likely to be obese than white girls (5), also enter puberty earlier (4, 6).

To better understand the influence of sex hormones on immune function, research has examined relationships between atopic conditions, characterized by immune alterations, and pubertal development (7, 8). Associations between early menarche and adult asthma (7, 9, 10) suggest that alterations in innate and adaptive immunity, including dysregulated type 2 immune responses, may be related to pubertal onset (11). Atopic asthma and allergic diseases typically appear early in life (8) are more prevalent among black and obese children and are influenced by sex hormones, as prevalence of asthma is higher in boys than girls during childhood, but reverses in adolescence (12).

Rates of childhood allergies, atopic dermatitis, and asthma have risen over the past 25 yr (13, 14). These temporal trends in asthma incidence have coincided with similarly dramatic secular changes in obesity and age at pubertal onset, with a trend toward earlier ages of breast and pubic hair development in the United States (3, 15).

In this study, we hypothesized that atopic conditions during childhood are associated with earlier pubertal onset and that relationships may vary by race/ethnicity. We examined associations of childhood asthma and other atopic diseases with breast or pubic hair development in a prospective multi-ethnic cohort study of young girls.

Methods

The Breast Cancer and Environment Research Program (BCERP) Puberty Study is a longitudinal study of girls enrolled at 6–8 yr of age who are being followed through puberty. Girls were enrolled at three sites from 2004 to 2007: Icahn School of Medicine at Mount Sinai (New York City), Cincinnati Children's Hospital (Cincinnati), and Kaiser Permanente Northern California (KPNC). Study protocols were approved by site institutional review boards (IRBs). A parent or guardian provided informed consent. Annual questionnaires collected demographic and medical information. Baseline and six subsequent years of follow-up data were used to assess prevalent and incident asthma, atopic dermatitis, and allergies. Study protocols for assessment of pubertal stages and anthropometry have been

described (4). We calculated age- (in months) and sex-specific body mass index percentiles (BMI percentile) based on CDC growth charts (CDC, 2000).

Definitions

We included 1055 girls who had data on atopic conditions and pubertal stages. Asthma was defined as ever/never diagnosis at baseline or at any follow-up visit, if it were diagnosed within the past year. Atopic dermatitis was defined as ever/never diagnosis and/or medication use at baseline or during follow-up. Allergies were defined (ever or never) at each visit from questions regarding allergy medications, rhinitis, or other allergy diagnosis. Allergy was coded as ever at a visit if reported at the current or any prior visit. We also created a variable 'any condition' that combined asthma, atopic dermatitis, and/or allergies together, because these conditions reflect an underlying propensity to become sensitized to environmental allergens and are characterized by dysregulated type 2 immune responses, even for non-allergic disease subtypes (8, 16). Pubertal age was defined as the midpoint between ages at the last stage 1 visit and the stage 2 visit for breast (B2: N = 871) or pubic hair (PH2: N = 870). If girls were stage B2 or PH2 at enrollment, age at stage 2 (n = 163 B2, 131 PH2) was assigned as 6 months earlier, hence the younger age category. Girls who were stage 1 at the last visit when seen were included in the older age category (n = 21 B2, 53 PH2). For statistical analyses, we first dichotomized ages at B2 and PH2 at the median for this study population (9.4 yr for B2 and 9.9 yr for PH2). A sensitivity analysis found the cutpoint for age at PH2 to be optimal when dichotomized at 10 yr, while age at B2 remained unchanged. Prevalence of atopic conditions is known to vary by race/ethnicity, being more common among blacks (17). Therefore, we conducted joint effects analyses to simultaneously examine race/ethnicity and asthma using a joint categorical variable (race/ethnicity $\times$ asthma status) with indicator variables for each subgroup (never asthma and black race as referents because there were black participants at all three sites). This approach allowed comparison of race/ethnicity, atopic conditions, or pubertal age in a single model. Joint effects analyses excluded Asians because of small numbers. Similar models were run for 'any condition'. Joint effect analyses were run for the GEE model with the joint categorical variable race/ethnicity $\times$ dichotomous age at B2 or PH2 (older age and black as referent). Secondhand tobacco smoke exposure was obtained from baseline questionnaires about smokers in and around the child's home, categorized as no exposure or exposure to at least one smoker (none vs. 1). Steroid use was obtained from yearly questions about use of oral or inhaled steroids for asthma; it was defined as ever used before the B2 or PH2 visit. We used BMI percentile at the final pubertal stage 1 visit preceding the stage 2 visit, to have a fairly consistent timeframe between body size measure and pubertal event.

Statistical methods

Analyses were conducted using SAS version 9.2 (Cary, NC, USA). Associations of covariates with allergic conditions were examined with the chi-square test (Table 1). Because the majority of girls reported asthma before puberty, we used log-linked binomial regression to evaluate associations of asthma or 'any atopic condition' with pubertal onset as the outcome; Prevalence ratios and 95% confidence intervals (PR and CI) were calculated for risk of younger age at puberty (vs. older age). In contrast to asthma, allergy prevalence

increased substantially throughout 7 yr of observation, mostly after puberty. Therefore, we analyzed risk for allergies as the outcome associated with puberty using longitudinal generalized estimating equation (GEE) models having compound symmetry correlation matrix (PROC GENMOD in SAS). This model can account for longitudinal change in reported allergies, possible non-independence in the data, and multiple varying data points for each girl (1–7 in our data). We reran models with smaller subsets that excluded girls whose asthma was reported after puberty or whose allergies were reported before puberty. Risk estimates and CIs were similar or identical to those for all conditions, which we present, as these estimates do not indicate direction or causality and because the assignments of atopy and pubertal ages are imprecise. Covariates based on known relationships with atopic conditions and pubertal development were race, caregiver education, enrollment site, BMI percentile, and secondhand smoke exposure. We tested whether oral or inhaled steroids for asthma was a confounder, if reported before B2 ($n = 34$) or PH2 ($n = 36$). Backward elimination was used to remove covariates that did not improve precision or alter the beta estimate by 10%. We examined the Breslow–Day statistic to assess homogeneity of ORs by secondhand smoke exposure. Final models included enrollment site, race/ethnicity, and BMI percentile. Because body size is a potential mediator between allergic asthma and earlier puberty, we also examined adjusted models with and without BMI percentile.

Results

The BCERP study enrolled girls at 6–8 yr of age with similar proportions of blacks, Hispanics, whites, and few Asians (Table 1). Approximately one-third of girls were overweight or obese (age- and sex-specific BMI ≥ 85 th percentile). Characteristics of girls in relation to atopic conditions are shown in Table 1. Asthma was reported by 210 girls at any time during the study, with most reported at baseline ($n = 185$, 88%) and few (< 11) after puberty. Puberty stage 2 was observed mainly after baseline (e.g., B2: $n = 892/1055$, 85%). Atopic dermatitis was reported by 38 girls, few after B2 (29%) or PH2 (32%; not shown). Allergies were reported by 166 girls, most during follow-up ($n = 127$) and after puberty (Fig. 1). Prevalence of each atopic condition was lowest among whites and did not differ by caregiver education. Atopic conditions were more common among overweight and obese girls and among girls with earlier age at B2 or PH2.

Age at B2 (≤ 9.4 yr vs. older) was not associated with asthma or any conditions in adjusted models (Table 2 and Table S1). White girls were less likely to have had any diagnosis of asthma or ‘any condition’ regardless of age at B2 or PH2 (Table 2 and Table S1).

Asthma or any atopic condition (ever vs. never) was associated with 14% increased risk for younger age at PH2 (≤ 10 yr), and estimates were only minimally attenuated after controlling for confounders including BMI percentile (Table 2 and Table S1). Effects were stronger among black girls, where those with asthma or any atopic condition had increased risk for younger age at PH2 compared to black girls with no condition. Hispanic girls with asthma were also at higher risk for earlier PH2 (≤ 10 yr) compared to those with no asthma (see note to Table 2).

At almost every year of age, the period prevalence of B2 and PH2 was higher among girls who had been diagnosed with allergies at that age or earlier than in girls the same age who had not been diagnosed (Fig. 1). Associations of age at B2 with allergies were null (Table 3). Increased risk for allergies with younger age at PH2 was little affected by adjustment for BMI percentile, and risk was more than doubled for black girls with younger age at PH2 compared to later age (Table 3). Hispanic and white girls had similar risk for allergy that did not differ by pubertal age. Secondhand smoke exposure did not confound the association between pubertal age and asthma or allergies, possibly because exposures were similar in girls with and without allergies (28%, 27%, respectively) and in girls with and without asthma (33%, 25%).

Discussion

In this longitudinal, multiracial/ethnic study of girls, asthma and any atopic conditions were associated with increased risk of younger age at PH2, but not B2. Associations were independent of BMI and were strongest for black girls who had earlier PH2 (approximately twofold increased risk for allergy compared with black girls having later PH2). No associations were observed among white girls. Hispanic girls with asthma had 36% increased risk of earlier pubarche compared to those without asthma, although risk of allergies was not significantly raised among girls with earlier PH2 compared to later PH2 (age > 10 yr).

We hypothesized that pubertal onset might be linked to childhood atopic conditions characterized by dysregulated type 2 immunity. Earlier studies show associations between early menarche and increased postmenarcheal asthma (9, 10, 18), which may be partly due to the role of female sex hormones in up-regulating pulmonary inflammation, histamine release, and Th2 cytokines (7). A British birth cohort found associations between early asthma at age 11 yr and early menarche (10). To our knowledge, ours is the first study to prospectively examine breast and pubic hair development, which typically occurs 2–3 yr before menarche, in relation to atopic conditions, and to examine these associations by race/ethnicity, accounting for body size.

Rising rates of childhood obesity have paralleled increasing rates of atopic conditions and earlier puberty, with obesity linked to both earlier pubertal development and allergic asthma (10), making it a potential confounder or mediator in our study. This issue may be particularly important among black girls, who have earlier pubertal onset and higher rates of asthma and obesity compared to whites (4–6). Adjustments for body size attenuated relationships with B2 in our analyses, but minimally affected the positive risk for younger PH2 with atopic conditions, suggesting that obesity does not mediate or confound the latter association. BMI, however, may confound associations with B2 because thelarche is triggered by rising estrogen levels, which are synthesized in peripheral adipose tissue; estrogen is less important for PH2, which is initiated by adrenal androgens (19, 20). Our findings were similar to the British cohort study, which found associations between early menarche and asthma to be minimally affected by adjustments for BMI (10).

Our observation that atopic conditions were associated with younger pubic hair development independent of obesity may indicate potential mechanisms linking asthma to early puberty, such as the insulin/IGF-1 pathway, which plays a critical role in the pathogenesis of asthma (21), and has been proposed to trigger the commencement of adrenarche, which precedes pubarche (22). This is also consistent with stronger associations we observed among black and Hispanic girls, who are more likely to have higher androgen levels (23).

Earlier pubertal onset in black compared with Hispanic and white girls has recently been shown in our cohort (4), and earlier age at menarche among black girls is well recognized (5, 6). Black children also experience 60% higher rates of asthma than white children (14). Evolutionary responses to endemic parasitic worm (helminths) exposure in sub-Saharan Africa have shifted immune responses toward a type 2 bias (24). Studies in West Africa and Asia show heritability for this immune phenotype (25); thus, blacks with upregulated T-helper type (Th2) immunity are more likely to develop allergies and asthma (26). Based on this, it is intriguing to speculate that racial disparities in pubertal onset may arise partly from genetic differences favoring a type 2 immune phenotype. Predisposition toward atopic conditions may be further exacerbated by racial variations in early pubertal onset, leading to hormonal upregulation of Th2 responses. In future, it will be important to examine the possible mutual influence of pubertal onset and immune function, including the role of other immune factors associated with allergy and Th2 dysregulation. Considerations include the counterbalancing effects of cytokines produced by Th1 and regulatory T cells, and the effects of allergy-driven inflammatory cytokines such as those within the Th17 pathways (11, 27).

Strengths of our study include its prospective design and relatively large study size with representation of different racial/ethnic groups and standardized assessments of body size and pubertal stages. A limitation of the study may be that allergic conditions were undiagnosed or underreported, which may have attenuated findings. Atopic dermatitis in particular was low (4%) compared with US data (11% among 10–17 yr olds) (13). In addition, there was very little incident asthma, and we did not have information on whether asthma cases were non-atopic, although the immunopathology with atopic and non-atopic asthma show similarities (11, 28), and non-atopic asthma tends to occur later in life, while asthma in our study was mostly diagnosed during childhood (28, 29). We could not adjust for parental allergy, which might be a confounder in relation to puberty, although both allergic and non-allergic forms of atopic diseases are associated with family history of allergy (16, 30). Risk estimates we provide indicate only association, not temporality, and sensitivity analyses suggest little influence of estimates by asynchronous outcome and exposure events.

We observed associations of younger age at puberty with atopic conditions during childhood that varied by race/ethnicity. If atopic diseases during childhood are confirmed to be associated with younger pubertal onset, important future research questions would be whether these conditions should be monitored closely during the pubertal transition and whether optimal control of these conditions will alter the pubertal trajectory. Few families of children with asthma (39%) report receiving an asthma management plan from their health care provider (14), and racial disparities currently exist in asthma control, with black

children having ~250% more emergency department visits and a ~500% higher death rate from asthma compared to white children (14). Many opportunities exist for interventions to improve asthma control.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.

Period prevalence of stage B2 and PH2 by age group among girls with and without allergies. Adjusted OR for PH2 association with allergies, 1.60 (CI 1.10–2.34); for B2, the adjusted ORs were null (see Table 3, GEE models). For girls with allergies, age is that at first diagnosis of allergy. Girls without allergies reported no diagnosis or medicine use at that age or prior. Girls with allergies reported diagnosis or medicine at that age or prior. Shown are all girls with allergies. Of these, most reported allergies were in the same timeframe as puberty or after puberty, B2 (108/166; 65%) and Ph2 (91/166; 55%). BCERP, 2004–2012.

Table 1
Prevalence of reported atopic conditions from 2004 to 2011 by baseline characteristics among 1055 BCERP girls

	Study site				Race/ethnicity				Caregiver education [†]			BMI percentile [‡]			Breast stage 2 onset			Pubic hair stage 2 onset [§]		
	All	MSSM	CIN	KPNC	Black	Hisp	Asian	White	HS	>HS	<85th	85th–95th	95th	9.4 yr	>9.4 yr	10 yr	>10yr			
N	1055	333	321	401	326	308	54	367	291	736	684	179	192	537	518	546	508			
Any conditional [¶]																				
Asthma, atopic dermatitis, & allergies																				
N	335	125	99	111*	135	97	24	79*	100	224	191	69	75*	186	149*	201	134*			
%	32	38	31	28	41	31	44	22	34	30	28	39	39	35	29	37	26			
No conditions																				
N	720	208	222	290	191	211	30	288	191	512	493	110	117	351	369	345	374			
%	68	62	69	72	59	69	56	78	66	70	72	61	61	65	71	63	74			
Asthma**																				
N	210	85	48	77*	91	66	13	40*	65	139	113	44	53*	117	93	131	79*			
%	20	26	15	19	28	21	24	11	22	19	17	25	28	22	18	24	16			
Allergies***																				
N	166	59	69	38*	66	43	9	48*	46	113	98	29	39*	93	73	102	64*			
%	16	18	21	9	20	14	17	13	16	15	14	16	20	17	14	19	13			

* Chi-Square p-value < 0.05 for condition vs. no condition within the characteristic category.

[†] Twenty eight girls missing parent education information.

[‡] BMI percentile at last stage B1 visit; PH1 BMI percentile was very similar to B1 BMI percentile.

[§] One girl missing PH2 staging.

[¶] N's represent prevalent conditions. They include total incident diagnoses (reported after enrollment) of asthma (N = 25), allergies (N = 127), asthma, atopic dermatitis, allergies (N = 129).

** There were 845 girls who never reported asthma; 889 never reported allergies.

Table 2

Associations of asthma (ever/never) with pubertal onset among 1055 BCERP girls, 2004–2011

Model 1: Log-binomial regression model adjusted for race/ethnicity, study site and BMI %ile									
Outcome	Asthma status	All girls (N)	Younger puberty (N)	Age at puberty (younger/older onset)					
				Unadjusted PR (95% CI)	Adjusted, without BMI %* PR (95% CI)	Adjusted, including BMI% [†] PR (95% CI)			
All girls	ALL	1055	537						
B2 Age (9.4 yr)	No asthma	845	420	1.0	1.0	1.0			
(ref >9.4 yr)	Asthma	210	117	1.12 (0.98, 1.29)	1.08 (0.96, 1.23)	1.03 (0.93, 1.14)			
Outcome [¶]		1054	546						
PH2 Age (10yr)	No asthma	844	415	1.0	1.0	1.0			
(ref >10 yr)	Asthma	210	131	1.27 (1.12, 1.44)	1.15 (1.04, 1.28)	1.13 (1.01, 1.25)			

Model 2: Log-binomial regression model joint race/ethnicity-asthma status variable									
Outcome	Joint variable	Race/ethnicity	ALL	Younger puberty (N)		Unadjusted PR (95% CI)	Adjusted [‡] PR (95% CI)	Adjusted [§] PR (95% CI)	
				1001	516				
B2 Age 9.4 yr(ref >9.4 yr)	Categories (referent Black, no asthma)	Black	No asthma	235	146	1.0	1.0	1.0	
		Black	Asthma	91	62	1.10 (0.92, 1.30)	1.10 (0.95, 1.28)	1.05 (0.92, 1.18)	
		Hispanic	No asthma	242	123	0.82 (0.70, 0.96)	0.92 (0.78, 1.08)	0.88 (0.76, 1.03)	
		Hispanic	Asthma	66	38	0.93 (0.74, 1.17)	1.07 (0.85, 1.36)	0.97 (0.77, 1.21)	
		White	No asthma	327	132	0.65 (0.55, 0.77)	0.65 (0.55, 0.77)	0.73 (0.62, 0.86)	
		White	Asthma	40	15	0.60 (0.40, 0.91)	0.64 (0.43, 0.96)	0.65 (0.44, 0.95)	
		Interaction p value ^{**}				0.50	0.41	0.64	

Outcome [¶]									
Outcome [¶]	Joint variable	Race/ethnicity	ALL						
				1000	537				
PH2 Age 10yr (ref >10 yr)	Categories (referent Black, no asthma)	Black	No asthma	235	172	1.0	1.0	1.0	
		Black	Asthma	91	76	1.14 (1.01, 1.29)	1.14 (1.02, 1.29)	1.13 (1.00, 1.27)	
		Hispanic	No asthma	242	113	0.64 (0.55, 0.75)	0.64 (0.55, 0.75)	0.63 (0.54, 0.73)	
		Hispanic	Asthma	66	42	0.87 (0.71, 1.06)	0.88(0.72, 1.08)	0.81 (0.67, 0.99)	
		White	No asthma	326	123	0.52 (0.44, 0.60)	0.53 (0.45, 0.62)	0.55 (0.47, 0.66)	
		White	Asthma	40	11	0.38 (0.23, 0.63)	0.39 (0.23, 0.64)	0.39 (0.24, 0.65)	

Model 2: Log-binomial regression model joint race/ethnicity-asthma status variable				
Outcome	Joint variable	Race/ethnicity	Younger puberty (N)	
			ALL	N
			516	1001
			Unadjusted PR (95% CI)	Adjusted [‡] PR (95% CI)
			<0.01	<0.01
			Adjusted [§] PR (95% CI)	<0.01

Bold PRs were significant, as CIs excluded the null.

Model with joint race/ethnicity-asthma status variable does not include 54 Asian girls.

Models for subset of girls with asthma reported before puberty (n = 201 B2, N = 202 PH2) were almost identical to asthma models shown above.

Model 2 was rerun with reference group Hispanic and no asthma; for Hispanic with Asthma and PH2-age, the unadjusted PR = 1.36 (95% CI: 1.09, 1.71); study site adjusted PR = 1.37 (95% CI: 1.10, 1.72); study site and BMI percentile adjusted PR = 1.29 (95% CI: 1.03, 1.61).

* Adjusted for race/ethnicity and study site.

[†] Adjusted for race/ethnicity, study site and BMI percentile.

[‡] Adjusted for study site.

[§] Adjusted for study site and BMI percentile.

[¶] One girl missing PH2 staging.

** Interaction term for the variable race/ethnicity*asthma status, Type III Fixed effect p value.

Table 3

Longitudinal analyses of associations between period prevalence of allergies and age at pubertal onset using GEE models among 1055 BCERP girls, 2004–2011

Allergy risk (yes vs. none reported)								
					Unadjusted OR (95% CI)	Adjusted, without BMI%* OR (95% CI)	Adjusted, including BMI%† OR (95% CI)	
Model 1: adjusted for race/ethnicity, study site and BMI%-ile								
	B2 Age, yr	All girls (N)	Allergies (N)					
All girls	1055	166						
	>9.4	518	73	1.0	1.0	1.0	1.0	
	9.4	537	93	1.31 (0.93, 1.84)	1.04 (0.73, 1.47)		0.96 (0.67, 1.37)	
	PH2 Age, yr¶	1054	166					
	>10	508	64	1.0	1.0	1.0	1.0	
	10	546	102	1.93 (1.36, 2.74)	1.69 (1.17, 2.44)		1.60 (1.10, 2.34)	
Model 2: joint race/ethnicity-stage 2 variable								
Joint variable	Race/Ethnicity	B2 Age, yr	N		Allergies (N)	Unadjusted OR (95% CI)	Adjusted‡ OR (95% CI)	Adjusted§ OR (95% CI)
			1001	157				
Categories (referent Black, B2 age >9.4 yr)	Black	>9.4	118	21	1.0	1.0	1.0	1.0
	Black	9.4	208	45	1.38 (0.77, 2.49)	1.30 (0.73, 2.34)	1.17 (0.65, 2.11)	
	Hispanic	>9.4	147	22	0.78 (0.40, 1.52)	0.86 (0.44, 1.70)	0.80 (0.40, 1.60)	
	Hispanic	9.4	161	21	0.66 (0.34, 1.29)	0.66 (0.33, 1.31)	0.59 (0.29, 1.19)	
	White	>9.4	220	24	0.55 (0.29, 1.06)	0.64 (0.32, 1.27)	0.65 (0.32, 1.30)	
	White	9.4	147	24	0.83 (0.43, 1.59)	0.76 (0.37, 1.55)	0.72 (0.35, 1.48)	
Interaction p value***					0.43	0.56	0.66	
Joint variable								
	Race/Ethnicity	PH2 Age, yr	1000	157				
Categories (referent Black, Ph age >10 yr)¶	Black	>10	78	8	1.0	1.0	1.0	
	Black	10	248	58	2.48 (1.12, 5.47)	2.59 (1.18, 5.69)	2.35 (1.06, 5.19)	
	Hispanic	>10	153	21	1.04 (0.43, 2.49)	1.25 (0.52, 3.00)	1.15 (0.47, 2.78)	
	Hispanic	10	155	22	1.38 (0.58, 3.28)	1.52 (0.64, 3.64)	1.35 (0.55, 3.31)	
	White	>10	232	28	0.90 (0.39, 2.09)	1.01 (0.43, 2.39)	1.02 (0.43, 2.41)	
	White	10	134	20	1.49 (0.62, 3.57)	1.61 (0.66, 3.93)	1.58 (0.65, 3.85)	
Interaction p value***					0.67	0.49	0.57	

Bold PRs were significant, as CIs excluded the null.

Model with race/ethnicity-stage 2 joint variable does not include 54 Asian girls.

Models were similar for the subset excluding observations in which allergies were reported before the puberty stage 2 visit, with some loss of precision for the fully adjusted estimates for PH2, likely due to shifting 75 girls (45%) from exposed to unexposed.

There for all observations (n=91 rather than 166 allergies, 22 >10 yr PH2-age, 69 10 yr PH2 age), the model not adjusted for BMI% showed OR 1.69 (0.76, 3.75), and fully adjusted OR 1.65 (0.75, 3.67).

Model 2 was rerun with reference group Hispanic and No Allergies; for Hispanic with Allergies and PH2-age, the unadjusted OR = 1.33 (95% CI: 0.69, 2.56); site adjusted OR = 1.22 (95% CI: 0.64, 2.35); site and BMI percentile adjusted OR = 1.18 (95% CI: 0.60, 2.30).

* Adjusted for race/ethnicity and study site

† Adjusted for race/ethnicity, study site and BMI percentile.

‡ Adjusted for study site.

§ Adjusted for study site and BMI percentile.

¶ One girl missing PH2 staging.

** Interaction term for the variable race/ethnicity*B2 or variable race/ethnicity*PH2, Type III p value from GEE model.