

Abbreviations used

AR: Allergic rhinitis

CRS: Chronic rhinosinusitis

when AR was present with sinusitis this predictive value was further increased.⁴ CRS and asthma frequently coexist: approximately 20% to 33% of patients with CRS have concomitant asthma, a prevalence 4-fold greater than that of the general population.^{5,6} Nearly 80% of patients with severe asthma will have

concomitant CRS.⁷ Moreover, treatment of AR and CRS has been shown to improve asthma symptoms, suggesting a common pathway.^{8,9} The concomitant expression of these conditions is believed to be driven by type 2 mediated inflammation resulting in elevated IgE, eosinophilic inflammation, and airway remodeling.¹⁰

The goal of this study was to identify early life risk factors for chronic sinusitis. Our aim was to use longitudinal data from the Tucson Children's Respiratory Study (TCRS) to investigate age of onset of symptoms, risk factors and the natural history of different forms of sinus disease from childhood to the fourth decade of life.

TABLE I. Early life risk factors for childhood sinusitis

Characteristic	Category	MD sinusitis at age 6 y				
		n	Percent	P value*	OR	95% CI
Sex	All	772	10.8			
	Male	366	10.4			
	Female	406	11.1	.753	1.08	0.68-1.70
Race/ethnicity	NHW	506	10.9			
	HW	172	8.1		0.73	0.39-1.34
	Other	94	14.9	.233	1.44	0.76-2.70
Maternal						
Asthma	No	680	9.6			
	Yes	83	20.5	.002	2.44	1.35-4.40
Smoking	No	657	10.7			
	Yes	115	11.3	.836	1.07	0.57-2.00
Education	≤12 y	186	10.2			
	>12 y	585	10.9	.781	1.08	0.63-1.85
Age	≤26	326	10.7			
	>26	446	10.8	.991	1.00	0.63-1.59
Paternal						
Asthma	No	636	9.6			
	Yes	94	16.0	.059	1.79	0.97-3.30
Smoking	No	551	10.3			
	Yes	211	10.9	.823	1.06	0.64-1.77
Education	≤12 y	177	11.3			
	>12 y	581	10.3	.712	0.90	0.53-1.55
Age	≤26	203	10.3			
	>26	559	10.6	.933	1.02	0.60-1.73
Child at 6 years						
Atopy	No	375	7.7			
	Yes	239	12.6	.048	1.71	0.99-2.93
Alternaria sensitization	No	511	8.6			
	Yes	102	14.7	.057	1.83	0.98-3.43
Bermuda sensitization	No	445	9.0			
	Yes	169	11.2	.397	1.28	0.72-2.28
Eosinophilia	<4%	307	8.8			
	≥4%	113	12.4	.271	1.47	0.74-2.91
Active asthma	No	697	9.8			
	Yes	69	20.3	.007	2.35	1.24-4.46
Active wheeze	No	577	8.7			
	Yes	190	16.8	.002	2.13	1.32-3.44
Ever eczema	No	648	9.6			
	Yes	117	18.0	.007	2.07	1.21-3.55
Ever hay fever	No	492	3.9			
	Yes	278	23.0	<.001	7.44	4.35-12.7
Colds*	MD allergic	24	8.3			
	0	581	8.6		1.04	0.24-4.53
	1-3	132	17.4		2.32	0.51-10.6
	4-9	29	27.6	.001	4.19	0.80-22.1

Boldface values are statistically significant.

HW, Hispanic white; NHW, non-Hispanic white.

*P value from chi-square statistic.

TABLE II. Early life risk factors for adult sinusitis

Characteristic	Category	n	Percent	X-ray-assessed adult sinusitis		
				P value*	OR	95% CI
Sex	All	772	12.2			
	Male	366	10.4		ref	
	Female	406	13.8	.148	1.4	0.9-2.1
Race/ethnicity	NHW	506	13.2		ref	
	HW	172	9.9		0.7	0.4-1.3
	Other	94	10.6	.452	0.8	0.4-1.6
Maternal						
Asthma	No	680	11.8		ref	
	Yes	83	16.9	.182	1.5	0.8-2.8
Smoking	No	657	12.3		ref	
	Yes	115	11.3	.757	0.9	0.5-1.7
Education	≤12 y	186	7.0		ref	
	>12 y	585	13.7	.015	2.1	1.1-3.9
Age	≤26	326	10.4		ref	
	>26	446	13.5	.204	1.3	0.9-2.1
Paternal						
Asthma	No	636	11.5		ref	
	Yes	94	16.0	.213	1.5	0.8-2.7
Smoking	No	551	11.4		ref	
	Yes	211	13.7	.381	1.2	0.8-2.0
Education	≤12 y	177	6.8		ref	
	>12 y	581	13.4	.017	2.1	1.1-4.0
Age	≤26	203	9.9		ref	
	>26	559	12.5	.313	1.3	0.8-2.2
Child at 6 years						
MD Sinusitis	No	689	9.9		ref	
	Yes	83	31.3	<.001	4.2	2.5-7.1
Atopy	No	375	9.3		ref	
	Yes	239	16.7	.006	2.0	1.2-3.2
Alternaria sensitization	No	511	10.8		ref	
	Yes	102	19.6	.013	2.0	1.2-3.6
Bermuda sensitization	No	445	10.8		ref	
	Yes	169	16.0	.079	1.6	0.9-2.6
Eosinophilia	<4%	307	11.4		ref	
	≥4%	113	18.6	.055	1.8	1.0-3.2
Active asthma	No	697	10.9		ref	
	Yes	69	23.2	.003	2.5	1.3-4.5
Active wheeze	No	577	9.9		ref	
	Yes	190	19.5	<.001	2.2	1.4-3.5
Ever eczema	No	648	11.3		ref	
	Yes	117	18.0	.043	1.7	1.0-2.9
Ever hay fever	No	492	8.5		ref	
	MD allergic reaction	278	18.7	<.001	2.5	1.6-3.8
Colds	0	24	16.7		ref	
	1-3	581	8.8		0.5	0.2-1.5
	4-5	132	22.7		1.5	0.5-4.6
	6-9	29	31.0	<.001	2.3	0.6-8.5

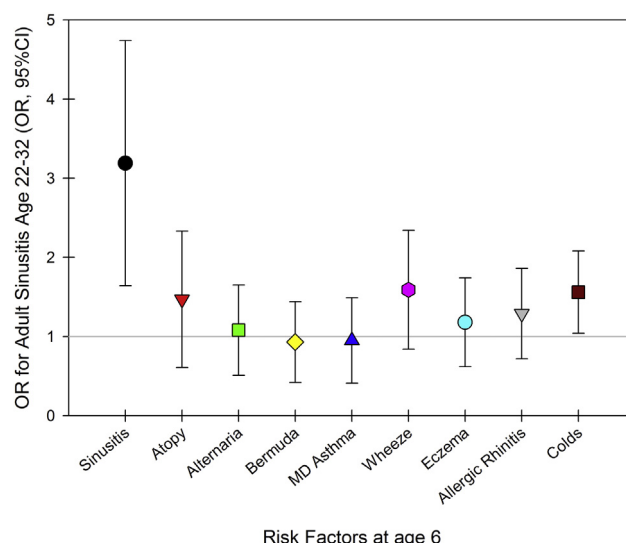
Boldface values are statistically significant.

*P value from chi-square statistic.

METHODS

Study design

Healthy infants were enrolled at birth in the TCRS between 1980 and 1984 (n = 1246).¹¹ At enrollment, parents completed a questionnaire describing their race and ethnicity, history of physician-diagnosed asthma, years of education, current age, and current smoking habits. Participant race and ethnicity was determined from this parental information and categorized as

**FIG 1.** Multivariable analysis of early life risk factors for adult sinusitis. MD Asthma, Physician diagnosed asthma; OR, odds ratio.

“non-Hispanic white” (both parents), “Hispanic white” (1 or both parents), and all other race/ethnic groups combined into “Other” (African American, Asian American, Native American, and other).

Diagnosis of sinusitis and definition of sinusitis phenotypes

The primary caregiver completed a respiratory health questionnaire for the child at age 6 that asked the following questions: Has this child ever had sinus trouble? Was it diagnosed by a doctor? Using this information, children were categorized into 2 groups: (1) “physician diagnosed sinus trouble”; (2) “no sinus trouble” at age 6.

At ages 22, 26, and 32, an affirmative response to “Have you ever had sinus x-rays taken?” was considered indicative of adult sinusitis. Additionally, participants who reported any sinus trouble between ages 22 and 32 and had sinus imaging performed at ages 16 or 18 were also considered to have adult sinusitis in adult life. All others were combined into a “no adult sinus trouble” group.

Participants were grouped into 4 phenotypes based on the natural history of disease: (1) no sinusitis: those without a history of childhood or adult sinusitis; (2) transient childhood sinusitis: those with physician-diagnosed sinusitis by age 6 but not as adults; (3) late-onset adult sinusitis: those without childhood sinusitis but with physician-diagnosed sinusitis requiring radiologic studies from ages 16 to 32; and (4) early onset chronic sinusitis: those with sinusitis both in childhood and as adults, as previously defined.

Aeroallergen skin testing

Skin prick tests were performed at age 6 and included Bermuda grass, careless weed, olive, mesquite, mulberry, house dust mix, and *Alternaria alternata* (Hollister-Stier Laboratories, Everett, Washington, DC) as previously reported.¹² Wheal sizes of 3 mm or greater, after subtracting the negative control, were considered positive. A subject was considered atopic if he/she had a positive skin test reaction to at least 1 aeroallergen.

IgE

A blood sample was collected when the child was 6 years old and a complete blood count was performed. Eosinophilia was defined as >4%. Total serum IgE was measured by Phadebas radioimmunosorbent test (PRIST) as previously reported.¹³

TABLE III. Total serum IgE levels at 9 months and age 6 for the sinusitis phenotypes

Sinusitis phenotypes	Total serum IgE IU/mL							
	9 mo				6 y			
	n	GM	95% CI	P value*	n	GM	95% CI	P value*
No	503	3.9	3.5-4.4	ref	349	34.4	28.6-41.3	ref
Transient childhood	46	3.0	2.1-4.4	.2	28	39.2	19.2-79.7	.7
Late-onset adult	51	3.9	2.7-5.6	.9	40	39.4	22.0-70.4	.6
Early onset chronic	18	7.5	2.9-19.7	.034	17	74.2	34.9-158	.078

GM, Geometric mean.

Boldface values are statistically significant.

*P value from linear regression of log total serum IgE with sinusitis phenotypes.

Respiratory health

Asthma was defined as a report of a physician diagnosis and reported symptoms (asthma episodes or attacks, and/or wheeze) during the past year. AR was defined as hay fever or runny, stuffy nose that a doctor said was an allergic reaction, and active wheeze was defined as symptoms during the past year. Recurrent cough was defined as 2 or more episodes of cough without a cold that lasted 1 week during the past year as previously reported for participants in this cohort.^{14,15} Additionally, at age 6, the number of colds during the past year was assessed by questionnaire. Adult active smoking was determined from questionnaire responses. A summary measure of the prevalence of each adult symptom (asthma, wheeze, cough) as well as smoking between ages 22 and 32 was defined as any positive report.

Statistical methods

Proportions between sinus phenotypes were compared using contingency tables. Logistic regression was used to adjust the relation between childhood sinusitis and adult sinusitis by covariates. Linear regression was used for the relation between sinusitis phenotypes and IgE. For the survival analysis, asthma was defined as the first age at which physician-diagnosed asthma was reported with symptoms during the past year. The oldest age that a questionnaire was completed without a diagnosis of asthma was used as the censored age. Cox regression was used to estimate hazard ratios and Kaplan-Meier method was used to plot the survival curves for the relation between sinusitis phenotypes and asthma. Stata 14 (StataCorp, College Station, Tex) and SPSS 24 (SPSS, Inc, Chicago, Ill) were used for analysis. Total serum IgE was log₁₀ transformed, and the geometric mean was reported.

This research was approved by the Institutional Review Board of the University of Arizona and informed consent/assent was obtained from/for all participants.

RESULTS

Of the 1246 participants enrolled at birth, 772 had information for sinusitis at age 6 and in adult life for ages 22 to 32 years. Participants with complete data (n = 772) were more likely to have nonsmoking parents with more years of education and to be non-Hispanic white, compared with those with incomplete data (n = 474; see Table E1 in this article's Online Repository at www.jacionline.org).

Characterization of participants with physician-diagnosed early life sinusitis

At age 6, 10.8% of children had physician-diagnosed sinusitis (83 of 772) (Table I). Similar proportions of males and females had sinusitis at age 6, and the prevalence of sinusitis was similar by race and ethnic group. Children with a history of maternal asthma were more likely to have sinusitis than were those without

such history. There was no difference, however, in the prevalence of early sinusitis by paternal asthma, parental smoking, or years of parental education. Children with atopy, active asthma, wheeze, eczema, AR (hay fever), and reports of 6 or more colds per year were significantly more likely to have sinusitis at age 6 than were those without such conditions (Table I).

Characterization of adult sinusitis

From 22 to 32 years of age, 12.2% of adults (94 of 772) with active sinusitis reported radiological assessment for sinusitis, as requested by their community physicians, in questionnaires obtained between ages 16 and 32 (Table II). The prevalence of adult sinusitis so defined was similar in men (10.4%) and women (13.8%). There was no difference in the prevalence of adult sinusitis by racial ethnic groups and current smoking status.

Early life risk for adult sinusitis

The strongest single independent risk factor for adult sinusitis was physician-diagnosed sinusitis at age 6: there was a 4-fold increased odds for adult sinusitis among participants who were diagnosed with sinusitis by a physician as a child (odds ratio = 4.2; 95% CI: 2.5-7.1; *P* < .0001; n = 772). Early life sinusitis remained significant and was the main independent risk factor for adult sinus disease after adjusting for previously identified risk factors at age 6 including atopy, asthma, wheeze, AR, eczema, and colds (odds ratio = 3.2; 95% CI: 1.6-6.2; *P* = .001; n = 599 in the model) (Fig 1). The only other significant predictor of adult sinusitis was the number of colds in the past year at age 6 with 1.6 times increased odds for adult sinusitis with increasing number of colds (odds ratio = 1.6; 95% CI: 1.1-2.3; *P* = .025) (Fig 1). Approximately one-third of all children diagnosed with sinusitis at age 6 received sinus imaging as adults (26 of 94).

Differences between sinusitis phenotypes

To assess predisposing factors for different sinusitis phenotypes, participants were classified into 4 groups based on the natural history of the disease: no sinusitis (n = 621), transient childhood sinusitis (n = 57), late-onset adult sinusitis (n = 68), and early onset chronic sinusitis (childhood and adult sinusitis, n = 26) (Table III, Fig 2). When compared with participants without sinusitis, those with early onset chronic sinusitis were more likely to have a maternal history of asthma and parents with more years of education (see Table E2 in this article's Online Repository at www.jacionline.org). At age 6, they were more likely to be skin prick test positive to *Alternaria* and to report

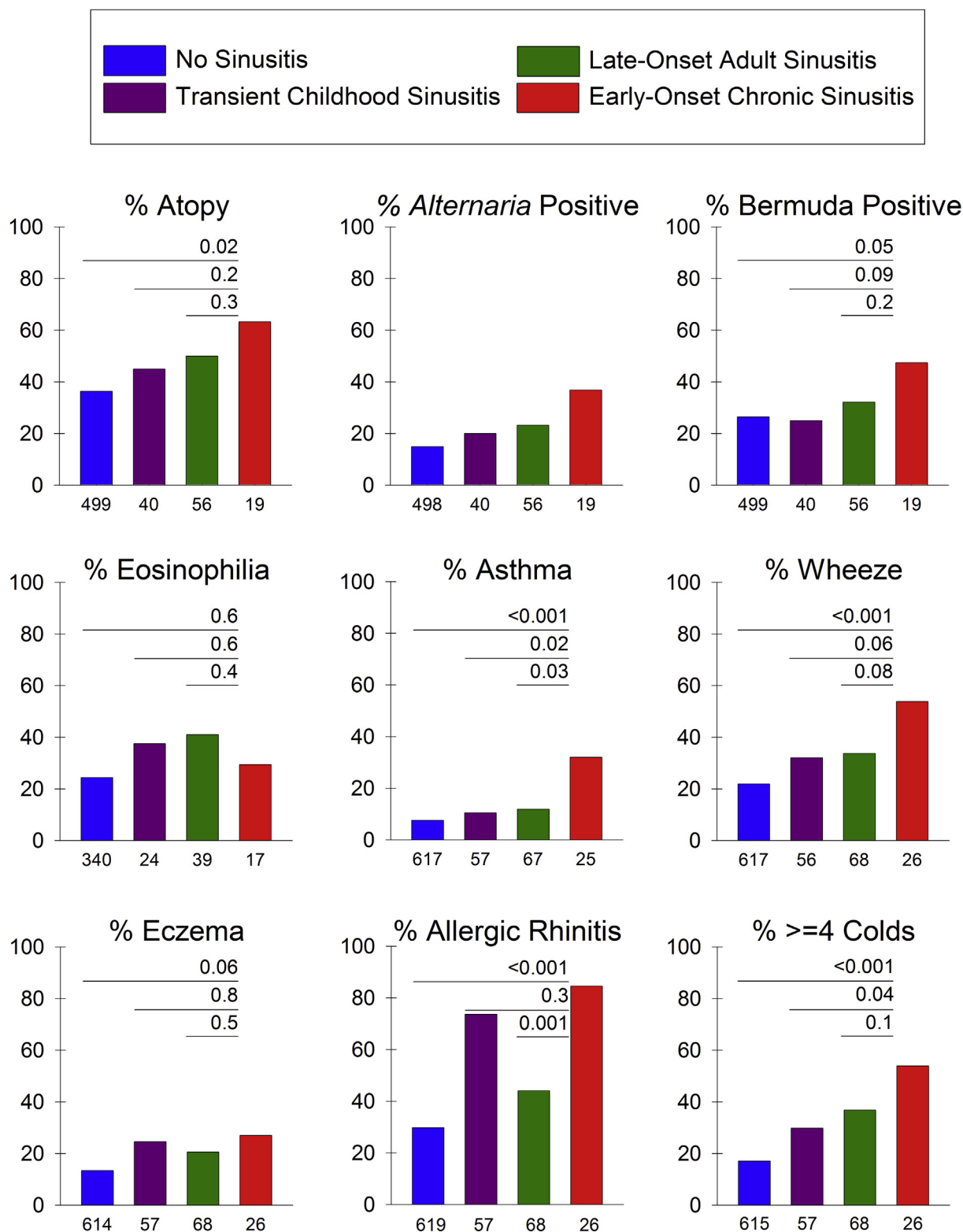


FIG 2. Age 6 characteristics of the sinusitis phenotypes.

eczema, AR, wheeze, asthma, and a higher number of colds. In addition, this group had increased total serum IgE levels (Table III) at 9 months of age. Participants with transient childhood sinusitis were significantly more likely to have eczema and AR than were those without sinusitis (data not shown), whereas no

early life characteristic differed significantly between late-onset adult sinusitis and no sinusitis.

Participants with early onset chronic sinusitis and with no asthma by age 6 were significantly more likely to report active physician-diagnosed asthma after the age of 6 than were those

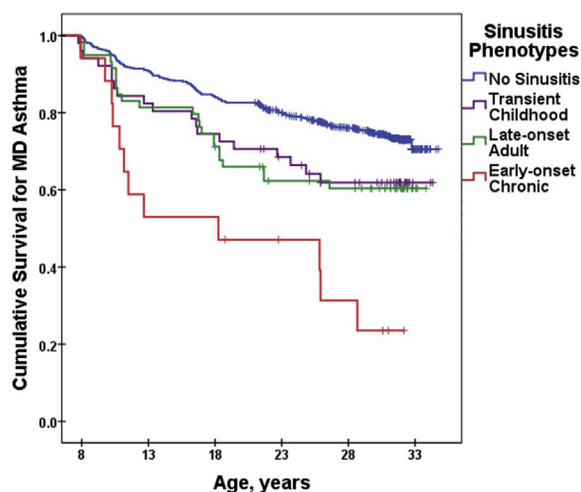


FIG 3. Survival curves for active MD asthma by the sinusitis phenotypes, limited to those without a diagnosis of asthma at age 6. Comparisons: early onset chronic sinusitis versus no sinusitis (hazard ratio [HR] = 4.2; 95% CI: 2.3-7.7; $P < .0001$); early onset chronic sinusitis versus transient childhood sinusitis (HR = 2.6; 95% CI: 1.3-5.4; $P = .009$); and versus late-onset adult sinusitis (HR = 2.5; 95% CI: 1.2-5.0; $P = .010$).

with no sinusitis (hazard ratio = 4.2; 95% CI: 2.3-7.7; $P < .0001$) (Fig 3). They were also more likely to have active asthma than the transient childhood sinusitis group was (hazard ratio = 2.6; 95% CI: 1.3-5.4; $P = .009$) and to the late-onset adult sinusitis group (hazard ratio = 2.5; 95% CI: 1.2-5.0; $P = .010$) (Fig 3).

As adults, those with early onset chronic sinusitis were significantly more likely to have asthma, wheeze, and cough than the no sinusitis group was (Table IV). There was no difference in the proportion of smokers for the sinusitis phenotypes.

DISCUSSION

In a longitudinal cohort of 772 individuals followed from early life up to the age of 32 years, we identified 3 longitudinal patterns of expression of sinusitis. Many children were diagnosed with sinusitis by the age of 6 years (11%), but for most, the condition was transient and did not persist into adult life. The main risk factor for this phenotype was AR and thus, given the subjective nature of the ascertainment, it is quite likely that these children had a severe form of AR that was diagnosed as “sinusitis” by their pediatricians. In a smaller group of participants with early life sinusitis (3% of the population), however, the condition persisted into adult life, as ascertained by the need to have imaging of the sinuses performed. Participants with this phenotype had increased serum IgE levels as early as at 9 months of age, were atopic (as assessed by skin prick test reactivity), and had eczema and/or AR at age 6, were more likely to have maternal asthma, and were markedly more likely to develop subsequent asthma. Finally, in participants with late-onset adult sinusitis (9%), no risk factor for this phenotype could be identified in this group in early life.

Although there have been many studies on risk factors for chronic sinusitis, to our knowledge there have been no previous studies on the natural history of sinus disease from childhood to adult life. Our study provides evidence indicating that a major phenotype for chronic sinusitis has its origins in the first years of life. In this phenotype, which we have called early onset chronic sinusitis, markers of a type 2 immune response can be detected as

early as during the first year of life. Moreover, the phenotype is strongly associated with maternal asthma and with subsequent development of asthma. The data thus suggest that a common pathogenesis may underlie these 3 conditions. There is strong evidence that early allergic sensitization plays a critical role in the development of early asthma,¹⁶ and our study suggests that it may also play a critical role in the development of early onset chronic sinusitis.

Early allergic sensitization appears to interact with susceptibility of the lower airway to rhinovirus infection in determining risk for asthma.¹⁷ Sensitivity to *Alternaria* has been associated with the development of AR¹⁸ and asthma.¹⁹⁻²² Further studies are required to determine whether this significant risk factor in the early onset chronic sinusitis group is related to specific exposure or as a marker of heightened type 2 immune response. Susceptibility to rhinovirus infection (especially to rhinovirus C) is in part determined by genetic variants in the cadherin-related family member 3 (*CDHR3*) gene.^{23,24} We found that subjects with early onset chronic sinusitis, but not those with transient childhood sinusitis, were more likely to have recurrent colds by the age of 6, but no viral studies were available. We have previously shown that adult CRS is associated with the same polymorphisms in *CDHR3* that were found to be associated with susceptibility to rhinovirus.²⁵ It is thus tempting to speculate that *CDHR3* may be a common risk factor for early onset chronic sinusitis and asthma, but there were too few subjects with this phenotype in this study to make an assessment of this association meaningful.

The major limitation of this study is the lack of accompanying medical information used in the diagnosis of sinusitis including endoscopy, specific radiologic findings, and medication usage. Access to medical records concerning sinusitis was not part of the study design and would have been difficult given the range of physicians, health sites, and the span of nearly 40 years in which this data were collected. A second limitation is that subjects may have been misdiagnosed as having sinusitis. The classification of childhood sinusitis was determined by a positive history of physician-diagnosed sinusitis. However, other disorders may mimic and contribute to the symptoms of pediatric sinusitis including adenoid hypertrophy and infection that cannot be excluded without nasal endoscopy. Our estimates of the prevalence of childhood sinusitis (10.8%) are in the range of other pediatric studies examining the rate of sinusitis as a complication of upper respiratory infections in children (6.5%-13%).²⁶⁻²⁸ The classification of adult sinusitis was determined by the need for radiographic studies. Radiographic studies for sinus disease are considered among the gold standards for diagnosis of adult CRS,²⁹⁻³¹ which also requires a diagnosis of rhinosinusitis made by a medical provider. Although there is a potential bias for physicians to order unnecessary studies in those with a previous history of rhinosinusitis, it would be extremely unlikely that physicians and/or patients would recall a medical diagnosis made in childhood and thus influence the diagnosis of adult disease. Finally, participants with adult sinusitis were not evaluated for the presence of nasal polyps. Although chronic rhinosinusitis is heterogeneous, the most common phenotypes for the disease are CRS with nasal polyps and CRS without nasal polyps. The early onset chronic sinusitis phenotype described herein seems to mirror that of CRS with nasal polyps, which has been associated with atopy, AR, and asthma. Moreover, the late onset chronic sinusitis phenotype also seems to mirror that of CRS without nasal polyps, which has often been found to be unrelated to

TABLE IV. Adult characteristics associated with the sinusitis phenotypes

Sinusitis Phenotypes	n	Adults ages 22-32											
		Asthma				Wheeze				Cough			
		Percent	OR	95% CI	P value	Percent	OR	95% CI	P value	Percent	OR	95% CI	P value
No	621	21.5	ref			52.2	ref			25.2	ref		
Transient childhood	57	33.3	1.8	1.0-3.3	.042	64.9	1.7	1.0-3.0	.068	31.6	1.4	0.8-2.5	.294
Late-onset adult	66	34.9	2.0	1.1-3.4	.015	65.2	1.7	1.0-2.9	.046	40.9	2.1	1.2-3.5	.007
Early onset chronic	25	72.0	9.4	3.9-23	<.001	84.0	4.8	1.6-14.2	.004	60.0	4.5	2.0-10	<.001

Boldface values are statistically significant.

markers of T_H2 deviation.³² However, given the lack of more detailed clinical characterization of our participants, we are unable to determine whether there is true overlap between the phenotypes described in this study and those identified in clinical studies of CRS.

In summary, our data suggest at least 2 presentations of sinusitis in adults: (1) early onset and associated with a type 2 immune response, susceptibility to viral infection and asthma; and (2) late onset that does not have early life correlates. Identification of molecular endotypes responsible for the pathophysiology of these 2 subtypes may lead to future therapies that can precisely target and potentially prevent the progression of the disease into adult sinusitis.

Clinical implications: Chronic sinusitis is frequently diagnosed in adults. This investigation of the natural history of sinusitis suggests an early onset chronic sinusitis phenotype associated with allergic sensitization, viral colds, asthma, and risk factors in childhood.

REFERENCES

- DeConde AS, Smith TL. Classification of chronic rhinosinusitis: working toward personalized diagnosis. *Otolaryngol Clin North Am* 2017;50:1-12.
- Caulley L, Thavorn K, Rudmik L, Cameron C, Kilty SJ. Direct costs of adult chronic rhinosinusitis by using 4 methods of estimation: results of the US medical expenditure panel survey. *J Allergy Clin Immunol* 2015;136:1517-22.
- Smith TL, Litvack JR, Hwang PH, Loehrl TA, Mace JC, Fong KJ, et al. Determinants of outcomes of sinus surgery: a multi-institutional prospective cohort study. *Otolaryngol Head Neck Surg* 2010;142:55-63.
- Guerra S, Sherrill DL, Martinez FD, Barbee RA. Rhinitis as an independent risk factor for adult-onset asthma. *J Allergy Clin Immunol* 2002;109:419-25.
- Joe SA, Thakkar K. Chronic rhinosinusitis and asthma. *Otolaryngol Clin North Am* 2008;41:297-309, vi.
- Pearlman AN, Chandra RK, Chang D, Conley DB, Tripathi-Peters A, Grammer LC, et al. Relationships between severity of chronic rhinosinusitis and nasal polypsis, asthma, and atopy. *Am J Rhinol Allergy* 2009;23:145-8.
- Bresciani M, Paradis L, Roches Des A, Vernhet H, Vachier I, Godard P, et al. Rhinosinusitis in severe asthma. *J Allergy Clin Immunol* 2001;107:73-80.
- Corren J, Adinoff AD, Buchmeier AD, Irvin CG. Nasal beclomethasone prevents the seasonal increase in bronchial responsiveness in patients with allergic rhinitis and asthma. *J Allergy Clin Immunol* 1992;90:250-6.
- Seybt MW, McMains KC, Kountakis SE. The prevalence and effect of asthma on adults with chronic rhinosinusitis. *Ear Nose Throat J* 2007;86:409-11.
- Bachert C, Patou J, Van Cauwenberge P. The role of sinus disease in asthma. *Curr Opin Allergy Clin Immunol* 2006;6:29-36.
- Taussig LM, Wright AL, Holberg CJ, Halonen M, Morgan WJ, Martinez FD. Tucson Children's Respiratory Study: 1980 to present. *J Allergy Clin Immunol* 2003;111:661-75, quiz: 676.
- Stern DA, Lohman IC, Wright AL, Taussig LM, Martinez FD, Halonen M. Dynamic changes in sensitization to specific aeroallergens in children raised in a desert environment. *Clin Exp Allergy* 2004;34:1563-669.
- Martinez FD, Stern DA, Wright AL, Taussig LM, Halonen M. Association of non-wheezing lower respiratory tract illnesses in early life with persistently diminished serum IgE levels. *Group Health Medical Associates. Thorax* 1995;50:1067-72.
- Sherrill DL, Guerra S, Minervini MC, Wright AL, Martinez FD. The relation of rhinitis to recurrent cough and wheezing: a longitudinal study. *Respir Med* 2005;99:1377-85.
- Wright AL, Holberg CJ, Morgan WJ, Taussig LM, Halonen M, Martinez FD. Recurrent cough in childhood and its relation to asthma. *Am J Respir Crit Care Med* 1996;153:1259-65.
- Simpson A, Soderstrom L, Ahlstedt S, Murray CS, Woodcock A, Custovic A. IgE antibody quantification and the probability of wheeze in preschool children. *J Allergy Clin Immunol* 2005;116:744-9.
- Jackson DJ, Gangnon RE, Evans MD, Roberg KA, Anderson EL, Pappas TE, et al. Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children. *Am J Respir Crit Care Med* 2008;178:667-72.
- Randriamanantany ZA, Annesi-Maesano I, Moreau D, Raheison C, Charpin D, Kopferschmitt C, et al. *Alternaria* sensitization and allergic rhinitis with or without asthma in the French Six Cities study. *Allergy* 2010;65:368-75.
- Nelson HS, Szefer SJ, Jacobs J, Huss K, Shapiro G, Sternberg AL. The relationships among environmental allergen sensitization, allergen exposure, pulmonary function, and bronchial hyperresponsiveness in the Childhood Asthma Management Program. *J Allergy Clin Immunol* 1999;104:775-85.
- Fernández C, Bevilacqua E, Fernández N, Gajate P, de la Cámara AG, Garcimartín M, et al. Asthma related to *Alternaria* sensitization: an analysis of skin-test and serum-specific IgE efficiency based on the bronchial provocation test. *Clin Exp Allergy* 2011;41:649-56.
- Halonen M, Stern DA, Wright AL, Taussig LM, Martinez FD. *Alternaria* as a major allergen for asthma in children raised in a desert environment. *Am J Respir Crit Care Med* 1997;155:1356-61.
- Perzanowski MS, Sporik R, Squillace SP, Gelber LE, Call R, Carter M, et al. Association of sensitization to *Alternaria alternans* with asthma among school-age children. *J Allergy Clin Immunol* 1998;101:626-32.
- Bønnelykke K, Sleiman P, Nielsen K, Kreiner-Møller E, Mercader JM, Belgrave D, et al. A genome-wide association study identifies CDHR3 as a susceptibility locus for early childhood asthma with severe exacerbations. *Nat Genet* 2014;46:51-5.
- Bochkov YA, Watters K, Ashraf S, Griggs TF, Devries MK, Jackson DJ, et al. Cadherin-related family member 3, a childhood asthma susceptibility gene product, mediates rhinovirus C binding and replication. *Proc Natl Acad Sci U S A* 2015;112:5485-90.
- Chang EH, Willis AL, McCrary HC, Noutsios GT, Le CH, Chiu AG, et al. Association between the CDHR3 rs6967330 risk allele and chronic rhinosinusitis. *J Allergy Clin Immunol* 2017;139:1990-2.e2.
- DeMuri GP, Gern JE, Moyer SC, Lindstrom MJ, Lynch SV, Wald ER. Clinical features, virus identification, and sinusitis as a complication of upper respiratory tract illness in children ages 4-7 years. *J Pediatr* 2016;171:133-9.e1.
- Wald ER, Guerra N, Byers C. Upper respiratory tract infections in young children: duration of and frequency of complications. *Pediatrics* 1991;87:129-33.
- Marom T, Alvarez-Fernandez PE, Jennings K, Patel JA, McCormick DP, Chonmaitee T. Acute bacterial sinusitis complicating viral upper respiratory tract infection in young children. *Pediatr Infect Dis J* 2014;33:803-8.
- Rosenfeld RM, Piccirillo JF, Chandrasekhar SS, Brook I, Ashok Kumar K, Kramper M, et al. Clinical practice guideline (update): adult sinusitis. *Otolaryngol Head Neck Surg* 2015;152:S1-39.
- Bhattacharyya N, Lee LN. Evaluating the diagnosis of chronic rhinosinusitis based on clinical guidelines and endoscopy. *Otolaryngol Head Neck Surg* 2010;143:147-51.
- Leung RM, Chandra RK, Kern RC, Conley DB, Tan BK. Primary care and upfront computed tomography scanning in the diagnosis of chronic rhinosinusitis: a cost-based decision analysis. *Laryngoscope* 2014;124:12-8.
- Akdis CA, Bachert C, Cingi C, Dykewicz MS, Hellings PW, Naclerio RM, et al. Endotypes and phenotypes of chronic rhinosinusitis: a PRACTALL document of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma & Immunology. *J Allergy Clin Immunol* 2013;131:1479-90.

TABLE E1. Characteristics of participants with complete data compared with those with incomplete data

Characteristic		Incomplete data (N = 474)		Complete data (N = 772)		P value
		Percent	n/n	Percent	n/n	
Sex	Male	52.1	247/474	47.4	366/772	.107
Race/ethnicity	NHW	48.1	228/474	65.5	506/772	
	HW	20.7	98/474	22.3	172/772	
	Other	31.2	148/474	12.2	94/772	<.001
Maternal						
Asthma	Yes	11.2	44/392	10.9	83/763	.859
Smoking	Yes	22.3	105/471	14.9	115/772	.001
Education	>12 y	55.7	262/470	75.9	585/771	<.001
Age	>26 y	48.0	227/473	57.8	446/772	.001
Paternal						
Asthma	Yes	10.4	38/364	12.9	94/730	.244
Smoking	Yes	37.5	174/464	27.7	211/762	<.001
Education	>12 y	59.9	275/459	76.7	581/758	<.001
Age	>26 Y	64.7	302/467	73.4	559/762	.001

Boldface values are statistically significant.

TABLE E2. Characterization of the sinusitis phenotypes

Characteristic	Category	No		Transient		Late onset		Early onset		P value
		Percent	n/n	Percent	n/n	Percent	n/n	Percent	n/n	
Sex	Male	48.6	302/621	45.6	26/57	38.2	26/68	46.2	12/26	.431
Race/ethnicity	NHW	64.7	402/621	64.9	37/57	72.1	49/68	69.2	18/26	
	HW	23.5	146/621	15.8	9/57	17.7	12/68	19.2	5/26	
	Other	11.8	73/621	19.3	11/57	10.3	7/68	11.5	3/26	.482
Maternal										
Asthma	Yes	9.8	60/613	16.1	9/56	8.8	6/68	30.8	8/26	.004
Smoking	Yes	15.0	93/621	15.8	9/57	13.2	9/68	15.4	4/26	.979
Education	>12 y	75.1	466/621	68.4	39/57	82.1	55/67	96.2	25/26	.026
Age	>26 y	56.7	352/621	59.7	34/57	67.7	46/68	53.9	14/26	.352
Paternal										
Asthma	Yes	11.9	70/589	17.0	9/53	13.9	9/65	26.1	6/23	.176
Smoking	Yes	27.0	166/615	29.1	16/55	32.8	22/67	28.0	7/25	.779
Education	>12 yr	76.0	465/612	67.9	38/56	84.9	56/66	91.7	22/24	.044
Age	>26 y	72.7	448/616	73.2	41/56	78.8	52/66	75.0	18/24	.764
At 6 years										
Atopy	Yes	36.3	181/499	45.0	18/40	50.0	28/56	63.2	12/19	.021
Alternaria sensitization	Yes	14.9	74/498	20.0	8/40	23.2	13/56	36.8	7/19	.032
Bermuda sensitization	Yes	26.5	132/499	25.0	10/40	32.1	18/56	47.4	9/19	.190
Eosinophilia	≥4%	24.4	83/340	37.5	9/24	41.0	16/39	29.4	5/17	.092
Active asthma	Yes	7.6	47/617	10.5	6/57	11.9	8/67	32.0	8/25	<.001
Active wheeze	Yes	21.9	135/617	32.1	18/56	33.8	23/68	53.9	14/26	<.001
Ever eczema	Yes	13.4	82/614	24.6	14/57	20.6	14/68	26.9	7/26	.021
Ever hay fever	MD allergic	29.7	184/619	73.7	42/57	44.1	30/68	84.6	22/26	<.001
Colds	0	3.3	20/615	0.0	0/57	2.9	2/68	7.7	2/26	
	1-3	79.7	490/615	70.2	40/57	60.3	41/68	38.5	10/26	
	4-5	14.5	89/615	22.8	13/57	29.4	20/68	38.5	10/26	
	6-9	2.6	16/615	7.0	4/57	7.4	5/68	15.4	4/26	<.001

Boldface values are statistically significant.