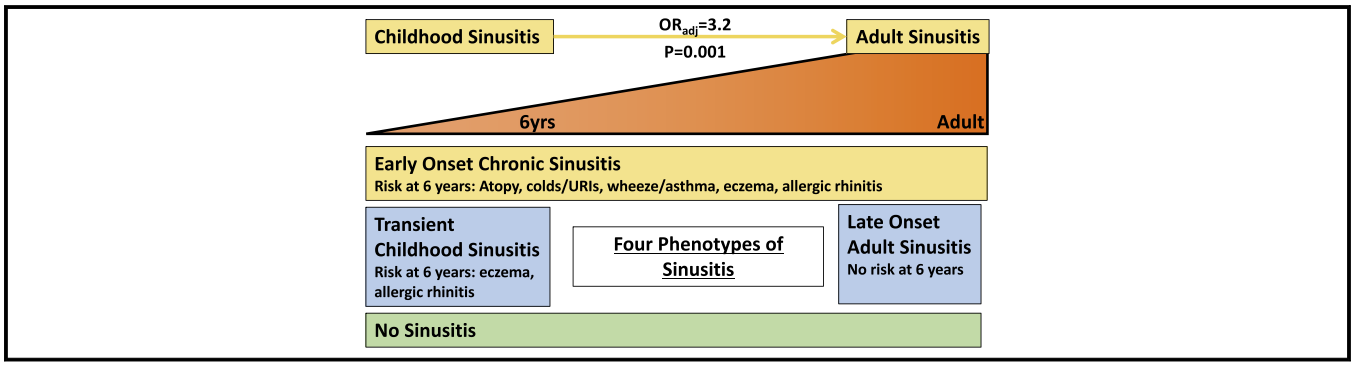
Early life risk factors for chronic sinusitis: A longitudinal birth cohort study

Eugene H. Chang, MD,[a,b] Debra A. Stern, MS,[b] Amanda L. Willis, MS,[a,b] Stefano Guerra, MD, PhD,[b] Anne L. Wright, PhD,[b] and Fernando D. Martinez, MD[b] *Tucson, Ariz*

GRAPHICAL ABSTRACT



Background: Chronic sinusitis is a commonly diagnosed condition in adults who frequently present with late-stage disease and irreversible changes to the sinus mucosa. Understanding the natural history of chronic sinusitis is critical in developing therapies designed to prevent or slow the progression of disease.

Objective: We sought to determine early life risk factors for adult sinusitis in a longitudinal cohort study (Tucson Children's Respiratory Study).

Methods: Physician-diagnosed sinusitis was reported at age 6. Adult sinusitis between 22 and 32 years was defined as self-reported sinusitis plus physician-ordered sinus radiologic films. Atopy was assessed by skin prick test. Individuals were grouped into 4 phenotypes: no sinusitis (n = 621), transient childhood sinusitis only (n = 57), late-onset adult sinusitis only (n = 68), and early onset chronic sinusitis (childhood and adult sinusitis, n = 26).

Results: Sinusitis was present in 10.8% of children and 12.2% of adults. Childhood sinusitis was the strongest independent risk factor for adult sinusitis (odds ratio = 4.2; 95% CI: 2.5-7.1; $P < .0001$; n = 772). Early onset chronic sinusitis was associated with increased serum IgE levels as early as at 9 months of age, atopy (assessed by skin prick test reactivity), childhood eczema and allergic rhinitis, frequent childhood colds, maternal asthma, and with increased prevalence of concurrent asthma. No association was found between late-onset adult sinusitis and any of the early life risk factors studied.

Conclusions: We identified an early onset chronic sinusitis phenotype associated with a predisposition to viral infections/colds in early life, allergies, and asthma. Elucidation of the molecular mechanisms for this phenotype may lead to future therapies to prevent the progression of the disease into adult sinusitis. (J Allergy Clin Immunol 2018;141:1291-7.)

Key words: *Sinusitis, asthma, allergy, viral, natural history*

The prevalence of chronic rhinosinusitis (CRS) is estimated to be 10% of the US population, with expenditures accounting for approximately 4.5% of total US health care dollars[1] ($60 billion annually).[2] Nevertheless, approximately 25% of individuals with maximal medical and surgical treatment fail to show significant clinical improvement.[3] This may be in part attributable to irreversible structural changes in the sinus mucosae, which perpetuate symptoms and hamper response to therapy. There is thus a critical need to develop strategies for the primary and secondary prevention of CRS, but very little is known about the natural history of the disease, the timing of the inception of the different subphenotypes of the disease, and the factors that determine its persistence.

From [a]the Department of Otolaryngology and [b]the Asthma and Airway Disease Research Center, University of Arizona.

Supported by National Institutes of Health grant NIH-R01 HL 132523 (E.H.C., S.G., A.L.W., F.D.M.).

Disclosure of potential conflict of interest: E. Chang has received grant NIH-R01 HL 132523 and has another NIH grant pending; consulting fees from Acclarent, Olympus; and payment for development of educational presentations from Novartis. S. Guerra has received a grant from NIH. A. L. Wright has received grants from NIH. F. D. Martinez has received grants from NIH/National Heart, Lung, and Blood Institute; and consulting fees from Copeval, Commense, Inc. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication August 4, 2017; revised October 23, 2017; accepted for publication November 30, 2017.

Available online February 21, 2018.

Corresponding author: Eugene H. Chang, MD, Department of Otolaryngology, University of Arizona, 1501 N Campbell Ave, PO Box 245074, Tucson, AZ 85724. E-mail: echang@oto.arizona.edu.

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0091-6749/$36.00

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https://doi.org/10.1016/j.jaci.2017.11.052

Abbreviations used
AR: Allergic rhinitis
CRS: Chronic rhinosinusitis

Allergic rhinitis (AR), asthma, and CRS often co-occur in the same individuals, and although the link between these disorders is multifactorial, there is evidence that AR and CRS can be risk factors for the development of asthma. In a longitudinal cohort study of 1655 households, AR was independently associated with a 3-fold increase in the development of adult-onset asthma, and 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]

TABLE I. Early life risk factors for childhood sinusitis

		MD sinusitis at age 6 y				
Characteristic	**Category**	**n**	**Percent**	***P* value***	**OR**	**95% CI**
	All	772	10.8			
Sex	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			
	MD allergic	278	23.0	**<.001**	7.44	4.35-12.7
Colds*	0	24	8.3			
	1-3	581	8.6		1.04	0.24-4.53
	4-5	132	17.4		2.32	0.51-10.6
	6-9	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

		X-ray-assessed adult sinusitis				
Characteristic	**Category**	**n**	**Percent**	***P* value***	**OR**	**95% CI**
	All	772	12.2			
Sex	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.

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.

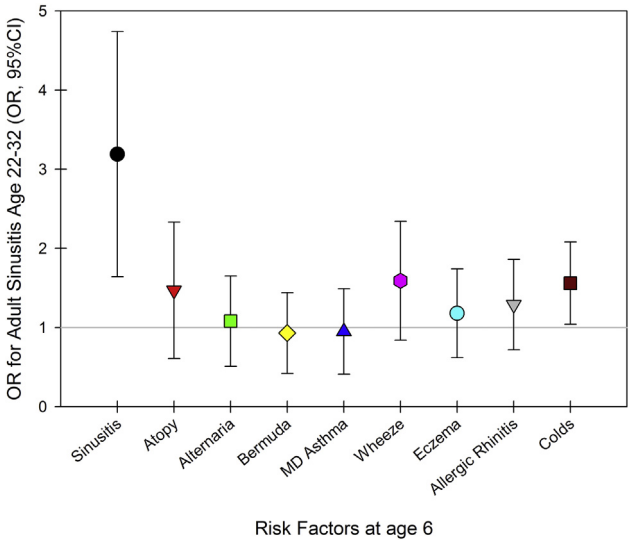


FIG 1. Multivariable analysis of early life risk factors for adult sinusitis. *MD Asthma*, Physician diagnosed asthma; *OR*, odds ratio.

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 "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.

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

	Total serum IgE IU/mL							
	9 mo				6 y			
Sinusitis phenotypes	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.

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 Phaedebas radioimmunosorbent test (PRIST) as previously reported.[13]

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 $\log_{10}$ 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

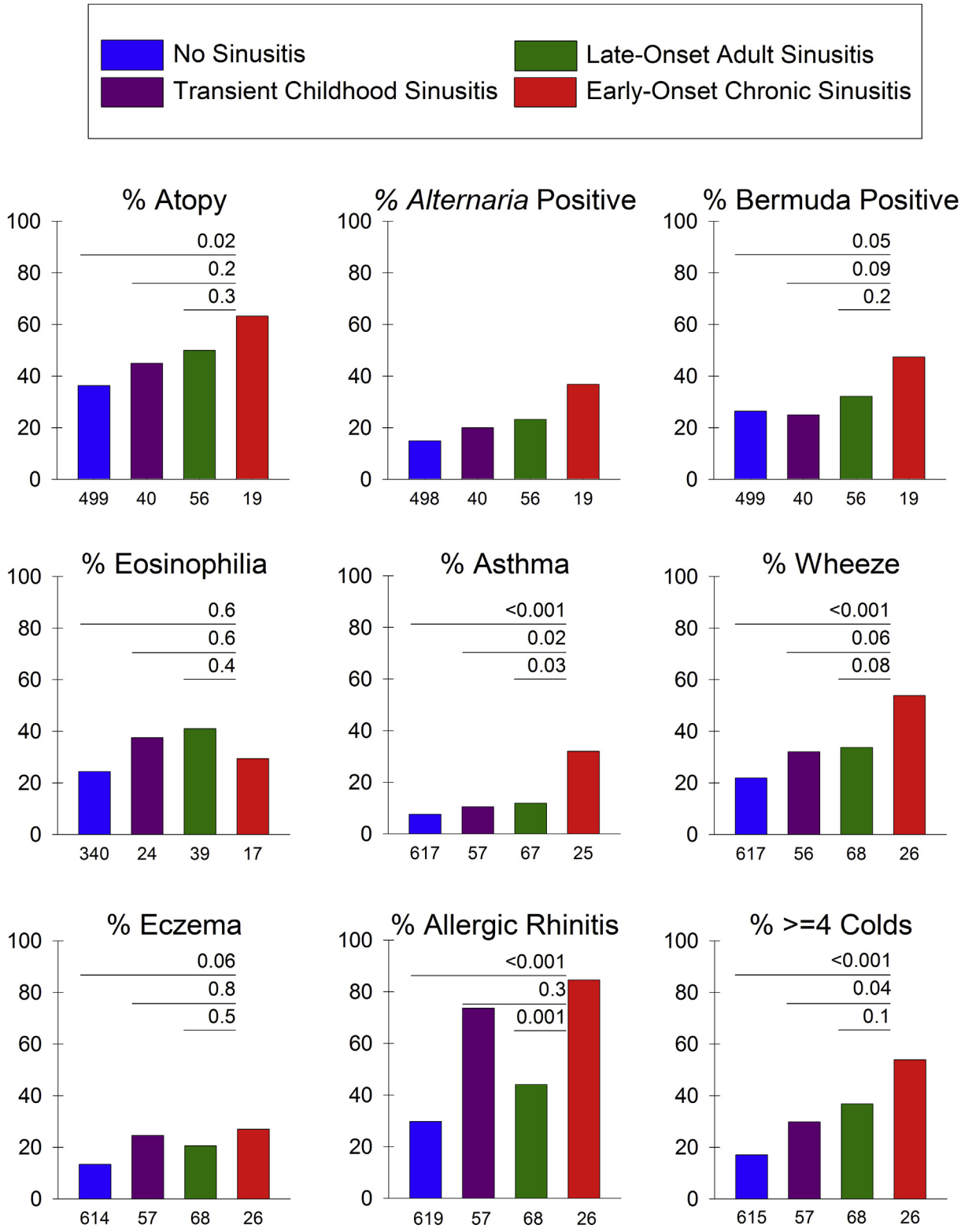


FIG 2. Age 6 characteristics of the sinusitis phenotypes.

likely to be skin prick test positive to *Alternaria* and to report 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

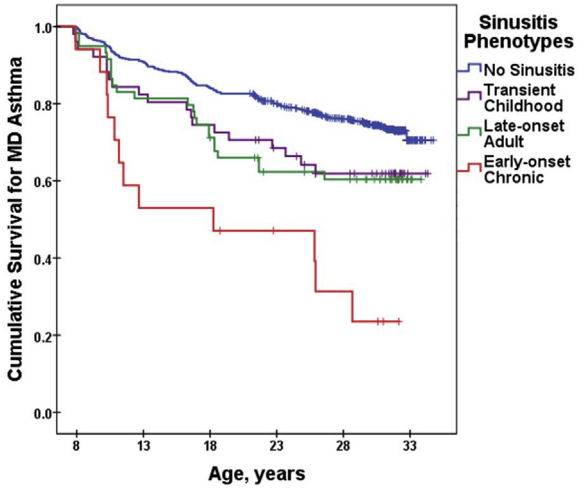


FIG 3. Survival curves for active MD asthma by the sinusitis phenotypes, limited to those without a diagnosis of asthma at age 6. Comparisons: early onset chronic sinusitis versus no sinusitis (hazard ratio [HR] = 4.2; 95% CI: 2.3-7.7; $P < .0001$); early onset chronic sinusitis versus transient childhood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

physician-diagnosed asthma after the age of 6 than were those 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 AR[18] 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	Adults ages 22-32												
		Asthma				Wheeze				Cough			
Phenotypes	n	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.

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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

		No		Transient		Late onset		Early onset		
Characteristic	**Category**	**Percent**	**n/n**	**Percent**	**n/n**	**Percent**	**n/n**	**Percent**	**n/n**	***P* value**
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.