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

Eugene H Chang MD[1,2], Debra A Stern MS[2], Amanda L Willis MSC[1,2], Stefano Guerra MD, PhD[2], Anne L Wright PhD[2], and Fernando D Martinez MD[2]

Department of Otolaryngology[1], University of Arizona, Tucson, AZ

Asthma and Airway Disease Research Center[2], University of Arizona, Tucson, AZ

Corresponding author:

Eugene H Chang MD

Department of Otolaryngology, University of Arizona

1501 N Campbell Ave

PO Box 245074

Tucson, AZ 85724

T: (520) 626-6673

Fax: (520) 626-6995

Email: echang@oto.arizona.edu

Sources of support: NIH –R01 HL132523 (EHC, SG, ALW, FDM)

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: 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 four 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 (OR=4.2, 95%CI:2.5, 7.1, $p<0.0001$, 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 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.

Discussion: 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.

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, and asthma and risk factors in childhood.

Capsule summary: This longitudinal study of the natural history of sinusitis identifies an early-onset chronic sinusitis phenotype associated with type 2 airway disease.

Key words: sinusitis; asthma; allergy; viral; natural history

Introduction

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 sub-phenotypes of the disease, and the factors that determine its persistence.

Allergic rhinitis (AR), asthma, and CRS often co-occur in the same individuals and although the link between these disorders is multi-factorial, 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 three-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 20-33% of patients with CRS have concomitant asthma, a prevalence four-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.

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' (one 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 which asked "Has this child ever had sinus trouble?" and was it "diagnosed by a doctor?". Using

this information, children were categorized into two 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 four 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 one aeroallergen.

IgE

A blood sample was collected when the child was 6 years old and a complete blood count performed. Eosinophilia was defined as greater than or equal to 4%. Total serum IgE was measured by 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. Allergic rhinitis was defined as hay fever or runny, stuffy nose that a doctor said was allergic and active wheeze was defined as symptoms during the past year. Recurrent cough was defined as two or more episodes of cough without a cold that lasted one 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 was used to plot the survival curves for the relation between sinusitis phenotypes and asthma. Stata 14 and SPSS 24 were used for analysis. Total serum IgE was log base 10 transformed and the geometric mean 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, n=772 had information for sinusitis at age 6 and in adult life for ages 22-32 years. Participants with complete data (n=772) were more likely to have non-smoking parents with more years of education and to be non-Hispanic White, compared to those with incomplete data (n=474; ETable 1).

Characterization of participants with physician-diagnosed early life sinusitis

At age 6, 10.8% of children had physician-diagnosed sinusitis (83/772) (Table 1). 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 compared to 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, allergic rhinitis (hay fever), and reports of 6 or more colds per year were significantly more likely to have sinusitis at age 6 compared to those without such conditions (Table 1).

Characterization of adult sinusitis

From 22 to 32 years of age, 12.2% of adults (94/772) with active sinusitis reported radiological assessment for sinusitis, as requested by their community physicians, in questionnaires obtained between ages 16 and 32 (Table 2). 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 (OR=4.2,

95%CI:2.5, 7.1, p<0.0001, 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 six including atopy, asthma, wheeze, allergic rhinitis, eczema and colds (OR=3.2, 95%CI:1.6, 6.2, p=0.001, n=599 in the model; Figure 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 (OR=1.6, 95%CI: 1.1, 2.3, p=0.025; Figure 1). Approximately one-third of all children diagnosed with sinusitis at age 6 received sinus imaging as adults (26/94).

Differences between sinusitis phenotypes

In order to assess predisposing factors for different sinusitis phenotypes, participants were classified into four 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 3 / Figure 2). When compared to 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 (ETable 2). At age 6 they were more likely to be skin test positive to *Alternaria*, and to report eczema, allergic rhinitis, wheeze, asthma and a higher number of colds. In addition, this group had increased total serum IgE levels (Table 3) at nine months of age. Participants with transient childhood sinusitis were significantly more likely to have eczema and allergic rhinitis than 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, compared to those with no sinusitis (HR=4.2, 95%CI: 2.3, 7.7, p<0.0001; Figure 3). They were also more likely to have active asthma compared to the transient childhood sinusitis group (HR=2.6, 95%CI:1.3, 5.4, p=0.009) and to the late-onset adult sinusitis group (HR=2.5, 95%CI: 1.2, 5.0, p=0.010; Figure 3).

As adults, those with early-onset chronic sinusitis were significantly more likely to have asthma, wheeze and cough compared to the no sinusitis group (Table 4). 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 allergic rhinitis and thus, given the subjective nature of the ascertainment, it is quite likely that these children had a severe form of allergic rhinitis 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 test reactivity) and had eczema and/or allergic rhinitis 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 three 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

252 associated with the development of allergic rhinitis[18] and asthma [19-22]. Further studies
253 are required to determine if this significant risk factor in the early-onset chronic sinusitis
254 group is related to specific exposure or as a marker of heightened type 2 immune
255 response. Susceptibility to rhinovirus infection (especially to rhinovirus C) is in part
256 determined by genetic variants in the cadherin related family member 3 (*CDHR3*)
257 gene.[23,24] We found that subjects with early-onset chronic sinusitis, but not those with
258 transient childhood sinusitis, were more likely to have recurrent colds by the age of 6,
259 but no viral studies were available. We have previously shown that adult chronic
260 rhinosinusitis is associated with the same polymorphisms in *CDHR3* that were found to
261 be associated with susceptibility to rhinovirus[25]. It is thus tempting to speculate that
262 *CDHR3* may be a common risk factor for early-onset chronic sinusitis and asthma, but
263 there were too few subjects with this phenotype in this study to make an assessment of
264 this association meaningful.
265
266 The major limitation of this study is the lack of accompanying medical information used
267 in the diagnosis of sinusitis including endoscopy, specific radiologic findings, and
268 medication usage. Access to medical records concerning sinusitis was not part of the
269 study design and would have been difficult given the range of physicians, health sites,
270 and the span of forty years in which this data were collected. A second limitation is that
271 subjects may have been misdiagnosed as having sinusitis. The classification of childhood
272 sinusitis was determined by a positive history of physician-diagnosed sinusitis. However,
273 other disorders may mimic and contribute to the symptoms of pediatric sinusitis

including adenoid hypertrophy and infection which 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 URIs 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 one of 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 chronic rhinosinusitis with nasal polyps and chronic rhinosinusitis without nasal polyps. The early-onset chronic sinusitis phenotype described herein seems to mirror that of chronic rhinosinusitis with nasal polyps, which has been associated with atopy, allergic rhinitis, and asthma. Moreover, the late onset chronic sinusitis phenotype also seems to mirror that of chronic rhinosinusitis without nasal polyps, which has often been found to be unrelated to markers of Th-2 deviation[32]. However, given the lack of more detailed clinical characterization of our participants, we are unable to determine if there is true overlap between the phenotypes described in this study and those identified in clinical studies of chronic rhinosinusitis.

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

References:

1. DeConde AS, Smith TL. Classification of Chronic Rhinosinusitis-Working Toward Personalized Diagnosis. Otolaryngol Clin North Am 2017;50:1–12.

2. 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.

3. 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.

4. 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.

5. Joe SA, Thakkar K. Chronic rhinosinusitis and asthma. Otolaryngol Clin North Am 2008;41:297–309–vi.

6. Pearlman AN, Chandra RK, Chang D, Conley DB, Tripathi-Peters A, Grammer LC, et al. Relationships between severity of chronic rhinosinusitis and nasal polyposis, asthma, and atopy. Am J Rhinol Allergy 2009;23:145–8.

7. 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.

8. 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.

9. 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.

10. Bachert C, Patou J, Van Cauwenberge P. The role of sinus disease in asthma. Curr Opin Allergy Clin Immunol 2006;6:29–36.

11. 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–quiz676.

12. 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.

13. 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.

14. 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.

15. 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.

16. 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.

17. 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.

18. Randriamanantany ZA, Annesi-Maesano I, Moreau D, Raherison 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.

19. Nelson HS, Szefler 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.

20. Fernández C, Bevilacqua E, Fernández N, Gajate P, la Cámara de 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.

21. 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.

22. Perzanowski MS, Sporik R, Squillace SP, Gelber LE, Call R, Carter M, et al. Association of sensitization to Alternaria allergens with asthma among school-age children. J Allergy Clin Immunol 1998;101:626–32.

23. 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.

24. 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 USA 2015;112:5485–90.

25. 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 2016;

26. 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.

27. Wald ER, Guerra N, Byers C. Upper respiratory tract infections in young children: duration of and frequency of complications. Pediatrics 1991;87:129–33.

28. Marom T, Alvarez-Fernandez PE, Jennings K, Patel JA, McCormick DP, Chonmaitree T. Acute bacterial sinusitis complicating viral upper respiratory tract infection in young children. Pediatr Infect Dis J 2014;33:803–8.

29. 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–S39.

30. Bhattacharyya N, Lee LN. Evaluating the diagnosis of chronic rhinosinusitis based on clinical guidelines and endoscopy. Otolaryngol Head Neck Surg 2010;143:147–51.

31. 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.

32. 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.

400 Table 1 – Early-life risk factors for childhood sinusitis

Characteristic	***MD Sinusitis at Age 6 yrs***					
	Category	**n**	**%**	**p-value***	**OR**	**95%CI**
	All	772	10.8			
Sex	Male	366	10.4			
	Female	406	11.1	0.753	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	0.233	1.44	0.76, 2.70
Maternal Asthma	No	680	9.6			
	Yes	83	20.5	**0.002**	2.44	1.35, 4.40
Smoking	No	657	10.7			
	Yes	115	11.3	0.836	1.07	0.57, 2.00
Education	<=12yr	186	10.2			
	>12yr	585	10.9	0.781	1.08	0.63, 1.85
Age	<=26	326	10.7			
	>26	446	10.8	0.991	1.00	0.63, 1.59
Paternal Asthma	No	636	9.6			
	Yes	94	16.0	0.059	1.79	0.97, 3.30
Smoking	No	551	10.3			
	Yes	211	10.9	0.823	1.06	0.64, 1.77
Education	<=12yr	177	11.3			
	>12yr	581	10.3	0.712	0.90	0.53, 1.55
Age	<=26	203	10.3			
	>26	559	10.6	0.933	1.02	0.60, 1.73
Child at 6 years: Atopy	No	375	7.7			
	Yes	239	12.6	**0.048**	1.71	0.99, 2.93
Alternaria *Sensitization*	No	511	8.6			

	Yes	102	14.7	0.057	1.83	0.98, 3.43
Bermuda Sensitization	No	445	9.0			
	Yes	169	11.2	0.397	1.28	0.72, 2.28
Eosinophilia	<4%	307	8.8			
	>=4%	113	12.4	0.271	1.47	0.74, 2.91
Active Asthma	No	697	9.8			
	Yes	69	20.3	**0.007**	2.35	1.24, 4.46
Active Wheeze	No	577	8.7			
	Yes	190	16.8	**0.002**	2.13	1.32, 3.44
Ever Eczema	No	648	9.6			
	Yes	117	18.0	**0.007**	2.07	1.21, 3.55
Ever Hay Fever	No	492	3.9			
	MD allergic	278	23.0	**<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	**0.001**	4.19	0.80, 22.1

401 Abbreviations: OR = odds ratio; CI = confidence interval; NHW = Non-Hispanic White;

402 HW = Hispanic White

403 *p-value from chi-square statistic

404

405 Table 2 – Early-life risk factors for adult sinusitis

Characteristic	***X-ray Assessed Adult Sinusitis***					
	Category	**n**	**%**	**p-value***	**OR**	**95%CI**
	All	772	12.2			
Sex	Male	366	10.4		ref	
	Female	406	13.8	0.148	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	0.452	0.8	0.4, 1.6
Maternal Asthma	No	680	11.8		ref	
	Yes	83	16.9	0.182	1.5	0.8, 2.8
Smoking	No	657	12.3		ref	
	Yes	115	11.3	0.757	0.9	0.5, 1.7
Education	<=12yr	186	7.0		ref	
	>12yr	585	13.7	**0.015**	2.1	1.1, 3.9
Age	<=26	326	10.4		ref	
	>26	446	13.5	0.204	1.3	0.9,2.1
Paternal Asthma	No	636	11.5		ref	
	Yes	94	16.0	0.213	1.5	0.8, 2.7
Smoking	No	551	11.4		ref	
	Yes	211	13.7	0.381	1.2	0.8, 2.0
Education	<=12yr	177	6.8		ref	
	>12yr	581	13.4	**0.017**	2.1	1.1, 4.0
Age	<=26	203	9.9		ref	
	>26	559	12.5	0.313	1.3	0.8, 2.2
Child at 6 years: MD Sinusitis	No	689	9.9		ref	
	Yes	83	31.3	**<0.001**	4.2	2.5, 7.1
Atopy	No	375	9.3		ref	
	Yes	239	16.7	**0.006**	2.0	1.2, 3.2

Alternaria Sensitization	No	511	10.8		ref	
	Yes	102	19.6	**0.013**	2.0	1.2, 3.6
Bermuda Sensitization	No	445	10.8		ref	
	Yes	169	16.0	0.079	1.6	0.9, 2.6
Eosinophilia	<4%	307	11.4		ref	
	>=4%	113	18.6	0.055	1.8	1.0, 3.2
Active Asthma	No	697	10.9		ref	
	Yes	69	23.2	**0.003**	2.5	1.3, 4.5
Active Wheeze	No	577	9.9		ref	
	Yes	190	19.5	**<0.001**	2.2	1.4, 3.5
Ever Eczema	No	648	11.3		ref	
	Yes	117	18.0	**0.043**	1.7	1.0, 2.9
Ever Hay Fever	No	492	8.5		ref	
	MD allergic	278	18.7	**<0.001**	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	**<0.001**	2.3	0.6, 8.5

406 Abbreviations: OR = odds ratio; CI = confidence interval; NHW = Non-Hispanic White;

407 HW = Hispanic White

408 *p-value from chi-square statistic

409 Table 3 - Total serum IgE levels at 9 months and age 6 for the sinusitis phenotypes

	Total Serum IgE IU/ml							
Sinusitis Phenotypes	**9 months**				**6 years**			
	n	**GM**	**95%CI**	**p***	**n**	**GM**	**95%CI**	**p***
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	0.2	28	39.2	19.2, 79.7	0.7
Late-onset adult	51	3.9	2.7, 5.6	0.9	40	39.4	22.0, 70.4	0.6
Early-onset chronic	18	7.5	2.9, 19.7	**0.034**	17	74.2	34.9, 158	0.078

410 Abbreviations: GM = geometric mean; OR = odds ratio; CI = confidence interval

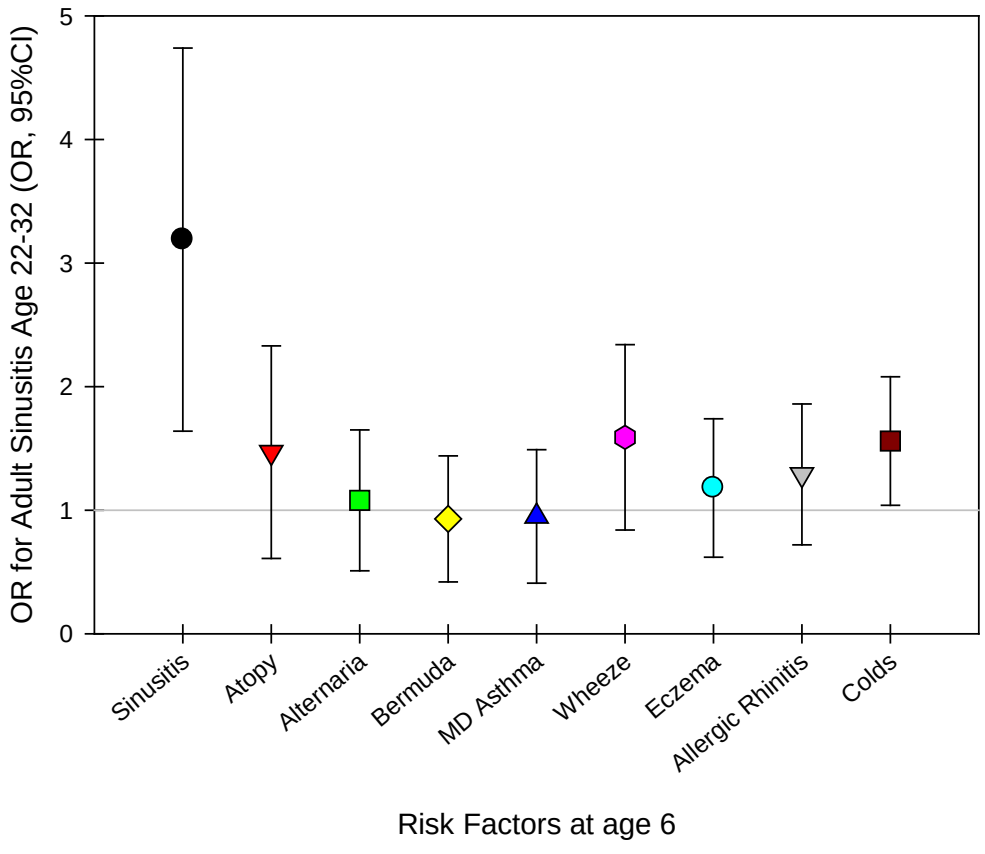
411 *p value from linear regression of log total serum IgE with sinusitis phenotypes

412 Table 4. Adult characteristics associated with the sinusitis phenotypes

Sinusitis	***Adult Age 22-32***												
Phenotypes	**Asthma**					**Wheeze**				**Cough**			
	n	**%**	**OR**	**95%CI**	**p**	**%**	**OR**	**95%CI**	**p**	**%**	**OR**	**95%CI**	**p**
No	621	21.5	ref			52.2	ref			25.2	ref		
Transient childhood	57	33.3	1.8	1.0, 3.3	**0.042**	64.9	1.7	1.0, 3.0	0.068	31.6	1.4	0.8, 2.5	0.294
Late-onset adult	66	34.9	2.0	1.1, 3.4	**0.015**	65.2	1.7	1.0, 2.9	**0.046**	40.9	2.1	1.2, 3.5	**0.007**
Early-onset chronic	25	72.0	9.4	3.9, 23	**<0.001**	84.0	4.8	1.6, 14.2	**0.004**	60.0	4.5	2.0. 10	**<0.001**

413 Abbreviations: OR = odds ratio; CI = confidence interval

414 **Figure 1**. Multivariable analysis of early life risk factors for adult sinusitis



415

Figure 2. Age 6 characteristics of the sinusitis phenotypes

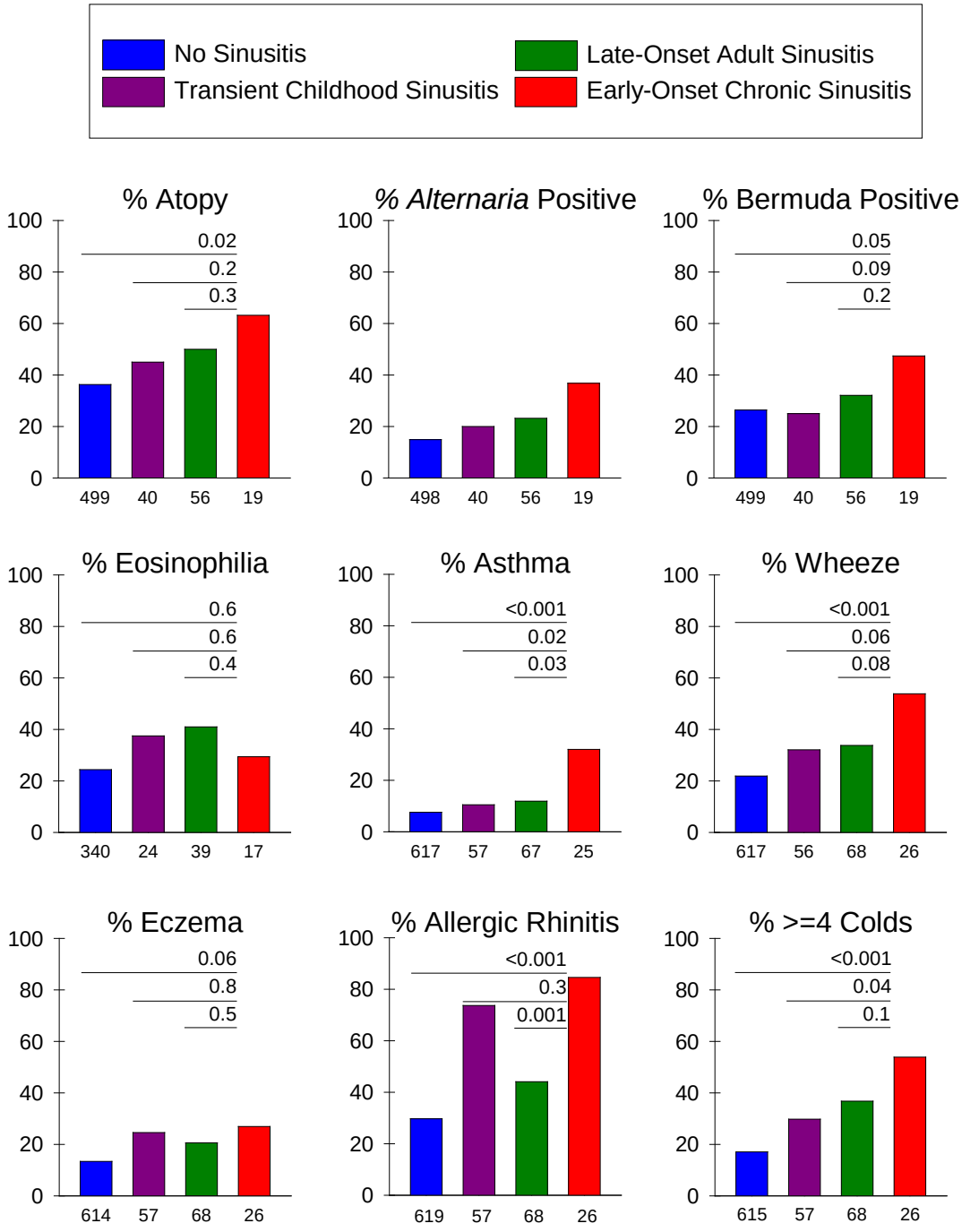
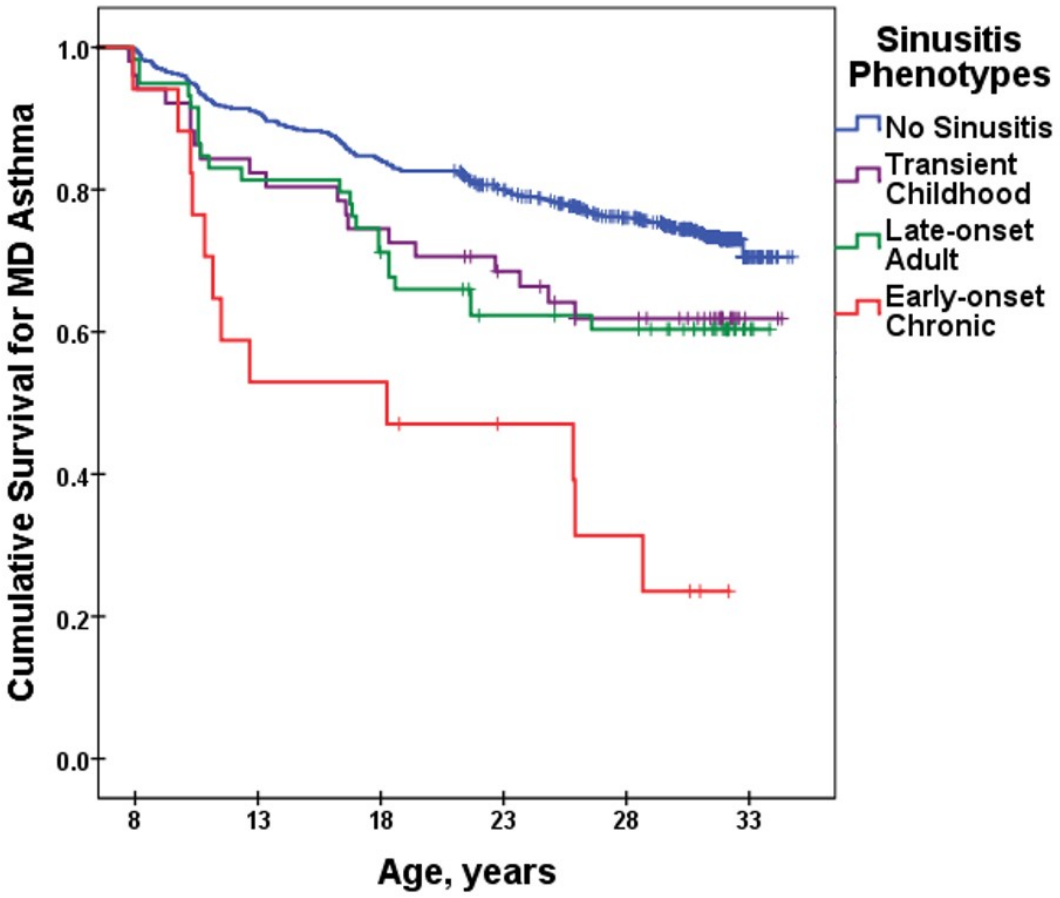


Figure 3. Survival curves for active MD asthma by the sinusitis phenotypes, limited to those without a diagnosis of asthma at age 6. Comparisons: early-onset chronic sinusitis vs. no sinusitis HR=4.2, 95%CI: 2.3, 7.7, p<0.0001; early-onset chronic sinusitis vs. transient childhood sinusitis HR=2.6, 95%CI:1.3, 5.4, p=0.009 and vs. late-onset adult sinusitis HR=2.5, 95%CI: 1.2, 5.0, p=0.010



Online Supplement

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

Eugene H Chang MD, Debra A Stern MS, Amanda L Willis MSC, Stefano Guerra MD, PhD, Anne L Wright MD, and Fernando D Martinez MD

ETable 1. Characteristics of participants with complete data compared to those with incomplete data

CHARACTERISTIC		INCOMPLETE DATA (N=474)		COMPLETE DATA (N=772)		P-VALUE
		%	n/N	%	n/N	
SEX	Male	52.1	247/474	47.4	366/772	0.107
RACE/ETHNICITY	Non-Hispanic White (NHW)	48.1	228/474	65.5	506/772	
	Hispanic White (HW)	20.7	98/474	22.3	172/772	
	Other	31.2	148/474	12.2	94/772	**<0.001**
MATERNAL						
ASTHMA	Yes	11.2	44/392	10.9	83/763	0.859
SMOKING	Yes	22.3	105/471	14.9	115/772	**0.001**
EDUCATION	>12yr	55.7	262/470	75.9	585/771	**<0.001**
AGE	>26yr	48.0	227/473	57.8	446/772	**0.001**
PATERNAL						
ASTHMA	Yes	10.4	38/364	12.9	94/730	0.244
SMOKING	Yes	37.5	174/464	27.7	211/762	**<0.001**
EDUCATION	>12yr	59.9	275/459	76.7	581/758	**<0.001**
AGE	**>26YR**	**64.7**	**302/467**	**73.4**	**559/762**	**0.001**

ETable 2. Characterization of the sinusitis phenotypes

Characteristic			*No*		*Transient*		*Late Onset*		*Early Onset*	
	Category	**%**	**n+/n**	**%**	**n+/n**	**%**	**n+/n**	**%**	**n+/n**	p
Sex	Male	48.6	302/621	45.6	26/57	38.2	26/68	46.2	12/26	0.431
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	0.482
Maternal										
Asthma	Yes	9.8	60/613	16.1	9/56	8.8	6/68	30.8	8/26	**0.004**
Smoking	Yes	15.0	93/621	15.8	9/57	13.2	9/68	15.4	4/26	0.979
Education	>12yr	75.1	466/621	68.4	39/57	82.1	55/67	96.2	25/26	**0.026**
Age	>26yr	56.7	352/621	59.7	34/57	67.7	46/68	53.9	14/26	0.352
Paternal										
Asthma	Yes	11.9	70/589	17.0	9/53	13.9	9/65	26.1	6/23	0.176
Smoking	Yes	27.0	166/615	29.1	16/55	32.8	22/67	28.0	7/25	0.779
Education	>12yr	76.0	465/612	67.9	38/56	84.9	56/66	91.7	22/24	**0.044**
Age	>26yr	72.7	448/616	73.2	41/56	78.8	52/66	75.0	18/24	0.764
At 6 Years:										

Atopy	Yes	36.3	181/499	45.0	18/40	50.0	28/56	63.2	12/19	**0.021**
Alternaria *Sensitization*	Yes	14.9	74/498	20.0	8/40	23.2	13/56	36.8	7/19	**0.032**
Bermuda Sensitization	Yes	26.5	132/499	25.0	10/40	32.1	18/56	47.4	9/19	0.190
Eosinophilia	>=4%	24.4	83/340	37.5	9/24	41.0	16/39	29.4	5/17	0.092
Active Asthma	Yes	7.6	47/617	10.5	6/57	11.9	8/67	32.0	8/25	**<0.001**
Active Wheeze	Yes	21.9	135/617	32.1	18/56	33.8	23/68	53.9	14/26	**<0.001**
Ever Eczema	Yes	13.4	82/614	24.6	14/57	20.6	14/68	26.9	7/26	**0.021**
Ever Hay Fever	MD allergic	29.7	184/619	73.7	42/57	44.1	30/68	84.6	22/26	**<0.001**
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	**<0.001**