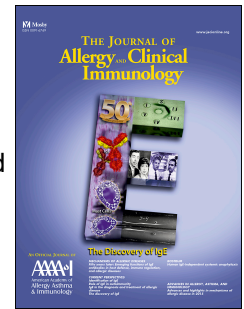


# Accepted Manuscript

Rhinitis in Children and Adolescents with Asthma: Ubiquitous, Difficult to Control, and Associated with Asthma Outcomes

Alkis Togias, MD, Peter J. Gergen, MD, MPH, Jack W. Hu, MS, Denise C. Babineau, PhD, MS, Robert A. Wood, Robyn T. Cohen, MD, MPH, Melanie M. Makhija, MD, Gurjit K. Khurana Hershey, MD, PhD, Carolyn M. Kercksmar, MD, Rebecca S. Gruchalla, MD, PhD, Andrew H. Liu, MD, Emily Wang, MD, Haejin Kim, MD, Carin I. Lamm, MD, Leonard B. Bacherier, MD, Dinesh Pillai, MD, Steve M. Sigelman, RN, MHA, James E. Gern, MD, William W. Busse, MD



PII: S0091-6749(18)31282-X

DOI: [10.1016/j.jaci.2018.07.041](https://doi.org/10.1016/j.jaci.2018.07.041)

Reference: YMAI 13609

To appear in: *Journal of Allergy and Clinical Immunology*

Received Date: 27 November 2017

Revised Date: 27 June 2018

Accepted Date: 31 July 2018

Please cite this article as: Togias A, Gergen PJ, Hu JW, Babineau DC, Wood RA, Cohen RT, Makhija MM, Khurana Hershey GK, Kercksmar CM, Gruchalla RS, Liu AH, Wang E, Kim H, Lamm CI, Bacherier LB, Pillai D, Sigelman SM, Gern JE, Busse WW, Rhinitis in Children and Adolescents with Asthma: Ubiquitous, Difficult to Control, and Associated with Asthma Outcomes, *Journal of Allergy and Clinical Immunology* (2018), doi: 10.1016/j.jaci.2018.07.041.

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# Rhinitis in Children and Adolescents with Asthma: Ubiquitous, Difficult to Control, and Associated with Asthma Outcomes

**Authors and affiliations:** Alkis Togias, MD<sup>1</sup>, Peter J. Gergen, MD, MPH<sup>1</sup>, Jack W. Hu, MS<sup>2</sup>, Denise C. Babineau, PhD, MS<sup>2</sup>, Robert A. Wood<sup>3</sup>, Robyn T. Cohen, MD, MPH<sup>4</sup>, Melanie M. Makhija, MD<sup>5</sup>, Gurjit K Khurana Hershey, MD, PhD<sup>6</sup>, Carolyn M. Kerckmar, MD<sup>6</sup>, Rebecca S. Gruchalla, MD, PhD<sup>7</sup>, Andrew H. Liu, MD<sup>8</sup>, Emily Wang, MD<sup>9</sup>, Haejin Kim, MD<sup>9</sup>, Carin I. Lamm, MD<sup>10</sup>, Leonard B. Bacherier, MD<sup>11</sup>, Dinesh Pillai, MD<sup>12</sup>, Steve M. Sigelman, RN, MHA<sup>1</sup>, James E. Gern, MD<sup>13</sup>, William W. Busse, MD<sup>13</sup>

<sup>1</sup>National Institute of Allergy and Infectious Diseases, Bethesda, MD

<sup>2</sup>Rho Federal Systems Division, Inc., Chapel Hill, NC

<sup>3</sup>Johns Hopkins University School of Medicine, Baltimore, MD

<sup>4</sup>Boston University School of Medicine, Boston, MA

<sup>5</sup>Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, IL

<sup>6</sup>Cincinnati Children's Hospital, Cincinnati, OH

<sup>7</sup>University of Texas Southwestern Medical Center, Dallas, TX

<sup>8</sup>National Jewish Health, Denver, CO, and Children's Hospital Colorado and University of Colorado School of Medicine, Aurora, CO

<sup>9</sup>Henry Ford Health System, Detroit, MI

<sup>10</sup>College of Physicians and Surgeons, New York, NY

<sup>11</sup>St. Louis Children's Hospital, St. Louis, MO

<sup>12</sup>Children's National Health System, Washington, DC

<sup>13</sup>University of Wisconsin School of Medicine and Public Health, Madison, WI

**Corresponding Author:**

Jack W Hu, MS

Rho Federal Systems Division, Inc.

6300 Quadrangle Drive

Chapel Hill, North Carolina 27517

UNITED STATES

9195951503

jack\_hu@rhoworld.com

**Abstract** (249 words)

**Background:** Rhinitis and asthma are linked, but substantial knowledge gaps in this relationship exist.

**Objective:** To determine the prevalence of rhinitis and its phenotypes in children and adolescents with asthma, assess symptom severity and medication requirements for rhinitis control, and investigate associations between rhinitis and asthma.

**Methods:** 749 children with asthma participating in the Asthma Phenotypes in the Inner-City study received baseline evaluations and were managed for 1 year with algorithm-based treatments for rhinitis and asthma. Rhinitis was diagnosed by questionnaire focusing on individual symptoms, and pre-defined phenotypes were determined by combining symptom patterns with skin testing and serum specific IgE.

**Results:** Analyses were done on 619 children with asthma who completed at least 4 of 6 visits. Rhinitis was present in 93.5%, and phenotypes identified at baseline were confirmed during the observation/management year. Perennial allergic rhinitis with seasonal exacerbations (PARSE) was most common (34.2%) and severe. Nonallergic rhinitis was least common (11.2%) and least severe. The majority of children remained symptomatic despite the use of nasal

corticosteroids  $\pm$  oral antihistamines. Rhinitis was worse in difficult-to-control vs. easy-to-control asthma and its seasonal patterns partially corresponded to those of difficult-to-control asthma.

**Conclusion:** Rhinitis is almost ubiquitous in urban children with asthma, and its activity tracks that of lower airway disease. PARSE is the most severe phenotype and most likely to be associated with difficult-to-control asthma. This study offers strong support to the concept that rhinitis and asthma represent the manifestations of one disease in two parts of the airways.

**Clinical Implications:** Clinicians should always query for rhinitis symptoms in children with asthma and should be aware that these symptoms will frequently remain uncontrolled with conventional treatment.

**Capsule Summary:** Almost all children and adolescents with asthma have rhinitis of various, stable phenotypes based on sensitization and seasonal pattern. Conventional medications control rhinitis symptoms only in a minority. Difficult-to-control asthma is associated with worse rhinitis.

**Key Words:** rhinitis prevalence, rhinitis phenotypes, rhinitis management, rhinoconjunctivitis, asthma

**Abbreviations:**

APIC – Asthma Phenotypes in the Inner City study

ARIA – Allergic Rhinitis and its Impact on Asthma

FeNO – Fractional Exhaled Nitric Oxide

FEV – Forced Expiratory Volume

IAR – Indeterminate Atopic Rhinitis

IgE – Immunoglobulin E

NAR – Non-Allergic Rhinitis

PAR – Perennial Allergic Rhinitis

PARSE – Perennial Allergic Rhinitis with Seasonal Exacerbations

SAR – Seasonal Allergic Rhinitis

V0 – Enrollment Visit

V1 – Follow-up Visit 1 (at 2 months)

V2 – Follow-up Visit 2 (at 4 months)

V3 – Follow-up Visit 3 (at 6 months)

V4 – Follow-up Visit 4 (at 8 months)

V5 – Follow-up Visit 5 (at 10 months)

V6 – Follow-up Visit 6 (at 12 months)

**Funding Sources:**

This project has been funded in whole or in part with Federal funds from the National Institute of Allergy and Infectious Diseases, National Institutes of Health, Department of Health and Human Services, under Contract numbers HHSN272200900052C and HHSN272201000052I. Additional support was provided by the National Center for Research Resources, and National Center for Advancing Translational Sciences, under grants NCRR/NIH UL1TR001079, UL1TR000451, UL1TR001105, 1UL1RR025780, UL1TR000075, NCATS/NIH UL1TR000150, UL1TR000077-04, UL1TR000154, UL1TR001082, and UL1TR000040. GlaxoSmithKline (GSK) provided Ventolin HFA, Flonase, Flovent, Advair under a clinical trial agreement with NIH NIAID.

**Conflict of Interest Disclosure Statement:**

L. Bacharier has consultant arrangements with Aerocrine, GlaxoSmithKline, Genentech/Novartis, Cephalon, Teva, and Boehringer Ingelheim; has received personal fees from Merck, DBV Technologies, AstraZeneca, WebMD/Medscape, Sanofi, Vectura, and Circassia. W. Busse has consultant arrangements with Novartis, GlaxoSmithKline, Genentech, Roche, Boehringer Ingelheim, Sanofi Genzyme, AstraZeneca, Teva, 3M, PrePBioPharm, Circassia, Regeneron, and PeptinNovate; serves as a board member for Boston Scientific DSMB and ICON Study Oversight Committee; and has received editor fees from Elsevier. J. Gern has consultant arrangements with Janssen, Regeneron, PReP Biosciences; and has received travel support from Boehringer Ingelheim. R. Gruchalla has received personal fees from the Consulting Massachusetts Medical Society; and serves as an unpaid special government employee for the Center for Biologics Evaluation and Research. C. Kercsmar has received personal fees from GlaxoSmithKline. A. Liu has received personal fees from Merck Sharp & Dohme; and has served as a Data Monitoring Committee member for GlaxoSmithKline. R. Wood has consultant arrangements with Stallergens; has received grants from DBV, Aimmune, Astellas, HAL-Allergy; and receives royalties from UpToDate. D. Babineau, R. Cohen, P. Gergen, G. K. Khurana Hershey, J. Hu, H. Kim, C. Lamm, M. Makhija, D. Pillai, S. Sigelman, A. Togias, and E. Wang have nothing outside of the submitted work to disclose.

## Introduction

Rhinitis and asthma are linked in various ways,<sup>1,2</sup> but substantial gaps in our knowledge of this relationship exist. The prevalence of rhinitis in asthma is high, but varies significantly from study to study.<sup>3-5</sup> The severity of rhinitis in asthma has not been well characterized, and the adequacy of conventional treatment with antihistamines and nasal corticosteroids to control the disease is not clear. There is evidence that the severity of rhinitis is associated with that of asthma,<sup>6-9</sup> but this relationship has not been examined in the context of seasonal variation nor in the context of different rhinitis phenotypes. This is important because seasonal variation in rhinitis is associated with various patterns of allergic sensitization, and clinical phenotyping of rhinitis has been based on those seasonality and sensitization patterns. All these knowledge gaps are evident in children and adolescents more so than in adults.

The Asthma Phenotypes in the Inner City (APIC) study was conducted by the National Institute of Allergy and Infectious Diseases-funded Inner-City Asthma Consortium to assess differences between easy-to-control and difficult-to-control phenotypes of childhood asthma.<sup>10</sup> The APIC study also collected data which allowed children and adolescents to be classified into pre-defined rhinitis phenotypes. The design of APIC included prospective management of both rhinitis and asthma under standardized algorithms. This allowed for the generation of a prospective and longitudinal dataset assessing the prevalence and severity of rhinitis and its relationship to asthma. The objectives of this study were to determine the prevalence of rhinitis and its phenotypes in children and adolescents with asthma, assess symptom severity and medication requirements for rhinitis control, and investigate associations between rhinitis and asthma.

## Methods

### Study Design

The details of the APIC study design have been previously published.<sup>10</sup> APIC was a prospective, longitudinal study of 6- to 17-year-olds from 9 urban areas with >20% poverty and with physician-diagnosed asthma of any severity or symptoms of asthma with albuterol use in the previous 12 months. The study was approved by each site's Institutional Review Board and written informed consent was obtained from a parent or guardian. The primary objective was to determine characteristics that would discriminate difficult-to-control from easy-to-control asthma. Difficult-to-control asthma was defined as requiring 500 µg/d of inhaled fluticasone with or without salmeterol in at least 4 out of the 6 post-baseline study visits. Easy-to-control asthma was defined as requiring 100 µg/d or less inhaled fluticasone or montelukast only or

no controller medication for asthma in at least 4 out of the 6 post-baseline visits. Secondary objectives included an unbiased approach to identify asthma phenotypes<sup>11</sup> and pathway analyses to identify factors contributing to asthma severity.<sup>12</sup>

The study involved a screening visit followed by enrollment (V0) and visits every 2 months for 12 months (V1–V6). At screening or enrollment, participants received comprehensive evaluations including skin prick testing, aeroallergen-specific IgE (Table E1), and assessments of rhinitis for diagnosis and management, as described below. Asthma was managed in accordance with a computerized algorithm that, based on various asthma control outcomes, determined the need for treatment step up or down, in accordance with Expert Panel Report-3 guidelines.<sup>10, 13</sup>

### Rhinitis Diagnosis and Phenotyping

To diagnose rhinitis, APIC used 2 standardized sets of questions. First, 5 questions addressed specific nasal/sinus symptoms over the past 12 months (sneezing, stuffy nose, runny nose, post-nasal drip, and sinus pressure or sinus headache). Second, 2 questions asked whether the participant was “ever told” by a doctor that he/she has “hay fever, or allergic rhinitis or allergies in the nose” or “sinus disease” (Supplemental Figure 2). Combinations of the number of reported symptoms and the responses to the doctor’s diagnosis questions were used to categorize each participant as having “no current rhinitis/rhinosinusitis”, “possible rhinitis/rhinosinusitis” and “probable rhinitis/rhinosinusitis” (Table E2). The term rhinitis/rhinosinusitis was used for categorization of questionnaire responses because one question refers to “sinus symptoms”. However, because differentiation between rhinitis and rhinosinusitis is not feasible on the basis of a questionnaire alone, and rhinosinusitis is of low prevalence in children (9% in APIC), the term rhinitis is used in this report with the understanding that some children may have, indeed, been suffering from chronic rhinosinusitis.

If a participant fulfilled criteria for possible\probable rhinitis\rhinosinusitis, another set of questions was delivered that assessed symptom seasonality (Supplemental Figure 3) and, in combination with the outcomes of skin testing and aeroallergen-specific serum IgE, led to the clinical phenotyping of rhinitis into 5 groups: seasonal allergic rhinitis (SAR), perennial allergic rhinitis<sup>14</sup>, perennial allergic rhinitis with seasonal exacerbations (PARSE), indeterminate atopic rhinitis (IAR) and nonallergic rhinitis<sup>14</sup>. (Table E3). For determining seasonality, and to take into account the known major aeroallergens of the 9 geographical areas where the study took place, the year was split into 6 “seasons” (early spring, late spring, summer, early fall, late fall, and winter). Based on our clinical experience, we reasoned that this makes a

retrospective recall easier. In addition to the common aeroallergens to which all participants were tested, some sites incorporated 1 or more area-specific aeroallergens (Table E1).

For some participants with evidence of sensitization to at least one aeroallergen, the tight relationship requirements between the seasonal pattern of symptoms and the pattern of allergic sensitization were not met; those were labeled IAR. All participants categorized as NAR were negative to all skin tests and all aeroallergen-specific IgE tests.

### Rhinitis Management

A rhinoconjunctivitis activity questionnaire, modified from the previously published Rhinitis Symptom Utility Index<sup>15</sup> was used to determine the frequency (how many days in the past 2 weeks) and the subjective magnitude (how bothersome) of each of 4 nasal symptoms (stuffy nose, runny nose, sneezing, itchy nose or throat) and 1 conjunctival symptom (itchy, watery eyes) at every visit (Supplemental Figure 4). For assessing the overall disease activity, a rhinoconjunctivitis total symptom score was calculated (up to 5 points for each symptom, total symptom score range of 0-25, Supplemental Table E4).

The responses to the rhinoconjunctivitis activity questions were used in a treatment algorithm which indicated whether rhinitis medications should be stepped up or down at each visit. We employed 3 rhinitis treatment steps: Step 0 (no medications), Step 1 (oral antihistamine - cetirizine) and Step 2 (nasal corticosteroid – fluticasone propionate- with or without oral antihistamine - cetirizine). This stepwise treatment was used on all rhinitis phenotypes with the exception of NAR in which 2 steps (no medication or nasal corticosteroid) were implemented (Table E5). For IAR, the site clinician was responsible for selecting which treatment algorithm (for allergic rhinitis or NAR) to use. Most IAR participants (74%) were treated as allergic rhinitis. The rhinitis management plan did not include montelukast, but a small number of children either entered the study or were subsequently placed on this agent. We did not change treatment step allocation if montelukast was used together with other medications. Seventeen participants who only received montelukast for one or more visits were designated Step 1 for the respective visit(s).

For the treatment algorithm, the symptom with the highest frequency and that with the highest degree of bother were combined to determine appropriate action (Table E6). Study physicians were allowed, with written justification, to override the algorithm and this occurred 8% of the time. Rhinitis medications, like medications for asthma, were provided

free to all participants. Adherence to treatment was recorded at every visit for those participants that were prescribed nasal fluticasone by asking them how many days in the previous 2 weeks they had used this medication.

### Statistical Analysis

Demographics and clinical characteristics were compared within or between rhinitis phenotypes using Kruskal-Wallis tests for continuous variables and  $\chi^2$  tests for categorical variables. Clinical characteristics measured repeatedly over time were compared between rhinitis phenotypes using generalized linear mixed models that included a random intercept to account for between-subject variability.

Generalized additive mixed models were used to estimate the seasonal patterns of rhinoconjunctivitis symptom score, asthma symptoms and exacerbations and pulmonary function within the rhinitis or asthma phenotypes of interest. A likelihood ratio test was used to determine the existence of a seasonal pattern within a rhinitis phenotype and to compare the seasonal patterns between phenotypes or outcomes of interest within a phenotype. Outcomes within a phenotype were standardized prior to estimating seasonal patterns to ensure that values were on the same scale. No adjustments were made to account for multiple comparisons between groups or between multiple variables due to the exploratory nature of those analyses. Consequently, all p-values are descriptive. We used SAS version 9.4 and R version 3.4.0.

## **Results**

### Rhinitis Prevalence, Phenotypes and Seasonal Symptom Patterns

The APIC study enrolled 749 children with asthma. Of those, 619 completed at least 4 of the 6 follow-up visits and were included in the primary analysis for asthma.<sup>10</sup> All had evaluable rhinitis data. Study participants were categorized as follows: “probable rhinitis” (78%), “possible rhinitis” (12%) and “no rhinitis” (10%) (Table E2). Age, sex and ethnicity/racial background did not vary among these 3 groups. However, compared to the “probable rhinitis” category, “possible rhinitis” had significantly lower rhinoconjunctivitis symptom scores ( $p=0.006$ ) and required less medication ( $p<0.001$ ) during the prospective observation/management year. Nineteen participants who were originally categorized as “no rhinitis” reported symptoms of rhinitis in subsequent visits and were re-categorized into rhinitis phenotypes. This is reflected in Figure 1, which shows the distribution of rhinitis phenotypes, and includes the final group of children with

“no rhinitis”. The most common phenotype was PARSE (34.2%) and the least common NAR (11.3%). No differences among the five rhinitis phenotypes were seen with regards to age, sex, or ethnicity/racial background ( $p \geq 0.05$ ). Compared to PAR, SAR, IAR, and NAR combined, PARSE had the highest number of aeroallergen sensitizations ( $p < 0.001$ ), as well as the highest total serum IgE ( $p < 0.001$ ). For total peripheral blood eosinophils and FeNO, NAR had significantly lower values compared to all allergic phenotypes combined ( $p < 0.001$ ). Significant differences between the allergic phenotypes were also detected (Table I). The rhinitis phenotypes were different with regards to the distribution of “possible rhinitis” versus “probable rhinitis”: SAR, IAR and NAR had higher percentages of children with “possible rhinitis” compared to PAR and PARSE, which, inversely, had higher percentages of children with “probable rhinitis” ( $p < 0.0001$ ).

Figure 2 presents the rhinoconjunctivitis total symptom score for each rhinitis phenotype over the calendar months of the observation/management year during which participants were offered free medications for optimal rhinitis pharmacotherapy. Several observations were made. First, the seasonal patterns of symptoms obtained prospectively over the 12-month period of the study matched the patterns identified using the baseline rhinitis phenotyping questionnaire. Comparing these curves to a linear model (which implies no seasonal pattern), PARSE and SAR demonstrated significant seasonal oscillations ( $p < 0.001$ ) with peaks in the spring and early fall and troughs in summer and winter. In PAR, seasonal oscillations were also identified, but of smaller magnitude and without statistical significance ( $p = 0.36$ ). Interestingly, children with IAR also showed seasonal peaks matching the peaks of PARSE and SAR ( $p = 0.021$ ). In NAR, seasonality was not confirmed statistically but a trend differing from the other phenotypes was observed. A non-significant seasonal pattern was also observed in the “no rhinitis” group, but the magnitude of symptoms was less than in the rhinitis phenotypes. When we compared the 5 rhinitis phenotypes as well as the “no rhinitis” group (Supplemental Figure 1), we found a significant difference among all 6 (or 5, if we remove the “no rhinitis” group). PARSE had the overall highest symptom levels and “no rhinitis” the lowest. In no group did rhinoconjunctivitis symptoms disappear at any time of the year, and, in all groups, summertime had the lowest symptoms.

Participants were assigned to IAR if their symptom pattern did not match that of aeroallergen sensitization. To better describe this group, we also examined whether they would have fit into phenotypes based only on baseline-reported symptoms. Using this approach, 56.8% would have been categorized as seasonal, 37.8% as perennial with seasonal exacerbations and only 5.4% as perennial. This matched their prospective experience during the observation period (Figure 2).

In an attempt to examine whether the pattern of seasonal oscillation seen in various magnitudes across all groups is purely due to seasonal allergen sensitization, we separately examined a subgroup of children that were only sensitized to perennial allergens and not to any seasonal allergens or molds, regardless of what seasonal pattern they had reported at baseline (N=80). The tracing of these children's average symptom score during the observation period was identical to that of PAR (data not shown).

#### Rhinitis Medication Requirements and Symptom Control

We examined medication requirements for each rhinitis phenotype at every study visit (Figure 3; left panel). Within each rhinitis phenotype, the percentage of children requiring no treatment, an antihistamine alone or a nasal corticosteroid  $\pm$  an antihistamine remained relatively stable over the study visits. On average, 71.5% of children with PAR and 84.2% with PARSE required a nasal corticosteroid  $\pm$  antihistamine, while 12.7% and 5.3%, respectively, needed no medications. In SAR and IAR, the average percentage of children requiring a nasal corticosteroid ( $\pm$  antihistamine) was 58% and 58.4%, respectively, while 18.1% and 26.5% required no medication. In NAR, 46.3% children required nasal corticosteroids and 50.3% no treatment. More children required nasal corticosteroids in PARSE compared to all other phenotypes ( $p<0.001$ ), while the proportion requiring no treatment was highest in NAR ( $p<0.001$ ). Also, the proportion requiring no treatment was higher in IAR, compared to SAR, PAR and PARSE ( $p\leq 0.002$ ). Among children with PARSE, PAR and SAR, 11.1-29% (depending on the phenotype) required only antihistamine.

The right panel of Figure 3 plots the percentage of children that remained symptomatic in each rhinitis phenotype and at every study visit, defined as meeting step-up treatment algorithm criteria despite having already been prescribed the highest treatment level, a nasal corticosteroid  $\pm$  oral antihistamine. This number remained relatively constant over the 7 study visits and was, on average, 67% in PARSE, 62% in PAR, 61% in SAR, 71% in IAR and 87% in NAR.

Self-reported adherence for nasal fluticasone averaged 61.6% with children with PARSE having the highest adherence (67.8%), while those with NAR the lowest (48.2%,  $p<0.001$ ).

#### Relationship between Rhinitis and Asthma

The easy-to-control vs difficult-to-control asthma groups<sup>10</sup> were compared in terms of the rhinoconjunctivitis symptom score and the percentage of children requiring nasal corticosteroids ( $\pm$  antihistamine) over the entire observation/management year (Figure 4). The mean rhinoconjunctivitis symptom score was higher in the children with difficult-to-control compared to easy-to-control asthma ( $p<0.001$ ). Also, the percentage of children using nasal corticosteroids ( $\pm$  antihistamine) was higher in difficult-to-control asthma, (range: 80% to 86%) compared to the easy-to-control group (range: 57% to 63%,  $p<0.001$ ). Finally, children with difficult-to-control asthma reported higher adherence to nasal corticosteroids compared to easy-to-control disease (66.3% vs 57.9%,  $p=0.027$ ).

The distribution of the 5 rhinitis phenotypes differed significantly between easy-to-control and difficult-to-control asthma ( $p=0.003$ ) with PARSE being more prevalent in the difficult-to-control (44.2%) than in the easy-to-control group (26.5%) (Table II). Inversely, compared to the other phenotypes, PARSE had more children with difficult-to-control asthma (65.6% vs  $<50\%$ ).

We examined whether seasonal fluctuations of rhinitis and asthma parallel each other by plotting (Figure 5) mean standardized rhinoconjunctivitis total symptom scores over the course of the year superimposed on mean standardized scores of each of the 4 outcomes used in the APIC study to monitor asthma (daytime and nighttime symptoms, exacerbations and FEV<sub>1</sub> % predicted). This depiction was confined to the combined PARSE and SAR group in difficult-to-control asthma because these rhinitis and asthma phenotypes were the only ones with clear seasonal rhinoconjunctivitis symptom fluctuations. Asthma exacerbations showed both a spring and fall seasonal pattern; daytime and nighttime asthma symptoms showed only a fall worsening pattern and FEV<sub>1</sub> % predicted did not show any significant seasonal oscillations. For rhinoconjunctivitis, the spring peak corresponded to that of the peak in asthma exacerbations. In the fall, the peak in rhinoconjunctivitis consistently preceded the peak in asthma symptoms and asthma exacerbations by 1-2 months.

## Discussion

This report presents our findings on rhinitis in a large sample of children and adolescents with asthma who participated in a 12-month prospective evaluation and management of both rhinitis and asthma. The conclusions can be summarized as follows: a) rhinitis is almost ubiquitous in children and adolescents with asthma; b) in the vast majority of children and

adolescents with asthma, we can reliably phenotype rhinitis on the basis of symptom seasonality and temporally relevant aeroallergen sensitization; c) conventional rhinitis medications (oral antihistamines and nasal corticosteroids) can completely control symptoms only in the minority of children and adolescents with rhinitis and asthma; d) PARSE is the most difficult to control rhinitis phenotype; e) rhinitis symptoms are more severe and more difficult to control in children and adolescents with difficult-to-control asthma; and f) seasonal oscillations of rhinitis symptoms partially reflect those of asthma outcomes.

In this urban population of children and adolescents with asthma, almost 95% had nasal symptoms despite the fact that none of the inclusion criteria targeted a population with rhinitis. Using almost identical diagnostic questionnaires, high prevalence of rhinitis has been previously reported in adults and adolescents asthma<sup>16</sup> but, in general, the numbers reported in the literature range from 50-85%, whether in children or adults;<sup>4, 17-19</sup> much lower rates have also been reported.<sup>20</sup> The reason behind these wide differences is not clear, but may be related to the fact that rhinitis is diagnosed on the basis of questionnaires and that the questionnaires used in different studies vary. Many studies tend to define rhinitis on the basis of a single question. Our approach was to query each rhinitis symptom separately (Supplemental Figure 2) because this allows the responder to focus on each component of the condition and not on a group of symptoms, which infers necessity for co-existence; we reasoned that this approach improves sensitivity. Concerns about accuracy are alleviated by the fact that the vast majority of the participants who had rhinitis (87%) were categorized as “probable rhinitis” (higher certainty), which turned out to be more symptomatic and required more medication than “possible rhinitis”. Furthermore, about 3/4 of all children with rhinitis, with the exception of NAR, required treatment (Figure 3).

Clinical phenotyping of rhinitis has traditionally combined aeroallergen sensitization with seasonal symptom patterns. In the ARIA guidelines, the terms “intermittent” and “persistent” rhinitis were introduced, but the season-based definitions were retained in the majority of clinical trials and have been re-introduced in the 2016 ARIA revision.<sup>14</sup> During the 12-month observation period, we confirmed the stability of the phenotype that was established at baseline by showing a clear symptom seasonality in SAR and PARSE, and minimal oscillation in PAR. IAR also showed a pattern of seasonal symptoms, which confirmed what 95% of these children had reported at baseline. It appears that IAR is a form of SAR or PARSE where either the diagnostic methods were not adequate to detect aeroallergen sensitization or the panel tested missed some locally important aeroallergens. Also, IAR may represent a form of local allergic rhinitis, where IgE for some offending aeroallergens is only produced in the nasal mucosa.<sup>21</sup> Even in the children with “no rhinitis”, low-level symptoms with a seasonal pattern were observed, albeit the seasonal variability was not statistically significant (Figure 2 and Supplemental Figure 1). A sub-group of those children may have had mild rhinitis, because children with one symptom only and no physician diagnosis were categorized as “no rhinitis” by the diagnostic questionnaire (Table E2);

also, some had allergen sensitizations (Table I). The overall pattern of seasonal oscillations that was seen in all phenotypes of rhinitis, albeit at varying magnitude, is of interest. To some extent, this could be due to the fact that, with the exception of NAR, all other phenotypes included children with varying frequencies of sensitization to seasonal allergens. However, the fact that the pattern remained the same when only children with sensitizations to perennial allergens were considered, raises the possibility that a component of rhinitis seasonality may reflect respiratory viral infections, since rhinovirus infections have a spring and fall predominance in temperate climates. A limitation of the APIC study is that it did not include sampling of nasal secretions for viral surveying.

A great majority of study participants required treatment for their rhinitis. This was most prominent in the allergic phenotypes and in IAR. In contrast, about 50% of children with NAR were asymptomatic at each study visit requiring no treatment (Figure 3, left panel) indicative of NAR being an overall milder disease in this population. Among participants prescribed the highest level of medication, a nasal corticosteroid  $\pm$  antihistamine, the majority remained symptomatic. Our algorithm did not include the use of a nasal antihistamine, which, combined with a corticosteroid, may offer a stronger therapeutic effect, at least in adolescents and adults,<sup>22</sup> nor were any of these children allowed to progress to allergen immunotherapy, which may have offered additional relief. Also, our data may reflect lower than optimal adherence to rhinitis treatment. Reported adherence to nasal corticosteroids was 66.1%, not very different from the objectively measured adherence to asthma controller treatment (Discus® counter), which was approximately 77%<sup>10</sup>. Given the optimal conditions for adherence that our study offered (free medications, education at every visit), the effects of rhinitis treatment would have been even more modest in a real-life situation. Another limitation is that this study was not designed to compare the rhinitis of children with asthma to that of children without asthma and that the population of this study was a convenience sample, probably inflated in terms of severe asthma. Nevertheless, the findings are compatible with a previous report in a seasonal rhinitis population<sup>23</sup> and are consistent with the fact that, even in randomized trials, the effect size on rhinitis symptoms of nasal corticosteroids versus placebo averages 11% in PAR and 22% in SAR.<sup>24</sup> Note that in NAR, more than 80% of the children who received a nasal corticosteroid (Figure 3, right panel) remained symptomatic. This suggests that this form of treatment is not effective for NAR in children. Although no randomized, placebo-controlled trials of nasal corticosteroids have been conducted in children with NAR, this finding reflects the controversy as to the usefulness of this form of treatment in trials that included both adults and older children.<sup>25, 26</sup>

Rhinitis symptom scores and the proportion requiring the highest level of medication were greater in PARSE and this was the most common phenotype in difficult-to-control asthma. In clinical practice or in clinical trials, PARSE is not recorded

and is lumped with either PAR or SAR, but based on these findings, we believe it needs to be treated as a separate phenotype.

The association between rhinitis and asthma has been established<sup>1,2</sup> and in the previous publications which presented the asthma analyses of the APIC study the role of rhinitis as a factor linked to asthma severity was clearly shown.<sup>10-12</sup> The work we have conducted herein deepens our knowledge by adding the element of time to this association. We showed that, during the course of the observation/management year, and regardless whether we examine symptom scores or the proportion of participants requiring the highest level of nasal medications, the activity of rhinitis in difficult-to-control versus easy-to-control asthma was consistently higher in the former (Figure 4). We further tried to increase the granularity of this finding by examining how each of four elements of asthma activity reflecting both impairment and risk relate to rhinitis over time. We found a partial temporal relationship where the spring peaks of some asthma outcomes coincided with those of rhinitis, whereas in the fall, a 1 to 2-month lag between rhinitis and asthma peaks was present. It is difficult to assign significance to the latter finding, but the data raise the hypothesis that, in the fall, increased rhinitis activity predisposes to increased asthma symptoms and exacerbations. We certainly do not know why this is not seen in the spring, but the mechanisms of spring versus fall asthma exacerbations may be different, as recently suggested.<sup>27</sup>

In conclusion, we have conducted a comprehensive study of rhinitis in urban children and adolescents with asthma and have determined various clinical characteristics of nasal airway disease phenotypes and their relationships to asthma. Rhinitis is almost ubiquitous in asthma and its clinical activity tracks that of lower airway disease. This study offers strong support to the concept that rhinitis and asthma represent the manifestations of one disease in two parts of the respiratory system.

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**Table I. Demographics by Rhinitis Phenotype  
(N=619)**

| Characteristic                                                           | Overall              | SAR<br>n=134   | PAR<br>n=81   | PARSE<br>n=212 | IAR<br>n=82   | NAR<br>n=70  | No Rhinitis<br>n=40 | P-value |
|--------------------------------------------------------------------------|----------------------|----------------|---------------|----------------|---------------|--------------|---------------------|---------|
| Age                                                                      | 12 and under         | 102 (76.1%)    | 56 (69.1%)    | 142 (67.0%)    | 57 (69.5%)    | 54 (77.1%)   | 34 (85.0%)          | 0.13    |
|                                                                          | Over 12              | 32 (23.9%)     | 25 (30.9%)    | 70 (33.0%)     | 25 (30.5%)    | 16 (22.9%)   | 6 (15.0%)           |         |
| Gender                                                                   | Female               | 45 (33.6%)     | 37 (45.7%)    | 87 (41.0%)     | 43 (52.4%)    | 33 (47.1%)   | 13 (32.5%)          | 0.07    |
|                                                                          | Male                 | 89 (66.4%)     | 44 (54.3%)    | 125 (59.0%)    | 39 (47.6%)    | 37 (52.9%)   | 27 (67.5%)          |         |
| Race*                                                                    | Black (non-Hispanic) | 81 (60.4%)     | 49 (60.5%)    | 147 (69.3%)    | 50 (61.0%)    | 45 (64.3%)   | 22 (55.0%)          | 0.21    |
|                                                                          | Hispanic             | 46 (34.3%)     | 22 (27.2%)    | 52 (24.5%)     | 23 (28.0%)    | 20 (28.6%)   | 14 (35.0%)          |         |
|                                                                          | Other/Mixed          | 2 (1.5%)       | 9 (11.1%)     | 10 (4.7%)      | 7 (8.5%)      | 4 (5.7%)     | 2 (5.0%)            |         |
|                                                                          | White (non-Hispanic) | 4 (3.0%)       | 0 (0%)        | 3 (1.4%)       | 2 (2.4%)      | 1 (1.4%)     | 1 (2.5%)            |         |
| No. of allergen sensitizations (panel of 22) at baseline 0 <sup>†‡</sup> |                      | 10 (7,15)      | 5 (2,10)      | 13 (9,17)      | 4 (2,8)       | 0 (0,0)      | 4 (1,9)             | <0.001  |
| Total serum IgE at baseline (kU/L) <sup>†</sup>                          |                      | 406 (166,1094) | 235 (92,622)  | 528 (190,1226) | 135 (36,402)  | 32 (13,71)   | 136 (43,549)        | <0.001  |
| Blood eosinophils count at baseline (cells/mm3) <sup>†</sup>             |                      | 326 (200,590)  | 295 (200,500) | 300 (200,500)  | 200 (100,400) | 100 (90,200) | 200 (100,400)       | <0.001  |

| Characteristic                      | Overall | SAR<br>n=134 | PAR<br>n=81 | PARSE<br>n=212 | IAR<br>n=82 | NAR<br>n=70 | No Rhinitis<br>n=40 | P-value |
|-------------------------------------|---------|--------------|-------------|----------------|-------------|-------------|---------------------|---------|
| FeNO at baseline (ppb) <sup>†</sup> |         | 20 (13,40)   | 20 (14,36)  | 23 (13,53)     | 17 (10,29)  | 11 (8,16)   | 18 (11,48)          | <0.001  |

*\*Three participants with missing race in SAR, PAR, and No Rhinitis group*

*<sup>†</sup>Median (with interquartile range); p-values are determined by Kruskal Wallis Rank Test*

*<sup>‡</sup>Sensitization is defined as having a positive skin prick test response, positive specific IgE level, and/or both*

**Table II. Distribution of rhinitis phenotypes in Difficult-to-Control and Easy-to-Control Asthmatics (N=453)**

| Characteristics                    | SAR<br>n=109 | PAR<br>n=63 | PARSE<br>n=163 | IAR<br>n=63 | NAR<br>n=55 | Total<br>n=453 | Overall<br>P-value |
|------------------------------------|--------------|-------------|----------------|-------------|-------------|----------------|--------------------|
| <b>Difficult-to-Control Asthma</b> | 53 (21.9%)   | 28 (11.6%)  | 107 (44.2%)    | 30 (12.4%)  | 24 (9.9%)   | 242            | 0.003              |
| <b>Easy-to-Control Asthma</b>      | 56 (26.5%)   | 35 (16.6%)  | 56 (26.5%)     | 33 (15.6%)  | 31 (14.7%)  | 211            |                    |

*Participants who could not be classified as either Difficult-to-Control or Easy-to-Control Asthmatics are excluded*

## Figure Legends

FIGURE 1. Numbers and percentages of participants in each rhinitis phenotype. Rhinitis phenotypes are denoted as Seasonal Allergic Rhinitis (SAR; red), Perennial Allergic Rhinitis (PAR; blue), Perennial Allergic Rhinitis with Seasonal Exacerbations (PARSE; green), Indeterminate Atopic Rhinitis (IAR, purple), Non-Allergic Rhinitis (NAR; orange). The percentage with No Rhinitis is included (gray).

FIGURE 2. Seasonal variation in rhinoconjunctivitis total symptom scores, stratified by rhinitis phenotype. Each line (shaded region) represents the mean (95% CI) of rhinoconjunctivitis total symptom scores over 12 months for participants with Seasonal Allergic Rhinitis (SAR; red line), Perennial Allergic Rhinitis (PAR; blue line), Perennial Allergic Rhinitis with Seasonal Exacerbation (PARSE; green line), Indeterminate Atopic Rhinitis (IAR; purple line), Non-Allergic Rhinitis (NAR; orange line). No Rhinitis (black) is also included. P-values correspond to statistical test of seasonal trend in each rhinitis phenotype.

FIGURE 3. Left Panel: percentage of participants at each treatment level and at each visit stratified by rhinitis phenotype. Treatment levels: no treatment (yellow), antihistamine alone (orange), and nasal steroid  $\pm$  antihistamine (purple).

Right Panel: percentage of participants receiving the highest treatment level (nasal steroid  $\pm$  antihistamine) at each visit who remained symptomatic (whose therapy would have been stepped-up if another level was available) or who did not (not symptomatic), stratified by rhinitis phenotype. Symptomatic is denoted by lined purples and not symptomatic by light purple.

FIGURE 4. Seasonal variation in rhinoconjunctivitis total symptom scores (left panel) and in the percentage of participants that were prescribed the highest treatment level (nasal steroid  $\pm$  antihistamine) (right panel), stratified by asthma severity. Each line (shaded region) represents the mean (95% CI) of rhinoconjunctivitis total symptom scores or percentage of participants (95% CI) that were prescribed nasal steroid  $\pm$  antihistamine over 12 months for participants with Difficult-to-Control Asthma (blue line) and with Easy-to-Control Asthma (green line). P-values correspond to a statistical test of the difference in the seasonal trend between Difficult-to-Control Asthma and Easy-to-Control Asthma.

FIGURE 5. Seasonal variation of asthma clinical severity measures superimposed on the rhinoconjunctivitis total symptom scores in the combined group of participants with Seasonal Allergic Rhinitis (SAR) and Perennial Allergic Rhinitis with Season Exacerbations (PARSE), who had Difficult-to-Control Asthma. Each line (shaded region) represents the mean (95% CI) of the respective outcome. Note that the same rhinoconjunctivitis total symptom score data (purple) are depicted in each panel for comparison with the respective asthma measure. Asthma measures: Asthma Day Symptom Score

measuring day symptoms and albuterol use in the last two weeks prior to a study visit (blue), Asthma Night Symptom Score measuring night symptoms and albuterol use in the last two weeks prior to a study visit (green), Asthma Exacerbation measuring exacerbation rates in the 2 months prior to a study visit (red) and FEV1 % predicted at each study visit (orange).

Figure 1

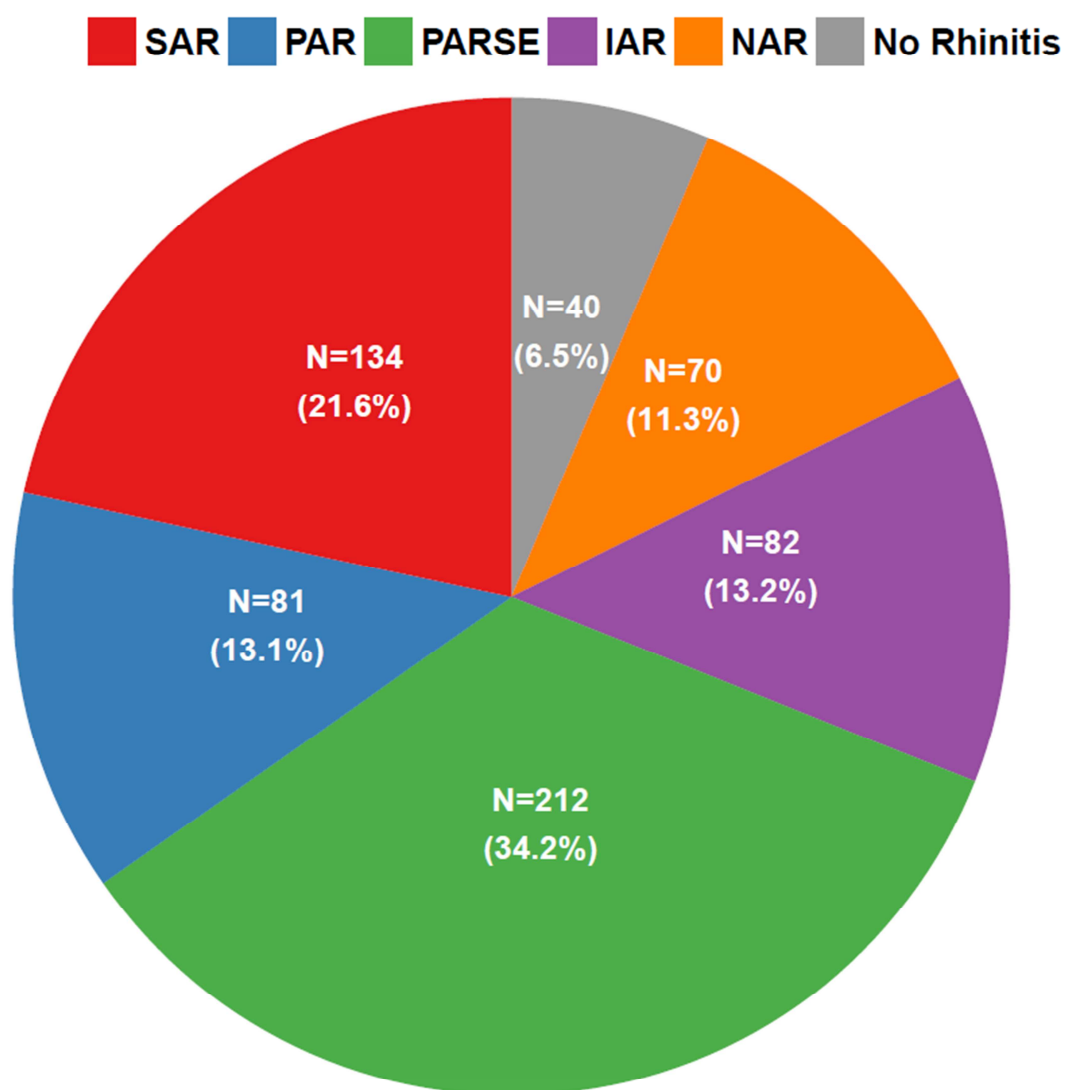


Figure 2

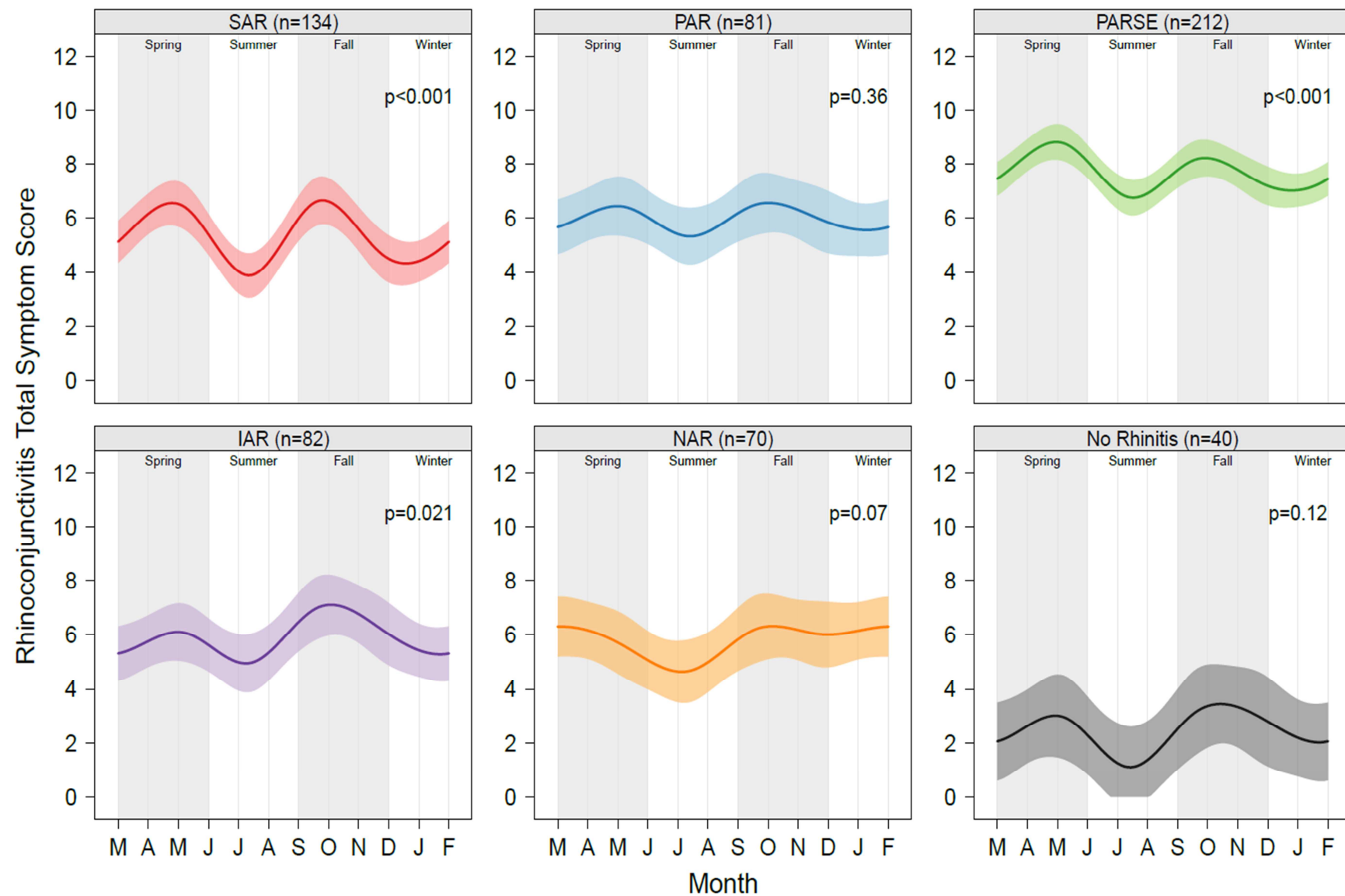


Figure 3

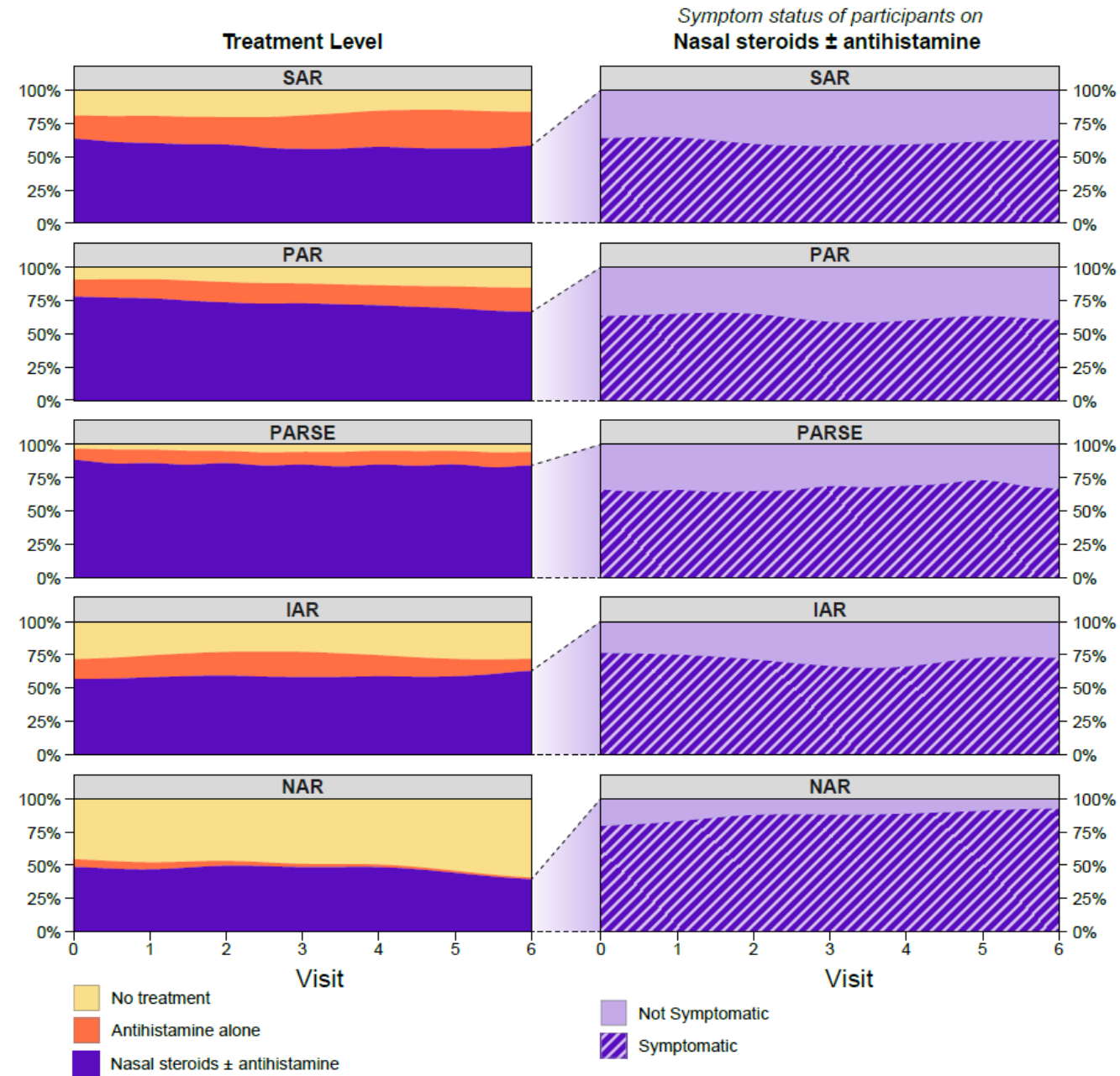


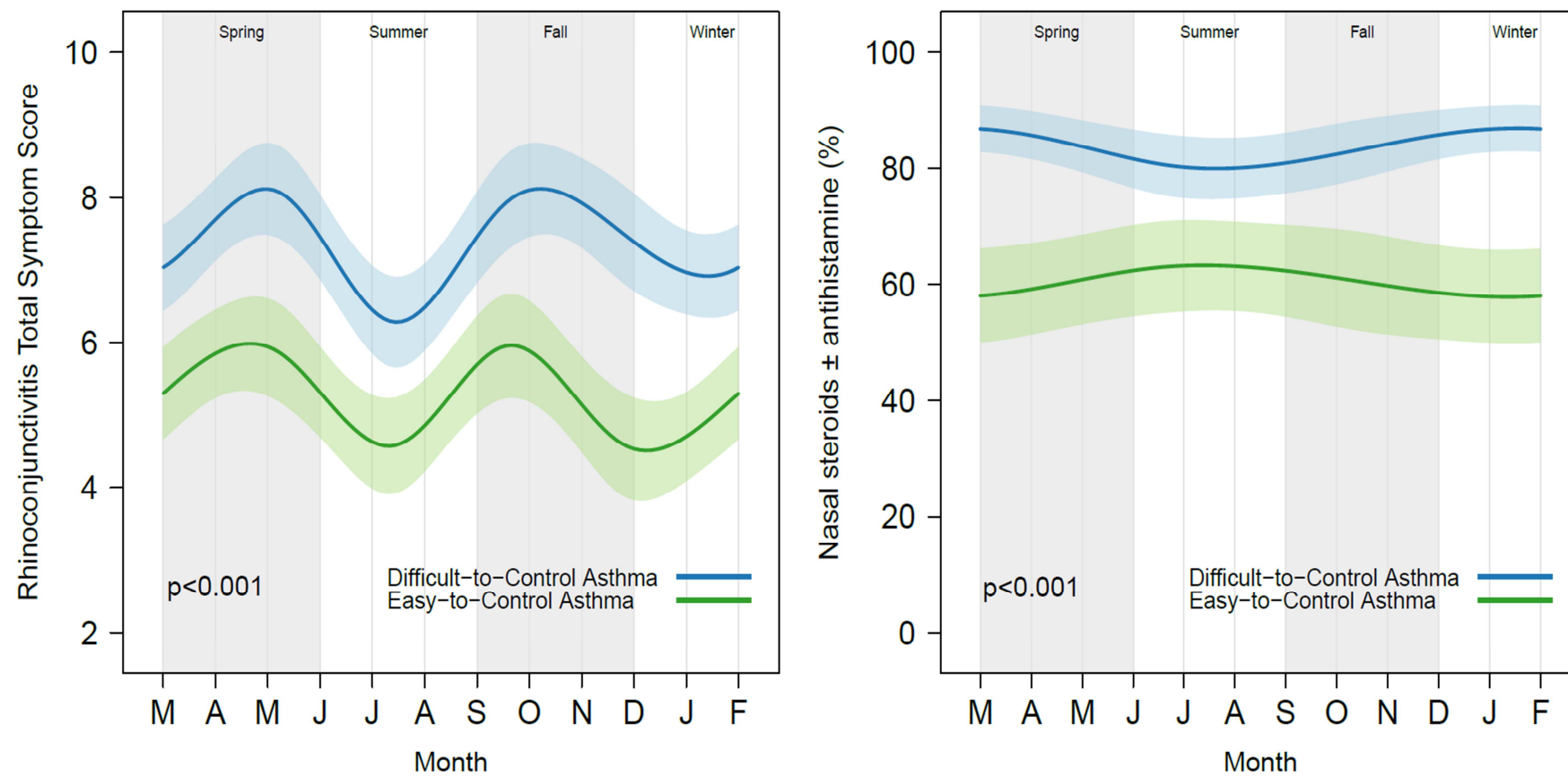
**Figure 4**

Figure 5

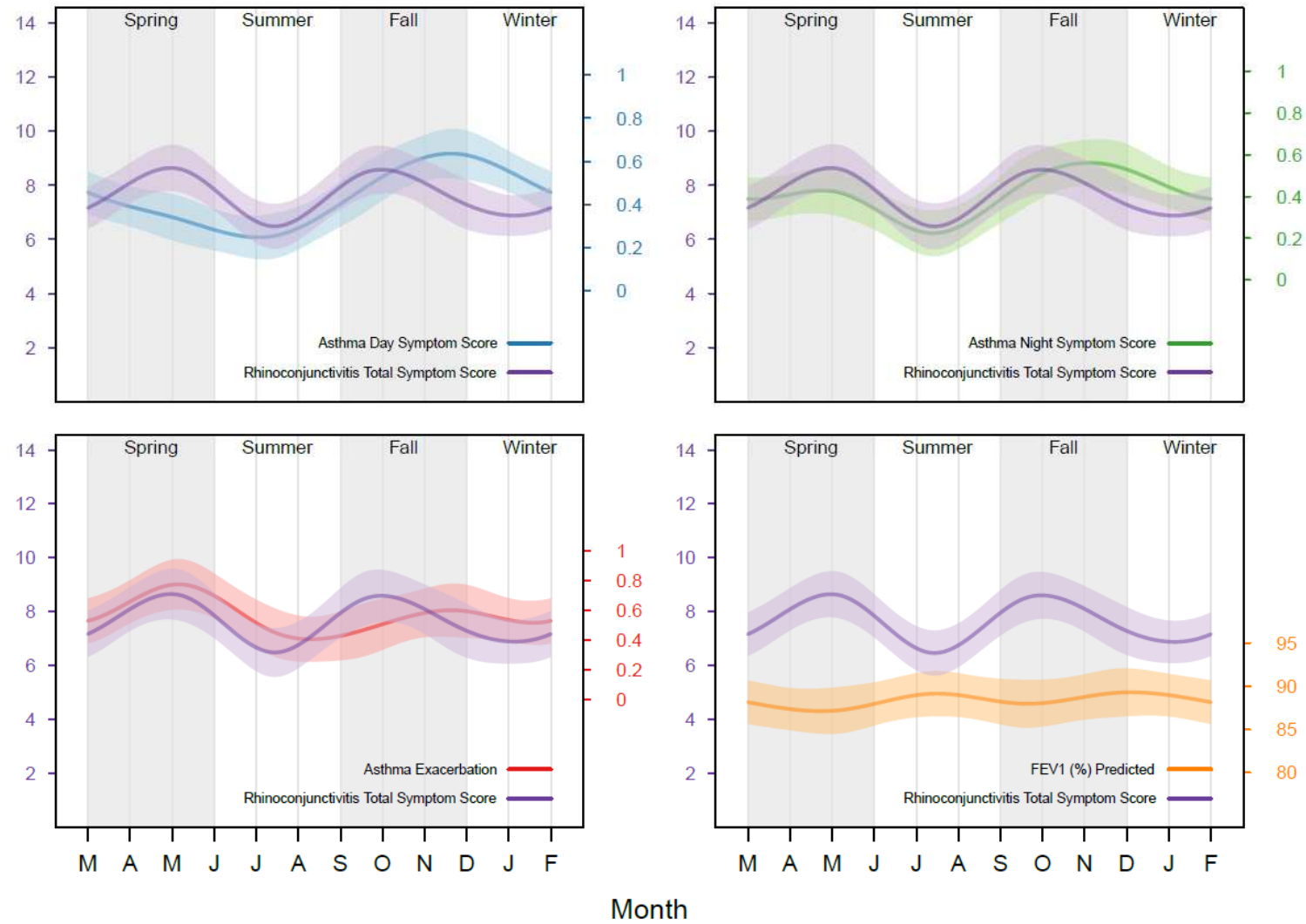


**Table E1****Evaluations for Aeroallergen Sensitization**

| <b>Skin Prick Tests</b>                                                                                                                        | <b>Serum Specific IgE</b>                 |
|------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|
| Mouse                                                                                                                                          | German Cockroach                          |
| Rat                                                                                                                                            | American Cockroach                        |
| Dog                                                                                                                                            | <i>D farinae</i>                          |
| Cat                                                                                                                                            | <i>D pteronyssinus</i>                    |
| Mite ( <i>D. pteronyssinus</i> <i>D. farinae</i> )                                                                                             | Cat dander                                |
| German Cockroach                                                                                                                               | Dog dander                                |
| American Cockroach                                                                                                                             | Mouse urine proteins                      |
| <i>Alternaria tenuis</i>                                                                                                                       | Rat urine proteins                        |
| <i>Aspergillus fumigatus</i>                                                                                                                   | <i>Alternaria alternate</i>               |
| Ragweed Mix                                                                                                                                    | <i>Aspergillus fumigatus</i>              |
| Eastern 8 tree mix (American Elm, American Beech, Eastern Cottonwood, Red Oak, Red/River Birch, Shagbark Hickory, White Ash, Maple Sugar/Hard) | Oak                                       |
| K-O-T grass mix (Kentucky, Blue/June, Orchard, Timothy)                                                                                        | Birch                                     |
| Bermuda Grass (only performed at the Dallas, Denver, and Washington DC sites)                                                                  | Maple – Box Elder ( <i>Acer negundo</i> ) |
| Juniper (only performed at the Cincinnati, Dallas, and Denver sites)                                                                           | <i>Cladosporium herbarum</i>              |
|                                                                                                                                                | Ragweed                                   |
|                                                                                                                                                | Timothy grass                             |

**Table E2****Rhinitis Diagnosis Algorithm**

| <b>Diagnosis</b>         | <b>Number of Symptoms Reported</b> | <b>Doctor's Diagnosis</b> |
|--------------------------|------------------------------------|---------------------------|
| <b>No Rhinitis</b>       | 0                                  | Yes                       |
|                          | 1                                  | No                        |
| <b>Possible Rhinitis</b> | 1                                  | Yes                       |
|                          | 2                                  | No                        |
| <b>Probable Rhinitis</b> | $\geq 2$                           | Yes                       |
|                          | $\geq 3$                           | No                        |

Participants were asked about 5 symptoms (see Appendix 1): sneezing, stuffy nose, runny nose, post-nasal drip, sinus pressure or sinus headaches

**Table E3****Rhinitis Phenotype Definitions****Perennial Allergic Rhinitis<sup>14</sup>****All 3 of the following need to be present for this diagnosis**

1. Possible or Probable Rhinitis/Rhinosinusitis based on Questionnaire
2. (Report nose and/or sinus symptoms all year around) **OR** (Deny nose and/or sinus symptoms all year around AND report symptoms in 5 out of the 6 seasons [early spring, late spring, summer, early fall, late fall, winter])
3. Positive skin test or specific IgE to any of the following: *D. pteronyssinus*/*D. farinae*, German Cockroach, American cockroach, rat, mouse, cat\*, dog\*  
**OR**, if negative to above list, positive to aeroallergens covering early and late spring, summer, and early and late fall

\*if only cat or dog skin tests or specific IgEs are positive, must have cat and/or dog at home

**Seasonal Allergic Rhinitis (SAR)****All 4 of the following need to be present for this diagnosis**

1. Possible or Probable Rhinitis/Rhinosinusitis based on Questionnaire
2. Deny nose and/or sinus symptoms all year around
3. Report at least 1 and less than 5 seasons (early spring, late spring, summer, early fall, late fall, winter) when nose and/or sinus symptoms are present
4. Positive by skin test or specific IgE to at least 1 seasonal pollen aeroallergen relevant to at least one of the symptomatic seasons.

**Perennial Allergic Rhinitis with Seasonal Exacerbations (PARSE)****All 4 of the following need to be present for this diagnosis**

1. Possible or Probable Rhinitis/Rhinosinusitis based on Questionnaire
2. (Report nose and/or sinus symptoms all year around) **OR** (Deny nose and/or sinus symptoms all year around AND report symptoms in 5 out of the 6 seasons [early spring, late spring, summer, early fall, late fall, winter])
3. Positive skin test or specific IgE to any of the following: *D. pteronyssinus*/*D. farinae*, German Cockroach, American cockroach, rat, mouse, cat\*, dog\*
4. Positive by skin test or specific IgE to at least 1 seasonal pollen aeroallergen relevant to at least one of the “worse” seasons.

\*if only cat or dog skin tests or specific IgE are positive, must have cat/dog at home

**Nonallergic Rhinitis****Both of the following need to be present for this diagnosis**

1. Possible or Probable Rhinitis/Rhinosinusitis based on Questionnaire
2. All skin tests and specific IgEs are negative

**Indeterminate Atopic Rhinitis**

**Both of the following need to be present for this diagnosis**

1. Possible or Probable Rhinitis/Rhinosinusitis based on Questionnaire
2. Positive skin test(s) or specific IgE(s), but nasal symptoms not seasonally relevant to any of the positive aeroallergens

**Table E4****Rhinitis Symptom Scoring System**

| <b>Days in past 2 weeks<br/>having a symptom<br/>(Frequency)</b> | <b>Score</b> |
|------------------------------------------------------------------|--------------|
| 0 Days                                                           | 0            |
| 1-3 Days                                                         | 1            |
| 4-7 Days                                                         | 2            |
| >7 Days                                                          | 3            |
|                                                                  |              |
| <b>Degree of Bother of<br/>that symptom<br/>(Severity)</b>       |              |
| Not Bothered                                                     | 0            |
| Somewhat Bothered                                                | 1            |
| Bothered a Lot                                                   | 2            |

The symptoms queried are: “stuffy or blocked nose”, “runny nose”, “sneezing” and “itchy, watery eyes” (see Appendix 3 for the questionnaire)

**Table E5****Standardized Rhinitis Treatment Steps**

| <b>Step</b> | <b>Allergic Rhinitis</b>                                                                                                                                                                                                                                                           | <b>Non-Allergic Rhinitis</b>                                         |
|-------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------|
| 0           | No medication                                                                                                                                                                                                                                                                      | No medication                                                        |
| 1           | cetirizine 10 mg PRN <b>or</b><br><br>montelukast 5 mg PO QD for 6 to 14 years of age; 10 mg PO QD for $\geq 15$ years of age<br>(treatment option only if this is a pre-study medication)                                                                                         | N/A                                                                  |
| 2           | fluticasone propionate nasal spray 200 mcg QD (2 sprays per nostril) <b>plus</b><br><br>cetirizine 10 mg PRN <b>or</b><br><br>montelukast 5 mg PO QD for 6 to 14 years of age; 10 mg PO QD for $\geq 15$ years of age<br>(treatment option only if this is a pre-study medication) | fluticasone propionate nasal spray 200 mcg QD (2 sprays per nostril) |

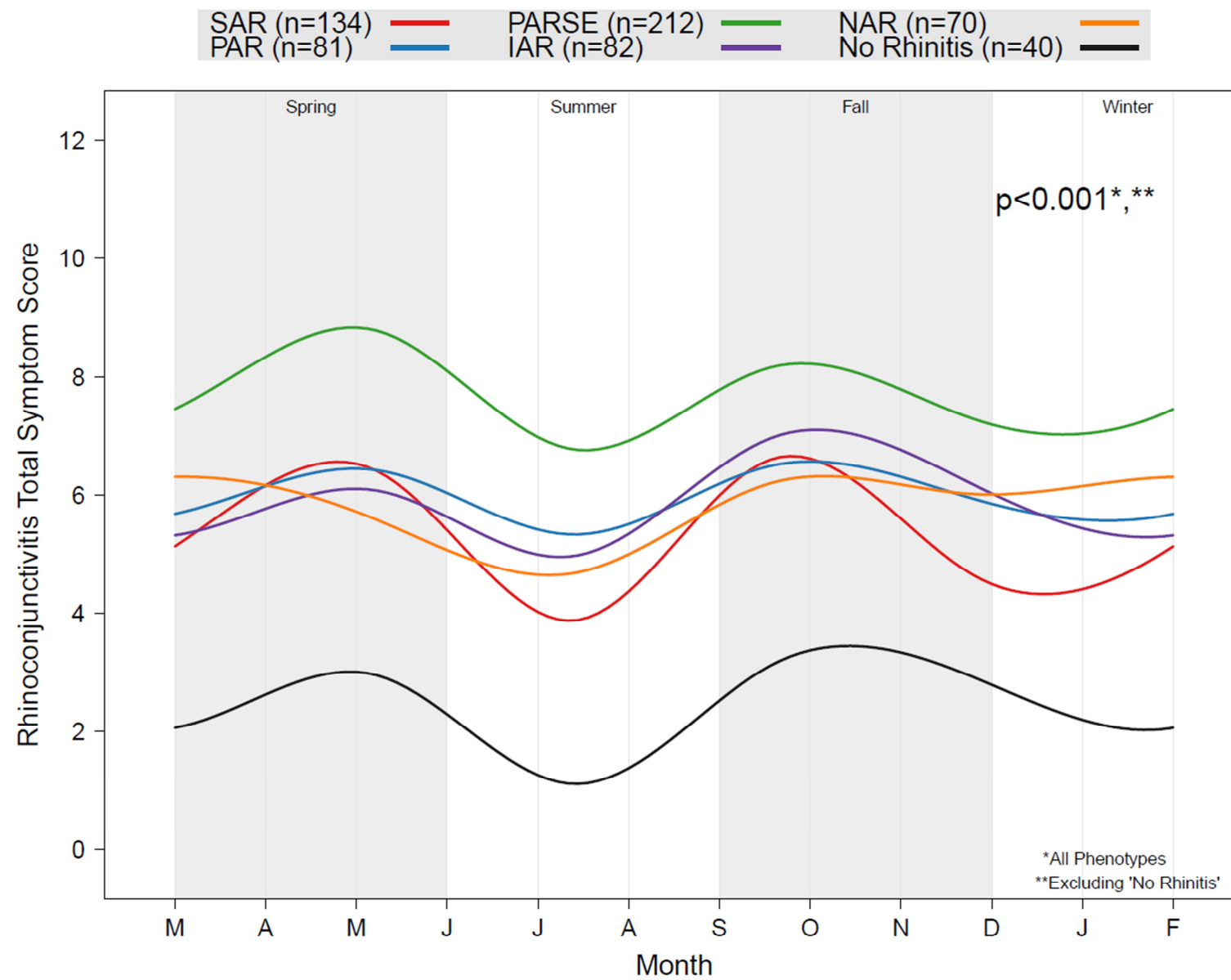
**Table E6****Rhinitis Treatment Algorithm**

| <b>Days in past 2 weeks<br/>having any symptoms<br/>(Frequency)</b> | <b>“Not Bothered”<br/>(Severity)</b> | <b>“Somewhat<br/>Bothered”<br/>(Severity)</b> | <b>“Bothered a<br/>Lot” (Severity)</b> |
|---------------------------------------------------------------------|--------------------------------------|-----------------------------------------------|----------------------------------------|
| 0 Days                                                              | Decrease to the<br>next lower step   |                                               |                                        |
| 1-3 Days                                                            | No change                            | No change                                     | Increase to the<br>next higher step    |
| 4-7 Days                                                            | No change                            | Increase to the<br>next higher step           | Increase to the<br>next higher step    |
| >7 Days                                                             | Increase to the<br>next higher step  | Increase to the<br>next higher step           | Increase to the<br>next higher step    |

**Supplemental Figure Legends**

SUPPLEMENTAL FIGURE 1. Seasonal variation in rhinoconjunctivitis total symptom scores by rhinitis phenotypes. The rhinitis phenotypes are denoted as Seasonal Allergic Rhinitis (SAR; red), Perennial Allergic Rhinitis (PAR; blue), Perennial Allergic Rhinitis with Seasonal Exacerbations (PARSE; green), Indeterminate Atopic Rhinitis (IAR, purple), Non-Allergic Rhinitis (NAR; orange), and No Rhinitis (black). P-values correspond to a comparison of seasonal trend across all phenotypes, with and without the No Rhinitis group

Figure E1



|                                                         |                                 |                               |                     |
|---------------------------------------------------------|---------------------------------|-------------------------------|---------------------|
| <b>Asthma Phenotypes in the Inner City</b>              |                                 |                               | Place ID label here |
| <b>RHINITIS/RHINOSINUSITIS DIAGNOSTIC QUESTIONNAIRE</b> |                                 |                               |                     |
| Participant's Initials<br>_____                         | Interviewer's Initials<br>_____ | Visit Date<br>_ _ / _ _ / _ _ | Visit<br>_____      |

[Form values are used in MEDS Program.]

[Interviewer] "Now I have some questions for you about [your/PARTICIPANT'S] nose and sinuses."

- Has a doctor ever told [you/PARTICIPANT] that [you have/PARTICIPANT has] hay fever or allergic rhinitis or allergies in the nose?  
 Yes .....1  
 No.....0
- Has a doctor ever told [you/PARTICIPANT] that [you have/PARTICIPANT has] chronic sinusitis, recurrent sinusitis or [do you/does PARTICIPANT] get **more than 2** episodes of acute sinusitis in one year for which a doctor prescribes treatment with antibiotics?  
 Yes .....1  
 No.....0
- Over the past 12 months, [do you/does PARTICIPANT] sneeze when [you do not/PARTICIPANT does not] have a cold or the flu?  
 Yes .....1  
 No.....0
- Over the past 12 months, [do you/does PARTICIPANT] get a stuffy nose when [you do not/PARTICIPANT does not] have a cold or the flu?  
 Yes .....1  
 No.....0
- Over the past 12 months, [do you/does PARTICIPANT] get a runny nose when [you do not/PARTICIPANT does not] have a cold or the flu?  
 Yes .....1  
 No.....0
- Over the past 12 months, [do you/does PARTICIPANT] have post-nasal drip (secretions dripping in the back of your throat) when [you do not/PARTICIPANT does not] have a cold or the flu?  
 Yes .....1  
 No.....0
- Over the past 12 months, [do you/does PARTICIPANT] get sinus pressure OR sinus headaches when [you do not/PARTICIPANT does not] have a cold or the flu?  
 Yes .....1  
 No.....0

|                                                  |                                 |                              |                     |
|--------------------------------------------------|---------------------------------|------------------------------|---------------------|
| Asthma Phenotypes in the Inner City              |                                 |                              | Place ID label here |
| RHINITIS/RHINOSINUSITIS DIAGNOSTIC QUESTIONNAIRE |                                 |                              |                     |
| Participant's Initials<br>_____                  | Interviewer's Initials<br>_____ | Visit Date<br>____/____/____ | Visit<br>_____      |

8. [Do you/Does PARTICIPANT] have nose and/or sinus symptoms all year round?

Yes ..... 1  
No ..... 0 [SKIP TO 11]

| 8a.  | Is/are any season(s) worse? | Yes | No |
|------|-----------------------------|-----|----|
| 8a1. | Early Spring .....          | 1   | 0  |
| 8a2. | Late Spring .....           | 1   | 0  |
| 8a3. | Summer .....                | 1   | 0  |
| 8a4. | Early Fall .....            | 1   | 0  |
| 8a5. | Late Fall .....             | 1   | 0  |
| 8a6. | Winter .....                | 1   | 0  |

[AFTER COMPLETION OF 8a, SKIP TO 11]

9. During which season or seasons [do you/does PARTICIPANT] get nose and/or sinus symptoms?

|                        | Yes | No |
|------------------------|-----|----|
| 9a. Early Spring ..... | 1   | 0  |
| 9b. Late Spring .....  | 1   | 0  |
| 9c. Summer .....       | 1   | 0  |
| 9d. Early Fall .....   | 1   | 0  |
| 9e. Late Fall .....    | 1   | 0  |
| 9f. Winter .....       | 1   | 0  |

10. Of the seasons selected above is/are any season(s) worse?

|                         | Yes | No | Not Applicable |
|-------------------------|-----|----|----------------|
| 10a. Early Spring ..... | 1   | 0  | [a]            |
| 10b. Late Spring .....  | 1   | 0  | [a]            |
| 10c. Summer .....       | 1   | 0  | [a]            |
| 10d. Early Fall .....   | 1   | 0  | [a]            |
| 10e. Late Fall .....    | 1   | 0  | [a]            |
| 10f. Winter .....       | 1   | 0  | [a]            |

11. [Do you/does PARTICIPANT] live with:

|                          | Yes | No |
|--------------------------|-----|----|
| 11a. Cats .....          | 1   | 0  |
| 11b. Dogs .....          | 1   | 0  |
| 11c. Other animals ..... | 1   | 0  |
| 11c1. Specify: _____     |     |    |

|                                         |                           |                                   |                     |
|-----------------------------------------|---------------------------|-----------------------------------|---------------------|
| Asthma Phenotypes in the Inner City     |                           |                                   | Place ID label here |
| MODIFIED RHINITIS SYMPTOM UTILITY INDEX |                           |                                   |                     |
| Participant's Initials<br>_____         | Staff's Initials<br>_____ | Completion Date<br>____/____/____ | Visit<br>_____      |

[Form values are used in MEDS Program.]

[Interviewer] "I would like to ask about symptoms [you/PARTICIPANT] may have had DURING THE PAST 2 WEEKS from [your/his/her] nose and eyes, how frequently [you/he/she] had these symptoms, and how bothered by these symptoms [you were/he/she was]."

It is important that the participant, with the assistance of the parent/guardian as needed, answer the questions.

1. How many days [have you/has PARTICIPANT] had a stuffy or blocked nose during the past 2 weeks?  
None.....0 [SKIP TO 3]  
1-3 days.....1  
4-7 days.....2  
8-14 days.....3
2. On average, how bothersome was [your/PARTICIPANT'S] stuffy or blocked nose during the past 2 weeks?  
Not bothered at all.....0  
Somewhat bothered.....1  
Bothered a lot.....2
3. How many days [have you/has PARTICIPANT] had a runny nose during the past 2 weeks?  
None.....0 [SKIP TO 5]  
1-3 days.....1  
4-7 days.....2  
8-14 days.....3
4. On average, how bothersome was [your/PARTICIPANT'S] runny nose during the past 2 weeks?  
Not bothered at all.....0  
Somewhat bothered.....1  
Bothered a lot.....2
5. How many days [have you/has PARTICIPANT] had sneezing during the past 2 weeks?  
None.....0 [SKIP TO 7]  
1-3 days.....1  
4-7 days.....2  
8-14 days.....3
6. On average, how bothersome was [your/PARTICIPANT'S] sneezing during the past 2 weeks?  
Not bothered at all.....0  
Somewhat bothered.....1  
Bothered a lot.....2
7. How many days [have you/has PARTICIPANT] had itching, watery eyes during the past 2 weeks?  
None.....0 [SKIP TO 9]  
1-3 days.....1  
4-7 days.....2  
8-14 days.....3
8. On average, how bothersome were [your/PARTICIPANT'S] itching, watery eyes during the past 2 weeks?  
Not bothered at all.....0  
Somewhat bothered.....1  
Bothered a lot.....2
9. How many days [have you/has PARTICIPANT] had itching nose or throat during the past 2 weeks?  
None.....0 [SKIP TO 11]  
1-3 days.....1  
4-7 days.....2  
8-14 days.....3
10. On average, how bothersome was [your/PARTICIPANT'S] itching nose or throat during the past 2 weeks?  
Not bothered at all.....0  
Somewhat bothered.....1  
Bothered a lot.....2

**Supplemental Figure Legends**

SUPPLEMENTAL FIGURE 1. Seasonal variation in rhinoconjunctivitis total symptom scores by rhinitis phenotypes. The rhinitis phenotypes are denoted as Seasonal Allergic Rhinitis (SAR; red), Perennial Allergic Rhinitis (PAR; blue), Perennial Allergic Rhinitis with Seasonal Exacerbations (PARSE; green), Indeterminate Atopic Rhinitis (IAR, purple), Non-Allergic Rhinitis (NAR; orange), and No Rhinitis (black). P-values correspond to a comparison of seasonal trend across all phenotypes, with and without the No Rhinitis group

SUPPLEMENTAL FIGURE 2. Questions used for diagnosis of rhinitis. The rhinitis diagnostic questions were administered to all participant at first visit. For those not classified as rhinitics at the first visit, the questions were re-administered at a later point in the APIC study when the participant reported rhinitis symptoms.

SUPPLEMENTAL FIGURE 3. Questions used for classifying rhinitis phenotypes. After a participant met the diagnostic criteria for rhinitis, these questions were administered to determine the seasonality of the symptoms and pet exposures. The responses were combined with the results of the participant's allergen skin test reactivity to classify the participant into one of the 5 rhinitis phenotypes.

SUPPLEMENTAL FIGURE 4. Questions used for monitoring rhinitis activity. At every visit the Modified Rhinitis Symptoms Utility Index questions were administered to determine the number of days a participant experienced symptoms of rhinitis and the impact on the participant's life.