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Original Article

High physician adherence to phenotype-specific asthma guidelines, but large variability in phenotype assessment in children.

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Abstract

Background: The implementation of international pediatric asthma guidelines hinges on the distinction between intermittent and persistent phenotypes and the prescription of recommended phenotype-specific pharmacotherapy.

Objectives: To ascertain key factors associated with specialist-confirmed phenotype and document physicians' adherence to practice recommendations in an academic pediatric asthma centre.

Design/Methods: Using electronic health records, we identified a cohort of children aged 1-17 years who presented to a tertiary-care Asthma Centre

between 2002-2007 and received a diagnosis of asthma from a pediatric specialist. Outcomes included: determinants of phenotypes and conformity with phenotype-specific treatment recommendations.

Results: Of the 3490 eligible children (11,119 visits), most (47%) were preschoolers, 35% were 6-11 years and 18%, 13-17 years. Of children with confirmed asthma, 59% were classified on presentation as having intermittent, 41% as persistent, asthma. The within-patient phenotype varied over time with a consistency index of 0.76 (best=1); the latter was significantly lower in preschoolers than older children ($p<0.0001$). The persistent phenotype was highly physician-dependent; it was also positively associated with child's age, asthma severity, multiple triggers, calendar year, and duration of follow-up. Compared to 33% of children with intermittent asthma, 82% of those with persistent asthma were prescribed a maintenance controller, most as monotherapy; combination therapy was usually prescribed after a trial of monotherapy.

Conclusion: Pediatric asthma specialists were highly adherent to phenotype-specific pharmacotherapy. However, even in an academic centre, the notable degree of intra-patient and between-physician variation in phenotype, particularly in preschoolers, was an important impediment to prescribing a maintenance controller. The findings underline the importance of developing validated and standardized means of assessing phenotypes, applicable to the whole pediatric age spectrum.

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ORIGINAL ARTICLE

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Keywords: asthma; children; asthma phenotype; intra-patient variability; pharmacotherapy; inhaled corticosteroids; physician prescription patterns

ABSTRACT

Background: The implementation of international pediatric asthma guidelines hinges on the distinction between intermittent and persistent phenotypes and the prescription of recommended phenotype-specific pharmacotherapy.

Objectives: To ascertain key factors associated with specialist-confirmed phenotype and document physicians' adherence to practice recommendations in an academic pediatric asthma centre.

Design/Methods: Using electronic health records, we identified a cohort of children aged 1-17 years who presented to a tertiary-care Asthma Centre between 2002-2007 and received a diagnosis of asthma from a pediatric specialist. Outcomes included: determinants of phenotypes and conformity with phenotype-specific treatment recommendations.

Results: Of the 3490 eligible children (11,119 visits), most (47%) were preschoolers, 35% were 6-11 years and 18%, 13-17 years. Of children with confirmed asthma, 59% were classified on presentation as having intermittent, 41% as persistent, asthma. The within-patient phenotype varied over time with a consistency index of 0.76 (best=1); the latter was significantly lower in preschoolers than older children ($p<0.0001$). The persistent phenotype was highly physician-dependent; it was also positively associated

with child's age, asthma severity, multiple triggers, calendar year, and duration of follow-up. Compared to 33% of children with intermittent asthma, 82% of those with persistent asthma were prescribed a maintenance controller, most as monotherapy; combination therapy was usually prescribed after a trial of monotherapy.

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Conclusion: Pediatric asthma specialists were highly adherent to phenotype-specific pharmacotherapy. However, even in an academic centre, the notable degree of intra-patient and between-physician variation in phenotype, particularly in preschoolers, was an important impediment to prescribing a maintenance controller. The findings underline the importance of developing validated and standardized means of assessing phenotypes, applicable to the whole pediatric age spectrum.

INTRODUCTION

Despite strong evidence-based asthma guidelines for the management of school-aged children and adults,¹⁻⁴ most children remained inadequately controlled with frequent symptoms, preventable hospitalizations, and impaired quality of life.⁵ Children with asthma, their family and healthcare professionals all share a role in achieving optimal asthma control. Our specific interest laid in ascertaining physicians' implementation of evidence-based practice guidelines in childhood asthma.

To optimally manage children with asthma, physicians must confirm the diagnosis, correctly ascertain the clinical presentation (hereafter termed "phenotype") and control, and prescribe appropriate phenotype-specific management. In school-aged children, the diagnosis of asthma is supported by objective documentation of both obstruction and airway hyperresponsiveness. However, in younger children, the diagnosis is usually based on a series of clinical criteria (symptom pattern, family history, physical findings) and the absence of an alternative diagnosis;^{1-4,6} some task forces even hesitate to diagnose asthma in young children.⁷ Correctly identifying the phenotype is a significant challenge due in part, to third party reporting of symptoms by parents and the variety (and increasing number) of available classifications, some amalgamating, others dissociating, temporal symptom pattern, triggers, and long-term prediction of outcome.^{1,7-11} Moreover, the distinction between persistent and intermittent asthma is not trivial, as it is directly associated with the recommendation or not to prescribe a daily controller.^{1-4,6} As specialists generally conform better than non-specialists on management decisions when surveyed using case scenarios,^{12,13} we hypothesize that, in settings where children were treated by asthma specialists with on-site access to lung function, allergy testing, and asthma education, one would expect accurate phenotype classification and pharmacologic management.

The objectives of the study were to ascertain the distribution and determinants of asthma phenotypes, based largely on the temporal pattern of airflow limitation as proposed by the Global Initiative for Asthma (GINA),^{14;15} explore the relationship with a trigger-based phenotype classification, and determine physicians' adherence to phenotype-specific practice guidelines in children treated in a tertiary-care pediatric asthma centre.

PATIENTS AND METHODS

Study design

We conducted a retrospective cohort study of children who presented to the Asthma Centre, a tertiary care pediatric consultation clinic between 2002 and 2007. Most patients were referred for diagnosis and management following emergency department visits, hospital admissions or by pediatricians, adult specialists, or general practitioners; less than 20% were self-referred. The protocol was approved by the Scientific Review Boards of the Montreal Children's Hospital and Sainte-Justine University Health Centre. Permission to access medical records without patient consent was granted by the Director of Professional Services of the Montreal Children's Hospital.

Data sources and collection

In 1999, the Asthma Centre adopted a structured clinic intake sheet to create electronic health records using automated data entry with Teleform (Cardiff Software v7, Inc., Vista, CA) with pre-programmed conditions to verify the quality of data entry; clinic sheets with incomplete, out-of-range or unclear critical fields were returned to the treating physician within 24 hours of the visit to ensure completeness

and accuracy of the data. We cross-checked electronic records with the computerized appointment database that logged all appointments and obtained missing clinic sheets. Between 2002 and 2007, the Asthma Centre electronic health records comprised 99% of all visits to our centre.

The electronic health records contained several critical variables including: patient demographics; physician assessment of asthma diagnosis, phenotype, severity and control; lung function, when applicable; and prescribed drugs. Asthma phenotype was defined as the absence (intermittent) or presence of airflow limitation between episodes (persistent) and the occurrence of airflow limitation solely during specific allergic seasons (seasonal), based on 2002 and 2005 Global Initiative for Asthma's definition;^{14;15} symptoms were used in children too young to cooperate to lung function testing. Airflow limitation was defined as a forced expiratory volume in 1 sec (FEV₁) of less than 80% of personnel best or, if not available, of predicted values and/or a reduced FEV₁/FVC ratio below that predicted for age and sex. In children too young to cooperate with spirometry, interim symptoms with effort or other triggers were explored; in their absence, the child was deemed as having intermittent asthma, and otherwise, persistent asthma. These criteria were standardized across physicians. In children taking daily controller medication, the absence of symptoms and normal lung function suggested adequate asthma control. Severity was assessed by the intensity and frequency of symptoms and/or on the amount of daily medication required to achieve control.^{1;4;16} The prospective documentation of triggers allowed *a posteriori* re-classification of children with two or more recognized triggers into multiple-trigger asthma, while those with single triggers were grouped under viral-only, allergic only or exercise-only asthma, in line with the 2008 PRACTALL and ERS task force.^{7;8} Prescribed controllers for maintenance therapy and step-up during exacerbations were recorded separately, with drug name, strength, and dose. Asthma Centre physicians were all academic pediatric asthma

specialists, with a certification in pediatrics (100%), allergy/immunology (20%) and/or respirology (10%) working in this multidisciplinary clinic; new patients were allocated to the first available physician, irrespective of specialty. Physicians' identifiers were coded to maintain confidentiality. The data was merged with that of the *Régie de l'assurance-maladie du Québec* (RAMQ) database that provided date, site, and International Classification of Diseases 9th version diagnostic codes of all acute care visits to ascertain healthcare utilization in the preceding year.

Subjects

Children presenting between January 1, 2002 and December 31, 2007 were eligible if they were: 1 to 17 years old; covered by the RAMQ health care; and diagnosed or suspected of asthma by an Asthma Centre physician who treated over 100 patients during the study period. The latter criterion served to eliminate trainees and locum physicians. Children with other chronic lung diseases were excluded. The date at which the patient first filled all inclusion criteria constituted the index date and the follow-up period ended at the last Asthma Centre visit or December 31, 2007, whichever occurred first. Patients were generally followed until control was achieved with the minimal effective dose, before returning to their treating physician.

Outcomes

The outcomes included distribution, determinants, and within-patient stability of phenotypes; prescription patterns of children with intermittent asthma; in children with persistent asthma, prescription conformity to: maintenance controller medication; trial of monotherapy trial prior to

combination therapy; use of long-acting β 2-agonist only in combination of a controller; and no initiation or dose increase of inhaled corticosteroids during exacerbations.

Statistical analyses

There was no sample calculation for this quality-of-care assessment. We examine differences in characteristics of children with different phenotypes, using unpaired t-tests, and analysis of variance for continuous variables, and chi-square tests for categorical variables. To examine the within-patient variability in phenotype and analogous to the continuity-of-care index¹⁷, we develop a consistency-of-phenotype index, defined as the ratio of sum of medical visits with a different phenotype over the product of total number of medical visits times the number of visits for each given phenotype (1 indicating the same phenotype in 100% of visits). Determinants of persistent phenotype on the index visit were examined with multivariate generalized linear regression models using binomial distribution. Candidate variables included age, gender, ethnicity, neighborhood financial income determined from 6-digit postal code as a surrogate,¹⁸ asthma severity, individual physicians or specialty, asthma triggers,⁷ year of visit (to account for potential secular changes in assessment or management), acute-care visits for asthma in the previous year, and spirometry, when available. We repeated the analysis using all patient visits, adding as candidate variables, the continuity-of-care index which reflects the extent to which a child saw the same physician during the observation period (1 indicating 100% of visits with the same physician),¹⁷ and duration of follow-up; we adjusted for within-patient correlation and an offset was used to account for varying person-time of observation, when applicable. P-values less than 0.05 indicated statistical significance, with no correction for multiple testing. Analyses were performed using SAS software (version 9.2, SAS Institute Inc., Cary, NC, USA).

RESULTS

Of 3874 patients who presented during the 6-year study period, 3490 eligible children made 11,119 visits and were attended by one or more of 10 physicians. Of these, (47%) were preschoolers, 35% were 6—11 years and 18%, 13—17 years. At the index visit, almost half of children were deemed to have intermittent asthma, 35%, persistent asthma, 14%, unconfirmed asthma, and only 1% had seasonal asthma. (Figure 1) Children with unconfirmed asthma, that is, in whom the physician was unable to confirm or infirm the diagnosis at the index visit, were predominantly preschoolers (66%), most (58%) having no identified triggers; and when cooperative with spirometry, they generally had normal lung function with no significant reversibility to bronchodilators; these children usually underwent a provocation test, therapeutic trial, or further observation to clarify the diagnosis.

Among children with confirmed asthma at the index visit, significant group differences were noted across phenotypes in child's age, ethnicity, severity, control, spirometry, triggers, acute-care visits, and physician specialty. (Table E1) Given the small proportion (1%) of children with seasonal asthma and their similar characteristics to those with persistent asthma, these two phenotypes were hereafter combined for analytical purposes, in line with 2007-2011 national and international guidelines; 59% of patients presented with the intermittent, and 41% with persistent, phenotype (Table 1).¹⁻⁴

During the observation period, 62% of patients visited the Asthma Centre more than once namely 75% of children with persistent, and 47% of those with intermittent, asthma ($P < 0.001$). Overall, a median (25%, 75%) of 3 (1, 5) visits were made by children with persistent asthma and 2 (1, 3) by patients with intermittent asthma, over 14 (5, 32) months. Among children with two or more visits, the median continuity-of-care index was 0.85 (0.48, 1.0) and 0.76 (0.40, 1.0) for patients with persistent and

intermittent asthma, respectively; approximately 21% of patients encountered different Asthma Centre physicians during follow-up.

Within patients, the asthma phenotype varied over time with a consistency index (best=1) of 0.76 (0.5, 1); the consistency index was not significantly different when several physicians assessed the patient, but it increased significantly with age, from 0.62 in children aged 1-5 years, to 0.79 and 0.85 among 6-11 years and 12-17 years old, respectively ($P < 0.0001$). Overall, 61% of patients maintained the same phenotype over time. When all visits were considered, the persistent phenotype was significantly associated with the child's age, (Figure 2) severity, triggers, calendar year, treating physician, and duration of follow-up. (Figure 3) The former five determinants remain significantly associated with phenotype when the analysis was restricted to the index visit (where follow-up duration was not relevant), underlying the robustness of findings. The same model held true when physicians were grouped by specialty. (Figure E1)

At the index visit, a maintenance controller was prescribed in 82% of children with persistent asthma; overall, most (59%) received monotherapy, usually inhaled corticosteroids. (Table 2) With rare exceptions, long-acting β_2 -agonist was systematically given with inhaled corticosteroids and used as preferred combination therapy in children aged 6 years and older; 83% of so-treated children had received a prior trial of monotherapy. Use of leukotriene receptor antagonists increased from 16% in 2002 to 26% in 2007, with a higher use as combination therapy than monotherapy. In contrast, the majority (67%) of children with intermittent asthma were not prescribed any daily controller. Similar figures were observed when all visits over the follow-up period were considered.

Almost half of children with persistent asthma were asked to step-up their daily dose of inhaled corticosteroids at the onset of a flare-up, whereas initiation of inhaled corticosteroids was preferred for children with intermittent asthma. Rescue oral corticosteroids were rarely recommended in either phenotype.

DISCUSSION

Our findings confirmed the high adherence to recommended phenotype-specific pharmacotherapy of pediatric specialists working in a tertiary care Asthma Centre. The proportion of children with a persistent phenotype based on the temporal pattern of airflow obstruction (or symptoms) increased with the child's age, asthma severity, multiple triggers, calendar year, duration of follow-up, and, importantly, also with specific physicians (or specialty). Despite only two main categories, the within-patient and between-physician variability in phenotype, rather than adherence to phenotype-specific therapy, appeared as a major obstacle to the standardization of care in children treated by asthma specialists.

The importance of an accurate phenotype rests in its impact on therapeutic decision. While various phenotype classifications have been proposed over the years to address the heterogeneity of childhood wheezing, three leading clinically-applicable classifications have emerged, all of which focused on preschool wheezing namely; the 2000 Asthma Predictive Index served to identify predictors of disease evolution,^{9;19} while the 2008 PRACTALL⁸ and ERS Task force⁷ hinged on current symptom pattern and triggers. In 2002, we endorsed the GINA classification based on temporal pattern of airflow limitation (and/or symptoms, in absence of lung function)

and allergic etiology to categorize children into intermittent, persistent (all severity levels combined), and seasonal asthma (a classification that remained unchanged in 2005).^{14;15} Our findings confirmed that the prevalence of the intermittent phenotype peaked at 1 year of age and decreased steadily thereafter, a timeline somewhat analogous to *early transient wheeze*.^{19 10} Similar to previous designations of *non-atopic* and *IgE-associated* wheezing/asthma, the persistent phenotype became most prevalent by 5 years.²² Very few children, however, had seasonal asthma. Of interest, the evolution of phenotypes with age closely resembles previously published hypothetical patterns, thus adding credibility to our findings.²³

In line with prior reports,²⁴ the notable within-subject variability in phenotype, with 39% of children changing phenotype over time, highlights the importance of prospective observation. Five main factors independently contributed to phenotype variation namely: age, follow-up duration, severity, calendar year, triggers, and physicians. Evidently, one would expect that the child's ability to demonstrate, and parents' skills to recognize, symptoms increased with age, as children become increasingly physically active, are exposed to stimuli, and are sensitized to various allergens; moreover, the use of lung function in older children likely improved accuracy and inter-rater variability of classification.²⁵ Children with persistent asthma or more severe asthma had more visits and longer follow-up in the Asthma Centre than those with intermittent asthma who improved spontaneously, explaining the association with persistent asthma and both severity and duration of follow-up. These observations are not surprising as the mandate of our centre is to confirm the diagnosis and management, educate patients and family, and provide guidance to referring physicians for subsequent care. As expected, children with mild episodic symptoms were more rapidly returned to the care of referring physicians than those with

persistent asthma. Perhaps, a secular trend in the increasing recognition of persistent asthma explained the association between calendar year and phenotype.

The temporal pattern of airflow limitation and/or symptoms was associated with triggers, albeit with substantial heterogeneity in the expected distribution of triggers, particularly for the intermittent phenotype (only 48% of whom had viral-only triggers). In fact, the overwhelming majority of children had multi-trigger symptoms (48%), followed by viral-induced (34%) asthma—with very few experiencing solely allergen-, or exercise-induced symptoms. Although phenotypes based on temporal symptom pattern and/or triggers were developed for preschool-aged children, they would appear to apply as well to older children. Perhaps a phenotype definition adding triggers to the temporal pattern of airflow obstruction (or symptoms), such as proposed by the 2008 PRACTALL and ERS task force,^{7;8} would have yield more homogeneous phenotype groups, although the test-retest reliability, the between-physician concordance, and importantly the validity of these expert, yet *ad hoc*, classifications remain to be ascertained. Validation may benefit from non-invasive measurement of lung function, expired nitric oxide, induced sputum, and/or genotype, as well as from documented response to specific pharmacotherapy.^{20;21}

While our study design did not allow us to explore the concordance between physicians for classifying phenotypes in children at the same point in time, physicians differ markedly in the proportion of their patients they diagnosed as having intermittent or persistent asthma; a difference that remained significant after adjustment for other determinants. Admittedly, persistent asthma has received several definitions referring to long-term prognosis,⁹ presence of interim symptoms, and/or multi-triggers.^{7;8}

We hypothesize that the physicians assessment of phenotype varied because of various weight given to different criteria, skill differences in eliciting triggers and symptoms, and variable use of allergy and lung function testing, all of which are components of more recent phenotype classifications.^{10,26} Although new patients were allocated to the next available physician, we cannot rule out the possibility that between-physician variability may reflect in part a different clientele. While this may explain the higher proportion of children identified as having persistent asthma by the two allergists who presumably obtained more allergy testing, it does not explain the opposite observation in the only respirologist. The latter would support the unselected assignment of patients to physicians, irrespective of their specialty. In the absence of a gold standard, these results neither supported nor refuted inaccuracies in individual physician's perception; however, they underlined the importance of a better classification than one based mainly on temporal pattern of airflow limitation and/or symptoms^{14;15} to decrease intra- and inter-physician (and inter-specialty) variability.^{24;27;28}

The overwhelming majority of children with persistent asthma were prescribed a daily controller. These figures are clearly superior to the 50% proportion reported in family physicians and paediatricians,²⁹ suggesting strong agreement with guidelines among academic pediatric asthma specialists. Yet, 18% of children were not prescribed daily controller at the initial visit: while we did not document reasons for these decisions, physicians generally favored a partnership decision approach with parents, in which they sometimes elected to refrain from treating a child (in face of resistant parents) and accept an observational period to better convince parents of the need for daily therapy. As recommended by guidelines,¹⁻⁴ inhaled corticosteroids were the preferred monotherapy; long-acting β 2-agonists, the favored adjunct therapy, was usually given after a trial of monotherapy, a value superior to other practice audits where 25% of combination therapy

were provided to steroid-naïve patients.³⁰ The use of leukotriene receptor antagonists was modest. As expected, only a minority of children with intermittent asthma were prescribed a daily controller.²⁸ Clearly, the phenotype classification has significant impact on the prescription or not of a daily asthma controller.

As home management of exacerbations, most children with persistent asthma were recommended by physicians to step-up their inhaled corticosteroids; this approach initially advocated by most guidelines, was only recently withdrawn in view of the lack of convincing evidence.^{31;32} Few children with persistent asthma were prescribed inhaled corticosteroids as rescue intermittent therapy, a popular yet unproven practice that is now under investigation.^{33;34} Preemptive use of oral corticosteroids was rare; this strategy has not been shown to be effective³⁵ and may be associated with immune suppression in children.³⁶ The heterogeneity in home management of exacerbations is not surprising given the paucity of solid phenotype-specific evidence, resulting in weak or lack of pediatric guidelines recommendations for both phenotypes.^{1;4;6}

The findings must be interpreted in light of the following strengths and limitations. The observational nature of this retrospective cohort allowed an unbiased assessment of phenotype and recommended management in children with confirmed asthma. The systematic documentation of specialist assessment of diagnosis, phenotype, and triggers represented a major advantage over patients' self-reports and pharmaco-epidemiologic using billing diagnoses. Clear documentation of whether therapy was prescribed for maintenance or intermittent use was superior to relying on drug claims. Triggers hinged on the quality of patient reporting and physician charting. Grouping mild, moderate and severe persistent asthma together and contrasting it to intermittent asthma resulted in two main phenotypes,

rather than four phenotypes proposed by the GINA guidelines or other phenotype classification;^{10;11} yet it correlated strongly with the prescription or not of a daily controller. While two phenotypes may be overly simplistic, it should have improved concordance; the remaining variability suggests that the greatest challenge lies in distinguishing between mild persistent and intermittent asthma. Finally, we did not specifically examine phenotype-specific morbidity during the observation period, because of the confounding effect of various treatments and adherence, as well as the complexity of dealing with intra-individual changes in phenotype.

The results of this study apply primarily to children with difficult-to-treat or a new diagnosis of asthma referred for diagnosis and management to pediatric asthma specialists with onsite access to lung function and allergy testing. In a similar cohort of children assessed by primary care physicians and non-pediatric specialists without access to specialized testing, one would expect the variability in the assessment of phenotype and the quality of prescribing to be worse than observed in our study.¹³

CONCLUSIONS

Tertiary-care asthma pediatric specialists adhered well to phenotype-specific asthma treatment guidelines. The ascertainment of phenotype as intermittent or persistent, based on temporal pattern of airflow obstruction or symptoms, was inconsistent in children, varying over time with age, severity, length of follow-up, calendar year, triggers, and importantly, physicians. Rather than adherence to phenotype-specific therapy, variability in phenotype appeared as a major obstacle to the standardization of care and prescription of daily controller in children treated by asthma specialists. The findings underline the importance of developing and validating

standardized tools for assessing phenotypes in children applicable as well, but not only, to preschoolers.

Transparency

Declaration of funding:

This work was funded through a research grant from the Childhood Asthma Foundation, Ontario, Canada.

Declaration of financial/other interest:

Francine M. Ducharme has disclosed that she has received unrestricted donations from Merck, Novartis, and Nycomed to support an electronic database of children with asthma. Jonathan Morin, G. Michael Davis, and Joanie Gingras have no relevant financial relationships to disclose. Francisco J.D. Noya has disclosed that he has received unrestricted grants for educational purposes from GSK, AstraZeneca, Merck, Novartis, and Nycomed. CMRO Peer reviewers on this manuscript have no relevant financial relationships to disclose.

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Legends

Figure 1

The cohort selection is depicted from screening to eligibility. Eligible patients are grouped according to the asthma phenotype recorded at the index visit and listed with their number of visits made subsequently by these patients, irrespective of whether or not they changed phenotype over time.

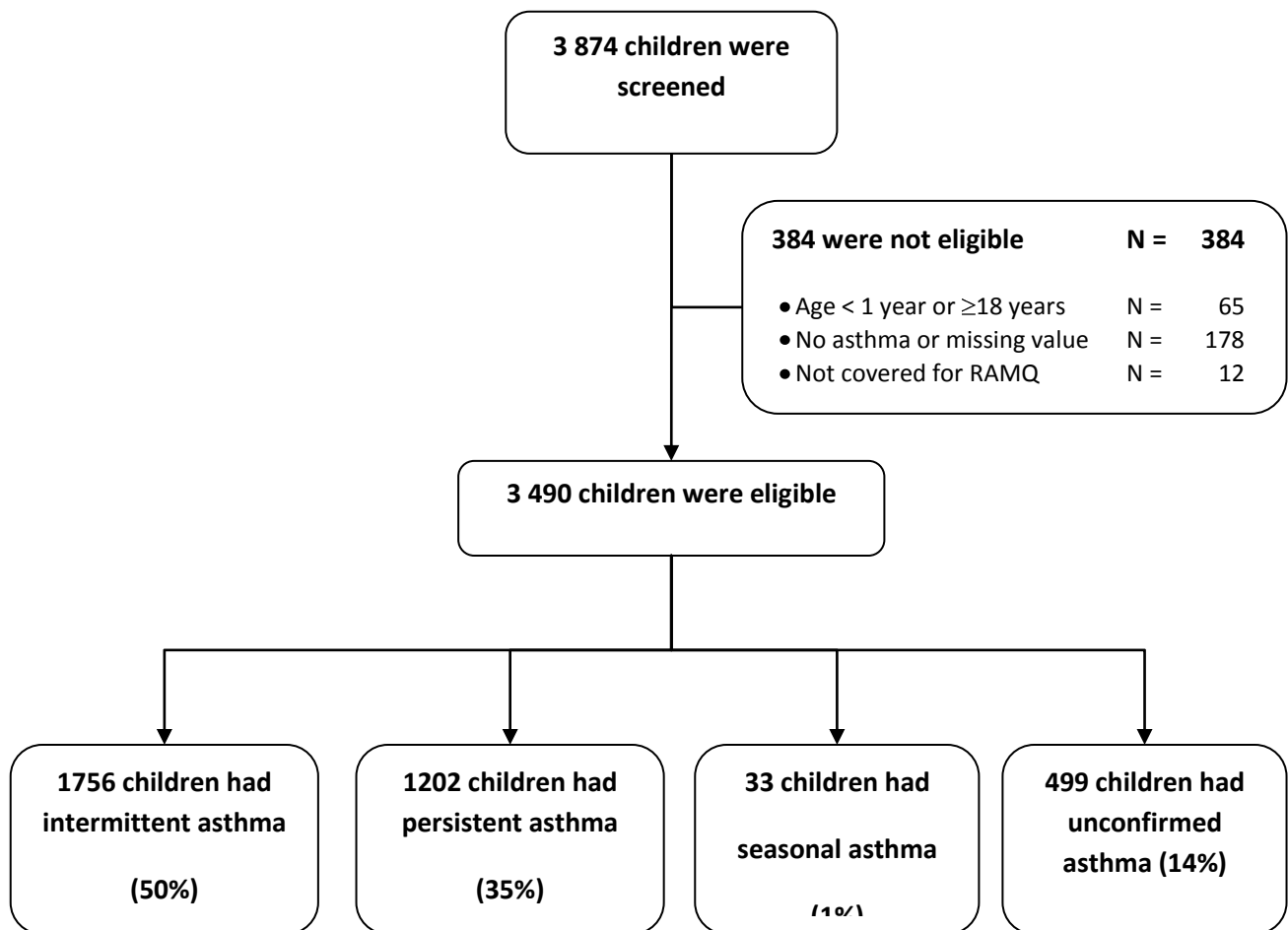


Figure 2

The figure displays the proportion of children labelled as intermittent (dash line) or persistent (solid line) on the y-axis, by age in years on the x-axis, including all visits made by children included in the cohort. The graphic was smooth using SAS GPlot, (version 9.2, SAS Institute Inc., Cary, NC, USA).

% of children

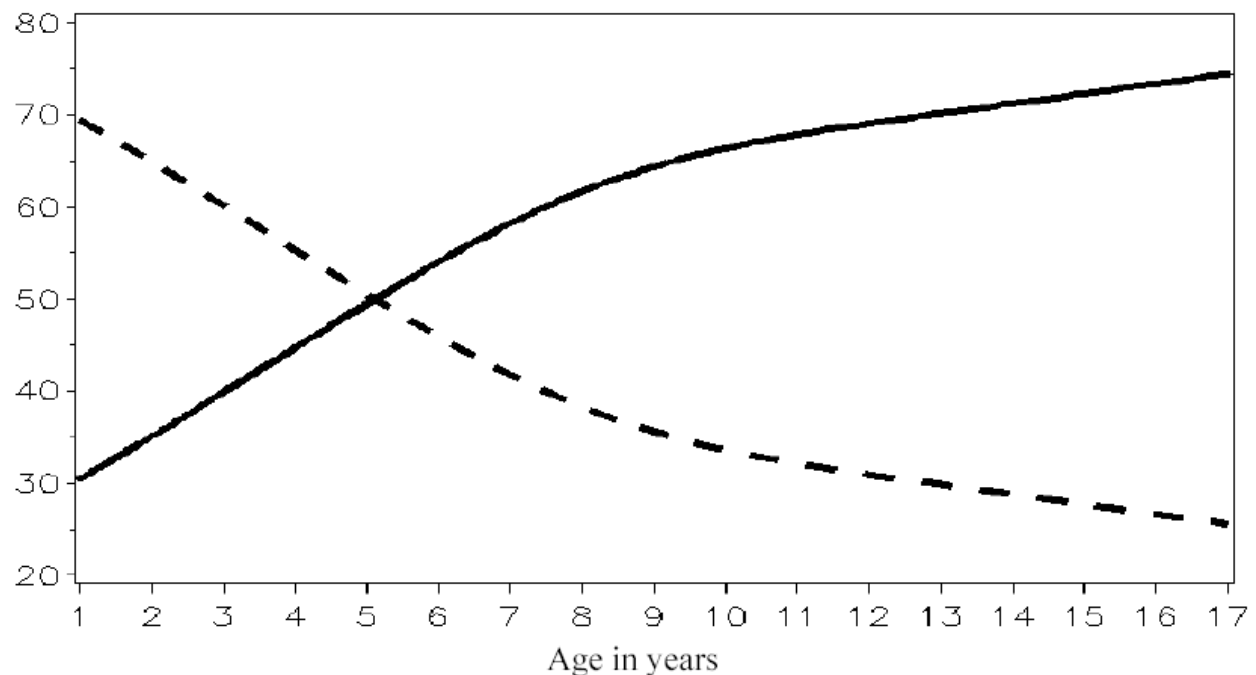


Figure 3

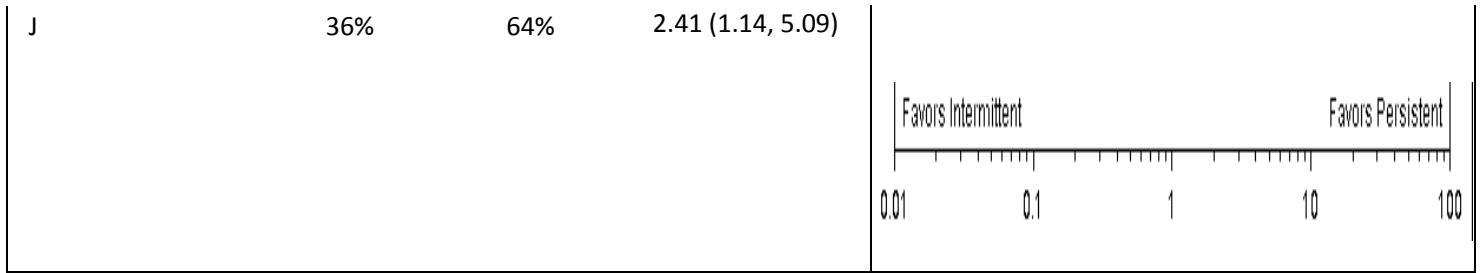
The figure displays the multivariate model predictive of the persistent phenotype. All visits were analyzed using Generalized Estimating Equations, adjusting for within-patient correlation. For each variable, the reference category is identified by an asterisk (*).

Figure 3. Determinants of phenotype

Parameters	Intermittent (%)	Persistent (%)	Adjusted OR (95% CI)	Adjusted OR (95% CI)
Patient-related				
1 to 5 years *	61%	39%		

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6 to 11 years	34%	66%	1.90 (1.50, 2.40)
12 to 17 years	27%	73%	1.61 (1.33, 1.94)
Asthma severity			
Mild *	46%	54%	
Moderate/severe	35%	65%	1.62 (1.38, 1.89)
Triggers			
Viral only*	75%	25%	
Allergic only	46%	54%	11.10 (6.50, 18.95)
Effort only	43%	57%	1.62 (1.38, 1.89)
Multiple triggers	26%	74%	12.94 (10.80, 15.51)
Year			1.16 (1.11, 1.23)
Length of follow-up			1.16 (1.07, 1.26)
MD-related			
Respirologist			
A*	60%	40%	
Pediatricians			
B	23%	77%	4.68 (2.25, 9.76)
C	82%	18%	0.14 (0.06, 0.32)
D	27%	73%	3.75 (1.72, 8.20)
E	59%	41%	0.37 (0.17, 0.80)
F	57%	43%	0.49 (0.22, 1.09)
G	42%	58%	1.52 (0.74, 3.13)
H	94%	6%	0.03 (0.01, 0.07)
Allergists			
I	24%	76%	2.08 (0.92, 4.71)



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Table 1. Characteristics of participants

Phenotype	Intermittent	Persistent/Seasonal	<i>P-value</i> *
	(n = 1756)	(n = 1235)	
Age—years			
1—5	980 (56%)	408 (33%)	< 0.0001
6—11	529 (30%)	509 (41%)	
12—17	247 (14%)	318 (26%)	
% male	1065 (61%)	709 (57%)	0.0757
Ethnicity	(n=1354)	(N=1154)	0.0016
Caucasian	934 (69%)	833 (72%)	
Black	138 (10%)	112 (10%)	
Asian	130 (10%)	64 (5%)	
Other	152 (11%)	145 (13%)	
Asthma severity	(N=1582)	(N=1154)	< 0.0001
Mild	1054 (67%)	717 (62%)	
Moderate	384 (24%)	361 (31%)	
Severe	144 (9%)	76 (7%)	

Asthma control	(N=412)	(N=1119)	
Good	197 (48%)	426 (38%)	
Satisfactory	186 (45%)	472 (42%)	< 0.0001
Poor	29 (7%)	221 (20%)	
Spirometry	(N=702)	(N=703)	
% predicted FEV1, median (25%, 75%)	100 (92, 108)	96 (87, 106)	< 0.0001
	(N=570)	(N=580)	
≥12% change post-bronchodilator	92 (16%)	143 (25%)	0.0009
Triggers			
Viral-induced	849 (48%)	164 (13%)	
Allergen-induced	53 (3%)	30 (2%)	
Exercise-induced	97 (6%)	79 (7%)	< 0.0001
Multiple triggers	593 (34%)	854 (69%)	
Unidentified	164 (9%)	108 (9%)	
Morbidity in the previous 12 months			
≥1 acute care visit	947 (54%)	585 (47%)	0.0004
Physician specialty			
Allergist	229 (13%)	325 (26%)	
Pulmonologist	52 (3%)	31 (3%)	< 0.0001
Pediatrician	1475 (84%)	879 (71%)	

* Represents the significance level for the group difference in the distribution of 2 or more categories for categorical variables or between means for continuous outcomes.

Table 2. Phenotype-specific prescribed management

	Intermittent		Persistent/Seasonal	
	Initial visit	All visits	Initial visit	All visits
	N=1756	N=4438	N=1235	N=5594
Daily maintenance				
No controller	1170 (67%)	2873 (65%)	223 (18%)	759 (14%)
Daily controller	586 (33%)	1565 (35%)	1012 (82%)	4835 (86%)
Monotherapy	500 (28%)	1317 (30%)	729 (59%)	2784 (50%)
<i>Inhaled corticosteroids</i>	435 (25%)	1100 (25%)	676 (55%)	2523 (45%)
<i>Leukotriene receptor antagonist</i>	58 (3%)	203 (5%)	51 (4%)	254 (0%)
<i>Long-acting β_2-agonists</i>	3 (0%)	5 (0%)	1 (0%)	4 (0%)
<i>Other monotherapy</i>	4 (0%)	9 (0%)	1 (0%)	3 (0%)
Combination therapy	86 (5%)	248 (3%)	283 (23%)	2051 (29%)
<i>ICS + LTRA</i>	39 (2%)	109 (2%)	78 (6%)	415 (7%)
<i>ICS + LABA</i>	40 (2%)	111 (3%)	180 (15%)	1358 (24%)
<i>Other combinations</i>	7 (0%)	28 (1%)	25 (2%)	278 (5%)
Management of exacerbations				
Inhaled corticosteroids				
None	431	898	109 (9%)	342 (6%)

	(25%)	(20%)		
Initiation	779 (44%)	2122 (48%)	143 (11%)	555 (10%)
Same dose	157 (9%)	362 (8%)	417 (34%)	1928 (35%)
Increase dose	389 (22%)	1056 (24%)	566 (46%)	2769 (50%)
Rescue oral corticosteroids	16 (1%)	33 (1%)	16 (1%)	101 (2%)
Monitoring				
Peak flow	0 (0%)	622 (14%)	5 (0 %)	1282 (23%)
Asthma diary	475 (27%)	861 (19%)	398 (32%)	1632 (29%)
Guided self-management				
Written action plan	460 (26%)	951 (21%)	428 (35%)	1979 (35%)
Asthma education	363 (21%)	538 (12%)	297 (24%)	756 (14%)
