Children with allergic and nonallergic rhinitis have a similar risk of asthma

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Background: Both allergic and nonallergic rhinitis have been associated with increased prevalence of asthma.
Objective: To characterize asthma and intermediary asthma endpoints in young children with allergic and nonallergic rhinitis.
Methods: Thirty-eight 7-year-old children with allergic rhinitis, 67 with nonallergic rhinitis, and 185 without rhinitis from the Copenhagen Prospective Study on Asthma in Childhood birth cohort were compared for prevalence of asthma, eczema, food sensitization, filaggrin null-mutations, total IgE, blood eosinophil count, fractional exhaled nitric oxide (FeNO), lung function, and bronchial responsiveness.
Results: Children with allergic rhinitis compared with asymptomatic controls had increased prevalence of asthma (21% vs 5%; $P = .002$), food sensitization (47% vs 13%; $P < .001$), and eczema (66% vs 43%; $P = .01$) and increased total IgE (155 kU/L vs 41 kU/L; $P < .001$), blood eosinophil count (0.46×10^9/L vs 0.30×10^9/L; $P = .01$), FeNO (15.9 ppb vs 6.6 ppb; $P < .001$), and bronchial hyperresponsiveness (23% vs 9%; $P = .008$). Filaggrin null-mutations were associated with allergic rhinitis (odds ratio, 3.3; 95% CI, 1.3-8.3) but did not modify these associations. Children with nonallergic rhinitis also had increased asthma prevalence (20% vs 5%; $P = .001$) but showed no association with filaggrin null-mutations, eczema, food sensitization, total IgE, blood eosinophil count, FeNO, or bronchial responsiveness.
Conclusion: Asthma is similarly associated with allergic and nonallergic rhinitis, suggesting a link between upper and lower airways beyond allergy associated inflammation. Only children with allergic rhinitis had increased bronchial responsiveness and elevated FeNO, suggesting different endotypes of asthma symptoms in young children with allergic and nonallergic rhinitis. (J Allergy Clin Immunol 2010;126:567-73.)

Key words: *Allergic rhinitis, nonallergic rhinitis, asthma, children, united airways*

Allergic rhinitis is defined by sensitization to inhaled allergens and symptoms such as rhinorrhea, nasal obstruction, nasal itching, and sneezing during exposure to relevant allergens,[1] whereas nonallergic rhinitis is a diagnosis of exclusion characterized by similar symptoms but without allergic sensitization relevant to symptoms and without signs of infection.[2] Studies of adults and adolescents have shown increased prevalence of asthma in subjects with allergic and nonallergic rhinitis.[3,4] We hypothesized that these may represent different endotypes of asthma. This has not been studied previously in young children.

We studied 290 seven-year-old children with allergic rhinitis, nonallergic rhinitis, and asymptomatic controls from the Copenhagen Prospective Study on Asthma in Childhood (COPSAC) birth cohort. We compared prevalence of asthma, eczema, sensitization to food allergens, frequency of filaggrin null-mutations, levels of total IgE, blood eosinophil count, fractional exhaled nitric oxide (FeNO), measures of lung function, and bronchial responsiveness.

The aim of the study was to describe asthma prevalence and intermediary asthma endpoints in children with allergic and nonallergic rhinitis.

METHODS

Design

The COPSAC is a birth cohort study of 411 children born to mothers with asthma, recruited in the region of greater Copenhagen, Denmark.[5-7] The infants were enrolled at 1 month of age and subsequently attended the clinical research unit at 6-month intervals and immediately on onset of any respiratory or skin-related symptom.

Ethics

The study was conducted according to the principles of the Declaration of Helsinki and was approved by the Copenhagen Ethics Committee (KF 01-289/96) and the Danish Data Protection Agency (2008-41-1754). Informed consent was obtained from both parents at enrollment.[5]

Objective measurements by age 7 years

Baseline lung function was assessed by measurement of specific resistance of airways (sRaw) by whole-body plethysmography.[8,9]

Reversibility of airway resistance was determined as the relative change of sRaw 15 minutes after inhaled β_2-agonist (2 puffs of terbutaline 0.25mg/dose in a pressurized metered-dose inhaler with a spacer).

Bronchial responsiveness was determined as the relative change of sRaw 4 minutes after hyperventilating –18°C cold dry air.[10,11]

Fractional exhaled nitric oxide level was measured by an online technique[12,13] in accordance with recognized guidelines.[14]

Blood samples were analyzed for eosinophil count, total IgE, and specific IgE levels.[15] Sensitization was defined as specific IgE ≥ 0.35 kU/L[15,16]; allergic

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Abbreviations used
COPSAC: Copenhagen Prospective Study on Asthma in Childhood
FeNO: Fractional exhaled nitric oxide
OR: Odds ratio
sRaw: Specific resistance of airways

sensitization to airborne allergens as any sensitization for cat, dog, horse, birch, timothy grass, mugwort, house dust mites, or molds; and food sensitization as any sensitization for hen's egg, cow's milk, fish, wheat, peanut, soybean, or shrimp.

Nasal eosinophilia was assessed by nasal scrapings and rated by 2 experienced cytologists according to the Meltzer semiquantitative scale[17] as previously detailed.[18]

Clinical diagnoses

Rhinitis was diagnosed by the COPSAC doctors on the basis of parent interviews (not questionnaires) on rhinitis symptoms in the child's seventh year of life. The interview addressed rhinitis symptoms (sneezing, blocked nose, runny nose, and nasal itching/rubbing), nasal steroid trials, limitation of daily activities and sleep disturbance, eye involvement (itching/watery and red eyes), suspected precipitating factors, and time of year with symptoms. According to these interviews, rhinitis was defined by troublesome sneezing or blocked or runny nose severely affecting the well being of the child in periods without common cold or flu.[19] Allergic rhinitis was diagnosed in children with sensitization to aeroallergens clearly related to the symptomatic periods (birch [April-May], grass [May-August], mugwort [July-August], molds [May-October], house dust mites [October-February], and animals [when exposed]). Nonallergic rhinitis was diagnosed in children without sensitization or without symptoms during periods of exposure to such allergens.[18]

In a secondary analysis, we analyzed (1) allergic rhinitis (rhinitis plus any sensitization to aeroallergens irrespective of association with symptoms) and nonallergic rhinitis (rhinitis without any sensitization to aeroallergens), (2) allergic rhinitis and nonallergic rhinitis stratified by presence of nasal eosinophilia, and (3) inflammatory rhinitis (rhinitis plus nasal eosinophilia) and noninflammatory rhinitis (rhinitis without nasal eosinophilia).

Current asthma in the seventh year of life was diagnosed according to international guidelines as previously detailed[7,20] on the basis of respiratory diary cards completed on a daily basis by the parents, symptoms judged by the COPSAC doctors to be typical of asthma (eg, exercise-induced symptoms, prolonged nocturnal cough, recurrent cough outside common cold, symptoms causing wakening at night); need for intermittent rescue use of inhaled β_2-agonist, response to a 3-month trial of inhaled corticosteroids, and relapse when stopping treatment.

Eczema ever in the first 7 years of life was diagnosed by the COPSAC doctors according to predefined morphology and localization at both scheduled and acute visits defined by the Hanifin-Rajka criteria as previously detailed.[21,22]

Genetics

Filaggrin genotyping for 2 independent common null-mutations (*R501X* and *2282del4*) was performed as previously detailed.[23] Children were assigned as having a filaggrin mutation if they carried at least 1 of the mutations.

Statistical analysis

The study group was categorized in 3 groups: allergic rhinitis, nonallergic rhinitis, and a control group (reference group) without persistent rhinitis symptoms. Odds ratios of asthma, eczema, and food sensitization were calculated by logistic regression, whereas associations between rhinitis diagnoses and continuous outcomes (total IgE, blood eosinophil count, FeNO, baseline sRaw, β_2-reversibility, and bronchial responsiveness to cold dry air) were analyzed by generalized linear models expressing results as β-coefficients. Total IgE, blood eosinophil count, and FeNO were log-transformed before analysis.

Results are reported with 95% CIs in brackets; a P value ≤ .05 was considered significant. All analyses were performed with SAS v. 9.2 (SAS Institute, Inc, Cary, NC).

Further details of the Methods are outlined in this article's Online Repository at www.jacionline.org.

RESULTS

Baseline characteristics

Complete follow-up by doctor interview on rhinitis symptoms in the seventh year of life and measurement of specific IgE was available for 290 of the cohort of 411 infants (see this article's Fig E1 in the Online Repository at www.jacionline.org). The study group had increased prevalence of recurrent wheeze in the first 1.5 year of life ($P < .001$) and higher income ($P < .001$) compared with the group without follow-up on these endpoints, whereas there were no differences in eczema, allergic sensitization to aeroallergens, sex, older siblings, or family history of allergic rhinitis (see this article's Table E1 in the Online Repository at www.jacionline.org).

Rhinitis was diagnosed in 105 children (36%) and allergic sensitization to inhaled allergens in 76 children (26%). Allergic rhinitis to aeroallergens was diagnosed in 38 children (13%) and nonallergic rhinitis in 67 children (23%). Five children classified as having nonallergic rhinitis were sensitized to aeroallergens but without symptoms during exposure. The control group without persistent rhinitis symptoms was made up of 185 children (64%).

The overall study group consisted of 142 boys (49%). Prevalence of asthma, food sensitization, eczema, nasal eosinophilia, and filaggrin mutations; levels of total IgE, FeNO, and blood eosinophil count; baseline sRaw, reversibility to β_2-agonist, and bronchial responsiveness to cold dry air are described in Table I.

Associations among asthma, eczema, and allergic and nonallergic rhinitis

The Venn diagrams illustrate the relationships among asthma, eczema, and allergic rhinitis (Fig 1, *A*) and nonallergic rhinitis (Fig 1, *B*). The overlapping areas illustrate that current asthma is equally frequent in children with allergic rhinitis (21%) and nonallergic rhinitis (20%). Accordingly, both allergic rhinitis (OR, 5.0; 95% CI, 1.8-14.0; $P = .002$) and nonallergic rhinitis (OR, 4.6; 95% CI, 1.9-11.4; $P = .001$) were significantly associated with current asthma (Table II). Likewise, asthma was significantly associated with rhinitis symptoms (OR, 4.8; 95% CI, 2.1-10.8; $P < .001$) without evidence of interaction with sensitization to aeroallergens (P value for interaction, 0.87).

The Venn diagrams also show that a history of eczema is a more frequent finding in children with allergic rhinitis than nonallergic rhinitis (66% vs 43%). The OR of eczema was 2.5 (95% CI, 1.2-5.1; $P = .01$) for children with allergic rhinitis and 1.0 (95% CI, 0.6-1.7; $P = .94$) for children with nonallergic rhinitis (Table II).

Allergic versus nonallergic rhinitis

Children with allergic rhinitis compared with nonallergic rhinitis more often had sneezing (79% vs 58%; $P = .03$), nasal rubbing/itching (66% vs 40%; $P = .01$), itchy/watery eyes (66% vs 42%; $P = .02$), and trials of nasal steroid treatments (37% vs 19%; $P = .05$), whereas blocked nose was more prevalent in children with nonallergic rhinitis (76% vs 58%; $P = .02$). Length of the rhinitis history was increased in allergic rhinitis

TABLE I. Phenotypic characteristics of the study group

Phenotypic characteristic	Allergic rhinitis N = 38	Allergic rhinitis without asthma N = 30	Nonallergic rhinitis N = 67	Nonallergic rhinitis without asthma N = 54	Controls N = 185
Binary variables					
Current asthma, no. (%)	8 (21)		13 (20)		9 (5)
Eczema ever, no. (%)	25 (66)	19 (63)	29 (43)	22 (41)	81 (44)
Food sensitization,* no. (%)	18 (47)	13 (43)	9 (13)	9 (17)	31 (17)
Filaggrin mutations,† no. (%)	9 (24)	8 (28)	7 (10)	4 (7)	16 (9)
Nasal eosinophilia, no. (%)	9 (28)	7 (27)	5 (8)	3 (6)	4 (2)
Continuous variables					
Total IgE (kU/L), median (Q1-Q3)	155 (72-384)	125 (60-133)	30 (11-71)	30 (11-71)	41 (17-99)
B-eosinophils (10^9 cells per liter); median (Q1-Q3)	0.46 (0.27-0.59)	0.43 (0.28-0.59)	0.36 (0.25-0.49)	0.38 (0.26-0.50)	0.30 (0.18-0.49)
FeNO (ppb), median (Q1-Q3)	15.9 (6.1-29.6)	13.1 (5.8-25.0)	6.8 (5.3-8.8)	7.0 (5.5-9.1)	6.6 (5.1-9.1)
Baseline sRaw (kPa/s), mean (SD)	1.33 (0.26)	1.27 (0.24)	1.33 (0.30)	1.28 (0.25)	1.34 (0.32)
β_2-reversibility,‡ mean (SD)	0.20 (0.14)	0.16 (0.13)	0.17 (0.13)	0.17 (0.11)	0.17 (0.14)
Cold dry air challenge,§ mean (SD)	0.23 (0.45)	0.22 (0.40)	0.14 (0.22)	0.12 (0.21)	0.09 (0.22)

*Specific IgE ≥0.35 kU/L for at least 1 of 7 food allergens (hen's egg, cow's milk, fish, wheat, peanut, soybean, shrimp).
†Filaggrin null-mutations: *R501X* or *2282del4*.
‡The relative change in sRaw before and after bronchodilator.
§The relative change in sRaw before and after cold dry air hyperventilation.

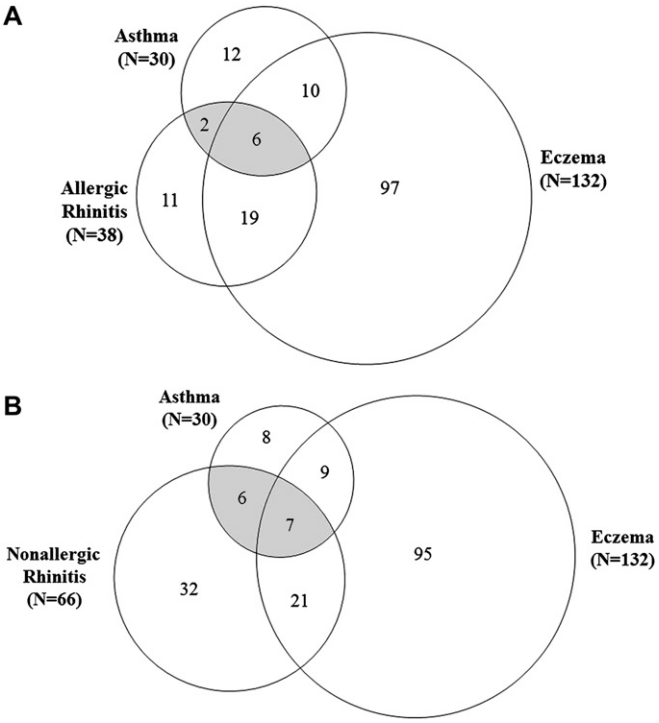

FIG 1. Venn diagrams illustrating the associations among asthma, eczema, and allergic rhinitis **(A)** and nonallergic rhinitis **(B)**. The size of the *circles* and overlapping areas are area-proportional with respect to the total study population. The overlapping areas between asthma and allergic and nonallergic rhinitis are *shaded*.

cases compared with nonallergic rhinitis (>2 years duration; 71% vs 33%; $P < .001$) (Fig 2).

Sensitization to food allergens was present in 47% (N=18) of children with allergic rhinitis, but only in 13% (N=9) of children with nonallergic rhinitis. Allergic sensitization to at least 1 of the tested food allergens was significantly associated with allergic rhinitis (OR, 4.5; 95% CI, 2.1-9.4; $P < .001$) but not with nonallergic rhinitis (OR, 0.8; 95% CI, 0.3-1.7; $P = .52$).

Children with allergic rhinitis had increased levels of total IgE (median values, 155 kU/L vs 41 kU/L; $P < .001$), increased blood eosinophil count (median values, 0.46×10^9/L vs 0.30×10^9/L; $P = .01$) and elevated FeNO level (median values, 15.9 ppb vs 6.6 ppb; $P < .001$) compared with children without persistent rhinitis. Subjects with nonallergic rhinitis were comparable to asymptomatic controls except for the increased asthma prevalence (Table II).

Children with allergic rhinitis had increased bronchial responsiveness to cold dry air challenge (relative change in sRaw, 23% vs 9%; $P = .008$), whereas children with nonallergic rhinitis were comparable to the controls. There were no differences in baseline sRaw or reversibility to β_2-agonist (Table II).

Allergic rhinitis defined as rhinitis plus any sensitization to aeroallergens (irrespective of relation to symptoms) and nonallergic rhinitis as rhinitis without sensitization did not modify the association with asthma or any of the other findings (see this article's Table E2 in the Online Repository at www.jacionline.org). We found similar associations with asthma and intermediary asthma endpoints in children with allergic rhinitis with and without nasal eosinophilia as well as in nonallergic rhinitis with and without nasal eosinophilia (see this article's Table E3 in the Online Repository at www.jacionline.org). The analysis of inflammatory versus noninflammatory rhinitis was comparable to allergic rhinitis versus nonallergic rhinitis except that response to cold dry air challenge was not increased in inflammatory rhinitis, probably because of low numbers (see this article's Table E4 in the Online Repository at www.jacionline.org).

Allergic versus nonallergic rhinitis in children with asthma

Asthma in children with allergic rhinitis is compared with asthma in children with nonallergic rhinitis in this article's Table E5 in the Online Repository at www.jacionline.org. Both children with allergic rhinitis and asthma and children with nonallergic rhinitis and asthma had increased baseline sRaw, whereas only children with allergic rhinitis and asthma had elevated FeNO, bronchial hyperresponsiveness, and reversibility to β_2-agonist.

TABLE II. Comparisons of allergic rhinitis with and without asthma, nonallergic rhinitis with and without asthma, and controls

Controls vs:	Allergic rhinitis		Allergic rhinitis without asthma		Nonallergic rhinitis		Nonallergic rhinitis without asthma	
Binary variables	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**
Current asthma	5.0 (1.8 to 14.0)	.002			4.6 (1.9 to 11.4)	.001		
Eczema ever	2.5 (1.2 to 5.1)	.01	2.2 (1.0 to 4.8)	.06	1.0 (0.6 to 1.7)	.94	0.9 (0.5 to 1.6)	.64
Food sensitization*	4.5 (2.1 to 9.4)	<.001	3.7 (1.6 to 8.5)	.002	0.8 (0.3 to 1.7)	.52	1.0 (0.4 to 2.2)	.95
Filaggrin mutations†	3.3 (1.3 to 8.3)	.01	3.8 (1.4 to 9.9)	.01	1.2 (0.5 to 3.1)	.69	0.8 (0.3 to 2.5)	.69
Continuous variables	**β-coefficient (95% CI)**	***P* value**	**β-coefficient (95% CI)**	***P* value**	**β-coefficient (95% CI)**	***P* value**	**β-coefficient (95% CI)**	***P* value**
Total IgE	1.34 (0.9 to 1.8)	<.001	1.13 (0.7 to 1.6)	<.001	−0.28 (−0.6 to 0.1)	.12	−0.33 (−0.7 to 0.1)	.10
Blood eosinophils	0.38 (0.1 to 0.6)	.01	0.41 (0.1 to 0.7)	.01	0.11 (−0.1 to 0.3)	.30	0.18 (−0.1 to 0.4)	.14
FeNO	0.72 (0.5 to 1.0)	<.001	0.62 (0.4 to 0.8)	<.001	−0.03 (−0.2 to 0.1)	.76	0.01 (−0.2 to 0.2)	.93
Baseline sRaw	−0.01 (−0.1 to 0.1)	.87	−0.05 (−0.2 to 0.1)	.32	−0.01 (−0.1 to 0.1)	.79	−0.04 (−0.1 to 0.1)	.42
β_2-reversibility‡	0.03 (−0.02 to 0.1)	.24	−0.00 (−0.1 to 0.1)	.90	0.00 (−0.04 to 0.04)	.99	0.01 (−0.04 to 0.1)	.78
Cold dry air challenge§	0.14 (0.04 to 0.2)	.008	0.14 (0.03 to 0.2)	.01	0.05 (−0.04 to 0.1)	.28	0.04 (−0.1 to 0.1)	.38

*Specific IgE ≥ 0.35kU/L for at least 1 of 7 food allergens (hen's egg, cow's milk, fish, wheat, peanut, soybean, shrimp).
†Filaggrin null-mutations: *R501X* or *2282del4*.
‡The relative change in sRaw before and after bronchodilator.
§The relative change in sRaw before and after cold dry air hyperventilation.

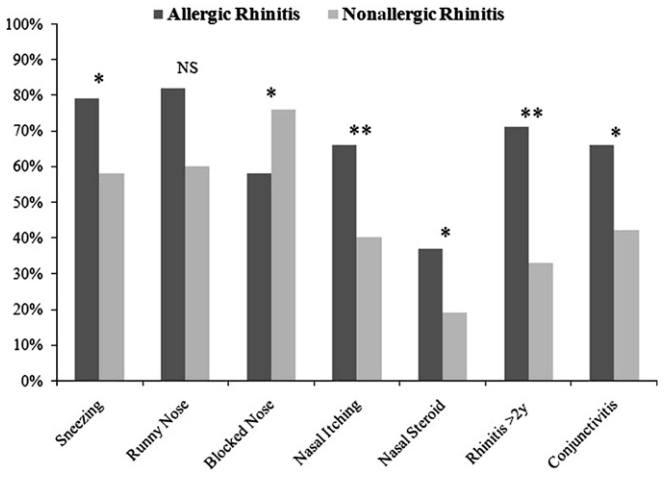

FIG 2. Diagram showing individual symptom patterns, nasal steroid trials, and length of rhinitis history in children with allergic rhinitis compared with nonallergic rhinitis. Comparisons are made with χ^2 statistics; *$P \leq .05$; ** $P \leq .01$. *NS,* Nonsignificant.

Allergic versus nonallergic rhinitis in children without asthma

We subsequently studied children with allergic and nonallergic rhinitis but no current asthma. Prevalence of eczema, food sensitization, total IgE and blood eosinophil count was increased in children with allergic rhinitis without concurrent asthma but not in nonallergic rhinitis. In particular, bronchial responsiveness to cold dry air challenge (relative change in sRaw, 22% vs 8%; $P = .01$) and FeNO level (median values, 13.1 ppb vs 6.6 ppb; $P < .001$) were increased in children with allergic rhinitis without asthma but not in children with nonallergic rhinitis (Table II).

Filaggrin null-mutations

Filaggrin mutations were strongly associated with allergic rhinitis by age 7 years (OR, 3.3; 95% CI, 1.3-8.3; $P = .01$) but not with nonallergic rhinitis (OR, 1.2; 95% CI, 0.5-3.1; $P = .69$). To investigate whether filaggrin mutations explained the differences between allergic and nonallergic rhinitis, we adjusted all significant associations for filaggrin mutations, which did not substantially alter the associations (see this article's Table E6 in the Online Repository at www.jacionline.org).

DISCUSSION

Main findings

First, asthma coexisted equally frequent in 7-year-old children with allergic and nonallergic rhinitis from the COPSAC birth cohort of mothers with asthma, suggesting a link between asthma and rhinitis beyond an allergy-driven mechanism.

Second, FeNO and bronchial hyperresponsiveness was increased in children with allergic rhinitis and asthma, but not in children with nonallergic rhinitis and asthma. This suggests different endotypes of asthma in children with allergic and nonallergic rhinitis.

Third, children with allergic rhinitis without asthma still exhibited increased bronchial responsiveness and FeNO, suggesting that the allergy-driven symptoms mark a disease process in both upper and lower airways even when symptoms only reveal as allergic rhinitis.

Together, these observations support the concept of a close connection between upper and lower airway disease partly from a common allergy-driven process but also from nonallergic (unknown) mechanisms.

Strengths and limitations of the study

A major strength of the study is the high diagnostic accuracy and sensitivity in this closely monitored birth cohort with comprehensive objective assessments and daily diary cards.[5-7] All diagnoses were made by the doctors employed at the COPSAC research unit, not the family practitioner, minimizing risk of misclassification. Rhinitis diagnosis was based on parent interviews (not questionnaires), allowing validation and interpretation of the symptom history. Similarly, asthma was diagnosed by the COPSAC research doctors based on clinical

assessments according to a predefined algorithm and daily diaries, not questionnaires. The diaries were reviewed by the COPSAC doctors at 6-monthly clinical sessions and immediately on onset of any respiratory symptom reducing risk of recall bias. Furthermore, the study is strengthened by the comprehensive objective assessments of atopic biomarkers, lung function, and bronchial reversibility and responsiveness, performed in accordance with standard operating procedures by highly trained research assistants at the COPSAC research unit.

The clinical follow-up rate of the cohort by age 7 years of 70% with clinical information on rhinitis, asthma, eczema, sensitization to food allergens, levels of total IgE, blood eosinophil count, nasal eosinophilia, FeNO, measures of lung function, and bronchial responsiveness is also a significant strength of the study.

The principal limitation of the study is the setting of a birth cohort of mothers with a history of asthma, which diminishes the generalizability of our findings. However, population-based studies of adolescents and adults with rhinitis have shown associations in agreement with our findings.[3,24]

We found that nonallergic rhinitis was twice as common as allergic rhinitis, which is different from studies of adults, among whom the proportion of subjects with nonallergic rhinitis is one third to one fourth of the rhinitis population.[3,4,24] It may be speculated that a subclinical allergic diathesis exists in a proportion of children with nonallergic rhinitis. Entopy—the presence of nasal mucosal but not systemic specific IgE—may explain early steps in the development of allergic rhinitis.[25,26] However, this remains speculative, and the evidence from our data shows that children with rhinitis without established sensitization to aeroallergens often have concurrent asthma.

Alternatively, misclassification may have occurred. However, we found well described differences in symptom presentation between children with allergic and nonallergic rhinitis[1] and reanalyzing data as allergic rhinitis (rhinitis plus any sensitization to aeroallergens irrespective of relation to symptoms) versus nonallergic rhinitis (rhinitis without any sensitization) as well as inflammatory rhinitis (rhinitis plus nasal eosinophilia) versus noninflammatory rhinitis did not modify our findings.

Another data approach would be to perform cluster analysis to discover potentially new endophenotypes of rhinitis. However, it was our aim to improve evidence of the associations within the triad of asthma and allergic and nonallergic rhinitis based on the currently recognized definitions.[1]

Interpretation

Increased prevalence of asthma was present in both children with allergic and nonallergic rhinitis, suggesting a link between symptoms from upper and lower airways beyond allergy-driven mechanisms. We recently demonstrated that upper and lower airway patency are strongly associated in children with allergic and nonallergic rhinitis.[27] Thus, generalized diminished airway dimensions may contribute to an increased propensity of coexisting rhinitis and asthma, possibly explained by shared genetic variants. In support of a nonallergic communality between upper and lower airways, a large proportion of adults with chronic rhinosinusitis has lung function abnormalities and reports having asthma.[28,29] Nasal symptoms are also frequently reported by patients with chronic obstructive pulmonary disease and bronchiectasis.[28,30,31]

Our finding of a similar asthma prevalence in children with allergic and nonallergic rhinitis is in accordance with findings in 5-year-old children[32] but in contrast with studies of adolescents and adults consistently showing a higher prevalence of asthma in subjects with allergic rhinitis compared with nonallergic rhinitis.[3,4,24] These findings suggest that a proportion of children with allergic rhinitis to aeroallergens will develop asthma later in life, which is consistent with longitudinal data from a recent report confirming allergic rhinitis as a determinant of adult-onset asthma.[33] In addition, some children with nonallergic rhinitis may develop allergy later in life. Both hypotheses support the Allergic Rhinitis and its Impact on Asthma (ARIA) recommendations[1] of testing for asthma in all children presenting symptoms of persistent rhinitis, whether allergic or nonallergic.

We also found that children with allergic rhinitis and asthma had an increased prevalence of bronchial hyperresponsiveness and elevated FeNO in comparison with children with nonallergic rhinitis and asthma, which suggests different endotypes of asthma symptoms in children with allergic and nonallergic rhinitis. Previous studies have shown bronchial hyperresponsiveness in one third to one half of adults with allergic rhinitis,[34,35] and one comparative study of mixed adults and adolescents reported airway hyperresponsiveness in a significantly greater proportion of subjects with allergic rhinitis compared with nonallergic rhinitis.[3] Our findings demonstrate different endotypes of asthma symptoms in children with allergic and nonallergic rhinitis and warrant increased awareness of children with coexisting asthma and allergic rhinitis because this phenotype is characterized by raised values of FeNO and bronchial hyperresponsiveness already at age 7 years. Further studies in children with allergic and nonallergic rhinitis comparing the prevalence of intermediary asthma endpoints are needed.[2]

Children with allergic rhinitis but no asthma still exhibited increased bronchial responsiveness and elevated FeNO levels, which has also been demonstrated in adults.[36,37] Furthermore, two cross-sectional studies of children with allergic rhinitis without asthma have also shown an increased prevalence of bronchial hyperresponsiveness.[38,39] However, one study is limited by low numbers (N=51) and a broad age range (6-15 years)[39] and the other by a subjective "auscultative" evaluation of response to methacholine challenge.[38] Our findings suggest a subclinical bronchial disease process in young children with allergic rhinitis and emphasize allergic rhinitis as a marker of a generalized airway disease.[33,40] This interpretation is supported by studies showing that nasal allergen challenge can cause bronchial inflammation[41,42] and that segmental bronchial provocation induces a nasal inflammatory response.[43] These findings may play an important role for the follow-up of children with allergic rhinitis without clinical asthma because asymptomatic bronchial hyperresponsiveness is described in association with subsequent development of asthma later in life.[44-46] Assessment of nasal eosinophilia does not seem to help the clinician identifying rhinitis children at particular risk of asthma because nasal eosinophilia was not a frequent finding in this age group, nor was nasal eosinophilia associated with any of the intermediary asthma endpoints.

As expected,[3,24] the allergic rhinitis phenotype had an increased prevalence of eczema and food sensitization, increased total IgE, and elevated blood eosinophil count, whereas these characteristics were not associated with the nonallergic rhinitis phenotype. In addition, filaggrin loss-of-function mutations were strongly associated with allergic rhinitis but not nonallergic

rhinitis. We have previously shown that filaggrin mutations are associated with the development of eczema[23] and allergic sensitization,[47] and others have reported an association with allergic rhinitis.[48] Therefore, a higher frequency of filaggrin mutations in children with allergic rhinitis could have accounted for the differences between the allergic and nonallergic rhinitis phenotypes. However, adjusting the analysis for filaggrin mutations did not modify our findings, assuring that the associations with asthma and intermediary asthma endpoints are not driven by differences in filaggrin genotypes.

In conclusion, asthma was equally frequent in children with allergic and nonallergic rhinitis, suggesting a link between upper and lower airway disease beyond an allergy-driven mechanism. Children with allergic rhinitis but not nonallergic rhinitis had increased bronchial responsiveness and FeNO, suggesting different endotypes of asthma associated with allergic and nonallergic rhinitis. Children with allergic rhinitis but no asthma also exhibited bronchial hyperresponsiveness and raised FeNO, suggesting a subclinical bronchial disease process and supporting the allergic disease process to involve both upper and lower airways. These observations lend support to a close connection between upper and lower airway disease partly from an allergy-driven process but also from nonallergic mechanisms.

We gratefully express our gratitude to the children and families of the COPSAC cohort study for all their support and commitment. We acknowledge and appreciate the unique efforts of the COPSAC research team.

Key messages

- **Asthma is equally frequent in young children with allergic and nonallergic rhinitis, suggesting a link between upper and lower airways beyond allergy-associated inflammation.**
- **Children with allergic rhinitis and asthma, but not nonallergic rhinitis and asthma, have increased bronchial responsiveness and FeNO, suggesting different endotypes of asthma in children with allergic and nonallergic rhinitis.**
- **Children with allergic rhinitis but no asthma also exhibited bronchial hyperresponsiveness and raised FeNO, suggesting a subclinical bronchial disease process and supporting the allergic disease process to involve both upper and lower airways.**

REFERENCES

1. Bousquet J, van CP, Khaltaev N. Allergic rhinitis and its impact on asthma. J Allergy Clin Immunol 2001;108(5 suppl):S147-334.
2. Bousquet J, Fokkens W, Burney P, Durham SR, Bachert C, Akdis CA, et al. Important research questions in allergy and related diseases: nonallergic rhinitis: a GA2LEN paper. Allergy 2008;63:842-53.
3. Molgaard E, Thomsen SF, Lund T, Pedersen L, Nolte H, Backer V. Differences between allergic and nonallergic rhinitis in a large sample of adolescents and adults. Allergy 2007;62:1033-7.
4. Rolla G, Guida G, Heffler E, Badiu I, Bommarito L, De SA, et al. Diagnostic classification of persistent rhinitis and its relationship to exhaled nitric oxide and asthma: a clinical study of a consecutive series of patients. Chest 2007;131:1345-52.
5. Bisgaard H. The Copenhagen Prospective Study on Asthma in Childhood (COPSAC): design, rationale, and baseline data from a longitudinal birth cohort study. Ann Allergy Asthma Immunol 2004;93:381-9.
6. Bisgaard H, Hermansen MN, Loland L, Halkjaer LB, Buchvald F. Intermittent inhaled corticosteroids in infants with episodic wheezing. N Engl J Med 2006;354:1998-2005.
7. Bisgaard H, Hermansen MN, Buchvald F, Loland L, Halkjaer LB, Bonnelykke K, et al. Childhood asthma after bacterial colonization of the airway in neonates. N Engl J Med 2007;357:1487-95.
8. Bisgaard H, Klug B. Lung function measurement in awake young children. Eur Respir J 1995;8:2067-75.
9. Bisgaard H, Nielsen KG. Plethysmographic measurements of specific airway resistance in young children. Chest 2005;128:355-62.
10. Nielsen KG, Bisgaard H. Lung function response to cold air challenge in asthmatic and healthy children of 2-5 years of age. Am J Respir Crit Care Med 2000;161:1805-9.
11. Nielsen KG, Bisgaard H. Cold air challenge and specific airway resistance in preschool children. Paediatr Respir Rev 2005;6:255-66.
12. Buchvald F, Bisgaard H. FeNO measured at fixed exhalation flow rate during controlled tidal breathing in children from the age of 2 yr. Am J Respir Crit Care Med 2001;163(3 pt 1):699-704.
13. Buchvald F, Baraldi E, Carraro S, Gaston B, De JJ, Pijnenburg MW, et al. Measurements of exhaled nitric oxide in healthy subjects age 4 to 17 years. J Allergy Clin Immunol 2005;115:1130-6.
14. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. Am J Respir Crit Care Med 2005;171:912-30.
15. Ballardini N, Nilsson C, Nilsson M, Lilja G. ImmunoCAP Phadiatop Infant—a new blood test for detecting IgE sensitisation in children at 2 years of age. Allergy 2006;61:337-43.
16. Wickman M, Ahlstedt S, Lilja G, van Hage HM. Quantification of IgE antibodies simplifies the classification of allergic diseases in 4-year-old children: a report from the prospective birth cohort study—BAMSE. Pediatr Allergy Immunol 2003;14:441-7.
17. Howarth PH, Persson CG, Meltzer EO, Jacobson MR, Durham SR, Silkoff PE. Objective monitoring of nasal airway inflammation in rhinitis. J Allergy Clin Immunol 2005;115(3 suppl. 1):S414-41.
18. Chawes BL, Kreiner-Moller E, Bisgaard H. Objective assessments of allergic and nonallergic rhinitis in young children. Allergy 2009;64:1547-53.
19. Braun-Fahrlander C, Wuthrich B, Gassner M, Grize L, Sennhauser FH, Varonier HS, et al. Validation of a rhinitis symptom questionnaire (ISAAC core questions) in a population of Swiss school children visiting the school health services. SCARPOL-team. Swiss Study on Childhood Allergy and Respiratory Symptom with respect to Air Pollution and Climate. International Study of Asthma and Allergies in Childhood. Pediatr Allergy Immunol 1997;8:75-82.
20. Bisgaard H, Bonnelykke K, Sleiman PM, Brasholt M, Chawes B, Kreiner-Moller E, et al. Chromosome 17q21 gene variants are associated with asthma and exacerbations but not atopy in early childhood. Am J Respir Crit Care Med 2009;179:179-85.
21. Bisgaard H, Simpson A, Palmer CN, Bonnelykke K, McLean I, Mukhopadhyay S, et al. Gene-environment interaction in the onset of eczema in infancy: filaggrin loss-of-function mutations enhanced by neonatal cat exposure. PLoS Med 2008;5:e131.
22. Halkjaer LB, Loland L, Buchvald FF, Agner T, Skov L, Strand M, et al. Development of atopic dermatitis during the first 3 years of life: the Copenhagen prospective study on asthma in childhood cohort study in high-risk children. Arch Dermatol 2006;142:561-6.
23. Palmer CN, Irvine AD, Terron-Kwiatkowski A, Zhao Y, Liao H, Lee SP, et al. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. Nat Genet 2006;38:441-6.
24. Bachert C, van CP, Olbrecht J, van SJ. Prevalence, classification and perception of allergic and nonallergic rhinitis in Belgium. Allergy 2006;61:693-8.
25. Powe DG, Jones NS. Local mucosal immunoglobulin E production: does allergy exist in non-allergic rhinitis? Clin Exp Allergy 2006;36:1367-72.
26. Takhar P, Smurthwaite L, Coker HA, Fear DJ, Banfield GK, Carr VA, et al. Allergen drives class switching to IgE in the nasal mucosa in allergic rhinitis. J Immunol 2005;174:5024-32.
27. Chawes BL, Kreiner-Moller E, Bisgaard H. Upper and lower airway patency are associated in young children. Chest 2010;137:1332-7.
28. Fokkens W, Lund V, Mullol J. European position paper on rhinosinusitis and nasal polyps 2007. Rhinol Suppl 2007;20):1-136.
29. Ragab A, Clement P, Vincken W. Objective assessment of lower airway involvement in chronic rhinosinusitis. Am J Rhinol 2004;18:15-21.
30. Hens G, Vanaudenaerde BM, Bullens DM, Piessens M, Decramer M, Dupont LJ, et al. Sinonasal pathology in nonallergic asthma and COPD: "united airway disease" beyond the scope of allergy. Allergy 2008;63:261-7.
31. Hurst JR, Wilkinson TM, Donaldson GC, Wedzicha JA. Upper airway symptoms and quality of life in chronic obstructive pulmonary disease (COPD). Respir Med 2004;98:767-70.

32. Marinho S, Simpson A, Lowe L, Kissen P, Murray C, Custovic A. Rhinoconjunctivitis in 5-year-old children: a population-based birth cohort study. Allergy 2007; 62:385-93.
33. Shaaban R, Zureik M, Soussan D, Neukirch C, Heinrich J, Sunyer J, et al. Rhinitis and onset of asthma: a longitudinal population-based study. Lancet 2008;372: 1049-57.
34. Ciprandi G, Cirillo I, Tosca MA, Vizzaccaro A. Bronchial hyperreactivity and spirometric impairment in patients with seasonal allergic rhinitis. Respir Med 2004; 98:826-31.
35. Downie SR, Andersson M, Rimmer J, Leuppi JD, Xuan W, Akerlund A, et al. Association between nasal and bronchial symptoms in subjects with persistent allergic rhinitis. Allergy 2004;59:320-6.
36. Ciprandi G, Cirillo I, Pistorio A. Impact of allergic rhinitis on asthma: effects on spirometric parameters. Allergy 2008;63:255-60.
37. Shaaban R, Zureik M, Soussan D, Anto JM, Heinrich J, Janson C, et al. Allergic rhinitis and onset of bronchial hyperresponsiveness: a population-based study. Am J Respir Crit Care Med 2007;176:659-66.
38. Choi SH, Yoo Y, Yu J, Rhee CS, Min YG, Koh YY. Bronchial hyperresponsiveness in young children with allergic rhinitis and its risk factors. Allergy 2007;62:1051-6.
39. Cuttitta G, Cibella F, La GS, Hopps MR, Bucchieri S, Passalacqua G, et al. Nonspecific bronchial hyper-responsiveness in children with allergic rhinitis: relationship with the atopic status. Pediatr Allergy Immunol 2003;14:458-63.
40. Bugiani M, Carosso A, Migliore E, Piccioni P, Corsico A, Olivieri M, et al. Allergic rhinitis and asthma comorbidity in a survey of young adults in Italy. Allergy 2005;60:165-70.
41. Bonay M, Neukirch C, Grandsaigne M, Lecon-Malas V, Ravaud P, Dehoux M, et al. Changes in airway inflammation following nasal allergic challenge in patients with seasonal rhinitis. Allergy 2006;61:111-8.
42. Gaga M, Lambrou P, Papageorgiou N, Koulouris NG, Kosmas E, Fragakis S, et al. Eosinophils are a feature of upper and lower airway pathology in non-atopic asthma, irrespective of the presence of rhinitis. Clin Exp Allergy 2000;30:663-9.
43. Braunstahl GJ, Kleinjan A, Overbeek SE, Prins JB, Hoogsteden HC, Fokkens WJ. Segmental bronchial provocation induces nasal inflammation in allergic rhinitis patients. Am J Respir Crit Care Med 2000;161:2051-7.
44. Brutsche MH, Downs SH, Schindler C, Gerbase MW, Schwartz J, Frey M, et al. Bronchial hyperresponsiveness and the development of asthma and COPD in asymptomatic individuals: SAPALDIA cohort study. Thorax 2006;61:671-7.
45. Ferdousi HA, Zetterstrom O, Dreborg S. Bronchial hyper-responsiveness predicts the development of mild clinical asthma within 2 yr in school children with hayfever. Pediatr Allergy Immunol 2005;16:478-86.
46. Stern DA, Morgan WJ, Halonen M, Wright AL, Martinez FD. Wheezing and bronchial hyper-responsiveness in early childhood as predictors of newly diagnosed asthma in early adulthood: a longitudinal birth-cohort study. Lancet 2008;372: 1058-64.
47. Bønnelykke K, Pipper CB, Tavendale R, Palmer CN, Bisgaard H. Filaggrin gene variants and atopic diseases in early childhood assessed longitudinally from birth. Pediatr Allergy Immunol 2010 Jun 21 [Epub ahead of print].
48. Weidinger S, O'Sullivan M, Illig T, Baurecht H, Depner M, Rodriguez E, et al. Filaggrin mutations, atopic eczema, hay fever, and asthma in children. J Allergy Clin Immunol 2008;121:1203-9.

METHODS

FeNO measurements

Fractional exhaled nitric oxide was measured at 7 years of age by an online technique[E1,E2] with NIOX FLEX (Aerocrine, Solna, Sweden) in accordance with American Thoracic Society and European Respiratory Society guidelines.[E3] The child was comfortably seated and breathing quietly for about 5 minutes to acclimatize. Thereafter, the child inhaled to near total lung capacity and immediately exhaled at a constant flow of 50 mL/s until a FeNO plateau of ≥2 seconds could be identified. An exhalation lasted at least 4 seconds, and the expiratory pressure was maintained at 5 to 20 cm H_2O to close the velum. During exhalation, the child was guided by an exhalation flow–driven animated computer program. Two repeated exhalations that agreed within 5% were completed with ≤30-second intervals, and mean FeNO was recorded.

Bronchial responsiveness to cold dry air

Cold dry air challenge was performed in the child's seventh year of life by hyperventilating –18°C cold dry air.[E4,E5] The air was generated by a Respiratory Heat Exchange System (Erich Jaeger GmbH, Würzburg, Germany). The test was done as a single-step isocapnic hyperventilation test lasting 4 minutes. An animated computer program guided the child to maintain an adequate frequency of breathing aiming at 1 L/min/kg body weight.[E4] A face mask fitted with a mouthpiece was used during hyperventilation, which ensured mouth breathing and prevented inhalation of room air.

Asthma diagnosis algorithm

Wheeze was defined from the daily diary cards as troublesome lower airway symptoms such as wheeze or whistling sounds, breathlessness, or persistent troublesome cough severely affecting the well being of the child.

A wheezy episode was defined by 3 consecutive days with troublesome lung symptoms, which led to a clinical evaluation of the child by the doctors at the COPSAC Research Unit.

The first COPSAC doctor-verified wheezy episode led to prescription of a short-acting β_2-agonist to be administered as needed for the current and following wheezy episodes.

If the child had 5 wheezy episodes within 6 months, had 4 consecutive weeks with wheeze, or met the criteria for acute severe asthma, a diagnosis of recurrent wheeze was established, and daily treatment for 3 months with inhaled corticosteroid ($100 \times 2 \times 2\mu g$ budesonide) was initiated, increasing to 6 and 12 months at subsequent relapses defined as 2 wheezy episodes within 3 months, 2 consecutive weeks with wheeze, or acute severe asthma.

Asthma was diagnosed at the first relapse after a 3-month trial of inhaled corticosteroids when symptoms judged by the COPSAC doctors were typical of asthma (eg, exercise-induced symptoms, prolonged nocturnal cough, recurrent cough outside common cold, symptoms causing wakening at night). The asthma diagnosis algorithm is given in details at www.copsac.com.

Allergic sensitization

At 6 years of age, specific IgE levels were determined by a screening method (ImmunoCAP, Phadiatop Infant; Pharmacia Diagnostics AB, Uppsala, Sweden) against the 15 most common inhalant and food allergens (cat, dog, horse, birch, timothy grass, mugwort, house dust mites, molds, egg, milk, fish, wheat, peanut, soybean, shrimp). Values of specific IgE ≥ 0.35kU/L were considered indicative of sensitization.[E6,E7]

Allergic sensitization to airborne allergens was considered relevant only when rhinitis symptoms were predominant during the appropriate exposure: birch (April-May), grass (May-August), mugwort (July-August), molds (May-October), house dust mites (October-February), and animals (when exposed).[E8]

Nasal eosinophilia

Nasal eosinophilia was assessed by nasal scraping in the child's sixth year of life and rated according to the Meltzer semiquantitative scale[E9] as previously detailed.[E10] Nasal eosinophilia was judged by experienced cytologists and defined as ≥1 eosinophil cells per high-power field (light microscopy, oil immersion, ×1000).

Total IgE

Total IgE was determined by ImmunoCAP (Phadia)[E6] with a detection limit of 2 kU/L.

Statistical analysis

The association between filaggrin null-mutations and rhinitis diagnoses was investigated by logistic regression. Filaggrin mutation–adjusted associations were calculated by adding filaggrin mutations (yes/no) as a covariate to the models.

REFERENCES

E1. Buchvald F, Bisgaard H. FeNO measured at fixed exhalation flow rate during controlled tidal breathing in children from the age of 2 yr. Am J Respir Crit Care Med 2001;163(3 pt 1):699-704.

E2. Buchvald F, Baraldi E, Carraro S, Gaston B, De JJ, Pijnenburg MW, et al. Measurements of exhaled nitric oxide in healthy subjects age 4 to 17 years. J Allergy Clin Immunol 2005;115:1130-6.

E3. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. Am J Respir Crit Care Med 2005;171):912-30.

E4. Nielsen KG, Bisgaard H. Cold air challenge and specific airway resistance in preschool children. Paediatr Respir Rev 2005;6:255-66.

E5. Nielsen KG, Bisgaard H. Lung function response to cold air challenge in asthmatic and healthy children of 2-5 years of age. Am J Respir Crit Care Med 2000;161:1805-9.

E6. Ballardini N, Nilsson C, Nilsson M, Lilja G. ImmunoCAP Phadiatop Infant—a new blood test for detecting IgE sensitisation in children at 2 years of age. Allergy 2006;61:337-43.

E7. Wickman M, Ahlstedt S, Lilja G, van Hage HM. Quantification of IgE antibodies simplifies the classification of allergic diseases in 4-year-old children: a report from the prospective birth cohort study—BAMSE. Pediatr Allergy Immunol 2003;14:441-7.

E8. Chawes BL, Kreiner-Moller E, Bisgaard H. Objective assessments of allergic and nonallergic rhinitis in young children. Allergy 2009;64:1547-53.

E9. Howarth PH, Persson CG, Meltzer EO, Jacobson MR, Durham SR, Silkoff PE. Objective monitoring of nasal airway inflammation in rhinitis. J Allergy Clin Immunol 2005;115(3 suppl. 1):S414-41.

E10. Chawes BL, Kreiner-Moller E, Bisgaard H. Upper and lower airway patency are associated in young children. Chest 2010;137:1332-7.

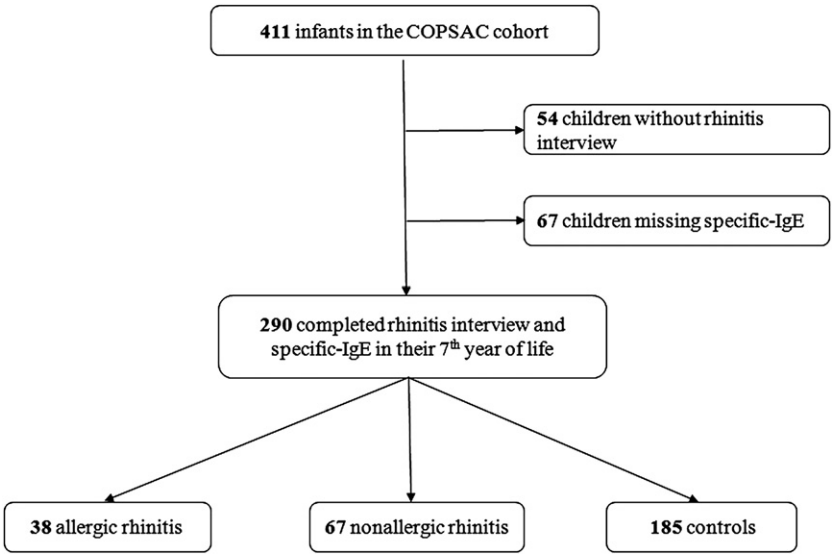

FIG E1. Study group flow chart.

TABLE E1. Comparison of study group versus children with incomplete data

Characteristic	Study group N = 290	Children with incomplete data N = 121	*P* value
Male sex, no. (%)	142 (49%)	60 (50%)	.79*
Recurrent wheeze, 0-1½ y, no. (%)	22 (8%)	0	<.001†
Eczema, 0-1½ y, no. (%)	99 (34%)	33 (27%)	.17*
Allergic sensitization to aeroallergens, 1½ y, no. (%)	10 (4%)	4 (5%)	.75†
Siblings at birth, no. (%)	118 (41%)	34 (35%)	.26*
Parental income at birth			<.001*
<400.000 Danish Kroner (dKr)	74 (26%)	38 (38%)	
400.000-600.000 dKr	138 (48%)	45 (46%)	
>600.000 dKr	74 (26%)	16 (16%)	
Father allergic rhinitis, no. (%)	94 (34%)	32 (28%)	.29*
Mother allergic rhinitis, no. (%)	222 (77%)	88 (73%)	.49*

*χ^2 test.
†Fisher exact test.

TABLE E2. Comparisons of allergic rhinitis and nonallergic rhinitis with and without asthma versus controls. Allergic rhinitis is defined as rhinitis plus sensitization to any tested aeroallergen (irrespective of association with symptoms), nonallergic rhinitis as rhinitis without sensitization to aeroallergens.

Controls vs: N = 185	Allergic rhinitis N = 43		Allergic rhinitis without asthma N = 34		Nonallergic rhinitis N = 62		Nonallergic rhinitis without asthma N = 50	
Binary variables	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**
Current asthma	5.0 (1.8 to 13.4)	.002	-	-	4.6 (1.8 to 11.5)	.001	-	-
Eczema ever	2.4 (1.2 to 4.8)	.01	2.0 (1.0 to 4.3)	.07	0.9 (0.5 to 1.7)	.80	0.8 (0.4 to 1.6)	.59
Food sensitization*	4.3 (2.1 to 8.8)	<.001	3.8 (1.7 to 8.4)	.001	0.6 (0.3 to 1.5)	.31	0.8 (0.3 to 1.9)	.61
Filaggrin mutations†	2.8 (1.2 to 6.9)	.02	3.2 (1.2 to 8.2)	.02	1.3 (0.5 to 3.4)	.56	0.9 (0.3 to 2.7)	.80
Continuous variables	**β-coefficient (95% CI)**	***P* value**	**β-coefficient (95% CI)**	***P* value**	**β-coefficient (95% CI)**	***P* value**	**β-coefficient (95% CI)**	***P* value**
Total IgE	1.24 (0.8 to 1.7)	<.001	1.08 (0.6 to 1.5)	<.001	−0.34 (−0.7 to 0.02)	.07	−0.41 (−0.8 to −0.02)	.04
B-eosinophils	0.39 (0.1 to 0.6)	.002	0.42 (0.1 to 0.7)	.004	0.09 (−0.1 to 0.3)	.44	0.15 (−0.1 to 0.4)	.23
FeNO	0.59 (0.4 to 0.8)	<.001	0.71 (0.5 to 0.9)	<.001	−0.09 (−0.2 to 0.1)	.52	−0.04 (−0.2 to 0.2)	.71
sRaw	−0.02 (−0.1 to 0.1)	.68	−0.06 (−0.2 to 0.04)	.23	−0.00 (−0.1 to 0.1)	.94	−0.03 (−0.1 to 0.1)	.54
β_2-reversibility‡	0.03 (−0.02 to 0.1)	.20	0.00 (−0.1 to 0.1)	.97	−0.00 (−0.1 to 0.04)	.87	0.00 (−0.04 to 0.1)	.87
Cold dry air challenge§	0.12 (0.02 to 0.2)	.02	0.11 (0.02 to 0.2)	.02	0.05 (−0.03 to 0.1)	.22	0.04 (−0.04 to 0.1)	.33

*Specific IgE ≥ 0.35 kU/L for at least 1 of 7 food allergens (hen's egg, cow's milk, fish, wheat, peanut, soybean, shrimp).

†Filaggrin null-mutations: *R501X* or *2282del4*.

‡The relative change in sRaw before and after bronchodilator.

§The relative change in sRaw before and after cold dry air hyperventilation.

TABLE E3. Comparisons of allergic rhinitis and nonallergic rhinitis with and without nasal eosinophilia versus controls

Controls vs: N = 165	Allergic rhinitis with nasal eosinophilia N = 9		Allergic rhinitis without nasal eosinophilia N = 23		Nonallergic rhinitis with nasal eosinophilia N = 5		Nonallergic rhinitis without nasal eosinophilia N = 54	
Binary variables	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**
Current asthma	4.9 (0.9 to 27.0)	.07	3.6 (1.0 to 12.8)	.05	5.7 (0.5 to 60.4)	.15	3.9 (1.5 to 10.2)	.01
Eczema ever	2.5 (0.6 to 10.2)	.21	3.5 (1.3 to 9.3)	.01	4.9 (0.5 to 45.0)	.16	0.8 (0.5 to 1.6)	.60
Food sensitization*	4.1 (1.0 to 16.2)	.05	3.9 (1.6 to 9.9)	.004	3.4 (0.5 to 21.4)	.19	0.6 (0.2 to 1.6)	.35
Filaggrin mutations†	3.3 (0.6 to 17.5)	.16	5.4 (1.9 to 15.6)	.002	2.9 (0.3 to 27.7)	.36	1.2 (0.4 to 3.5)	.77
Continuous variables	**β-coefficient (95% CI)**	***P* value**	**β-coefficient (95% CI)**	***P* value**	**β-coefficient (95% CI)**	***P* value**	**β-coefficient (95% CI)**	***P* value**
Total IgE	0.82 (−0.02 to 1.7)	.06	1.18 (0.6 to 1.7)	<.001	−0.62 (−1.7 to 0.5)	.27	−0.30 (−0.7 to 0.1)	.13
B-eosinophils	0.26 (−0.2 to 0.8)	.31	0.38 (0.04 to 0.7)	.03	−0.10 (−0.8 to 0.6)	.78	0.17 (−0.1 to 0.4)	.18
FeNO	0.93 (0.5 to 1.3)	<.001	0.57 (0.3 to 0.9)	<.001	0.27 (−0.3 to 0.8)	.33	−0.06 (−0.2 to 0.1)	.54
sRaw	−0.14 (−0.4 to 0.1)	.18	0.04 (−0.1 to 0.2)	.54	−0.09 (−0.4 to 0.3)	.63	−0.02 (−0.1 to 0.1)	.71
β_2-reversibility‡	0.02 (−0.1 to 0.1)	.69	0.03 (−0.04 to 0.1)	.38	−0.03 (−0.2 to 0.1)	.68	0.01 (−0.03 to 0.1)	.73
Cold dry air challenge§	0.21 (0.1 to 0.4)	.01	0.16 (0.04 to 0.3)	.01	0.15 (−0.1 to 0.4)	.26	0.03 (−0.1 to 0.1)	.48

*Specific IgE ≥ 0.35 kU/L for at least 1 of 7 food allergens (hen's egg, cow's milk, fish, wheat, peanut, soybean, shrimp).
†Filaggrin null-mutations: *R501X* or *2282del4*.
‡The relative change in sRaw before and after bronchodilator.
§The relative change in sRaw before and after cold dry air hyperventilation.

TABLE E4. Comparison of inflammatory rhinitis, noninflammatory rhinitis versus controls

Controls vs: N = 165	**Inflammatory rhinitis N = 14**		**Noninflammatory rhinitis N = 77**	
Binary variables	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**
Current asthma	5.1 (1.2 to 22.0)	.03	3.8 (1.6 to 9.2)	.003
Eczema ever	3.1 (0.9 to 10.2)	.07	1.3 (0.7 to 2.2)	.40
Food sensitization*	3.8 (1.2 to 11.9)	.02	1.3 (0.7 to 2.7)	.40
Continuous variables	**β-coefficient (95% CI)**	***P* value**	**β-coefficient (95% CI)**	***P* value**
Total IgE	0.30 (−0.4 to 1.0)	.41	0.14 (−0.2 to 0.5)	.43
B-eosinophils	0.14 (−0.3 to 0.6)	.51	0.23 (−0.02 to 0.4)	.13
FeNO	0.71 (0.4 to 1.0)	<.001	0.10 (−0.1 to 0.3)	.27
sRaw	−0.13 (−0.3 to 0.1)	.16	0.00 (−0.1 to 0.1)	.99
β_2-reversibility†	0.01 (−0.1 to 0.1)	.90	0.01 (−0.03 to 0.1)	.47
Cold dry air challenge‡	0.05 (−0.1 to 0.2)	.54	0.07 (−0.01 to 0.2)	.07

Inflammatory rhinitis is defined as rhinitis with nasal eosinophilia, noninflammatory rhinitis as rhinitis without nasal eosinophilia.

*Specific IgE ≥ 0.35 kU/L for at least 1 of 7 food allergens (hen's egg, cow's milk, fish, wheat, peanut, soybean, shrimp).

†The relative change in sRaw before and after bronchodilator.

‡The relative change in sRaw before and after cold dry air hyperventilation.

TABLE E5. Comparison of asthma in children with allergic rhinitis and nonallergic rhinitis versus controls

Controls vs: N = 169	Asthma and allergic rhinitis N = 8		Asthma and nonallergic rhinitis N = 13	
Variables	**β-coefficient (95% CI)**	***P* value**	**β-coefficient (95% CI)**	***P* value**
FeNO	0.40 (0.03 to 0.8)	.03	−0.12 (−0.5 to 0.2)	.47
Baseline sRaw	0.25 (0.1 to 0.5)	.01	0.17 (0.01 to 0.3)	.04
β_2-reversibility*	0.18 (0.1 to 0.3)	.001	0.01 (−0.1 to 0.1)	.80
Cold dry air challenge†	0.18 (0.02 to 0.4)	.05	0.12 (−0.04 to 0.3)	.13

*The relative change in sRaw before and after bronchodilator.
†The relative change in sRaw before and after cold dry air hyperventilation.

TABLE E6. Significant characteristics of allergic and nonallergic rhinitis adjusted for filaggrin null-mutations

Phenotypic characteristic	Allergic rhinitis vs controls				Nonallergic rhinitis vs controls			
	Crude		Adjusted for *FLG** mutations		Crude		Adjusted for *FLG* mutations	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Current asthma	5.0 (1.8-14.0)	.002	5.7 (2.0-16.8)	.001	4.6 (1.9-11.4)	.001	5.1 (2.0-13.0)	.001
Eczema ever	2.5 (1.2-5.1)	.01	2.0 (1.0-4.3)	.07	-	-	-	-
Food sensitization*	4.5 (2.1-9.4)	<.001	4.4 (2.0-9.6)	<.001	-	-	-	-
	β-coefficient (95% CI)	*P* value	β-coefficient (95% CI)	*P* value	β-coefficient (95% CI)	*P* value	β-coefficient (95% CI)	*P* value
Total-IgE	1.34 (0.9-1.8)	<.001	1.33 (0.9-1.8)	<.001	-	-	-	-
Blood eosinophil count	0.38 (0.1-0.6)	.01	0.31 (0.04-0.6)	.02	-	-	-	-
FeNO	0.62 (0.4-0.8)	<.001	0.60 (0.4-0.8)	<.001	-	-	-	-
Cold dry air challenge†	0.14 (0.04-0.2)	.008	0.15 (0.04-0.3)	.007	-	-	-	-

FLG, Filaggrin null-mutations: *R501X* or *2282del4*.

*Food sensitization, specific IgE ≥ 0.35 kU/L for at least 1 of 7 food allergens (hen's egg, cow's milk, fish, wheat, peanut, soybean, shrimp).

†Cold dry air challenge, the relative change in sRaw before and after cold dry air hyperventilation.