

ORIGINAL ARTICLE

Airways Disease

Impact of IgE sensitization and rhinitis on inflammatory biomarkers and lung function in adolescents with and without asthma

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Abstract

Background: Both allergic and non-allergic rhinitis are associated with worse asthma control. However, it is unclear how IgE sensitization and/or rhinitis are associated with lung function. We therefore evaluated the effect of rhinitis and sensitization on lung function, including the periphery of the airway system, and inflammatory biomarkers in individuals with and without asthma.

Methods: Participants in the BAMSE longitudinal birth cohort study underwent measures of spirometry, impulse oscillometry, and FeNO at age 16 years. Questionnaires were used to obtain data on asthma and rhinitis. Blood samples were analyzed for eosinophils and allergen-specific IgE.

Results: Groups based on the combination of asthma, rhinitis, and sensitization were compared to a healthy reference group. Lower FEV₁/FVC levels were seen for groups with asthma only (adjusted mean difference -2.8% units (95% CI -4.7; -1.0), $P < 0.01$), asthma with sensitization (-2.0 (-3.9; -0.2), $P < 0.05$), and asthma with sensitization and rhinitis (-2.5 (-3.6; -1.4), $P < 0.001$). The index of peripheral airway resistance R_{5-20} was higher in groups with asthma and sensitization (adjusted median difference 94.9 Pa L⁻¹ s⁻¹ (95% CI 60.4; 129.3), $P < 0.001$), as well as asthma with sensitization and rhinitis (36.9 (15.0; 58.8), $P < 0.01$). These groups also had increased FeNO and blood eosinophil levels.

Conclusions: We found signs of peripheral airway obstruction and increased levels of inflammatory biomarkers in the presence of allergic asthma, irrespective of rhinitis

status. Despite having a reduced FEV_1/FVC , peripheral airway engagement was not seen in non-sensitized adolescents with asthma. We suggest that small airway disease is a feature related to the eosinophilic inflammation in allergic asthma in adolescence.

KEYWORDS

asthma, BAMSE, impulse oscillometry, rhinitis, sensitization, spirometry

1 | INTRODUCTION

Asthma and rhinitis are two of the most common chronic diseases in childhood and adolescence, with worldwide prevalence rates up to 15%.¹ Rhinitis is considered a risk factor for later asthma development,²⁻⁴ and in children who already have asthma, rhinitis has been associated with worse symptom control and more airway inflammation, but not with lung function impairment.^{5,6} Concomitant IgE sensitization to airborne allergens is common in both asthma and rhinitis patients,⁷ which are then referred to as having allergic asthma or rhinitis. Individuals without sensitization are traditionally referred to as having non-allergic disease.

The obstruction of the airways in asthma involves both the larger central and the smaller peripheral airways,⁸ and studies in adults and children have suggested that peripheral airway function is a good indicator of asthma control.^{9,10} Given that spirometry does not adequately reflect peripheral airway function,¹¹ measuring further aspects of lung function beyond spirometry could contribute to the understanding of the interplay between asthma and its comorbidities. Impulse oscillometry (IOS) is a non-invasive method that provides information on the resistance and reactance of the peripheral airways,¹² and has been used to describe the peripheral airway engagement in asthma in both children and adults.¹³⁻¹⁵

We have previously shown that both transient and active asthma were negatively associated with FEV_1 in adolescence, while IOS measurements showed that only active asthma was associated with small airway impairments.¹³ Two of the major differences between these groups are the markedly higher prevalences of sensitization and rhinitis in the group with active symptoms. We therefore hypothesize that rhinitis and sensitization per se may have a negative effect on lung function, attributed to ongoing inflammation and peripheral airway obstruction.

To our knowledge, no other large-scale study has assessed the peripheral airway dysfunction in relation to both sensitization and rhinitis in asthmatic children or adolescents. The aim was therefore to evaluate the effect of rhinitis and sensitization on inflammatory biomarkers and lung function, including the periphery of the airway system, in 16-year-old individuals with and without asthma.

2 | MATERIAL AND METHODS

2.1 | Study subjects

The BAMSE (Swedish abbreviation for Children, Allergy, Milieu, Stockholm, Epidemiology) study is a prospective birth cohort

including 4089 Swedish children.¹⁶ Parents of all infants born between 1994 and 1996 in predefined areas of Stockholm including inner city, urban, and suburban districts were asked to participate in the study. The original cohort consists of 75% of eligible children. Baseline characteristics were collected by parental questionnaires when the children were approximately 2 months of age (time of inclusion). Parental reports on respiratory symptoms and medication were obtained by questionnaires answered at the age of 1, 2, 4, 8, and 16 years. In addition, smoking habits and symptom severity were reported by the adolescents at 16 years. Response rates ranged from 96% to 78% at each occasion. At 16 years of age, all subjects were invited to attend a clinical follow-up.

2.2 | Clinical examination

The clinical examination at 16 years included anthropometry, blood sampling, measurements of exhaled nitric oxide, spirometry, and impulse oscillometry.¹³

FE_{NO} was measured with a chemiluminescence analyzer (EcoMedics Exhalyzer® CLD 88sp with Denox 88; Eco Medics, Duernten, Switzerland). The procedure was performed in accordance with published guidelines.¹⁷

Spirometry and impulse oscillometry (IOS) were performed using the Jaeger MasterScreen-IOS system (Carefusion Technologies, San Diego, CA, USA). IOS was performed by superimposing pressure waves of different frequencies (5-35 Hz) onto normal tidal breathing to determine the resistance and reactance of the respiratory system. The area of reactance, A_x , is the integrated area of negative reactance from 5 Hz to the frequency where reactance equals zero. R_{5-20} is calculated as the difference between resistance at 5 and 20 Hz. The measurements were performed according to current international recommendations.¹⁸ The subjects performed tidal breathing with their lips tightly sealed around the mouthpiece while supporting the cheeks with their hands to avoid impulse pressure loss due to upper airway shunt. At least two artifact-free measurements of 20 seconds were required. Measurements with coherence at below 0.8 at 10 Hz were excluded. For analysis, mean values of each parameter were calculated.

Maximal expiratory flow volume (MEFV) measurements were performed following IOS. Forced vital capacity (FVC) and forced expiratory volume in 1 seconds (FEV_1) were assessed according to ATS/ERS criteria.¹⁹ FEV_1/FVC ratios were expressed as percentages.

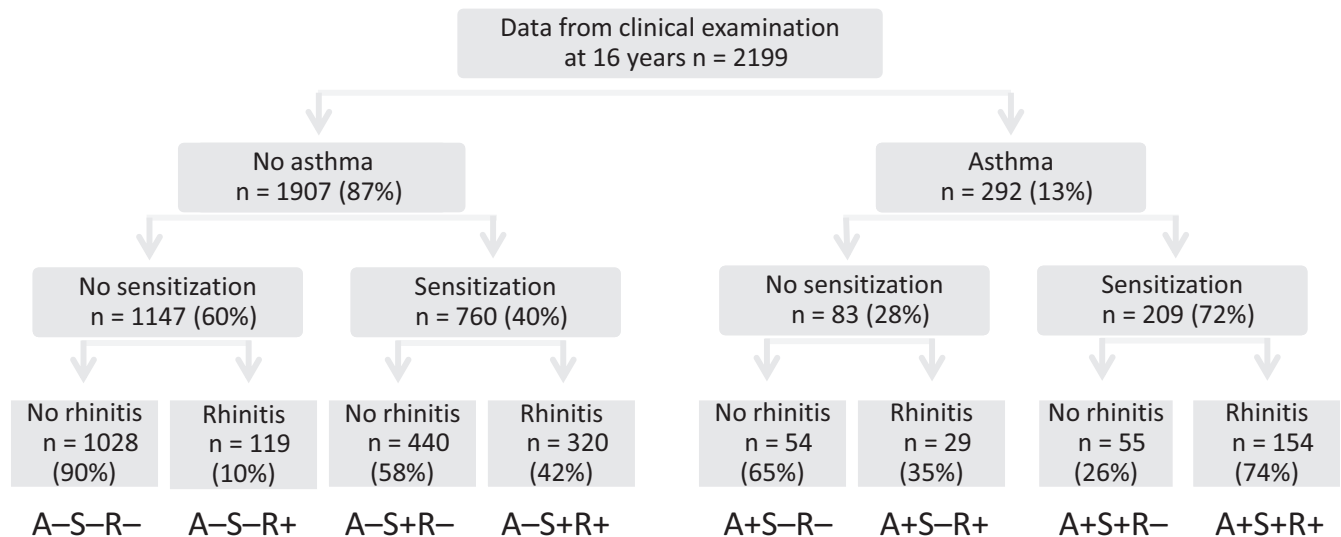


FIGURE 1 Flowchart of individuals with and without asthma (A), sensitization (S), and rhinitis (R) at 16 y of age in BAMSE. Percentage relates to the group directly above

2.3 | Blood analyses

Peripheral blood samples were analyzed for eosinophil cell count (Department of Clinical Chemistry, Karolinska University Hospital, Stockholm, Sweden).

Sera were analyzed for immunoglobulin E (IgE) reactivity to a mix of common inhalant allergens (birch, timothy, cat, dog, horse, mold, house dust mite, and mugwort) using Phadiatop® (Thermo Fisher Scientific/Phadia AB, Uppsala, Sweden; Department of Clinical Immunology, Karolinska University Hospital, Stockholm).

2.4 | Definitions of exposure

Rhinitis was defined as sneezing or a runny or blocked nose without common cold in the last 12 months at the 16-year follow-up questionnaire.²⁰

Asthma was defined as a positive answer to at least two of the following: (a) wheeze in the last 12 months, (b) reported use of asthma medication occasionally or regularly in the last 12 months, and (c) a doctor's diagnosis of asthma ever.²¹

Sensitization was defined as an IgE level of ≥ 0.35 kU_A/L to Phadiatop®.

Participants were grouped according to asthma status, with further subdivision by presence or absence of rhinitis and sensitization status, resulting in eight mutually exclusive groups (Figure 1). Groups are referred to with "+" representing the presence and "-" the absence of A, asthma; S, sensitization; and R, rhinitis.

2.5 | Statistical analysis

Comparisons between groups regarding background variables, FE_{NO}, eosinophil count, and prevalence of specific symptoms were performed by the chi-square test. Associations between groups and lung function

variables were assessed using multiple linear regression adjusting for sex, age, height, and weight at examination. *P*-values of <0.05 were considered statistically significant. Analyses were performed using the Stata 12.1 software package (StataCorp LP, College Station, TX, USA).

The BAMSE study was approved by the Regional Ethical Review Board in Stockholm, and all parents and participants provided consent to participate in the study.

3 | RESULTS

3.1 | Baseline characteristics

Of the 4089 children in the original BAMSE cohort, 2605 participated in the clinical follow-up at 16 years of age. Successful lung function test and blood sampling at 16 years of age were performed in 2199 subjects (54% of original cohort). Of these, 13% and 28% fulfilled the asthma and rhinitis criteria within the last 12 months, respectively. Sensitization to any of the screened inhalant allergens was found in 44% of participants. Subgroups depending on asthma, sensitization, and rhinitis status can be found in Figure 1. Background characteristics are summarized in Table 1.

3.2 | Lung function

We evaluated lung function in individuals with and without asthma, further divided into groups according to rhinitis and sensitization status. The group with no asthma, no sensitization, and no rhinitis (A-S-R-) was used as reference. Spirometry data for each group are presented in Table 2 and IOS data in Table 3. In the absence of asthma, neither sensitization, nor rhinitis, nor the combination of the two had an effect on spirometry or IOS parameters. An obstructive pattern indicated by significantly lower FEV₁ and FEV₁/FVC ratios was observed in all asthma groups (A+S-R-, A+S+R-, A+S+R+), with the exception of the small (n = 29) non-sensitized asthma and rhinitis

TABLE 1 Background characteristics of the different groups. Results are presented as n (%)

	A-S-R- (n = 1028)	A-S-R+ (n = 119)	A-S+R- (n = 440)	A-S+R+ (n = 320)	A+S-R- (n = 54)	A+S-R+ (n = 29)	A+S+R- (n = 55)	A+S+R+ (n = 154)
Male	448 (43.6)	54 (45.4)	246 (55.9)	183 (57.2)	20 (37.0)	4 (13.8)	22 (40.0)	84 (54.6)
	Ref.	P = 0.71	P < 0.001	P < 0.001	P = 0.34	P = 0.001	P = 0.60	P = 0.011
Birth <37 gestational weeks	59 (5.7)	7 (5.9)	19 (4.3)	15 (4.7)	9 (16.7)	2 (6.9)	4 (7.3)	10 (6.5)
	Ref.	P = 0.95	P = 0.27	P = 0.47	P = 0.001	P = 0.79	P = 0.64	P = 0.71
High socioeconomic index ^a	882 (86.6)	96 (81.4)	367 (84.2)	280 (88.3)	44 (83.0)	22 (75.9)	47 (85.5)	121 (80.1)
	Ref.	P = 0.12	P = 0.23	P = 0.41	P = 0.46	P = 0.10	P = 0.82	P = 0.035
Parental allergic heredity	233 (22.9)	43 (36.1)	161 (36.9)	140 (44.0)	16 (29.6)	13 (46.4)	25 (46.3)	76 (50.3)
	Ref.	P = 0.001	P < 0.001	P < 0.001	P = 0.25	P = 0.004	P < 0.001	P < 0.001
Maternal smoking during pregnancy	108 (10.5)	23 (19.3)	49 (11.1)	20 (6.3)	5 (9.3)	5 (17.2)	8 (14.6)	21 (13.6)
	Ref.	P = 0.004	P = 0.72	P = 0.02	P = 0.77	P = 0.25	P = 0.35	P = 0.25
Passive smoking at 16 y	171 (17.4)	24 (21.4)	76 (18.0)	50 (16.2)	14 (26.4)	9 (36.0)	12 (23.1)	25 (16.9)
	Ref.	P = 0.29	P = 0.761	P = 0.64	P = 0.09	P = 0.016	P = 0.29	P = 0.88
Self-reported active smoking at 16 y	43 (4.2)	5 (4.3)	19 (4.3)	8 (2.5)	4 (7.6)	2 (6.9)	0	4 (2.6)
	Ref.	P = 0.95	P = 0.90	P = 0.17	P = 0.24	P = 0.48	P = 0.12	P = 0.36

"+" represents the presence and "-" the absence of A, asthma; S, sensitization; and R, rhinitis.

^aSocioeconomic status at birth for the household according to dominance order in two classes (0 = blue-collar worker; and 1 = white-collar worker [incl. liberal professional practitioner with university graduate jobs]).

TABLE 2 Difference in adjusted mean spirometry values and 95% CI at 16 y between groups

	FVC (mL)		FEV ₁ (mL)		FEV ₁ /FVC (%)	
	Diff. (95% CI)	P-values ^a	Diff. (95% CI)	P-values ^a	Diff. (95% CI)	P-values ^a
A-S-R-	—	Ref.	—	Ref.	—	Ref.
A-S-R+	-55 (-157; 46)	0.28	-28 (-119; 63)	0.56	0.5 (-0.8; 1.8)	0.46
A-S+R-	-27 (-87; 32)	0.37	-23 (-77; 31)	0.40	0.003 (-0.8; 0.8)	0.99
A-S+R+	-56 (-124; 12)	0.11	-16 (-77; 46)	0.62	0.7 (-0.2; 1.6)	0.12
A+S-R-	-64 (-207; 80)	0.38	-195 (-324; -66)	0.003	-2.8 (-4.7; -1.0)	0.003
A+S-R+	137 (-46; 320)	0.14	72 (-93; 237)	0.39	-1.0 (-3.4; 1.4)	0.40
A+S+R-	-77 (-218; 65)	0.29	-171 (-299; -44)	0.009	-2.0 (-3.9; -0.2)	0.032
A+S+R+	-108 (-195; -22)	0.014	-216 (-294; -139)	<0.001	-2.5 (-3.6; -1.4)	<0.001

“+” represents the presence and “-” the absence of A, asthma; S, sensitization; and R, rhinitis.

^aFrom multiple linear regression on the mean, adjusting for sex, height, age, and weight at examination.

group (A+S-R+). IOS showed increased R_{5-20} and Ax in groups of asthma with sensitization (A+S+R+ and A+S+R-) compared to the healthy reference group.

3.3 | Inflammatory parameters

In sensitized asthmatic patients (A+S+R-, A+S+R+), the proportions of individuals with elevated levels of FE_{NO} and eosinophil levels were significantly higher than in the reference group, whereas this was not the case for non-sensitized asthmatic patients (Table 4). In addition, sensitization was associated with elevated FE_{NO} in non-asthmatic patients (A-S+R-, A-S+R+), while increased eosinophils was seen only for the non-asthmatic group with sensitization without rhinitis (A-S+R-).

3.4 | Symptoms

Prevalences of specific respiratory and nasal symptoms in the different groups are presented in Table S1. In subjects fulfilling the asthma criteria, the proportion of individuals having experienced more than three episodes of wheeze in the last 12 months was significantly more common in the two groups with concomitant rhinitis (A+S-R+,

46.4%, $P = 0.03$; A+S+R+, 38.5%, $P = 0.049$), when compared with the reference group without sensitization or rhinitis (A+S-R-, 22.9%). Having 12 episodes of wheeze or exercise-induced asthma symptoms did not differ significantly by sensitization or rhinitis status.

Activity avoidance and disturbed sleep due to nasal symptoms as an indication of rhinitis severity were most prevalent in groups with concomitant sensitization.

4 | DISCUSSION

In the present study, we show an association between asthma with sensitization in adolescence and peripheral airway obstruction measured by IOS, irrespective of rhinitis status. Asthmatic subjects with sensitization also had significantly elevated levels of inflammatory biomarkers measured as FE_{NO} and blood eosinophils. Despite having a reduced FEV₁/FVC, peripheral airway engagement was not seen in non-sensitized asthmatic patients. Finally, neither sensitization nor rhinitis was associated with lung function in the absence of asthma.

We found that airway obstruction indicated by a low FEV₁/FVC ratio was related to asthma status, rather than presence of rhinitis

	R_{5-20} (Pa·L ⁻¹ ·s ⁻¹)		Ax (Pa L ⁻¹)	
	Diff. (95% CI)	P-values ^a	Diff. (95% CI)	P-values ^a
A-S-R-	—	Ref.	—	Ref.
A-S-R+	5.0 (-3.9; 13.9)	0.28	11.5 (-12.9; 36.0)	0.36
A-S+R-	-1.0 (-6.2; 4.2)	0.71	3.9 (-10.4; 18.2)	0.59
A-S+R+	0.3 (-5.5; 6.2)	0.91	11.3 (-4.8; 27.4)	0.17
A+S-R-	6.6 (-6.2; 19.3)	0.31	31.5 (-3.2; 66.3)	0.08
A+S-R+	2.4 (-14.9; 19.7)	0.78	-15.9 (-63.1; 31.4)	0.51
A+S+R-	17.2 (4.6; 29.8)	0.007	94.9 (60.4; 129.3)	<0.001
A+S+R+	12.1 (4.1; 20.1)	0.003	36.9 (15.0; 58.8)	0.001

“+” represents the presence and “-” the absence of A, asthma; S, sensitization; and R, rhinitis.

^aFrom multiple linear regression on the median, adjusting for sex, height, age, and weight at examination.

TABLE 3 Difference in adjusted median IOS values and 95% CI at 16 y between groups

TABLE 4 Proportion of individuals with elevated inflammatory biomarkers

	FeNO >25 ppb		Eosinophils >0.5 × 10 ⁹ /L	
	n (%)	P-values	n (%)	P-values
A-S-R-	96 (11.6)	Ref.	23 (2.4)	Ref.
A-S-R+	11 (11.2)	0.91	1 (0.9)	0.31
A-S+R-	93 (26.0)	<0.001	19 (4.6)	0.026
A-S+R+	109 (40.9)	<0.001	11 (3.6)	0.24
A+S-R-	6 (12.0)	0.93	1 (1.9)	0.84
A+S-R+	4 (17.4)	0.39	1 (3.4)	0.70
A+S+R-	20 (47.6)	<0.001	5 (9.8)	0.001
A+S+R+	62 (50.0)	<0.001	18 (12.1)	<0.001

FeNO, forced exhaled nitric oxide; "+" represents the presence and "-" the absence of A, asthma; S, sensitization; and R, rhinitis.

or sensitization. The lack of influence of these comorbidities on lung function measured by resting spirometry is in concordance with results from the UK-based MAAS cohort and the German MAS cohort, where it was reported that FEV₁/FVC did not differ by absence or presence of rhinitis.^{5,22} Further in accordance with our results, de Groot et al⁶ analyzed the effect of allergic rhinitis in a selected patient sample of asthmatic children aged 5-18 years and found poorer asthma control, but no difference in FEV₁ or FVC. In a paper by Luzak et al,²³ sensitization was not associated with any spirometric parameter considered in 15-year-old subjects with allergic rhinitis, asthma, or neither disease.

In our study, peripheral airway disease as indicated by increased frequency dependence of resistance and reactance measured by IOS was found solely in the groups of adolescents with allergic asthma (ie, both sensitization and asthma) with or without rhinitis. In a considerably smaller but very detailed study of adults, evidence of peripheral airway dysfunction was seen in non-asthmatic patients with allergic rhinitis. In their study, airway function was assessed via ventilation distribution measured by multiple-breath washout, and after bronchoprovocation, making comparisons difficult.²⁴ We do however acknowledge that IOS reflects the mechanics of the peripheral airways with preference to the better functioning units, and might therefore not be as sensitive as methods such as multiple-breath washout, where weight is given to relatively poorly ventilated lung units.¹⁴ Nevertheless, the finding in the current study that FVC was lower than expected in the asthma group with sensitization is indirectly giving further support to the presence of peripheral airway involvement. FVC has been shown to correlate inversely with the ratio between residual volume and total lung volume (RV/TLC), indicating that a reduction of FVC can be considered a marker of air trapping, as small airway abnormalities lead to peripheral heterogeneity of the ventilation and to premature airway closure and air trapping.^{25,26}

We found that sensitization per se, rather than rhinitis, was positively associated with FE_{NO} and blood eosinophils. In the study by de Groot et al,⁶ presence of rhinitis was associated with higher FE_{NO}, but since over 97% of their rhinitis population was sensitized to aeroallergens, it was not possible to discriminate non-allergic

rhinitis and is plausible that the FE_{NO} reflects sensitization rather than rhinitis. In the COPSAC study of children at high risk of allergic disease, the effect of sensitization was indirectly examined in 7-year-old asthmatic children with allergic and non-allergic rhinitis and it was found that FE_{NO} was increased only in those with sensitization.² Further in concordance, it was reported by Deliu et al⁵ that FE_{NO} (after adjustment for atopy) did not differ by absence or presence of rhinitis in school children with asthma.

4.1 | Strengths and limitations

A major strength of the study is that the use of IOS measures provides additional insight into the lung physiology beyond spirometry.

A limitation is the questionnaire-based symptoms criteria used to define disease, which however is typical for large epidemiological studies. The results should be considered in light of the relatively young age of the population, as time may be an important factor in the relation between the different disease entities and development of lung function impairment.

4.2 | Interpretation

The results from this study suggest two distinct phenotypes related to the observed airway obstruction measured by spirometry in adolescents with current asthma. Allergic asthma, here defined as asthma (according to criteria) in combination with sensitization to aeroallergens, was characterized by atopic heredity, eosinophilic inflammation, and small airway dysfunction. A small airway asthma subtype characterized by low FEV₁ and high blood eosinophils has previously been suggested in adults by Kjellberg et al.¹⁴ Our data show that a similar pattern can be found in adolescence.

In comparison, the non-allergic asthma group also presented with reduced FEV₁/FVC ratios, but not eosinophilic inflammation or small airway disease. We hypothesize that other factors may influence lung function impairment in this group, such as preterm birth and early life events.²⁷ Unfortunately, the design of the current study does not allow for the assessment of whether the lung function impairment in this group is more static and less related to hyper-reactivity.

The current study further highlights the need of disentangling the effect of sensitization and rhinitis on respiratory symptoms and lung function. In the non-allergic rhinitis and asthma group, lung function assessed with both IOS and spirometry showed values similar to or better than those of the reference group. Nevertheless, they reported more respiratory symptoms than any other group. It should be noted that this group was small (n = 26) and differed notably from the others in sex distribution and exposure to passive smoking.

In conclusion, we show an association between asthma with sensitization in adolescence and peripheral airway obstruction measured by IOS, irrespective of rhinitis status. Asthmatic subjects with sensitization also had significantly elevated levels of inflammatory biomarkers measured as FE_{NO} and blood eosinophils. We suggest that small airway disease is a feature related to the eosinophilic inflammation in allergic asthma in adolescence.

CONFLICT OF INTEREST

JH and MW have received a speakers' fee from MEDA AB. MvH has received speakers' fees from ALK and Thermo Fisher Scientific and consultant fee from Hycor Biomedical LLC, CA, USA. EM has received speakers' fees from MEDA AB and Thermo Fisher Scientific. IK, AB, GL, CA, and NB have no potential conflict of interests to disclose.

AUTHOR CONTRIBUTION

JH carried out the data acquisition and analysis together with EM. IK, NB, CA, MW, GL, MvH, and AB participated in the design and planning of the study, as well as in the interpretation of the results. JH and EM drafted the manuscript. All authors read and approved the final manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Supplementary data

Impact of IgE sensitization and rhinitis on inflammatory biomarkers and lung function in adolescents with and without asthma.

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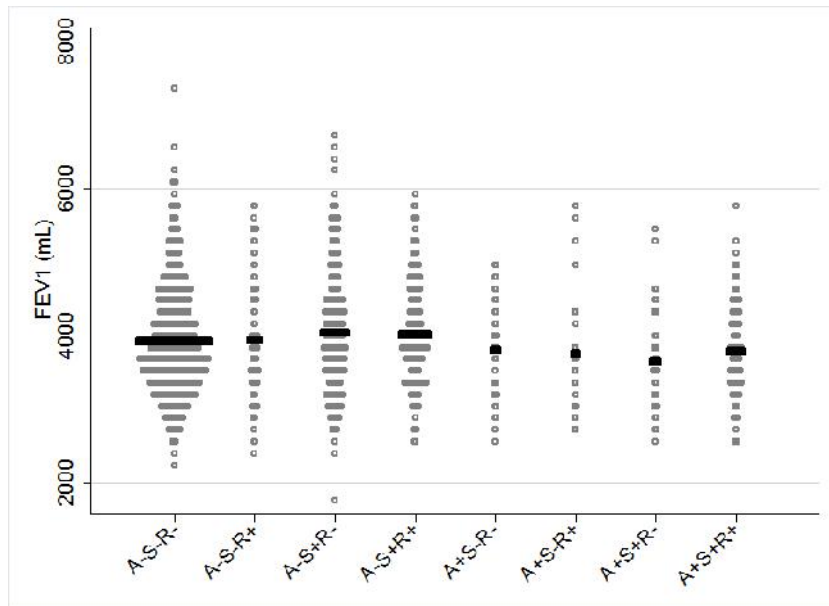
Online Table 1. Self reported asthma and rhinitis symptoms in the last 12 months. Data presented as n(%).

Asthma symptoms	A+S-R-	A+S-R+	A+S+R-	A+S+R+
>3 wheeze episodes	11(22.9)	13(46.4)	17(31.5)	57(38.5)
>12 wheeze episodes	5(10.4)	5(17.9)	7(13.0)	19(12.8)
Exercise induced wheeze	24(52.2)	17(65.4)	30(60.0)	81(61.8)
Rhinitis symptoms	A-S-R+	A+S-R+	A-S+R+	A+S+R+
Activity avoidance due to nasal symptoms	2(4.8)	1(16.7)	46(38.0)	13(31.0)
Disturbed sleep due to nasal symptoms	19(32.2)	4(44.4)	72(49.0)	41(58.6)

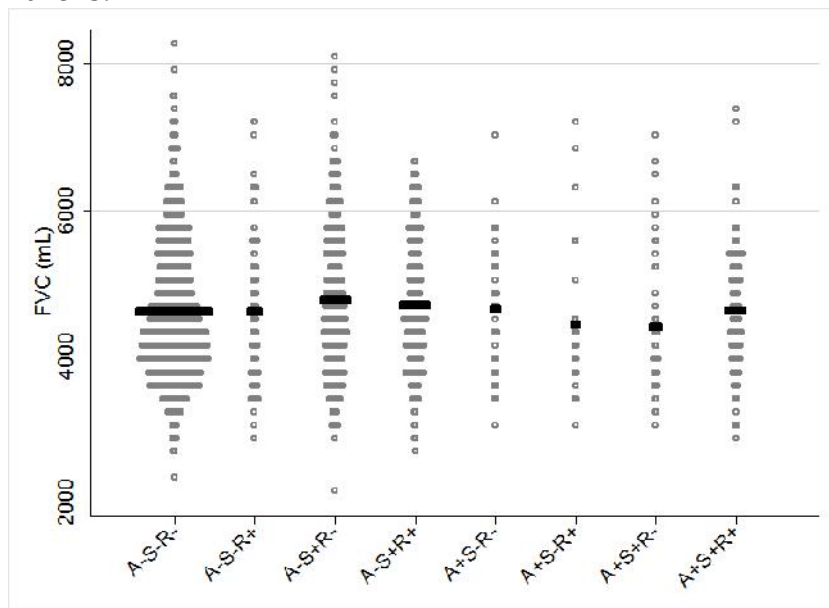
Abbreviations: “+” represents presence and “-“ for absence of A, asthma; S, sensitization; and R, rhinitis.

Online Figure 1a-c. Comparative scatterplot of crude lung function by group. Each dot represents an individuals value and the horizontal line the mean of the group.

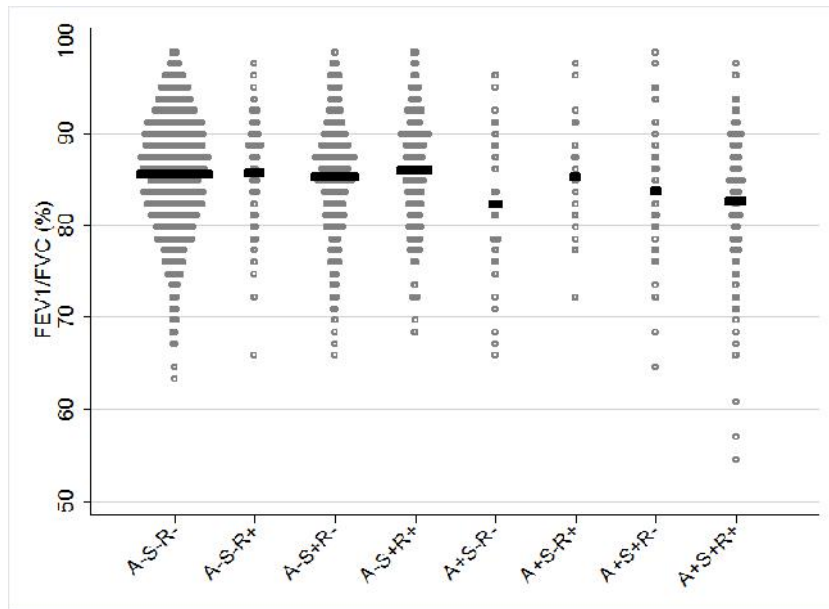
Panel a.



Panel b.



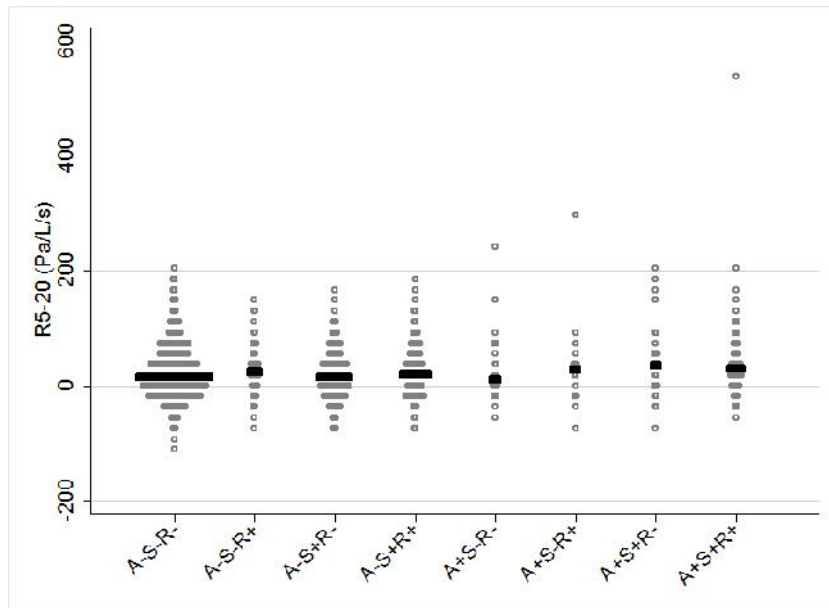
Panel c.



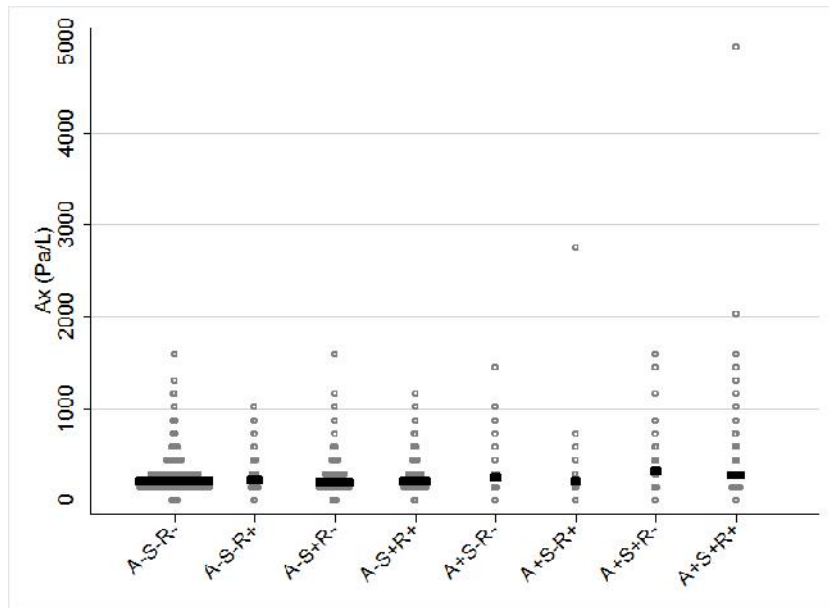
Abbreviations: “+” represents presence and “-“ for absence of A, asthma; S, sensitization; and R, rhinitis.

Online Figure 2a-b. Comparative scatterplot of crude lung function by group. Each dot represents an individuals value and the horizontal line the median of the group.

Panel a.



Panel b.



Abbreviations: “+” represents presence and “-“ for absence of A, asthma; S, sensitization; and R, rhinitis.