

Lower airway flow influences peak nasal inspiratory flow in school-aged children*

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Background: Rhinitis and asthma frequently coexist. Peak nasal inspiratory flow (PNIF) objectively evaluates nasal obstruction. Lower airway flow's impact on PNIF has seldom been analysed in children. We aimed to study the associations between PNIF and: (1) forced expiratory volume in one second (FEV₁) and peak expiratory flow (PEF) in children with allergic rhinitis and asthma and healthy controls; (2) allergic rhinitis and asthma control subjective evaluation.

Methods: Sequential assessments of PNIF before and after nasal decongestion and spirometry with bronchodilation test were performed in 65 children (6-12 years) with allergic rhinitis and asthma, and 24 gender, age-matched healthy controls. The Control of Allergic Rhinitis and Asthma Test in children (CARATkids) was used for control assessment. Associations were investigated by multiple linear regression models.

Results: Baseline and decongested PNIF correlated with baseline and post-bronchodilation FEV₁ and PEF, observed independently of rhinitis and asthma diagnosis. The best model for PNIF included PEF, age and gender. No association was found between PNIF and CARATkids scores, except for nasal obstruction self-report.

Conclusion: In school-aged children, besides age and gender, PEF values should ideally be known to interpret PNIF values. PNIF can be complementary to subjective control assessment in children with allergic rhinitis and asthma.

Key words: asthma, children, Peak Expiratory Flow (PEF), Peak Nasal Inspiratory Flow (PNIF), rhinitis

Introduction

Rhinitis and asthma frequently coexist⁽¹⁻⁴⁾. Allergic rhinitis is an independent risk factor for asthma persistence^(1,5); asthma prevalence is increased when rhinitis symptoms are persistent and severe^(1,6,7). Nasal obstruction is one of the main complaints in these patients^(2-4,8), due to mucosal inflammation. The use of validated subjective scoring tools is highly recommended for the evaluation of rhinitis and asthma control⁽⁹⁻¹²⁾. Furthermore, the assessment of a patient suffering of nasal obstruction should be based upon subjective and objective measurements, as both may not correlate well^(9,11-13). The Control of Allergic Rhinitis and Asthma Test (CARAT) is a simple and validated questionnaire that has the advantage of enabling the self-reported subjective concurrent assessment of rhinitis and asthma control in adults and in children (CARATkids)⁽¹⁴⁻¹⁶⁾. How-

ever, no data exist on the association between CARAT questionnaires and objective measures of nasal patency.

Peak nasal inspiratory flow (PNIF) is a simple and validated measure of nasal airflow^(11,12), successfully used for the objective evaluation of rhinitis and its control⁽¹⁷⁻²⁰⁾, including in children^(21,22). Reference values for the paediatric population have been published, all measured in non-decongested noses⁽²³⁻²⁷⁾. Yet, it is important to measure PNIF values before and after decongestion to elicit the role of mucosal swelling^(11,12).

The impact of lower airway patency on PNIF should be considered^(11,12,28-30). A bivariate correlation between baseline PNIF and peak expiratory flow (PEF) has been described in healthy children⁽²⁶⁾, but no multivariable analysis including PEF was reported. Since a continuous increase in PNIF values has been consistently reported with children's age⁽²³⁻²⁷⁾, it is important to exclude that

the observed association between PNIF and PEF is not a simple reflection of the normal growth (i.e., older children have larger airways and correspondingly higher nasal airflow).

Thus, we have investigated the association between PNIF before and after topical nasal alpha-adrenergic use and lower airway patency before and after inhaled beta₂-agonist, in children with allergic rhinitis and asthma and healthy controls, when adjusted for possible confounders. We have also evaluated the association between PNIF and CARATkids questionnaire results, multiple sensitization to aeroallergens and exhaled nitric oxide levels (FeNO).

Subjects and methods

Study design and participants

Cross-sectional, exploratory study of 65 children (6-12 years) with allergic rhinitis and asthma recruited among patients attending the Allergy Center at CUF Descobertas Hospital in Lisbon, from May until October 2015. Rhinitis was defined as the presence of nasal itching/rhinorrhea/sneezing and/or nasal obstruction, occurring during ≥ 2 consecutive days for > 1 hour on most days^(1,8). Allergic rhinitis was considered in children with rhinitis and self-reported symptoms upon aeroallergen exposure with positive skin prick test (SPT). Allergic rhinitis was classified according to the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines^(1,8). Asthma was diagnosed by a history of respiratory symptoms in the previous year, such as wheeze, breathlessness, chest tightness and cough that varied over time and in intensity, together with documented positive bronchodilator reversibility testing⁽¹⁰⁾. A convenience-driven sampling was used, stratified by asthma control defined according to the Global Initiative for Asthma (GINA) guidelines⁽¹⁰⁾; children with controlled, partly controlled and uncontrolled asthma were recruited in an approximate 1:1:1 ratio.

Children with any other diagnosed respiratory or cardiac disease were excluded from this study. These encompassed diagnosed congenital or perinatal diseases including cardiopulmonary or neuromuscular diseases, pneumonia/pneumonitis, aspiration, cystic fibrosis, immunodeficiency, gastro-oesophageal reflux disease, adenoid hypertrophy, nasal septum deviation or nasal polyps. Children with asthma exacerbation, systemic corticosteroids use or acute disease (including respiratory infection) within four weeks of the study visit were also excluded.

Age and gender-matched controls without rhinitis and asthma were screened by no positive answers on the International Study of Asthma and Allergies in Childhood questionnaire⁽³¹⁾. Included children were non-atopic, without history of other diseases likely to interfere with the study (such as those described above) and no acute disease within the previous four weeks.

All diagnoses were validated by medical specialists, based on anamnesis, clinical files and medical examination including anterior rhinoscopy (performed in all children).

Informed consent was obtained from each child's parent/legal guardian. This study was approved by the Ethics Committee of CUF Descobertas Hospital and by the Portuguese Data Protection Authority.

Measurements

Prior to study visit, subjects had not taken any asthma or topical nasal medication for at least 12 hours and anti-histamines for seven days. Study visits occurred during the morning.

1. CARATkids questionnaire

All children with asthma and rhinitis and their parents answered the CARATkids before all other measurements⁽¹⁵⁾. Total score (0 – best control to 13 – worst control) was recorded, as well as, nasal obstruction report by the children and CARATkids total nasal score (varying from 0 to 3, obtained by the sum of positive answers regarding nasal symptoms of “blocked nose”, “sneezing” and “runny nose”, in the past two weeks).

2. Anthropometric measurements

Accurate height (cm) and weight (Kg) were registered without shoes for all the included children.

3. Respiratory function tests

All nasal and lung function tests were performed by trained lung function technicians, all awarded with the European Respiratory Society Spirometry Driving Licence.

Bilateral PNIF was assessed using a nasal flow meter (In-Check Nasal, Clement Clarke International Ltd., Edinburgh, England). After mildly blowing their noses, the children were instructed to do a nasal inspiration with their mouths closed, from residual volume to total lung capacity, while using the facial mask without leakage of air or nose compression. The highest value out of three satisfactory maximal inspiration measurements was recorded. All measurements were taken with children sitting in an upright position.

Lower airway flow was assessed by forced expiratory volume in one second (FEV₁) and PEF, obtained by spirometry test (Jaeger MasterScreen™ system from Carefusion with a Flow Spirometer (Lilly Pneumotacograph) with Software version - JLAB 5.31.0.83), performed and interpreted according to international recommendations⁽³²⁾. Global Lung Initiative normative data was used. Bilateral topical nasal phenylephrine chlorhydrate at 2.5mg/ml was applied and a bronchodilation test was performed with 400µg of inhaled salbutamol administered using a chamber⁽³²⁾. Then, decongested PNIF was obtained using the same procedure, as well as post-bronchodilator PEF and FEV₁.

Nasal reversibility was calculated by the Nasal Congestion Index (NCI)⁽³³⁾, as follows: $NCI = [(decongested\ PNIF - baseline\ PNIF) / baseline\ PNIF] \times 100$.

For the PNIF measurements recorded, the z-scores for age and

Table 1. Study group characteristics.

Characteristic	All study participants (n=89)	Healthy controls (n=24)	Controlled asthma (n=20)	Partly controlled asthma (n=21)	Uncontrolled asthma (n=24)	p
Gender male, n (%)	50 (56.2)	12 (50.0)	10 (50.0)	15 (71.4)	13 (54.2)	0.439
Age months, median (min-max)	115 (73.0-155.0)	116 (73.0-155.0)	105 (74.0-155.0)	115 (76.0-148.0)	128 (78.0-155.0)	0.106
Height cm, median (min-max)	135 (113.0-165.0)	133 (114.5-155.0)	134 (116.0-150.5)	134 (113.0-162.3)	143 (117.0-165.0)	0.154
Weight Kg, median (min-max)	34 (17.0-67.0)	31 (17.0-48.0)	31 (20.0-53.0)	35 (17.0-54.0)	39 (22.0-67.0)	0.103
Allergic rhinitis classification (ARIA)*						0.028
Mild intermittent, n (%)	5 (5.6)	0 (0.0)	4 (20.0)	1 (4.8)	0 (0.0)	
Moderate-severe intermittent, n (%)	2 (2.3)	0 (0.0)	0 (0.0)	2 (9.5)	0 (0.0)	
Mild persistent, n (%)	11 (12.4)	0 (0.0)	5 (25.0)	3 (14.3)	3 (12.5)	
Moderate-severe persistent, n (%)	47 (52.8)	0 (0.0)	11 (55.0)	15 (71.4)	21 (87.5)	
Nasal topic corticosteroid use*#, n (%)	23 (33.8)	0 (0.0)	6 (30.0)	8 (38.1)	9 (37.5)	0.832
Oral montelukast use*#, n (%)	7 (7.9)	0 (0.0)	0 (0.0)	3 (14.3)	4 (16.7)	0.201
Inhaled corticosteroid use*#, n (%)	37 (41.6)	0 (0.0)	12 (60.0)	14 (66.7)	11 (45.8)	0.351
Inhaled LABA use*#, n (%)	20 (22.5)	0 (0.0)	6 (30.0)	4 (19.0)	10 (41.7)	0.259
Multiple sensitization*, n (%)	39 (60.0)	0 (0.0)	11 (55.0)	13 (61.9)	15 (62.5)	0.860

ARIA – allergic rhinitis and its impact on asthma guidelines; min – minimum; max – maximum; LABA – long-acting beta₂ agonist; * - considering only children with rhinitis and asthma, # – medication use reported by caregiver

gender were calculated according to the PNIF reference values proposed by Papachristou and collaborators⁽²⁴⁾.

4. Fractional exhaled nitric oxide measurement

The FeNO was measured with the NIOX Vero® system (Aerocrine, Sweden) using a single-breathing online method before respiratory function tests, according to current guidelines^(34, 35).

5. Skin prick tests

The SPT were performed according to international recommendations^(9, 36). The skin was pricked with steel lancets (Prick Lancetter®, Hollister-Stier Laboratories, Spokane, WA, USA), and the following allergen extracts were applied: *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Lepidoglyphus destructor*, *Parietaria*, grass pollen mixture, olive tree, *Alternaria*, dog and cat epithelium (Bial-Aristegui®, Bilbao, Spain). Histamine hydrochloride (10 mg/ml) was used as a positive control; a saline solution was the negative control. A wheal mean diameter ≥3 mm was considered a positive test.

Atopy was considered when at least one SPT was positive. Multiple sensitization was defined when SPT were positive to two or more of the following aeroallergen groups: house dust mites, pollens, moulds or pets.

Statistical analysis

Normal distribution of variables was assessed using the Shapiro-Wilk or Kolmogorov-Smirnov tests and histogram visual analysis.

Categorical variables were expressed as absolute and relative frequencies. Comparisons were performed with the Pearson's chi-square test. Continuous variables were expressed as the mean and standard deviation (SD), or median and extreme values in case of no normal distribution. Comparisons were performed with parametric independent t-test or one-way ANOVA or non-parametric Mann-Whitney or Kruskal-Wallis tests, followed by post-hoc multiple comparisons according to Bonferroni test. Correlations were analysed using Pearson's coefficient or Spearman's rank coefficient. Associations were further investigated by multivariable linear regression models for baseline and decongested PNIF; assumption of normally distributed residuals was fulfilled. Results were reported as beta-coefficients with 95% confidence intervals (95%CI).

P values <0.05 were considered significant. Data analyses were performed with SPSS® version 24.0 for Windows (IBM SPSS, Chicago, IL, USA).

Results

Participants characteristics

A total of 89 children were included. Participants' characteristics are summarized in Table 1. All children were Caucasian. No statistically significant differences were found regarding demographic and anthropometric parameters. Most patients had moderate-severe persistent allergic rhinitis (72.3%). Allergic rhinitis classification by ARIA was associated with asthma control assessed according to GINA guidelines (Table 1).

Table 2. Control of Allergic Rhinitis and Asthma Test for children (CARATkids) results.

CARATkids	Total of asthmatic children (n=65)		Controlled asthma (n=20)		Partly controlled asthma (n=21)		Uncontrolled asthma (n=24)		p
Global score, median (min-max)	4	(0-10)	1	(0-8)	4	(0-10)	6	(2-10)	<0.001
Nasal obstruction, n (%)	38	(58.5)	9	(45.0)	12	(57.1)	17	(70.8)	0.221
Nasal score, n (%)									0.121
0	10	(15.4)	4	(20.0)	4	(19.0)	2	(8.3)	
1	12	(18.5)	7	(35.0)	4	(19.0)	1	(4.2)	
2	22	(33.8)	4	(20.0)	7	(33.3)	11	(45.8)	
3	21	(32.3)	5	(25.0)	6	(28.6)	10	(41.7)	

min – minimum; max – maximum

Table 3. Study group objective airway function and exhaled nitric oxide assessment.

Characteristic	All study participants (n=89)		Healthy controls (n=24)		Controlled asthma (n=20)		Partly controlled asthma (n=21)		Uncontrolled asthma (n=24)		p
Baseline PNIF L/min, median (min-max)	100.0	(40.0-170.0)	100.0	(60.0-150.0)	100.0	(40.0-150.0)	100.0	(50.0-150.0)	100.0	(40.0-170.0)	0.747
Decongested PNIF L/min, median (min-max)	110.0	(50.0-210.0)	110.0	(80.0-190.0)	110	(50.0-200.0)	120.0	(60.0-190.0)	120.0	(80.0-210.0)	0.339
Baseline PNIF z-score, mean (SD)	-0.77	(0.94)	-0.70	(0.94)	-0.80	(1.06)	-0.65	(0.66)	-0.93	(1.06)	0.630
Decongested PNIF z-score, mean (SD)	-0.07	(0.93)	-0.05	(1.05)	-0.16	(1.00)	0.12	(0.82)	-0.17	(0.87)	0.617
Nasal congestion index %, median (min-max)	21.43	(-10.00-175.00)	23.61	(0.00-66.67)	19.26	(-10.00-100.00)	20.00	(-10.00-83.33)	22.48	(-4.55-175.00)	0.984
Baseline PEF L/s, mean (SD)	3.95	(0.97)	3.96	(0.87)	3.98	(0.96)	3.98	(1.26)	3.90	(0.83)	0.993
Baseline PEF z-score, mean (SD)	-0.41	(0.94)	-0.25	(0.79)	-0.07	(1.08)	-0.49	(0.85)	-0.77	(0.96)	0.070
Post-beta ₂ agonist PEF L/s, mean (SD)	4.30	(0.99)	4.28	(0.83)	4.27	(1.02)	4.17	(1.25)	4.47	(0.87)	0.776
Post-beta ₂ agonist PEF z-score, mean (SD)	0.01	(0.81)	0.21	(0.77)	0.22	(0.92)	-0.20	(0.91)	-0.18	(0.59)	0.135
Baseline FEV ₁ L, mean (SD)	1.88	(0.47)	1.91	(0.48)	1.93	(0.47)	1.86	(0.57)	1.83	(1.89)	0.894
Baseline FEV ₁ z-score, mean (SD)	0.32	(1.58)	0.85	(1.07)	1.26	(1.65)	0.19	(1.30)	-0.88	(1.42)	<0.001
Post-beta ₂ agonist FEV ₁ L, mean (SD)	2.05	(0.51)	1.98	(0.47)	2.04	(0.53)	2.01	(0.59)	2.15	(0.48)	0.698
Post-beta ₂ agonist FEV ₁ z-score, mean (SD)	1.22	(1.35)	1.30	(1.09)	1.79	(1.47)	1.11	(1.35)	0.75	(1.36)	0.079
Positive bronchodilation test, n (%)	25	(28.1)	1	(4.2)	0	(0.0)	6	(28.6)	18	(75.0)	<0.001
FeNO ppb, median (min-max)	12	(0-104)	5	(0-24)	10	(0-87)	15	(0-94)	29	(7-104)	<0.001

PNIF – peak nasal inspiratory flow; PEF – peak expiratory flow; FEV₁ – forced expiratory volume in one second; FeNO – exhaled nitric oxide; min – minimum; max – maximum; SD – standard deviation

Table 4. Correlation coefficients between Peak Nasal Inspiratory Flow and demographic/anthropometric and lung function variables.

Variables	Baseline PNIF (L/min)		Decongested PNIF (L/min)	
	rho	p	rho	p
Age (months)	0.281	(0.008)	0.445	(<0.001)
Height (cm)	0.288	(0.006)	0.452	(<0.001)
Weight (Kg)	0.358	(0.001)	0.488	(<0.001)
Baseline FEV ₁ (L)	0.322	(0.002)	0.453	(<0.001)
Baseline FEV ₁ (z-score)	-	ns	-	ns
Post-beta ₂ agonist FEV ₁ (L)	0.299	(0.004)	0.475	(<0.001)
Post-beta ₂ agonist FEV ₁ (z-score)	-	ns	-	ns
Baseline PEF (L/s)	0.404	(<0.001)	0.482	(<0.001)
Baseline PEF (z-score)	0.321	(0.002)	-	ns
Post-beta ₂ agonist PEF (L/s)	0.341	(0.001)	0.476	(<0.001)
Post-beta ₂ agonist PEF (z-score)	0.226	(0.033)	-	ns

rho – Spearman rank correlation coefficient; PNIF – peak nasal inspiratory flow; FEV₁ – forced expiratory volume in one second; PEF – peak expiratory flow; ns – not significant

CARATkids scores

The median CARATkids score in children with rhinitis and asthma was 4, varying from 0 to 10. This score was associated with asthma control but no statistically significant differences were found regarding CARATkids nasal score or nasal obstruction self-report (Table 2).

The CARATkids score was associated with ARIA rhinitis classification, the worst values in moderate-severe persistent rhinitis (Bonferroni post-hoc testing, $p=0.002$).

Objective measurements

Table 3 summarizes the upper and lower airway function and FeNO assessment results. No statistically significant differences were found in PNIF values or NCI comparing healthy children versus children with rhinitis and asthma, either reporting nasal obstruction or not. Children with rhinitis and asthma reporting nasal obstruction in the past two weeks in the CARATkids questionnaire had mean baseline PNIF z-scores of -1.02 (SD 1.01) versus -0.68 (SD 0.95) in healthy children ($p=0.185$).

Obstructive lower airway flow limitation was found in 27% of the children, with FEV₁ z-score varying from -3.49 to 1.17. Lower FEV₁ z-score and higher FeNO levels were found in children with asthma, the worst values in uncontrolled asthmatics (Bonferroni post-hoc testing, $p\leq 0.006$). No associations were found between PNIF and asthma control (assessed according to GINA guidelines) or ARIA classification of allergic rhinitis.

Association between PNIF and CARATkids scores

In children with rhinitis and asthma, those reporting nasal obstruction in the CARATkids questionnaire had lower baseline PNIF z-scores (mean -1.02 (SD 1.01) versus mean -0.49 (SD 0.73), $p=0.018$). This association was independent of PEF and FEV₁. No other associations were found between PNIF and CARATkids scores.

Association between PNIF and demographic/anthropometric variables

Baseline and decongested PNIF values correlated with age, height and weight (Table 4). Both values were higher in boys, although this difference was not statistically significant (median decongested PNIF 120.0L/min (70.0L/min-210.0L/min) in boys versus 110.0L/min (50.0L/min-190.0L/min) in girls, $p=0.117$).

Association between PNIF, lung function variables and FeNO

Baseline and decongested PNIF correlated with baseline and post-beta₂ agonist FEV₁ and PEF (Table 4). After adjusting the models for gender and age, the estimated change in decongested PNIF per 1L increase in post-beta₂ FEV₁ or 1L/s increase in PEF (beta-coefficients) were 29.73L/min (95%CI 17.80-41.67, adjusted $r^2=0.248$, $p<0.001$) and 17.12L/min (95%CI 11.06-23.19, adjusted $r^2=0.293$, $p<0.001$), respectively. Baseline values of PNIF were also significantly associated with FEV₁ (beta-coefficient 15.78L/min; 95%CI 3.92-27.64, adjusted $r^2=0.105$, $p=0.008$) and PEF (beta-coefficient 10.40L/min; 95%CI 4.77-16.02, adjusted

$r^2=0.164$, $p<0.001$).

The backward elimination procedure eliminated the variables height and weight. The associations between PNIF and FEV₁ or PEF were observed independently of rhinitis and asthma diagnosis, CARATkids scores, multiple sensitization and montelukast, nasal or inhaled corticosteroid or long-acting beta₂-agonist use. The best equation for decongested PNIF (L/min) was (adjusted $r^2=0.309$, $p<0.001$): $30.32 + 11.38 \times \text{baseline PEF (L/s)} + 0.34 \times \text{age (months)} + 14.89 \times \text{gender [0=female; 1=male]}$.

A correlation was found between baseline PNIF (L/min) and PEF z-score (Table 4). Baseline PNIF z-score was also associated with FEV₁ z-score ($r=0.228$, $p=0.031$) and PEF z-score ($r=0.307$, $p=0.003$); this was observed independently of nasal obstruction report. There was no association between reversibility of the upper and lower airways. No association was found between PNIF and FeNO levels.

Discussion

A consistent and independent correlation between PNIF and lower airway patency was found in school-aged children. Thus, this study strengthens that, ideally, it is important to consider at least PEF values, besides age and gender, when assessing nasal airflow by means of PNIF in children. PNIF can provide complementary objective information to subjective control assessment in children with allergic rhinitis and asthma.

We have evaluated the association between PNIF and lower airway patency measures in school-aged children, when adjusted to potential confounders. Sequential upper and lower airway standardized evaluations of the same individual were performed, reporting PNIF values before and after nasal topical alpha-adrenergic use and PEF and FEV₁ values before and after inhaled beta₂-agonist. A balanced sample of patients comprising different asthma control levels was studied, together with age and gender-matched healthy controls. Consistent correlations between upper and lower airway flow were found. These correlations persisted after adjusting to age, gender, height and weight, suggesting that the association between upper and lower airflow measures is independent and not a simple reflection of growth or body size. The correlations found between PNIF and PEF expressed in z-scores (which is age, gender and height-independent) also support our conclusions. Furthermore, this study strengthens that objective measurements of nasal flow and subjective symptoms scores may not be correlated, as we found no associations between PNIF and the CARATkids questionnaire scores, except for nasal obstruction self-report in the past two weeks and PNIF expressed in z-scores in children with allergic rhinitis and asthma.

This study's main limitations are its cross-sectional, exploratory design and the lack of children with asthma or rhinitis alone. Most children with asthma also have rhinitis^(1, 5, 9, 10), and we did

include asthmatic children with different levels of disease control and lung function tests results, but still inclusion of children with asthma or rhinitis only is relevant. Another limitation is the lack of children of other ethnicity, which limits our results only to Caucasians. Further studies with larger heterogeneous samples are needed to confirm our results. Despite the fact that all diagnoses were validated by medical specialists (based on anamnesis, clinical files and medical examination including anterior rhinoscopy), no nasal endoscopy or imaging techniques were performed in this study. Therefore, we could not firmly rule out adenoid hypertrophy or nasal septum deviation, but only excluded children with known or suspected diagnosis or with observable anatomical nasal abnormality on anterior rhinoscopy. Although baseline PNIF correlated with PEF and FEV₁ before and after bronchodilator use, we did not retest for PNIF after the single use of bronchodilator and therefore the clinical usefulness of PNIF after bronchodilator only was not tested.

The fact that nasal flow can be influenced by lower airway status has long been a concern⁽¹²⁾. Studies in adults have suggested an independent correlation between PNIF and PEF⁽²⁸⁾, or FEV₁⁽²⁹⁾.

Although initially considered a limitation of PNIF, the concept of a single disease of the airways has changed this view, and the impact of the lower airways is now taken into consideration in the study of nasal function^(12, 37). The correlation between PNIF and PEF has been reported in healthy children⁽²⁶⁾, but no multivariable analysis including PEF values was reported and FEV₁ wasn't evaluated. As previously described⁽²⁴⁻²⁶⁾, we have found a correlation between PNIF and age, height and weight. PNIF values were higher in boys compared to girls but, as reported by Papachristou et al., this difference did not reach statistical significance until the age of 12 years⁽²⁴⁾. Since age was the only variable consistently reported in the literature to be correlated with PNIF⁽²³⁻²⁷⁾, multivariable linear models for PNIF using this variable were presented. We chose to include baseline PEF rather than FEV₁ in the final model since baseline PEF is more easily obtained, even with only a peak flow meter and without the need to use bronchodilators. After accounting for these variables, there still remains a large degree of variability in PNIF values, suggesting that further variables, such as anatomic variations or possibly nasal inflammation may refine the modelling of data. Using acoustic rhinometry (before and after alpha-agonist) and spirometry with bronchodilation test, Chawes and collaborators found an independent and consistent correlation between nasal volume and FEV₁ in children aged six years⁽³⁸⁾. In accordance to our results, the correlation between upper and lower airways measures were observed independently of rhinitis and asthma diagnosis⁽³⁸⁾. This suggests that the independent correlation is a consistent finding in healthy and asthmatic children. Our results further support the hypothesis that the correlation between upper and lower airways may reflect a physiologic background for the common asthma-rhinitis multimorbidity⁽³⁸⁾.

Pathologic mechanisms could also be involved. A continuous nasobronchial inflammation process has been described in rhinitis and asthma^(9, 10). However, we found no association between PNIF and FeNO levels or between reversibility of the upper and lower airways, also in agreement with Chawes et al findings⁽³⁸⁾. We also found no differences in PNIF according to multiple sensitization to aeroallergens, as described before^(38, 39). Nevertheless, Chawes and collaborators reported an association between blood eosinophil counts and nasal eosinophilia with nasal patency⁽³⁸⁾, which we did not evaluate. Our baseline PNIF values were similar to the reported values in healthy children in Brazil^(25, 26). Prescott et al. and van Spronsen et al. reported slightly lower PNIF values^(23, 27), while Papachristou et al., who analysed the largest sample of healthy children, reported higher PNIF values⁽²⁴⁾. The discrepancy between study results could be due to different studied populations and to different methods (for instance, not performing the PNIF manoeuvre from the residual volume until reaching total lung capacity⁽²³⁾, or PNIF values collected while sitting^(23, 27), or standing up⁽²⁴⁻²⁶⁾). A recent study in adults showed a trend towards a positive effect of the standing position on PNIF, although not statistically significant⁽⁴⁰⁾. To our knowledge, the effect of body position on PNIF in children has not been analysed. Papachristou et al. published PNIF values were similar to our observed decongested PNIF values⁽²⁴⁾, which we used as a reference. In our study, no association was found between PNIF values and GINA asthma control or ARIA rhinitis classifications, or with CARATkids total or nasal scores. Previous studies with children have found an agreement between objective and subjective measures of nasal obstruction^(21, 41), while others report the opposite⁽⁴²⁾. The reason for this disagreement in multiple studies is probably multifactorial. For instance, given the known influence of other variables including age, gender and anthropometric variables in upper airway function in children, it is important to use reference values to obtain predicted percentages or ideally z-scores to interpret the results. We found an association between PNIF expressed in z-scores (for age and gender) and nasal obstruction self-report in the CARATkids questionnaire in children with allergic rhinitis and asthma. This association was also independent of PEF. Evaluating each nostril individually instead of bilateral measurements has been shown to allow stronger correlations between objective and subjective measurements in adults⁽¹³⁾, and also described in children using rhinomanometry⁽⁴²⁾. On the other hand, the subjective scoring tool influences the results. Scales with fewer score options seem to increase the probability of an association between objective and subjective measurements⁽⁴³⁾. The exact questions and time of symptoms evaluation may also affect this association. In our study, we didn't find statistically significant differences in PNIF comparing healthy children and children with rhinitis and asthma reporting nasal obstruction in the CARATkids question-

naire. This needs to be analysed in future studies with larger samples, but it could be influenced by the fact that CARATkids questionnaire considers nasal symptoms self-reported by the children regarding the last two weeks and not necessarily current symptoms at the time of PNIF measurement. Moreover, in a previous study in adults, patients with asthma significantly rated their nasal obstruction by visual analogue scale more seriously than non-asthmatic controls with comparable PNIF values⁽²⁹⁾. Apparently, the sensation of nasal obstruction in asthmatics may be different from controls despite being in the same PNIF group⁽²⁹⁾. On the opposite direction, children on long-term treatment for chronic rhinitis may underreport the amount of nasal congestion⁽⁴⁴⁾, and it has been reported that children may be more accepting of mouth-breathing than adolescents⁽⁴³⁾. Last but definitely not least, children might also be influenced by their parents or guardians' perceptions during the subjective assessments, which may also contribute to this disagreement⁽⁴²⁾. Therefore, as in asthma, objective and subjective assessments appear to evaluate different parameters that may not be directly related, and PNIF may provide complementary information to the subjective evaluation of rhinitis and asthma in children. Since the subjective feeling of nasal obstruction may be valued differently by individual subjects, future research studies addressing PNIF in children with rhinitis and asthma may take advantage of additional comparisons with other measures of nasal patency, namely using the "golden standard" rhinomanometry.

Conclusion

In conclusion, the independent correlation between PNIF and lower airways patency measures in school-aged children suggests that, ideally, at least PEF values should be considered, besides age and gender, when evaluating nasal obstruction by means of PNIF in this age group. This study supports PNIF as a complementary objective measurement to the subjective assessment of allergic rhinitis and asthma control in children.

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Authorship contribution

HP participated in study conception, data collection, analysis and interpretation and wrote the manuscript draft. LP, ACH, IM, CC, AVL and IA participated in data collection. MB provided critical review. MMA critically analysed the project, with guidance throughout its stages and tasks. All authors have reviewed and approved the final manuscript.

Conflict of interest

None.

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