



Upper and Lower Airway Patency Are Associated in Young Children

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Background: Although allergic rhinitis and asthma frequently coexist, the nature of this association is poorly understood. Therefore, we examined whether upper and lower airway patency are associated.

Methods: We investigated 221 6-year-old children from the Copenhagen Prospective Study on Asthma in Childhood birth cohort, assessing upper airway patency by acoustic rhinometry before and after α -agonist, and lower airway patency by spirometry before and after β_2 -agonist. Furthermore, we measured blood eosinophil count, nasal eosinophilia, total IgE, and fraction of exhaled nitric oxide. Associations were investigated by generalized linear models.

Results: Decongested nasal airway patency and post- β_2 FEV₁ were significantly associated ($P = .007$). The association remained significant after adjustments for sex, body size, FVC, and atopic diseases (β -coefficient 2.85 cm³; 95% CI, 0.42 to 5.29; $P = .02$). Baseline values of upper and lower airway patency were also significantly associated (β -coefficient 0.89 cm³; 95% CI, 0.26-1.51; $P = .01$). In addition, blood eosinophil count and nasal eosinophilia were inversely associated with decongested nasal airway patency, β -coefficient -0.42 cm³ (95% CI, -0.77 to -0.07 ; $P = .02$) and β -coefficient -0.47 cm³ (95% CI, -0.89 to -0.05 ; $P = .03$), respectively.

Conclusions: We found a strong and consistent association between upper and lower airway patency. This may be due to a common pathology, as suggested by the inverse association between decongested nasal airway patency, blood eosinophil count, and nasal eosinophilia. Alternatively, the association between upper and lower airway patency might reflect a physiologic background for the common comorbidity.

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Abbreviations: COPSAC = Copenhagen Prospective Study on Asthma in Childhood; FENO = fraction of exhaled nitric oxide

The upper and lower airways present mucosal and immunologic similarities as well as functional complementarity.¹⁻³ Cross-sectional surveys have demonstrated that asthma and allergic rhinitis often

coexist,^{1,4} and longitudinal data have established rhinitis as an important predictor of adult-onset asthma.⁵ Furthermore, subjects with COPD show increased nasal symptoms, suggesting a link between the upper and lower airways beyond asthma- and allergy-associated inflammation.⁶

Clinical studies have shown that a significant proportion of nonasthmatic allergic rhinitis subjects have impaired FEV₁ and increased bronchial responsiveness.⁷⁻⁹ Moreover, bronchial inflammation can result from nasal allergen challenge in patients with allergic rhinitis experiencing nasal symptoms alone,¹⁰ and segmental bronchial provocation has been shown to induce nasal inflammation.¹¹

The aim of the current study was to compare upper and lower airway patency. We investigated 221 6-year-old children from the Copenhagen Prospective Study on Asthma in Childhood (COPSAC) birth cohort by acoustic rhinometry before and after topical

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α -adrenergic treatment, and by spirometry before and after inhaled β_2 -agonist.

MATERIALS AND METHODS

Design

The study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.¹² It was nested in the COPSAC birth cohort, a single-center, prospective, clinical birth cohort study of 411 children born to asthmatic mothers, enrollment of which was described in detail previously.¹³⁻¹⁵ The children attended the COPSAC clinical research unit every 6 months for scheduled clinical investigations according to standard operating procedures, and additional visits were arranged immediately upon onset of any respiratory symptom.¹³⁻¹⁵ The families used only the doctors employed at the clinical research unit, rather than their family practitioners, for diagnosis and treatment of any respiratory symptom.

Ethics

The study was conducted in accordance with 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).¹⁵ Before enrollment, informed consent was obtained from both parents of each subject.

Objective Measurements

Upper Airway Patency: Upper airway patency was assessed by acoustic rhinometry in the child's sixth year of life according to standardized international guidelines.¹⁶ Trained research assistants at the COPSAC clinical research unit performed all measurements using the SRE 2100 continuous wide-band acoustic rhinometer with a small-sized adult anatomic nose adapter (RhinoMetrics; Interacoustics A/S; Assens, Denmark). The child was seated facing the examiner and stopped breathing for about 5 s with the probe tube applied to the nostril. Three independent measurements with SD < 5% were obtained from each nostril before, and 15 min after, decongestion from topical α -agonist (one puff of intranasal xylometazoline, 1 mg/mL).

Decongested nasal volume 1 to 4 cm into the nasal cavity was selected as the primary end point as a measure of irreversible upper airway obstruction based on previous sensitivity analyses.¹⁷ Baseline nasal volume 1 to 4 cm into the nasal cavity was used as the secondary end point.

Lower Airway Patency: Maximum FEV₁ was assessed by spirometry from up to five technically acceptable maneuvers, in accordance with international criteria for reproducibility,¹⁸ using the MasterScope system 754916 spirometer (Erich Jäger; Würzburg, Germany). Spirometry was performed in the child's sixth year of life, at baseline and 15 min after use of an inhaled β_2 -agonist (two puffs of terbutaline, 0.25 mg/dose, in a pressurized metered dose inhaler with a spacer). All measurements were obtained with a computer-animated, volume-driven incentive well known to the children.

Post- β_2 FEV₁ was chosen as the primary end point as a measure of irreversible lower airway obstruction. Baseline FEV₁ was used as the secondary end point.

Atopic Biomarkers: Fraction of exhaled nitric oxide (FENO) was assessed by an online technique¹⁹ using NIOX FLEX (Aerocrine;

Solna, Sweden). Blood was sampled at age 6 years for measurement of eosinophil count (10⁹/L) and total IgE. The level of total IgE was determined by ImmunoCAP (Pharmacia Diagnostics AB; Uppsala, Sweden)²⁰ with a detection limit of 2kU/L. Nasal eosinophilia was assessed by nasal scraping in the child's sixth year of life and was rated according to Meltzer semiquantitative scale,²¹ as detailed previously.¹⁷ Nasal eosinophilia was judged by experienced cytologists and defined as ≥ 1 eosinophil cell per high-power field (light microscopy, oil immersion, $\times 1,000$).

Allergic Sensitization: Specific IgE was determined at age 6 years against eight common inhalant allergens (cat, dog, horse, birch, timothy grass, mugwort, house dust mites, and molds) by ImmunoCAP (Pharmacia Diagnostics AB; Uppsala, Sweden). Values ≥ 0.35 kU/L were defined as sensitization²⁰ and were analyzed as a dichotomized measurement.

Anthropometry: Height, weight, and head circumference were measured the same day as acoustic rhinometry and spirometry. BMI was calculated as weight (kg)/height (m)².

Clinical Diagnoses

Rhinitis: Rhinitis was diagnosed by the COPSAC doctors at the scheduled 6-year-visit to the clinical research unit, based on parent interviews on rhinitis symptoms in that year. Rhinitis was defined as troublesome sneezing or blocked or runny nose affecting the well-being of the child in the past 12 months in periods without accompanying cold or flu.²² Allergic rhinitis was defined as rhinitis with allergic sensitization against inhaled allergens and symptom periods congruent with exposure; nonallergic rhinitis was defined as rhinitis with no sensitization or sensitization to allergens without relevant association between symptoms and exposure.

Current Asthma: Current asthma during the sixth year of life was diagnosed according to the Global Initiative for Asthma guidelines as previously detailed,¹⁴ based on respiratory symptom diaries filled in on a daily basis by the parents; symptoms judged by the doctors at the clinical research unit to be typical of asthma (eg, exercise-induced symptoms, prolonged nocturnal cough, recurrent cough outside common cold, symptoms causing waking at night); need of intermittent rescue use of inhaled β_2 -agonist; response to a 3-month course of inhaled corticosteroids and relapse when treatment stopped.

Statistical Analysis

Associations between upper and lower airway patency were studied using generalized linear models with decongested nasal volume 1 to 4 cm into the nasal cavity as the continuous outcome variable and post- β_2 FEV₁ as the continuous explanatory variable. We adjusted the models for sex, allergic sensitization, rhinitis, asthma, nasal and inhaled steroid usage, height, weight, head circumference, BMI, and FVC by adding the variables as covariates to the models. Interactions with sex, allergic sensitization, rhinitis, and asthma and the studied associations between upper and lower airway patency were tested by adding cross-products to the models. Associations between upper airway patency and atopic biomarkers, and between lower airway patency and atopic biomarkers, were investigated using generalized linear models corrected for sex, nasal steroid usage, and inhaled steroid usage.

Results are reported as β -coefficients with 95% CI; a *P* value ≤ 0.05 is considered significant. All analyses were performed using SAS version 9.1 for Windows (SAS Institute; Cary, NC).

Baseline

We investigated 276 of the cohort of 411 infants by acoustic rhinometry and spirometry in their sixth year of life; 253 completed baseline FEV₁ the same day as nasal airway patency and 221 had concomitant post-β₂ FEV₁ and decongested nasal airway patency. The study group flowchart is illustrated in the online supplement (Figure E1).

The study group was characterized by significantly more wheeze in the first 18 months of life compared with the drop-out group, whereas the number of subjects with allergic sensitization against inhaled allergens was distributed equally. The study group had higher income and more fathers with asthma, whereas there were no significant differences regarding sex, older siblings, and family history of allergic rhinitis and allergic sensitization against inhaled allergens (data not shown).

Allergic sensitization against inhaled allergens was found in 59 children (27%). Rhinitis was diagnosed in 74 children (33%); allergic rhinitis could be categorized in 21 (10%) and nonallergic rhinitis in 53 (24%). Thirty-three children (15%) were diagnosed with asthma at age 6 years. Study group characteristics and objective assessments are given in Table 1.

Upper and Lower Airway Patency

Decongested nasal airway patency was significantly associated with post-β₂ FEV₁ ($P = .007$) (Fig 1). After adjusting the model for sex, height, weight, head circumference, BMI, FVC, allergic sensitization, rhinitis, asthma, nasal and inhaled steroid usage, the estimated change in decongested nasal airway patency per 1 L increase in post-β₂ FEV₁ (β-coefficient) was 2.85 cm³ (95% CI, 0.42-5.29; $r^2 = 0.16$; $P = .02$). There was no evidence of interaction between sex ($P = .64$), allergic sensitization ($P = .37$), rhinitis ($P = .50$), or asthma ($P = .83$) and upper and lower airway patency.

Figure 2 and Figure E2 online show the three-dimensional relationships between decongested nasal airway patency, post-β₂ FEV₁, height, and FVC. The figures illustrate that the association between upper and lower airway patency is independent of height and FVC.

Baseline nasal airway patency was also significantly associated with baseline FEV₁ ($P < .001$) (Figure E3 online). After adjusting for sex, height, weight, head circumference, BMI, FVC, allergic sensitization, rhinitis, asthma, nasal steroid usage and inhaled steroid usage, the association remained significant (β-coefficient 0.89 cm³; 95% CI, 0.26-1.51; $r^2 = 0.18$; $P = .01$). There was no association between reversibility of the upper and lower airways (Table E1 online).

Table 1—Study Group Characteristics

Covariate	Study Group (N = 221)
Male, No. (%)	103 (47)
Age, y, mean (SD)	5.3 (0.3)
Height, cm, mean (SD)	113.9 (4.9)
Weight, kg, mean (SD)	20.3 (2.8)
Head circumference, cm, mean (SD)	51.9 (1.4)
BMI, kg/m ² , mean (SD)	15.7 (1.3)
Allergic sensitization, ^a No. (%)	59 (27)
Allergic rhinitis, No. (%)	21 (10)
Nonallergic rhinitis, No. (%)	53 (24)
Asthma, ^b No. (%)	33 (15)
Baseline nasal airway patency, cm ³ , mean (SD)	2.86 (0.66)
Decongested nasal airway patency, cm ³ , mean (SD)	4.70 (0.80)
Nasal reversibility to α-agonist, ^c mean (SD)	+ 68.7 (30.4)
FEV ₁ , L, mean (SD)	1.16 (0.19)
Post-β ₂ FEV ₁ , L, mean (SD)	1.17 (0.16)
Bronchial reversibility to β ₂ -agonist, ^d %, mean (SD)	+ 2.7 (11.8)
FENO, ^e ppb, GM (95% CI)	7.3 (2.7-19.7)
Blood eosinophil count, 10 ⁹ /L, GM (95% CI)	0.33 (0.08-1.30)
Total IgE, kU/L, GM (95% CI)	44.8 (3.2-629.2)
Nasal eosinophilia, ^f No. (%)	16 (8)

FENO = fraction of exhaled nitric oxide; GM = geometric mean; ppb = parts per billion.

^aAllergic sensitization is any sensitization (specific IgE ≥ 0.35 kU/L) toward birch, timothy grass, mugwort, house dust mites, molds, cat, dog, and horse.

^bAsthma status missing for 2 subjects.

^cNasal reversibility = [(decongested nasal airway patency – baseline nasal airway patency)/baseline nasal airway patency] × 100.

^dBronchial reversibility = [(post-β₂ FEV₁ – FEV₁)/FEV₁] × 100.

^eFENO measurement missing for 77 subjects.

^fNasal scrape missing for 17 subjects.

Upper and Lower Airway Patency and Atopic Biomarkers

Blood eosinophil count was inversely associated with decongested nasal airway patency (Fig 3), whereas there was no such association with post-β₂ FEV₁ (Table E2 online). After adjusting the model for sex, nasal steroid usage, and inhaled steroid usage, the estimated decrease in decongested nasal airway patency (ie, increased nasal airway obstruction) per 1 × 10⁹/L increase in eosinophil count was 0.42 cm³ (β-coefficient – 0.42 cm³; 95% CI, – 0.77 to – 0.07; $r^2 = 0.17$; $P = .02$).

In addition, nasal eosinophilia was inversely associated with decongested nasal airway patency, but not with post-β₂ FEV₁ (Table E2 online). The adjusted analysis showed that subjects with nasal eosinophilia had a 0.47 cm³ decrease in decongested nasal airway patency compared with subjects without nasal eosinophilia (β-coefficient – 0.47 cm³; 95% CI, – 0.89 to – 0.05; $r^2 = 0.14$; $P = .03$). Neither FENO nor total IgE was associated with upper airway or lower airway patency (Table E2 online).

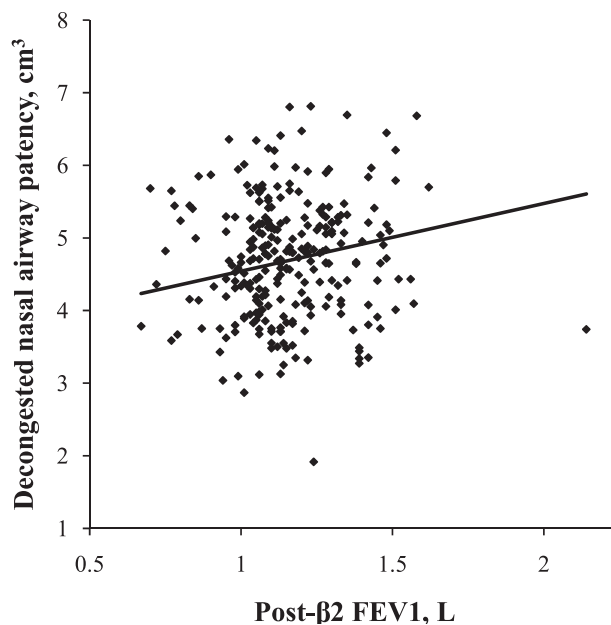


FIGURE 1. Association between decongested nasal airway patency and post- β 2 FEV₁.

DISCUSSION

Principal Findings

We have shown a significant association between upper and lower airway patency in 6-year-old children from the COPSAC birth cohort. The association was consistent for both baseline values of nasal airway patency and FEV₁, and for decongested nasal airway patency and post- β 2 FEV₁. The association remained significant after adjustments for body size and FVC, and was independent of sex and atopic diseases.

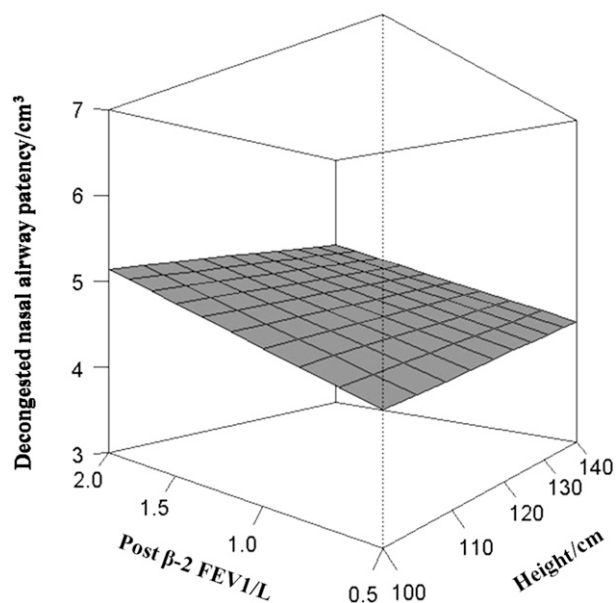


FIGURE 2. Three-dimensional relationship between decongested nasal airway patency, post- β 2 FEV₁ and height.

Decongested nasal airway patency was inversely associated with blood eosinophil count and nasal eosinophilia, suggesting its association with upper airway inflammation. These findings also suggest an association between pathophysiology of upper and lower airways.

Strengths and Limitations of the Study

The major strength of this study is the diagnostic specificity in the COPSAC cohort due to comprehensive prospective investigations based on standard operating procedures and investigator diagnosed clinical end points following predefined algorithms,^{13,14} assuring that the observed association between upper and lower airway patency is not due to misclassification. Furthermore, the study is strengthened by the highly standardized objective assessments. Acoustic rhinometry is a noninvasive method for objective measurements of upper airway patency,¹⁶ it has been validated against CT,²³ and the technique is well tolerated by children.²⁴⁻²⁶ The children of the COPSAC birth cohort are investigated repeatedly from birth¹⁵ and are thus highly trained and cooperate with assessments by acoustic rhinometry and spirometry, and all objective measurements are made by trained research assistants at the COPSAC clinical research unit.

The external validity of the study is limited by the setting of a high-risk cohort (all mothers have a history of asthma) because upper and lower airway patency results might differ from the background population. However, an unselected study of 1,735 6-year-old children²⁷ reported FEV₁ values in accordance with our results, and a cross-sectional survey of 137 healthy 5-year-old children²⁶ presented baseline nasal volumes similar to our findings. Furthermore, our analyses are based on comparisons between upper and lower airway patency within individuals, which is unlikely to be affected by increased risk of atopic disease.

Interpretation

The observed association between upper and lower airway patency could be a reflection of body dimensions (ie, tall children have larger airways²⁷ and correspondingly larger nasal volumes).²⁸ However, this would be an unlikely explanation for the observed association because we studied children in the narrow age range of 5 to 6 years. Furthermore, we adjusted the observed association for FVC and for measurements of body size, including height, weight, head circumference, and BMI. The association between upper and lower airway patency persisted after such adjustments, assuring that the finding is not a simple reflection of body size.

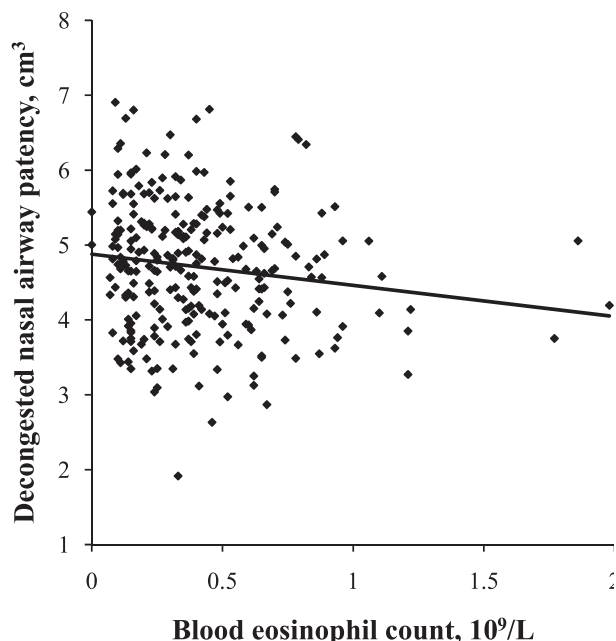


FIGURE 3. Inverse association between decongested nasal airway patency and blood eosinophil count.

The association between upper and lower airway patency was independent of allergic sensitization, rhinitis, and asthma and therefore was a consistent finding in both healthy and atopic children. This may reflect a continuous nasobronchial airway inflammation process from healthy to diseased airways, which was supported by the independent associations between blood eosinophil count, nasal eosinophilia, and upper airway patency. In agreement with this, the thickness of the nasal reticular basement membrane correlates with that of the bronchial tissue in both healthy controls and subjects with coexisting allergic rhinitis and asthma.²⁹ Both respiratory and systemic pathways have been proposed as accounting for the interaction between upper and lower airways.³⁰ Loss of the protective functions of the nose may account for the nasobronchial cross-talk. Alternatively, the absorption of inflammatory mediators (eg, interleukin-5 and eotaxin) from sites of inflammation into the systemic circulation has been shown to induce the release of eosinophils from bone marrow and prolonged blood eosinophilia, and thereby possible systemic propagation of inflammation from nose to lung and *vice versa*.³¹ Our finding of a significant association between decongested nasal airway patency (irreversible nasal airway obstruction) and blood eosinophil count is supportive of this hypothesis and suggests that nasal inflammation is not a local phenomenon, but that the entire respiratory tract is involved, even in the absence of clinical asthma.

Nevertheless, blood eosinophil count and nasal eosinophilia were not associated with lower airway

patency and neither FENO nor total IgE were significantly related to upper or lower airway patency. This seems to contradict the theory that the association between upper and lower airway patency reflects a common pathology. Alternatively, our data may be interpreted as supportive of an association between upper and lower airway patency as the physiologic background for the common comorbidity. A possible explanation could be that diminished airway patency contributed to an increased disease propensity.

CONCLUSIONS

This study shows an association between upper and lower airway patency in children at age 6 years and an association between blood eosinophils, nasal eosinophilia, and nasal airway patency. This finding may support the notion of a common pathophysiology in asthma and allergic rhinitis.

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Mr Kreiner-Møller: contributed to data acquisition, analysis, and interpretation and writing of the manuscript.

Dr Bisgaard: contributed to the conception, design, and conduct of the study; data acquisition, analysis, and interpretation; and writing of the manuscript.

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