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ORIGINAL ARTICLE

# Small-airway dysfunction precedes the development of asthma in children with allergic rhinitis

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**KEYWORDS**
Allergic rhinitis;
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Children

**Abstract**
*Background:* Epidemiological evidence suggests the existence of a direct link between allergic rhinitis (AR) and asthma. Several studies also support the presence of small-airway dysfunction (SAD) in non-asthmatic children with AR. However, it remains unknown whether SAD can predict the progression of AR to asthma. Our objective was to explore the existence of SAD in non-asthmatic children with AR and to assessed its ability to predict the development of asthma.
*Methods:* Seventy-three 6-year-old children with intermittent moderate-severe AR but without asthma symptoms/medication within the last two years, underwent spirometry and measurement of respiratory resistance (Rrs) and reactance (Xrs) before and after bronchodilation (BD) (300 mcg salbutamol). Lung function measurements were performed in the absence of nasal symptoms and repeated at AR exacerbation. SAD was defined as >30% decrease in Rrs or >50% increase in Xrs at 6 or 8 Hz post-BD. Participants were followed for five years.
*Results:* Twenty-three children (31.5%) developed asthma; this group presented significant post-BD changes in Rrs and Xrs, but only at AR exacerbation. The ability of these changes to predict the development of asthma was exceptional and superior to that of the spirometric parameters. SAD (22 children, 30.1%), emerged as the single most efficient predictor of asthma, independently of other risk factors such as parental asthma, personal history of eczema and type of allergic sensitisation.
*Conclusion:* SAD precedes the development of asthma in children with AR. Changes in respiratory impedance at AR exacerbation may assist in identifying those at risk to progress to asthma.


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## Introduction

The concept of ''united airways disease''[1] supports the existence of a direct link between allergic rhinitis (AR) and asthma. Indeed, epidemiological evidence shows that the two disorders often overlap; the vast majority of patients with asthma experience nasal symptoms, whereas up to 40% of those with AR are also diagnosed with asthma.[2] Allergic rhinitis is a recognised risk factor for the development of asthma in both adults[3] and children,[4] while the severity of nasal symptoms in these patients correlates to the level of asthma control.[5,6] Given the above clinical interactions and the well-described pathophysiological mechanisms which support the functional cross-talk between nose and bronchi,[2,7] the Allergic Rhinitis and Its Impact on Asthma (ARIA) workgroup proposes that bronchial involvement should be considered in all individuals with AR.[8,9]

A growing body of evidence suggests that small-airway dysfunction (SAD), as determined by means of subtle spirometric changes, bronchial hyper-reactivity and/or airway inflammation, is an early characteristic of bronchial involvement in non-asthmatic adults with rhinitis.[10] Several cross-sectional studies also support the presence of SAD in non-asthmatic children with AR.[11–15] However, the evidence on whether SAD is predictive of the development of asthma, remains sparse and controversial[16,17]; this may be partly attributed to the fact that spirometric parameters cannot reliably detect mild reversible airway obstruction in such patients.[14] On the other hand, subclinical changes in respiratory impedance, as determined by the forced oscillations technique (FOT), have been proven superior to spirometry in detecting SAD in non-asthmatic children with AR.[14] Nevertheless, no longitudinal study to date has explored the ability of subclinical abnormalities in respiratory impedance to predict the development of asthma in these children.

The aim of the present study was to explore the existence of small-airway involvement, as determined by means of spirometry and FOT, in non-asthmatic school-aged children with AR, and to assess the ability of SAD in predicting subsequent development of asthma.

## Materials and methods

### Study design and population

This is a longitudinal study of non-asthmatic children with moderate-severe intermittent AR at the age of six years who were regularly followed for development of asthma up to the age of 11 years. All participants were recruited between June 2008 and May 2011.

Eligible patients were non-asthmatic children cared for in the Paediatric Pulmonology and Allergy Unit of the University Hospital of Patras, Greece, who at the calendar year of their sixth birthday presented symptoms suggestive of AR (i.e., rhinorrhoea, nasal obstruction, nasal itching, and/or sneezing) lasting less than four days per week or less than four consecutive weeks, with troublesome impact on their daily activity (school, sports, social life). Children with mild or persistent forms of AR according to the ARIA classification,[8,9] were excluded. Eligible subjects were also required to have positive skin prick tests (SPTs) to common local inhalant allergens (grass pollen mixture, *Cynodon dactylon*, *Olea Europaea*, cypress, *Parietaria*, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Alternaria tensis*, *Cladosporium herbarum*, *Aspergillus fumingatus*, dog dander, and cat epithelium). SPTs were performed by a paediatric allergy specialist (MT), using a commercial panel of allergenic extracts (Laboratorios LETI, Madrid, Spain). Allergic sensitisation was classified as *seasonal* when the subject was sensitised only to pollens or *perennial* when the participant had positive SPTs to dust mites, moulds and/or animals. Presence of positive SPTs to three or more aeroallergens was defined as multiple sensitisation. The absence of current asthma at the age of six years was ascertained by a specialist in paediatric pulmonology (SF), based on the following criteria: (a) no history of parent- or doctor-reported symptoms suggestive of asthma (wheezing, dyspnoea, relapsing cough) within the last two years, (b) no prescription of asthma-related medication within the last two years and, (c) normal spirometry at enrolment. A third specialist in paediatric allergy and pulmonology (KD) independently reviewed the data and confirmed that all participants fulfilled the eligibility criteria.

The study was approved by the ethics committee of the University Hospital of Patras, and written informed consent was obtained from the parents of the children prior to enrolment. The study flow is presented in Fig. 1.

### Study protocol

**Visit 1: baseline lung function when asymptomatic**
Eligible children were asked to visit our unit when they were completely free of AR and other respiratory symptoms for at least four weeks, and not receiving any relevant medication (i.e., intranasal corticosteroids, antihistamines, leukotriene receptor antagonists). After a thorough clinical examination, all children underwent a set of lung function measurements, performed in the following order: (a) measurement of exhaled nitric oxide fraction (FeNO) (NObreath, Bedfont Scientific, UK); (b) Measurement of respiratory impedance using a multifrequency (4–48 Hz) pseudorandom noise FOT (i2m device, Chess Medical, Ghent, Belgium) according to standard recommendations.[18] For each subject, the mean Rrs and Xrs at 6 and 8 Hz of five technically acceptable measurements were recorded; (c) spirometry, performed using a MicroLab™ spirometer (CareFusion, San Diego, CA, USA). The best forced expiratory volume at 1 s ($FEV_1$), forced vital capacity (FVC) and forced expiratory flow between 25 and 75% of FVC ($FEF_{25-75}$) of three technically acceptable measurements were recorded; and (d) Bronchial reversibility test, after administration of 300 mcg of inhaled salbutamol (Aerolin™ 100 mcg/dose, GlaxoSmithKline, Greece) via a holding chamber (Aerochamber™, Trudell Medical International, Canada). FOT followed by spirometric measurements were repeated 15 min after bronchodilation (BD) and post-BD $FEV_1$, FVC, $FEF_{25-75}$, Rrs at 6 and 8 Hz, and Xrs at 6 and 8 Hz, were recorded.

**Visit 2: lung function at AR exacerbation**
The parents of the participants were instructed to bring their child to our unit at the first exacerbation of AR, within 48 h from the beginning of the symptoms and prior

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