

## Comparison of pulmonary functions of children who outgrew asthma symptoms with pulmonary functions of children without asthma

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### ABSTRACT

**Background:** Asthma treatment guidelines recommend that inhaled corticosteroids (ICS) can be stopped in children if they remain asymptomatic on its lowest dose. However, the effect of stopping steroids on their pulmonary function largely remains unknown. **Objective:** The objective of the study was to compare the lung function parameters of children with persistent asthma, who were treated with ICS for at least 1 year and are now remaining asymptomatic after stopping them for  $\geq 1$  year (children who outgrew asthma), with the lung function parameters of children in same age group without asthma. **Materials and Methods:** The study design was cross-sectional comparative study, and it was conducted in the pediatric asthma clinic of a tertiary level teaching hospital in South India from August 2017 to July 2018. The study included 54 children in the age group of 6–18 years with asthma, now remaining asymptomatic after stopping ICS for  $\geq 1$  year and 54 children in same age group without asthma. Spirometry was done in both groups. Post-bronchodilator reversibility testing was done for children with asthma. **Results:** The median values of forced expiratory volume in one second (FEV1), FEV1%, FEV1/forced vital capacity (FVC) ratio, peak expiratory flow (PEF), PEF%, forced expiratory flow 25-75 (FEF25-75), and FEF25-75% were observed to be significantly lower in children who outgrew asthma symptoms, when compared with children without asthma. A statistically significant number of children who outgrew their asthma had FEV1%  $< 80\%$ , FEV1/FVC ratio  $< 80\%$ , PEF%  $< 80\%$ , and FEF25-75%  $< 80\%$  when compared to children without asthma. After inhalation of short-acting beta-agonist, 18 children (33.3%) who had outgrown asthma symptoms had FEV1 reversibility more than 12%. **Conclusion:** The pulmonary functions of children with bronchial asthma who were remaining asymptomatic for more than 1 year after stopping ICS were significantly lower than children without asthma.

**Key words:** Inhaled corticosteroids, Lung function, Pediatric asthma, Post-bronchodilator reversibility, Spirometry

Asthma is a chronic inflammatory disease of the airways, characterized by the presence of variable and recurring respiratory symptoms, airflow limitation, and airway hyper-responsiveness [1]. All children with wheezing do not have asthma, as small children might develop wheezing even with lower respiratory infections due to small airway caliber. Asthma can remain undiagnosed in early childhood [1].

Maximal expiratory flow-volume curves are considered the gold standard for the assessment of lung function in children with asthma [2]. Regular assessment of pre- and post-bronchodilator forced expiratory volume in one second (FEV1) might help to identify children at risk for developing a progressive decline in airflow [3]. Epidemiological studies have consistently shown a tracking of FEV1 and FEV1/forced vital capacity (FVC) ratio from childhood to adulthood [2]. Children with persistent wheezing phenotypes have more lung function impairment compared with other phenotypes [4,5]. In school-aged children, objective measurement of lung functions by spirometry is essential for evaluation of asthma, as symptoms alone are not reliable [6].

Persistent asthma is defined by National Asthma Education and Prevention Program (NAEPP) as the presence of daytime asthma symptoms and needs for reliever drugs on more than 2 days per week, nighttime awakenings more than twice in a month and interference with normal activity [1]. Children with persistent asthma are treated with controller drugs, and inhaled corticosteroids (ICS) are the most effective and commonly used drug [1]. If the patient has good control of asthma symptoms for 6 months, ICS are stepped down. Global initiative for asthma guideline recommends that if the child remains symptom free on lowest dose of ICS and does not have any risk factor for exacerbation or fixed airway obstruction, ICS might be discontinued. However, the same guideline does not recommend discontinuation in adults with asthma [7]. Long-term cessation of ICS treatment is rarely successful in adults but might be achieved in children [8].

ICS treatment can be discontinued in a large group of children who initially had persistent asthma symptoms. Most of these children may remain asymptomatic, though some may develop a

recurrence of symptoms later in life. The aim of the study was to compare the lung function parameters of children with persistent asthma, treated with ICS for at least 1 year and now remaining free of symptoms after stopping treatment for  $\geq 1$  year, with those in the same age group without asthma.

## MATERIALS AND METHODS

This cross-sectional comparative study was conducted in the pediatric asthma clinic of a tertiary level teaching hospital in South India over a period of 1 year from August 2017 to July 2018. The study population consisted of two groups: Group 1 consisted of children in the age group of 6–18 years with persistent asthma (by NAEP classification), who were treated with ICS for at least 1 year and are now remaining free of symptoms after stopping treatment for  $\geq 1$  year. These children were referred as those who outgrew their asthma symptoms for descriptive purpose. Group 2 consisted of healthy children in the age group of 6–18 years without asthma.

Children with intermittent asthma or who had other comorbidities or acute illness and who were unable to produce valid spirometry were excluded from the study. The study was approved by the Institutional Ethics Committee. The children without asthma were recruited from the school children who attended a medical exhibition at our institution. The children who outgrew their asthma symptoms were recruited from the respiratory clinic. Informed consent from parents and assent from children were obtained before recruiting the children for the study.

The parents of children in both groups were interviewed with the help of a questionnaire. The questionnaire had four parts, including demographic details, frequency, and severity of asthma symptoms, family history of asthma and allergic diseases, and treatment history. A detailed treatment history including the age of initiation of ICS maximum dose needed for control, any other drugs needed for control of symptoms, duration of ICS treatment, age at stopping treatment, and recurrence of symptoms after stopping ICS was obtained from parents of children with asthma. The details of the treatment and details about asthma symptoms were also obtained from their records in the asthma clinic.

Pulmonary function tests were done using spirometry. All children were made to do the forced expiratory maneuver using Vitalograph alpha spirometer. Spirogram satisfying the American Thoracic Society criteria [9] for a valid test only was selected for the study. Global lung function 2012 reference values were used [10]. FVC, FEV1, FEV1/FVC ratio, peak expiratory flow (PEF), and forced expiratory flow 25-75 (FEF25-75) were obtained from the volume – time graphs and flow-volume loops. FVC, FEV1, PEF, and FEF25-75 were also expressed as percentage of predicted values based on age, gender, ethnicity, height, and weight. They were termed as FVC%, FEV1%, PEF%, and FEF25-75%, respectively. Post-bronchodilator reversibility testing was also done for children who outgrew their asthma symptoms. After doing the baseline spirometry, these children were given 200  $\mu$ g of salbutamol

using metered dose inhaler with spacer. A repeat spirometry was done after 15 min.

The data were analyzed with the help of SPSS 21. The lung functions of children who outgrew their asthma were compared with the lung functions of children without asthma. The data were expressed as Mean (Standard deviation [SD]) for normal distribution and median (QD) for skewed distribution. Means were compared using t-test. Nonparametric tests were used for analyzing skewed data.

## RESULTS

The study included 54 children who had outgrown asthma symptoms and 54 children without asthma. Their baseline characteristics and family history of asthma and allergic diseases are described in Table 1. There was a significant difference between the two groups with respect to the presence of other allergic diseases in the child and presence of asthma or other allergic diseases in the first degree relatives.

The group of children who outgrew asthma symptoms was analyzed with respect to their initial asthma symptoms and treatment needed for symptom control. The mean age at the onset of asthma symptoms was 2.43 (1.79) years. The mean age at starting ICS was 5 (2.8) years. The steroids were started after a mean delay of 2.56 (2.7) years after the onset of symptoms. According to NAEP classification, 23 children (42.6%) had mild persistent asthma symptoms and 31 children (57.4%) had moderate persistent symptoms. For control of asthma, 12 children (22%) attained symptom control at low dose of ICS ( $\leq 200$  mcg/day), 29 children (54%) required medium dose

**Table 1: Baseline characteristics and family history of asthma and allergic diseases**

Parameter	Children without asthma n=54	Children who outgrew asthma symptoms n=54	p-value
Male: female	38:16	31:23	0.163
Age (year) Mean (SD)	9.69 (2.25)	10.40 (2.93)	0.153
Height (cm) Mean (SD)	131.30 (12.39)	136.19 (15.45)	0.073
Weight (kg) Mean (SD)	27.8 (8.169)	31.06 (9.85)	0.099
BMI (kg/m <sup>2</sup> ) Mean (SD)	15.30 (2.87)	16.21 (3.47)	0.142
Family history of asthma			
Yes	7	29	<0.0001
No	47	25	
Family history of allergic diseases			
Yes	11	35	<0.0001
No	43	19	
Other allergic diseases in the child			
Yes	4	20	0.0004
No	50	34	

SD: Standard deviation, BMI: Body mass index

(200–400 mcg/day), and 13 children (24%) required high dose (>400 mcg/day). Long-acting beta-agonists along with ICS were required in 19 children (35%) for symptom control. The average duration of ICS use was 3.98 (1.58) years, and the mean age of stopping the steroids was 9.06 (3.09) years.

Table 2 describes the median (QD) values of the forced expiratory maneuver parameters of the two groups. The median values of pulmonary function parameters were significantly lower in children who outgrew asthma symptoms when compared with children without asthma. Figure 1 is a boxplot comparing FEV1% of the two groups. Figure 2 compares the FEF25-75% of the two groups.

Expiratory airflow limitation was quantitated by comparing the FEV1%, PEF%, and FEF25-75% with predicted values based on age, gender, weight, and ethnicity. A value <80% when compared to the predicted value was considered as abnormal. FEV1/FVC ratio <80% is considered as the parameter, which consistently indicates airway obstruction.

Table 3 compares the frequency of abnormal lung function values between the two groups. A statistically significant number of children who outgrew their asthma had abnormal FEV1%, FEV1/FVC ratio, PEF%, and FEF25-75% <80% when compared to children without asthma.

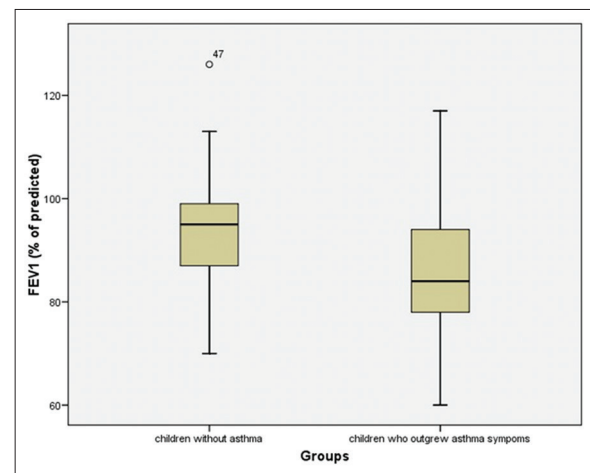
Post-bronchodilator reversibility testing was done in the group who had outgrown their asthma symptoms. The FEV1, PEF, and FEF25-75 values obtained were compared with the baseline values. Mean increase in FEV1 after bronchodilatation was 110.4 (9.9) ml and 7.67% (0.82%) in children who outgrew asthma symptoms. PEF increased by 394.8 (49.4) ml and 16.24% (2.4%) and FEF25-75 increased by 432.2 (35.8) ml and 29.7% (2.9%) after bronchodilatation.

After inhalation of short-acting beta-agonist, 18 children (33.3%) who had outgrown asthma symptoms had FEV1 reversibility more than 12% or 200 ml. Among them, 7 children (13%) had post-bronchodilator increase in FEV1 >15%, which is considered as high reversibility. Nineteen children (35%) had PEF reversibility more than 20% and 34 children (63%) had FEF25-75 reversibility more than 20%

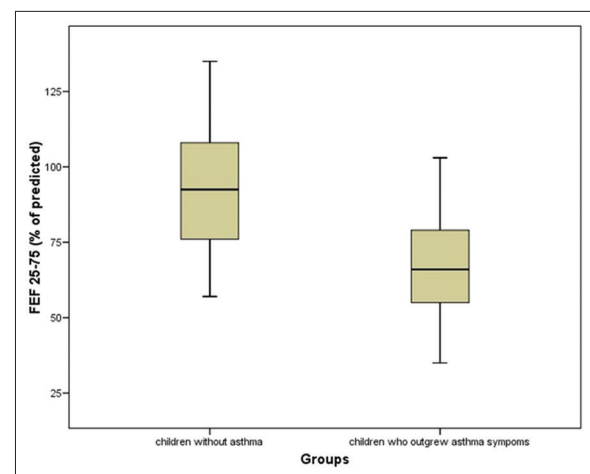
**Table 2: Comparison of forced expiratory maneuver parameters**

Pulmonary function parameter	Children without asthma median (QD)	Children who outgrew asthma symptoms median (QD)	p-value
FVC (L)	1.69 (0.25)	1.57 (0.42)	0.922
FVC%	89 (6.5)	89 (8.5)	0.472
FEV1 (L)	1.52 (0.26)	1.29 (0.34)	0.151
FEV1%	95 (6.5)	84 (8.5)	0.001
FEV1/FVC ratio	87.2 (4.1)	84.75 (3.7)	0.000
PEF (L/s)	3.25 (0.68)	3.14 (0.77)	0.124
PEF%	89 (9)	76.5 (13.5)	0.000
FEF25-75 (L/s)	1.93 (0.28)	1.43 (0.32)	0.000
FEF25-75%	92.50 (16.5)	66 (12)	0.000

FVC: Forced vital capacity, PEF: Peak expiratory flow



**Figure 1: Boxplot – forced expiratory volume in one s% of children without asthma and children who outgrew asthma symptoms**



**Figure 2: Boxplot – forced expiratory flow 25-75% of children without asthma and children who outgrew asthma symptoms**

after bronchodilatation. The improvement in the pulmonary function studies after bronchodilatation indicates the presence of bronchospasm in these children, even though they do not have any symptoms.

The pulmonary functions of the children who outgrew their asthma symptoms were further analyzed to look for factors associated with abnormal lung function values. The onset of asthma symptoms below the age of 3 years was associated with persistent post-bronchodilator reversibility in FEV1 by more than 12% ( $p=0.026$ ), and presence of other allergic diseases in the child was significantly associated with low FEV1 (<80% of predicted) ( $p=0.044$ ). Girls had a lower PEF% than boys ( $p=0.002$ ). There was no significant association between other factors studied and abnormal lung function values.

## DISCUSSION

The lung function parameters of children who outgrew asthma symptoms were significantly lower when compared to children without asthma. The median values of FEV1%, median FEV1:FVC ratio, PEF%, and FEF25-75 of children who outgrew their asthma

**Table 3: Comparison of abnormal pulmonary function parameters between the two groups**

Pulmonary function parameter (%)	Children without asthma	Children who outgrew asthma symptoms	p-value
FVC			
>80	44	41	0.639
<80	10	13	
FEV1			
>80	49	36	0.0056
<80	5	18	
FEV1/FVC ratio			
>80	53	44	0.008
<80	1	10	
PEF			
>80	44	23	<0.0001
<80	10	31	
FEF25-75			
>80	39	12	<0.0001
<80	15	42	

FVC: Forced vital capacity, PEF: Peak expiratory flow

symptoms were significantly less than the corresponding median values of children without asthma. The lung function parameter with the greatest difference between the two groups was FEF25-75, which indicates small airway obstruction. We were able to demonstrate a statistically significant increase in all the lung function parameters after inhalation of 200 mcg salbutamol in the group of children who outgrew asthma symptoms. In the present study, 33.3% had a post-bronchodilator increase in FEV1 by >12% or 200 ml, which is the hallmark of reversible airway obstruction. This demonstrates that even though these children are remaining asymptomatic, they still have bronchial obstruction and smooth muscle spasm, demonstrable by spirometry.

There is paucity of similar studies in literature, which have compared lung functions of children who currently do not have asthma symptoms with children without asthma. A birth cohort study by Sears *et al.* compared the lung function in patients with persistent asthma (both in remission and symptomatic), intermittent asthma and transient wheezing with children without asthma [11]. They found that the mean difference in FEV1 of persons with persistent wheezing in remission was 5% lesser than persons without asthma at the age of 26 years [11]. They found no significant difference between FEV1:FVC ratio of patients in remission and persons without asthma. The mean FEV1/FVFC ratio of persons in remission was lower by 0.8 in males and 2.3 in females when compared to persons without asthma in their study [11].

Morgan *et al.* found that the FEV1 of infrequent persistent wheezers was 66 ml (p=0.02) lower than children without asthma [12]. Henderson *et al.* found that FEV1 of children without asthma was higher by 0.14 SD units than children with infrequent wheezing at the age of 8–9 years [4]. They also found that FEF25-75 of children without asthma was higher by 0.18 SD units than children with infrequent wheezing at the age of 8–9 years [4]. In

the birth cohort study by Stern *et al.*, lung functions were studied at 22 years of age. They found that the post-bronchodilator increase in FEV1:FVC ratio was 0.5 in persons with inactive asthma [13,14].

Agertoft and Pedersen found that the delay in initiating treatment after the onset asthma symptoms significantly affected the lung functions. Children who received budesonide after 5 years from the onset of symptoms had a lower FEV1% (96%) than children who were initiated within 2 years of onset of symptoms (101%) [15]. In the present study, delay in initiation of treatment was not significantly associated with abnormal lung function. The onset of symptoms below 3 years and the presence of other allergic diseases were found to have significant association with abnormal lung functions.

A recent study comparing the use of 200 and 400 µg of salbutamol for reversibility testing in Korean children, found that the use of 400 µg of salbutamol produces more bronchodilatation [16]. Hence, the significant post-bronchodilator reversibility demonstrated with 200 µg of salbutamol in the present study implies that more children might have bronchodilator reversibility at the standard dose of 400 µg of salbutamol. The degree of reversibility has been correlated with the degree of airway inflammation [17]. Children with high post-bronchodilator reversibility are at increased risk for airway remodeling and hence loss of lung function overtime [18]. Spirometry is a poorly utilized tool in management of pediatric asthma [19]. Stout *et al.* have demonstrated that addition of lung functions to the symptom frequency will result in reclassification of asthma symptoms to a higher severity in a significant proportion of patients [20].

The authors suggest that a lung function study should be done before stopping controller medications in children with asthma, and controllers should be stopped only if lung functions, including post-bronchodilator reversibility is normal. The sub-group of children in whom the controller treatment is stopped should be kept under follow-up, with yearly lung function studies. They need to be assessed to see if the growth in their lung function is within normal limits. Treating physicians should also be on the lookout for an early or rapid decline in lung functions with age.

This study was not designed to identify the risk factors associated with low lung functions in children who outgrew their asthma. Further studies with higher sample size and detailed evaluation of risk factors will help to identify the factors associated with low lung function parameters in children who had outgrown their asthma symptoms.

## CONCLUSION

The lung function parameters of children who were remaining asymptomatic for more than 1 year after stopping ICS were significantly lower than the parameters of children without asthma. Total 33% of the children, who remained asymptomatic after stopping ICS, had a post-bronchodilator increase in FEV1 by >12% or 200 ml, which is an indicator of reversible airway obstruction, the hallmark of asthma.



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