Relationship between FEV_1/FVC and age in children with asthma

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March 28, 2024

Abstract

FEV_1/FVC normally decreases through childhood, increases briefly during early adolescence, and then declines throughout life. The physiology behind this temporary increase during early adolescence is not well understood. The objective of this study was to determine if this pattern also occurs in children with asthma. **Design:** Single-center, cross-sectional, retrospective analysis of pulmonary function tests (PFTs) obtained over a 5-year period in children 5 to 18 years of age with persistent asthma. **Results:** 1,793 patients satisfied all inclusion and exclusion criteria. Mean age ($\pm$ SD) was 10.4 $\pm$ 3.8 years. 48% were female. Mean FEV_1 /FVC was 0.83 $\pm$ .09. FEV_1 /FVC in children with persistent asthma declined from age 5 to age 11 by 5.7 % compared to 7.3% in healthy girls, and 5.8% compared to 9.4% in healthy boys. FEV_1/FVC increased by 1.2% until age 16 in children with asthma, compared to 2.2% in healthy girls, and 2.5% compared to 2.3% in healthy boys. The ratio was lower in obese children with asthma at all ages but demonstrated the same curvilinear shape as in healthy children. In absolute terms, FEV_1 grew proportionately more than FVC during early adolescence, so the ratio of FEV_1/FVC increased during that period. The curvilinear shape of the curve remained in postbronchodilator testing, though significantly blunted. **Conclusions**: The "Shepherd's Hook" pattern in the FEV_1/FVC curve is preserved in children with persistent asthma. This was also true in obese patients with asthma, although their FEV_1/FVC ratios were lower throughout all stages of childhood and adolescence.

Introduction

The Global Lung Function Initiative (GLI), an international collaboration with the goal of developing universal reference equations for children and adults11**References**Cooper BG, Stocks J, Hall GL, Culver B, Steenbruggen I, Carter KW, Thompson BR, Graham BL, Miller MR, Ruppel G, Henderson J, Vaz Fragoso CA, Stanojevic S. The Global Lung Function Initiative (GLI) Network: bringing the world's respiratory reference values together. Breathe (Sheff). 2017 Sep;13(3): e56-e64., published reference equations for spirometry in 201222Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, Enright PL, Hankinson JL, Ip MS, Zheng J, Stocks J; ERS Global Lung Function Initiative. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J. 2012 Dec;40(6):1324-43.. These reference equations, obtained from healthy children, may potentially add to a better understanding of lung growth. A careful analysis of changes in the forced expiratory volume in the first second of the maneuver (FEV_1) as a proportion of the forced vital capacity (FVC), or the FEV_1/FVC ratio, with age through childhood and adolescence demonstrated a remarkable shape to the curve33Quanjer PH, Stanojevic S, Stocks J, Hall GL, Prasad KV, Cole TJ, Rosenthal M, Perez-Padilla R, Hankinson JL, Falaschetti E, Golshan M, Brunekreef B, Al-Rawas O, Kühr J, Trabelsi Y, Ip MS; Global Lungs Initiative. Changes in the FEV1/FVC ratio during childhood and adolescence: an intercontinental study. Eur Respir J. 2010 Dec;36(6):1391-9.. Figure 1a demonstrates that the mean ratio of FEV_1/FVC rapidly decreases through childhood in healthy children, at least up to about 10-12 years of age, followed by a small increase during early adolescence, before resuming an inexorable downhill decrease throughout life44Quanjer PH, Stocks J, Polgar G, Wise M, Karlberg J, Borsboom G. Compilation of reference values for lung function measurements in children. Eur Respir J Suppl. 1989 Mar; 4:184S-261S.. It is generally accepted that FEV_1/FVC decreases from childhood to old age55Quanjer PH, Stocks J, Polgar G, Wise M, Karlberg J, Borsboom G. Compilation of reference values for lung function measurements in children. Eur Respir J Suppl. 1989 Mar;4:184S-261S.,falling with both age and height66Stanojevic S, Wade A, Cole TJ, Lum S, Custovic A, Silverman M, Hall GL, Welsh L, Kirkby J, Nystad W, Badier M, Davis S, Turner S, Piccioni P, Vilozni D, Eigen H, Vlachos-Mayer H, Zheng J, Tomalak W, Jones M, Hankinson JL, Stocks J; Asthma UK Spirometry Collaborative Group. Spirometry centile charts for young Caucasian children: the Asthma UK Collaborative Initiative. Am J Respir Crit Care Med. 2009 Sep 15;180(6):547-52.. The reasons for this "Shepherd's Hook" appearance in early adolescence are not well understood. One suggestion is that this age-dependent increase in the ratio may be due to well-recognized changes in thoracic configuration, and as a result, decreased chest-wall compliance in adolescents77Merkus PJ, ten Have-Opbroek AA, Quanjer PH. Human lung growth: a review. Pediatr Pulmonol. 1996 Jun;21(6):383-97.,[viii,ix,x] , particularly during the adolescent growth spurt and puberty88Schrader PC, Quanjer PH, van Zomeren BC, Wise ME. Changes in the FEV1-height relationship during pubertal growth. Bull Eur Physiopathol Respir. 1984 Jul-Aug;20(4):381-8.. This might result in slower growth in measured vital capacity relative to $FEV_1$99Degroodt EG, Quanjer PH, Wise ME, et al. Changing relationships between stature and lung volumes during puberty. Respir Physiol 1986; 65: 139-153.,1010Smeets M, Brunekreef B, Dijkstra L, Houthuijs D. Lung growth of pre-adolescent children. Eur Respir J. 1990 Jan;3(1):91-6..

The primary objective of this study was to analyze the relationship between FEV_1/FVC and age in children and adolescents with asthma. The cross-sectional area of the airways may not increase relative to alveolar volume in adolescents with asthma, as much as in healthy adolescents. If so, this might result in a reduced FEV_1/FVC ratio. If individuals with asthma do not have this temporary adolescent growth spurt in FEV_1/FVC ratio noted in healthy adolescents, the trajectory of FEV_1/FVC throughout adulthood might remain permanently lower. Secondary objectives were to assess the role of gender, obesity, and measurements of lung volumes on the relationship between age and FEV_1/FVC.

Methods

This study was exempt from IRB review by the New York Medical College Institutional Review Board under federal guidelines 45CFR46.104, section 4ii, as the data was de-identified, and the investigators did not contact or re-identify the subjects. A retrospective data extraction of all children with a diagnosis of asthma who underwent complete pulmonary function tests (PFTs) over a 5-year period (January 2014 to January 2019) from the Pediatric Pulmonary Function Laboratory at Maria Fareri Children's Hospital at Westchester Medical Center was performed, and subsequently, a review of individual clinical records was conducted. Patients were selected if they met the following inclusion criteria: age 5 and older, physician-defined persistent asthma, documented ongoing symptoms within the past year, and on treatment with an asthma controller. Patients were excluded if they had any diagnoses other than asthma that might affect pulmonary function; or had acute symptoms at the time of the PFTs. After deidentification, demographic data and all pulmonary function data, before and after inhaled albuterol, were extracted from the most recent pulmonary function test performed by each patient. FEV_1 and FVC, expressed as % of predicted values, were recalculated with the 2022 GLI global reference equations11Bowerman C, Bhakta NR, Brazzale D, Cooper BR, Cooper J, Gochicoa-Rangel L, Haynes J, Kaminsky DA, Lan LTT, Masekela R, McCormack MC, Steenbruggen I, Stanojevic S. A Race-neutral Approach to the Interpretation of Lung Function Measurements. Am J Respir Crit Care Med. 2023 Mar 15;207(6):768-774.. Lung volumes and specific airway conductance (sGaw) were estimated with whole body plethysmography22Dubois AB, Botelho SY, Comroe JH Jr. A new method for measuring airway resistance in man using a body plethysmograph: values in normal subjects and in patients with respiratory disease. J Clin Invest. 1956 Mar;35(3):327-35.. Total Lung Capacity (TLC) and Residual Volume (RV) are expressed as % of predicted as determined by standard reference equations33Zapletal A, Chalupová J, Kucera J. Lung volumes in healthy children and adolescents: methods, reference values. Monaldi Arch Chest Dis. 1995 Feb;50(1):6-18.,44Zapletal A, Šamánek M, Paul T. Lung Function in Children and Adolescents. Methods, reference values. Progress in Respiratory Research,

Vol. 22, Basel: Karger, 1987.,55Stocks J, Quanjer PH. Reference values for residual volume, functional residual capacity and total lung capacity. ATS Workshop on Lung Volume Measurements. Official Statement of The European Respiratory Society. Eur Respir J. 1995 Mar;8(3):492-506..

Statistical Methods

Means and standard deviations (SD) are reported for the entire cohort and stratified by gender. Proportions were compared using chi-square tests and unpaired t-tests were used to compare means between groups. Obese patients (BMI $>$ 95thpercentile for age) were compared to patients with normal BMI (5th to $<$ 85thpercentile). Pulmonary function tests were graphed against age, in years. Percent changes in the ratio of FEV_1/FVC were compared for differences between children with asthma and healthy children as previously reported, as well as between obese children and children with a BMI within the normal range. Two-sided p values were considered statistically significant. Statistical analyses were performed using STATA 15.0 (Statacorp LLC, TX, USA).

Results

3,854 children completed pulmonary function tests during the 5-year period, of which 1,793 met all inclusion and exclusion criteria (Fig 2). Lung volumes and specific airway conductance obtained via plethysmography were obtained in 1,790 patients. Patient characteristics and pulmonary function tests are in Table 1. The cohort included a higher proportion of boys, who were on average, slightly younger than girls, and more likely to be obese. There were no significant gender differences by ancestry. Children with asthma had lower pulmonary function on average than healthy children at all ages. Mean FEV_1, % predicted, for children with asthma was 94.8 + 16.5 prebronchodilator and 99.7 + 16.9 postbronchodilator ($p < 0.001$). Mean FEV_1/FVC was .83 + .09 prebronchodilator and .87 + .08 postbronchodilator ($p < 0.001$). Patients had, on average, low specific conductance, which was reversed with an inhaled bronchodilator. Specific conductance remained remarkably steady throughout the age range of this study. TLC was within the normal range, but RV was on average, higher than the normal reference range and RV/TLC ratio mildly elevated (Table 1). FEV_1/FVC at age 16 in male children with asthma was 5.6% lower than healthy children, 5.4 % lower in females (Table 2). Postbronchodilator FEV_1/FVC in 16-year-old male children with asthma was 1.1% lower than healthy children and 3.3% lower in females. Female patients had a higher FEV_1/FVC ratio than males at all ages.

Figure 1b demonstrates that the curvilinear shape to the relationship between FEV_1/FVC and age was preserved in children with asthma. Similar to healthy children, FEV_1/FVC decreased from age 5 to around age 11, increased until about the age of 13, and remained stable or even increased until the age of 18. Post-bronchodilator, these trajectories remained, though blunted.

Table 2 demonstrates that the decrease from age 5 to age 11 in FEV_1/FVC in children with asthma was proportionately less than reported in healthy children in the GLI cohort, -5.8% compared to about -9.4% in boys, and -5.7% compared to -7.3% in girls. This difference from healthy children was even more striking postbronchodilator, with a - 4.1% decrease from age 5 to 11 in boys with asthma and -2.1% decrease in girls with asthma.

The increase in FEV_1/FVC from age 11 to age 16 was similar in children with asthma as compared to healthy children. FEV_1/FVC increased 2.5% in boys with asthma from age 11 to age 16, compared to 2.3% in healthy boys; and 1.2% in girls with asthma, as compared to 2.2% in healthy girls. Postbronchodilator, the increase in the ratio in children with asthma was 2.6% in boys and 1.0% in girls. At age 16, FEV_1/FVC was 7.3% less than at age 5 in boys with asthma compared to 5.2% less in healthy boys, and 4.5% less than at age 5 in girls with asthma compared to 5.2% less in healthy girls. Obese children with asthma had, on average, an 8.1% decrease in the FEV1/FVC ratio between ages 5 and 11, as compared to +1.1% in children with a BMI within the normal range.

Figure 3 demonstrates that the curvilinear shape to the graph appears similar regardless of gender. In this cross-sectional cohort of children with asthma, there do not appear to be gender differences in the age of onset of the increase in FEV_1/FVC ratio that were reported for healthy children.

FEV_1/FVC of obese patients was lower as compared to patients with BMIs in the normal range, .80 + .09 versus .84+ .09, p< 0.0001, prebronchodilator; and .85 +.08 compared to .88 + .08. p < 0.0001, postbronchodilator. Children with asthma that were obese maintained a curvilinear shape to the relationship between FEV_1/FVC and age but differed from patients with a normal BMI. (Figure 4). At 16 years of age, their mean FEV_1/FVC was .79 compared to .86 in children with a BMI in the normal range, p< 0.0001.

In absolute terms, FVC increased proportionally more than TLC between age 5 and age 11, 101.5% compared to 88.9%, which resulted in a decrease in mean RV/TLC ratio from .34 to .29. Between age 11 and age 16, FVC and TLC increased similarly, 45.1% compared to 43.8%, so mean RV/TLC ratio in 16-year-old children with asthma was .28. The growth in FEV_1 was quite similar to TLC, increasing 90.3% between ages 5 and 11, and 49.3% from 11 to 16. From age 11 to age 16, FEV_1 grew, on average, by 49.3%, compared to a 45.0% increase in FVC, consistent with an increase in the ratio of the two during early adolescence.

Discussion

The primary finding of this study is that the ratio of FEV_1/FVC in children with persistent asthma appears to follow the same curvilinear curve through childhood as reported in healthy children. The ratio steadily decreased from age 5 to around age 11, then increased briefly during early adolescence before settling out and remaining fairly steady until age 18. This is true both before and after an inhaled bronchodilator, though the curve is somewhat blunted postbronchodilator. Not surprisingly, the ratio remains lower in children with asthma in all ages than healthy children, consistent with their overall pulmonary function. Sitting height/standing height ratio decreases from age 5 to 11[3], which suggests that during this period, leg length is growing faster than chest cavity height or size. Then, the ratio decreases from age 11 to 16, which suggests that the chest cavity, i.e., TLC, grows more rapidly than legs. If this is true, then both FVC and TLC should have the same curvilinear shape as FEV_1/FVC. Just as reported by Quanjer PH, et al[3] in healthy children, FVC increased proportionally more than TLC and FEV_1 in this cohort of children with asthma from age 5 to 11, then proportionally less from age 11 to 16. The difference in relative growth during early adolescence in FEV_1 and FVC is consistent with the ratio increasing, not decreasing as it does throughout life.

The overall decrease in FEV_1/FVC in children with asthma, from age 5 to age 11, was proportionally less than reported in the GLI global reference results for healthy children[3]. This was true for both boys and girls. However, the ratio was already significantly lower than normal by 5 years of age. Children with asthma demonstrated a similar proportional increase in FEV_1/FVC to healthy children during their adolescent growth spurt. One contributing factor to the decrease in the ratio during early childhood may be the number and size of alveoli may continue to increase, which is likely to lead to a faster increase in lung volume than in airway caliber11Ochs M, Nyengaard JR, Jung A, Knudsen L, Voigt M, Wahlers T, Richter J, Gundersen HJ. The number of alveoli in the human lung. Am J Respir Crit Care Med. 2004 Jan 1;169(1):120-4..

Girls had overall slightly better pulmonary function than boys, consistent with previous studies22Hibbert M, Lannigan A, Raven J, Landau L, Phelan P. Gender differences in lung growth. Pediatr Pulmonol. 1995 Feb;19(2):129-34.. The early adolescent increase in FEV_1/FVC ratio was not shifted to an earlier age in girls compared to boys, as reported by Quanjer PH et al[3]. There was a gender difference when comparing 5-year-old to 16-year-old children with asthma. FEV_1/FVC was 7.3% lower in 16-year-old boys compared to 5-year-old boys. The ratio was higher in 5-year-old girls with asthma than boys and was only 4.5% lower at age 16.

The relationship between age and postbronchodilator FEV_1/FVC as seen in figures 1 and 3 are intriguing. The curvilinear shape persists but the decrease from age 5 to 11 is less than that reported for healthy children, so that the curve is almost flat. It could be very interesting to repeat this analysis in healthy children before and after an inhaled bronchodilator.

Children with asthma who were obese demonstrated the most significant differences in the relationship between FEV_1/FVC and age. There was an overall change in the ratio from age 5 to age 16 in obese children with asthma of -8.1%, compared to +1.1% in children with asthma with normal weight. Studies on the effects of obesity on pulmonary function in children have reported conflicting results33Huang L, Wang ST, Kuo HP, Delclaux C, Jensen ME, Wood LG, Costa D, Nowakowski D, Wronka I, Oliveira PD, Chen YC, Chen YC, Lee YL. Effects of obesity on pulmonary function considering the transition from obstructive to restrictive pattern from childhood to young adulthood. Obes Rev. 2021 Dec;22(12): e13327.›44Forno E, Han YY, Mullen J, Celedón JC. Overweight, Obesity, and Lung Function in Children and Adults-A Meta-analysis. J Allergy Clin Immunol Pract. 2018 Mar-Apr;6(2):570-581.e10.›55Tantisira KG, Litonjua AA, Weiss ST, Fuhlbrigge AL; Childhood Asthma Management Program Research Group. Association of body mass with pulmonary function in the Childhood Asthma Management Program (CAMP). Thorax. 2003 Dec;58(12):1036-41.. In this cohort of patients with obesity and persistent asthma, obese patients had poorer lung function. Their FEV_1/FVC ratio dropped more steeply from age 5 to 11 and did not recover very much from age 11 to age 16. A lower FEV_1/FVC in children with obesity and asthma has been shown to be associated with increased hospitalizations and oral steroid bursts66Starr S, Wysocki M, DeLeon JD, Silverstein G, Arcoleo K, Rastogi D, Feldman JM. Obesity-related pediatric asthma: relationships between pulmonary function and clinical outcomes. J Asthma. 2023 Jul;60(7):1418-1427..

Similar to healthy children, TLC, expressed as a % of predicted value, declined very gradually from age 5 to 11 then slowly increased. RV/TLC was higher at all ages than as reported in healthy children, slowly decreased from age 5 to age 11, and then remained relatively stable through adolescence. Whereas in a longitudinal study in healthy children, the RV/TLC ratio gradually increased through adolescence77Merkus PJ, Borsboom GJ, Van Pelt W, Schrader PC, Van Houwelingen HC, Kerrebijn KF, Quanjer PH. Growth of airways and air spaces in teenagers is related to sex but not to symptoms. J Appl Physiol 1985. 1993 Nov;75(5):2045-53..

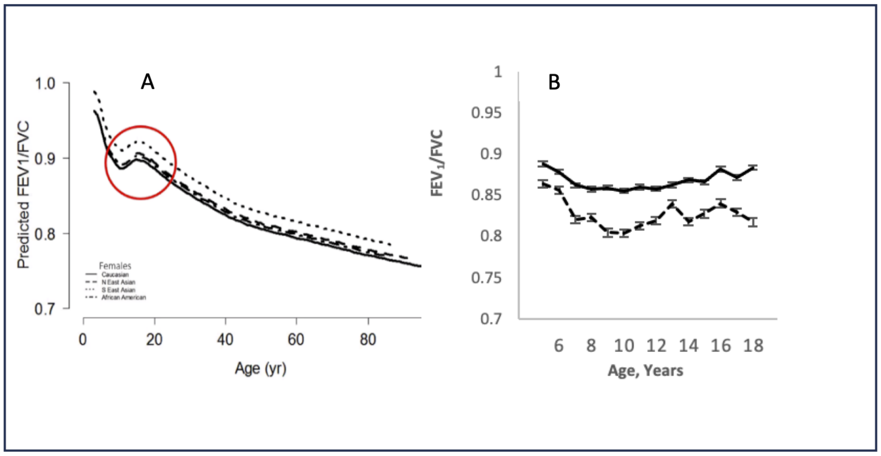
We chose to compare our cohort of children with persistent asthma to the recently published GLI global reference values, which have been race-corrected88Kanj AN, Scanlon PD, Yadav H, Smith WT, Herzog TL, Bungum A, Poliszuk D, Fick E, Lee AS, Niven AS. Application of GLI Global Spirometry Reference Equations Across a Large, Multicenter Pulmonary Function Lab Population. Am J Respir Crit Care Med. 2023 Jul 31., or sometimes referred to as race-neutral99 Baugh A, Adegunsoye A, Connolly M, Croft D, Pew K, McCormack MC, Georas SN. Towards a Race-Neutral System of Pulmonary Function Test Results Interpretation. Chest. 2023 Jun 17: S0012-3692(23).. One reason this decision was made was that 38% of our patients either declined to indicate race/ethnicity or chose to identify as “other”.

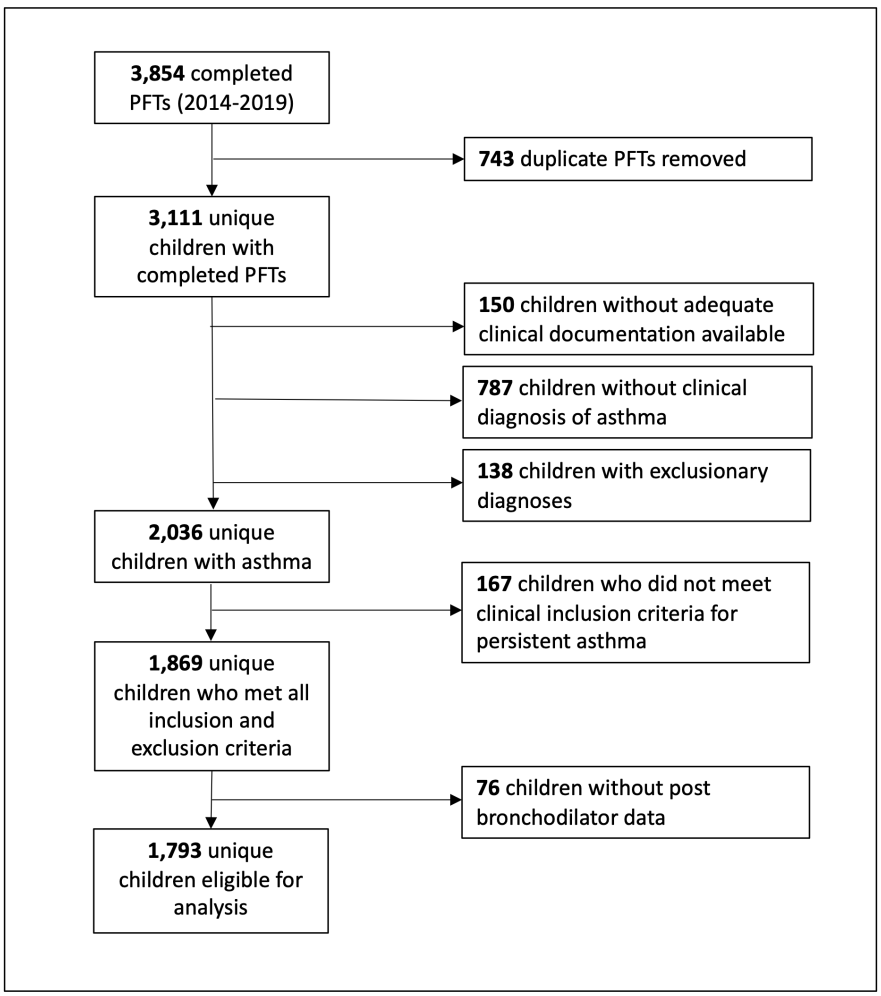
There are many limitations to this study. We do not have our own healthy control patients who performed their pulmonary function tests in the same laboratory with the same technicians. Our data is cross-sectional not longitudinal data. This is also true of the healthy children reference values. In healthy children, the ratio appears to begin to decline in late adolescence, while in our data, the ratio remains stable until 18 years of age. We only enrolled subjects up to their nineteenth birthday, so we have no information about what happens to the ratio after that age. Children with asthma who were obese had decreased ratios compared to children with normal BMIs, but we do not have measurements on children with just obesity and not asthma.

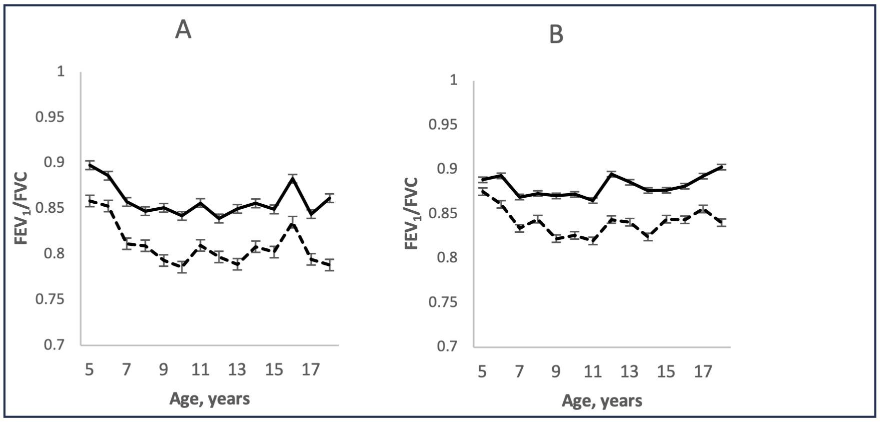
The major strengths of this study are the large sample size; and that we were able to examine the clinical charts of each patient and carefully characterize and enroll subjects who had persistent asthma but without acute symptoms. We limited our study to patients who meet criteria for persistent asthma, so this may not be generalizable for patients with milder disease.

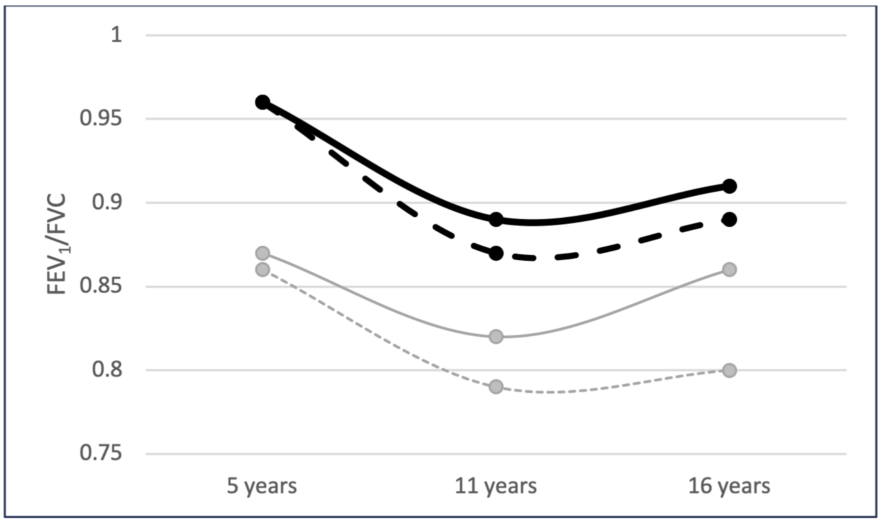
In summary, in this cross-sectional retrospective study, children with persistent asthma had increased obstruction compared to healthy children, but they demonstrated a similar “Shepherd’s Hook” shape to the curve of FEV_1/FVC compared to age, increasing in early adolescence. While the ratio was lower in obese patients with asthma, the curvilinear shape of this curve in early adolescence was preserved. Similar to what was seen in healthy children, FVC grew proportionally more than TLC and FEV_1 from age 5 to 11, and proportionally more from age 11 to 16. There are subtle differences of unknown clinical or physiological significance between this cohort of children with persistent asthma and the data obtained on healthy children by Quanjer PH et al[3], which merit confirmation with prospective studies.

Acknowledgements: The authors acknowledge the important role of Zachary Messer, MPH, Division Research and Regulatory manager. This study was funded by intramural funds of the Division of Pediatric Pulmonology, Allergy, Immunology, and Sleep Medicine of Boston Children's Health Physicians.









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