Does lung function change in the months after an asthma exacerbation in children?

Joanne Martin1, Marielle W Pijnenburg2, Graham C Roberts3, Katherine C Pike4, Helen Petsky5, Anne B Chang6, Stanley J Szefler7, Peter Gergen8, Francoise Vermeulen9, Robin Vael10, Steve Turner1.

1Child Health, University of Aberdeen, UK

2Department of Paediatric Respiratory Medicine and Allergology, University Medical Centre Rotterdam, Erasmus MC – Sophia Children’s Hospital, Rotterdam, Netherlands

3Clinical and Experimental Science, University of Southampton Faculty of Medicine, Southampton, UK

4Bristol Royal Hospital for Children, Bristol, UK

5School of Nursing and Midwifery, Griffith University; Menzies Health Institute Queensland, Brisbane, Australia

6Department of Respiratory and Sleep Medicine, Queensland Children's Hospital, Queensland University of Technology, Brisbane; Child Health Division, Menzies School of Health Research, Charles Darwin University, Darwin, Australia

7Breathing Institute, Children’s Hospital Colorado, Department of Pediatrics, University of Colorado School of Medicine, Anschutz Medical Campus, Aurora, Colorado, USA

8National Institute of Allergy and Infectious Diseases, Bethesda, MD USA

9Department of Paediatrics, Hôpital Erasme, Université Libre de Bruxelles (U.L.B.), Brussels, Belgium

10Department of Paediatrics, Antwerp University Hospital, Antwerp, Belgium

Running title: Lung function post asthma exacerbation

Corresponding author: Professor Steve Turner, Child Health, Royal Aberdeen Children’s Hospital, Aberdeen, UK, AB25 2ZG. Tel +44 1224 438470. [s.w.turner@abdn.ac.uk](mailto:s.w.turner@abdn.ac.uk)

Word count: 2489

Number of tables and figures: 6

This paper has material in the electronic repository

1. Statement of conflicts of interest. None of the authors has a real or perceived conflict of interest to declare
2. Financial support. This project had no financial support
3. **ABSTRACT**

Background. There are limited data describing lung function changes in children after an asthma exacerbation. Our hypothesis was that lung function does not fully recover in children in the months following an asthma exacerbation.

Methods. We used a dataset of children with asthma where lung function (including FEV1, FEV1/FVC ratio and FEF25-75) was measured at three-month intervals over a year. Mixed level models compared spirometry measured on two occasions three-months apart before a single exacerbation (assessments 1 and 2) to measurements made on two occasions after the exacerbation (assessments 3 and 4), with adjustment for covariates. Changes in spirometry over a year were also analysed across those with exacerbations in no, one or more than one three-month periods.

Results. For the 113 children who had a single exacerbation, spirometry measured made at assessment 1 or 2 did not differ at assessments 3 or 4 when the whole population was considered. When categorised into tertiles by change in %FEV1 between assessments 2 and 3, those with the greater reduction were more likely to be treated with long acting beta agonist, but in this category %FEV1 at assessment 4 had returned to the value at assessment 1. %FEV1 did not change over a 12month period within and between the three exacerbation categories (n=809).

Conclusion. One or more asthma exacerbation was not associated with a fall in lung function for the whole population. Lung function does fall after an exacerbation in some individuals but after a period of months returns to pre-exacerbation values.

Key words. Asthma, Child, Exacerbation, Nitric oxide, Pulmonary function testing

**Key message**

We find no evidence that lung function is reduced in the months following an asthma attack in childhood

**Author contribution**

ST conceived the idea and lead on data analysis. JM and ST undertook the analysis and wrote the initial draft of the manuscript. MW, JdJ, GR, KP, HP, AC, SS, PG, FV and RV contributed data. All authors made meaningful contributions to the final version of the manuscript. ST is the guarantor of this work.

**Conflict statement**

None of the authors has a real or perceived conflict of interest to declare

1. **Main Text**

**INTRODUCTION**

Asthma is a chronic respiratory condition which affects 1.1 million children in the UK1 and 5.5 million in the USA2 and globally is in the top ten causes of conditions affecting children’s quality of life3 . Children with asthma typically have intermittent wheeze and shortness of breath, obstructed lung function and airway eosinophilia, and all these features worsen during an asthma exacerbation 4. There is evidence from studies in mice that lung function does not fully recover after an exacerbation5, and in adults lung function declines more rapidly post asthma exacerbation6-8. Airway remodelling may be important to the mechanism where exacerbations adversely affect lung function9,10. In children there is limited literature addressing the relationship between asthma exacerbations with any subsequent decline in lung function. One randomised clinical trial (RCT) of inhaled corticosteroids (ICS) in steroid-naïve asthmatics, which included a subset of children, observed that FEV1 became lower after an asthma exacerbation for those receiving placebo but not among those randomised to ICS8.

The relationship between asthma exacerbations and spirometry in children is complicated by the fact that reduced FEV1 is a risk factor for an exacerbation;11,12 which raises the question’ does the exacerbation precede reduced lung function or *vice versa*?’ One method to understand the temporal relationship between asthma exacerbations and changes in lung function is to prospectively and regularly measure spirometry over a period in children with asthma, and then compare measurements before and after an exacerbation.

Our group has collaborated to form a dataset of children and young people with asthma, aged 6-20 years managed in primary and secondary care who were predominantly treated with ICS and who participated in seven RCTs13-19 which compared using measurements of fractional exhaled nitric oxide (FeNO, an index of airway eosinophilia) to guide asthma treatment with treatment based on standard clinical assessment12,20,21. Measurements of spirometry (and FeNO) were made at approximately three-month intervals over one year. There were three aims of the present study: first, to identify individuals with a single exacerbation were spirometry was measured on two occasions before and after the exacerbation and test the hypothesis that lung function does not fully recover in children in the months following an asthma exacerbation; second, in those with a single exacerbation to stratify individuals by change in spirometry after an exacerbation and compare characteristics of those with highest and lowest change against those whose lung function did not change; third to describe longitudinal changes in spirometry over a year for individuals who had no, one or two three-month periods where at least one exacerbation occurred.

**METHODS**

**Study design**

This was a retrospective multicentre study which analysed spirometry data from children with asthma who were predominantly atopic and followed up for twelve months as part of RCTs designed to investigate the utility of FeNO in guiding asthma treatment. Data from six13-18 of the seven cohorts in our dataset were included and measurements made at baseline and three, six, nine and twelve months afterwards were related to one asthma exacerbation. The study by Fritsch *et al*22 was a six-month duration study and thus excluded in our analysis. The definition of an asthma exacerbation was one requiring treatment with oral corticosteroid23. Where absolute spirometry measurements were provided, values were expressed as % predicted standardised to the global lung initiative (GLI) reference24. Height was measured at each assessment and spirometry standardised accordingly. In two cohorts16,25 we used the provided non-GLI standardised % predicted values (absolute spirometry values were not available) \*\*state which reference populations were used\*\*. FEV1 was the primary spirometric index. Additional spirometric indices were FEV1/FVC and FEF25-75 (available in a subset of participants).  Supplement table one described the definitions of asthma control used in the different cohorts. Ethical approval was obtained for each RCT and was not necessary for the present analysis.

**Populations included**

Peirsman *et al*13. Ninety-nine atopic children aged 5-14 years with mild to severe persistent asthma according to GINA guidelines attending hospital asthma clinics in Belgium were recruited and assessed every three months over a year. FeNO was only measured in participants allocated to the intervention arm, and individuals in the control arm were not eligible. Absolute FEV1 data were available in all participants (but not FEV1/FVC and FEF25-75).

Petsky *et al* 14. Sixty-three children aged >4 years with persistent asthma according to the National Asthma Council of Australia attending asthma clinics in Australia and Hong Kong were recruited and assessed at intervals which included three, six ten and twelve months after baseline. The measurements taken at ten months were assigned the nine-month assessment. Absolute FEV1 and FEV1/FVC data were available (but not FEF25-75).

Pijnenburg *et al* 15. Eighty-six children aged 6-18 years with atopic asthma attending hospital asthma clinics in the Netherlands were recruited and assessed every three months over a year. No absolute spirometric measurements were provided, instead only non-GLI percent predicted FEV1 values were available.

Pike *et al* 16. Ninety patients aged 6-17 years with asthma treated with ≥400 microg BUD equivalent daily treatment and with a positive bronchodilator response were recruited from hospitals in Southampton and the surrounding area within the UK. Assessments took place every two months. For the present analysis, measurements taken at two and ten months after baseline were assigned the three- and nine-month assessment respectively. No absolute spirometric measurements were provided, instead only non-GLI %FEV1 was available.

Szefler *et al* 17. Here 546 children and young adults aged 12-20 years with diagnosed asthma which was uncontrolled according to National Asthma Education and prevention Programme guidelines living in inner city areas of ten US cities and of African or Hispanic ancestry were recruited. In our analysis, measurements taken at 14, 22, 30 and 46 weeks after baseline were assigned three, six, nine and twelve months respectively. Absolute FEV1, FEV1/FVC and FEF25-75 data were available

Voorend-van Bergen *et al* 18. Children with allergic asthma aged 4-18 years with a positive bronchodilator response or airway hyperresponsiveness attending hospital clinics in the Netherlands were recruited. There were 181 participants. Assessments took place four, eight and twelve months after baseline which were assigned three, six and nine months for our analysis. Spirometry was only measured at baseline and twelve months. Absolute FEV1, FEV1/FVC and FEF25-75 data were available. In light of the missing spirometry data, a sensitivity analysis excluded this RCT from the main analysis

**Analysis**

There were three stages to the analysis. First, we identified participants with no exacerbation or with a single asthma exacerbation which occurred after two assessments and before another two assessments, figure 1. Knowing that increasing FeNO is a risk factor for an exacerbation26 we analysed FeNO and spirometry measurements in the period before and after this single exacerbation. Mixed level models (MLM) were used to relate the four measurements of spirometry and FeNO to the four time points. Covariates were added individually do determine whether they were associated with % predicted FEV1 and were included in the final model where p<0.2. Measurements at assessment two were also used as the reference to compare against values at assessment three and four. Covariates were: sex, age, obesity, ethnicity, dose of ICS (budesonide equivalent), treatment with long acting beta agonists (LABA), treatment with leukotriene receptor antagonist (LTRA) and current asthma control (defined as per each trial’s protocol). Additionally the interval between assessments and whether the child received standard or intervention treatment were considered. Obesity was defined by International Obesity Task Force Criteria27. Hispanic ethnicity was the most common (38%) across all participants and was therefore the reference ethnic group; other ethnic groups included “white” (35%), “black” (12%), “other white” (9%).

Second, individuals with a single exacerbation (as previously described) were ranked into tertiles by change in spirometry at assessments before and after an exacerbation. Characteristics across tertiles were analysed using chi square and ANOVA. Significant characteristics were included in a multinomial logistic model.

Third, all individuals in the dataset were categorised as: no exacerbation, those with a single one three month period during which ≥one exacerbation took place and those with more than one three month period during which ≥one exacerbation took place. An MLM was used to analyse differences in spirometry between categories and time: this model included an interaction term between category and time. IBM/SPSS version 25.0 software was used and a p value of <0.05 was considered significant for multivariate models.

**RESULTS**

**Study population**

Data were available in 1065 individuals, mean age (SD) 12.6y (3.1). The mean (SD) baseline %FEV1 was 94 (18), the median (IQR) daily ICS dose was 400 (400, 1000) microg BUD equivalent and 58% were prescribed long acting beta agonists, table one. There were 745 children with no exacerbations and 320 with ≥one exacerbation in a single three-month period (including the 113 where the exacerbation occurred between assessments two and three)and 64 with ≥one exacerbation in >one three-month period.

**Change in spirometric measurements after single exacerbation**

The mean age of individuals with a single exacerbation between assessments two and three was 12.7 years and 58% were male, table 1. Compared to the whole dataset, individuals with a single exacerbation were more likelyto receive LABA and LTRA treatment, to receive a higher dose of ICS and to have higher FeNO and lower %FEV1, table 1. At assessment one, FeNO data were available in 113 individuals, % predicted FEV1 in 103 and % predicted FEV1/FVC and % predicted FEF25-75 in 71. Supplemental table two shows how the covariates considered were related to spirometry and FeNO. There was no difference between % predicted FEV1,(table 2 and figure 2), % predicted FEV1/FVC or % predicted FEF25-75 (supplemental table three) on assessments three and four relative to assessment one. Similarly there were no differences between spirometric measurements made on assessments three and four relative to assessment two. The results were not substantially changed when data from the study Voorend-van Bergen *et al* 18 were excluded from the analysis, supplemental table four.

There was a trend of borderline significance for FeNO values to differ across the four assessments (p=0.049), table 2 and supplemental figure 1. FeNO values at assessment four were 21% higher than on assessment one [95% confidence interval -5, +54].

**Characteristics of participants stratified by change in % predicted FEV1 between assessments two and three**

In 92 of the 113 individuals in the above analysis where %FEV1 was determined before and after the exacerbation.. In unadjusted analyses, the proportions with obesity, atopy and on LABA treatment differed across tertiles, table 3. In a multivariate model, and with reference to the intermediate change in %predicted FEV1, the group with greatest fall were more likely to be treated with LABA (OR 6.8 [95% CI 1.1, 41.7], p=0.039) and the group with greatest rise were more likely to be obese (OR 3.5 [95% CI 1.0, 11.8], p=0.048). These results were unchanged when the two individuals not treated with inhaled corticosteroids were removed from the analysis

**Change in spirometric measurements over 12 months across exacerbation categories**

Between groups, % predicted FEV1 was higher in the no exacerbation category compared to the ≥one exacerbation in a single three-month category (mean difference 4.2 [95% CI 1.5, 6.9]) p=0.002, supplemental table five. In all three groups, % predicted FEV1 did not differ between the start and the end of the 12 month period (supplemental table 4). Although the interaction between time and exacerbation category was significant (p=0.045, supplemental table five), this was explained by a fall in % predicted FEV1 after three months in the category with exacerbations in more than one three-month period (figure 3).

**DISCUSSION**

The main finding of this study was that we found no evidence of a change in spirometry measurements in the months after an asthma exacerbation in children who continue to be prescribed asthma preventer medication. When we created a subgroup of children who did experience a reduction in % predicted FEV1 within three months of an exacerbation, their % predicted FEV1 had recovered to pre-exacerbation values within six months. We saw no consistent evidence that measurements of lung function changed over time across groups stratified by the burden of exacerbations.

Our results are consistent with those of O’Byrne *et al*8 who, in a subset of 138 children within a larger population of adults and children, report that those taking ICS had no decline in lung function following exacerbation. Our study population had more severe asthma than participants in the earlier study8 and our findings are therefore relevant to children with more severe asthma. O’Byrne *et al*8 reported that children randomised to no ICS had a 4% decrease in %FEV1 after an exacerbation, and in our study there were only two participants not treated with ICS so we are not able to confirm whether ICS protect against reductions in lung function after an exacerbation.

Our findings are also consistent with cohort studies of children with and without asthma and which demonstrate tracking of lung function from infancy or childhood into adulthood28,29. Although individuals with the lowest lung function tend to have a greater burden of respiratory symptoms compared to their peers with higher lung function, growth in lung function over time is parallel across groups with low, intermediate and high initial lung function measurements.

In contrast to our findings in children, adults with frequent exacerbations have an accelerated decline in FEV1 in comparison to individuals with no asthma or well controlled asthma6,8,30 and there may be a linear relationship between the number of exacerbations and FEV1 decline7. Only some adults with asthma may experience an accelerated decline in lung function after an exacerbation31, for example those with severe6,8 or frequent32 exacerbations.

Our study was not designed to explain why lung function is permanently reduced after an exacerbation in adults but apparently not in children. In addition to the limitations of our study (described later, possible explanations for differences between adults and children include different asthma phenotypes in children and adults33, active smoking in adults but not children and ongoing growth in lung volumes protecting against or repairing damage to lung tissue during an exacerbation. Additional factors could include differences in treatment adherence, short duration of asthma and/or low number of lifetime exacerbations in children compared to adults.

One limitation to our study is that the number of participants with a single exacerbation was relatively small, and it is possible that our study was underpowered to detect a small decline in lung function after a single exacerbation. We are not aware of other sources of data for a power calculation and have used the data available to us from our dataset. For those with no exacerbations during follow up, the mean % predicted FEV1 at baseline was 95.17% and the standard deviation between baseline and nine months was 11.23. Populations of 11, 44 and 121 individuals would be required to detect changes of 10%, 5% and 3% (assuming 80% power and a p value of 0.05), meaning that the sample size was underpowered to detect a change in FEV1 of 1.9 between assessments one and four in 113 individuals (table two). A second limitation is that although all exacerbations were treated with oral corticosteroids, we do not know how severe the exacerbation was. Third, we did not have post bronchodilator % predicted FEV1 which is an index of fixed airway obstruction and therefore a better index of airway remodelling than the pre bronchodilator % predicted FEV1 which was available to us. A further limitation is that our duration of follow up was relatively short so we cannot be certain of the long lasting effect of an exacerbation on subsequent lung function, although lung function did return to pre-exacerbation values the group with a post-exacerbation fall in lung function. Our study was not designed to determine whether different triggers (or combinations of triggers)34 for exacerbation have a different impact on lung function. Finally we do not know the exact date of the exacerbation only that it occurred between assessments two and three, and together with the different follow up periods in some included RCTs this lack of precision means that assessment three for some individuals will have been several weeks after the exacerbation whereas for others the interval may have been only several days.

Our study design allowed us to see that in this subgroup, which was enriched with non-atopic individuals, %predicted FEV1 did recover to pre-exacerbation values within months indicating a delayed but nonetheless apparently complete recovery in % predicted FEV1. The children we identified as having the greatest fall in % predicted FEV1 post exacerbation were more likely to be treated with LABA and this association may represent reverse causation. Our subgroup analysis also found that those with the greatest rise in % predicted FEV1 after an exacerbation were more likely to be obese; this was an unexpected finding and should be interpreted with caution.

Among those with one exacerbation, FeNO concentrations differed over the period do follow up with values being highest at the fourth assessment compared to the first assessment. The delay between exacerbation and rising FeNO seems unlikely to be causally related. Our participants were exacerbation-prone and the delayed rise in FeNO values may be due to oral corticosteroids temporarily suppressing airway eosinophilia but over time the same factors which contribute to the exacerbation contribute to rising FeNO, e.g. inadequate ICS treatment, treatment adherence.

In summary, we find no evidence that an asthma exacerbation leads to a lasting reduction in lung function for all children. Our results could reassure patients, parents and clinicians that children with asthma requiring higher doses of ICS and additional therapies do not seem to have a “loss” of lung function after an exacerbation. Future research utilising data from studies with longer follow up than the present study are required, ideally studies which include severe asthmatics where exacerbations are more frequent and more likely to show any impact over time.

1. **ACKNOWLEDGEMENTS**

We thank our colleagues Dr Maria Fritsch and Prof Thomas Frischer for sharing data from their study with us and which have been used in other analyses, but not the present analysis. We are also grateful to Dr Delapo Ayansina for his comments on the statistical approach taken for the analysis.

1. **IMPACT STATEMENT**

Asthma attacks in adults are associated with a persistent reduction in lung function, but there is limited understanding of whether this is also seen in children with asthma. In our study we analysed data collected over 12 months in children with asthma to study the relationship between lung function and asthma exacerbations. We found no evidence that lung function was persistently reduced after a single or multiple exacerbation. We believe that these findings make a useful addition to the literature.

1. **REFERENCES**

1. Asthma UK. Asthma facts and FAQs. <https://www.asthma.org.uk/about/media/facts-and-statistics/>. Updated 2020. Accessed 04/12, 2020.

2. Centres for Disease Control and Prevention. Asthma stats. <https://www.cdc.gov/asthma/asthma_stats/documents/AsthmaStats_Asthma_Uncontrolled_Child_PDF_Cleared_H.pdf>. Updated 2019. Accessed 06/16, 2020.

3. Asher I, Pearce N. Global burden of asthma among children. *International Journal of Tuberculosis & Lung Disease*. 2014;18(11):1269-1278.

4. British Thoracic Society and Scottish Intercollegiate Guidelines Network. SIGN 158.  the british guideline on the management of asthma. <https://www.brit-thoracic.org.uk/quality-improvement/guidelines/asthma/>. Updated 2019. Accessed 07/27, 2019.

5. Kumar RK, Herbert C, Foster PS. Mouse models of acute exacerbations of allergic asthma. *Respirology*. 2016;21(5):842-849.

6. Bai TR, Vonk JM, Postma DS, Boezen HM. Severe exacerbations predict excess lung function decline in asthma. *European Respiratory Journal*. 2007;30(3):452-456.

7. Ortega H, Yancey SW, Keene ON, Gunsoy NB, Albers FC, Howarth PH. Asthma exacerbations associated with lung function decline in patients with severe eosinophilic asthma. *The Journal of Allergy & Clinical Immunology in Practice*. 2018;6(3):980-986.e1.

8. O'Byrne PM, Pedersen S, Lamm CJ, Tan WC, Busse WW, START Investigators Group. Severe exacerbations and decline in lung function in asthma. *American Journal of Respiratory & Critical Care Medicine*. 2009;179(1):19-24.

9. Fehrenbach H, Wagner C, Wegmann M. Airway remodeling in asthma: What really matters. *Cell & Tissue Research*. 2017;367(3):551-569.

10. Grainge CL, Lau LCK, Ward JA, et al. Effect of bronchoconstriction on airway remodeling in asthma. *N Engl J Med*. 2011;364(21):2006-2015.

11. Fuhlbrigge AL, Kitch BT, Paltiel AD, et al. FEV(1) is associated with risk of asthma attacks in a pediatric population. *Journal of Allergy & Clinical Immunology*. 2001;107(1):61-67.

12. Fielding S, Pijnenburg M, de Jongste JC, et al. Change in FEV1 and feno measurements as predictors of future asthma outcomes in children. *Chest*. 2019;155(2):331-341.

13. Peirsman EJ, Carvelli TJ, Hage PY, et al. Exhaled nitric oxide in childhood allergic asthma management: A randomised controlled trial. *Pediatr Pulmonol*. 2014;49(7):624-631.

14. Petsky HL, Li AM, Au CT, Kynaston JA, Turner C, Chang AB. Management based on exhaled nitric oxide levels adjusted for atopy reduces asthma exacerbations in children: A dual centre randomized controlled trial. *Pediatr Pulmonol*. 2015;50(6):535-543.

15. Pijnenburg MW, Bakker EM, Hop WC, De Jongste JC. Titrating steroids on exhaled nitric oxide in children with asthma: A randomized controlled trial. *American Journal of Respiratory & Critical Care Medicine*. 2005;172(7):831-836.

16. Pike K, Selby A, Price S, et al. Exhaled nitric oxide monitoring does not reduce exacerbation frequency or inhaled corticosteroid dose in paediatric asthma: A randomised controlled trial. *The clinical respiratory journal*. 2013;7(2):204-213.

17. Szefler SJ, Mitchell H, Sorkness CA, et al. Management of asthma based on exhaled nitric oxide in addition to guideline-based treatment for inner-city adolescents and young adults: A randomised controlled trial. *Lancet*. 2008;372(9643):1065-1072.

18. Voorend-van Bergen S, Vaessen-Verberne AA, Brackel HJ, et al. Monitoring strategies in children with asthma: A randomised controlled trial. *Thorax*. 2015;70(6):543-550.

19. Fritsch M, Uxa S, Horak FJ, et al. Exhaled nitric oxide in the management of childhood asthma: A prospective 6-months study. *Pediatr Pulmonol*. 2006;41(9):855-862.

20. Fielding S, Pijnenburg MW, de Jongste JC, et al. **Does treatment guided by fractional exhaled nitric oxide improve outcomes in subgroups of children with asthma?** *Eur Respir J*. 2020;doi 10.1183/13993003.01879-2019.

21. Fielding S, Pijnenburg M, de Jongste J, et al. What is a clinically meaningful change in exhaled nitric oxide for children with asthma?. *Pediatr Pulmonol*. 2020;55(3):599-606.

22. Fritsch M, Uxa S, Horak FJ, et al. Exhaled nitric oxide in the management of childhood asthma: A prospective 6-months study. *Pediatr Pulmonol*. 2006;41(9):855-862.

23. Reddel HK, Taylor DR, Bateman ED, et al. An official american thoracic society/european respiratory society statement: Asthma control and exacerbations: Standardizing endpoints for clinical asthma trials and clinical practice. *American Journal of Respiratory & Critical Care Medicine*. 2009;180(1):59-99.

24. Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: The global lung function 2012 equations. *European Respiratory Journal*. 2012;40(6):1324-1343.

25. Pijnenburg MW, Bakker EM, Hop WC, De Jongste JC. Titrating steroids on exhaled nitric oxide in children with asthma: A randomized controlled trial. *American Journal of Respiratory & Critical Care Medicine*. 2005;172(7):831-836.

26. Zeiger RS, Schatz M, Zhang F, et al. Elevated exhaled nitric oxide is a clinical indicator of future uncontrolled asthma in asthmatic patients on inhaled corticosteroids. *Journal of Allergy & Clinical Immunology*. 2011;128(2):412-414.

27. Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: International survey. *BMJ*. 2000;320(7244):1240-1243.

28. McGeachie MJ, Yates KP, Zhou X, et al. Patterns of growth and decline in lung function in persistent childhood asthma. *N Engl J Med*. 2016;374(19):1842-1852.

29. Belgrave DCM, Granell R, Turner SW, et al. Lung function trajectories from pre-school age to adulthood and their associations with early life factors: A retrospective analysis of three population-based birth cohort studies. *The Lancet Respiratory Medicine*. 2018;6(7):526-534.

30. Matsunaga K, Hirano T, Oka A, et al. Progression of irreversible airflow limitation in asthma: Correlation with severe exacerbations. *The Journal of Allergy & Clinical Immunology in Practice*. 2015;3(5):759-64.e1.

31. Dougherty RH, Fahy JV. Acute exacerbations of asthma: Epidemiology, biology and the exacerbation-prone phenotype. *Clinical & Experimental Allergy*. 2009;39(2):193-202.

32. Koga T, Oshita Y, Kamimura T, Koga H, Aizawa H. Characterisation of patients with frequent exacerbation of asthma. *Respir Med*. 2006;100(2):273-278.

33. Turner S, Upham JW. Asthma in children and adults- what are the differences and what can they tell us about asthma? *Front Pediatr*. 2020;doi: 10.3389/fped.2020.00141.

34. Dick S, Doust E, Cowie H, Ayres JG, Turner S. Associations between environmental exposures and asthma control and exacerbations in young children: A systematic review. *BMJ Open*. 2014;4(2):e003827.

1. **TABLES**

Table 1. Characteristics of the whole population, individuals with no exacerbations and individuals where spirometry was measured twice before and twice after an exacerbation.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | | Whole population (denominator=1065 unless stated) | No exacerbation (denominator=745 unless stated) | One exacerbation with two spirometry measurements before and after (denominator=113 unless stated) |
| Mean age (SD), y | | 12.6 (3.1) | 12.1 (3.0) | 12.7 (3.1) |
| Proportion (number) male | | 58% (615) | 59% (441) | 58% (66) |
| Proportion (number) of Hispanic ethnic group | | 38% (340/899) | 33% (247/582) | 46% (45/99) † |
| Proportion atopic | | 92% (944/1030) | 92% (683/734) | 93% (97/104) |
| Proportion obese | | 18% (183/1038) | 14 % (103/729) | 20% (22/112)† |
| Mean baseline % predicted FEV1 (SD) | | 94 (18) n=1030 | 95 (17) n=715 | 91 (20) n=111† |
| Mean baseline % predicted FEV1/FVC(SD) | | 92 (10) n=702 | 93 (9) n=472 | 90 (10) n=75 |
| Mean baseline % predicted FEF25-75 (SD) | | 78 (30) n=699 | 82 (29) n=426 | 73 (30) n=75 |
| Median baseline FeNO (IQR), ppb | | 21 (11, 42) n=1011 | 21 (11, 40) n=696 | 24 (13, 46) n=111† |
| Proportion in standard treatment arm of trial | | 50% (536) | 49% (364) | 58% (66) |
| Proportion (number) not prescribed inhaled corticosteroids at baseline | | 3% (32) | 4% (26/734) | 2% (2/113) |
| Median (IQR) dose of inhaled corticosteroid (BUD equivalent) at baseline, microg | | 400 (400, 1000) n=1053 | 400 (400, 970) n=734 | 800 (400, 2000)\*† |
| Proportion (number) prescribed long acting beta agonist at baseline | | 58% (616/1060) | 50% (374/740) | 72% (81)\*† |
| Proportion (number) prescribed leukotriene receptor antagonist at baseline | | 20% (214/1060) | 17% (124/740) | 21% (24)† |
| Median number of exacerbations (IQR) | | 0 (0, 1) | 0 (0, 0) | 1 (1, 1)\* |
| Mean %FEV1 (SD) | Baseline | 94 (18) n=1030 | 95 (17) n=715 | 91 (20) n=103‡ |
| Three months | 93 (20) n=771 | 95 (17) n=517 | 90 (20) n=92‡ |
| Six months | 94 (20) n=740 | 95 (18) n=508 | 91 (20) n=93‡ |
| Nine months | 94 (19) n=714 | 96 (18) n=461 | 92 (19) n=96‡ |
| Twelve months | 95 (18) n=941 | 97 (17) n=653 | Not applicable |
| Median FeNO (IQR), ppb | Baseline | 21 (11, 42) n=1011 | 21 (11, 40) n=696 | 22 (13,51) n=110‡ |
| Three months | 23 (12, 49) n=982 | 22 (12, 43) n=678 | 25 (14, 57) n=109‡ |
| Six months | 24 (13, 51) n=952 | 22 (13, 47) n=673 | 25 (13, 46) n=110‡ |
| Nine months | 27 (13, 53) n=750 | 26 (13, 50) n=476 | 31 (14, 63) n=98‡ |
| Twelve months | 28 (13, 53) n=895 | 27 (13, 50) n=614 | Not applicable |
| Proportion (number) with controlled asthma symptoms | Baseline | 77% (723/941) | 77% (465/608) | 72% (72/100)‡ |
| Three months | 77% (739/964) | 79% (502/632) | 80% (82/103)‡ |
| Six months | 79% (745/945) | 82% (516/633) | 71% (72/102)‡ |
| Nine months | 79% (584/739) | 82% (390/476) | 76% (77/102)‡ |
| Twelve months | 79% (723/911) | 82% (516/632) | Not applicable |
| Proportion (number) from each cohort\* | Peirsman13 | 9% (99) | 12% (92) | 2% (2) |
| Petsky14 | 6% (63) | 7% (50) | 5% (5) |
| Pijnenburg15 | 8% (86) | 8% (61) | 7% (8) |
| Pike16 | 8% (90) | 6% (48) | 19% (21) |
| Szefler17 | 49% (546) | 40% (297) | 58% (65) |
| Voorend-van Bergen18 | 16% (181) | 21% (154) | 11% (12) |

SD=standard deviation, IQR=interquartile range, ppb=parts per billion, BUD=budesonide equivalent. \*p<0.01 for difference between group with one exacerbation and the whole population. †<0.05 for difference between group with one exacerbation and no exacerbation. ‡For the subgroup where spirometry was measured on two occasions before and after an exacerbation, baseline=assessment one, three months =assessment two, six months=assessment three and nine months=assessment four (see figure one).

Table 2. Results from four mixed level models which related spirometric or exhaled nitric oxide (FeNO) measurements made at assessments 1-4 where an asthma exacerbation occurred between assessments 2 and 3. The numbers provided are mean difference in percent predicted lung function or percentage change in FeNO. The values in square brackets are 95% confidence intervals. Covariates were included if p<0.1 in univariate analysis and therefore some cells in the table are empty (see supplemental table two). LABA=long acting beta agonist. LTRA=leukotriene receptor antagonist. BUD: budesonide equivalent.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | | Mean change in %FEV1 | Mean change in %FEV1/FVC | Mean change in %FEF25-75 | % change in FeNO |
| Assessment number variable | Overall trend | p=0.396 | p=0.445 | p=0.473 | p=0.049 |
| Ass 2 vs 1 | 0.8 [-1.2, 3.2] | 0.2 [-1.3, 1.7] | -0.5 [-4.7, 3.7] | 10 [-7, 29] |
| Ass 3 vs 1 | 0.3 [-2.7, 3.2] | -0.6 [-2.6, 1.4] | -1.1 [-6.8, 4.6] | -2 [-21, 20] |
| Ass 4 vs 1 | 1.9 [-1.4, 5.2] | 0.5 [-1.9, 2.8] | 2.4 [-4.2, 9.1] | 21 [-5, 54] |
| Male sex | |  |  |  | 24 [-9, 66] p=0.143 |
| Age (y) | |  |  |  | 3 [-2, 9] p=0.203 |
| Hispanic relative to other ethnic group | | -18.7 [-24.6, -12.8] p<0.001 |  | -28 [-16, -39] p<0.001 | 24 [-2, 44] p=0.068 |
| Obese relative to non-obese | |  | -3.7 [-8.0, 0.6] p=0.088 |  |  |
| Atopic relative to non-atopic | |  | -9.4 [-17.8, -1.1] p=0.029 | -27 [-4, -51] p=0.024 | 62 [26, 80] p=0.005 |
| Asthma controlled relative to uncontrolled | | 2.6 [0.1, 5.0] p=0.040 | 2.5 [0.7, 4.4] p=0.006 | 10 [5, 15] p<0.001 |  |
| LABA relative to no LABA treatment | | 6.3 [-0.6, 13.1] p=0.07 | 5.5 [1.1, 10.0] p=0.016 | 14 [1, 26] p=0.029 |  |
| LTRA relative to no LTRA treatment | |  | -7.5 [-13.6, -1.5] p=0.016 |  |  |
| Inhaled corticosteroid dose (microg BUD) | |  |  |  | -7 [-19, 6] p=0.291 |

Table 3. Comparison of details across individuals stratified by fall in %FEV1 before and after an exacerbation. \*p<0.05 for trend across three groups

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | | Tertile of % change in FEV1 between assessments two and three | | |
| Greatest negative change in %FEV1  n=30 unless stated | Intermediate change in %FEV1 n=31 unless stated | Greatest positive change in %FEV1  n=31 unless stated |
| Mean change in %FEV1 between assessments 2 and 3 (SD) | | -8.6% (9.7) | 0.1 (1.3) | 8.8 (6.6) |
| Mean %FEV1 (SD) | Assessment 1 | 92.8 (22.6) | 84.9 (16.0) | 93.2 (23.3) |
| Assessment 2 | 95.9 (21.5) | 84.7 (14.4) | 90.8 (21.1) |
| Assessment 3 | 87.3 (23.7) | 84.8 (14.4) | 99.6 (18.5) |
| Assessment 4 | 92.8 (20.7) n=28 | 87.1 (15.4) n=30 | 96.5 (21.7) n=29 |
| Mean age (SD), y | | 13.3 (3.0) | 13.1 (3.0) | 12.7 (3.0) |
| Proportion (number) male | | 57% (17) | 65% (20) | 61% (19) |
| Proportion (number) of Hispanic ethnic group | | 43% (13) | 55% (17) | 48% (15) |
| Proportion (number) obese\* | | 17% (5) | 16% (5) | 39% (12) |
| Proportion atopic\* | | 82% (22/27) | 96% (27/28) | 96% (27/28) |
| Median FeNO at assessment 2(IQR), ppb | | 22 (9,86) n=29 | 32 (19,66) n=30 | 18 (13,41) |
| Proportion with controlled asthma on assessment two | | 77% (23) | 72% (21/29) | 68% (19/28) |
| Proportion (number) prescribed long acting beta agonist at baseline\* | | 90% (27) | 74% (23) | 68% (21) |
| Proportion (number) prescribed leukotriene receptor antagonist at baseline | | 30% (9) | 10% (3) | 26% (8) |
| Median (IQR) dose of inhaled corticosteroid (BUD equivalent) at assessment two, microg | | 1234 (n=30) | 837 (n=31) | 1060 (n=31) |
| Mean interval between assessments two and three (SD) | | 99 (29) n=20 | 102 (32) n=25 | 94 (28) n=27 |

1. **FIGURE LEGENDS**

Figure 1. Schematic diagram showing how spirometry and fractional exhaled nitric oxide measurements data from the five visits as part of their respective randomised controlled trial were allocated to assessments 1, 2, 3 and 4 with the asthma exacerbation occurring between assessments 2 and 3. The exacerbation was taken as “time zero” and two time points prior to this and two time points after, irrespective of when “time zero” actually fell in the time course of that particular study. Data were not included in this analysis if the exacerbation occurred early or late in the course of the trial meaning that they had only one or no assessments before or after the exacerbation.

Figure 2. Diagram comparing %FEV1 measured on four assessments at three-month intervals and where there was an asthma exacerbation between the second and third assessment. The circles represent the mean relative difference and the vertical lines represent the 95% confidence interval. There were no differences between % FEV1 values on the four assessments.

Figure 3. Diagram comparing %FEV1 measured on five occasions at three-month intervals for individuals stratified by having no, one or more than one three-month period during which there was an exacerbation. %FEV1 was significantly lower throughout for those with exacerbation(s) in one period compared to no exacerbations (p=0.002). Within groups there was a difference between % FEV1 at baseline and three months among the category with more than one three-month period during which there was an exacerbation (p=0.040).