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

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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 data set of children with asthma where lung function (including FEV₁, FEV₁/FVC ratio and FEF₂₅₋₇₅) was measured at 3-month intervals over a year. Mixed-level models compared spirometry measured on two occasions 3 months apart before a single exacerbation (assessments 1 and 2) with 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 3-month periods.

**Results:** For the 113 children who had a single exacerbation, spirometry measured at assessments 1 or 2 did not differ from measurements at assessments 3 or 4 when the whole population was considered. When stratified 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 12-month 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. In a subset of individuals, lung function does fall after an exacerbation but returns to pre-exacerbation values after a period of months.

**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.
1 | INTRODUCTION

Asthma is a chronic respiratory condition, which affects 1.1 million children in the UK \(^1\) and 5.5 million in the USA, \(^2\) and globally is in the top ten causes of conditions affecting children’s quality of life. \(^3\) 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. \(^6\) There is evidence from studies in mice that lung function does not fully recover after an exacerbation, \(^5\) and in adults, lung function declines more rapidly post-asthma exacerbation. \(^6\) Airway remodelling may be important to the mechanism where exacerbations adversely affect lung function. \(^9\) In children, there is limited literature addressing the relationship between asthma exacerbations with any subsequent decline in lung function. One randomized clinical trial (RCT) of inhaled corticosteroids (ICS) in steroid-naïve children with asthma, which included a subset of children, observed that FEV \(_1\) became lower after an asthma exacerbation for those receiving placebo but not among those randomized to ICS. \(^8\) The relationship between asthma exacerbations and spirometry in children is complicated by the fact that reduced FEV \(_1\) is a risk factor for an exacerbation, \(^11\) raising 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 repeatedly 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 data set 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 RCTs, \(^13\) which compared using measurements of fractional exhaled nitric oxide (FeNO, an index of airway eosinophilia) to guide asthma treatment. \(^12\) Measurements of spirometry (and FeNO) were made at approximately 3-month intervals over 1 year. Here, we used our data set to achieve three aims: (i) to identify individuals with a single exacerbation where 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; (ii) in those with a single exacerbation described in (i), 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; and (iii) to describe longitudinal changes in spirometry over a year for individuals who had no, one or two 3-month periods during which at least one exacerbation occurred.

2 | METHODS

2.1 | Study design

This was a data set from prospective multicentre RCTs where the spirometry data were retrospectively analysed from children with asthma who were predominantly atopic and followed up for 12 months as part of RCTs designed to investigate the utility of FeNO in guiding asthma treatment. Data from six \(^13\) of the seven cohorts in our original data set were included, and spirometry (and FeNO) measurements made at baseline and 3, 6, 9 and 12 months afterwards were used. The study by Fritsch et al \(^19\) was a 6-month duration study and thus excluded in our analysis. The definition of an asthma exacerbation was one requiring treatment with oral corticosteroid. \(^22\) Where absolute spirometry measurements were provided, values were expressed as % predicted standardized to the global lung initiative (GLI) reference. \(^23\) Height was measured at each assessment and spirometry standardized accordingly. In two cohorts \(^15,16\), where absolute spirometry values were not available, we used the provided non-GLI standardized % predicted values from Zapletal et al \(^24\) and Rosenthal et al \(^25\). FEV \(_1\) was the primary spirometric index. Additional spirometric indices were FEV \(_1\)/FVC and FEF \(_{25-75}\) (available in a subset of participants). Supplement Table S1 describes 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.

2.2 | Populations included

Peirsman et al \(^13\) Ninety-nine atopic children aged 5-14 years with mild to severe persistent asthma according to the GINA guidelines attending hospital asthma clinics in Belgium were recruited and assessed every 3 months over a year. FeNO was only measured in participants allocated to the intervention arm. Absolute FEV \(_1\) data were available in all participants (but not FEV \(_1\)/FVC and FEF \(_{25-75}\)).

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 3, 6, 10 and 12 months after baseline. The measurements taken at 10 months were assigned the 9-month assessment. Absolute FEV \(_1\) and FEV \(_1\)/FVC data were available (but not FEF \(_{25-75}\)).

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 3 months over a year.

Pike et al \(^16\) Ninety patients aged 6-17 years with asthma treated with 3400 microg BUD equivalent daily treatment and with a positive bronchodilator response were recruited from hospitals in Southampton and the surrounding area. Assessments took place every 2 months. For the present analysis, measurements taken at 2 and 10 months after baseline were assigned the 3- and 9-month assessment, respectively.

Szefer et al \(^17\) Here, 546 children and young adults aged 12-20 years with diagnosed asthma, which was uncontrolled according to the 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 3, 6, 9
and 12 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 in two trial arms. Individuals in a third web-based trial arm were not included in the present analysis. Assessments took place 4, 8 and 12 months after baseline, which were assigned 3, 6 and 9 months for our analysis. Spirometry was only measured at baseline and 12 months. Absolute FEV₁, FEV₁/FVC and FEF₂₅₋₇₅ data were available. Due to the missing spirometry data, a sensitivity analysis excluded this RCT from the main analysis.

2.3 | 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 exacerbation,²⁶ we analysed FeNO and spirometry measurements in the period before and after this single exacerbation. Mixed-level models (MLMs) were used to relate the four measurements of spirometry and FeNO to the four time points. Covariates were added individually to determine whether they were associated with % predicted FEV₁ and were included in the final model where \( P < .2 \). Measurements at assessment 2 were also used as the reference to compare against values at assessments 3 and 4. Covariates were as follows: sex, age, obesity, ethnicity, dose of ICS (budesonide equivalent), treatment with long-acting beta-agonists (LABAs), 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 the International Obesity Task Force Criteria.²⁷ 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%) and ‘other White’ (9%).

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

Third, all individuals in the data set were categorized as: no exacerbation, those with a single 3-month period during which zone exacerbation took place and those with more than one 3-month period during which zone 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 < .05 was considered significant for multivariate models.

3 | RESULTS

3.1 | Study population

Data were available in 1065 individuals, with a mean age (SD) of 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 1). There were 745 children with no exacerbations and 320 with ≥one exacerbation in a single 3-month period (including the 113 where the exacerbation occurred between assessments 2 and 3) and 64 with ≥one exacerbation in >one 3-month period.

![Figure 1](image-url)  
Schematic diagram showing how spirometry and fractional exhaled nitric oxide measurement data from the five visits as part of their respective randomized 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. The exacerbation may have occurred after three or six months. Data were not included in this analysis if the exacerbation occurred before three or after six months in the course of the trial since they had only less than two assessments before or after the exacerbation.
### TABLE 1  Characteristics of the whole population, individuals with no exacerbations and individuals where spirometry was measured twice before and after an exacerbation

<table>
<thead>
<tr>
<th></th>
<th>Whole population (denominator = 1065 unless stated)</th>
<th>No exacerbation (denominator = 745 unless stated)</th>
<th>One exacerbation with two spirometry measurements before and after (denominator = 113 unless stated)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean age (SD), y</strong></td>
<td>12.6 (3.1)</td>
<td>12.1 (3.0)</td>
<td>12.7 (3.1)</td>
</tr>
<tr>
<td><strong>Proportion (number) of male</strong></td>
<td>58% (615)</td>
<td>59% (441)</td>
<td>58% (66)</td>
</tr>
<tr>
<td><strong>Proportion (number) of Hispanic ethnic group</strong></td>
<td>38% (340/899)</td>
<td>33% (247/782)</td>
<td>46% (45/99)</td>
</tr>
<tr>
<td><strong>Proportion of obese</strong></td>
<td>18% (183/1038)</td>
<td>14% (103/729)</td>
<td>20% (22/112)</td>
</tr>
<tr>
<td><strong>Mean baseline % predicted FEV₁ (SD)</strong></td>
<td>94 (18) n = 1030</td>
<td>95 (17) n = 715</td>
<td>91 (20) n = 111</td>
</tr>
<tr>
<td><strong>Mean baseline % predicted FEV₁/FVC(SD)</strong></td>
<td>92 (10) n = 702</td>
<td>93 (9) n = 472</td>
<td>90 (10) n = 75</td>
</tr>
<tr>
<td><strong>Mean baseline % predicted FEF 2 5 - 7 5 (SD)</strong></td>
<td>78 (15) n = 699</td>
<td>82 (12) n = 426</td>
<td>73 (13) n = 75</td>
</tr>
<tr>
<td><strong>Median baseline FeNO (IQR), ppb</strong></td>
<td>21 (11, 42) n = 1011</td>
<td>21 (11, 40) n = 696</td>
<td>24 (13, 46) n = 111</td>
</tr>
<tr>
<td><strong>Proportion (number) of patients with controlled asthma symptoms</strong></td>
<td>77% (723/941)</td>
<td>77% (465/608)</td>
<td>72% (72/100)</td>
</tr>
<tr>
<td><strong>Proportion (number) of patients from each cohort</strong></td>
<td>9% (99)</td>
<td>12% (92)</td>
<td>2% (2)</td>
</tr>
</tbody>
</table>

**Abbreviations:** SD, standard deviation; IQR, interquartile range; ppb, parts per billion; BUD, budesonide equivalent.

*P < .01 for difference between group with one exacerbation and the whole population; †P < 0.05 for difference between groups with one exacerbation and no exacerbation; ‡For the subgroup where spirometry was measured on two occasions before and after an exacerbation, baseline = assessment 1, 3 mo = assessment 2, 6 mo = assessment 3 and 9 mo = assessment 4 (see Figure 1).
### 3.2 Change in spirometric measurements after single exacerbation

The mean age of individuals with a single exacerbation between assessments 2 and 3 was 12.7 years, and 58% were male (Table 1). Compared with the whole data set, individuals with a single exacerbation were more likely to receive LABA and LTRA treatment, to receive a higher dose of ICS and to have higher FeNO and lower %FEV₁ (Table 1). At assessment 1, FeNO data were available in 113 individuals, % predicted FEV₁ in 103 and % predicted FEV₁/FVC and % predicted FEF₂₅-₇₅ in 71. Supplemental Table S2 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 S3) on assessments 3 and 4 relative to assessment 1. Similarly, there were no differences between spirometric measurements made on assessments 3 and 4 relative to assessment 2. The results were not substantially changed when data from the study Voorend-van Bergen et al.¹⁸ were excluded from the analysis (supplemental Table S4).

### 3.3 Characteristics of participants stratified by change in % predicted FEV₁ between assessments 2 and 3

In 92 of the 113 individuals in the above analysis, %FEV₁ was determined before and after the exacerbation, i.e. assessments two and three. In unadjusted analyses, the proportions with obesity, atopy and LABA treatment differed across tertiles (Table 3). In a multivariate model, and with reference to the intermediate change in %predicted FEV₁, the group with the greatest fall were more likely to be treated with LABA (OR 6.8 [95% CI 1.1, 41.7], P = .039) and the group with the greatest rise were more likely to

### 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

<table>
<thead>
<tr>
<th>Assessment number variable</th>
<th>Mean change in %FEV₁</th>
<th>Mean change in %FEV₁/FVC</th>
<th>Mean change in %FEF₂₅-₇₅</th>
<th>% change in FeNO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall trend</td>
<td>P = .396</td>
<td>P = .445</td>
<td>P = .473</td>
<td>P = .049</td>
</tr>
<tr>
<td>Ass 2 vs 1</td>
<td>0.8 [-1.2, 3.2]</td>
<td>0.2 [-1.3, 1.7]</td>
<td>-0.5 [-4.7, 3.7]</td>
<td>10 [-7.29]</td>
</tr>
<tr>
<td>Ass 3 vs 1</td>
<td>0.3 [-2.7, 3.2]</td>
<td>-0.6 [-2.6, 1.4]</td>
<td>-1.1 [-6.8, 4.6]</td>
<td>-2 [-21, 20]</td>
</tr>
<tr>
<td>Ass 4 vs 1</td>
<td>1.9 [-1.4, 5.2]</td>
<td>0.5 [-1.9, 2.8]</td>
<td>2.4 [-4.2, 9.1]</td>
<td>21 [-5, 54]</td>
</tr>
<tr>
<td>Male sex</td>
<td></td>
<td></td>
<td></td>
<td>24 [-9, 66]</td>
</tr>
<tr>
<td>Age (y)</td>
<td></td>
<td></td>
<td></td>
<td>P = .143</td>
</tr>
<tr>
<td>Hispanic relative to other ethnic group</td>
<td>-18.7 [-24.6, -12.8]</td>
<td>-28 [-16, -39]</td>
<td>-24 [-2, 44]</td>
<td>P = .068</td>
</tr>
<tr>
<td>Obese relative to non-obese</td>
<td>-3.7 [-8.0, 0.6]</td>
<td></td>
<td></td>
<td>P = .088</td>
</tr>
<tr>
<td>Atopic relative to non-atopic</td>
<td>-9.4 [-17.8, -1.1]</td>
<td>-27 [-4, -51]</td>
<td></td>
<td>62 [26, 80]</td>
</tr>
<tr>
<td>Asthma controlled relative to uncontrolled</td>
<td>2.6 [0.1, 5.0]</td>
<td>2.5 [0.7, 4.4]</td>
<td>10 [5, 15]</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td>LABA relative to no LABA treatment</td>
<td>6.3 [-0.6, 13.1]</td>
<td>5.5 [1.1, 10.0]</td>
<td>14 [1, 26]</td>
<td>P = .029</td>
</tr>
<tr>
<td>LTRA relative to no LTRA treatment</td>
<td>-7.5 [-13.6, -1.5]</td>
<td>-5 [-19.6]</td>
<td></td>
<td>P = .291</td>
</tr>
</tbody>
</table>

Note: The numbers provided are mean difference in per cent predicted lung function or percentage change in FeNO. The values in square brackets are 95% confidence intervals. Covariates were included if P < .1 in univariate analysis, and therefore, some cells in the table are empty (see supplemental Table S2).

Abbreviations: LABA, long-acting beta-agonist; LTRA, leukotriene receptor antagonist; BUD, budesonide equivalent.
be obese (OR 3.5 [95% CI 1.0, 11.8], P = .048). These results were unchanged when the two individuals not treated with inhaled corticosteroids were removed from the analysis.

### 3.4 | Change in spirometric measurements over 12 months across exacerbation categories

Between groups, % predicted FEV₁ was higher in the no exacerbation category compared with the ≥ one exacerbation in a single 3-month category (mean difference 4.2 [95% CI 1.5, 6.9], P = .002; supplemental Table S5). In all three groups, % predicted FEV₁ did not differ between the start and the end of the 12-month period (supplemental Table S4). Although the interaction between time and exacerbation category was significant (P = .045; supplemental Table S5), this was explained by a fall in % predicted FEV₁ after 3 months in the category with exacerbations in more than one 3-month period (Figure 3).

**TABLE 3** Comparison of details across individuals stratified by fall in %FEV₁ before and after an exacerbation

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

*P < .05 for trend across three groups.
FIGURE 3 Diagram comparing %FEV₁ measured on five occasions at 3-month intervals for individuals stratified by having no, one or more than one 3-month period during which there was an exacerbation. %FEV₁ was significantly lower throughout for those with exacerbation(s) in one period compared with no exacerbations (P = .002). Within groups, there was a difference between %FEV₁ at baseline and 3 months among the category with more than one 3-month period during which there was an exacerbation (P = .040).

4 | 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 preventive medication. When we created a subgroup of children who did experience a reduction in % predicted FEV₁ within 3 months of an exacerbation, their % predicted FEV₁ had recovered to pre-exacerbation values within 6 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, 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 an exacerbation. Our study population had more severe asthma than participants in the earlier study, and our findings are therefore relevant to children with more severe asthma. O’Byrne et al reported that children randomized 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 and adults with asthma which demonstrate tracking of lung function from infancy or childhood into adulthood. Although individuals with the lowest lung function tend to have a greater burden of respiratory symptoms compared with 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 with individuals with no asthma or well-controlled asthma and there may be a linear relationship between the number of exacerbations and FEV₁ decline. Only some adults with asthma may experience an accelerated decline in lung function after an exacerbation, for example those with severe or frequent 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 adults, 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 with 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 irreversible 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 data set. For those with no exacerbations during follow-up, the mean % predicted FEV₁ at baseline was 95.17% and the standard deviation for change in %FEV₁ between baseline and 3 months was 9.87. Populations of 10, 33 and 125 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% between assessments.

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, compared with 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 in the group with a post-exacerbation fall in lung function. Our study was not designed to determine whether different triggers (or combinations of triggers) 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 2 and 3, and together with the different follow-up periods in some included RCTs, this lack of precision means that assessment 3 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 a subgroup, which was enriched with non-atopic individuals, %predicted FEV$_1$ did fall but then recover to pre-exacerbation values within months indicating a delayed but nonetheless apparently complete recovery in %predicted FEV$_1$. The children we identified as having the greatest fall in %predicted FEV$_1$ 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 FEV$_1$ 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 of follow-up with values being the highest at the fourth assessment compared with 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 that contribute to the exacerbation contribute to rising FeNO, for example inadequate ICS treatment and incomplete 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 utilizing data from studies with longer follow-up than the present study is required, ideally studies that include children with severe asthma where exacerbations are more frequent and more likely to show any impact over time.

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CONFLICTS OF INTEREST

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

AUTHOR CONTRIBUTION

Joanne Martin: Data curation (lead); Formal analysis (lead); Methodology (lead); Writing-original draft (lead); Writing-review & editing (equal). Mariëlle W Pijnenburg: Resources (equal); Writing-review & editing (equal). Graham Roberts: Resources (equal); Writing-review & editing (equal). Katy Pike: Resources (equal); Writing-review & editing (equal). Helen Petsky: Resources (equal); Writing-review & editing (equal). Anne Chang: Resources (equal); Writing-review & editing (equal). Stanley J Szeffler: Resources (equal); Writing-review & editing (equal). Peter Gerger: Resources (equal); Writing-review & editing (equal). Francoise Vermeulen: Resources (equal); Writing-review & editing (equal). Robin Vael: Resources (equal); Writing-review & editing (equal). Steve Turner: Conceptualization (lead); Data curation (lead); Formal analysis (lead); Methodology (lead); Project administration (lead); Supervision (lead); Writing-original draft (equal); Writing-review & editing (equal).

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REFERENCES


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