# Asthma Exacerbations are Associated with a decline in Lung Function: A Longitudinal Population-Based Study

Seyi Soremekun[1,2], Liam G. Heaney[3], Derek Skinner[1,2], Lakmini Bulathsinhala[1,2], Victoria Carter[1,2], Isha Chaudhry[1,2], Naeimeh Hosseini[1,2], Neva Eleangovan[1,2], Ruth Murray[1,2], Trung N. Tran[4], Benjamin Emmanuel[4], Esther Garcia Gil[5], Andrew Menzies-Gow[6], Matthew Peters[7], Njira Lugogo[8], Rupert Jones[2,9], David Price[1,2,10]

[1]Optimum Patient Care, Cambridge, UK; [2]Observational and Pragmatic Research Institute, Singapore, Singapore; [3]UK Severe Asthma Network and National Registry, Queen's University Belfast, Belfast, Northern Ireland; [4]AstraZeneca, Gaithersburg, MD, USA; [5]AstraZeneca, Barcelona, Spain; [6]UK Severe Asthma Network and National Registry, Royal Brompton & Harefield NHS Foundation Trust, London, UK; [7]Department of Thoracic Medicine, Concord Hospital, Sydney, Australia; [8]Department of Medicine, Division of Pulmonary and Critical Care Medicine, University of Michigan, Ann Arbor, MI, USA; [9]Faculty of Medicine & Dentistry, University of Plymouth, Plymouth, UK; [10]Centre of Academic Primary Care, Division of Applied Health Sciences, University of Aberdeen, Aberdeen, UK

**Corresponding author**

Professor David B. Price
Academic Primary Care
Division of Applied Health Sciences
University of Aberdeen
Polwarth Building
Foresterhill
Aberdeen AB25 2ZD
UK
E-mail: dprice@opri.sg
Tel: +65 6802 9724

**Target Journal suggestions**

*Thorax*

**Word count: 4,326 words**

# Abstract

**Rationale** Progressive lung function (LF) decline in patients with asthma contribute to worse outcomes. Asthma exacerbations are thought to contribute to this decline; however evidence is limited with mixed results.

**Methods** This historical cohort study of a broad asthma patient population in the Optimum Patient Care Research Database, examined asthma patients with 3+ eligible post-18th birthday peak expiratory flow rate (PEF) records (primary analysis), or records of forced expiratory flow in 1 second ($FEV_1$) (sensitivity analysis). Adjusted linear growth models tested the association between mean annual exacerbation rate (AER) and lung function trajectory.

**Results** We studied 109,182 patients with follow-up ranging from 5-50 years, of which 75, 280 had data for all variables included in the adjusted analyses. For each additional exacerbation an estimated additional -1.34 L/min PEF per year (95% CI -1.23, -1.50) were lost. Patients with AERs >2/year and aged 18-24 years at baseline lost an additional -5.95 L/min PEF/year (95% CI -8.63, -3.28) compared to those with AER 0. These differences in the rate of LF decline between AER groups became progressively smaller as age at baseline increased. The results using $FEV_1$ were consistent with the above.

**Conclusion** To our knowledge this study is the largest nationwide cohort of its kind and demonstrates that asthma exacerbations are associated with faster lung function decline. This was more prominent in younger patients, but was evident in older patients when it was related to lower starting lung function, suggesting a persistent deteriorating phenotype that develops in adulthood over time. Earlier intervention with appropriate management in younger asthma patients could be of value to prevent excessive lung function decline.

**KEY MESSAGES BOX (Thorax):**

**What is already known on this topic?**

Although some studies have previously assessed the link between exacerbations and accelerated lung function decline in asthma, these studies have included mostly small numbers of patients often with severe disease and/or with short follow-up times that may not adequately capture true underlying lung status. Results have been mixed, and variable between studies.

**What this study adds**

This study provides the most robust estimate of year-on-year loss of lung function with increasing exacerbation burden for the average adult patient with asthma. This association and speed of lung function decline was stronger in younger patients aged 18-39 years, persisted even in patients on higher average daily ICS doses, and was consistent for trajectories based on either PEF or $FEV_1$.

**How this study might affect research, practice or policy**

Our findings underline the need for earlier intervention (before 40 years of age) in the management of asthma, particularly in frequently exacerbating patients who are at risk of accelerated lung function decline.

# Introduction

Many asthma patients experience significant irreversible deterioration of their lung function over time,[1] which is associated with features of severe disease including persistent dyspnoea, poor quality of life (QoL), increased healthcare costs and premature death.[1,2] Childhood factors such as starting lung function and environmental factors, like cigarette smoke and lifestyle choices, can play a part in predicting lung function and the speed of decline in lung function in adulthood.[3,4] However, symptomatic asthma and particularly exacerbations severe enough to require oral corticosteroids (OCS) or resulting in hospitalisation are thought to be major, potentially modifiable causes of lung function decline over time. The causal pathways arise from the inflammatory processes underlying exacerbation episodes, which can lead to permanent structural changes in lung tissue known as airway remodelling, described extensively elsewhere.[5] Exacerbations may also contribute to other deterioration pathways including mucus hypersecretion and emphysema.[6,7]

Whilst a handful of studies have assessed the link between exacerbations and accelerated lung function decline in asthma, these studies have mostly included small numbers of patients often with severe disease and/or with short follow-up times that may not adequately capture true underlying lung status.[8–12] The results have been mixed, and even where an association was found, estimates of the additional exacerbation-associated loss in lung function were highly variable between studies.[8–12] This highlights the need for large scale, robust studies that can track the course of lung function in a representative population of patients over the long term. Such studies can indicate whether early intervention with measures that prevent exacerbations, including targeted lifestyle management and newer classes of asthma medications, may have an impact on slowing or reversing accelerated lung function decline. Crucially, lung function develops over time, increasing in children, then plateauing in adolescence and slowly declining in adulthood. The long-term impact of exacerbations during adulthood is therefore thought to be phase-dependent, with the largest impact in older patients whose lung function is in the decline phase;[8] however no study has investigated this assumption.

Using primary care electronic medical record (EMR) data is one way to answer this question given the availability of long-term clinical and therapy information for patients with chronic conditions, including lung function test results for asthma and chronic obstructive pulmonary disease (COPD) patients. In the United Kingdom the Quality Outcomes Framework (QoF), a performance-based incentive programme for general practitioners, requires annual recording of peak expiratory flow rate (PEF) in patients with asthma,[13,14] making PEF ideal for longitudinal lung function studies. The aim of our study was to test the hypothesis that exacerbation burden is associated with age-specific, long-term lung function trajectory. We used PEF data from anonymised primary care EMR data for asthma patients from 650 primary care practices covering England, Scotland, Wales, and Northern Ireland in the Optimum Patient

Care Research Database (OPCRD). There is no equivalent QoF requirement for lung function monitoring using forced expiratory volume in 1 second ($FEV_1$), which is infrequently measured in asthma patients beyond diagnostic spirometry or testing for obstruction in older patients.[15] Nonetheless, studies suggest that PEF and $FEV_1$ values are highly correlated[16,17] thus as an exploratory objective, this study additionally assessed the association of exacerbations and $FEV_1$ decline in a sensitivity analysis in patients with $FEV_1$ data available.

# Methods

### Study Design

This was an observational, historical, UK-wide cohort study of patients with active asthma, managed in primary care. The study received ethical approval from the Anonymised Data Ethics and Protocol Transparent Committee[18] (ADEPT1319) and is registered with The European Union Electronic Register of Post-Authorisation Studies (ENCEPP ID: EUPAS31386).

All patient data for this study were extracted from the UK OPCRD between June and November 2019.

### Data source

The OPCRD is one of the largest enhanced healthcare databases providing de-identified data from over 800 general practices and approximately 12 million patients in the UK. It was established in 2005, contains data from over 800 general practices and approximately 12 million patients in the UK. It was established in 2005, contains regularly inputted data from 1988 and retrospectively inputted data from 1950 and is maintained by Optimum Patient Care Ltd (OPC UK), a UK based social enterprise.[19,20] The index date (starting point) for each patient was the first eligible lung function record at, or after their 18$^{th}$ birthday, and lung function trajectories were constructed using all eligible lung function readings following this point.

Baseline variables included demographic, clinical and medication data, and were measured in the 2-year period prior to the index date unless specified otherwise (**S-Table 1).**

### Patients

Patients were required to have a QoF diagnostic Read code for asthma and ≥2 prescriptions for asthma medication, made on ≥2 separate occasions, at any point during the baseline line year or follow-up period which ran for a total of 69 years from 1950-2019. This was done not as a measure of asthma severity, but as an indicator of active disease, in line with the work of Nissen et al 2017.[21] Only those with at least 3 lung function measurements (of the same type) that covered a period of at least 5 years after age 18 were included. We focused on patients aged ≥18 years in order to assess the relationship with exacerbation burden once lungs reached close to full development; childhood-only trajectories or trajectories that traverse childhood and adulthood may not be reliably modelled with the linear statistical approach used in this analysis.

Those with COPD or other chronic respiratory conditions at baseline were excluded.

### Outcome

The primary outcome was PEF measured in litres per minute and a feasibility analysis of the correlation between PEF and $FEV_1$ measured on the same date was performed **(S-Table 2).** A supplementary analysis using percent predicted PEF based on formulas in Hankinson et al 1999[22] and using $FEV_1$ was also performed (online supplement).

*Lung function trajectory*

Lung function trajectory was assessed by measuring the slope created by multiple recordings of PEF over time. Lung function readings within 14 days of an exacerbation were dropped. Trajectories were smoothed by retaining the highest absolute values of PEF within each subsequent 1-year (yr) period (or highest $FEV_1$ in each 6-month period) starting from the index date (online supplement).

**Asthma exacerbations**

The annual exacerbation rate (AER) was assessed using all exacerbations from the start of the baseline period until the end of the follow up period. An asthma exacerbation was defined according to the ERS/ATS task force definition,[23] i.e. an asthma-related hospital attendance/admission and/or primary care consultation and/or an asthma-related A&E attendance and/or an acute OCS course of ≥3 days. Only 1 exacerbation per 14-day period was included in the calculation of AER.[11,12] The AER is presented as a continuous variable and additionally categorised into annual rates as described in the analytical methods section below.

**Age, gender, and inhaled corticosteroid usage**

The relationship between AER and lung function decline was assessed according to patient age at first lung function reading (18-24, 25-39 and 40+ years) and mean annual inhaled corticosteroid (ICS) dosage (using tercile cut points: 147.1 mcg/day and 463.7 mcg/day). To be entirely predictive of overall ICS usage throughout the follow-up period, we calculated yearly dosage of ICS based on both baseline and follow-up data and used the average of all yearly doses to categorise patients into the above terciles. All ICS dosages were converted to beclomethasone dipropionate equivalent dosages, and tercile cut-points were identified on the combined sample of all patients. An additional gender-stratified analysis was performed (adjusted for covariates excluding gender as outlined in the analytical methods section below) and included in the supplementary file.

**Sensitivity analyses**

A sensitivity analysis was performed using $FEV_1$ (absolute volume and % predicted) to investigate lung function trajectory in patients with longitudinal $FEV_1$ records fitting the same eligibility criteria (3+ readings over 5+ years of follow-up).

Two additional sensitivity analyses restricted the cohort to (i) patients with first eligible lung function reading on or after 1990 in order to coincide with the digitisation of medical records where patterns of

data input may have changed, and (ii) with first reading on or after 2005 following scale changes to UK peak flow meters.[24]

**Analytical Methods**

Baseline characteristics are presented as percentages (categorical indicators) or medians/means with interquartile range or standard deviations (continuous indicators). Linear growth models were used to assess the association of AER and lung function trajectory, achieved by estimating the interaction between AER (continuous and categorical) and time in the model, whilst also allowing for random variation in trajectories of lung function at the patient level. This method of trajectory estimation was used for ease of interpretation and for consistency with similar published studies.[8–10] Cut-offs for AER in the categorical model were 0/year, >0-1/year, >1-2/year and >2/year. Final models are adjusted for age at baseline, gender, smoking status at baseline, smoking status during follow-up, body mass index (BMI) at baseline, length of follow-up, lung function at baseline, and time-varying height (where the outcome is absolute PEF or $FEV_1$). Definitions for all covariates are provided in S-Table 1. These adjustments were made because these covariates are thought to be independently associated with lung function and may be unevenly distributed within our sample particularly by exacerbation burden. Crude (unadjusted) models for all analyses are also available in the supplementary data file. Patients with missing data (for smoking or BMI) were excluded from the adjusted analysis.

# Results

**Patient disposition and characteristics**

A total of 109,182 patients followed for a median of 10.4 years were eligible for inclusion in the PEF cohort (**Figure 1,Table 1 and S-Table 3)** and were included in the unadjusted analyses. Approximately 30% of patients did not have smoking status/BMI recorded (this proportion remained consistent across exacerbation categories), 72,604 patients with full data were included in the adjusted analyses. See **S-Figure 1** and **S-Table 4** for patient disposition and baseline characteristics, respectively, for the $FEV_1$ cohort. Patients with higher AER started with lower lung function at baseline and had more frequent asthma symptoms or severe disease at time of first recorded lung function (**Table 1 and S-Table 3)**. These patients were characterised by higher eosinophil counts, older age, higher BMI, more short-acting $\beta_2$-agonist (SABA) and OCS prescriptions and higher total dosages of ICS at baseline. There was no clear trend of smoking status or age at first asthma diagnosis in patients with higher compared to lower AERs. The overall trajectory of PEF with time in all patients was negative with a loss of -3.73L/min/year (95% CI -3.77, -3.69) of PEF or 0.27% predicted points of PEF/year (95% CI 0.25, 0.29).

**Association between annual exacerbation rate and PEF decline**

There was a significant, acceleration in PEF decline associated with every additional exacerbation per year, estimated as -0.21% predicted PEF/year (95% CI -0.25, -0.18; p<0.0001) and -1.34 L/min/year (95% CI -1.2, -1.5; p<0.001). Patients with exacerbation rates of >0-1/year, >1-2/year, and >2/year all had significant, additional yearly loss of lung function compared to those with an exacerbation rate of 0/year, whether assessed as the absolute change in PEF (**Figure 2A**) or % predicted PEF (**Figure 2B**). This ranged from an additional -0.81 L/min/year decline (95% CI -0.93, -0.70; p≤0.001) for those with AER >0-1/year to an additional -2.46 L/min/year decline (95% CI -3.06, -1.85; p≤0.001) for those with AER >2 compared to those with none (**Figure 2A**). **S-Figure 2** shows the model-predicted crude (unadjusted) association of exacerbations on (A) PEF (L) and (B) % predicted PEF, illustrating the difference between exacerbation categories in baseline lung function. Those with the highest exacerbation burden had the lowest starting percent predicted lung function (**Table 1 and S-Table 3)**. Those who smoked (either sustained smoker or mixed smoker/ex-smoker) and even sustained ex-smokers had a significantly greater PEF decline (both % predicted and absolute flow) compared to those who had never smoked (**S-Table 5**).

**Exacerbations and PEF decline by baseline age**

The association between exacerbation rate and PEF (L) decline persisted as above for patients stratified by age at baseline (**Figure 3**). The largest effect occurred in patients aged 18-24 and 25-39 years at baseline. The rate of lung function decline in patients in these age groups experiencing 2+ exacerbations/year was 3-6 times greater than the non-exacerbators; these differences were much

greater than the same group of patients with 2+ exacerbations/year versus none aged ≥40 years (**Figure 3).** Unadjusted results (**S-Figure 3**) further indicate that baseline lung function was lower in patients with higher AERs, but only in older patient groups (aged ≥25 years). A similar pattern of accelerated decline with increasing AER was observed for % predicted PEF, stratified by age at baseline (adjusted: **S-Figure 4**; unadjusted: **S-Figure 5**).

**Exacerbations and PEF decline by yearly average ICS dosage**

The association between exacerbation rate and PEF (L) decline persisted as above for patients stratified by mean yearly ICS dose (**Figure 4**). Higher average ICS dose/year was associated with declining PEF trajectories, irrespective of AER. Higher AER consistently resulted in a faster decline in PEF trajectory in patients in the medium and highest mean yearly ICS dosage terciles. Small numbers of patients with AER >2 in the lowest ICS dosage group resulted in large errors around the point estimates of lung function decline; these patients did not experience a significantly accelerated decline compared to those with an exacerbation rate of 0/year (**Figure 4**). Unadjusted results are provided in **S-Figure 6**. A similar pattern of accelerated decline with increasing AER was observed for % predicted PEF stratified by mean annual ICS dose (adjusted: **S-Figure 7**; unadjusted: **S-Figure 8**).

**Exacerbations and lung function decline in males and females**

Male and female-specific trajectories for both PEF and $FEV_1$ are included in the supplementary file (**S-Tables 6 and 7**). Lung function decline measured by PEF tended to be faster in females compared to males, irrespective of exacerbation category. However, the impact of exacerbations on lung function trajectories was more marked in men (males: >2 AER versus 0 AER/year: -3.35 L/min/year (95% CI -4.59, -2.11); females: >2 AER vs 0 AER: -1.62 L/min/year (95% CI -2.25, -0.99); **S-Table 6**). $FEV_1$-measured decline in lung function did not demonstrate this trend, and the majority of the between exacerbation group comparisons were not significant (**S-Table 7**).

**Sensitivity analysis with $FEV_1$**

There were 10,943 patients in the $FEV_1$ cohort (**S-Figure 1**) followed for a median of 8.1 years (**S-Table 4**) who were included in the unadjusted analyses, and 8172 with data on all covariates included in the adjusted analysis. Compared to the PEF cohort, patients in the $FEV_1$ cohort were older at baseline with shorter follow-up times, were more likely to be diagnosed with asthma as older adults, have a higher prevalence of COPD diagnosed later in follow-up, and were in generally poorer health as assessed by a number of metrics (**S-Table 4**). Being older on average and with shorter follow-up, the $FEV_1$ cohort had already experienced significant decline by the index date in contrast to the PEF cohort. The association between AER and $FEV_1$ trajectories showed the same overall pattern of accelerated decline in patients with higher AERs (**S-Figure 9**). As with PEF, the overall $FEV_1$ trajectory decreased over time:

25.5mL/year (95% CI -26.3, -24.6) and -0.13%/year (95% CI -17.0, 10.4) for $FEV_1$ volume and percent predicted, respectively. Unadjusted results are shown in **S-Figure 10**.

Because of low patient numbers, patients aged 18-39 years were combined into a single stratum; the association between exacerbations and $FEV_1$ (L) decline was greatest for patients in this age group (**S-Figure 11**). Patients with AER >2 lost an additional -39.3mL $FEV_1$ per year compared to patients with no exacerbations (95% CI -65.2, -13.4; p = 0.008). In patients aged ≥40 years there was no significant association of AER on the lung function trajectories. Results were similar for % predicted $FEV_1$ (**S-Figure 12**). Because of low numbers, patients in the lowest two terciles for ICS dosage/year were combined into a single stratum (terciles 1+2). The relationship between exacerbations and $FEV_1$ (L) decline persisted in patients in the highest tercile of ICS dosage/year (**S-Figure 13**). Patients with exacerbation rate >2/year lost an additional 7.9 mL/year $FEV_1$ compared to patients with no exacerbations (95% CI -16.1, 0.2; p = 0.056). Results were similar for % predicted $FEV_1$ (**S-Figure 14**).

**Sensitivity analyses of sub-sample cohorts with post-age 18 years lung function records starting post-1990 and post 2004**

There were 108, 958 patients with their first post-age 18 years PEF reading on or after 1 January 1990 (unadjusted cohort) and 72,576 in the adjusted cohort. This represented a loss of 0.2% of patients from the full 1950-2019 cohort. Post-1990 PEF trajectories and the relationship with exacerbations were practically identical to the results of the full cohort (**S-Table 8**). The post-1990 $FEV_1$ trajectories (representing 99.95% of patients from the full 1950-2019 cohort) were identical to the results of the full cohort (**S-Table 9**).

To account for change in PEF measurement practices in 2004, an additional sensitivity analysis of the PEF cohort was performed on a sub-sample of 37,029 (unadjusted) and 26, 873 (adjusted) patients with first lung function reading on or after 1 January 2005 (**S-Table 8**). Follow-up in this group was markedly shorter than in the full cohort (median 7.6 years IQR 6.1-9.6). However, the association between exacerbations and lung function decline was, again, similar to the full 1950-2019 cohort, although the additional loss of lung function in patients experiencing more exacerbations versus none was slightly attenuated (>2 AER vs 0 AER: -1.929 L/year (-3.29, -0.57) p =0.0054; **S-Table 8**).

# Discussion

To our knowledge, this is the first study to show, in a broad asthma cohort including over 100,000 patients across the UK tracked for 5 to 60 years, that more frequent exacerbations are associated with long-term lung function decline. Our study provides the most robust estimate of year-on-year loss of lung function with increasing exacerbation burden for the average adult patient with asthma. We observed that the greater the AER, the lower the starting lung function and the more negative the trajectory over time. After adjustment for key confounders including starting lung function, this association persisted and was stronger in younger patients aged 18-39 years than in patients aged 40+ years, which was consistent for trajectories based on either PEF or $FEV_1$. This finding underlines the need for a review of the management of patients at risk of accelerated decline before reaching 40 years of age; patients with fastest decline tended to already be on the highest Global Initiative for Asthma (GINA) therapies (ie, GINA 3+), suggesting that many may be less responsive to ICS or to OCS, the long-term use of which are associated with significant negative side effects in asthma and COPD.[25,26] Such patients would benefit from earlier intervention/review of therapy and lifestyle to consider alternatives. Our study also demonstrates the potential value of using PEF to compare long-term lung function trajectories in groups of patients with asthma, in contrast to previous studies of exacerbations and lung function decline that use $FEV_1$.[8–10,12] The barriers to the availability of frequent, long-term recording of $FEV_1$ in routinely collected primary care data make the potential for longitudinal studies using PEF more attractive and feasible.

The relationship between accelerated lung function decline and exacerbations of COPD has been studied extensively and demonstrated reliably, in relatively large populations.[27–30] However, evidence of this relationship in asthma prior to this study have been less conclusive. Six published studies have used $FEV_1$ to assess lung function and exacerbations mostly in very severe or difficult-to-treat patients and showed considerable variation in association.[2,8–12] Nonetheless, even in this small evidence base a general trend of greater decline with increasing exacerbation burden was more commonly than not observed, with declines of between 25 and 50mL $FEV_1$ per year in exacerbating patients. Two of these previous studies made the reasonable case that use of ICS may diminish the association of exacerbations on decline, and therefore focused on ICS-naïve patients.[8,11] As a result, these studies tended to show some of the larger effect sizes seen across the previous literature on this subject; one reporting excess loss of 30.2mL $FEV_1$ per year in 93 ICS-naïve patients,[8] and the other an additional loss of 1.34% predicted $FEV_1$ per year in 3368 ICS-naïve patients.[11] This second study found no difference in decline in patients on ICS. Such studies are ethically impossible to reproduce prospectively, and difficult to reproduce in observational cohorts as large numbers of long-term ICS-naïve yet frequently exacerbating patients do not naturally occur. Results from our heterogenous asthma population may be more applicable to primary care as we observed that fastest decliners were usually

already on the highest dosages of ICS medication, suggesting that increasing dosage of ICS and other medications because of disease severity does not entirely protect some patients from the associated faster decline in lung function with exacerbations, or from faster lung function decline in general.

The value of our study within the context of this background literature is in the evaluation of a very large and heterogenous asthma cohort, with long-term follow-up, and a focus on trajectories stratified by patient age. The Bai et al 2007 study of 93 patients with asthma all aged <40 years speculated that the greatest association of exacerbation rate and lung function may be seen in older patients whose lung function would be in the decline phase.[8] Our study demonstrates that, in fact, the opposite is true; lung function declines more quickly in younger adults compared to older patients who have had the same number of exacerbations. The corollary is that in the under 18 age group, patients with exacerbations should show an even greater decline in lung function. This has not been extensively investigated, but recent studies suggest that function deteriorates more rapidly in children who have exacerbations[31,32] and may be attenuated by preventative asthma medication.[32] Others have found that childhood impairment of lung function and male sex were the most significant predictors of both abnormal longitudinal patterns of lung function growth and of decline.[33] Comparative studies of lung function decline with exacerbations in childhood and adulthood could shed further light on the life course impacts of exacerbations.

In adults, we observed that asthma patients aged 18-39 years at baseline who have exacerbations experience an additional loss of PEF that is 10-120 additional litres/minute in absolute terms or 2.25% expressed as change in precent predicted PEF over 20 years compared to patients with no exacerbations over the same period. Contrasted with this are patients aged ≥40 years at baseline who experienced a mean total loss of up to 20 litres/min of PEF (or 7 percentage points of predicted PEF) over 20 years. The results in our $FEV_1$ sensitivity cohort were consistent with this. A meta-analysis of 27 trials estimated that each 10% drop in predicted $FEV_1$ is associated with an approximate 2-point drop in patient QoL using the Asthma Quality of Life questionnaire (AQLQ)[34]; this is 4 times the minimal clinical difference for the AQLQ.[35] The difference in percent predicted PEF and $FEV_1$ in frequent exacerbators versus those without exacerbations in younger exacerbating patients in our study was more than 8 times the minimal clinical difference for QoL after 20 years, highlighting the real-life implications of accelerated lung function deterioration in this group.

Faced with these findings, potential key questions for clinicians managing patients with asthma in primary care are: when to intervene to minimise the potential long-term negative impact of exacerbations on lung function; what early intervention should look like; and in which patients. Whilst we allow that further studies are required, to fully quantify the causal relationship between exacerbations and decline if any, many healthcare professionals will find it encouraging that the majority of patients

with asthma in this study experienced little to no acceleration in lung function decline. We estimated that the overall rate of decline in non-exacerbating patients was 2.93 L/year PEF or 20.2mL/year $FEV_1$ (irrespective of age or ICS dosage) making this group comparable with patients without asthma who are estimated to experience an average decline of 22.4mL $FEV_1$/year, as reported in a recent meta-analysis of 16 cohort studies of more than 30,000 patients with no known chronic respiratory disease.[36] In patients who do exacerbate, however, our study highlights the potential value of addressing exacerbation burden when patients are still in the growth and plateau phases of lung trajectory before 40 years of age. Our unadjusted results suggest that younger patients often start with similar lung function, irrespective of exacerbation burden at baseline, whilst patients who were older at the time of their first lung function reading and who had higher exacerbation burdens had relatively poorer baseline lung function. This indicates that at the population level an earlier adult-period history of exacerbations and other factors play a big part in decline, above childhood factors. Our findings thus strongly suggest that the group who are likely to experience the greatest gain from earlier intervention for long-term benefit are those aged below 40 years. This may include a more pro-active approach to lifestyle changes and trigger avoidance, as well as a review of ICS-based therapy or consideration of newer classes of biologic therapy.[37–41] Currently anti–IL-5, anti–IL-14/13 and anti-IgE biologic medications are only indicated for subgroups of patients with severe asthma,[41] who are often in later life. Patients with frequent exacerbations may benefit from earlier targeted therapy. To our knowledge there are, as yet, no longitudinal studies of exacerbations and lung function trajectory in patients on biologic medications.

This large-scale study covering all four countries of the United Kingdom, provides insights into lung function decline in patients with asthma followed for up to 60 years within the period 1950-2019. Our findings are robust, not simply due to the large sample size, but also due to the inclusion of a broad UK-wide group of adult patients with asthma, which is likely more generalizable to the general population than previous studies.[2,8–12] Additionally, our long follow up time spanning 69 years of recording (one of the longest maximum follow-up periods of any of the previous studies discussed), enabled us to quantify the long-term association between exacerbations and lung function in sufficient numbers of patients, even in sub-group analyses. Notably, this allowed for rate of decline comparisons in younger, middle and older aged adults with good levels of certainty (including >10,000 patients/age group) highlighting the possible effect of age on this relationship. We have controlled for variation in individual patient trajectories and other key factors that may independently impact lung function, including baseline lung function which may be viewed as a proxy for severity and for earlier life factors which were not directly measured in this study.

Our study intended to estimate the long-term association of exacerbations and lung function trajectory in a disease characterised by short-term variability in lung function; therefore, we did not include patients

with short term trajectories (<5 years of lung function data) that may impact the representativeness of our results. However, we argue that inclusion of such patients would not keep within the aim of our study to assess long-term association between exacerbation burden and lung function. We included patients with eligible data from as early as 1950. Whilst digitisation of medical records was not introduced until the early 1990s, OPCRD, the Clinical Practice Datalink (CPRD) and other primary care databases store electronic records of patient outcomes from prior to this era due to the retrospective digitisation of paper-based patient records by many practices.[42] Such records use Read Codes later selected for QoF monitoring. Importantly this enabled us to include a sub-sample of patients with longer-term trajectories (>20 years) including two patients born in the early 1920s with first PEF readings dated in 1950 and 1956. Commercial peak flow meters were not widely available until the early 1960s however earlier models were in general usage,[43] and so we saw no reason to exclude older patients such as these, with otherwise excellent data (who represented 0.002% of the dataset). Nonetheless, our sensitivity analyses excluding patients with readings prior to 1990 or prior to 2005 (to coincide with scale changes in UK PEF meters) had small to negligible impacts on point estimates (which in the case of the 2004 cohort are likely to be partially due to the shorter follow-up times) and no impact on the overall inferences.

Whilst our study demonstrated a clear link between exacerbations and lung function decline, we highlight the need for studies to fully quantify the chronology of this relationship and assess causality. This could be achieved either with causal modelling approaches which would include the inputs of a range of additional potential confounders that could impact the results over the course of follow-up and/or interventional studies of treatments which target exacerbations and track lung function over time.

We restricted the cohorts to adult lung function to focus on the relationship between exacerbations and decline once lungs reach their development peak and begin the natural decline phase. This results in a tendency towards later median age at onset of asthma, as childhood asthma may well resolve or attenuate before adulthood. Lung function trajectories that traverse childhood and adulthood are not linear and therefore require different modelling approaches to the linear models used in this paper. However, previous studies have highlighted the importance of childhood factors, including childhood exacerbations, smoking, and childhood asthma diagnosis amongst others;[31,44,45] undoubtedly lung capacity by early adulthood will be influenced by these factors. Whilst we have not included childhood risk factors, we have allowed for varying starting adult lung function and the impact of this on subsequent adult lung function trajectory. Nonetheless, the specific association (if any) of exacerbations and lung function in children is an area of great importance that warrants further investigation. Although patients with missing data for smoking or BMI were excluded from the adjusted analyses, the amount of missing data was typical of routinely collected primary care record data in the UK (especially data with such a long look-back as that presented in the current study) and less than previously published.[46,47] We also excluded patients with a COPD diagnosis at baseline.[8] However, it is possible that some older

patients will have had either undiagnosed or unrecorded but diagnosed COPD at the start of their lung function recording period. Patients who already had significant obstruction at baseline may not be as sensitive to further changes in AER, and therefore the estimated effect sizes in the overall cohort may be underestimated. Finally, although EMR data are prone to misclassification (eg, lack of information on pre- or post-bronchodilator status of lung function tests, lack of location data, and potential underreporting of exacerbations), these issues are most likely to cumulatively bias the results towards the null. However, after applying noise-reduction techniques and adjustment for known confounders, we still observed highly significant associations, suggesting not only the advantages of sample size and duration of this dataset, but also the strength of the relationship between exacerbations and lung function. Overall, this highlights the value of the use of routine data for large-scale, long-term analyses of this type.

In conclusion, we have demonstrated the association between exacerbations and lung function decline, after adjusting for, and stratifying by, possible alternative causes of decline that might confound the relationship including starting lung function, BMI, gender, smoking status and other key variables. We do this whilst addressing key evidence gaps in sample size, patient representativeness, duration of follow-up and analysis methodology. Future analyses that further explore these associations under a causal framework and within other key subgroups of gender, ethnicity, location, and other lifestyle factors will be highly valuable to address remaining evidence gaps. A key new finding is that the greatest association of exacerbations is found in younger patients with lung function in the plateau or start of decline phase, and that whilst the association is much more modest in older patients, many have also already experienced significant decline in lung function, particularly those with higher exacerbation burdens. This finding has important implications for earlier therapeutic intervention in frequently exacerbating patients prior to middle age before permanent deterioration in lung function has occurred.

**Acknowledgements**

The authors thank the UK primary care sites that contributed anonymised patient data to this study; Drs Jaco Voorham and Marjan Kerkhof for their contributions to the preparation and analysis of the data; and Audrey Ang and Andrea Teh Xin Yi for coordinating logistical and administrative support for the development of this manuscript. We also thank our Thorax peer reviewers for their in-depth comments and suggestions which greatly improved the quality of this article.

**Funding**

This study was conducted by the Observational and Pragmatic Research Institute (OPRI) Pte Ltd and was partially funded by Optimum Patient Care Global and AstraZeneca Ltd. No funding was received by the Observational & Pragmatic Research Institute Pte Ltd (OPRI) for its contribution.

**Contributors**

SS, DP, LH and TT conceived the study analysis which was developed with input from all authors from inception. Data preparation and analysis was performed by SS and DS. SS and RM produced the first draft of the manuscript to which all authors contributed. The final version of the manuscript has been fully reviewed and approved by all authors.

**Patient consent for publication**

Not required.

**Ethics Approval**

The study received ethical approval from the Anonymised Data Ethics and Protocol Transparent Committee (ADEPT1319) and is registered with The European Union Electronic Register of Post-Authorisation Studies (ENCEPP ID: EUPAS31386).

**Data availability statement**

The dataset supporting the conclusions of this article was derived from the Optimum Patient Care Research Database (www.opcrd.co.uk). The OPCRD has ethical approval from the National Health Service (NHS) Research Authority to hold and process anonymised research data (Research Ethics Committee reference: 15/EM/0150). This study was approved by the Anonymised Data Ethics Protocols and Transparency (ADEPT) committee – the independent scientific advisory committee for the OPCRD. The authors do not have permission to give public access to the study dataset; researchers may request access to OPCRD data for their own purposes. Access to OCPRD can be made via the OCPRD website (https://opcrd.co.uk/our-database/data-requests/) or via the enquiries email info@opcrd.co.uk.

**Competing Interests**

At the time this research was conducted:

**Derek Skinner**, **Victoria Carter**, and **Neva Eleangovan** are employees of Optimum Patient Care, and **Seyi Soremekun**, **Lakmini Bulathsinhala**, **Isha Chaudhry**, and **Naeimeh Hosseini** were employees of Optimum Patient Care. Optimum Patient Care is a co-funder of the International Severe Asthma Registry.

**Liam G. Heaney** declares he has received grant funding, participated in advisory boards and given lectures at meetings supported by Amgen, AstraZeneca, Boehringer Ingelheim, Circassia, Hoffmann la Roche, GlaxoSmithKline, Novartis, and Teva; he has taken part in asthma clinical trials sponsored by Boehringer Ingelheim, Hoffmann la Roche, and GlaxoSmithKline for which his institution received remuneration; he is the Academic Lead for the Medical Research Council Stratified Medicine UK Consortium in Severe Asthma which involves industrial partnerships with a number of pharmaceutical companies including Amgen, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Hoffmann la Roche, and Janssen.

**Ruth Murray** declares no conflict of interest.

**Trung N. Tran** and **Benjamin Emmanuel** are employees of AstraZeneca, and **Esther Garcia Gil** was an employee of AstraZeneca. AstraZeneca is a co-funder of the International Severe Asthma Registry.

**Andrew Menzies-Gow** has attended advisory boards for AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Sanofi and Teva, and has received speaker fees from AstraZeneca, Boehringer Ingelheim, Novartis, Roche, Teva and Vectura. He has participated in research with AstraZeneca for which his institution has been remunerated and has attended international conferences with Teva. He has had consultancy agreements with AstraZeneca, Sanofi, and Vectura.

**Matthew Peters** declares personal fees and non-financial support from AstraZeneca and GlaxoSmithKline.

**Njira Lugogo** consulted for AstraZeneca and GSK; served on protocol committee with AstraZeneca; and served on advisory board with AstraZeneca, GSK, Sanofi, Novartis, Genentech and Teva.

**Rupert Jones** reports grants, personal fees, and non-financial support from AstraZeneca and OPRI, personal fees and non-financial support from Boehringer Ingelheim, grants, personal fees, and non-financial support from GSK, grants and non-financial support from Novartis, non-financial support from Nutricia, and personal fees from Pfizer outside the submitted work.

**David Price** has advisory board membership with Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Circassia, Mylan, Mundipharma, Novartis, Regeneron Pharmaceuticals, Sanofi Genzyme, Teva Pharmaceuticals, Thermofisher; consultancy agreements with Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Mylan, Mundipharma, Novartis, Pfizer, Teva Pharmaceuticals, Theravance; grants and unrestricted funding for investigator-initiated studies (conducted through Observational and Pragmatic Research Institute Pte Ltd) from AstraZeneca, Boehringer Ingelheim,

549 Chiesi, Circassia, Mylan, Mundipharma, Novartis, Pfizer, Regeneron Pharmaceuticals, Respiratory
550 Effectiveness Group, Sanofi Genzyme, Teva Pharmaceuticals, Theravance, UK National Health Service;
551 payment for lectures/speaking engagements from AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla,
552 GlaxoSmithKline, Kyorin, Mylan, Mundipharma, Novartis, Regeneron Pharmaceuticals, Sanofi Genzyme,
553 Teva Pharmaceuticals; payment for the development of educational materials from Mundipharma,
554 Novartis; payment for travel/accommodation/meeting expenses from AstraZeneca, Boehringer
555 Ingelheim, Mundipharma, Mylan, Novartis, Thermofisher; funding for patient enrolment or completion of
556 research from Novartis; stock/stock options from AKL Research and Development Ltd which produces
557 phytopharmaceuticals; owns 74% of the social enterprise Optimum Patient Care Ltd (Australia and UK)
558 and 74% of Observational and Pragmatic Research Institute Pte Ltd (Singapore); 5% shareholding in
559 Timestamp which develops adherence monitoring technology; is peer reviewer for grant committees of
560 the Efficacy and Mechanism Evaluation programme, and Health Technology Assessment; and was an
561 expert witness for GlaxoSmithKline.

## References


1 Sears MR. Lung function decline in asthma. *Eur Respir J* 2007;**30**:411–3. doi:10.1183/09031936.00080007

2 Calhoun WJ, Haselkorn T, Miller DP, *et al.* Asthma exacerbations and lung function in patients with severe or difficult-to-treat asthma. *J Allergy Clin Immunol* 2015;**136**:1125-1127.e4. doi:10.1016/j.jaci.2015.05.014

3 Bui DS, Lodge CJ, Burgess JA, *et al.* Childhood predictors of lung function trajectories and future COPD risk: a prospective cohort study from the first to the sixth decade of life. *Lancet Respir Med* 2018;**6**:535–44. doi:10.1016/S2213-2600(18)30100-0

4 Arshad SH, Hodgekiss C, Holloway JW, *et al.* Association of asthma and smoking with lung function impairment in adolescence and early adulthood: the Isle of Wight Birth Cohort Study. *Eur Respir J* 2020;**55**. doi:10.1183/13993003.00477-2019

5 Bai TR, Knight DA. Structural changes in the airways in asthma: observations and consequences. *Clin Sci (Lond)* 2005;**108**:463–77. doi:10.1042/CS20040342

6 Vonk JM, Jongepier H, Panhuysen CIM, *et al.* Risk factors associated with the presence of irreversible airflow limitation and reduced transfer coefficient in patients with asthma after 26 years of follow up. *Thorax* 2003;**58**:322–7. doi:10.1136/thorax.58.4.322

7 Shen Y, Huang S, Kang J, *et al.* Management of airway mucus hypersecretion in chronic airway inflammatory disease: Chinese expert consensus (English edition). *Int J Chron Obstruct Pulmon Dis* 2018;**13**:399–407. doi:10.2147/COPD.S144312

8 Bai TR, Vonk JM, Postma DS, *et al.* Severe exacerbations predict excess lung function decline in asthma. *Eur Respir J* 2007;**30**:452–6. doi:10.1183/09031936.00165106

9 Coumou H, Westerhof GA, de Nijs SB, *et al.* Predictors of accelerated decline in lung function in adult-onset asthma. *Eur Respir J* 2018;**51**. doi:10.1183/13993003.01785-2017

10 Newby C, Agbetile J, Hargadon B, *et al.* Lung function decline and variable airway inflammatory pattern: longitudinal analysis of severe asthma. *J Allergy Clin Immunol* 2014;**134**:287–94. doi:10.1016/j.jaci.2014.04.005

11 O'Byrne PM, Pedersen S, Lamm CJ, *et al.* Severe exacerbations and decline in lung function in asthma. *Am J Respir Crit Care Med* 2009;**179**:19–24. doi:10.1164/rccm.200807-1126OC

12 Ortega H, Yancey SW, Keene ON, *et al.* Asthma Exacerbations Associated with Lung Function Decline in Patients with Severe Eosinophilic Asthma. *J Allergy Clin Immunol Pract* 2018;**6**:980-986.e1. doi:10.1016/j.jaip.2017.12.019

13 NHS England 2019/20 General Medical Services (GMS) contract Quality and Outcomes Framework (QOF). Guidance for GMS contract 2019/20 in England. Published Online First: April 2019.https://www.england.nhs.uk/wp-content/uploads/2019/05/gms-contract-qof-guidance-april-2019.pdf

14 Quality and Outcomes Framework (QOF) business rule v39 2018-2019 baseline release. https://digital.nhs.uk/data-and-information/data-collections-and-data-sets/data-collections/quality-and-outcomes-framework-qof/quality-and-outcome-framework-qof-business-rules/quality-and-outcomes-framework-qof-business-rule-v39-2018-2019-baseline-release

15 Chronic obstructive pulmonary disease in over 16s: diagnosis and managment. *National Institute for Health and Care Excellence*;:2019.

16 Halpin DMG, Meltzer EO, Pisternick-Ruf W, *et al.* Peak expiratory flow as an endpoint for clinical trials in asthma: a comparison with FEV(1). *Respir Res* 2019;**20**:159. doi:10.1186/s12931-019-1119-6

17 Gautrin D, D'Aquino LC, Gagnon G, *et al.* Comparison between peak expiratory flow rates (PEFR) and FEV1 in the monitoring of asthmatic subjects at an outpatient clinic. *Chest* 1994;**106**:1419–26. doi:10.1378/chest.106.5.1419

18 ADEPT Committee. REG - Respiratory Effectiveness Group. https://www.regresearchnetwork.org/adept-committee/

19 NHS HRA. Optimum Patient Care Research Database Approval. /planning-and-improving-research/application-summaries/research-summaries/optimum-patient-care-research-database/

20 Optimum Patient Care Research Database. https://opcrd.co.uk/

21 Nissen F, Morales DR, Mullerova H, *et al.* Validation of asthma recording in the Clinical Practice Research Datalink (CPRD). *BMJ Open* 2017;**7**:e017474. doi:10.1136/bmjopen-2017-017474

22 Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med* 1999;**159**:179–87. doi:10.1164/ajrccm.159.1.9712108

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. *Am J Respir Crit Care Med* 2009;**180**:59–99. doi:10.1164/rccm.200801-060ST

24 Miller M. Peak expiratory flow meter scale changes: implications for patients and health care professionals. *The Airways Journal* 2004;**2**:80–2.

25 Falk JA, Minai OA, Mosenifar Z. Inhaled and systemic corticosteroids in chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2008;**5**:506–12. doi:10.1513/pats.200707-096ET

26 Volmer T, Effenberger T, Trautner C, *et al.* Consequences of long-term oral corticosteroid therapy and its side-effects in severe asthma in adults: a focused review of the impact data in the literature. *Eur Respir J* 2018;**52**. doi:10.1183/13993003.00703-2018

27 Halpin DMG, Decramer M, Celli BR, *et al.* Effect of a single exacerbation on decline in lung function in COPD. *Respir Med* 2017;**128**:85–91. doi:10.1016/j.rmed.2017.04.013

28 Dransfield MT, Kunisaki KM, Strand MJ, *et al.* Acute Exacerbations and Lung Function Loss in Smokers with and without Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2017;**195**:324–30. doi:10.1164/rccm.201605-1014OC

29 Kerkhof M, Voorham J, Dorinsky P, *et al.* Association between COPD exacerbations and lung function decline during maintenance therapy. *Thorax* 2020;**75**:744–53. doi:10.1136/thoraxjnl-2019-214457

30 Donaldson GC, Seemungal TAR, Bhowmik A, *et al.* Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. *Thorax* 2002;**57**:847–52. doi:10.1136/thorax.57.10.847

31 Belgrave DCM, Buchan I, Bishop C, *et al.* Trajectories of lung function during childhood. *Am J Respir Crit Care Med* 2014;**189**:1101–9. doi:10.1164/rccm.201309-1700OC

32 Martin J, Pijnenburg MW, Roberts G, *et al.* Does lung function change in the months after an asthma exacerbation in children? *Pediatr Allergy Immunol* Published Online First: 15 March 2021. doi:10.1111/pai.13503

33 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**:1842–52. doi:10.1056/NEJMoa1513737

34 Carranza Rosenzweig JR, Edwards L, Lincourt W, *et al.* The relationship between health-related quality of life, lung function and daily symptoms in patients with persistent asthma. *Respir Med* 2004;**98**:1157–65. doi:10.1016/j.rmed.2004.04.001

35 Juniper EF. Asthma Quality of Life Questionnaire (AQLQ). https://www.thoracic.org/members/assemblies/assemblies/srn/questionaires/aqlq.php

36 Thomas ET, Guppy M, Straus SE, *et al.* Rate of normal lung function decline in ageing adults: a systematic review of prospective cohort studies. *BMJ Open* 2019;**9**:e028150. doi:10.1136/bmjopen-2018-028150

37 Liu Y, Zhang S, Li D, *et al.* Efficacy of anti-interleukin-5 therapy with mepolizumab in patients with asthma: a meta-analysis of randomized placebo-controlled trials. *PLoS ONE* 2013;**8**:e59872. doi:10.1371/journal.pone.0059872

38 Noonan M, Korenblat P, Mosesova S, *et al.* Dose-ranging study of lebrikizumab in asthmatic patients not receiving inhaled steroids. *Journal of Allergy and Clinical Immunology* 2013;**132**:567-574.e12. doi:10.1016/j.jaci.2013.03.051

39 Korenblat P, Kerwin E, Leshchenko I, *et al.* Efficacy and safety of lebrikizumab in adult patients with mild-to-moderate asthma not receiving inhaled corticosteroids. *Respir Med* 2018;**134**:143–9. doi:10.1016/j.rmed.2017.12.006

40 McGregor MC, Krings JG, Nair P, *et al.* Role of Biologics in Asthma. *Am J Respir Crit Care Med* 2019;**199**:433–45. doi:10.1164/rccm.201810-1944CI

41 Busse WW. Biological treatments for severe asthma: A major advance in asthma care. *Allergol Int* 2019;**68**:158–66. doi:10.1016/j.alit.2019.01.004

42 Information sheet for use of CPRD services to support studies funded by NIHR data-enabled trials grant. *Medicines & Healthcare Products Regulatory Agency*http://www.CPRD.com

43 WRIGHT BM, McKERROW CB. Maximum forced expiratory flow rate as a measure of ventilatory capacity: with a description of a new portable instrument for measuring it. *Br Med J* 1959;**2**:1041–6. doi:10.1136/bmj.2.5159.1041

44 Covar RA, Spahn JD, Murphy JR, *et al.* Progression of asthma measured by lung function in the childhood asthma management program. *Am J Respir Crit Care Med* 2004;**170**:234–41. doi:10.1164/rccm.200308-1174OC

45 Apostol GG, Jacobs DRJ, Tsai AW, *et al.* Early life factors contribute to the decrease in lung function between ages 18 and 40: the Coronary Artery Risk Development in Young Adults study. *Am J Respir Crit Care Med* 2002;**166**:166–72. doi:10.1164/rccm.2007035

46 Price D, Kemp L, Sims E, *et al.* Observational study comparing intranasal mometasone furoate with oral antihistamines for rhinitis and asthma. *Prim Care Respir J* 2010;**19**:266–73. doi:10.4104/pcrj.2010.00040

47 Ryan D, Heatley H, Heaney LG, *et al.* Potential severe asthma hidden in UK primary care. *J Allergy Clin Immunol Pract* 2021;**9**:1612–23. doi:10.1016/j.jaip.2020.11.053

48 Global Strategy for Asthma Prevention and Treatment. 2018 update. 2018.https://ginasthma.org/wp-content/uploads/2018/04/wms-GINA-2018-report-V1.3-002.pdf.

**Tables and Figures – Exacerbations and Lung Function Decline in Broad Asthma patient population**

**Table 1** Characteristics of 109,182 patients in the PEF cohort – overall and by annual exacerbation rate (AER)

| Patient characteristics | **Overall (n=109,182)** | **AER 0/yr (n=44,107)** | **AER >0-1/yr (N=60,927)** | **AER >1-2/yr (N=3,236)** | **AER >2/yr (N=912)** |
|---|---|---|---|---|---|
| ***Baseline lung function*** | | | | | |
| Median years of follow-up (IQR) | 10.4 (7.5 – 14.1) | 9.3 (6.9-12.8) | 11.2 (8.1-15.1) | 10.9 (7.9-14.7) | 10.6 (7.7-14.1) |
| Mean baseline % predicted PEF (SD) | 94.8 (18.6) | 95.7 (17.7) | 94.5 (19.0) | 90.9 (21.1) | 87.1 (21.2) |
| ***Vital statistics*** | | | | | |
| Median age at baseline (IQR) | 42 (30-55) | 39 (28-53) | 43 (32-57) | 50 (37-61) | 47 (37-60) |
| Male, N (%) | 44697 (40.9) | 20791 (47.1) | 22577 (37.1) | 1007 (31.1) | 322 (35.3) |
| Median eosinophil count at baseline cells/mm3 (IQR)[a] | 225 (148-350) | 213 (140-335) | 230 (150-350) | 250 (156-400) | 287 (180-433) |
| ***Asthma status at baseline*** | | | | | |
| Median age of onset of asthma (IQR) | 35 (18-51) | 32 (16-48) | 37 (21-53) | 42 (25-56) | 39 (22-53) |
| Median years with asthma prior to index date (IQR)[b] | 4.5 (0.1-14.2) | 5.1 (0.1-14.7) | 4.0 (0.1-13.7) | 5.6 (0.6-15.7) | 7.1 (0.9-18.4) |
| Median number of exacerbations at baseline (IQR) | 0.2 (0.6) | 0.00 (0-0) | 0.0 (0-0) | 0.0 (0-1) | 1.0 (0-3) |
| Non-smoker, n (%) | 38287 (35.1) | 16637 (37.7) | 20388 (33.5) | 983 (30.4) | 279 (30.6) |
| Ex-smoker, n (%) | 20120 (18.4) | 7865 (17.8) | 11436 (18.8) | 637 (19.7) | 20.0 (182) |
| Current smoker, n (%) | 16873 (15.5) | 6381 (14.5) | 9818 (16.1) | 524 (16.2) | 150 (16.5) |
| Smoking status not recorded, n (%) | 33902 (31.1) | 13224 (30.0) | 19285 (31.7) | 1092 (33.8) | 301 (33.0) |
| Median SABA prescriptions in baseline year (IQR) | 2 (1-4) | 2 (1-4) | 2 (1-5) | 3 (2-7) | 5 (2-9) |
| Median ICS dosage/day over follow-up in mcg (IQR) | 260.5 (91.8-556.96) | 161.8 (48.6379.7) | 322.7 (133.7-633.5) | 783.5 (446.4-1241.9) | 1054.7 (599.6-1586.8) |

| | | | | | |
|---|---|---|---|---|---|
| Median OCS prescriptions/year over follow-up (IQR) | 0.3 (0.1-0.6) | 0.1 (0.1-0.2) | 0.3 (0.1-0.5) | 2.1 (1.6-2.9) | 4.3 (3.3-5.8) |
| Asthma Severity: GINA Step at baseline[c] | | | | | |
| Step 0 (no prescriptions), n (%) | 8723 (14.69) | 8781 (19.91) | 10665 (17.5) | 375 (11.6) | 82 (15.0) |
| Step 1 (SABA only), n (%) | 7952 (13.4) | 9760 (22.1) | 10389 (17.1) | 280 (8.7) | 67 (7.4) |
| Step 2 (low dose ICS), n (%) | 11675 (19.7) | 15349 (34.8) | 19517 (32.0) | 709 (21.9) | 121 (13.3) |
| Step 3 (low dose ICS+ LABA), n (%) | 12805 (21.7) | 7267 (16.5) | 12912 (21.2) | 840 (26.0) | 210 (23.0) |
| Step 4 or 5 (med/high dose ICS+ LABA + add ons), n (%) | 18228 (30.7) | 2950 (6.7) | 7444 (12.2) | 1032 (31.9) | 432 (47.4) |

[a]Most recent eosinophil reading within 5 years of baseline and up to 2nd year of follow-up

[b]See Appendix 2 for more information on calculation of age of onset of asthma

[c]GINA step: Based on 2018 guidelines for stepped therapy for asthma (GINA)[48]

BMI: body mass index; GINA: Global Initiative for Asthma; ICS: inhaled corticosteroid; IQR: inter-quartile range; OCS: oral corticosteroid; PEF: peak expiratory flow rate; SABA: short acting $\beta_2$-agonist; SD: standard deviation

**Legend to Figures**

**Figure 1**: Patient disposition

COPD: chronic obstructive pulmonary disease; $FEV_1$: forced expiratory volume in one second; LF: lung function; PEF(R): peak expiratory flow rate; QoF: quality outcome framework-defined asthma diagnosis read codes. ** ≥2 separate prescriptions on ≥occasions during follow up; *** smoothing methods described in online supplement.

**Figure 2**:

a) Adjusted 20-year PEF trajectories (L/yr) by annual exacerbation rate (AER; n=109,182). CI: confidence interval; PEF: peak expiratory flow rate
b) Adjusted 20-year percent predicted PEF trajectories (%/yr) by annual exacerbation rate (AER; n=109,182). CI: confidence interval; PEF: peak expiratory flow rate

Final models are adjusted for age at baseline, gender, fixed smoking status at baseline, time-varying smoking status during follow-up, BMI at baseline, length of follow-up, lung function at baseline, and time-varying height. CI: confidence interval; PEF: peak expiratory flow

**Figure 3:** Adjusted 20-year PEF trajectories (L/yr) by annual exacerbation rate (AER) stratified by patient age at baseline (18-24 years, n= 16,482; 25-39 years, n=32,892; ≥40 years, n=59,808). Final models are adjusted for age at baseline, gender, fixed smoking status at baseline, time-varying smoking status during follow-up, BMI at baseline, length of follow-up, lung function at baseline, and time-varying height. CI: confidence interval; PEF: peak expiratory flow rate

**Figure 4**: 20-year PEF trajectories (L/yr) by annual exacerbation rate (AER) stratified by mean daily ICS dose (33.3% centiles); Lowest dose: n=37,652; medium dose: n=37,770; highest dose: n=33,760). Final models are adjusted for age at baseline, gender, fixed smoking status at baseline, time-varying smoking status during follow-up, BMI at baseline, length of follow-up, lung function at baseline, and time-varying height. CI: confidence interval; PEF: peak expiratory flow.