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Asthma exacerbations are associated with a decline in lung function: a longitudinal population-based study

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ABSTRACT

Rationale Progressive lung function (LF) decline in patients with asthma contributes 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 s (FEV_1) (sensitivity analysis). Adjusted linear growth models tested the association between mean annual exacerbation rate (AER) and LF trajectory.

Results We studied 1 09 182 patients with follow-up ranging from 5 to 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 to −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 to −3.28) compared with 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 LF decline. This was more prominent in younger patients but was evident in older patients when it was related to lower starting LF, suggesting a persistent deteriorating phenotype that develops in adulthood over time. Earlier intervention with appropriate management in younger patients with asthma could be of value to prevent excessive LF decline.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Previous studies have assessed the link between exacerbations and accelerated lung function decline in asthma with variable results. Most studies included small numbers of patients often with severe disease and/or short follow-up times that may not adequately capture lung function status.

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 were stronger in younger patients aged 18–39 years, persisted even in patients on higher average daily inhaled corticosteroid 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 patients with asthma 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]

While 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 are 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 patients with chronic obstructive pulmonary disease (COPD). In the UK, 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 patients with asthma 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 s (FEV_1), which is infrequently measured in patients with asthma 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.

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 deidentified 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 (UK), a UK-based social enterprise.[18 19 20] The index date (starting point) for each patient was the first eligible lung function record at, or after their 18th 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 (online supplemental 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 to 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*[21] Only those with at least three 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 (online supplemental table 2). A supplementary analysis using per cent predicted PEF based on formulas in Hankinson *et al*[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 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] that is, an asthma-related hospital attendance/admission and/or primary care consultation and/or an asthma-related Accident and Emergency (A&E) attendance and/or an acute OCS course of ≥3 days. Only one 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.

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 μg/day and 463.7 μg/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 online supplemental file 1.

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 (1) 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 (2) with first reading on or after 2005 following scale changes to UK peak flow metres.[24]

Analytical methods

Baseline characteristics are presented as percentages (categorical indicators) or medians/means with IQR or SDs (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, while 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 online supplemental 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 online supplemental 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 online supplemental figure 1 and online supplemental 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 online supplemental table 3). These patients were characterised by higher eosinophil counts, older age, higher BMI, more short-acting β_2 agonist and OCS prescriptions and higher total dosages of ICS at baseline. There was no clear trend of smoking status

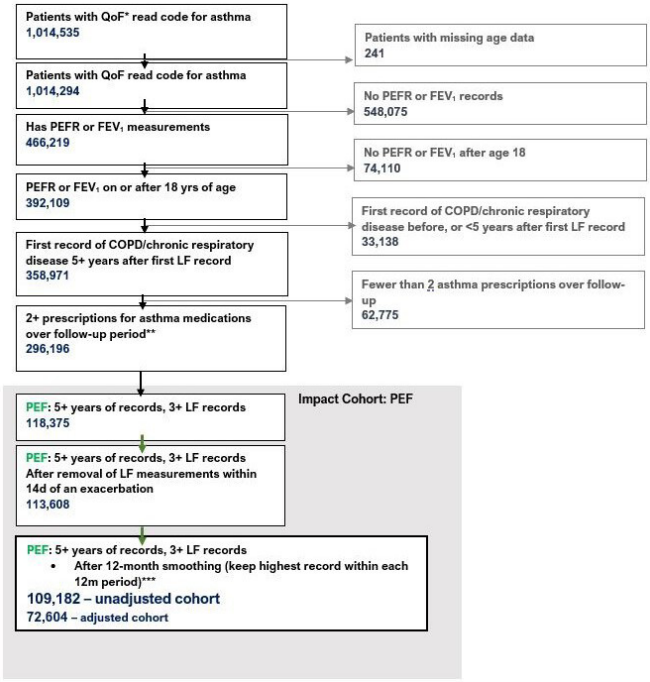


Figure 1 Patient disposition. COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in one second; LF, lung function; PEF(R), peak expiratory flow rate; QoF, quality outcome framework-defined asthma diagnosis read codes. **≥2 separate prescriptions on ≥occasions during follow-up. ***Smoothing methods described in online supplement.

or age at first asthma diagnosis in patients with higher compared with lower AERs. The overall trajectory of PEF with time in all patients was negative with a loss of −3.73 L/min/year (95% CI −3.77 to −3.69) of PEF or 0.27% predicted points of PEF/year (95% CI 0.25 to 0.29).

Association between AER 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 to −0.18; p<0.0001) and −1.34 L/min/year (95% CI −1.2 to −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 with 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 to 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 to −1.85; p≤0.001) for those with AER >2 compared with those with none (figure 2A). Online supplemental 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 per cent-predicted lung function (table 1 and online supplemental 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 with those who had never smoked (online supplemental table 5).

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

Patient characteristics	Overall (n=1 09 182)	AER 0/year (n=44 107)	AER>0–1/year (N=60 927)	AER>1–2/year (N=3236)	AER>2/year (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 (%)	44 697 (40.9)	20 791 (47.1)	22 577 (37.1)	1007 (31.1)	322 (35.3)
Median eosinophil count at baseline cells/mm^3 (IQR)*	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)†	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 (%)	38 287 (35.1)	16 637 (37.7)	20 388 (33.5)	983 (30.4)	279 (30.6)
Ex-smoker, n (%)	20 120 (18.4)	7865 (17.8)	11 436 (18.8)	637 (19.7)	20.0 (182)
Current smoker, n (%)	16 873 (15.5)	6381 (14.5)	9818 (16.1)	524 (16.2)	150 (16.5)
Smoking status not recorded, n (%)	33 902 (31.1)	13 224 (30.0)	19 285 (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‡					
Step 0 (no prescriptions), n (%)	8723 (14.69)	8781 (19.91)	10 665 (17.5)	375 (11.6)	82 (15.0)
Step 1 (SABA only), n (%)	7952 (13.4)	9760 (22.1)	10 389 (17.1)	280 (8.7)	67 (7.4)
Step 2 (low dose ICS), n (%)	11 675 (19.7)	15 349 (34.8)	19 517 (32.0)	709 (21.9)	121 (13.3)
Step 3 (low dose ICS +LABA), n (%)	12 805 (21.7)	7267 (16.5)	12 912 (21.2)	840 (26.0)	210 (23.0)
Step 4 or 5 (med/high dose ICS +LABA + add ons), n (%)	18 228 (30.7)	2950 (6.7)	7444 (12.2)	1032 (31.9)	432 (47.4)

*Most recent eosinophil reading within 5 years of baseline and up to second year of follow-up.
†See online supplemental appendix 2 for more information on calculation of age of onset of asthma.
‡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; OCS, oral corticosteroid; PEF, peak expiratory flow rate; SABA, short-acting β_2 agonist.

Exacerbations and PEF decline by baseline age

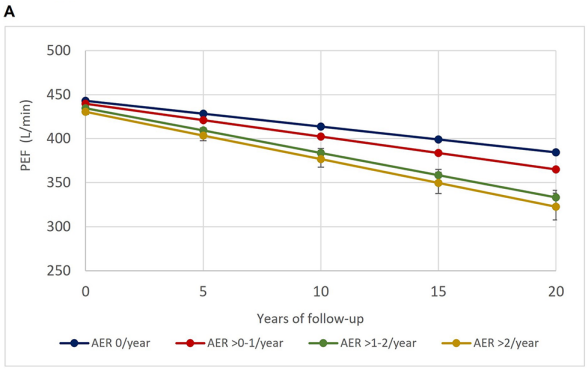
The association between exacerbation rate and PEF (L) decline persisted as above for patients stratified by age at baseline (figure 3). The largest effect occurred in patients aged 18–24 and 25–39 years at baseline. The rate of lung function decline in patients in these age groups experiencing 2+ exacerbations/year 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 (online supplemental 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: online supplemental figure 4; unadjusted: online supplemental figure 5).

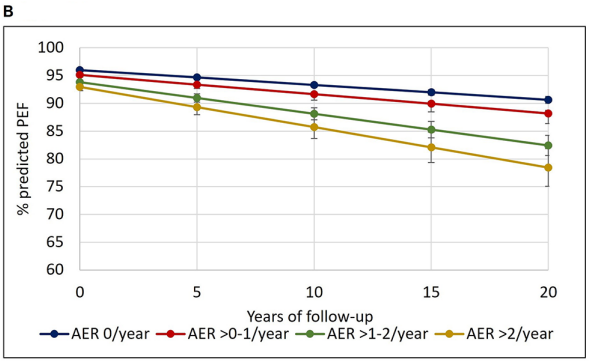
Exacerbations and PEF decline by yearly average ICS dosage

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 with those with an exacerbation rate of 0/year (figure 4). Unadjusted results are provided in online supplemental figure 6. A similar pattern of accelerated decline with increasing AER was observed for % predicted PEF stratified by mean annual ICS dose (adjusted: online supplemental figure 7; unadjusted: online supplemental 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 (online supplemental tables 6 and 7). Lung function decline measured by PEF tended to be faster in women compared with men, irrespective of exacerbation category. However, the impact of exacerbations on lung function trajectories was more marked in men (men: >2 AER vs 0 AER/year: −3.35 L/min/year (95% CI −4.59 to −2.11); women: >2 AER vs 0 AER: −1.62 L/min/year (95% CI −2.25 to −0.99); online supplemental 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 (online supplemental table 7).





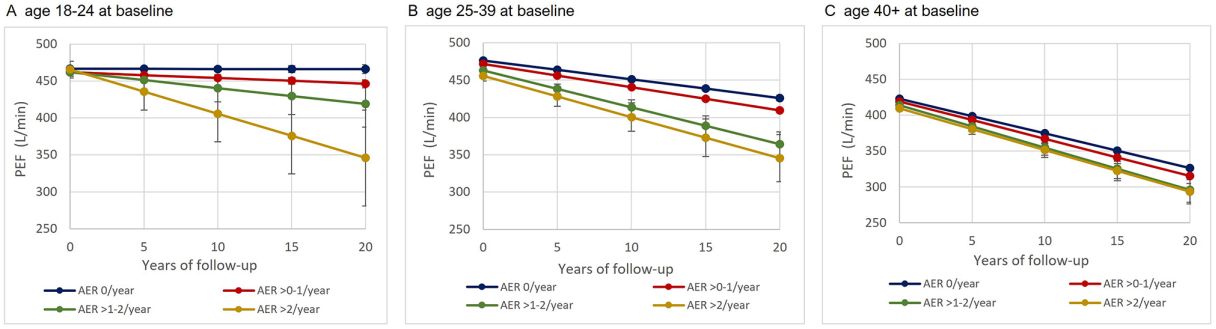
Annual exacerbation rate	Decline in PEF L/min/yr (95% CI)	Average difference in PEF L/min/yr decline between AER categories (95% CI; p)
0/yr	**-2.93** L/min/yr (-3.04, -2.82)	
>0-1/yr	**-3.74** L/ min/yr (-3.84, -3.64)	-0.81 L (-0.93, -0.70) p ≤0.001
>1-2/yr	**-5.05** L/ min/yr (-5.38, -4.73)	-2.13 L (-2.46, -1.80) p ≤0.001
>2/yr	**-5.38** L/ min/yr (-5.98, -4.78)	-2.46 L (-3.06, -1.85) p ≤0.001

Annual exacerbation rate	Decline in % predicted PEF (95% CI)	Average difference in % predicted PEF decline between AER categories (95% CI; p)
0/yr	**-0.27** %/yr (-0.29, -0.24)	
>0-1/yr	**-0.35** %/yr (-0.37, -0.32)	-0.08 %/yr (-0.10, -0.05) p ≤0.001
>1-2/yr	**-0.57** %/yr (-0.64, -0.50)	-0.03 %/yr (-0.38, -0.23) p ≤0.001
>2/yr	**-0.72** %/yr (-0.86, -0.59)	-0.46 %/yr (-0.59, -0.32) p ≤0.001

Figure 2 (A) Adjusted 20-year PEF trajectories (L/year) by annual exacerbation rate (AER; n=109 182). (B) Adjusted 20-year per cent-predicted PEF trajectories (%/year) by annual exacerbation rate (AER; n=109 182). 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. AER, annual exacerbation rate; BMI, body mass index; PEF, peak expiratory flow.

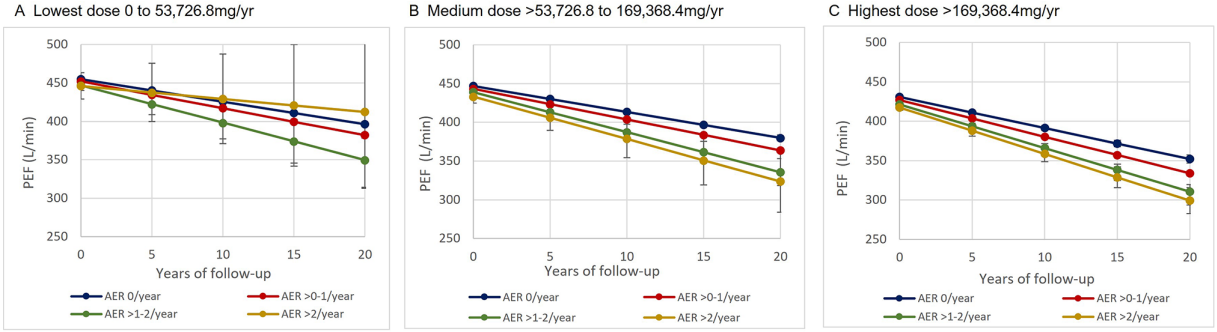
Sensitivity analysis with FEV_1

There were 10 943 patients in the FEV_1 cohort (online supplemental figure 1) followed for a median of 8.1 years (online supplemental table 4) who were included in the unadjusted analyses, and 8172 with data on all covariates included in the adjusted analysis. Compared with 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 (online supplemental 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 (online supplemental figure 9). As with



AER	18 – 24 years old at baseline		25 – 39 years old at baseline		40+ years old at baseline	
	Decline in PEF L/min/yr (95% CI)	Average difference in PEF L/min/yr decline (95% CI; p)	Decline in PEF L/min/yr (95% CI)	Average difference in PEF L/min/yr decline (95% CI; p)	Decline in PEF L/min/yr (95% CI)	Average difference in PEF L/min/yr decline (95% CI; p)
0/yr	**-0.02** L/min/yr (-0.26, 0.22)	**comparator**	**-2.52** L/min/yr (-2.67, -2.36)	**comparator**	**-4.82** L/min/yr (-4.94, -4.7)	**comparator**
>0-1/yr	**-0.77** L/min/yr (-1.00, -0.54)	**-0.75** L/min/yr (-1.08, -0.41) p<0.001	**-3.11** L/min/yr (-3.24, -2.98)	**-0.59** L/min/yr (-0.79, -0.39) p<0.001	**-5.20** L/min/yr (-5.29, -5.11)	**-0.38** L/min/yr (-0.53, -0.23) p<0.001
>1-2/yr	**-2.15** L/min/yr (-3.43, -0.88)	**-2.13** L/min/yr (-3.43, -0.83) p = 0.001	**-4.93** L/min/yr (-5.57, -4.28)	**-2.41** L/min/yr (-3.07, -1.75) p<0.001	**-5.89** L/min/yr (-6.25, -5.53)	**-1.07** L/min/yr (-1.45, -0.69) p<0.001
>2/yr	**-5.98** L/min/yr (-8.64, -3.31)	**-5.95** L/min/yr (-8.63, -3.28) p<0.001	**-5.51** L/min/yr (-6.75, -4.27)	**-2.99** L/min/yr (-4.24, -1.74) p<0.001	**-5.82** L/min/yr (-6.5, -5.14)	**-1.00** L/min/yr (-1.69, -0.31) p = 0.005

Figure 3 Adjusted 20-year PEF trajectories (L/year) 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. AER 0/year- no exacerbations, AER >0-1/yr - greater than 0 and up to 1 exacerbation per year, AER >1-2/yr - greater than 1 and up to 2 exacerbations per year, AER >2/yr - greater than 2 exacerbations per year. BMI, body mass index; PEF, peak expiratory flow rate.



AER	Lowest dose (mean yearly dosage 0- 53,726.8mg)		Medium dose (mean yearly dosage >53,726.8 to 169,368.4mg)		Highest dose (mean yearly dosage >169,368.4mg)	
	Decline in PEF L/min/yr (95% CI)	Average difference in PEF L/min/yr decline (95% CI; p)	Decline in PEF L/min/yr (95% CI)	Average difference in PEF L/min/yr decline (95% CI; p)	Decline in PEF L/min/yr (95% CI)	Average difference in PEF L/min/yr decline (95% CI; p)
0/yr	**-2.93** L/min/yr (-3.07, -2.8)	**comparator**	**-3.36** L/min/yr (-3.51, -3.21)	**comparator**	**-3.93** L/min/yr (-4.13, -3.73)	**comparator**
>0-1/yr	**-3.51** L/min/yr (-3.66, -3.37)	**-0.58** L/min/yr (-0.78, -0.38) p<0.001	**-3.96** L/min/yr (-4.08, -3.85)	**-0.61** L/min/yr (-0.8, -0.42) p<0.001	**-4.65** L/min/yr (-4.77, -4.53)	**-0.72** L/min/yr (-0.95, -0.48) p<0.001
>1-2/yr	**-4.87** L/min/yr (-6.29, -3.45)	**-1.94** L/min/yr (-3.37, -0.51) p =0.008	**-5.15** L/min/yr (-5.85, -4.46)	**-1.80** L/min/yr (-2.51, -1.08) p<0.001	**-5.55** L/min/yr (-5.92, -5.19)	**-1.62** L/min/yr (-2.04, -1.21) p<0.001
>2/yr	**-1.69** L/min/yr (-5.81, 2.44)	**1.25** L/min/yr (-2.88, 5.37) p = 0.554	**-5.48** L/min/yr (-7.06, -3.89)	**-2.12** L/min/yr (-3.71, -0.53) p=0.009	**-5.92** L/min/yr (-6.58, -5.27)	**-1.99** L/min/yr (-2.67, -1.31) p<0.001

Figure 4 20-year PEF trajectories (L/year) 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. AER 0/year, no exacerbations; AER >0-1/yr, greater than 0 and up to 1 exacerbation per year; AER >1-2/yr, greater than 1 and up to 2 exacerbations per year; AER >2/yr, greater than 2 exacerbations per year; BMI, body mass index; PEF, peak expiratory flow.

PEF, the overall FEV_1 trajectory decreased over time: 25.5 mL/year (95% CI −26.3 to −24.6) and −0.13%/year (95% CI −17.0 to 10.4) for FEV_1 volume and percent predicted, respectively. Unadjusted results are shown in online supplemental 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 (online supplemental figure 11). Patients with AER >2 lost an additional −39.3 mL FEV_1 per year compared with patients with no exacerbations (95% CI −65.2 to −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 (online supplemental 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 (online supplemental figure 13). Patients with exacerbation rate >2/year lost an additional 7.9 mL/year FEV_1 compared with patients with no exacerbations (95% CI −16.1 to 0.2; p=0.056). Results were similar for %-predicted FEV_1 (online supplemental figure 14).

Sensitivity analyses of subsample cohorts with postage 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 (online supplemental 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 (online supplemental table 9).

To account for change in PEF measurement practices in 2004, an additional sensitivity analysis of the PEF cohort was performed on a subsample of 37 029 (unadjusted) and 26 873 (adjusted) patients with first lung function reading on or after 1 January 2005 (online supplemental 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 to −0.57) p=0.0054; online supplemental 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 5–60 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 has 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 50 mL 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 30.2 mL 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 heterogeneous 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 heterogeneous asthma cohort, with long-term follow-up, and a focus on trajectories stratified by patient age. Bai *et al* 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 with 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 was 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 patients with asthma aged 18–39 years at baseline who have exacerbations experience an additional loss of PEF, that is, 10–120 additional L/min in absolute terms or 2.25% expressed as change in per cent-predicted PEF over 20 years compared with 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 L/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 four times the minimal clinical difference for the AQLQ.[35] The difference in per cent-predicted PEF and FEV_1 in frequent exacerbators versus those without exacerbations in younger exacerbating patients in our study was more than eight 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. While 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 20.2 mL/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 22.4 mL 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, while 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 proactive 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 UK 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 generalisable 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 subgroup 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. While digitisation of medical records was not introduced until the early 1990s, OPCRD, the Clinical Practice Datalink 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 subsample 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 metres 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 metres) 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.

While 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 among others[31 44 45]; undoubtedly lung capacity by early adulthood will be influenced by these factors. While 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 prebronchodilator or postbronchodilator 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 while 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 while 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.

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Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by 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). Participants gave informed consent to participate in the study before taking part.

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Data availability statement Data are available upon reasonable request. 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.

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