Online supplement

Methods

OPCRD info

Data were obtained from the Optimum Patient Care Research Database (OPCRD)[1]. The OPCRD dataset comprises medical records of more than 11 million patients from over 800 general practices across the UK (approximately 8% of the total UK population), and integrates with all UK clinical systems (EMIS, TPP SystmOne, InPS Vision, Microtest Evolution). It benefits from a long retrospective period (median time in the database is 19.8 (12.8-25.7) years, going back to birth for summary diagnostic data in many cases), and contains linked patient-completed respiratory questionnaires for approximately 10% of asthma patients included.[1] The OPCRD is approved by the UK National Health Service for clinical research use (Research Ethics Committee reference: 15/EM/0150).

S-Table 1: Variables collected from OPCRD at baseline (1 year before the index date)

Variable	Description
Fixed variables measured on index date or at/close to baseline	
Age at start of lung function record	Age in years on index date.
Gender	Female or Male
Height	Measurement in metres (m) on reading closest to index date, in adulthood
Body Mass Index (BMI)	Defined as the ratio of weight (kg) to squared height (m^2) on index date (or closest date). Categorised as: Underweight <18.5 Normal w eight 18.5 to <25 Overweight 25 to <30 Obese 30 and over
Age of Asthma Onset	Age of onset of asthma was estimated as the first date where a diagnostic code for asthma was recorded in the patient EMR, excluding patients who fit the following criteria, for whom age of onset was defined as missing due to insufficient data: • First asthma diagnosis record is <3 years from patient registration at the GP practice (possible active asthma prior to registration) • First asthma diagnosis record is ≥3 years from patient registration at the GP practice but inhalers are prescribed in registration year (possible active asthma prior to registration) • First asthma diagnosis record is <5 years from patient registration, AND first post-diagnostic inhaler prescription in >90 days from diagnosis (possible resurgence of asthma in remission)
Proxies of asthma severity	Patients categorised by highest GINA Treatment Step in baseline year, using on 2018 guidelines for stepped therapy for asthma (GINA) (reference 21 in main paper)

Variable	Description
Blood eosinophil count (BEC)	Mean count of blood eosinophils (10^9cells/L) in baseline year (or mean of all counts in closest year within 5 years of baseline).
Lung function	Percent predicted PEF at index date. Categorised Percent predicted FEV_1 at index date. Categorised
Total years of follow-up	Total follow-up time in years between dates of first and last eligible lung function records (calculated for FEV_1 and PEF separately)
Diagnosis of COPD during follow-up	Any patient with a first diagnostic record for COPD during follow-up. Patients with a diagnosis of COPD before the index date or up to 5 years after the index date have been excluded from the eligible patient population.
Number of SABA prescriptions (asthma control)	Total number of SABA prescriptions in baseline year or first year of follow up (i.e. either in the year prior or following the index date) – whichever is the greater number.
Time-varying variables measured during follow-up	
Maintenance oral corticosteroids	Cumulative sum of prescriptions up until end of follow up as a proportion of total years of follow up
ICS	Mean annualised dosage of inhaled corticosteroids in mg up until end of follow up (includes ICS-only inhalers and ICS in combination with long-acting beta agonist inhalers). Categorised into terciles: Lowest tercile (up to 53726.8 mg/yr) Middle tercile (>53726.8 to 169368.4mg/yr) Highest tercile (>169368.4mg/yr)
Other maintenance therapy	Cumulative sum of prescriptions up until the end of follow up as a proportion of total years of follow up for LABA, LAMA, LTRA, anti-IL-5, anti-IgE and anti-IL-13 medications.
SABA prescriptions	Cumulative sum of short acting beta agonist prescriptions up until the end of follow up as a proportion of total years of follow up
Smoking status	Categorised at the end of follow up as: -never smoker, -variable smoker, -continuous smoker -smoking status unknown

EMR: Electronic Medical Record; FEV_1; forced expiratory volume in one second; GINA: Global Initiative for Asthma; ICS: inhaled corticosteroid; LABA: long-acting β_2-agonist; LAMA: long-acting muscarinic antagonist; LTRA: leukotriene receptor antagonist; PEF: peak expiratory flow rate; SABA: short acting β_2 agonist

Smoothing of Lung Function Trajectories

PEF and FEV_1 vary considerably over time, may be measured using different instruments, and can show periods of rapid decline and recovery, which can be difficult to differentiate from the underlying lung function trajectory (i.e contribute significant 'noise' to analysis models). This inherent variability was accounted for by (i) smoothing and (ii) excluding lung function values that were 14 days wither side of an exacerbation. Smoothing was achieved by taking the highest eligible readings of absolute and % predicted lung function readings within each 12-month period for PEF or 6-month period for FEV_1, starting from the index date. By taking the highest value the aim was to mimic the effect of analysing a dataset containing readings taken during times of 'normal/best' lung function.

Estimation of lung function trajectory: a discussion of different models

Our first key assumption, that a linear model is able to appropriately characterise lung function trajectory is in line with other published studies of lung function trajectory in asthma and COPD patients.[2–4] An alternative quadratic model (including time and time) was considered, particularly for younger participants (as lung function peaks in early adulthood (18-25 years) and declines thereafter). However, a comparison of the information criteria (AIC and BIC) showed that the differences between linear and quadratic models of the study population were small and not consistent between PEF and FEV_1 trajectories; quadratic models were negligibly better (AIC: 8686422 BIC: 8686479) for PEF (L) and the linear model was negligibly better (AIC: 47046.24 BIC: 47091.2) for FEV_1 volume. Similar results were observed for % predicted PEF and FEV_1.

Our second assumption was that the data we were modelling was normal. Both baseline and follow-up lung function distributions did not appear to deviate significantly from normal.

Results

S-Table 2: Correlation between FEV_1 and PEF (4 different significance tests) in a subset of 6083 patients with 25,359 PEF and FEV_1 test results measured on the same dates

Objective	**Correlation between:**	**Coefficient (95% CI) p (change in dependent variable for unit increase in predictor)**	**R_square**	**Interpretation**
Relationship between absolute FEV_1 and PEF	PEF (predictor) and FEV_1 (outcome variable)	+2.7mL (2.6, 2.8) p<0.001	0.7	Significantly correlated, predictor explains most of variation in outcome
Change in relationship between PEF and FEV_1 over time	PEF * time (predictor) and FEV_1 (outcome variable)	-0.000005 (-000012, 0.000002) p = 0.131	0.7	No significant change in relationship between FEV_1 and PEF over time, Model explains most of variation in outcome

CI: confidence interval; FEV1: forced expiratory volume in one second; PEF: peak expiratory flow rate

S-Table 3: Additional 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					
Mean baseline PEF in L/min, (SD)	441.0 (107.0)	440 (106.8)	430.0 (104.5)	393.0 (106.8)	385.0 (102.2)
Vital statistics					
Aged 18-24 years, N (%)	16482 (15)	8228 (19)	7954 (13)	235 (7)	65 (7)
Aged 25-39 years, N (%)	32892 (30)	14490 (33)	17471 (29)	727 (22)	204 (22)
Aged 40+ years, N (%)	59808 (55)	21389 (48)	35502 (58)	2274 (70)	643 (71)
Median BMI at baseline (IQR)[a]	27.0 (24.0-30.9)	26.3 (23.5-29.9)	27.5 (24.3-31.6)	28.1 (24.6-32.6)	28.1 (24.4-32.9)
% Insufficient data to calculate BMI N (%)	3892 (3.6)	1970 (4.5)	1803 (3.0)	99 (3.1)	20 (2.2%)
Missing recent/no eosinophil data[b] N (%)	68485 (62.7)	29029 (65.8)	37129 (60.94)	1812 (56.0)	515 (56.5)
Asthma status at baseline					
age of onset of asthma >30yrs[c], N (%)	54464 (49.9)	19970 (45.3)	32150 (52.8)	1857 (57.4)	487 (53.4)
Missing date of asthma diagnosis N (%)	15765 (14.4)	6503 (14.7)	8663 (14.2)	462 (14.3)	137 (15.0)
Median annual exacerbation rate (IQR)	0.08 (0.0-0.25)	0.00 (0.00)	0.18 (0.1-0.35)	1.33 (1.17-1.6)	2.55 (2.25-3.13)
Smoking status					
Smoking status during follow-up[d]					
Non-smoker, n (%)	35759 (32.8)	15865 (36.0)	18751 (30.8)	885 (27.4)	258 (28.3)
Sustained ex-smoker, n (%)	23470 (21.5)	9180 (20.8)	13348 (21.9)	742 (22.9)	200(21.9)
Intermittent smoker, n (%)	20020 (18.3)	7184 (16.3)	11945 (19.6)	683 (21.1)	208 (22.8)
Sustained smoker, n (%)	5622 (5.2)	2435 (5.5)	3036 (5.0)	114 (3.5)	37 (4.1)
No smoking data recorded in follow-up period, n (%)	24311 (22.3)	9443 (21.4)	13847 (22.7)	812 (25.1)	209 (22.9)

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)**
Asthma prescriptions (control/severity)					
Mean ICS dosage/year categorised[e]					
lowest tercile ICS (0-147.1 mcg/day), n (%)	37652 (34.5)	20950 (47.5)	16488 (27.1)	181 (5.6)	33 (3.6)
medium tercile ICS (147.1-463.7 mcg/day, n (%)	37770 (34.6)	14693 (33.3)	22264 (36.5)	686 (21.2)	127 (13.9)
highest tercile (>463.7mcg), n (%)	33760 (30.9)	8464 (19.2)	22175 (36.4)	2369 (73.2)	752 (82.5)

AER: annual exacerbation rate; BMI: body mass index; ICS: inhaled corticosteroid; IQR: interquartile range; PEF: peak expiratory flow rate; SD: standard deviation

[a]Most recent BMI recorded up to 10 yrs prior to baseline or up to 5 years after index date.

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

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

[d]Baseline: Smoking status up to 10 years prior to baseline. Follow-up: Latest smoking status at baseline or during follow-up.

[e]patients were ranked by mean yearly ICS dosage in mg into 33.33% percentile groups. Bottom tercile ICS: 0-53,726.8 mg/yr; middle tercile ICS: >53,726.8 to 169,368.4 mg/yr; top tercile (>169,368.4 mg/yr)

S-Table 4: Characteristics of 10,943 patients in the FEV_1 cohort – overall and by annual exacerbation rate (AER)

Patient characteristics	**Overall**	**AER 0/yr**	**AER >0-1/yr**	**AER >1-2/yr**	**AER >2/yr**
Distribution of patients N %	10943 (100)	2961 (27.1)	6730 (61.5)	940 (8.6)	312 (2.9)
Baseline lung function					
Median years of follow-up (IQR)	8.1 (6.8 – 11.9)	7.4 (6.0-9.5)	8.5 (6.6-11.2)	8.5 (6.7-11.1)	8.2 (6.3-10.7)
Mean baseline FEV_1 in L/1s (SD)	2.2 (0.8)	2.5 (0.8)	2.2 (0.8)	1.9 (0.7)	1.8 (0.7)
Mean baseline % predicted FEV_1 (SD)	81.5 (20.7)	85.4 (19.0)	81.3 (20.7)	75.2 (22.4)	70.3 (22.6)
Vital statistics					
Median age at baseline (IQR)	58 (48-66)	57 (46-66)	59 (48-67)	60 (50-68)	56 (48-66)
Aged 18-39 years N (%)	1223 (11.2)	399 (13.5)	711 (10.6)	78 (8.3)	35 (11.2)
Aged 40+ years N (%)	9720 (88.8)	2562 (6.5)	6019 (89.4)	862 (91.7)	277 (88.8)
Male N (%)	4747 (43.4)	1517 (51.2)	2792 (41.5)	334 (35.5)	104 (33.3)
Median BMI at baseline (IQR)[a]	28.0 (24.9-31.8)	27.6 (24.6-31.0)	28.1 (25.0-31.9)	28.3 (24.9-32.4)	28.3 (25-32.9)
% Insufficient anthropometric data to calculate BMI N (%)	156 (1.43)	48 (1.6)	89 (1.3)	13 (1.4)	6 (1.9)
Median eosinophil count at baseline cells/mm3 (IQR)[b]	225 (150-334)	216 (150-320)	225 (150-330)	249 (165-378)	288 (178-406)
Missing/no recent eosinophil data [b]	3256 (29.7)	1019 (34.4)	1957 (29.1)	204 (21.7)	76 (24.4)
Asthma status at baseline					
Median age of onset of asthma (IQR)	51 (37-62)	51 (36-62)	52 (39-63)	50 (37-61)	44 (30-58)
Age of onset of asthma >30yrs[c] N (%)	7657 (70.0)	(031 (68.6)	4786 (71.1)	70.3 (661)	57.4 (179)

Patient characteristics	Overall	AER 0/yr	AER >0-1/yr	AER >1-2/yr	AER >2/yr
Onset not possible to ascertain N (%)	1569 (14.3)	419 (14.2)	953 (14.2)	137 (14.6)	60 (19.3)
Median years with asthma prior to index date (IQR) [c]	5.8 (0.0-14.1)	5.1 (0.0-13.5)	5.4 (0.0-13.7)	8.4 (1.4-16.9)	12.3 (4.0-21.0)
Median number exacerbations at baseline (IQR)	0 (0-0)	0 (0-0)	0 (0-0)	1 (0-2)	2 (1-4)
Median annual exacerbation rate	0.2 (0.0-0.6)	0.00 (0.0-0.0)	0.3 (0.1-0.5)	1.4 (1.2-1.7)	2.6 (2.3-3.2)
Diagnosis of COPD during follow-up N (%)	3516 (32.1)	536 (18.1)	2312 (34.4)	507 (53.9)	161 (51.6)
Smoking status					
Evidence of smoking at baseline[e]					
Non-smoker N (%)	2393 (21.8)	694 (23.4)	1422 (21.1)	196 (20.9)	81 (26.0)
Ex-smoker N (%)	3674 (33.6)	1018 (34.4)	2226 (33.1)	327 (34.8)	(103 (33.0)
Current smoker N (%)	2247 (20.5)	577 (19.5)	1416 (21.0)	197 (21.0)	57 (18.3)
No smoking data recorded in baseline period N (%)	2629 (24.02)	672 (22.7)	1666 (24.8)	220 (23.4)	71 (22.8)
Evidence of smoking during follow-up****					
Non-smoker N (%)	2146 (19.6)	637 (21.5)	1258 (18.7)	175 (18.6)	76 (24.4)
Sustained ex-smoker N (%)	3376 (30.9)	960 (32.4)	2047 (30.4)	281 (30.0)	88 (28.2)
Mixed smoker/ex-smoker (n)	2357 (21.5)	526 (17.8)	1521 (22.6)	235 (25.0)	75 (24.0)
Sustained smoker (n)	798 (7.3)	246 (8.3)	487 (7.2)	54 (5.7)	11 (3.5)
No smoking data recorded in follow-up period (n)	2266 (20.7)	592 (20.1)	1417 (21.1)	195 (20.7)	62 (19.9)
Asthma prescriptions (control/severity)					

Patient characteristics	Overall	AER 0/yr	AER >0-1/yr	AER >1-2/yr	AER >2/yr
Median SABA prescriptions in baseline year (IQR)	3 (1-6)	2 (1-5)	3 (1-6)	4 (2-8)	7 (3-11)
Median SABA prescriptions/yr in follow-up period	2.9 (1.3-6.0)	1.9 (0.8-4.4)	3.0 (1.4-5.9)	5.1 (2.7-8.5)	6.7 (4.0-11.4)
Median ICS dosage/year over follow-up in mcg (IQR)	514.8 (220.5-965.0)	324.1 (104.8-645.4)	544.2 (249.9-960)	576.7 (997.0-1498.8)	1322.2 (785.1-1781.4)
Mean ICS dosage/year categorised[e]					
Lowest 2 terciles for ICS dose/yr (0-463.7mcg/day)	3073 (28.1)	973 (32.9)	952 (29 (1)	126 (13.4)	30 (7.1)
Highest tercile for ICS dose/yr (>463.7 mcg)	5880 (53.7)	1077 (36.4)	3744 (55.6)	777 (82.7)	282 (90.4)
Median OCS prescriptions/year over follow-up (IQR)	0.5 (0.2-1.3)	1 (1-2)	4 (2-7)	20 (14-32)	36 (26-60)
Asthma Severity: GINA Step at baseline[f]					
Step 0 (no prescriptions) (n)	1631 (14.9)	603 (20.4)	985 (14.6)	59 (6.3)	9 (2.9)
Step 1 (SABA only) (n)	1587 (14.5)	495 (16.7)	990 (14.7)	85 (9.0)	17 (5.5)
Step 2 (low dose ICS) (n)	2227 (20.4)	748 (25.3)	1351 (20.1)	107 (11.4)	21 (6.7)
Step 3 (low dose ICS+ LABA) (n)	2272 (20.8)	619 (20.9)	1441 (21.4)	158 (16.8)	29 (**9.3**)
Step 4 or 5 (med/high dose ICS+ LABA + add ons) (n)	3226 (29.5)	496 (16.8)	1963 (29.2)	531 (56.5)	236 (75.6)

[a]Most recent BMI recorded up to 10 yrs prior to baseline or up to 5 years after index date.
[b]Most recent eosinophil reading within 5 years of baseline and up to 2nd year of follow-up
[c]See S-Table 1 for more information on calculation of age of onset of asthma
[d]Baseline: Smoking status up to 10 years prior to baseline. Follow-up: Latest smoking status at baseline or during follow-up.
[e]patients were ranked by mean yearly ICS dosage in mg into 33.33% percentile groups. Bottom tercile ICS: 0-53,726.8 mg/yr; middle tercile ICS: >53,726.8 to 169,368.4 mg/yr; top tercile (>169,368.4 mg/yr)
[f]GINA step: Based on 2018 guidelines for stepped therapy for asthma (GINA).(see reference 21 in main paper)
AER: annual exacerbation rate; BMI: body mass index; COPD: chronic obstructive pulmonary disease; FEV_1; forced expiratory volume in one second; GINA: Global Initiative for Asthma; ICS: inhaled corticosteroid; IQR: inter-quartile range; LABA: long-acting β_2-agonist; OCS: oral corticosteroid; SABA: short acting β_2-agonist; SD: standard deviation

S-Table 5: Overall impact of smoking status on lung function trajectory (multivariate model with continuous exacerbation rate, time, duration of follow-up and baseline BMI)

Smoking category	% predicted (95% CI) p value	PEF, L/min (95% CI) p-value
Baseline smoking status		
Never smoker	Comparison group	
Ex-smoker	-3.1% (1.2%, -7.3%) p=0.155	1.0 (-0.06, 2.07) p=0.064
Smoker	-11.7% (7.0%, 16.5%) p<0.0001	-0.5 (-1.7, 0.7) p=0.387
Follow-up smoking status		
Never smoker	Comparison group	
Sustained ex-smoker	5.0% (0.8%, 9.3%) p=0.020	1.3 (0.2, 2.4) p=0.016
Mixed smoker/ex-smoker	-6.6% (-2.1%, 11.2%) p=0.004	-2.69 (-3.8, -1.5) p<0.0001
Sustained smoker	-49.5% (-42.7%, -56.2%)	-6.2 (-7.9, -4.6) p<0.0001

BMI: body mass index; CI: confidence interval; PEF: peak expiratory flow rate

S-Table 6. Adjusted PEF trajectories (L/min/year) by AER stratified by gender

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-value)
Males (N=29,056)		
0/yr	-1.65 (-1.85, -1.45)	reference
>0-1/yr	-3.02 (-3.22, -2.82)	-1.37 (-1.58, -1.16) p<0.001
>1-2/yr	-4.77 (-5.45, -4.09)	-3.12 (-3.8, -2.43) p<0.001
>2/yr	-5.00 (-6.24, -3.77)	-3.35 (-4.59, -2.11) p<0.001
Females (N=43,548)		
0/yr	-3.87 (-3.99, -3.74)	reference
>0-1/yr	-4.07 (-4.17, -3.96)	-0.20 (-0.33, -0.07)p =0.0027
>1-2/yr	-5.14 (-5.47, -4.81)	-1.27 (-1.61, -0.93) p <0.001
>2/yr	-5.49 (-6.12, -4.86)	-1.62 (-2.25, -0.99) p <0.001

AER: annual exacerbation rate; CI: confidence interval; PEF: peak expiratory flow rate

S-Table 7. adjusted FEV_1 trajectories (mL/yr) by AER stratified by gender

Annual exacerbation rate	Decline in FEV_1, mL/yr, (95% CI)	Average difference in FEV_1, mL/yr, decline between AER categories (95% CI), p-value
Males (n=3,508)		
0/yr	-22.2(-27.8, -16.7)	reference
>0-1/yr	-25.4 (-30.5, -20.3)	-3.9 (-8.6, 0.8) p = 0.102
>1-2/yr	-26.4 (-35.3, -17.6)	-4.9 (-13.5, 3.7) p = 0.264
>2/yr	-15.8 (-30.8, -0.9)	5.7 (-9.2, 20.6) p = 0.454
Females (n=4,664)		
0/yr	-18.8 (-22.2, -15.4) p = 0	Reference
>0-1/yr	-19.9 (-22.6, -17.2) p = 0	-1.1 (-4.3, 2) p = 0.486
>1-2/yr	-22.5 (-27, -17.9) p = 0	-3.7 (-8.5, 1.2) p = 0.138
>2/yr	-28.1 (-35.3, -20.9) p = 0	-9.3 (-16.8, -1.9) p = 0.014

AER: annual exacerbation rate; CI: confidence interval; FEV_1: forced expiratory volume in one second

S-Table 8. Adjusted and unadjusted PEF trajectory (L/min/yr) by AER in patients with lung function records starting from 1990 and from 2005

	Starting 1990 to 2019		Starting 2005 to 2019	
Annual exacerbation rate	**PEF Decline, L/min/yr (95% CI)**	**Average PEF difference (L/min/yr) decline between AER categories (95% CI; p-value)**	**PEF Decline, L/min/yr (95% CI)**	**Average PEF difference(L/min/yr) decline between AER categories (95% CI; p-value)**
	PEF unadjusted (N=108,958)		**PEF unadjusted (n=37,029)**	
0/yr	-3.22 (-3.29, -3.16)	**reference**	-1.69 (-1.83, -1.55) p =0	reference
>0-1/yr	-4.06 (-4.11, -4.01)	-0.84 (-0.92, -0.75) p = <0.001	-2.47 (-2.59, -2.35) p =0	-0.78 (-0.96, -0.59) p <0.001
>1-2/yr	-5.45 (-67, -5.23)	-2.22 (-2.45, -2.00) p = <0.001	-4.21 (-4.74, -3.68) p =0	-2.52 (-3.07, -1.97) p <0.001
>2/yr	-5.82 (-6.24, -5.41)	-2.60 (-3.02, -2.17) p = <0.001	-3.87 (-4.84, -2.89) p =0	-2.17 (-3.16, -1.19) p <0.001
	PEF adjusted (N=72,576)		**PEF adjusted (n=26,873)**	
0/yr	-2.93 (-3.04, -2.81)	reference	-1.40 (-1.63, -1.17) p <0.001	reference
>0-1/yr	-3.74 (-3.84, -3.64)	-0.81 (-0.93, -0.70) p = <0.001	-2.10 (-2.32, -1.88) p <0.001	-0.695 (-0.95, -0.44) p <0.001
>1-2/yr	-5.05 (-5.38, -4.73)	-2.13 (-2.46, -1.80) p = <0.001	-3.60 (-4.36, -2.84) p <0.001	-2.197 (-2.96, -1.43) p <0.001
>2/yr	-5.38 (-5.98, -4.78)	-2.46 (-3.06, -1.85) p = <0.001	-3.31 (-4.68, -1.98) p <0.001	-1.929 (-3.29, -0.57) p =0.0054

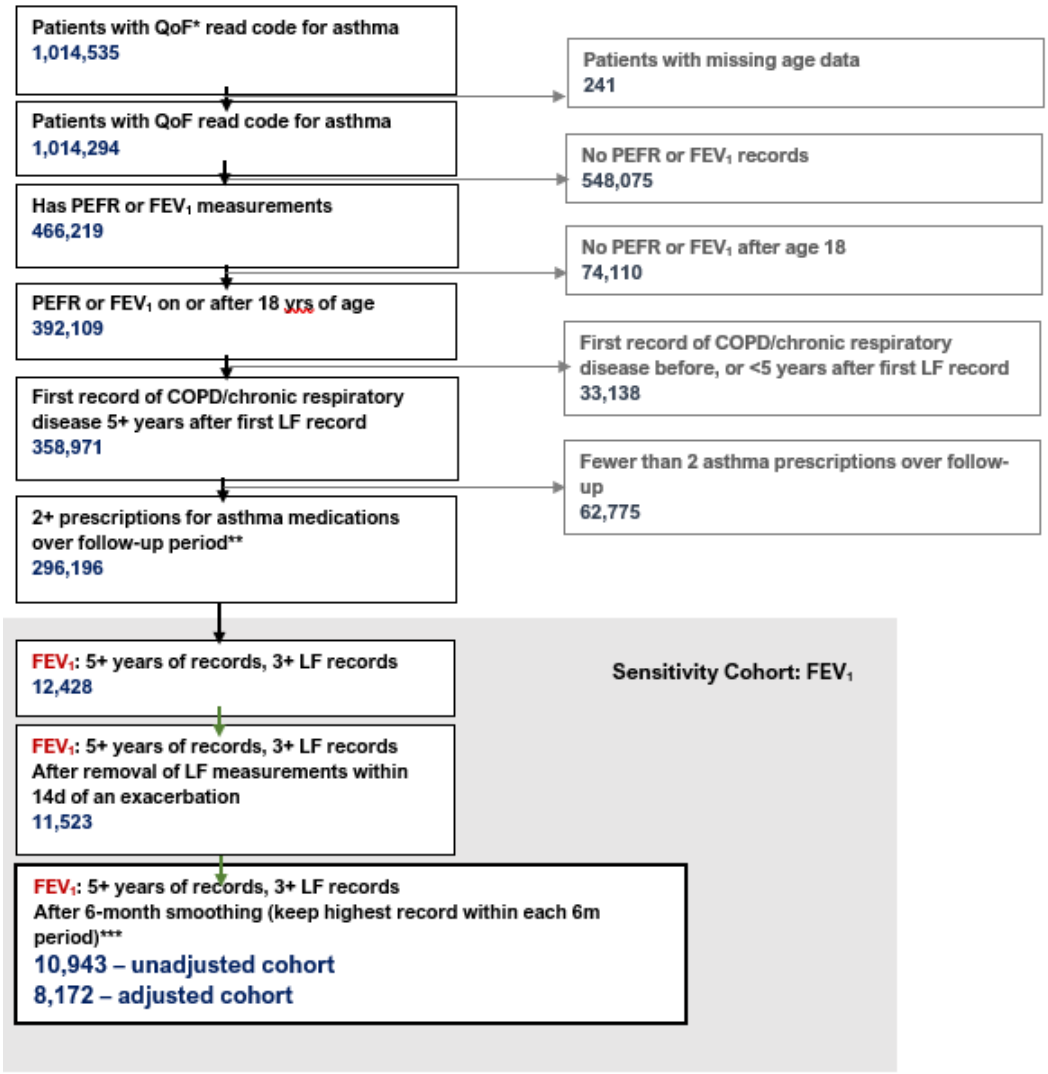
AER: annual exacerbation rate; CI: confidence interval; PEF: peak expiratory flow rate

S-Table 9 Adjusted and unadjusted FEV_1 trajectory (mL/yr) by AER in patients with lung function records starting from 1990

Annual exacerbation rate	Decline in FEV_1, mL/yr (95% CI)	Average difference in FEV_1, mL/yr, decline between AER categories (95% CI; p, value)
	Unadjusted (n=10,907)	
0/yr	-25.31 (-27.00, -23.61)	reference
>0-1/yr	-27.81 (-28.85, -26.76)	-2.50 (-4.49, -0.51) p = 0.0138
>1-2/yr	-29.56 (-32.34, -26.78)	-4.25 (-7.51, -0.99) p = 0.0105
>2/yr	-27.66 (-32.60, -22.73)	-2.60 (-7.57, 0.28) p = 0.3762
	Adjusted (n=8,169)	
0/yr	-20.2 (-23.3, -17.2)	reference
>0-1/yr	-21.8 (-24.4, -19.2)	-1.9 (-4.6, 0.9) p = 0.179
>1-2/yr	-23.4 (-27.8, -19.0)	-3.4 (-7.9, 1.1) p = 0.135
>2/yr	-23.8 (-31.0, -16.7)	-3.8 (-11, 3.4) p = 0.300

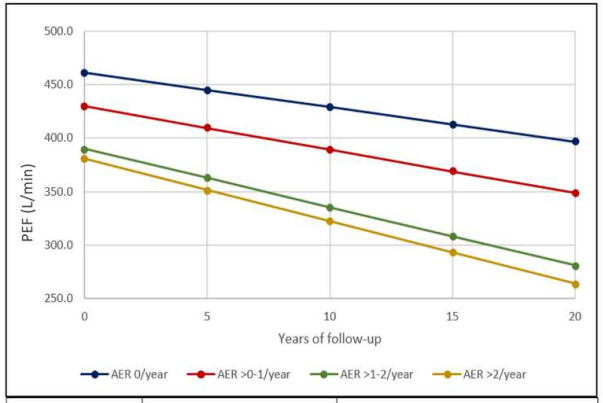
AER: annual exacerbation rate; CI: confidence interval; FEV_1: forced expiratory volume in one second

S-Figure 1: Patient disposition for FEV_1 cohort

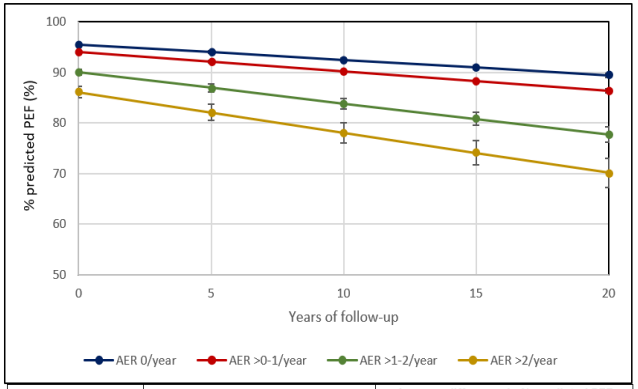


COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in one second; LF: lung function; PEF: peak expiratory flow rate; QoF: Quality Outcomes Framework

S-Figure 2: Unadjusted 20-year change in (**A) PEF** (L/min) and (B) **% predicted** (%/year) trajectories by annual exacerbation rate



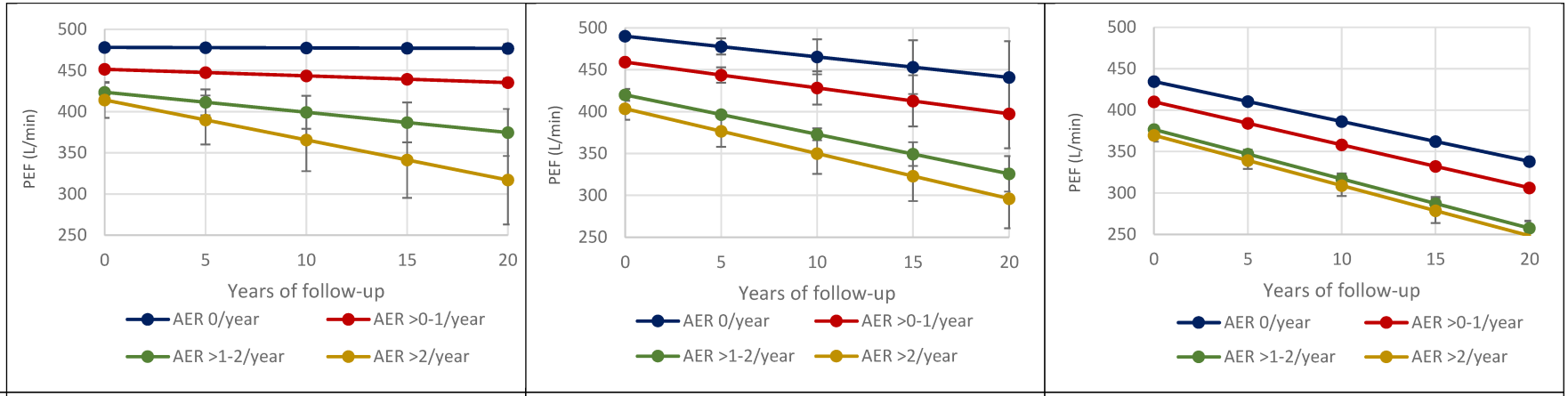
Annual exacerbation rate	Decline in PEF volume/yr (95% CI)	Average difference in PEF volume decline in L/min yr^{-1} between AER categories (95% CI; p)
0/yr	-3.223 L/min yr^{-1} (-3.29, -3.16)	**comparator**
>0-1/yr	-4.056 L/min yr^{-1} (-4.11, -4.01)	-0.83 (-0.92, -0.75) p <0.0001
>1-2/yr	-5.45 L/min yr^{-1} (-5.67, -5.23)	-2.23 (-2.46, -2.00) p <0.0001
>2/yr	-5.824 L/min yr^{-1} (-6.24, -5.4)	-2.60 (-3.03, -2.18) p <0.0001



Annual exacerbation rate (AER)	Decline in % predicted PEF (95% CI)	Average difference in % predicted PEF decline between AER categories (95% CI; p)
0/yr	-0.30 %/yr (-0.32, -0.29)	**reference**
>0-1/yr	-0.38 %/yr (-0.39, -0.37)	-0.08 %/yr (-0.10, -0.06) p<0.0001
>1-2/yr	-0.614%/yr (-0.66, -0.57)	-0.31 %/yr (-0.36, -0.26) p<0.0001
>2/yr	-0.80 %/yr (-0.89, -0.71)	-0.49 %/yr (-0.59, -0.40) p<0.0001

AER: annual exacerbation rate; CI: confidence interval PEF: peak expiratory volume

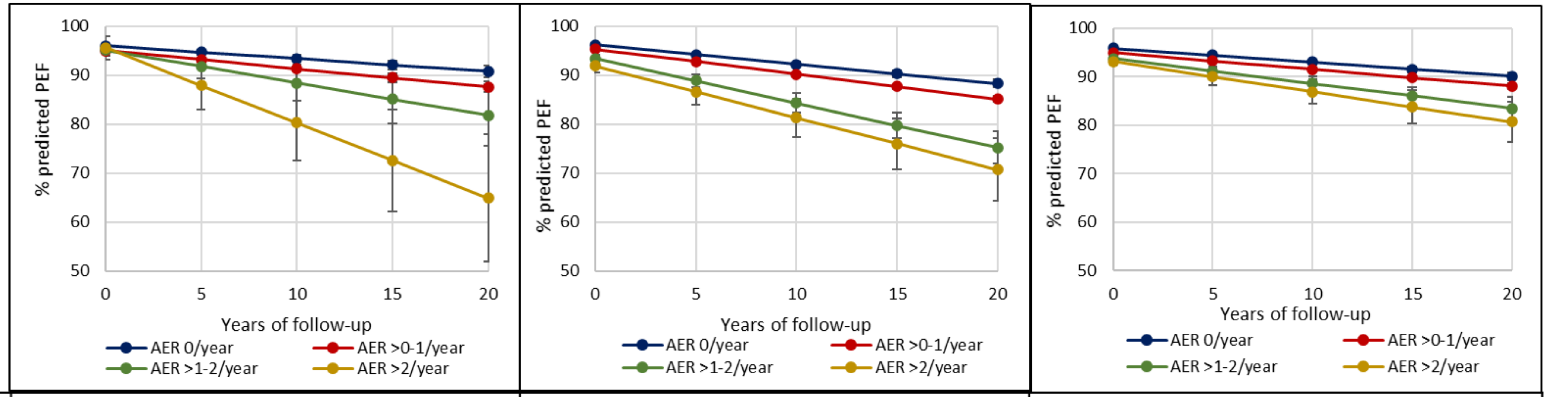
S-Figure 3: Unadjusted 20-year **PEF** (L/min) trajectories by annual exacerbation rate **stratified by patient age** at baseline



AER	18 – 24 years old at baseline		25 – 39 years old at baseline		40+ years old at baseline	
	Decline in PEF L/min (95% CI)	Average difference in PEF decline in **L**/min yr^{-1} (95% CI; p)	Decline in PEF L/min (95% CI)	Average difference in PEF L/min decline (95% CI; p)	Decline in PEF L/min (95% CI)	Average difference in PEF decline in **L**/min yr^{-1} (95% CI; p)
0/yr	-0.058 L/min y^{1} (-0.22, 0.10)	**comparator**	-2.465 L/min y^{1} (-2.57, -2.36)	**comparator**	-4.82 L/min y^{1} (-4.91, -4.73)	**comparator**
>0-1/yr	-0.808 L/min y^{1} (-0.96, -0.66)	-0.75 (-0.97, -0.53) p <0.0001	-3.086 L/min y^{1} (-3.17, -3.00)	-0.62 (-0.76, -0.48) p <0.0001	-5.19 L/min y^{1} (-5.25, -5.13)	-0.37 (-0.48, -0.27) p <0.0001
>1-2/yr	-2.447 L/min y^{1} (-3.30, -1.59)	-2.39 (-3.26, -1.52) p <0.0001	-4.711 L/min y^{1} (-5.14, -4.28)	-2.25 (-2.69, -1.80) p <0.0001	-5.96 L/min y^{1} (-6.20, -5.71)	-1.14 (-1.40, -0.87) p <0.0001
>2/yr	-4.861 L/min y^{1} (-6.47, -3.25)	-4.80 (-6.43, -3.18) p <0.0001	-5.365 L/min y^{1} (-6.17, -4.56)	-2.90 (-3.71, -2.09) p <0.0001	-6.07 L/min y^{1} (-6.54, -5.59)	-1.25 (-1.73, -0.76) p <0.0001

AER: annual exacerbation rate; CI: confidence interval; PEF: peak expiratory flow rate

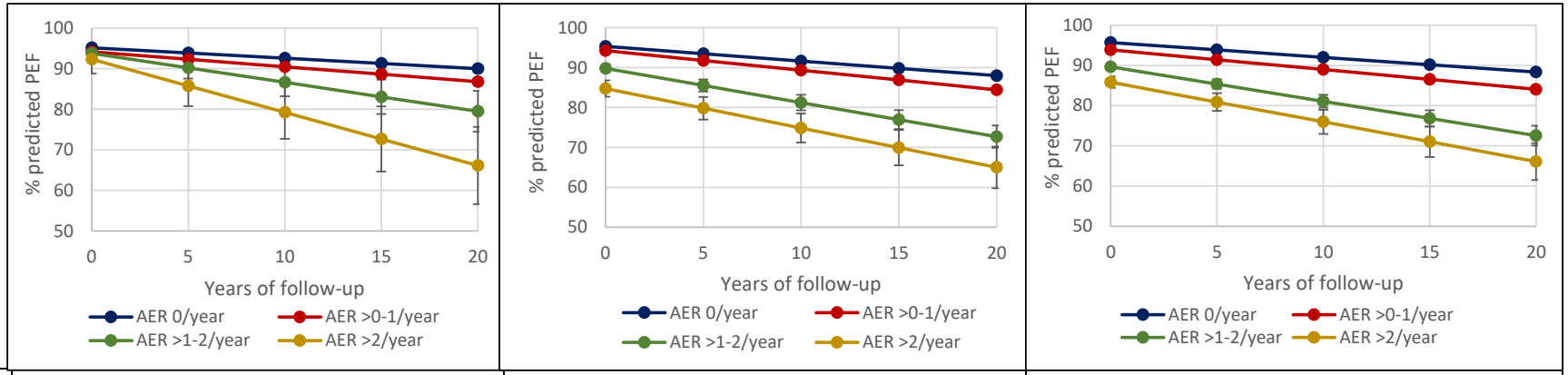
S-Figure 4: Adjusted 20 year **% predicted PEF** trajectories by annual exacerbation rate for patients **stratified by patient age** at baseline



AER	18 – 24 years old at baseline		25 – 39 years old at baseline		40+ years old at baseline	
	Decline in ppPEF/yr (95% CI)	Average difference in ppPEF decline/yr (95% CI)	Decline in ppPEF/yr (95% CI)	Average difference in ppPEF decline/yr (95% CI)	Decline in ppPEF/yr (95% CI)	Average difference in ppPEF decline (95% CI)
0/yr	**-0.26** (-0.31, -0.21)	**comparator**	**-0.39** (-0.43, -0.36)	**comparator**	**-0.29** (-0.32, -0.26)	**comparator**
>0-1/yr	**-0.37** (-0.41, -0.32)	**-0.11** (-0.18, -0.04) p = 0.001	**-0.51** (-0.54, -0.48)	**-0.11** (-0.16, -0.07) p <0.001	**-0.35** (-0.37, -0.32)	**-0.06** (-0.09, -0.02) p = 0.003
>1-2/yr	**-0.67** (-0.92, -0.41)	**-0.41** (-0.67, -0.14) p = 0.002	**-0.91** (-1.04, -0.78)	**-0.52** (-0.65, -0.38) p <0.001	**-0.51** (-0.6, -0.42)	**-0.22** (-0.32, -0.13) p <0.001
>2/yr	**-1.53** (-2.07, -1.0)	**-1.27** (-1.81, -0.73) p <0.001	**-1.06** (-1.31, -0.81)	**-0.67** (-0.92, -0.41) p <0.001	**-0.62** (-0.79, -0.45)	**-0.33** (-0.5, -0.16) p <0.001

AER: annual exacerbation rate; CI: confidence interval; PEF: peak expiratory flow rate; ppPEF: percent predicted peak expiratory flow rate

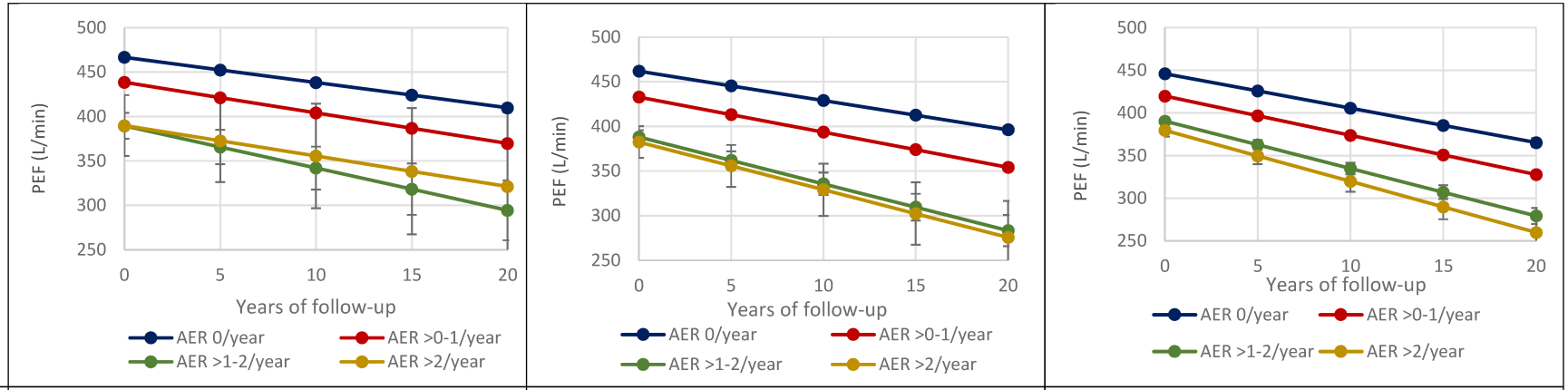
S-Figure 5: **Unadjusted** 20-year **% predicted** PEF trajectories by annual exacerbation rate stratified **by patient age** at baseline



AER	18 – 24 years old at baseline		25 – 39 years old at baseline		40+ years old at baseline	
	Decline in % predicted PEF (95% CI)	Average difference in % predicted PEF decline in (95% CI; p)	Decline in % predicted PEF (95% CI)	Average difference in % predicted PEF decline (95% CI; p)	Decline in % predicted PEF (95% CI)	Average difference in % predicted PEF decline (95% CI; p)
0/yr	-0.26 %/yr (-0.29, -0.23)	**comparator**	-0.37 %/yr (-0.39, -0.34)	**comparator**	-0.28 %/yr (-0.30, -0.26)	**comparator**
>0-1/yr	-0.37 %/yr (-0.4, -0.34)	-0.11 (-0.15, -0.07) p <0.0001	-0.49 %/yr (-0.51, -0.47)	-0.12 (-0.15, -0.10) p <0.0001	-0.34 %/yr (-0.35, -0.32)	-0.06 (-0.09, -0.03) p <0.0001
>1-2/yr	-0.71 %/yr (-0.87, -0.56)	-0.46 (-0.62, -0.3) p <0.0001	-0.86 %/yr (-0.94, -0.77)	-0.49 (-0.58, -0.40) p <0.0001	-0.53 %/yr (-0.59, -0.47)	-0.25 (-0.31, -0.18) p <0.0001
>2/yr	-1.31 %/yr (-1.61, -1.01)	-1.05 (-1.36, -0.75) p <0.0001	-0.99 %/yr (-1.15, -0.83)	-0.62 (-0.78, -0.46) p <0.0001	-0.679 %/yr (-0.80, -0.56)	-0.40 (-0.52, -0.28) p <0.0001

AER: annual exacerbation rate; CI: confidence interval; ppPEF: percent predicted peak expiratory flow

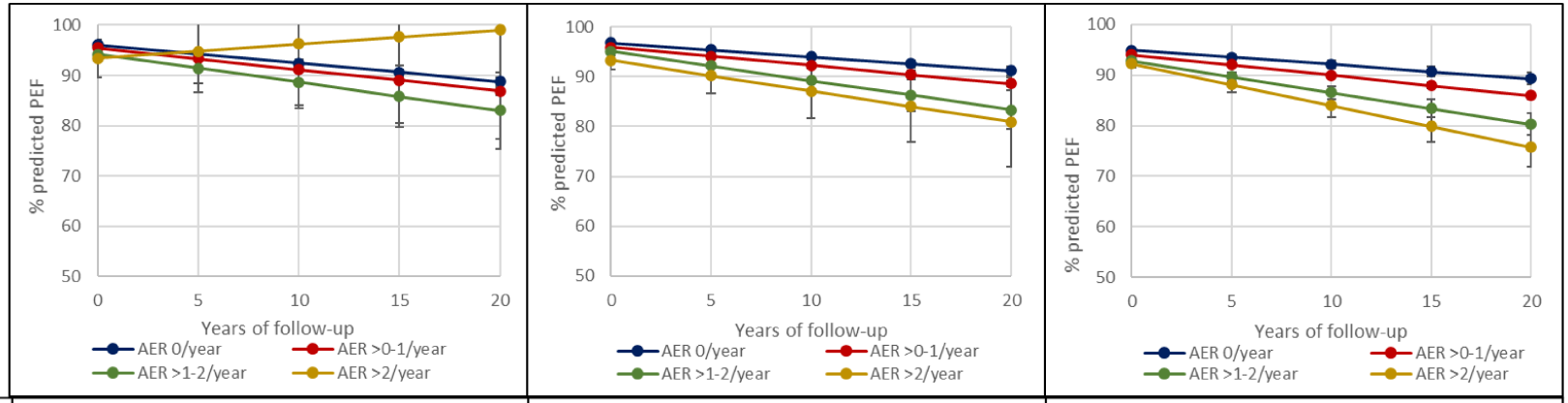
S-Figure 6: **Unadjusted** 20-year **PEF** (L/min) trajectories by annual exacerbation rate **stratified by yearly ICS dose**



AER	Lowest dose (mean daily dosage 0-147.1 mcg/day)		Medium dose (mean daily dosage >147.1-463.7 mcg/day)		Highest dose (mean daily dosage >463.7mcg)	
	Decline in PEF L/min (95% CI)	Average difference in PEF decline in L/min yr^{1} (95% CI; p)	Decline in PEF L/min (95% CI)	Average difference in PEF decline in L/min yr^{1} (95% CI; p)	Decline in PEF L/min (95% CI)	Average difference in PEF decline in L/min yr^{1} (95% CI; p)
0/yr	-2.84 L/min yr^{1} (-2.93, -2.74)	**comparator**	-3.29 L/min yr^{1} (-3.4, -3.18)	**reference**	-4.03 L/min yr^{1} (-4.18, -3.88)	**reference**
>0-1/yr	-3.44 L/min yr^{1} (-3.54, -3.34)	-0.60 (-0.74, -0.47) p <0.0001	-3.93 L/min yr^{1} (-4.02, -3.85)	-0.64 (-0.78, -0.51) p <0.0001	-4.60 L/min yr^{1} (-4.69, -4.52)	-0.57 (-0.74, -0.4) p<0.0001
>1-2/yr	-4.76 L/min yr^{1} (-5.71, -3.8)	-1.92 (-2.88, -0.95) p <0.0001	-5.24 L/min yr^{1} (-5.73, -4.75)	-1.95 (-2.45, -1.45) p <0.0001	-5.56 L/min yr^{1} (-5.81, -5.3)	-1.53 (-1.82, -1.23) p<0.0001
>2/yr	-3.43 L/min yr^{1} (-5.89, -0.97)	-0.59 (-3.05, 1.87) p = 0.637	-5.34 L/min yr^{1} (-6.48, -4.19)	-2.05 (-3.2, -0.89) p = 0.001	-5.98 L/min yr^{1} (-6.45, -5.52)	-1.95 (-2.44, -1.46) p<0.0001

AER: annual exacerbation rate; CI: confidence interval; ppPEF: percent predicted peak expiratory flow

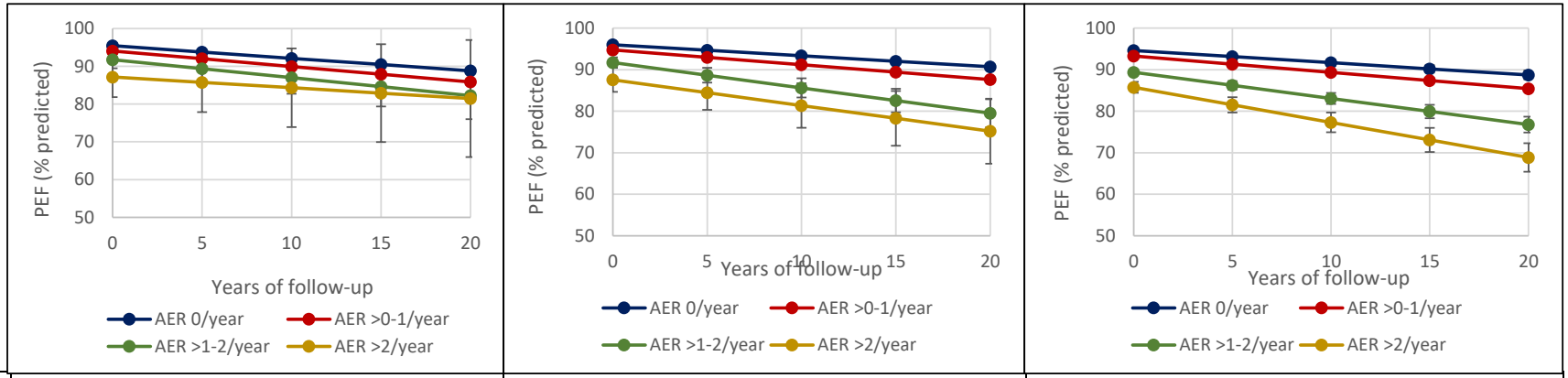
S-Figure 7: **adjusted** 20-year **% predicted PEF** by annual exacerbation rate for patients stratified **by mean yearly ICS dose**



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 ppPEF/yr (95% CI)	Average difference in ppPEF decline/yr (95% CI)	Decline in ppPEF/yr (95% CI)	Average difference in ppPEF decline/yr (95% CI)	Decline in ppPEF/yr (95% CI)	Average difference in ppPEF decline/yr (95% CI)
0/yr	**-0.36** (-0.39, -0.33)	**comparator**	**-0.28** (-0.31, -0.25)	**comparator**	**-0.28** (-0.33, -0.23)	**Comparator**
>0-1/yr	**-0.43** (-0.46, -0.4)	**-0.06** (-0.11, -0.02) p = 0.004	**-0.37** (-0.39, -0.34)	**-0.08** (-0.13, -0.04) p <0.001	**-0.41** (-0.43, -0.38)	**-0.13** (-0.18, -0.07) p <0.001
>1-2/yr	**-0.56** (-0.87, -0.25)	**-0.20** (-0.5, 0.11) p = 0.216	**-0.59** (-0.74, -0.43)	**-0.31** (-0.47, -0.15) p <0.001	**-0.63** (-0.72, -0.55)	**-0.35** (-0.45, -0.25) p <0.001
>2/yr	**0.28** (-0.61, 1.18)	**0.65** (-0.25, 1.54) p = 0.157	**-0.62** (-0.98, -0.26)	**-0.34** (-0.7, 0.02) p = 0.062	**-0.83** (-0.98, -0.67)	**-0.55**(-0.71, -0.39) p <0.001

AER: annual exacerbation rate; CI: confidence interval; PEF: peak expiratory flow rate; ppPEF: percent predicted peak expiratory flow rate

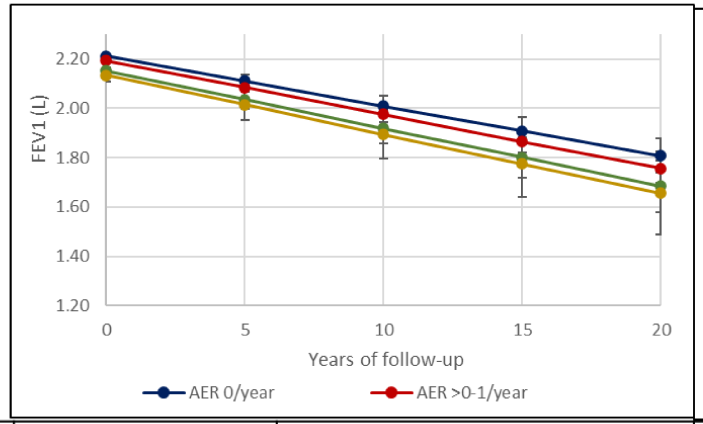
S-Figure 8: **Unadjusted** 20-year **% predicted PEF** trajectories by annual exacerbation rate stratified **by yearly ICS dose**

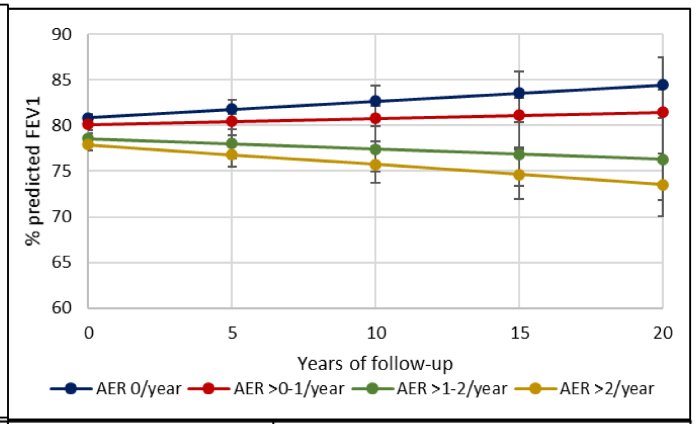


AER	Lowest dose (mean daily dosage 0-147.1 mcg/day)		Medium dose (mean daily dosage >147.1-463.7 mcg/day)		Highest dose (mean daily dosage >463.7mcg)	
	Decline in % predicted PEF (95% CI)	Average difference in % predicted PEF decline in (95% CI; p)	Decline in % predicted PEF (95% CI)	Average difference in % predicted PEF decline (95% CI; p)	Decline in % predicted PEF (95% CI)	Average difference in % predicted PEF decline (95% CI; p)
0/yr	-0.33 %/yr (-0.35, -0.31)	**comparator**	-3.29 %/yr (-3.4, -3.18)	**comparator**	-0.294 %/yr (-0.33, -0.26)	**comparator**
>0-1/yr	-0.41 %/yr (-0.43, -0.39)	-0.08 (-0.1, -0.05) p <0.0001	-3.93 %/yr (-4.02, -3.85)	-0.64 (-0.78, -0.51) p <0.0001	-0.393 %/yr (-0.41, -0.37)	-0.10 (-0.14, -0.06) p<0.0001
>1-2/yr	-0.48 %/yr (-0.67, -0.28)	-0.14 (-0.34, 0.06) p = 0.16	-5.24 %/yr (-5.73, -4.75)	-1.95 (-2.45, -1.45) p <0.0001	-0.629 %/yr (-0.69, -0.57)	-0.34 (-0.4, -0.27) p<0.0001
>2/yr	-0.29 %/yr (-0.79, 0.22)	0.05 (-0.46, 0.56) p = 0.85	-5.34 %/yr (-6.48, -4.19)	-2.05 (-3.2, -0.89) p = 0.0010	-0.844 %/yr (-0.95, -0.74)	-0.55 (-0.66, -0.44) p<0.0001

AER: annual exacerbation rate; CI: confidence interval; ppPEF: percent predicted peak expiratory flow

S-Figure 9: **adjusted** 20-year **FEV_1(L) and % predicted trajectories** by annual exacerbation rate (n=10,943)

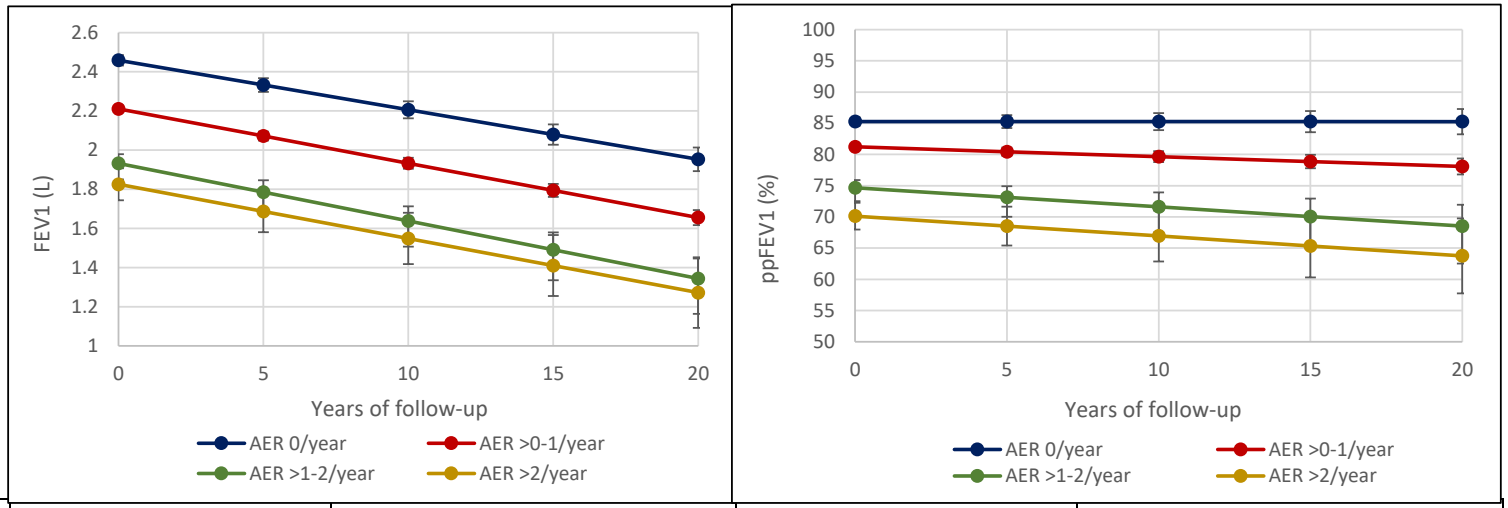




Annual exacerbation rate	Decline in FEV_1 mL/yr (95% CI)	Average difference in FEV_1 mL/yr decline between AER categories (95% CI)	Decline in $ppFEV_1$/yr (95% CI)	Average difference in $ppFEV_1$decline between AER categories (95% CI)
0/yr	**-20.22** (-29.19, -7.66)	**comparator**	**0.18** (0.04, 0.31)	**comparator**
>0-1/yr	**-21.85** (-24.43, -19.27)	**-1.93** (-4.66, 0.80) p = 0.167	**0.07** (-0.05, 0.18)	-0.11 % points (-0.23, 0.009) p = 0.070
>1-2/yr	**-23.43** (-27.84, -19.03)	**-3.46** (-7.96, 1.03) p = 0.131	**-0.11** (-0.31, 0.08)	-0.29 % points (-0.49, -0.91) p = 0.004
>2/yr	**-23.85** (-30.97, -16.74)	**-3.86** (-11.08, 3.36) p = 0.295	**-0.22** (-0.54, 0.09)	-0.40 % points (-0.72, -0.08) p = 0.014

AER: annual exacerbation rate; CI: confidence interval; $ppFEV_1$: percent predicted forced expiratory volume in one second

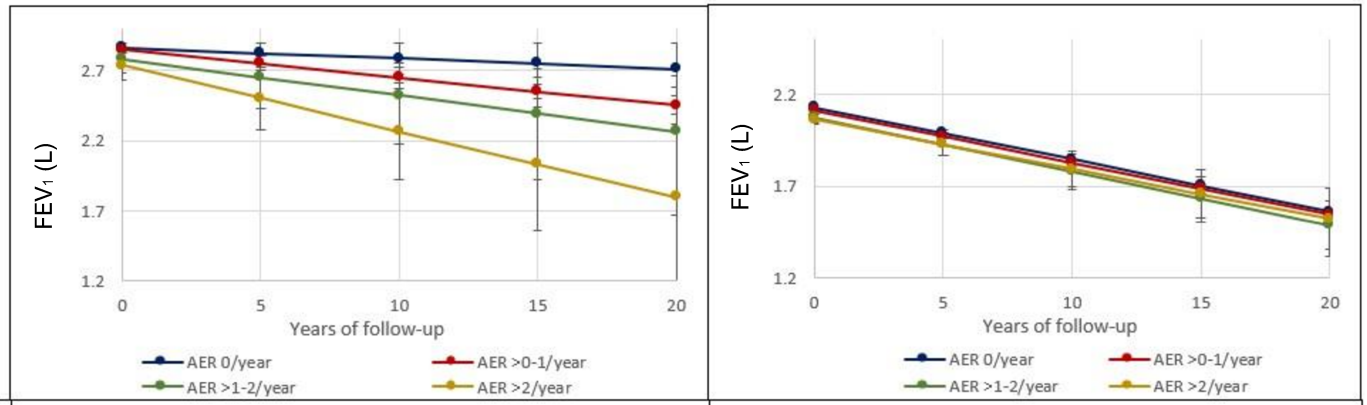
S-Figure 10: unadjusted change in 20-year **FEV_1 (L/1 sec)** and **% predicted** trajectories by annual exacerbation rate (n=10,943)



	Decline in FEV_1 mL/yr (95% CI)	Average difference in FEV_1 mL/yr decline between AER categories (95% CI; p)	Decline in $ppFEV_1$/yr (95% CI)	Average difference in $ppFEV_1$ decline between AER categories (95% CI; p)
0/yr	-25.3 mL/yr (-27.0, -23.6)	**comparator**	-0.001 %/yr (-0.07, 0.07)	**comparator**
>0-1/yr	-27.8 mL/yr (-28.8, -26.7)	-2.5 (-4.5, -0.5) p = 0.014	-0.158 %/yr (-0.2, -0.12)	-0.16 (-0.23, -0.08) p <0.0001
>1-2/yr	-29.4 mL/yr (-32.2, -26.6)	-4.1 (-7.4, -0.9) p = 0.013	-0.307 %/yr (-0.42, -0.2)	-0.31 (-0.43, -0.18) p <0.0001
>2/yr	-27.7 mL/yr (-32.6, -22.7)	-2.4 (-7.6, 2.8) p = 0.372	-0.318 %/yr (-0.51, -0.13)	-0.32 (-0.52, -0.11) p = 0.002

AER: annual exacerbation rate; CI confidence interval; FEV_1: forced expiratory volume in one second; $ppFEV_1$: percent predicted forced expiratory volume in one second

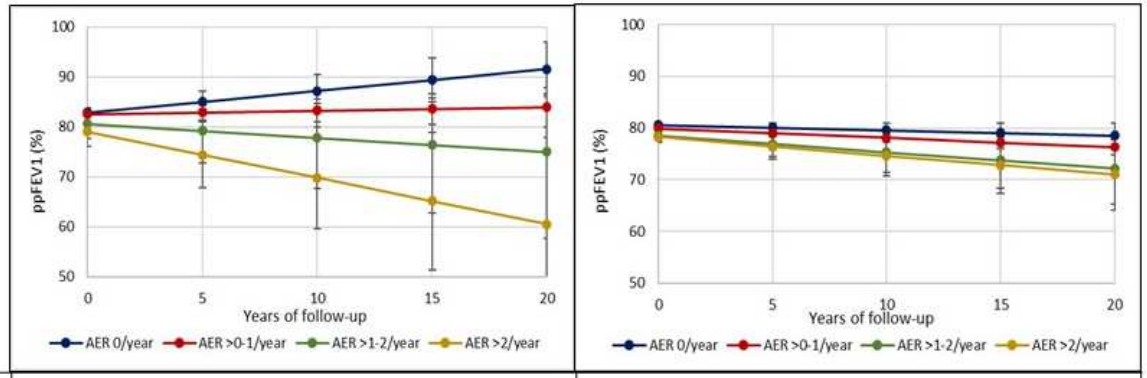
S-Figure 11: **Adjusted** 20-year **FEV_1** (L) trajectories by annual exacerbation rate stratified **by patient age at baseline**



AER	18 – 39 years old at baseline		40+ years old at baseline	
	Decline in FEV_1 volume (95% CI)	Average difference in FEV_1 volume decline (95% CI; p)	Decline in FEV_1 volume (95% CI)	Average difference in FEV_1 volume decline (95% CI; p)
0/yr	**-7.5** mL/yr (-15.3, 0.2)	**comparator**	**-28.5** mL/yr (-30.8, -26.1)	**comparator**
>0-1/yr	**-20**.0 mL/yr (-25.5, -14.4)	**-12.4** mL/yr (-22.0, -2.9) p = 0.011	**-28.4** mL/yr (-29.9, -26.9)	**0.1** mL/yr (-2.7, 2.9) p = 0.963
>1-2/yr	**-25.7** mL/yr (-42.2, -9.2)	**-18.2** mL/yr (-36.4, 0.0) p = 0.050	**-29.3** mL/yr (-33.2, -25.5)	**-0.9** mL/yr (-5.4, 3.7) p = 0.708
>2/yr	**-46.8** mL/yr (-71.5, -22.2)	**-39.3** mL/yr (-65.2, -13.4) p = 0.003	**-27.0** mL/yr (-34.0, -20.0)	**1.5** mL/yr (-5.9, 8.9) p = 0.697

AER: annual exacerbation rate; CI: confidence interval; $ppFEV_1$: percent predicted forced expiratory volume in one second

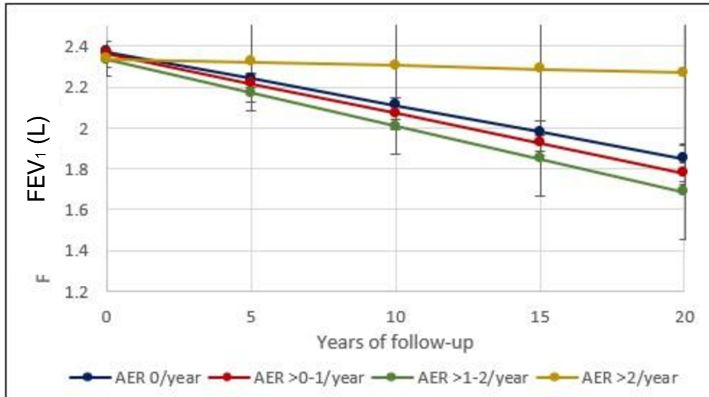
S-Figure 12: **Adjusted** 20-year **% predicted FEV_1** trajectories by annual exacerbation rate stratified *by patient age at baseline*

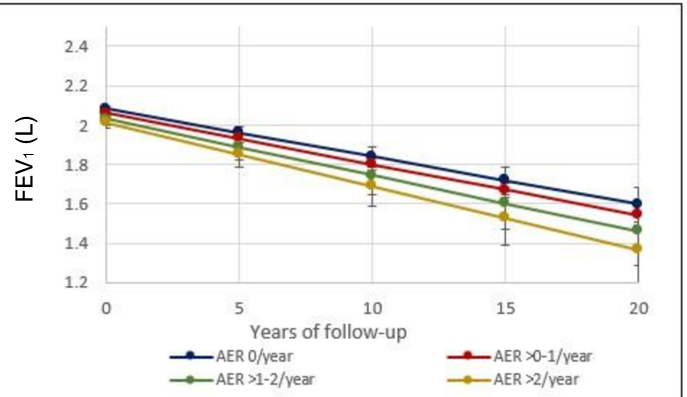


AER	18 – 39 years old at baseline		40+ years old at baseline	
	Decline in ppFEV$_1$/yr (95% CI)	Average difference in ppFEV$_1$decline/yr between AER categories (95% CI)	Decline in ppFEV$_1$/yr (95% CI)	Average difference in ppFEV$_1$decline/yr between AER categories (95% CI)
0/yr	**0.43** (0.21, 0.66)	**comparator**	**-0.10** (-0.20, 0.00)	**comparator**
>0-1/yr	**0.07** (-0.09, 0.23)	**-0.37**(-0.64, -0.09), p = 0.010	**-0.18** (-0.24, -0.12)	**-0.08** (-0.20, 0.03), p = 0.170
>1-2/yr	**-0.28** (-0.76, 0.20)	**-0.72** (-1.25, -0.18), p = 0.008	**-0.32** (-0.48, -0.16)	**-0.22** (-0.41, -0.03), p = 0.021
>2/yr	**-0.93** (-1.65, -0.20)	**-1.36** (-2.12, -0.6), p <0.001	**-0.36** (-0.65, -0.07)	**-0.26** (-0.57, 0.04), p = 0.092

AER: annual exacerbation rate; CI: confidence interval; ppFEV$_1$; percent predicted forced expiratory volume in one second

S-Figure 13: Adjusted 20-year **FEV_1** (L) trajectories by annual exacerbation rate **stratified by yearly ICS dose**

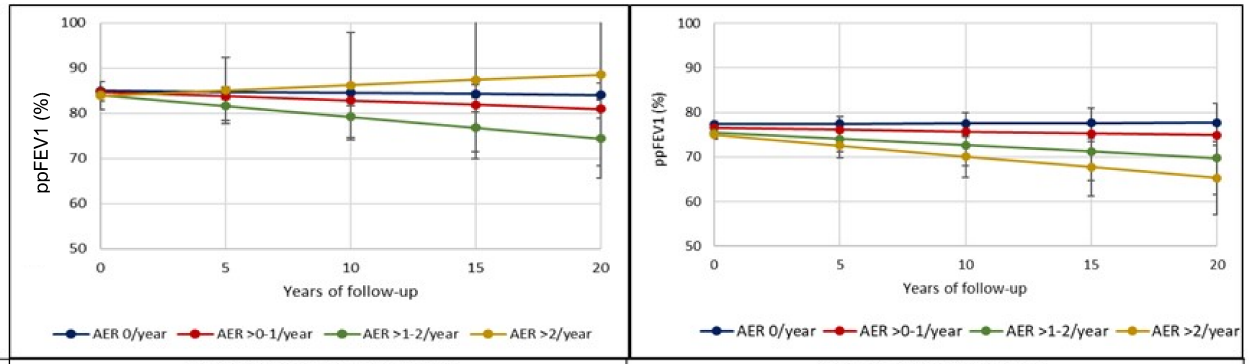




AER	Lowest two terciles ICS dosage (mean yearly dosage 0-169,368.4mg/yr)		Highest tercile ICS dosage (mean yearly dosage >169,368.4mg/yr)	
	Decline in FEV_1 volume (95% CI)	Average difference in FEV_1 volume decline (95% CI; p)	Decline in FEV_1 volume (95% CI)	Average difference in FEV_1 volume decline (95% CI; p)
0/yr	**-26.2** mL/yr (-29.1, -23.3)	**comparator**	**-24.4** mL/yr (-28.2, -20.6)	**comparator**
>0-1/yr	**-29.3** mL/yr (-31.5, -27.1)	**-3.1** mL/yr (-6.7, 0.6) p = 0.097	**-25.9** mL/yr (-27.9, -24)	**-1.6** mL/yr (-5.9, 2.7) p = 0.475
>1-2/yr	**-32.3** mL/yr (-42, -22.6)	**-6.1** mL/yr (-16.2, 4.0) p = 0.237	**-28.5** mL/yr (-32.7, -24.3)	**-4.1** mL/yr (-9.8, 1.5) p = 0.153
>2/yr	**-3.4** mL/yr (-25.6, 18.9)	**+22.9** mL/yr (0.4, 45.3) p = 0.046	**-32.3** mL/yr (-39.5, -25.1)	**-7.9** mL/yr (-16.1, 0.2) p = 0.056

AER: annual exacerbation rate; CI: confidence interval; $ppFEV_1$: percent predicted forced expiratory volume in one second:

S-Figure 14: **Adjusted** 20-year **% predicted FEV_1** trajectories by annual exacerbation rate **stratified by mean yearly ICS dose**



AER	Lowest two terciles ICS dosage (mean yearly dosage 0-169,368.4mg/yr)		Highest tercile ICS dosage (mean yearly dosage >169,368.4mg/yr)	
	Decline in $ppFEV_1$/yr (95% CI)	Average difference in $ppFEV_1$ decline/yr between AER categories (95% CI)	Decline in $ppFEV_1$/yr (95% CI)	Average difference in $ppFEV_1$ decline/yr between AER categories (95% CI)
0/yr	**-0.05** (-0.16, 0.06)	**Comparator**	**0.01** (-0.14, 0.16)	**comparator**
>0-1/yr	**-0.19** (-0.28, -0.11)	**-0.15** (-0.28, -0.01), p = 0.038	**-0.12** (-0.2, -0.04)	**-0.13** (-0.3, 0.04) p = 0.141
>1-2/yr	**-0.48** (-0.85, -0.11)	**-0.43** (-0.82, -0.05), p = 0.026	**-0.29** (-0.46, -0.12)	**-0.30** (-0.53, -0.07) p = 0.010
>2/yr	**0.23** (-0.61, 1.08)	**0.28** (-0.57, 1.13), p = 0.522	**-0.50** (-0.8, -0.21)	**-0.51** (-0.84, -0.18) p = 0.002

AER: annual exacerbation rate; CI: confidence interval; ICS: inhaled corticosteroid; $ppFEV_1$; percent predicted forced expiratory volume in one second

References

1 Optimum Patient Care Research Database (OPCRD. optimumpatientcare.org/database-overview/ (accessed 5 Jul 2019).

2 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

3 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**:1701785. doi:10.1183/13993003.01785-2017

4 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