Exacerbation risk and characterisation of the UK's asthma population, from infants to old age

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Summary box

What is the key question?

What are the characteristics of the UK's general asthma population, including all phenotypes and ages, and how are these associated with the risk of an exacerbation?

What is the bottom line?

Many differences in demographics, clinical characteristics, and exacerbation rates, were found between the four generations of asthma patients; the oldest (≥55 years) cohort, followed by the youngest (<5 years) cohort, had the most severe asthma with the highest exacerbation rates.

Why read on?

This is the first description of the UK's general asthma population and includes all those with current asthma, from infants to old age.

Abstract

BACKGROUND:

Few studies have examined the characteristics of a general asthma population; most have focussed on more severe patients or severe exacerbations.

METHODS:

This population-based cohort study, April 2007 to September 2015, used linked primary and secondary care electronic healthcare records (Clinical Practice Research Datalink, Hospital Episode Statistics). Characteristics of four age cohorts: 'Under 5s', '5 to 17s', '18 to 54s', '55+', were described. Exacerbation risk factors, including asthma severity (measured by the British Thoracic Society stepwise approach), were assessed using Poisson regression.

RESULTS:

424,326 patients with current asthma were eligible (N, median follow-up: 'Under 5s'=17,320, 1 year; '5 to 17s'=82,707, 3.3 years; '18 to 54s'=210,724, 4 years; '55+'=113,575, 5.1 years). Over 60% of the total study population had mild asthma (BTS steps 1/2). There were differences between the cohort's characteristics, including by gender, disease severity and exacerbation pattern. The rate of exacerbations was highest in the oldest cohort and lowest in the '5 to 17s' cohort (rate per 10 person-years, (95% CI), 'Under 5s'=4.27 (4.18-4.38), '5 to 17s'=1.48 (1.47-1.50), '18 to 54s'=3.22 (3.21-3.24), '55+'=9.40 (9.37-9.42)). In all cohorts, exacerbation rates increased with increasing asthma severity, after adjusting for confounders including gender, socioeconomic status, smoking, BMI, atopy, rhinitis, gastroesophageal reflux, anxiety, depression and COPD.

CONCLUSION:

The majority of UK asthma patients had mild asthma and did not experience an exacerbation during follow-up. Patients aged >55 years had the lowest proportion with mild asthma and highest rate of exacerbations; the opposite was found in patients aged between 5 to 18 years.

Introduction

Asthma is a common disease and its lifetime prevalence in the UK continues to rise[1]. Internationally, the UK ranks as having one of the highest prevalence and mortality rates in Europe[2,3]. Asthma causes a significant burden to the NHS across the spectrum of ages, with 5.4 million people receiving treatment and approximately 65,000 hospital admissions yearly[4]. In addition it leads to a significant societal burden including absence from work and school.

Most asthma patients do not require secondary care intervention yet there is limited knowledge on the characterisation of national asthma populations. To date, epidemiological studies have focussed on patients with more severe disease, distinct phenotypes, or have separated those with childhood-onset from adult-onset asthma. In addition, most published reports on exacerbations have analysed only hospital admissions or Accident & Emergency (A&E) visits. Currently, we do not have comprehensive knowledge on the UK's general asthma population; this is needed to help us understand the natural history of asthma and guide population-level public health measures.

Over 98% of the UK population is registered with a general practitioner (GP)[5]. Most asthma patients first present to their GP who makes the diagnosis based on their respiratory symptoms, signs and test results; in patients with insufficient evidence, such as children under 5 years who cannot perform spirometry, a period of watchful waiting or monitored treatment may be advocated. Primary care electronic healthcare records, originating from routine clinical practice, capture this and a huge amount of other clinical and demographic information in a longitudinal record.

We have used national electronic healthcare records to describe, for the first time, the UK's asthma population, laying out the differences and similarities that exist between the generations using four consecutive age cohorts between infancy and old age. We have assessed several factors that may be associated with an increased risk of an exacerbation.

Methods

Data sources

Clinical Practice Research Datalink (CPRD) included 674 GP practices and current coverage of over 11.3 million patients who represent the UK's population with respect of age, gender, BMI and ethnicity[6]. Approximately 60% of CPRD practices have patient-level linkage to Hospital Episode Statistics (HES) data (collected during a patient's visit to an NHS hospital), Index of Multiple Deprivation (IMD) and Office of National Statistics mortality data.

Study design and population

We conducted a population-wide open cohort study. The study population consisted of patients in CPRD linked practices with validated Read codes (a clinical terminology system) indicating prevalent or incident asthma[7]. Patients were eligible if a code for asthma had been recorded at ≤2 years prior to study entry if aged <18 years, or ≤3 years if aged ≥18 years (Figure 1). Patients entered the study at

the latest of their asthma diagnosis date, the date the practice began recording research quality data, or 1st April 2007. Patient follow-up was censored at the earliest of 30th September 2015, death, transfer out of CPRD practice, linkage end date or practice last collection date. The patient's age at study entry dictated which cohort they entered. Age categories were based on the age distinctions used in the BTS asthma guidance[8]: under 5 years old, 5-12 years old and adolescents were combined in the 5-17s year cohort, and the adult cohort was split into two cohorts due to the possible confounding from COPD after 55 years old.

Outcome and variables

The main outcome was asthma exacerbations. An exacerbation was defined as ≤300mg oral corticosteroids (OCS) (not prescribed during an annual asthma review), or an A&E visit, or hospital admission. A cut-off of ≤150mg OCS was used for children <5 years old. Exacerbations recorded within 14 days after the index one were considered part of the same exacerbation. Level of care of each exacerbation was documented as the highest level per episode. Incident lower respiratory tract infections treated with antibiotics (Ax-LRTIs) were also measured, by identifying specific Read codes (available upon request) with same day prescription of appropriate antibiotics.

Body mass index (BMI) was measured using kg/m^2 (z-scores were used if <5 years old). A history of atopy, rhinitis, gastroesophageal reflux (reflux), anxiety and depression were recorded using appropriate Read codes (available upon request). COPD was classified by Read codes, a smoking history, and age >35 years[9]. The British Thoracic Society (BTS) stepwise approach (incorporating inhaler class and dose) is a recommended evidence-based method of measuring asthma severity[8]. Using the 2016 guidelines, patients were classified by their highest BTS step (most severe asthma) using all medications prescribed during the year before their study start date. Step 6 is 'continuous or frequent' OCS use; we defined this as ≥6 annual OCS prescriptions that must have occurred in ≥2 yearly-quarters (a yearly-quarter was 3 consecutive months). Approximately 20% of inhaled corticosteroid (ICS) prescriptions did not have a precise dose recorded; using the BTS guidelines and the type of ICS device and dosage prescribed the ICS dose levels were imputed with good accuracy.

Statistical analysis

Baseline characteristics were tabulated for each cohort. To take into account multiple exacerbations, a repeated measures Poisson regression model was used to calculate crude rate ratios of exacerbations. This model was also used to determine the relative rates of exacerbations by BTS step, adjusting for: gender, age, IMD (socioeconomic index, 1 is least deprived), BMI, smoking status, atopy, rhinitis, reflux, anxiety, depression and COPD status. Where >20% of the data were missing the variable was excluded from the regression model. The data were also modelled using Poisson regression and time to first exacerbation during study follow-up; results were displayed by Kaplan-Meier graphs.

Ethics

The protocol for this research was approved by the Independent Scientific Advisory Committee (ISAC) for MHRA Database Research (protocol 16_067), the approved protocol was made available during peer review. Generic ethical approval for observational research using the CPRD with approval from ISAC has been granted by a Health Research Authority Research Ethics Committee (East Midlands – Derby, REC reference number 05/MRE04/87).

Results

Patient characteristics

In the total study population there were 424,326 patients with current asthma. The number of patients and follow-up varied between cohorts, the smallest and shortest follow-up was in the 'Under 5s' and the largest, with a longer follow-up, was the '18 to 54s' cohort ('Under 5s' N=17,320, IQR 0.5-1.8 years; '5 to 17s' N=82,707, IQR 1.4-5.8; '18 to 54s' N=210,724, IQR 1.7-6.9 years; '55+' N=113,575, IQR 2.4-7.6) (Table 1). Female prevalence increased with increasing cohort age and became the dominant gender from 18 years onwards (Table 1). Over 70% in the 'Under 5s' cohort were aged between 3 and 5 years old (Table 1). In the '55+' cohort the numbers of patients were inversely proportional to the age group. The highest percentage of smokers were in the '18 to 54s' cohort (current 25.9%) and ex-smokers in the '55+' cohorts (ex-smoker 49.2%) (Table 1). Recorded BMI was predominantly either normal or underweight if cohort age was <18 years, but normal or above if cohort age was ≥ 18 years (Table 1).

Taking the total cohort as a whole (all ages), 35% (149,338) of patients were not taking regular asthma medication and 27% (112,937) were taking an ICS at the lowest dose appropriate for their age. The proportion in each BTS step varied with each cohort (Table 1 & Figure 2). Around 70% of patients <55 years old were in BTS step 1 or 2, only in the 'Under 5s' cohort were there more in BTS step 2 than 1 (Table 1). The '55+' cohort had the smallest proportion with patients on BTS steps 1 or 2 (44%). All the cohorts had a very low proportion in BTS step 6 (< 2%).

The proportion of patients with atopy was highest in the two youngest cohorts (<18 years) (Table 1). The proportion of patients with rhinitis, reflux, anxiety or depression was highest in the two oldest cohorts (≥18 years) (Table 2). Just under one quarter aged ≥ 55 years had a co-existent diagnosis of COPD (Table 1), of these 66% had a COPD diagnosis after their asthma diagnosis.

Exacerbation characteristics

The rate of exacerbations was highest in the oldest age group, followed by the youngest age group, and lowest in the '5 to 17s' cohort (exacerbations per 10 person years: '55+'=9.4 (95%CI 9.37-9.42), 'Under 5s'=4.27 (95%CI 4.18-4.38), '18 to 54s'=3.22 (95% CI 3.21-3.24), '5 to 17s'= 1.48 (95% CI 1.47-1.5)) (Table 2). Of those who did exacerbate, the majority had ≤1 exacerbation per year, in cohorts aged ≥5 years (Ann. Freq. ≤1/year: '5 to 17s'=86.9%; '18 to 54s'=81.3%; '55+'=65%); the opposite was found in the 'Under 5s' cohort, in whom just over half experienced >1 exacerbation per year (54.7%) (Table 2 & Figure 3). Around 85% of exacerbations in each cohort did not require over-night hospitalisation ('Under 5s'= 85.6%, '5 to 17s'= 85.2%, '18 to 54s'= 83.1%, '55+'= 88.7%). All patients were most likely to see their GP as their maximum level of care; the oldest age cohort had a lower proportion of hospitalised exacerbations, but highest proportion of asthma deaths (Table 2).

The rate of Ax-LRTIs was much lower than the rate of exacerbations; the rate was highest in the '55+' cohort and lowest in the '5 to 17s' cohort ('55+'=1.93 (95% CI 1.92-1.94) exacerbations per 10 person-years, '5 to 17s'=0.22 (95% CI 0.21-0.22) exacerbations per 10 person-years). Of those with an Ax-LRTI, <10% occurred at the time of, or 14 days after an exacerbation ('Under 5s'= 5%, '5 to 17s'= 4.9%, '18 to 54s'= 8.3%, '55+'= 7.3%) and ≤1% of Ax-LRTIs preceded an exacerbation within 14 days ('Under 5s'= 0.6%, '5 to 17s'= 0.4%, '18 to 54s'= 0.9%, '55+'= 1%).

The rate of exacerbations increased with increasing asthma severity (BTS step) in every cohort, with the lowest rate, 0.73 (95% CI 0.7-0.77) exacerbations per 10 person-years, in BTS step 1 in '5 to 17s' cohort and the highest rate, 60.2 (95% CI 57.97-62.52) exacerbations per 10 person-years, in BTS step 6 in the '55+' cohort (Table 3).

Effect of demographic and clinical characteristics on exacerbation rates (univariable analysis)

Female gender was significantly associated with exacerbation risk in all cohorts except for the '5 to 17s' cohort; the relative rate decreased in the 'Under 5s' but increased in the oldest two cohorts (Female: 'Under 5s' IRR=0.84 (95% CI 0.76-0.92), '18 to 54s' IRR=1.67 (95% CI 1.64-1.71), '55+' IRR=1.11 (95% CI 1.09-1.13), p<0.001). Within the oldest two cohorts, as age increased exacerbations rates also increased, the opposite occurred in the youngest two cohorts (Table S1-4). Current and ex-smoking was significantly associated with an increased rate in patients' ≥18 years (Table S1-4). Patients with a 'non-normal' BMI (underweight, overweight or obese) had higher exacerbation rates in the '5 to 17s' and '18 to 54s' cohort (Table S1-4). Having atopy, rhinitis, reflux, anxiety, or depression increased the relative rate of exacerbations in all cohorts (Table S1-4). Exacerbation rates were also higher in asthma patients with COPD (Table S3-4).

Effect of asthma severity on exacerbation rates (multivariable analysis modelling on all exacerbations)

Each increase in BTS step was significantly associated with an increased rate of exacerbations compared to BTS step 1 (Figure 4). This effect was seen in all cohorts, but the largest adjusted rate ratios were found in the youngest cohort, and the smallest were found in the oldest cohort ('Under 5s' cohort: step 2 IRR=2.3 (95% CI 2.0-2.6), step 3 IRR=4.5 (95% CI 3.7-5.5), step 4 IRR=4 (95% CI 3.5-4.7), step 5 IRR=4.7 (95% CI 2.7-8.1), step 6 IRR=16.3 (95% CI 0.8-348), adjusted for age, gender, IMD, atopy, rhinitis, reflux and anxiety; '55+' cohort: step 2 IRR=1.3 (95% CI 1.2-1.3), step 3 IRR=1.6 (95%CI 1.5-1.6), step 4 IRR=2 (95% CI 1.9-2), step 5 IRR=2.3 (2.2-2.3), step 6 IRR=10 (95% CI 9.3-10.7), adjusted for age, gender, IMD, BMI, atopy, rhinitis, reflux, anxiety, depression and COPD (Figure 4).

Effect of asthma severity on time to first exacerbation during study follow-up

Time to first exacerbation analysis revealed a comparable pattern to analyses including all exacerbations. The Kaplan-Meier curves were steepest, with the shortest median times to first exacerbation, with each increasing BTS step (Figure 5 & Table S2). In general, the curves were also steepest in the following cohort order: '55+', 'Under 5s', '18 to 54s' and '5 to 17s' (Figure 5 & Table S2).

Discussion

We have undertaken the first descriptive study of the UK's general asthma population and found many similarities and differences between the characteristics of cohorts representing: infants to preschoolers (Under 5s), young children to teenagers (5 to 17s), younger adults to middle age (18 to 54s), and middle to old age (55+). One clear difference was gender; males were found to be more prevalent in the younger cohorts, <18 years but the opposite was found in the older cohorts; these results are in agreement with other prevalence, as well as incidence, asthma studies[10,11]. Smoking prevalence increased between the '5 to 17s' and '18 to 54s' cohort but fell in the '55+' cohort, in keeping with UK smoking data[12]. Adult BMI (≥ 18 years) increased with increasing cohort age, compatible with published national data[13]. Atopy prevalence was highest in the two youngest cohorts (< 18 years), which appears consistent with studies showing that late-onset asthma is less likely to be allergic asthma[14]. A history of rhinitis and reflux both showed a steady increase with age; presently there is a paucity of published data on the relationship between age and these disorders.

The majority of asthma patients (>60% of the total study population) had mild asthma, BTS step 1 or 2; it is notable that this cohort only included patients with current asthma and excluded patients who

had not visited their GP practice for their asthma in the last 2 or 3 years (depending on their age). However, the level of severity varied considerably between the age cohorts. The youngest and oldest cohorts, <5 years old and ≥ 55 years old, had the lowest proportion on BTS step 1. Only in the 'Under 5s' cohort were patients more likely to have BTS step 2 than 1; this may be related to the difficulty in diagnosing asthma in children <5 years old (spirometry is often not possible and it can be difficult distinguishing asthma from 'recurrent wheeze') and a reluctance to diagnose until a child is more symptomatic. Asthma was more severe in the '55+' cohort, in keeping with other older asthma populations[15]. Nearly a quarter of the '55+' cohort had a record indicating concurrent COPD, in keeping with other epidemiology studies[16]; this could be due to misdiagnosis or the presence of features of both diseases (the '55+' cohort had a high proportion with a smoking history), nearly two-thirds had their COPD diagnosed after their asthma diagnosis. Currently, there is no published study on the general UK population, but the proportion in each BTS step was similar to a study of a selected sample of UK asthma patients[17].

This is the first study to look comprehensively at exacerbation rates in a general asthma population. Rates were highest in the '55+' cohort and lowest in the '5 to 17s' cohort; in those patients that did exacerbate, the 'Under 5s' cohort had the highest proportion of frequent exacerbators. Although the multivariable analysis was adjusted for COPD there may have been residual confounding in the '55+' cohort, including from undiagnosed COPD. For all cohorts, the majority of exacerbations were treated within primary care. The number of asthma deaths were in keeping with reported national statistics[18]. The rate of antibiotic treated LRTIs in association with an exacerbation was low, supporting BTS guidance not to use antibiotics for an asthma exacerbation, unless clearly clinically indicated[8].

Many factors significantly changed the rates of an exacerbation, including gender, age, socioeconomic deprivation, smoking history, BMI, atopy history, rhinitis history, reflux history, anxiety history, depression history and COPD history. After adjusting for these factors, increasing BTS step still significantly increased exacerbation rates. The effect was notable in all cohorts, but was more marked, for each incremental BTS step, in those aged <18 years compared to those ≥ 18 years old; suggesting that in childhood asthma the risk of an exacerbation is more influenced by the underlying disease severity than it is in adult asthma.

Cluster analysis has identified a specific phenotype of older asthma patients with more severe symptoms and worse lung function[19], but it is unclear how many older asthma patients are represented by this phenotype. Our study of a large general asthma cohort (where the age of disease-onset is unknown) also suggests a poorer outcome for older patients (≥ 55 years), with both increased disease severity and exacerbation activity. The increase in exacerbations could be explained by the higher proportion with more severe disease, which in turn could be related to the higher proportion with asthma-severity risk factors, including a smoking history, co-existent COPD diagnosis, and reflux[20–22]. It has also been postulated to be related to the effects of aging (including worsening lung function, impaired response to bronchodilators and some changes in immune function), and to longer disease duration in those with early-onset asthma[15,23]. Furthermore, the opposite was found for the '5 to 17s' cohort which had the least severe asthma and lowest exacerbation activity. There is some evidence to suggest that childhood-onset asthma exhibits a better treatment response and prognosis than adult-onset asthma[24], but there is a lack of knowledge regarding a general adult cohort, which would consist of patients with both early- and late-onset asthma.

Our findings have shown that there is a strong association between levels of asthma treatment and exacerbation risk. Although this has not been assessed directly elsewhere, it is in keeping with another UK study, and a US study that showed high exacerbation rates in patients despite high-intensity therapy[17,25]. All patients should be on the lowest level of treatment required to achieve their best level

of control. Therefore, the question remains whether these findings are due to suboptimal management, poor compliance, poor inhaler technique or other environmental factors, or, if some of these patients have a specific poorly-responding phenotype despite maximal pharmacological management.

Limitations

A possible limitation was misclassification of asthma patients, but as the Read codes used have a high positive predictive value of 86% (paper in press), this study may have excluded some asthma patients but is unlikely to have included many patients who did not have asthma. The study did not include mild exacerbations, e.g. treated by the patient themselves, as these are not routinely recorded within CPRD. Using a cut-off of 300mg for exacerbations may have excluded some exacerbations that were treated for more prolonged periods with high OCS doses, however from a sensitivity analysis changing the cut-off had little effect (Table S6). From 2007 until 2015 only 62% of A&E data were captured by CPRD; this would have reduced the number of A&E exacerbations in this study, but these were only a small proportion of total exacerbations, so any deficit is unlikely to have significantly affected the findings.

There were some potential limitations in respect to the measurement of BTS step. Firstly, a defined period of one year prior to study entry was chosen, but it is possible that some patients' BTS step changed during their follow-up. Secondly, it is possible some GP practices did not follow BTS guidelines, although most alternative national treatment guidelines (including local Clinical Commissioning Groups guidance, NICE guidelines and the British National Formulary) are created using the BTS guideline. It was notable only a small percentage of patients were not prescribed medication that fitted with the BTS stepwise approach. Lastly, the medications prescribed may not be the medication used, yet it would be expected that the prescription itself indicated the GP's evaluation of the patient's disease severity. The 2016 BTS guidelines are spread over 6 steps, and were not the ones used by GP practices during the study time period, which predated these guidelines. The 2016 guidelines were selected due to the improved clarity in correlating ICS dosage to asthma severity. Due to the large amount of missing BMI data in the 'Under 5s' and '5 to 17s' cohorts, the multivariate regression models for these cohorts did not include BMI.

Conclusions

The majority of asthma patients within the UK have mild disease and infrequent exacerbations, which are managed within primary care. There are distinct differences in characteristics across the generations of asthma patients, including gender, smoking history, atopy and asthma severity. After adjusting for multiple risk factors, the rates of exacerbations are strongly associated with disease severity, as measured using the BTS stepwise approach.

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Table 1. Description of each cohort

	Under 5s		5 to 17s		18 to 54s		55+	
	N	%	N	%	N	%	N	%
Total	17,320		82,707		210,724		113,575	
F/U median (IQR, years)	1 (0.5-1.8)		3.3 (1.4-5.8)		4.0 (1.7-6.9)		5.1 (2.4-7.6)	
Gender								
Female	6,635	38.3	35,993	43.5	120,910	57.4	67,865	59.8
Age cat*								
1	943	5.4	13,687	16.6	37,322	17.7	46,232	40.7
2	3,738	21.6	19,370	23.4	59,239	28.1	37,226	32.8
3	5,606	32.4	27,619	33.4	62,750	29.8	23,460	20.7
4	7,033	40.6	22,031	26.6	51,413	24.4	6,657	5.9
IMD**								
1	3,472	20.1	17,987	21.8	45,058	21.4	24,310	21.4
2	3,367	19.4	17,044	20.6	45,241	21.5	27,151	23.9
3	3,102	17.9	15,585	18.8	41,377	19.6	23,458	20.7
4	3,772	21.8	16,765	20.3	42,673	20.3	21,356	18.8
5	3,552	20.5	15,283	18.5	36,212	17.2	17,220	15.2
Missing	55	0.3	43	0.1	163	0.1	80	0.1
Smoking								
Never	N/A	N/A	61,506	74.4	102,684	48.7	42,815	37.7
Current	N/A	N/A	3,476	4.2	54,669	25.9	14,826	13.1
Ex	N/A	N/A	1,151	1.4	53,052	25.2	55,903	49.2
Missing	N/A	N/A	16,574	20.0	319	0.2	31	0.0
BMI								
Normal	7,980	46.1	23,068	27.9	69,020	32.8	29,495	26.0
Overweight	1,018	5.9	6,393	7.7	58,786	27.9	39,274	34.6
Obese	638	3.7	4,105	5.0	54,702	26.0	36,189	31.9
Underweight	683	3.9	24,589	29.7	3,879	1.8	2,212	2.0
Missing	7,001	40.4	24,552	29.7	24,337	11.6	6,405	5.6
BTS step								
BTS1	4,889	28.2	33,109	40.0	86,360	41.0	24,980	22.0
BTS2	6,856	39.6	26,766	32.4	54,773	26.0	24,542	21.6

BTS3	979	5.7	3,785	4.6	18,661	8.9	12,321	10.9
BTS4	2,227	12.9	11,782	14.3	32,821	15.6	25,714	22.6
BTS5	97	0.6	1,148	1.4	14,663	7.0	19,425	17.1
BTS6	<5	0.0	22	0.0	623	0.3	1,629	1.4
Non-BTS	480	2.8	2,020	2.4	2,547	1.2	4,613	4.1
Missing	1,790	10.3	4,075	4.9	276	0.1	351	0.3
Atopy								
Yes	4,883	28.2	25,714	31.1	54,205	25.7	25,629	22.6
Rhinitis								
Yes	629	3.6	6,948	8.4	23,740	11.3	14,366	12.7
GERD								
Yes	764	4.4	1,854	2.2	17,150	8.1	19,755	17.4
Anxiety								
Yes	290	1.7	4,260	5.2	32,844	15.6	19,610	17.3
Depression								
Yes	N/A	N/A	2,238	2.7	45,489	21.6	23,397	20.6
COPD								
Yes	N/A	N/A	N/A	N/A	5,756	2.7	25,781	22.7

*age categories are for 'Under 5s': 1 (1-1.9 years), 2 (2-2.9 years), 3 (3-3.9 years), 4(4-4.9 years), '5 to 17s': 1 (5-7 years), 2 (8-10 years), 3 (11-13 years), 4(14-17 years), '18 to 54s': 1 (18-24 years), 2 (25-34 years), 3 (35-44 years), 4(45-54 years), '18 to 54s': 1 (55-64 years), 2 (65-74 years), 3 (75-84 years), 4 (≥85 years); **socioeconomic deprivation scale, 1 is least deprived. BTS steps are defined as 1 = no regular preventer, 2 = lowest ICS dose appropriate for age (or LTRA alone if <5 years), 3 = Add LABA (add LTRA if <5 years), 4 = increase ICS dose to next level (medium in adults, low dose in children), may add in other therapy (adults: LTRA, theophylline, LAMA; children: LTRA), 5 = increase ICS dose (high in adults, medium in children), add fourth drug (adults: LTRA, theophylline, beta agonist tablet, LAMA, children: theophylline), 6 = same ICS dose and continuous or frequent use of oral steroids. LTRA = leukotriene receptor antagonist, LABA = long-acting beta-2 agonist, LAMA = long-acting muscarinic antagonist; children are patients aged under 12 years old.

Table 2. Summary of exacerbations and presumed bacterial LRTIs for each cohort

	Under 5s		5 to 17s		18 to 54s		55 +	
	Patients (%)	**Rate per 10 person years (95% CI)**	**Patients (%)**	**Rate per 10 person years (95% CI)**	**Patients (%)**	**Rate per 10 person years (95% CI)**	**Patients (%)**	**Rate per 10 person years (95% CI)**
Total cohort	17,320		82,707		210,724		113,575	
Exacerbations	7,574	4.27 (4.18-4.38)	39,970	1.48 (1.47-1.50)	245,077	3.22 (3.21-3.24)	435,029	9.40 (9.37-9.42)
Patients that exacerbated	3,706 (21.4*)		18,449 (22.3*)		80,041 (38*)		70,954 (62.5*)	
Annual exacerbation freq.								
≤ 0.5	553		12,433		47,588		29,620	
0.5- 1	1,131		3,600		17,423		16,439	
1.1 - 3	1,577		2,047		12,156		17,569	
3.1 - 6	369		292		2,121		4,419	
>6	76		77		753		2,907	
Level of care								
GP only	*5,211*		*26,543*		*155,054*		*334,850*	
A&E	*232*		*984*		*2,257*		*561*	
Hosp (<1 day)	*966*		*6,515*		*46,227*		*50,385*	
Hosp (≥1 day)	*1,165*		*5,925*		*41,502*		*49,015*	
Died	*<5*		*< 5*		*37*		*218*	
Antibiotic treated LRTIs	2,179	0.61 (0.58-0.64)	11,488	0.22 (0.21-0.22)	81,084	0.71 (0.71-0.72)	171,352	1.93 (1.92-1.94)
Patients with Ax-LRTI	1,612 (9.3*)		8,252 (10*)		41,874 (19.9*)		34,656 (30.5*)	

* % of total cohort, all other percentages are % of patients that exacerbated in that age category cohort; annual frequency is number of patients who exacerbated within each band of annual frequency. Ax-LRTI = antibiotic treated lower respiratory tract infection.

Table 3. Exacerbations by patient's BTS step and age cohort

	Under 5s		5 to 17s		18 to 54s		55 +		Mean population rate per BTS step
	N (% of BTS)	Rate (95% CI)	N (% of BTS)	Rate (95% CI)	N (% of BTS)	Rate (95% CI)	N (% of BTS)	Rate (95% CI)	
BTS 1	656 (13.4)	2.01 (1.89-2.14)	4,849 (14.6)	0.73 (0.70-0.77)	26,607 (30.8)	1.82 (1.78-1.86)	11,805 (47.3)	5.01 (4.84-5.20)	2.39 (2.30-2.49)
BTS 2	1439 (21.0)	4.12 (3.98-4.29)	5,958 (22.3)	1.41 (1.36-1.46)	19,704 (36.0)	2.79 (2.74-2.85)	14,041 (57.2)	6.60 (6.41-6.80)	3.73 (3.62-3.85)
BTS 3	343 (35.0)	8.57 (8.01-9.17)	1,141 (30.1)	2.51 (2.30-2.76)	8,003 (42.9)	3.88 (3.75-4.01)	8,155 (66.2)	8.53 (8.26-8.82)	5.87 (5.58-6.19)
BTS 4	663 (29.8)	7.52 (7.16-7.91)	4,028 (34.2)	2.53 (2.41-2.66)	15,362 (46.8)	5.16 (5.03-5.29)	17,638 (68.6)	10.83 (10.59-11.08)	6.51 (6.30-6.74)
BTS 5	35 (36.1)	10.59 (8.59-13.05)	508 (44.3)	5.18 (4.57-5.88)	8,494 (57.9)	8.07 (7.84-8.31)	14,575 (75.0)	13.27 (13.00-13.55)	9.28 (8.50-10.20)
BTS 6	<5 (0.0)	31.89 (13.27-76.6)	21 (95.5)	56.36 (42.40-77.21)	547 (87.8)	42.1 (39.2-45.4)	1,531 (94.0)	60.19 (57.97-62.52)	47.64 (38.21-65.43)
NonBTS	131 (27.3)	5.58 (4.96-6.28)	649 (32.1)	3.11 (2.75-3.52)	1,211 (47.6)	6.90 (6.32-7.55)	2,986 (64.7)	12.07 (11.43-12.75)	6.92 (6.37-7.53

N is total number of patients that exacerbated, % of patients with exacerbations in that BTS category in that cohort; rates are per 10 person years.

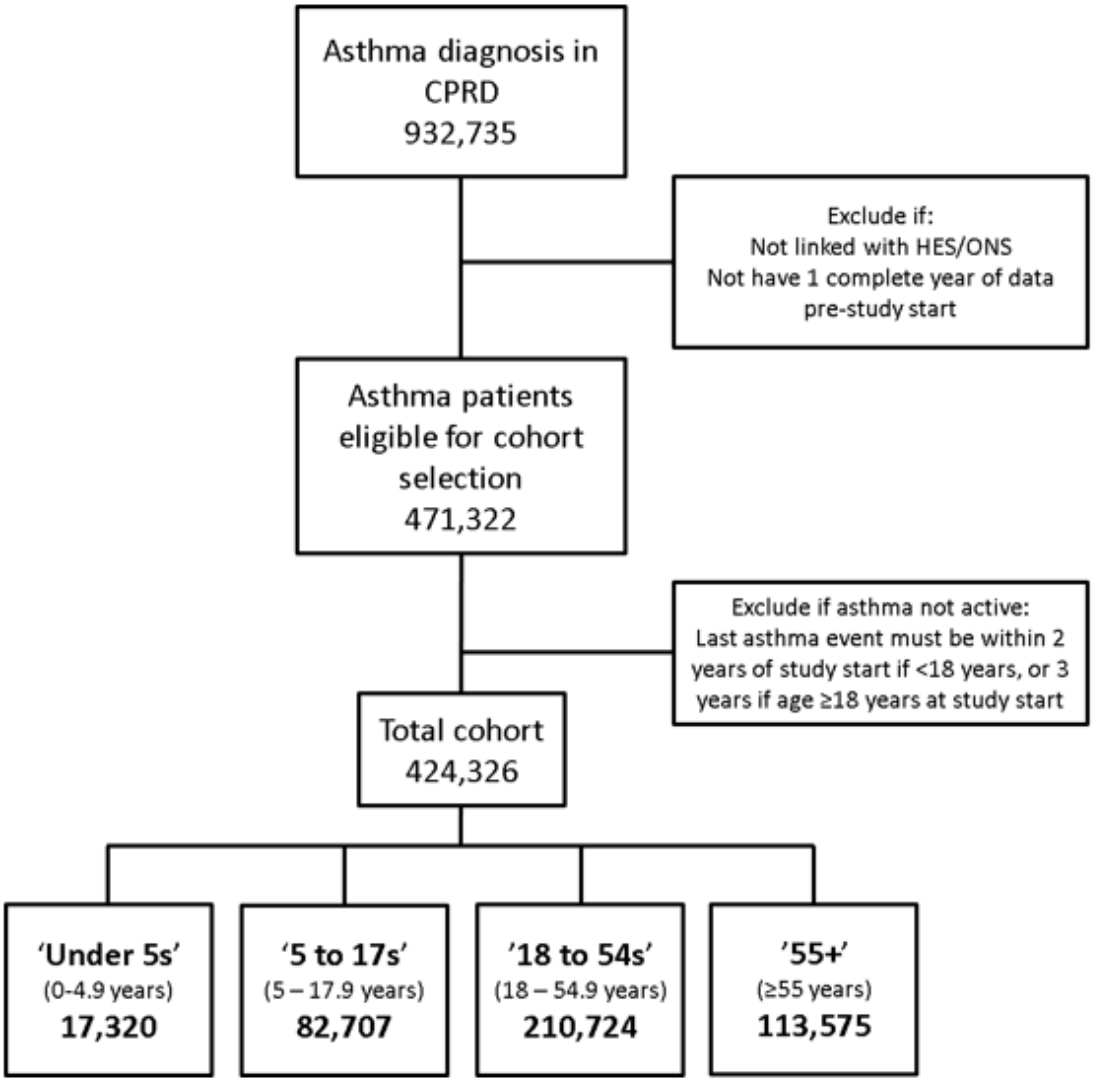
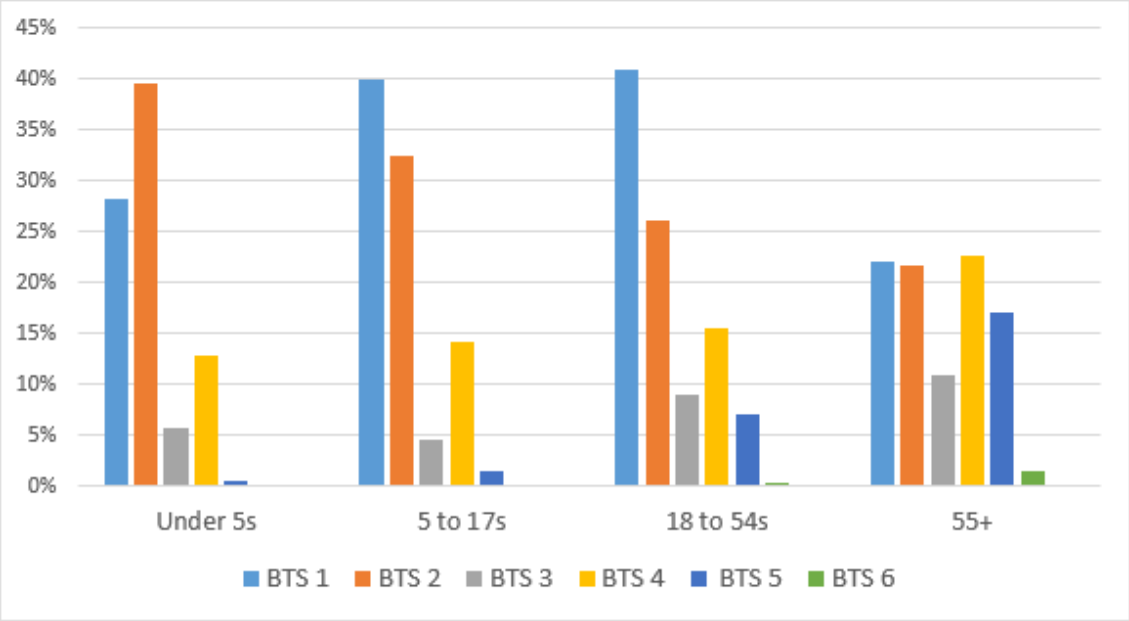

Asthma diagnosis in CPRD
932,735
Exclude if:
Not linked with HES/ONS
Not have 1 complete year of data pre-study start
Asthma patients eligible for cohort selection
471,322
Exclude if asthma not active:
Last asthma event must be within 2 years of study start if <18 years, or 3 years if age ≥18 years at study start
Total cohort
424,326
'Under 5s'
(0-4.9 years)
17,320
'5 to 17s'
(5 – 17.9 years)
82,707
'18 to 54s'
(18 – 54.9 years)
210,724
'55+'
(≥55 years)
113,575

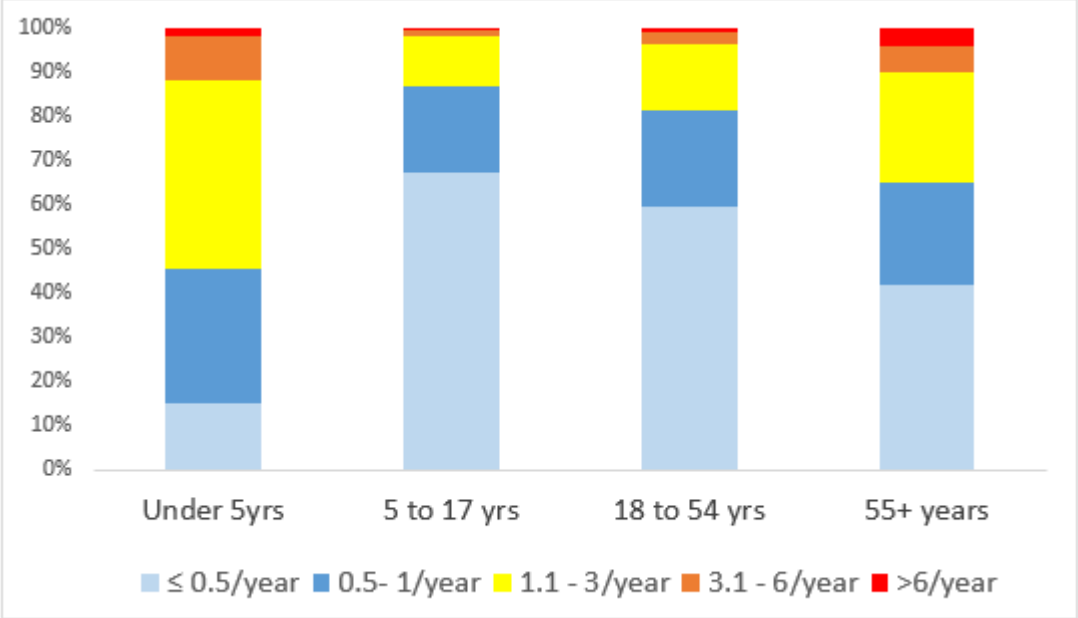
Figure 1



382

383 Figure 2

384



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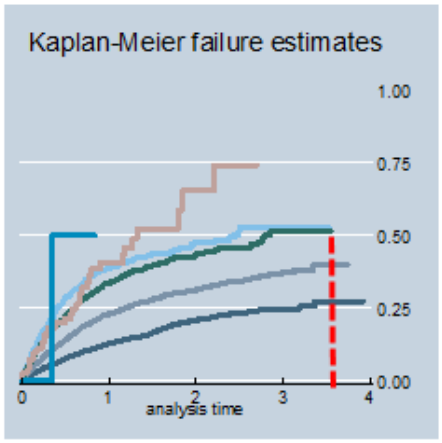
386 Figure 3

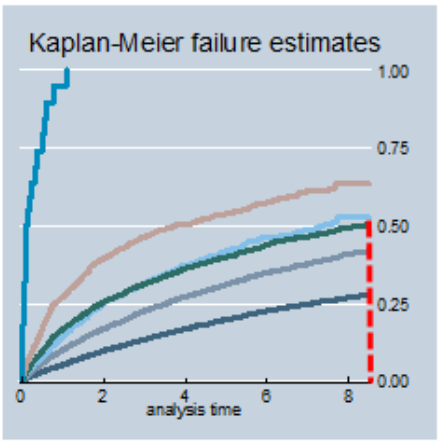
387

Under 5s



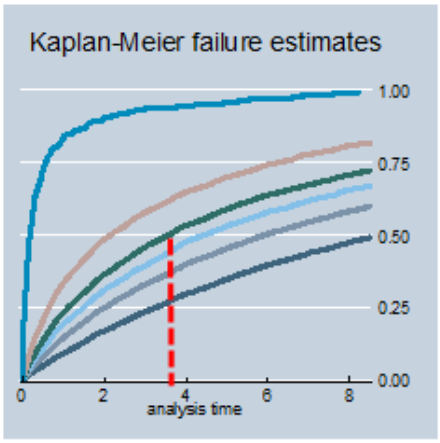
(median = 2.8 yrs)

5 to 17s



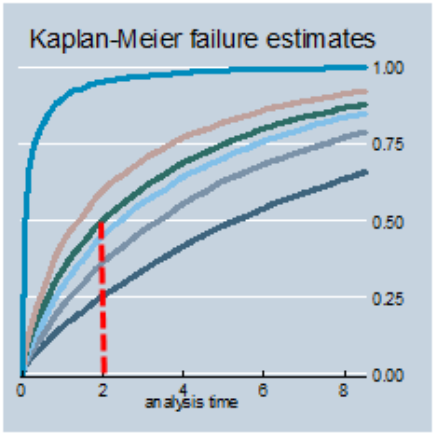
(median = 8.4 yrs)

18 to 54s

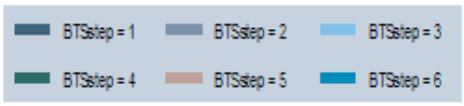


(median = 3.6 yrs)

55+



(median = 2 yrs)



median time to an exacerbation in BTS step 4

388

389 Figure 5

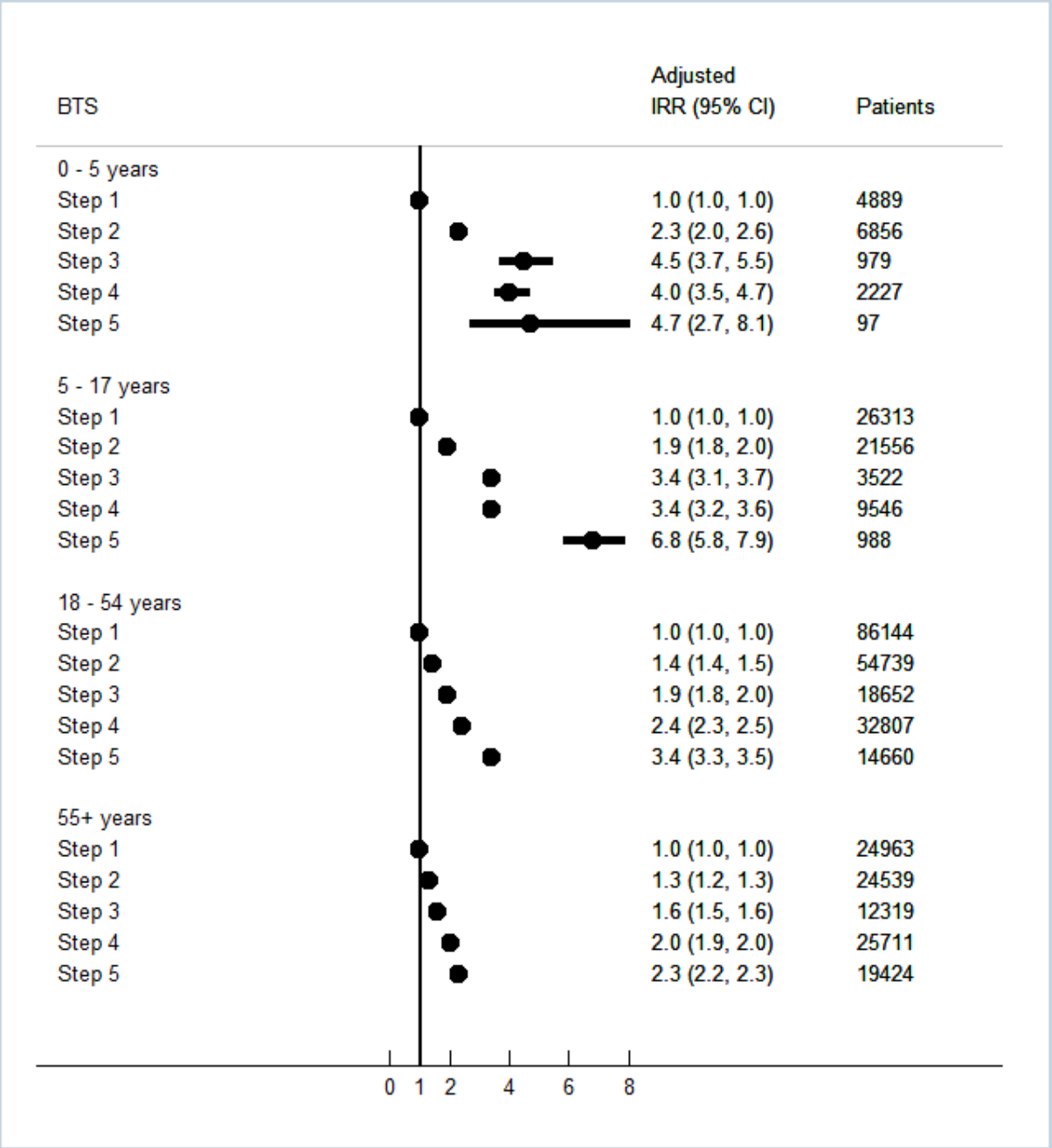


Figure 6

Supplementary Table S1. Univariate analysis of demographic and clinical characteristics in 'Under 5s' cohort

Characteristic	N	100 person-years	Rate (95% CI) per 100 person years	Crude IRR (95% CI)
Gender				
Male	4997	111	45 (42.8-47.4)	Ref
Female	2577	66	39.2 (36.4-42.2)	0.84 (0.76-0.92)*
Age cat (years)				
1-1.9	884	20	43.9 (38-50.9)	Ref

2-2.9	3026	62	48.7 (45.4-52.3)	1.09 (0.9-1.32)"
3-3.9	2694	64	42.3 (39.6-45.2)	0.93 (0.77-1.13)"
4-4.9	970	31	31.5 (29-34.3)	0.6 (0.49-0.73)*
IMD				
1	1227	36	33.7 (30.7-37.2)	Ref
2	1550	34	45.3 (41-50.1)	1.26 (1.09-1.46)*
3	1306	31	42.3 (38.6-46.5)	1.23 (1.06-1.44)^
4	1744	38	45.7 (42-49.7)	1.3 (1.13-1.5)*
5	1743	37	47.3 (43.3-51.9)	1.3 (1.13-1.5)*
BMI				
Normal	3903	81	48.5 (45.9-51.4)	Ref
Overweight	483	10	47.7 (40.9-55.8)	1.06 (0.88-1.27)"
Obese	275	6	45 (37.3-54.8)	0.97 (0.77-1.22)"
Underweight	633	8	77.9 (66.2-92.3)	1.45 (1.19-1.78)*
BTS step				
BTS 1	1123	56	20.2 (18.4-22.2)	Ref
BTS 2	2808	68	41.3 (38.7-44.2)	2.17 (1.93-2.44)*
BTS 3	829	10	85.7 (75.6-97.7)	4.57 (3.76-5.55)*
BTS 4	1552	21	75.3 (68.4-83)	3.86 (3.33-4.47)*
BTS 5	88	1	106 (69-171.7)	4.36 (2.54-7.46)*
BTS 6	5	0	31.89 (13.27-76.6)	13.03 (0.58-294.9)”
Non BTS	277	5	55.8 (45.6-69.1)	3.04 (2.32-3.98)*
Atopy				
No	4941	129	38.5 (36.6-40.4)	Ref
Yes	2633	48	54.5 (50.7-58.8)	1.33 (1.21-1.47)*
Reflux				
No	7135	169	42.4 (40.6-44.2)	Ref
Yes	439	8	52.2 (43.4-63.3)	1.12 (0.9-1.38)"
Anxiety				
No	7416	174	42.6 (40.9-44.5)	Ref
Yes	158	3	56.9 (39.8-84.1)	1.22 (0.87-1.72)"
Season				
Winter	2018	9	219.3 (209.9-229)	Ref
Spring	1900	8	243.1 (232.4-254.3)	1.11 (1.1-1.12)*
Summer	1348	6	218.3 (207-230.3)	1.09 (1.08-1.1)*
Autumn	2308	11	206.6 (198.4-215.2)	1 (0.99-1.01)"

N exacerbations; rate: per 100 person years; p-values: * p<0.001, ^ p<0.05, “p>0.05; IMD, 1 is least deprived

Supplementary Table S2. Univariate analysis of demographic and clinical characteristics in '5 – 17s' cohort

Characteristic	N	100 person-years	Rate (95% CI) per 100 person years	Crude IRR (95% CI)
Gender				
Male	22772	1555	14.7 (14.3-15.1)	Ref
Female	17198	1141	15.1 (14.6-15.7)	1 (0.95-1.04)"
Age cat (years)				
5-7	14755	772	19.2 (18.4-20)	Ref
8-10	12393	830	15 (14.3-15.7)	0.75 (0.71-0.79)*
11-13	8807	743	11.9 (11.4-12.5)	0.58 (0.55-0.62)*
14-17	4015	352	11.5 (10.8-12.1)	0.51 (0.48-0.54)*
IMD				
1	7827	624	12.6 (11.9-13.3)	Ref
2	7957	557	14.3 (13.6-15.1)	1.13 (1.06-1.21)*
3	7508	501	15 (14.2-15.9)	1.2 (1.12-1.28)*
4	8405	535	15.8 (15-16.6)	1.23 (1.15-1.32)*
5	8255	478	17.3 (16.4-18.3)	1.39 (1.3-1.49)*
Smoking				
Never	33471	2154	15.6 (15.2-16)	Ref
Current	856	64	13.4 (12.2-14.9)	0.96 (0.85-1.08)"
Ex	368	22	16.9 (13.8-20.9)	1.18 (0.97-1.43)"
BMI				
Normal	11209	709	15.9 (15.2-16.6)	Ref
Overweight	3232	186	17.4 (16.1-19)	1.15 (1.06-1.25)*
Obese	2251	126	18 (16.4-19.7)	1.13 (1.02-1.24)^
Underweight	16256	913	17.9 (17.1-18.6)	1.2 (1.14-1.27)*
BTS step				
BTS 1	8196	11000	7.3 (6.9-7.7)	Ref
BTS 2	11301	8000	14.1 (13.6-14.6)	2.05 (1.95-2.16)*
BTS 3	2740	1100	25.1 (23-27.6)	3.37 (3.07-3.71)*
BTS 4	10732	4200	25.3 (24.1-26.6)	3.76 (3.54-4)*
BTS 5	1858	359	51.8 (45.7-58.8)	7.21 (6.18-8.41)*
BTS 6	387	7	563.6 (424-772.1)	60.71 (23.13-159.36)*
Non BTS	1793	577	31.1 (27.5-35.2)	4.45 (3.93-5.04)*
Atopy				
No	24132	1824	13.3 (12.9-13.7)	Ref
Yes	15838	873	18.2 (17.5-18.9)	1.36 (1.3-1.42)*
Reflux				
No	38493	2637	14.6 (14.3-15)	Ref
Yes	1477	59	25.1 (21.1-30)	1.59 (1.39-1.83)*
Anxiety				
No	37510	2554	14.7 (14.4-15.1)	Ref
Yes	2460	143	17.3 (15.5-19.3)	1.09 (1-1.2)"

Depression				
No	38790	2636	14.8 (14.4-15.1)	Ref
Yes	1180	60	19.6 (17.2-22.5)	1.18 (1.03-1.34)^
COPD				
No	39781	2688	0 (0-0)	Ref
Yes	189	8	0 (0-0)	1.4 (0.97-2.02)"
Season				
Winter	10430	145	71.9 (70.6-73.3)	Ref
Spring	9877	126	78.2 (76.7-79.7)	1.12 (1.08-1.16)*
Summer	8589	113	76.2 (74.6-77.9)	1.08 (1.04-1.12)*
Autumn	11074	146	76 (74.6-77.4)	1.02 (0.99-1.05)"

401 N exacerbations; rate: per 100 person years; p-values: * p<0.001, ^ p<0.05, “p>0.05; IMD, 1 is least
402 deprived
403

404 Supplementary Table S3. Univariate analysis of demographic and clinical characteristics in '18 – 54s'
405 cohort

Characteristic	N	100 person-years	Rate (95% CI) per 100 person years	Crude IRR (95% CI)
Gender				
Male	76254	3351	22.8 (22.3-23.3)	Ref
Female	168823	4240	39.9 (39.3-40.4)	1.67 (1.64-1.71)*
Age cat (years)				
18-24	28503	1334	21.4 (20.8-22)	Ref
25-34	57976	2115	27.5 (26.9-28.1)	1.22 (1.19-1.26)*
35-44	91169	2637	34.6 (33.9-35.3)	1.51 (1.47-1.55)*
45-54	67429	1505	44.9 (43.8-45.9)	1.97 (1.91-2.03)*
IMD				
1	39105	1729	22.7 (22.1-23.3)	Ref
2	46958	1648	28.6 (27.8-29.3)	1.23 (1.19-1.27)*
3	47393	1473	32.2 (31.4-33.1)	1.39 (1.35-1.44)*
4	55104	1497	36.9 (35.9-37.8)	1.58 (1.53-1.62)*
5	56391	1239	45.6 (44.5-46.7)	1.93 (1.87-1.99)*
Smoking				
Never	100753	3822	26.4 (25.9-26.9)	Ref
Current	80844	1933	41.9 (41-42.7)	1.57 (1.54-1.61)*
Ex	63469	1829	34.8 (34-35.6)	1.32 (1.29-1.35)*
BMI				
Normal	69182	2501	27.7 (27.1-28.3)	Ref
Overweight	66585	2161	30.9 (30.2-31.5)	1.12 (1.1-1.15)*
Obese	89918	1958	46 (45.1-46.9)	1.63 (1.59-1.67)*
Underweight	5084	136	37.4 (34-41.3)	1.33 (1.24-1.42)*
BTS step				
BTS 1	62730	35000	18.2 (17.8-18.6)	Ref
BTS 2	50228	18000	27.9 (27.4-28.5)	1.51 (1.47-1.55)*
BTS 3	24359	6400	38.8 (37.5-40.1)	2.05 (1.99-2.12)*
BTS 4	54192	11000	51.6 (50.3-52.9)	2.68 (2.61-2.75)*
BTS 5	39217	4900	80.7 (78.4-83.1)	4.1 (3.96-4.25)*
BTS 6	8450	200	421.3 (391.7-453.6)	20.88 (18.17-23.98)*
Non BTS	5369	798	69 (63.2-75.5)	3.54 (3.27-3.82)*
Atopy				
No	167639	5544	30.3 (29.9-30.7)	Ref
Yes	77438	2047	37.9 (37.1-38.7)	1.21 (1.18-1.23)*
Reflux				
No	208090	6939	30 (29.7-30.4)	Ref
Yes	36987	652	56.8 (54.9-58.8)	1.78 (1.72-1.84)*
Anxiety				
No	187540	6339	29.6 (29.2-30)	Ref
Yes	57537	1252	46 (44.9-47.2)	1.5 (1.46-1.54)*
Depression				

No	163724	5928	27.7 (27.3-28.1)	Ref
Yes	81353	1663	49 (48-50)	1.71 (1.68-1.75)*
COPD				
No	227779	7443	30.7 (30.3-31)	Ref
Yes	17298	148	116.9 (111.5-122.6)	3.4 (3.21-3.6)*
Season				
Winter	65630	817	80.3 (79.7-80.9)	Ref
Spring	59958	691	86.8 (86.1-87.5)	1.1 (1.09-1.12)*
Summer	56396	646	87.3 (86.5-88)	1.07 (1.06-1.09)*
Autumn	63093	757	83.4 (82.7-84)	1 (0.98-1.01)"

406 N exacerbations; rate: per 100 person years; p-values: * p<0.001, ^ p<0.05, “p>0.05; IMD, 1 is least
407 deprived
408

409 Supplementary Table S4. Univariate analysis of demographic and clinical characteristics in '55+'
410 cohort

Characteristic	N	100 person-years	Rate (95% CI) per 100 person years	Crude IRR (95% CI)
Gender				
Male	161258	1845	87.5 (85.8-89.2)	Ref
Female	273771	2785	98.3 (96.8-99.9)	1.11 (1.09-1.13)*
Age cat (years)				
55-64	151439	2012	75.3 (73.8-76.8)	Ref
65-74	161024	1576	102.2 (100.2-104.3)	1.36 (1.33-1.39)*
75-84	103650	869	119.3 (116.3-122.4)	1.63 (1.59-1.68)*
85+	18916	173	109.3 (103.6-115.3)	1.64 (1.57-1.71)*
IMD				
1	82641	1042	79.4 (77.1-81.7)	Ref
2	101774	1119	91 (88.8-93.3)	1.13 (1.1-1.16)*
3	89705	942	95.3 (92.7-97.9)	1.19 (1.16-1.23)*
4	84986	847	100.4 (97.7-103.1)	1.23 (1.2-1.27)*
5	75663	676	111.9 (108.8-115.1)	1.36 (1.32-1.41)*
Smoking				
Never	141855	1817	78.1 (76.5-79.9)	Ref
Current	64605	580	111.5 (108.3-114.8)	1.37 (1.33-1.41)*
Ex	228533	2233	102.4 (100.7-104.1)	1.29 (1.26-1.31)*
BMI				
Normal	114822	1189	96.6 (94.3-99.1)	Ref
Overweight	151104	1666	90.7 (88.9-92.6)	0.91 (0.89-0.94)*
Obese	144957	1521	95.3 (93.5-97.3)	0.96 (0.93-0.98)*
Underweight	9407	67	140.2 (129.1-152.5)	1.49 (1.39-1.6)*
BTS step				
BTS 1	55299	1100	50.1 (48.4-52)	Ref
BTS 2	64519	978	66 (64.1-68)	1.28 (1.24-1.31)*
BTS 3	43565	511	85.3 (82.5-88.2)	1.63 (1.58-1.69)*
BTS 4	110858	1000	108.3 (105.9-110.8)	2.06 (2-2.11)*
BTS 5	103228	778	132.7 (130-135.5)	2.47 (2.4-2.55)*
BTS 6	35276	59	601.9 (579.7-625.2)	11.52 (10.71-12.38)*
Non BTS	20206	167	120.7 (114.3-127.5)	2.25 (2.14-2.36)*
Atopy				
No	321078	3507	91.6 (90.3-92.9)	Ref
Yes	113951	1123	101.5 (99.1-104)	1.08 (1.05-1.1)*
Reflux				
No	339108	3775	89.9 (88.7-91.1)	Ref
Yes	95921	855	112.3 (109.4-115.2)	1.21 (1.18-1.24)*
Anxiety				
No	342657	3792	90.4 (89.2-91.7)	Ref
Yes	92372	839	110.2 (107.3-113.2)	1.2 (1.17-1.23)*
Depression				

No	329034	3673	89.6 (88.4-90.9)	Ref
Yes	105995	957	110.8 (108.1-113.6)	1.21 (1.19-1.24)*
COPD				
No	304241	3754	81.1 (79.9-82.3)	Ref
Yes	130788	876	149.3 (146.2-152.5)	1.78 (1.74-1.82)*
Season				
Winter	114083	866	131.7 (130.9-132.4)	Ref
Spring	112214	765	146.6 (145.7-147.5)	1.11 (1.10-1.12)*
Summer	102679	671	152.9 (152-153.9)	1.09 (1.08-1.10)*
Autumn	106053	749	141.6 (140.8-142.5)	1.00 (0.99-1.01)”

N exacerbations; rate: per 100 person years; p-values: * p<0.001, ^ p<0.05, “p>0.05; IMD, 1 is least deprived

Table S5. Median time to first exacerbation by age group and BTS step

	Median time without an exacerbation (years)			
	Under 5s	**5-17s**	**18-54s**	**55+**
BTS 1	> 4	>8.5	>8.5	5.3
BTS 2	> 4	>8.5	5.9	3.4
BTS 3	2.4	7.4	4.4	2.5
BTS 4	2.8	8.4	3.6	2
BTS 5	1.3	3.8	2.1	1.4
BT S6	0.34	0.1	0.2	0.1

Log-rank test $p<0.001$