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# 1 Exacerbation risk and characterisation of the UK's asthma population, 2 from infants to old age

3 C.I. Bloom<sup>1</sup>, F Nissen<sup>2</sup>, I.J. Douglas<sup>2</sup>, L. Smeeth<sup>2</sup>, P. Cullinan<sup>1</sup>, J.K.Quint<sup>1</sup>

4 <sup>1</sup>Imperial College, <sup>2</sup>London School of Hygiene and Tropical Medicine

## 6 **Summary box**

### 7 **What is the key question?**

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

### 10 **What is the bottom line?**

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

### 14 **Why read on?**

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

## 18 **Abstract**

### 19 **BACKGROUND:**

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

### 22 **METHODS:**

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

### 28 **RESULTS:**

29 424,326 patients with current asthma were eligible (N, median follow-up: 'Under 5s'=17,320, 1 year;  
30 '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  
31 total study population had mild asthma (BTS steps 1/2). There were differences between the cohort's  
32 characteristics, including by gender, disease severity and exacerbation pattern. The rate of  
33 exacerbations was highest in the oldest cohort and lowest in the '5 to 17s' cohort (rate per 10 person-  
34 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),  
35 '55+'=9.40 (9.37-9.42)). In all cohorts, exacerbation rates increased with increasing asthma severity,  
36 after adjusting for confounders including gender, socioeconomic status, smoking, BMI, atopy, rhinitis,  
37 gastroesophageal reflux, anxiety, depression and COPD.

38 **CONCLUSION:**

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

42

43

**Introduction**

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

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

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

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

66

67

**Methods**

68 **Data sources**

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

74 **Study design and population**

75 We conducted a population-wide open cohort study. The study population consisted of patients in  
76 CPRD linked practices with validated Read codes (a clinical terminology system) indicating prevalent  
77 or incident asthma<sup>7</sup>. Patients were eligible if a code for asthma had been recorded at  $\leq 2$  years prior to  
78 study entry if aged <18 years, or  $\leq 3$  years if aged  $\geq 18$  years (Figure 1). Patients entered the study at

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

## 86 **Outcome and variables**

87 The main outcome was asthma exacerbations. An exacerbation was defined as  $\leq 300$ mg oral  
88 corticosteroids (OCS) (not prescribed during an annual asthma review), or an A&E visit, or hospital  
89 admission. A cut-off of  $\leq 150$ mg OCS was used for children  $< 5$  years old. Exacerbations recorded within  
90 14 days after the index one were considered part of the same exacerbation. Level of care of each  
91 exacerbation was documented as the highest level per episode. Incident lower respiratory tract  
92 infections treated with antibiotics (Ax-LRTIs) were also measured, by identifying specific Read codes  
93 (available upon request) with same day prescription of appropriate antibiotics.

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

## 105 **Statistical analysis**

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

## 114 **Ethics**

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

120

121

## **Results**

122 **Patient characteristics**

123 In the total study population there were 424,326 patients with current asthma. The number of  
124 patients and follow-up varied between cohorts, the smallest and shortest follow-up was in the 'Under  
125 5s' and the largest, with a longer follow-up, was the '18 to 54s' cohort ('Under 5s' N=17,320, IQR 0.5-  
126 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,  
127 IQR 2.4-7.6) (Table 1). Female prevalence increased with increasing cohort age and became the  
128 dominant gender from 18 years onwards (Table 1). Over 70% in the 'Under 5s' cohort were aged  
129 between 3 and 5 years old (Table 1). In the '55+' cohort the numbers of patients were inversely  
130 proportional to the age group. The highest percentage of smokers were in the '18 to 54s' cohort  
131 (current 25.9%) and ex-smokers in the '55+' cohorts (ex-smoker 49.2%) (Table 1). Recorded BMI was  
132 predominantly either normal or underweight if cohort age was <18 years, but normal or above if  
133 cohort age was ≥ 18 years (Table 1).

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

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

144 **Exacerbation characteristics**

145 The rate of exacerbations was highest in the oldest age group, followed by the youngest age group,  
146 and lowest in the '5 to 17s' cohort (exacerbations per 10 person years: '55+'=9.4 (95%CI 9.37-9.42),  
147 '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-  
148 1.5)) (Table 2). Of those who did exacerbate, the majority had ≤1 exacerbation per year, in cohorts  
149 aged ≥5 years (Ann. Freq. ≤1/year: '5 to 17s'=86.9%; '18 to 54s'=81.3%; '55+'=65%); the opposite was  
150 found in the 'Under 5s' cohort, in whom just over half experienced >1 exacerbation per year (54.7%)  
151 (Table 2 & Figure 3). Around 85% of exacerbations in each cohort did not require over-night  
152 hospitalisation ('Under 5s'= 85.6%, '5 to 17s'= 85.2%, '18 to 54s'= 83.1%, '55+'= 88.7%). All patients  
153 were most likely to see their GP as their maximum level of care; the oldest age cohort had a lower  
154 proportion of hospitalised exacerbations, but highest proportion of asthma deaths (Table 2).

155 The rate of Ax-LRTIs was much lower than the rate of exacerbations; the rate was highest in the '55+'  
156 cohort and lowest in the '5 to 17s' cohort ('55+'=1.93 (95% CI 1.92-1.94) exacerbations per 10 person-  
157 years, '5 to 17s'=0.22 (95% CI 0.21-0.22) exacerbations per 10 person-years). Of those with an Ax-LRTI,  
158 <10% occurred at the time of, or 14 days after an exacerbation ('Under 5s'= 5%, '5 to 17s'= 4.9%, '18  
159 to 54s'= 8.3%, '55+'= 7.3%) and ≤1% of Ax-LRTIs preceded an exacerbation within 14 days ('Under 5s'=  
160 0.6%, '5 to 17s'= 0.4%, '18 to 54s'= 0.9%, '55+'= 1%).

161 The rate of exacerbations increased with increasing asthma severity (BTS step) in every cohort, with  
162 the lowest rate, 0.73 (95% CI 0.7-0.77) exacerbations per 10 person-years, in BTS step 1 in '5 to 17s'  
163 cohort and the highest rate, 60.2 (95% CI 57.97-62.52) exacerbations per 10 person-years, in BTS step  
164 6 in the '55+' cohort (Table 3).

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

166 Female gender was significantly associated with exacerbation risk in all cohorts except for the '5 to  
167 17s' cohort; the relative rate decreased in the 'Under 5s' but increased in the oldest two cohorts  
168 (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+'  
169 IRR=1.11 (95% CI 1.09-1.13),  $p<0.001$ ). Within the oldest two cohorts, as age increased exacerbations  
170 rates also increased, the opposite occurred in the youngest two cohorts (Table S1-4). Current and ex-  
171 smoking was significantly associated with an increased rate in patients'  $\geq 18$  years (Table S1-4). Patients  
172 with a 'non-normal' BMI (underweight, overweight or obese) had higher exacerbation rates in the '5  
173 to 17s' and '18 to 54s' cohort (Table S1-4). Having atopy, rhinitis, reflux, anxiety, or depression  
174 increased the relative rate of exacerbations in all cohorts (Table S1-4). Exacerbation rates were also  
175 higher in asthma patients with COPD (Table S3-4).

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

178 Each increase in BTS step was significantly associated with an increased rate of exacerbations  
179 compared to BTS step 1 (Figure 4). This effect was seen in all cohorts, but the largest adjusted rate  
180 ratios were found in the youngest cohort, and the smallest were found in the oldest cohort ('Under  
181 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-  
182 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,  
183 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  
184 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  
185 for age, gender, IMD, BMI, atopy, rhinitis, reflux, anxiety, depression and COPD (Figure 4).

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

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

192

193 **Discussion**

194 We have undertaken the first descriptive study of the UK's general asthma population and found many  
195 similarities and differences between the characteristics of cohorts representing: infants to  
196 preschoolers (Under 5s), young children to teenagers (5 to 17s), younger adults to middle age (18 to  
197 54s), and middle to old age (55+). One clear difference was gender; males were found to be more  
198 prevalent in the younger cohorts,  $<18$  years but the opposite was found in the older cohorts; these  
199 results are in agreement with other prevalence, as well as incidence, asthma studies<sup>10,11</sup>. Smoking  
200 prevalence increased between the '5 to 17s' and '18 to 54s' cohort but fell in the '55+' cohort, in  
201 keeping with UK smoking data<sup>12</sup>. Adult BMI ( $\geq 18$  years) increased with increasing cohort age,  
202 compatible with published national data<sup>13</sup>. Atopy prevalence was highest in the two youngest cohorts  
203 ( $< 18$  years), which appears consistent with studies showing that late-onset asthma is less likely to be  
204 allergic asthma<sup>14</sup>. A history of rhinitis and reflux both showed a steady increase with age; presently  
205 there is a paucity of published data on the relationship between age and these disorders.

206 The majority of asthma patients ( $>60\%$  of the total study population) had mild asthma, BTS step 1 or  
207 2; it is notable that this cohort only included patients with current asthma and excluded patients who

208 had not visited their GP practice for their asthma in the last 2 or 3 years (depending on their age).  
209 However, the level of severity varied considerably between the age cohorts. The youngest and oldest  
210 cohorts, <5 years old and  $\geq 55$  years old, had the lowest proportion on BTS step 1. Only in the 'Under  
211 5s' cohort were patients more likely to have BTS step 2 than 1; this may be related to the difficulty in  
212 diagnosing asthma in children <5 years old (spirometry is often not possible and it can be difficult  
213 distinguishing asthma from 'recurrent wheeze') and a reluctance to diagnose until a child is more  
214 symptomatic. Asthma was more severe in the '55+' cohort, in keeping with other older asthma  
215 populations<sup>15</sup>. Nearly a quarter of the '55+' cohort had a record indicating concurrent COPD, in keeping  
216 with other epidemiology studies<sup>16</sup>; this could be due to misdiagnosis or the presence of features of  
217 both diseases (the '55+' cohort had a high proportion with a smoking history), nearly two-thirds had  
218 their COPD diagnosed after their asthma diagnosis. Currently, there is no published study on the  
219 general UK population, but the proportion in each BTS step was similar to a study of a selected sample  
220 of UK asthma patients<sup>17</sup>.

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

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

236 Cluster analysis has identified a specific phenotype of older asthma patients with more severe  
237 symptoms and worse lung function<sup>19</sup>, but it is unclear how many older asthma patients are  
238 represented by this phenotype. Our study of a large general asthma cohort (where the age of disease-  
239 onset is unknown) also suggests a poorer outcome for older patients ( $\geq 55$  years), with both increased  
240 disease severity and exacerbation activity. The increase in exacerbations could be explained by the  
241 higher proportion with more severe disease, which in turn could be related to the higher proportion  
242 with asthma-severity risk factors, including a smoking history, co-existent COPD diagnosis, and  
243 reflux<sup>20-22</sup>. It has also been postulated to be related to the effects of aging (including worsening lung  
244 function, impaired response to bronchodilators and some changes in immune function), and to longer  
245 disease duration in those with early-onset asthma<sup>15,23</sup>. Furthermore, the opposite was found for the  
246 '5 to 17s' cohort which had the least severe asthma and lowest exacerbation activity. There is some  
247 evidence to suggest that childhood-onset asthma exhibits a better treatment response and prognosis  
248 than adult-onset asthma<sup>24</sup>, but there is a lack of knowledge regarding a general adult cohort, which  
249 would consist of patients with both early- and late-onset asthma.

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

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

## 258 **Limitations**

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

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

## 282 **Conclusions**

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

288

## 289 **References**

- 290 1. Simpson, C. R. & Sheikh, A. Trends in the epidemiology of asthma in England: a national study  
291 of 333,294 patients. *J. R. Soc. Med.* **103**, 98–106 (2010).
- 292 2. To, T. *et al.* Global asthma prevalence in adults: findings from the cross-sectional world health  
293 survey. *BMC Public Health* **12**, 204 (2012).
- 294 3. International Study of Asthma and Allergies in Childhood (ISAAC). The Global Asthma Report  
295 2011. The Global Asthma Report 2014. *Int. Study Asthma Allerg. Child. Int. Union against*  
296 *Tuberc. Lung Dis. (The Union)* (2014).



- 297 4. Royal College of Physicians. *Why asthma still kills*. (2014).
- 298 5. Health and Social Care Information Centre. Attribution Data Set GP-Registered Populations  
299 Scaled to ONS Population Estimates – 2011 2012. Available at:  
300 <http://content.digital.nhs.uk/catalogue/PUB05054>.
- 301 6. Herrett, E. *et al.* Data Resource Profile: Clinical Practice Research Datalink (CPRD). *Int. J.*  
302 *Epidemiol.* **44**, 827–836 (2015).
- 303 7. Nissen, F. *et al.* Validation of the Recording of Asthma Diagnosis in UK Electronic Health  
304 Records (Clinical Practice Research Datalink). *Am. Thorac. Soc.* (2017).
- 305 8. British Thoracic Society. BTS/SIGN British guideline on the management of asthma. (2016).  
306 Available at: [https://www.brit-thoracic.org.uk/standards-of-care/guidelines/btssign-british-](https://www.brit-thoracic.org.uk/standards-of-care/guidelines/btssign-british-guideline-on-the-management-of-asthma/)  
307 [guideline-on-the-management-of-asthma/](https://www.brit-thoracic.org.uk/standards-of-care/guidelines/btssign-british-guideline-on-the-management-of-asthma/).
- 308 9. Quint, J. K. *et al.* Validation of chronic obstructive pulmonary disease recording in the Clinical  
309 Practice Research Datalink (CPRD-GOLD). *BMJ Open* **4**, e005540–e005540 (2014).
- 310 10. Anderson, H. R., Pottier, A. C. & Strachan, D. P. Asthma from birth to age 23: incidence and  
311 relation to prior and concurrent atopic disease. *Thorax* **47**, 537–42 (1992).
- 312 11. Schatz, M. & Camargo, C. A. The relationship of sex to asthma prevalence, health care  
313 utilization, and medications in a large managed care organization. *Ann. Allergy. Asthma*  
314 *Immunol.* **91**, 553–8 (2003).
- 315 12. Health & Social Care Information Centre, O. of N. S. Statistics on Smoking. (2016).
- 316 13. Health Survey England. Adult Weight. *Natl. Obes. Obs.* (2011).
- 317 14. Craig, T. J. Aeroallergen sensitization in asthma: Prevalence and correlation with severity.  
318 *Allergy Asthma Proc.* **31**, 96–102 (2010).
- 319 15. Quadrelli, S. A. & Roncoroni, A. Features of asthma in the elderly. *J. Asthma* **38**, 377–89  
320 (2001).
- 321 16. Postma, D. S. & Rabe, K. F. The Asthma–COPD Overlap Syndrome. *N. Engl. J. Med.* **373**, 1241–  
322 1249 (2015).
- 323 17. Price, D. *et al.* Predicting frequent asthma exacerbations using blood eosinophil count and  
324 other patient data routinely available in clinical practice. *J. Asthma Allergy* **9**, 1–12 (2016).
- 325 18. Office of National Statistics. Asthma deaths in England and Wales, 2001 to 2015 occurrences -  
326 Office for National Statistics. (2016). Available at:  
327 [https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths](https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/adhocs/005955asthmadeathsinenglandandwales2001to2015occurrences)  
328 [/adhocs/005955asthmadeathsinenglandandwales2001to2015occurrences](https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/adhocs/005955asthmadeathsinenglandandwales2001to2015occurrences).
- 329 19. Haldar, P. *et al.* Cluster analysis and clinical asthma phenotypes. *Am. J. Respir. Crit. Care Med.*  
330 **178**, 218–24 (2008).
- 331 20. Harding, S. M. Recent clinical investigations examining the association of asthma and  
332 gastroesophageal reflux. *Am. J. Med.* 39S–44S (2003).
- 333 21. Hardin, M. *et al.* The clinical features of the overlap between COPD and asthma. *Respir. Res.*  
334 **12**, 127 (2011).
- 335 22. Thomson, N. C., Chaudhuri, R. & Livingston, E. Asthma and cigarette smoking. *Eur. Respir. J.*  
336 **24**, 822–833 (2004).

- 337 23. Hanania, N. A. *et al.* Asthma in the elderly: Current understanding and future research needs-  
 338 -a report of a National Institute on Aging (NIA) workshop. *J. Allergy Clin. Immunol.* **128**, S4-24  
 339 (2011).
- 340 24. de Nijs, S. B., Venekamp, L. N. & Bel, E. H. Adult-onset asthma: is it really different? *Eur.*  
 341 *Respir. Rev.* **22**, (2013).
- 342 25. Schatz, M., Meckley, L. M., Kim, M., Stockwell, B. T. & Castro, M. Asthma Exacerbation Rates  
 343 in Adults Are Unchanged Over a 5-Year Period Despite High-Intensity Therapy. *J. Allergy Clin.*  
 344 *Immunol. Pract.* **2**, 570–574.e1 (2014).

345

346

Table 1. Description of each cohort

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	Under 5s		5 to 17s		18 to 54s		55+	
	N	%	N	%	N	%	N	%
<b>Total</b>	17,320		82,707		210,724		113,575	
<b>F/U median</b> (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)	
<b>Gender</b>								
Female	6,635	38.3	35,993	43.5	120,910	57.4	67,865	59.8
<b>Age cat*</b>								
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
<b>IMD**</b>								
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
<b>Smoking</b>								
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
<b>BMI</b>								
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
<b>BTS step</b>								
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
<b>Atopy</b>								
Yes	4,883	28.2	25,714	31.1	54,205	25.7	25,629	22.6
<b>Rhinitis</b>								
Yes	629	3.6	6,948	8.4	23,740	11.3	14,366	12.7
<b>GERD</b>								
Yes	764	4.4	1,854	2.2	17,150	8.1	19,755	17.4
<b>Anxiety</b>								
Yes	290	1.7	4,260	5.2	32,844	15.6	19,610	17.3
<b>Depression</b>								
Yes	N/A	N/A	2,238	2.7	45,489	21.6	23,397	20.6
<b>COPD</b>								
Yes	N/A	N/A	N/A	N/A	5,756	2.7	25,781	22.7

348 \*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  
349 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-  
350 34 years), 3 (35-44 years), 4(45-54 years), '18 to 54s': 1 (55-64 years), 2 (65-74 years), 3 (75-84  
351 years), 4 (≥85 years); \*\*socioeconomic deprivation scale, 1 is least deprived. BTS steps are defined as  
352 1 = no regular preventer, 2 = lowest ICS dose appropriate for age (or LTRA alone if <5 years), 3 = Add  
353 LABA (add LTRA if <5 years), 4 = increase ICS dose to next level (medium in adults, low dose in  
354 children), may add in other therapy (adults: LTRA, theophylline, LAMA; children: LTRA), 5 = increase  
355 ICS dose (high in adults, medium in children), add fourth drug (adults: LTRA, theophylline, beta  
356 agonist tablet, LAMA, children: theophylline), 6 = same ICS dose and continuous or frequent use of  
357 oral steroids. LTRA = leukotriene receptor antagonist, LABA = long-acting beta-2 agonist, LAMA =  
358 long-acting muscarinic antagonist; children are patients aged under 12 years old.

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

365

	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)
<b>Total cohort</b>	17,320		82,707		210,724		113,575	
<b>Exacerbations</b>	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)
<b>Patients that exacerbated</b>	3,706 (21.4*)		18,449 (22.3*)		80,041 (38*)		70,954 (62.5*)	
<b>Annual exacerbation freq.</b>								
≤ 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	
<b>Level of care</b>								
<i>GP only</i>	5,211		26,543		155,054		334,850	
<i>A&amp;E</i>	232		984		2,257		561	
<i>Hosp (&lt;1 day)</i>	966		6,515		46,227		50,385	
<i>Hosp (≥1 day)</i>	1,165		5,925		41,502		49,015	
<i>Died</i>	<5		< 5		37		218	
<b>Antibiotic treated LRTIs</b>	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)
<b>Patients with Ax-LRTI</b>	1,612 (9.3*)		8,252 (10*)		41,874 (19.9*)		34,656 (30.5*)	

366

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

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

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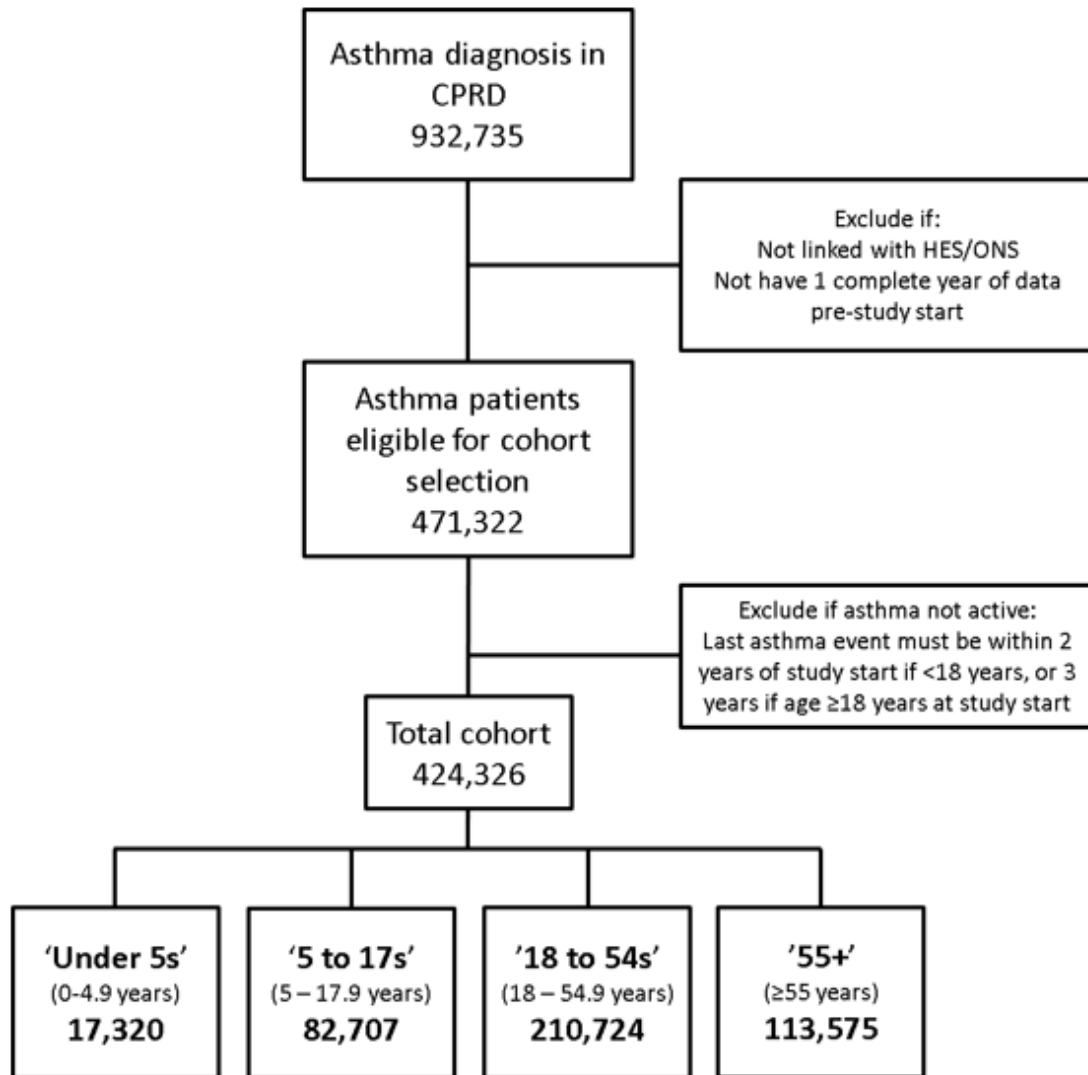
	Under 5s		5 to 17s		18 to 54s		55 +		Mean population rate per BTS step
	N (% of BTS)	Rate (95% CI)	N (% of BTS)	Rate (95% CI)	N (% of BTS)	Rate (95% CI)	N (% of BTS)	Rate (95% CI)	
<b>BTS 1</b>	656 (13.4)	2.01 (1.89-2.14)	4,849 (14.6)	0.73 (0.70-0.77)	26,607 (30.8)	1.82 (1.78-1.86)	11,805 (47.3)	5.01 (4.84-5.20)	2.39 (2.30-2.49)
<b>BTS 2</b>	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)
<b>BTS 3</b>	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)
<b>BTS 4</b>	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)
<b>BTS 5</b>	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)
<b>BTS 6</b>	<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)
<b>NonBTS</b>	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)

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

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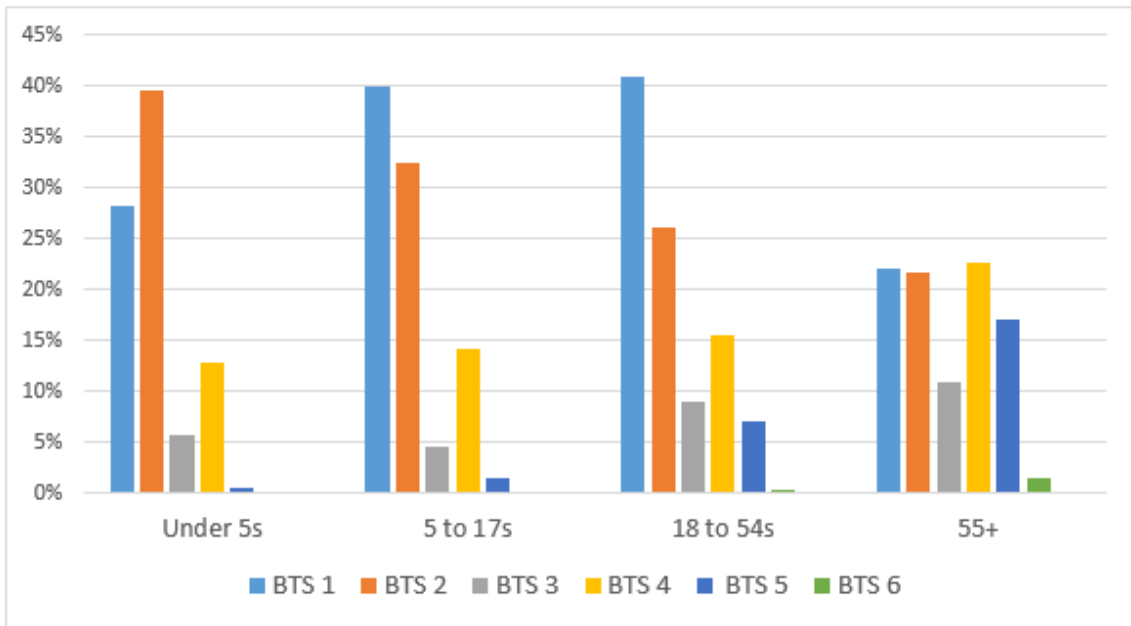


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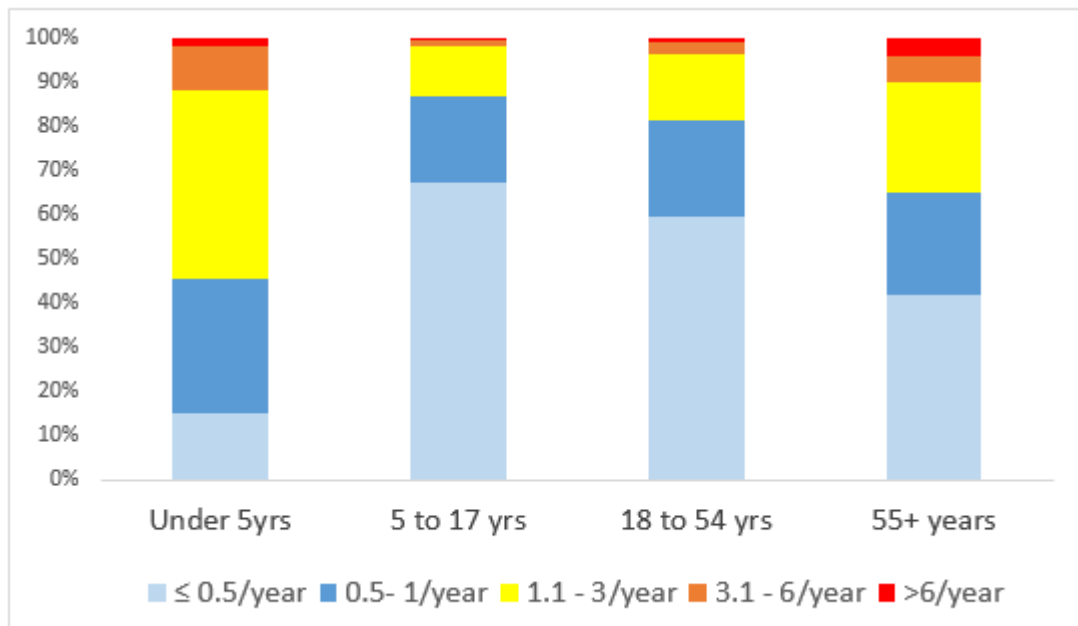
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380 Figure 1

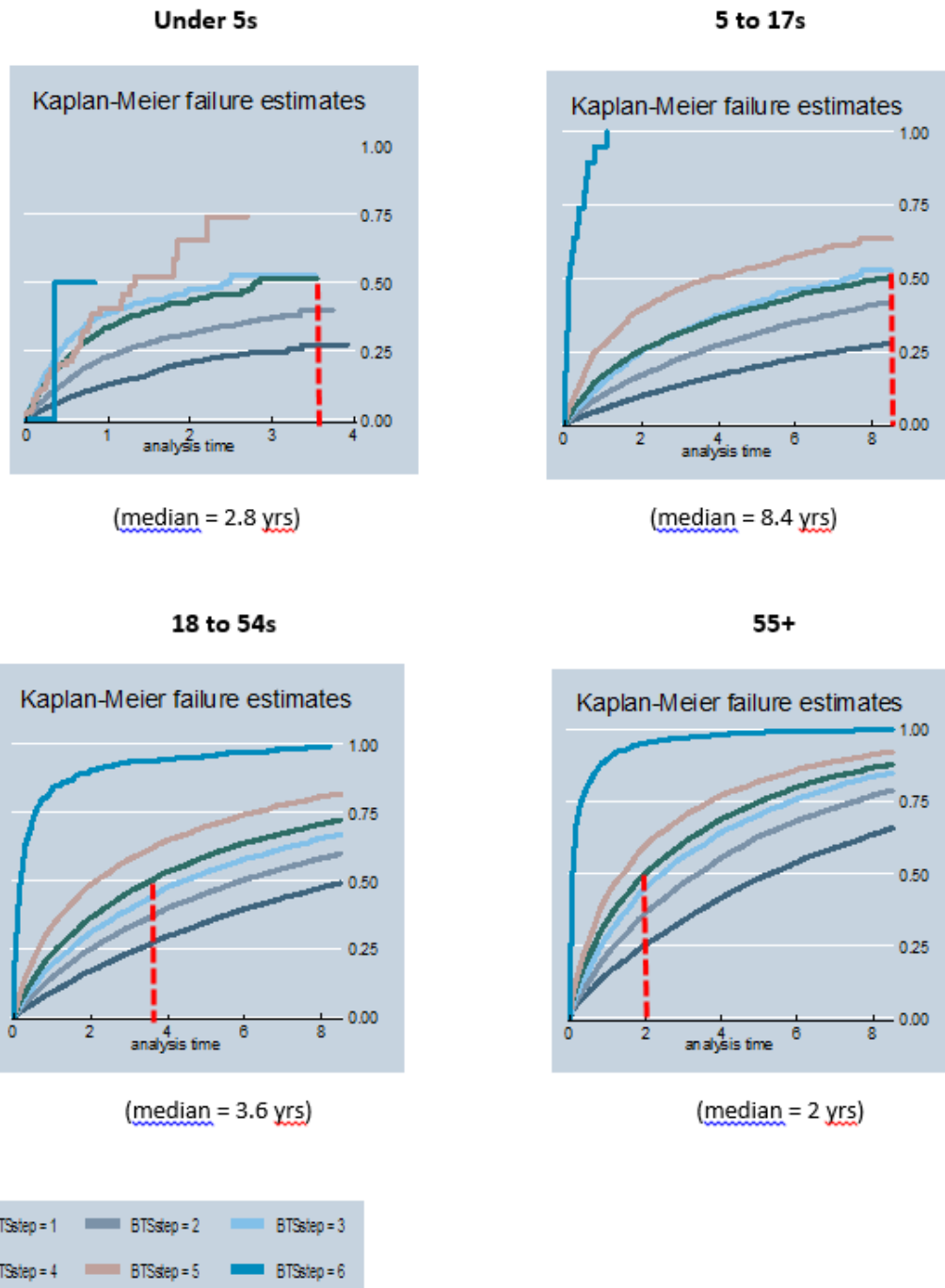
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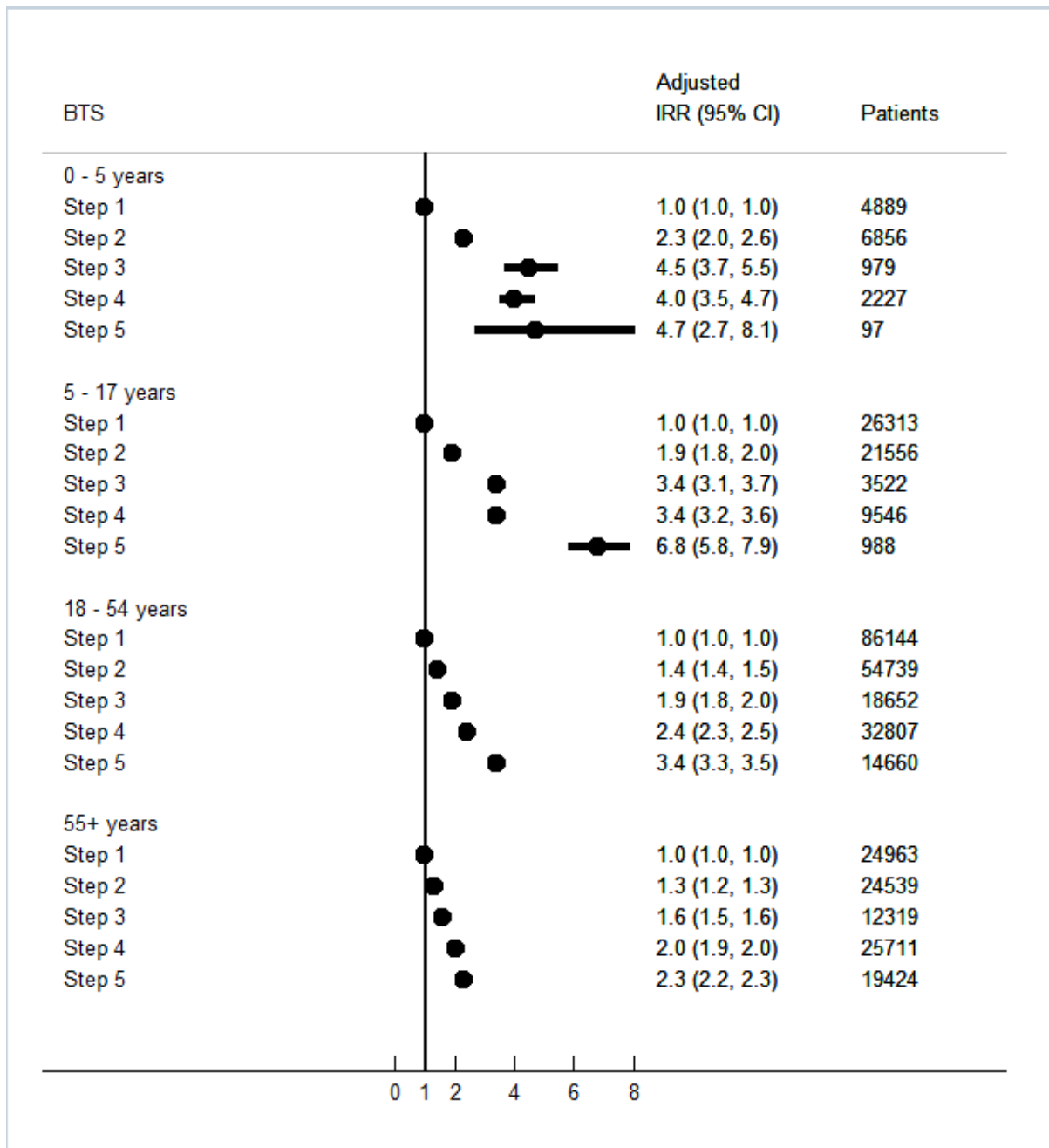



 median time to an exacerbation in BTS step 4

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389 Figure 5





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391 Figure 6

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

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

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

395 N exacerbations; rate: per 100 person years; p-values: \* p<0.001, ^ p<0.05, "p>0.05; IMD, 1 is least  
396 deprived  
397

398  
399  
400

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)
<b>Gender</b>				
Male	22772	1555	14.7 (14.3-15.1)	Ref
Female	17198	1141	15.1 (14.6-15.7)	1 (0.95-1.04)"
<b>Age cat (years)</b>				
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)*
<b>IMD</b>				
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)*
<b>Smoking</b>				
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)"
<b>BMI</b>				
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)*
<b>BTS step</b>				
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)*
<b>Atopy</b>				
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)*
<b>Reflux</b>				
No	38493	2637	14.6 (14.3-15)	Ref
Yes	1477	59	25.1 (21.1-30)	1.59 (1.39-1.83)*
<b>Anxiety</b>				
No	37510	2554	14.7 (14.4-15.1)	Ref
Yes	2460	143	17.3 (15.5-19.3)	1.09 (1-1.2)"

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

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

Characteristic	N	100 person-years	Rate (95% CI) per 100 person years	Crude IRR (95% CI)
<b>Gender</b>				
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)*
<b>Age cat (years)</b>				
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)*
<b>IMD</b>				
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)*
<b>Smoking</b>				
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)*
<b>BMI</b>				
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)*
<b>BTS step</b>				
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)*
<b>Atopy</b>				
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)*
<b>Reflux</b>				
No	208090	6939	30 (29.7-30.4)	Ref
Yes	36987	652	56.8 (54.9-58.8)	1.78 (1.72-1.84)*
<b>Anxiety</b>				
No	187540	6339	29.6 (29.2-30)	Ref
Yes	57537	1252	46 (44.9-47.2)	1.5 (1.46-1.54)*
<b>Depression</b>				

<b>No</b>	163724	5928	27.7 (27.3-28.1)	Ref
<b>Yes</b>	81353	1663	49 (48-50)	1.71 (1.68-1.75)*
<b>COPD</b>				
<b>No</b>	227779	7443	30.7 (30.3-31)	Ref
<b>Yes</b>	17298	148	116.9 (111.5-122.6)	3.4 (3.21-3.6)*
<b>Season</b>				
<b>Winter</b>	65630	817	80.3 (79.7-80.9)	Ref
<b>Spring</b>	59958	691	86.8 (86.1-87.5)	1.1 (1.09-1.12)*
<b>Summer</b>	56396	646	87.3 (86.5-88)	1.07 (1.06-1.09)*
<b>Autumn</b>	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+' cohort  
 410

<b>Characteristic</b>	<b>N</b>	<b>100 person- years</b>	<b>Rate (95% CI) per 100 person years</b>	<b>Crude IRR (95% CI)</b>
<b>Gender</b>				
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)*
<b>Age cat (years)</b>				
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)*
<b>IMD</b>				
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)*
<b>Smoking</b>				
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)*
<b>BMI</b>				
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)*
<b>BTS step</b>				
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)*
<b>Atopy</b>				
No	321078	3507	91.6 (90.3-92.9)	Ref
Yes	113951	1123	101.5 (99.1-104)	1.08 (1.05-1.1)*
<b>Reflux</b>				
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)*
<b>Anxiety</b>				
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)*
<b>Depression</b>				

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

411 N exacerbations; rate: per 100 person years; p-values: \* p<0.001, ^ p<0.05, "p>0.05; IMD, 1 is least  
412 deprived  
413



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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+
<b>BTS 1</b>	> 4	>8.5	>8.5	5.3
<b>BTS 2</b>	> 4	>8.5	5.9	3.4
<b>BTS 3</b>	2.4	7.4	4.4	2.5
<b>BTS 4</b>	2.8	8.4	3.6	2
<b>BTS 5</b>	1.3	3.8	2.1	1.4
<b>BT S6</b>	0.34	0.1	0.2	0.1

415 Log-rank test  $p < 0.001$

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