

## Trends in moderate and severe exacerbations among COPD patients in the UK from 2005 to 2013

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DOI:

[10.1016/j.rmed.2018.09.010](https://doi.org/10.1016/j.rmed.2018.09.010)

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*Document Version*

Peer reviewed version

*Citation for published version (Harvard):*

Oshagbemi, OA, Keene, S, Driessen, JHM, Jordan, R, Wouters , EFM, de Boer , A, de Vries, F & Franssen, FME 2018, 'Trends in moderate and severe exacerbations among COPD patients in the UK from 2005 to 2013', *Respiratory Medicine*. <https://doi.org/10.1016/j.rmed.2018.09.010>

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## **Trends in moderate and severe exacerbations among COPD patients in the UK from 2005 to 2013.**

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**Declarations of interest:** none

**Keywords**

Chronic obstructive pulmonary disease, general practice, exacerbations, trends.

## **Abstract (311)**

### **Introduction**

Exacerbations of chronic obstructive pulmonary disease are characterised by increased symptoms such as dyspnoea, cough and sputum production and/or purulence, leading to greater risk of hospitalisation and mortality. Very few studies have measured long term trends in the incidence of exacerbations of chronic obstructive pulmonary disease. We therefore investigated the incidence of moderate and severe exacerbations in the UK general population.

### **Methods**

A population based-study including Clinical Practice Research Datalink (CPRD) patients  $\geq 40$  years of age with a current diagnosis of COPD within the United Kingdom from 2004 to 2013 was conducted. Individuals with a history of asthma were excluded from main analyses. We calculated the incidence rates for any, moderate, and severe exacerbations. Patients contributed time at risk from January 1st up to the date of the first outcome within each year. The incidence rate for any, moderate and severe exacerbations for COPD in each calendar year was calculated as follows: the sum of any or moderate or severe exacerbations for COPD in that year divided by the total duration of follow-up in the same calendar year from 2005 through to 2013. We then analysed these rates by gender and age categories (40-59 years, 60-79 years and  $\geq 80$  years).

### **Results**

Among 213,561 with incident COPD diagnosis, 86,300 patients were included in the study. From 2005 to 2013, the incidence rate of any exacerbations increased from 89 to 98 per 1000 person years (PYs) ( $p=0.005$ ). Women had significantly higher incidence rates of any exacerbation for each calendar year when compared to men ( $p<0.0001$ ). The incidence rate of any and moderate exacerbations increased with age from 2005 to 2007. For severe exacerbations incidence decreased from 2005 to 2007 before increasing from 2008 until the end of follow-up (43 per 1000 PYs (95% confidence interval, 42-45/1000PYs) in 2013). Incidence rates of severe exacerbations were similar by gender and patients aged 80+ years had a higher incidence rate of severe exacerbation from 2005 to 2008 after which their incident rate dropped in subsequent years.

### **Conclusion**

This is the first study that reports the long-term changes in the incidence rates of moderate and severe exacerbations within the UK general practice. **Women showed a substantially higher risk of any COPD exacerbations, and their risk is increasing. The incidence rates of any exacerbations increased during the study period, while severe exacerbations were variable. Furthermore, incidence rates varied substantially by age group.**

## **Introduction (313)**

Exacerbations of chronic obstructive pulmonary disease (COPD) are defined as acute episodes of increased respiratory symptoms necessitating additional therapy [1]. Main symptoms are increased dyspnea, cough and sputum production and/or purulence. Exacerbations of COPD negatively impact on lung function [2] health status [3] and muscle function [4]. Also, they are important drivers of hospitalisations [5] and are associated with high mortality risk [6]. Hence, prevention of exacerbations of COPD is one of the main goals of pharmacologic treatment of the disease and multiple options for drug therapy are available [7]. In the United Kingdom (UK), £253 million British Pounds (GBP) is spent yearly on COPD management, with more than 50% of the costs attributed to exacerbations [8]. Also, COPD-related mortality has increased from 2004-2012 (29, 000 died in 2012) while incidence of COPD decreased and then remained stable over the same period (115, 000 new diagnosed COPD in 2012). There are over a million bed days and 140,000 hospital admissions each year in the UK due to COPD (1.7% of all hospital admissions and bed days) [9].

The role of demographic characteristics in shaping the trends in exacerbations and related hospitalisations over time has not been adequately described in a UK population. Understanding trends in acute exacerbations and related hospitalisations can help redirect healthcare policies and interventions to subgroups most affected by Exacerbations of COPD , allow comparison between countries to aid healthcare planning, predict future healthcare challenges, and provide a basis for improving future management. Thus, there is a need to understand the constantly changing trends and to subsequently target health planning and policies towards groups who are at high risk of exacerbations of COPD [10]. Management of patients with COPD in the UK is performed mainly within the primary care setting [11]. Therefore this study aims to describe the incidence rates of moderate and severe exacerbations for COPD by age and gender within the UK primary care setting from 2005-2013.

## Methods (726)

### *Data source*

This study was conducted with data from the Clinical Practice Research Datalink (CPRD), formerly known as the General Practice Research Database (GPRD). CPRD contains computerized medical records of 674 primary care practices in the UK. Data collection started in January 1987 and over 11 million persons are currently included, corresponding with 7% of the UK population [12][13]. The introduction of the Quality and Outcomes Framework (QOF) in April 2004, was aimed at facilitating quality reporting of various diseases by GPs, including COPD and its related outcomes [14]. The quality management system uses indicators recorded by GPs to monitor effectiveness in COPD reporting and to reduce the rate of misdiagnosis. Indeed, a high positive predictive value in identifying patients with COPD based on these read codes has been reported [12] and the CPRD has been used in various studies on COPD [15–17]. Using CPRD ensured that our results are generalizable within the UK population. The independent scientific advisory committee of the Medicines and Healthcare product Regulatory Agency (MHRA) database research approved this study. (ISAC protocol No: 18\_046R).

### *Study population*

We selected all patients aged  $\geq 40$  years with a diagnosis of COPD as recorded by read codes within the CPRD. The study period was from 1<sup>st</sup> January 2004 until 31<sup>st</sup> December 2013 corresponding to the period since the introduction of the Quality and Outcomes Framework (QOF). However, we calculated the incidence rates from 2005 through to 2013. For the main analyses, we excluded all patients with a history of asthma from the study and COPD diagnosis prior to 2004. Follow-up ended at the earliest of the study end date (31<sup>st</sup> December 2013), or the patient's death or transfer out of the practice. The primary endpoint was the first acute exacerbation of COPD in a given calendar year, identified using validated read codes for exacerbations of COPD [18] from the referral and/or clinical files. We defined this as any exacerbations of COPD. The secondary outcomes were defined as follows: (i) exacerbations of COPD without hospitalisations/accident and emergency (A&E) visits evaluated using validated Read codes for exacerbations of COPD from the clinical file only. This was defined as moderate exacerbations of COPD. (ii) COPD-related hospitalisations/A&E visit evaluated using Read codes for hospitalisation/A&E visits for COPD from both clinical and/or referral file in addition with validated read codes for exacerbations of COPD from the referral file. This was defined as severe exacerbations of COPD. Referral files contains referral details recorded by GPs while the clinical file contains all the medical history data entered by the GP.[19]

### *Statistical analysis*

For our main analyses we only counted the first outcome of interest within a given calendar year (i.e. patients with an outcome only contributed time at risk from January 1<sup>st</sup> up to the date of the first outcome within each year). The incidence rates for moderate/severe, moderate and severe exacerbations for COPD in each calendar year was calculated as follows: the sum of any or moderate or severe exacerbations for COPD in that year divided by the total duration of follow-up in the same calendar year. We only calculated incidence rates from 2005 through to 2013. The incidence rates were expressed as the number of exacerbations per 1000 person-years (PY). We then analysed these rates by gender and age categories (40-59 years, 60-79 years and  $\geq 80$  years). The incidence rates are accompanied by 95% confidence intervals (CI). Using chi-square test, we compared the changes in trends with statistically significant difference determined at  $p < 0.05$  between calendar year, gender and age categories. All analyses were carried out using SAS 9.4 (SAS Institute, Cary, NC).

### *Sensitivity analysis*

We performed two sensitivity analyses. As far as we know, there are no established methods to estimate incidence rates of moderate and severe exacerbations among COPD patients. In the first sensitivity analysis we no longer counted the first event within a given calendar year, but we added up all exacerbations that occurred in a calendar year. To overcome the problem of potentially counting the same event more than once, we stipulated a gap of at least 30 days between consecutive events of any exacerbations of COPD. This sensitivity analysis was carried out to depict the overall trend of any exacerbations of COPD using validated read codes from referral or/and clinical files (see supplementary appendix: eTable1). In the second sensitivity analysis, we included patients with a history of asthma and estimated the incidence rates of any exacerbations taking only the first exacerbation into consideration. (see supplementary appendix: eTable2).

## Results (685)

We identified 213,561 patients with COPD diagnosis within the CPRD of whom 86,300 met the inclusion criteria. The mean age of patients in our study was 68 years and 45.5% (n=39,241) were women (see supplementary appendix: eTable 1).

### *Trends of any exacerbations for COPD*

We observed 30,996 any exacerbation for COPD during the study period. Table 1 shows the overall incidence rates of any exacerbations for COPD. From 2005 to 2007, the incidence rate of the primary any exacerbations remained stable at around 88 per 1000PYs. A rise in incidence rate of any exacerbations was noted from 2008 to 2012 (112 per 1000PYs (95%CI, 109-114/1000PYs)). However, we observed a decrease in the incidence of any exacerbations to 98 per 1000 PYs in 2013. Overall, there was a 10% increase in any exacerbations from 2005 to 2013, which was statistically significant (p=0.005). Gender specific incidence rates are shown in Figure 1a. In both men and women, any exacerbations incidence rates followed a somewhat similar pattern of year-to-year change. The incidence rates for both men and women increased from 84 and 95 in 2005 to 90 and 107 per 1000 PYs in 2013 respectively. Women had greater incidence rates of any exacerbations in each calendar year compared to men (p<0.0001).

Figure 2a shows the incidence rates of any exacerbations by age. There was an increasing incidence rate of any exacerbations with increasing age group from 2005 to 2007, which disappeared from 2009 to 2013. In 2008 the incidence rates of any exacerbations were the same among patients 40-59 and 60-79 years old. We observed a decrease in year-to-year incidence rates of any exacerbations for 80+ year-old patients. In contrast, any exacerbation rates increased across the study period for patients in the 40-59 and the 60-79 year old age groups.

### *Trends of moderate exacerbations for COPD*

From 2005 until 2013, a total of 30,973 moderate exacerbations were observed in our study population. Table 2 shows the annual incidence rates of moderate exacerbations for COPD. The general trend of moderate exacerbation was similar to that of any exacerbations for COPD by age and gender (see appendix). From 2005 to 2007, the incidence rate of the moderate exacerbations remained stable at around 88 per 1000PYs before increasing to 112 per 1000 PYs (95%CI, 109-114/1000PYs) in 2012. We found a significant increase in moderate exacerbations for COPD by 10% from 2005 to 2013 (p=0.005).

### *Trends of severe exacerbations for COPD*

Between 2005 and 2013 we found 8032 severe COPD exacerbations. From 2005 to 2007 we found a decline in the incidence of severe exacerbations for COPD from 18 to 11 per 1000 PYs. However, there was a steady increase from 2008 until the end of the study period. In 2013, the incidence rate was



43 per 1000 PYs. Figure 1b shows the incidence rates of severe exacerbations by gender (Table 3). Similar to the overall trend, both men and women showed a flattened 'U' shaped decrease in hospitalisation/A&E incidence rates before an increase from 2008 to their peak rates in 2013. Women and men had similar incidence rates in each calendar year of the study ( $p=0.747$ ).

Figure 2b shows the incidence rates of severe exacerbations for COPD by age. We noticed an increasing incidence rate of severe exacerbations for COPD by age from 2005 to 2008. In 2012 and 2013 patients aged 60-79 years had a significantly higher incidence rate compared to other age groups ( $p<0.0001$ ). For each age group, the incidence rates for severe exacerbations decreased from 2005 to 2007 before increasing from 2008 to 2013 (Figure 2b). For all age groups, the rates in 2009 were similar.

#### *Sensitivity analysis of trends of any exacerbations of COPD.*

For the first sensitivity analysis we considered multiple events in a given calendar year. A total of 37,160 any exacerbations of COPD were observed during the study period. The trends were similar to that observed for moderate/severe exacerbations of COPD when we evaluated only one event in a calendar year. However, we found a non-significant increase of 3% in the incidence rates of any COPD exacerbations from 2005 to 2013. (see supplementary appendix: eTable2). In the second sensitivity analysis we included patients with a history of asthma. The incident rates declined gradually until 2007 and remained the same from 2008 to 2009. The incident rates dropped from 119 to 103 per 1000 PYs from 2011 to 2013. Overall, there was a 2% decrease in the incidence rates of any COPD exacerbations, which was not statistically significant ( $p=0.577$ ). (see supplementary appendix: eTable3).

## **Discussion (1380)**

### *Summary of main findings*

Using the world's largest primary care database, this study showed a significant increase in the incidence rates from 2005 to 2013 for the primary endpoint, any exacerbations of COPD. For severe exacerbations, incidence rates increased from 2008 to 2013. Women had higher incidence rates of any exacerbations compared to men patients throughout the study period but they had similar incidence rates of severe exacerbations for COPD from 2005 to 2013. The incidence rate of any exacerbations for COPD was higher in patients 80+ years from 2005 to 2008, after which this trend was not observed.

### *Comparison with existing literature*

To the best of our knowledge there has been no previous large-scale population based studies on the trends of moderate to severe exacerbations of COPD in the UK. Previous studies have focused mainly on prevalence rates of COPD [20–22] with no emphasis on the trends of acute exacerbations of COPD. Using the Health Improvement Network database, Snell et al [9] reported a 27% increase in the prevalence of COPD in the UK from 2004 to 2012. This increase in prevalence of COPD is correlated with the increase in incidence of moderate and severe exacerbations of COPD in our study. A study conducted among 423 COPD patients within the Dutch general practice from 1980 to 2006 reported a reduction in overall annual exacerbation rates which is contrary to our findings [10]. The study also observed that the decreasing trends was independent of age and sex [10]. It is difficult to draw a definite conclusion for the declining trends of acute exacerbations of COPD in their study, but it might be related to changes in treatment guidelines for COPD and increased emphasis on vaccination during the study period [10]. In our study, we also found that the incidence rates of acute exacerbations increased with increasing age in certain years. This might be due to disease progression and severity of the disease state. Investigators have reported a relationship between age and underreporting of acute exacerbations [23], which means that the incidence rates might be underestimated among older patients.

Although, few studies have focused on incidence rates of moderate exacerbations of COPD more have focused on COPD exacerbation requiring hospitalisations (severe exacerbations). Furhrrmal et al [24], examined the temporal trends in acute exacerbations related hospitalisation from 1998 to 2007 in France, and found that admission rates increased significantly, especially among females. Although, our study also reported an increase in severe exacerbations there was only slight differences by gender for all years. Another study conducted in Brazil found no changes in hospitalisation rates from 1998 to 2009 [25]. The Hospital Episode Statistics published by the UK department of health from 1998 to 2003 showed an increase in the number of admissions for COPD [26], with 140,000 hospital admissions each year [9]. It has been reported that 30% of patients hospitalised for exacerbations will

be seen again and possibly admitted with another exacerbation within 8 weeks [26]. Contrary to our findings, a study investigating the incidence of COPD which defined COPD diagnosis based on A&E visit and hospitalisation in Canada reported a reduction in the incidence of COPD from 1996 to 2007 [20]. Similarly, Kinnula et al [27] reported a decrease in the rates of hospitalisations associated with COPD in Finland from 1998 to 2007. The exact reason for the low incidence rates of severe exacerbations in our study is not completely understood. However, this might be related to the fact that most COPD patients die from various fatal comorbidities associated with COPD severity before they could be hospitalised for an acute exacerbations of COPD [28]. Another explanation is that many patients have problems in identifying symptom aggravation and fail to report exacerbations to health experts [29,30], resulting in spontaneous hospitalisations and A&E visits. Additionally, GPs often record COPD hospitalisation using less specific read codes. [31]. Merinopoulou et al [32], reported that the rates of COPD-related hospitalisations from 2011 to 2013 were higher in patients with more severe disease state, with most severe patients (GOLD D) having 3 times the number of exacerbations compare to least severe groups (GOLD A). The lack of information on disease stage in our study made it impossible to corroborate their finding.

Whilst emphasis has been on adherence to treatment guidelines among COPD patients in different GOLD guidelines as a means of reducing prevalence of COPD-related exacerbations, a significant dissociation has been reported between adherence to guidelines and actual management of COPD patients [33]. A study conducted among 24,957 COPD patients in the UK showed that the patients were not managed in accordance to GOLD and National Institute for Health and Care Excellence recommendations, with substantial amount of patients not receiving appropriate medications [34]. Despite current developments with LAMA/LABA and ICS in treatment of COPD patients we found no objective reduction in exacerbations in our study. **Although, low adherence to therapy [35], and improper inhaler technique among COPD patients [7] may have contributed to the trend observed. Furthermore variation in the incidence of exacerbations seems to follow the incidence of influenza A during the study period, suggesting that this might have had an impact our study [36]. It is also important to note that the use of long acting agents was low in our study cohort.**

#### *Strengths and limitations*

A major strength of this study was the inclusion of patients from one of the world's largest primary care databases, thus providing a very large sample size. Second, we were able to assess the incidence rates of moderate and severe exacerbations over a long period. Third, we consider periods since the introduction of the QOF ensuring greater quality and validity of data recording. Fourth, we used validated read codes for acute exacerbations of COPD. **Lastly, a validity study of COPD patients in the CPRD concluded that patients with COPD can be identified easily using specific read codes [37].**

Despite the numerous strengths, this study had some limitations. The use of the read codes for acute

exacerbation may have underestimated the true incidence rates of COPD exacerbations. However, the read codes used have been reported to have a high positive predictive value (PPV) of 96% in identifying patients with COPD exacerbation in the CPRD [18] and we explored both clinical and referral files to ensure all exacerbations were identified. Nevertheless, we may have missed a considerable amount of exacerbations that may be miscoded e.g. as respiratory tract infections or pneumonia. Although we excluded asthma patients from the main analyses, it was impossible to rule out the inclusion of patients with reversible airflow limitation in this study [38]. Furthermore, the PPV of approximately 50.2% and a sensitivity of 5.4% in identifying hospitalisations for COPD within the CPRD is arguably low, which may have resulted from GPs recording hospitalisation for COPD by generic hospitalisation codes and/or acute exacerbation read codes [31]. As such the incidence rate for severe exacerbations is likely to be an underestimate of the true incidence in the UK. While the method of diagnosis of COPD has not changed since 2005, GPs ability to identify exacerbations of COPD might have changed over time [32], which may have had an effect on our findings.

#### *Implication for future research and clinical practice*

The introduction of QOF in 2004 was aimed at ensuring quality recording of diagnosis and treatment of COPD and other chronic diseases [39]. Although, approximately equal numbers of patients were diagnosed with COPD annually during the study period. The higher incidence rates of any exacerbations among women and among older patients suggests emphasis be placed on adherence to treatment guidelines and other interventions among these patient groups. The increased incidence of any exacerbations in our study since the introduction of QOF is concerning. This coincides with sceptics questioning the relevance of QOF in aiding holistic clinical care [39], although it cannot be denied that its introduction has resulted in a modest reduction in overall emergency admission rates for long-term conditions [39]. ECLIPSE investigators, suggest that patients with two or more exacerbations in a year represent a distinct “frequent exacerbators” phenotype, and have increased risk of future exacerbation events [40]. Though these group of patients could not be identified in our study. Fundamentally, it is important for GPs to identify these patients by carefully exploring patient’s history and targeting interventions based on recommendations from clinical guidelines. Also a greater emphasis should be made on treatment adherence by COPD patients, as “frequent exacerbators” and patients with history of hospitalisation have been reported to be less likely to adhere to therapy [35].

#### *Conclusion*

This is the first study that reports the long-term changes in the incidence rates of moderate and severe exacerbations as recorded by UK general practitioners. Women showed a substantially higher risk of any COPD exacerbations, and their risk is increasing. The incidence rates of any exacerbations increased during the study period, while severe exacerbations were variable. Furthermore, incidence rates varied substantially by age group. In addition, these findings have the potential to help redirect

healthcare policies, planning and interventions to target subgroups more effectively, and may provide a basis for improving overall COPD management in the future.

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#### **Author Contributions:**

Conception or design: all authors equally contributed.

Analysis of data: OO, JHM

Interpretation of data: all authors equally contributed.

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Final approval of the version to be published: all authors equally contributed.



## Results

Table 1. Incidence rates* of any exacerbations for COPD from 2005-2013 <sup>¶</sup>			
Year	No. of any exacerbations n=30996	PY at risk	IR /1000 PY (95% CI)
2005	1110	12514.4	89 (84-95)
2006	1678	18981.8	88 (84-93)
2007	2194	24905.1	88 (85-92)
2008	2838	30441.4	93 (90-97)
2009	3356	35161.5	95 (92-99)
2010	4315	40319.5	107 (104-110)
2011	4839	44777.5	108 (105-111)
2012	5500	49260.1	112 (109-114)
2013	5166	52893.7	98 (95-100)

\* Only one event per calendar year was counted.

Abbreviations: AECOPD, acute exacerbation chronic obstructive pulmonary disease; IR, incidence rate; HR, hazard ratio; A&E, accident & emergency; PY, person-years; CI, confidence interval.

<sup>¶</sup> using validated read codes for AECOPD from clinical and/or referral files.

Table 2. Incidence rates\* of moderate exacerbations for COPD from 2005-2013<sup>¶</sup>

Year	No. of moderate exacerbations n=30973	PY at risk	IR /1000 PY (95% CI)
2005	1110	12514.8	89 (84-94)
2006	1676	18983.3	88 (84-92)
2007	2193	24905.2	88 (85-92)
2008	2835	30443.4	93 (90-96)
2009	3352	35164.4	95 (92-98)
2010	4313	40320.7	107 (104-110)
2011	4835	44779.7	108 (105-111)
2012	5496	49261.5	112 (109-114)
2013	5163	52895.7	98 (95-100)

\* Only one event per calendar year was counted.

Abbreviations: AECOPD, acute exacerbation chronic obstructive pulmonary disease; IR, incidence rate; HR, hazard ratio; A&E, accident & emergency; PY, person-years; CI, confidence interval.

<sup>¶</sup> using validated read codes for AECOPD from clinical file only.

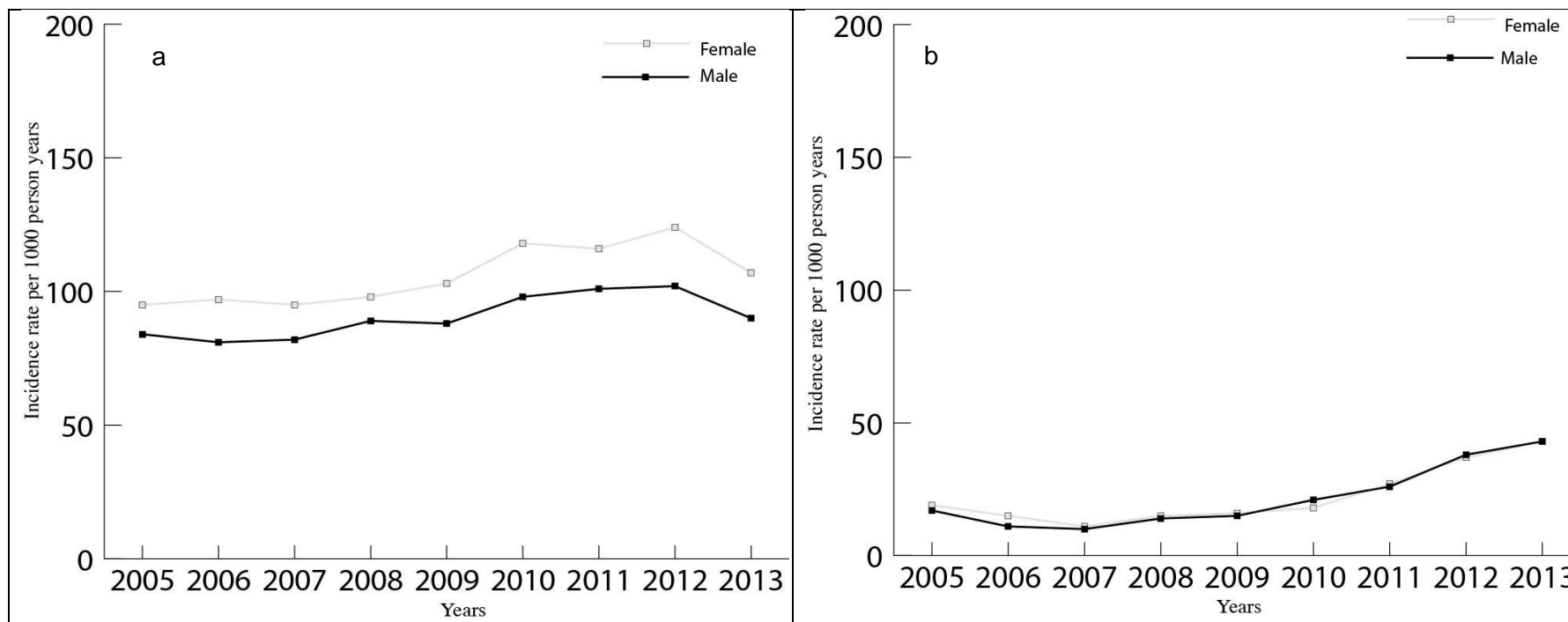
Table 3. Incidence rates of severe exacerbations for COPD from 2005-2013<sup>¶</sup>

Year	No. of severe exacerbations* n=8032	PY at risk	IR /1000 PY (95% CI)
2005	229	12896.0	18 (16-20)
2006	248	19646.9	13 (11-14)
2007	277	25792.1	11 (10-12)
2008	455	31421.6	14 (13-16)
2009	556	36382.1	15 (14-17)
2010	821	41713.3	20 (18-21)
2011	1224	46192.4	26 (25-28)
2012	1902	50388.8	38 (36-39)
2013	2320	53691.0	43 (42-45)

\* Only one event per calendar year was counted.

Abbreviations: AECOPD, acute exacerbation chronic obstructive pulmonary disease; IR, incidence rate; HR, hazard ratio; A&E, accident & emergency; PY, person-years; CI, confidence interval.

<sup>¶</sup> using read codes for hospitalisation/A&E visits for COPD from clinical and/or referral files in addition with validated read codes for AECOPD from referral file.

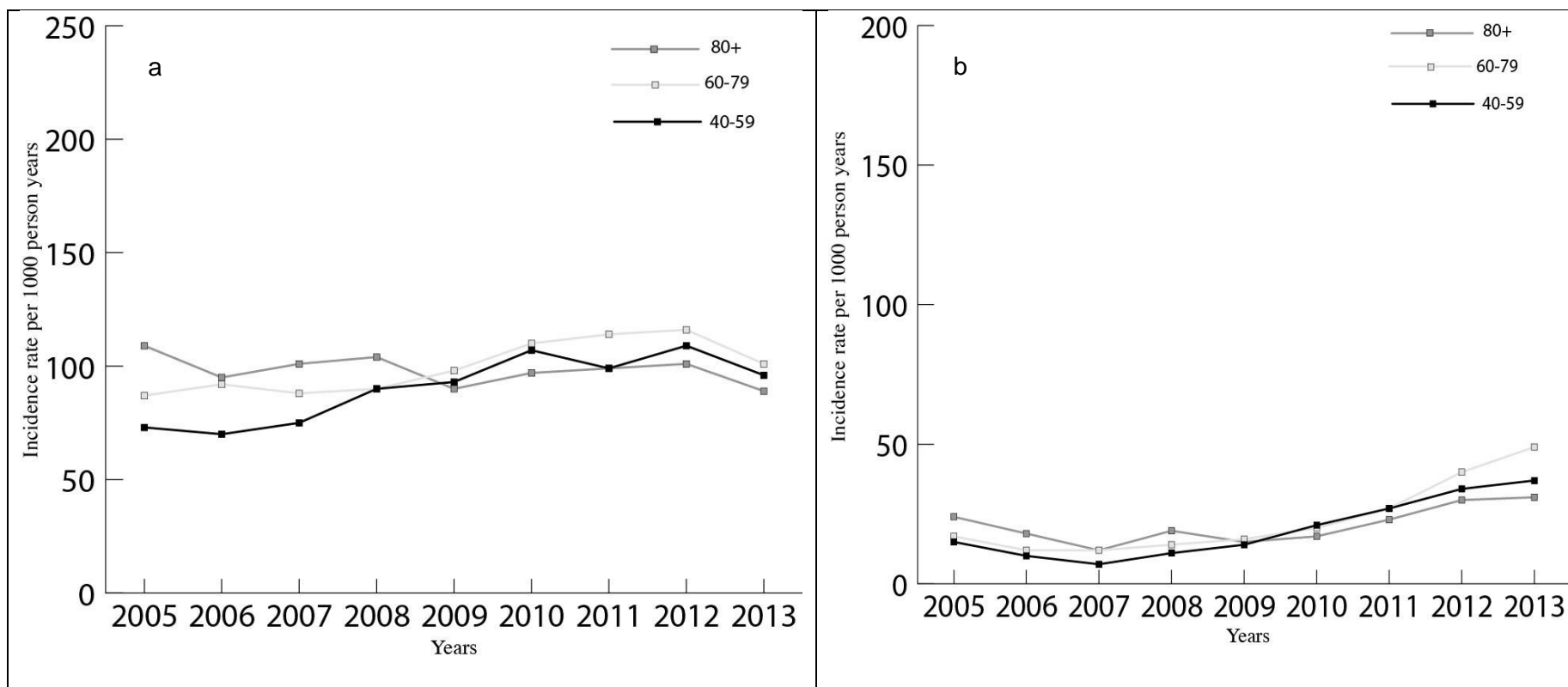


**Figure 1. Incident rates of (a) any exacerbations<sup>†</sup> or (b) severe exacerbations\* for COPD by gender.**

Abbreviations: AECOPD, acute exacerbation chronic obstructive pulmonary disease; A&E, accident & emergency; PY, person-years.

<sup>†</sup> using validated read codes for AECOPD from clinical and/or referral files.

\* using read codes for hospitalisation/A&E visits for COPD from clinical and/or referral files in addition with validated read codes for AECOPD from referral file.



**Figure 2. Incident rates of (a) any exacerbations<sup>¶</sup> or (b) severe exacerbations\* for COPD by age.**

Abbreviations: AECOPD, acute exacerbation chronic obstructive pulmonary disease; A&E, accident & emergency; PY, person-years.

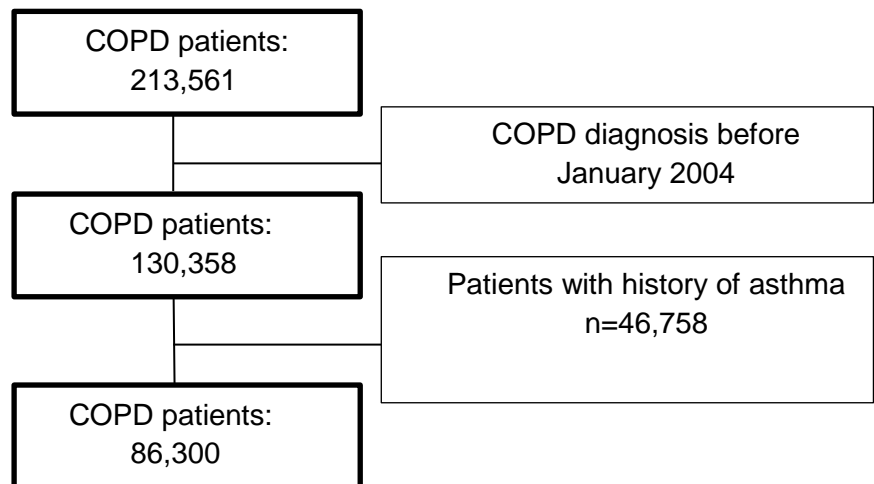
<sup>¶</sup> using validated read codes for AECOPD from clinical and/or referral files.

\* using read codes for hospitalisation/A&E visits for COPD from clinical and/or referral files in addition with validated read codes for AECOPD from referral file.

# Supplementary appendix

This appendix forms part of the original submission.

**Trends in moderate and severe exacerbations among COPD patients in the UK from 2005 to 2013.**



**eFigure 1: Flow chart showing the selection of eligible patients**

eTable1: Baseline characteristics	COPD patients (n=86,300)	
	<b>n</b>	<b>(%)</b>
Females	39,241	45.5
Mean age (years, SD)	68.1	11.3
Age category (years)		
40-59	19,475	22.6
60-79	51,982	60.2
80+	14,843	17.2
BMI (kg/m <sup>2</sup> ) in the past 6 months		
Underweight (BMI < 18.5 kg/m <sup>2</sup> )	4,784	5.5
Normal weight (BMI 18.5-24.9 kg/ m <sup>2</sup> )	29,808	34.5
Overweight (BMI 25.0-29.9kg/ m <sup>2</sup> )	26,529	30.7
Obese (BMI ≥ 30,0 kg/ m <sup>2</sup> )	20,938	24.4
Missing	4,241	4.9
Smoking status at index date		
Never	9,005	10.4
Current	38,207	44.3
Former	38,662	44.8
Missing	426	0.5
Drug use (in the past 6 months)		
SABAs	48,624	56.3
LABAs	7,542	8.7
SAMAs	7,576	8.8
LAMAs	15,102	17.5
Xanthine derivatives	770	0.3
Antidepressants	17,063	19.8
History of co-morbidities		
Diabetes Mellitus	9,619	11.1
Anxiety	12,267	14.2
Osteoporosis	15,063	5.9
Malignancies excluding non-melanoma skin cancer	12,357	14.3
Chronic liver disease	292	0.3
Ischaemic heart disease	12,493	14.5
Abbreviations: SD, standard deviation; COPD, chronic obstructive pulmonary disease; BMI, body mass index; SABAs, short-acting beta-2 agonists; LABAs, long-acting beta-2 agonists; SAMAs, short-acting muscarinic antagonists; LAMAs, long-acting muscarinic antagonists; ICS, inhaled corticosteroids.		

eTable 2. Incidence rates\* of any exacerbations for COPD from 2005-2013<sup>¶</sup>

Year	No. of any exacerbations n=30996	PY at risk	IR /1000 PY (95% CI)
2005	1471	13350.9	110 (105-116)
2006	2260	20607.8	109 (105-114)
2007	3034	27540.5	110 (107-114)
2008	3934	34209.7	114 (112-118)
2009	4760	40181.9	118 (115-122)
2010	6247	46885.5	133 (130-136)
2011	7137	52995.1	134 (132-138)
2012	8090	59217.2	137 (134-139)
2013	7250	64304.4	113 (110-115)

\* We counted all events occurring 30 days between consecutive events within a calendar year.

Abbreviations: AECOPD, acute exacerbation chronic obstructive pulmonary disease; IR, incidence rate; HR, hazard ratio; A&E, accident & emergency; PY, person-years; CI, confidence interval.

<sup>¶</sup> using validated read codes for AECOPD from clinical and/or referral files.



eTable 3. Incidence rates\* of any exacerbations for COPD from 2005-2013 among COPD patients with history of asthma<sup>†</sup>

Year	No. of any exacerbations n=53514	PY at risk	IR /1000 PY (95% CI)
2005	2098	19984.5	105 (101-109)
2006	3100	30311.7	102 (99-106)
2007	4082	39632.7	103 (100-106)
2008	5106	48203.1	106 (103-109)
2009	5858	55284.1	106 (103-109)
2010	7390	63121.3	117 (115-120)
2011	8273	69617.8	119 (116-121)
2012	9204	76043.7	121 (119-123)
2013	8403	81196.9	103 (101-106)

\* Only one event per calendar year was counted.

Abbreviations: AECOPD, acute exacerbation chronic obstructive pulmonary disease; IR, incidence rate; HR, hazard ratio; A&E, accident & emergency; PY, person-years; CI, confidence interval.

<sup>†</sup> using validated read codes for AECOPD from clinical and/or referral files.

eTable 4. Incidence rates of any exacerbations of COPD from 2005-2013 by gender<sup>¶</sup>

	Men			Women		
Year	No of any exacerbations n=15609	PY at risk	IR /1000 PY	No of any exacerbations n=15387	PY at risk	IR /1000 PY
2005	579	6902.9	84 (78-91)	531	5611.5	95 (87-103)
2006	856	10465.5	82 (77-87)	822	8516.2	97 (90-103)
2007	1132	13676.2	83 (78-88)	1062	11228.9	95 (89-100)
2008	1487	16628.7	89 (85-93)	1351	13812.7	98 (93-103)
2009	1698	19195.5	88 (85-93)	1658	15966.0	104 (99-109)
2010	2154	21933.4	98 (94-102)	2161	18386.1	118 (113-122)
2011	2451	24244.7	101 (97-105)	2388	20532.8	116 (112-121)
2012	2700	26598.9	102 (98-105)	2800	22661.1	124 (119-128)
2013	2552	28494.1	90 (86-93)	2614	24399.5	107 (103-111)

Abbreviations: AECOPD, acute exacerbation chronic obstructive pulmonary disease; IR, incidence rate; PY, person-years.

<sup>¶</sup> using validated read codes for AECOPD from clinical and/or referral files

eTable 5. Incidence rates of moderate exacerbations of COPD from 2005-2013 by gender<sup>¶</sup>

	Men			Women		
Year	No of moderate exacerbations n=15599	PY at risk	IR /1000 PY	No of moderate exacerbations n=15374	PY at risk	IR /1000 PY
2005	579	6903.4	84 (78-91)	531	5611.5	95 (87-103)
2006	856	10465.6	82 (77-87)	820	8517.7	96 (90-103)
2007	1132	13676.2	83 (78-88)	1061	11229.1	94 (89-100)
2008	1485	16630.6	89 (85-94)	1350	13812.8	98 (93-103)
2009	1697	19195.8	88 (84-93)	1655	15968.5	104 (99-108)
2010	2152	21934.6	98 (94-102)	2161	18386.1	118 (113-122)
2011	2450	24245.1	101 (97-105)	2385	20534.6	116 (112-121)
2012	2698	26599.4	101 (98-105)	2798	22662.1	124 (119-128)
2013	2550	28495.4	90 (86-93)	2613	24400.3	107 (103-111)

Abbreviations: AECOPD, acute exacerbation chronic obstructive pulmonary disease; IR, incidence rate; PY, person-years.

<sup>¶</sup> using validated read codes for AECOPD from clinical file only

eTable 6. Incidence rates of severe exacerbations of COPD from 2005-2013 by gender<sup>¶</sup>

	Men			Women		
Year	No of severe exacerbations n=4318	PY at risk	IR /1000 PY	No of severe exacerbations n=3714	PY at risk	IR /1000 PY
2005	119	7108.1	17 (14-20)	110	5787.9	19 (16-23)
2006	115	10811.4	11 (9-13)	133	8835.5	15 (13-18)
2007	149	14116.3	11 (9-12)	128	11675.8	11 (9-13)
2008	238	17150.8	14 (12-16)	216	14270.9	15 (13-17)
2009	299	19806.7	15 (13-17)	258	16575.4	16 (14-18)
2010	467	22577.2	21 (19-23)	354	19136.1	18 (17-21)
2011	656	24941.7	26 (24-28)	568	21250.8	27 (25-29)
2012	1029	27054.8	38 (36-40)	873	23334.1	37 (35-40)
2013	1246	28788.9	43 (41-46)	1074	24902.7	43 (41-46)

Abbreviations: AECOPD, acute exacerbation chronic obstructive pulmonary disease; IR, incidence rate; PY, person-years.

<sup>¶</sup> using read codes for hospitalisation/A&E visits for COPD from clinical and/or referral files in addition with validated read codes for AECOPD from referral file.

