Respiratory Medicine 144 (2018) 1–6

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

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

Olorunfemi A. Oshagbemi[a,b,c,d,1], Spencer J. Keene[b,d,e,1], Johanna H.M. Driessen[a,b,c,g], Rachel Jordan[e], Emiel F.M. Wouters[d,f], Anthonius de Boer[c], Frank de Vries[a,b,c,*], Frits M.E. Franssen[d,f]

[a] Department of Clinical Pharmacy and Toxicology, Maastricht University Medical Centre+, Maastricht, the Netherlands
[b] Department of Epidemiology, Care and Public Health Research Institute (CAPHRI), Maastricht University, the Netherlands
[c] Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute of Pharmaceutical Sciences, Utrecht, the Netherlands
[d] CIRO+, Centre for Specialised Treatments Chronic Respiratory Diseases, Horn, the Netherlands
[e] Institute of Applied Health Research, College of Medical and Dental Sciences, University of Birmingham, Birmingham, United Kingdom
[f] Department of Respiratory Medicine, Maastricht University Medical Centre (MUMC+), Maastricht, the Netherlands
[g] NUTRIM School for Nutrition and Translational Research in Metabolism, Maastricht University, Maastricht, the Netherlands

ARTICLE INFO

Keywords:
Chronic obstructive pulmonary disease
General practice
Exacerbations
Trends

ABSTRACT

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 ≥ 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 ≥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.

* Corresponding author. Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, the Netherlands.
E-mail address: f.devries@uu.nl (F. de Vries).
[1] OO and SK are joint first authors.

https://doi.org/10.1016/j.rmed.2018.09.010
Received 18 July 2018; Received in revised form 4 September 2018; Accepted 11 September 2018
Available online 17 September 2018

1. Introduction

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 to 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 to 2013.

2. Methods

2.1. 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).

2.2. Study population

We selected all patients aged ≥40 years with a diagnosis of COPD as recorded by read codes within the CPRD. The study period was from 1st January 2004 until 31st 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 (31st 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].

2.3. 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 1st 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 ≥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).

2.4. 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 form referral or/and clinical files (see supplementary appendix: eTable 1). 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: eTable 2).

3. Results

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).

3.1. 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

Table 1
Incidence rates[a] of any exacerbations for COPD from 2005 to 2013[b].

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)

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

[a] Only one event per calendar year was counted.

[b] Using validated read codes for AECOPD from clinical and/or referral files.

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 Fig. 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 to 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).

Fig. 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.

3.2. 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).

3.3. 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. Fig. 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).

Fig. 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 (Fig. 2b). For all age groups, the rates in 2009 were similar.

3.4. 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: eTable 2). 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: eTable 3).

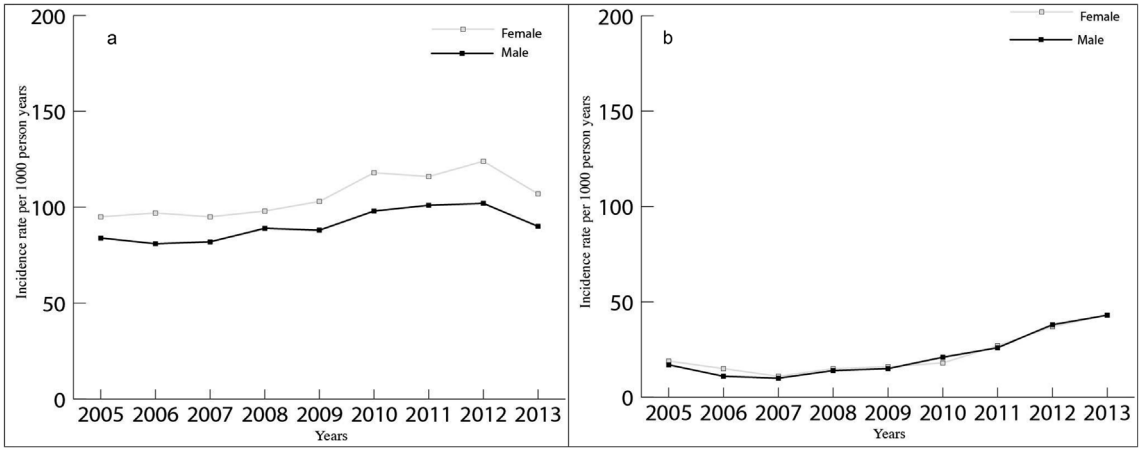

Fig. 1. Incident rates of (a) any exacerbations ¶ or (b) severe exacerbations* for COPD by gender.
AbbreviationsAECOPD, acute exacerbation chronic obstructive pulmonary disease; A&E, accident & emergency; PY, person-years.
¶ using validated read codes for AECOPD from clinical and/or referral files.
* 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.

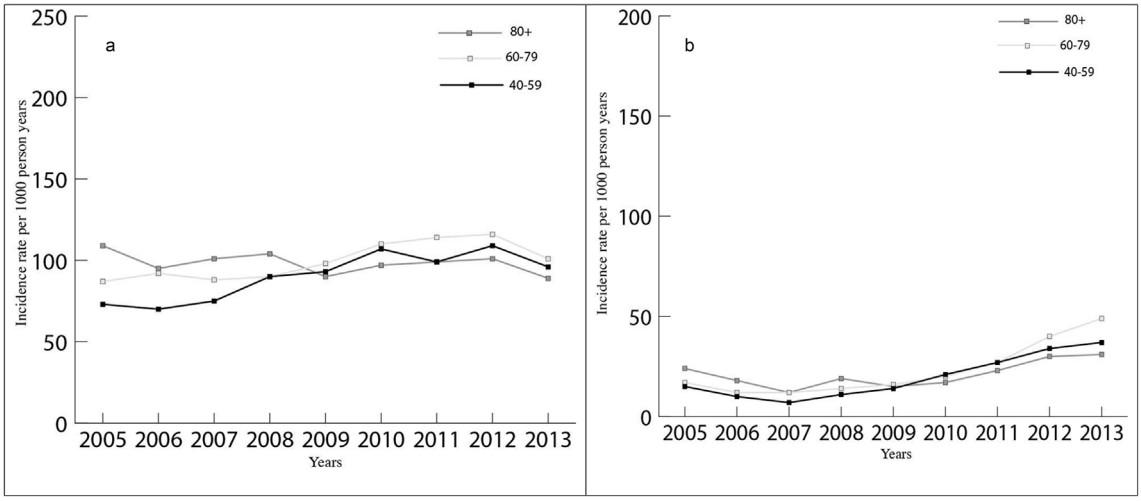

Fig. 2. Incident rates of (a) any exacerbations ¶ or (b) severe exacerbations* for COPD by age.
Abbreviations: AECOPD, acute exacerbation chronic obstructive pulmonary disease; A&E, accident & emergency; PY, person-years.
¶ using validated read codes for AECOPD from clinical and/or referral files.
* 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.

Table 2
Incidence rates[a] of moderate exacerbations for COPD from 2005 to 2013[b].

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)

Abbreviations: AECOPD, acute exacerbation chronic obstructive pulmonary disease; IR, incidence rate; HR, hazard ratio; A&E, accident & emergency; PY, person-years; CI, confidence interval.
[a] Only one event per calendar year was counted.
[b] Using validated read codes for AECOPD from clinical file only.

Table 3
Incidence rates of severe exacerbations for COPD from 2005 to 2013[b].

Year	No. of severe exacerbations[a] 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)

Abbreviations: AECOPD, acute exacerbation chronic obstructive pulmonary disease; IR, incidence rate; HR, hazard ratio; A&E, accident & emergency; PY, person-years; CI, confidence interval.
[a] Only one event per calendar year was counted.
[b] 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.

4. Discussion

4.1. 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.

4.2. 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.

4.3. 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 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.

4.4. 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].

5. 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.

Declarations of interest

None.

Conception or design

All authors equally contributed.

Analysis of data

OO, JHM.

Interpretation of data

All authors equally contributed.

Drafting the work

OO, SK, FF, FV, RJ.

Final approval of the version to be published

All authors equally contributed.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2018.09.010.

References

[1] J.A. Wedzicha, T.A. Seemungal, COPD exacerbations: defining their cause and prevention, Lancet 370 (2007) 786–796, https://doi.org/10.1016/S0140-6736(07)61382-8.

[2] M.T. Dransfield, K.M. Kunisaki, M.J. Strand, A. Anzueto, S.P. Bhatt, R.P. Bowler, et al., Acute exacerbations and lung function loss in smokers with and without chronic obstructive pulmonary disease, Am. J. Respir. Crit. Care Med. 195 (2017) 324–330, https://doi.org/10.1164/rccm.201605-1014OC.

[3] T a Seemungal, G.C. Donaldson, E a Paul, J.C. Bestall, D.J. Jeffries, J a Wedzicha, Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease, Am. J. Respir. Crit. Care Med. 157 (1998) 1418–1422, https://doi.org/10.1164/ajrccm.157.5.9709032.

[4] M.A. Spruit, R. Gosselink, T. Troosters, A. Kasran, G. Gayan-Ramirez, P. Bogaerts, et al., Muscle force during an acute exacerbation in hospitalised patients with COPD and its relationship with CXCL8 and IGF-I, Thorax 58 (2003) 752–756, https://doi.org/10.1136/thorax.58.9.752.

[5] J. Foo, S.H. Landis, J. Maskell, Y.M. Oh, T. Van Der Molen, M.L.K. Han, et al., Continuing to confront COPD international patient survey: economic impact of COPD in 12 countries, PLoS One 11 (2016), https://doi.org/10.1371/journal.pone.0152618.

[6] C. Obstructive, P. Disease, J.J. Soler-Cataluña, M a Martínez-García, P. Román Sánchez, E. Salcedo, et al., Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease, Thorax 60 (2005) 925–931, https://doi.org/10.1136/thx.2005.040527.

[7] C.F. Vogelmeier, G.J. Criner, F.J. Martinez, A. Anzueto, P.J. Barnes, J. Bourbeau, et al., Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report. GOLD executive summary, Am. J. Respir. Crit. Care Med. 195 (2017) 557–582, https://doi.org/10.1164/rccm.201701-0218PP.

[8] H. Qureshi, A. Sharafkhaneh, N.A. Hanania, Chronic obstructive pulmonary disease exacerbations: latest evidence and clinical implications, Ther. Adv. Chronic. Dis. 5 (2014) 212–227, https://doi.org/10.1177/2040622314532862.

[9] N. Snell, D. Strachan, R. Hubbard, J. Gibson, K. Gruffydd-Jones, I. Jarrold, S32 Epidemiology of chronic obstructive pulmonary disease (COPD) in the UK: findings from the british lung foundation's “respiratory health of the nation” project, Thorax 71 (2016), https://doi.org/10.1136/thoraxjnl-2016-209333.38 A20.1-A20.

[10] E.W.M.A. Bischoff, T.R.J. Schermer, H. Bor, P. Brown, C. Van Weel, W.J.H.M. Van Den Bosch, Trends in COPD prevalence and exacerbation rates in Dutch primary care, Br. J. Gen. Pract. 59 (2009) 927–933, https://doi.org/10.3399/bjgp09X473079.

[11] G.D. James, G.C. Donaldson, J.A. Wedzicha, I. Nazareth, Trends in management and outcomes of COPD patients in primary care, 2000-2009: a retrospective cohort study, NPJ Prim. Care. Respir. Med. (2014), https://doi.org/10.1038/npjpcrm.2014.15.

[12] J.K. Quint, H. Müllerova, R.L. DiSantostefano, H. Forbes, S. Eaton, J.R. Hurst, et al., Validation of chronic obstructive pulmonary disease recording in the Clinical Practice Research Datalink (CPRD-GOLD), BMJ Open 4 (2014), https://doi.org/10.1136/bmjopen-2014-005540.

[13] E. Herrett, A.M. Gallagher, K. Bhaskaran, H. Forbes, R. Mathur, T. Staa van, et al., Data resource profile: clinical practice research Datalink (CPRD), Int. J. Epidemiol. 44 (2015) 827–836, https://doi.org/10.1093/ije/dyv098.

[14] J.S. Taggar, T. Coleman, S. Lewis, L. Szatkowski, The impact of the Quality and Outcomes Framework (QOF) on the recording of smoking targets in primary care medical records: cross-sectional analyses from the Health Improvement Network (THIN) database, BMC Publ. Health 12 (2012) 1–11, https://doi.org/10.1186/1471-2458-12-329.

[15] M.F. Barakat, H.I. McDonald, T.J. Collier, L. Smeeth, D. Nitsch, J.K. Quint, Acute kidney injury in stable COPD and at exacerbation, Int. J. Chronic Obstr. Pulm. Dis. 10 (2015) 2067–2077, https://doi.org/10.2147/COPD.S88759.

[16] H. Mullerova, A. Shukla, A. Hawkins, J. Quint, Risk factors for acute exacerbations of COPD in a primary care population: a retrospective observational cohort study, BMJ Open 4 (2014) e006171, https://doi.org/10.1136/bmjopen-2014-006171.

[17] K.E. Wurst, A. Shukla, H. Muellerova, K.J. Davis, Respiratory pharmacotherapy use in patients newly diagnosed with chronic obstructive pulmonary disease in a primary care setting in the UK: a retrospective cohort study, COPD 11 (2014) 521–530 https://doi.org/10.3109/15412555.2014.922064.

[18] K.J. Rothnie, H. Müllerová, J.R. Hurst, L. Smeeth, K. Davis, S.L. Thomas, et al., Validation of the recording of acute exacerbations of COPD in UK primary care electronic healthcare records, PLoS One 11 (2016), https://doi.org/10.1371/journal.pone.0151357.

[19] S. Padmanabhan, CPRD GOLD Data Specification, (2015) https://www.ed.ac.uk/files/atoms/files/cprd_gold_full_data_specification.pdf , Accessed date: 15 May 2018.

[20] A.S. Gershon, C. Wang, A.S. Wilton, R. Raut, T. To, Trends in chronic obstructive pulmonary disease prevalence, incidence, and mortality in ontario, Canada, 1996 to 2007: a population-based study, Arch. Intern. Med. 170 (2010) 560–565, https://doi.org/10.1001/archinternmed.2010.17.

[21] N. Terzikhan, K.M.C. Verhamme, A. Hofman, B.H. Stricker, G.G. Brusselle, L. Lahousse, Prevalence and incidence of COPD in smokers and non-smokers: the Rotterdam Study, Eur. J. Epidemiol. 31 (2016) 785–792, https://doi.org/10.1007/s10654-016-0132-z.

[22] R. De Marco, S. Accordini, I. Cerveri, A. Corsico, J.M. Antó, N. Künzli, et al., Incidence of chronic obstructive pulmonary disease in a cohort of young adults according to the presence of chronic cough and phlegm, Am. J. Respir. Crit. Care Med. 175 (2007) 32–39, https://doi.org/10.1164/rccm.200603-381OC.

[23] L. Langsetmo, R.W. Platt, P. Ernst, J. Bourbeau, Underreporting exacerbation of chronic obstructive pulmonary disease in a longitudinal cohort, Am. J. Respir. Crit. Care Med. 177 (2008) 396–401, https://doi.org/10.1164/rccm.200708-1290OC.

[24] C. Fuhrman, N. Roche, A. Vergnenègre, M. Zureik, C. Chouaid, M.C. Delmas, Hospital admissions related to acute exacerbations of chronic obstructive pulmonary disease in France, 1998-2007, Respir. Med. 105 (2011) 595–601, https://doi.org/10.1016/j.rmed.2010.11.014.

[25] F.P. Antunes, M. da CN. Costa, J.S. Paim, L.M. Vieira-da-Silva, CA. de ST. Santos, Á.A. Cruz, et al., Trends in hospitalizations for respiratory diseases in salvador, bahia state, Brazil, 1998-2009, Cad. Saúde Pública 28 (2012) 869–877, https://doi.org/10.1590/S0102-311X2012000500006.

[26] G.C. Donaldson, J.A. Wedzicha, COPD exacerbations .1: Epidemiology, Thorax 61 (2006) 164–168, https://doi.org/10.1136/thx.2005.041806.

[27] V.L. Kinnula, T. Vasankari, E. Kontula, A. Sovijarvi, O. Saynajakangas, A. Pietinalho, The 10-year COPD programme in Finland: effects on quality of diagnosis, smoking, prevalence, hospital admissions and mortality, Prim. Care Respir. J. 20 (2011) 178–183, https://doi.org/10.4104/pcrj.2011.00024.

[28] J. Lykkegaard, R. De Pont Christensen, J.R. Davidsen, H. Støvring, M. Andersen, J. Søndergaard, Trends in the lifetime risk of COPD exacerbation requiring hospitalisation, Eur. Respir. J. (2013), https://doi.org/10.1183/09031936.00129312.

[29] R. Kessler, E. Ståhl, C. Vogelmeier, J. Haughney, E. Trudeau, C.-G. Löfdahl, et al., Patient understanding, detection, and experience of COPD exacerbations: an observational, interview-based study, Chest 130 (2006) 133–142, https://doi.org/10.1378/CHEST.130.1.133.

[30] T.M.A. Wilkinson, G.C. Donaldson, J.R. Hurst, T.A.R. Seemungal, J.A. Wedzicha, Early therapy improves outcomes of exacerbations of chronic obstructive pulmonary disease, Am. J. Respir. Crit. Care Med. 169 (2004) 1298–1303, https://doi.org/10.1164/rccm.200310-1443OC.

[31] K.J. Rothnie, H. Müllerová, S.L. Thomas, J.S. Chandan, L. Smeeth, J.R. Hurst, et al., Recording of hospitalizations for acute exacerbations of COPD in UK electronic health care records, Clin. Epidemiol. 8 (2016) 771–782, https://doi.org/10.2147/CLEP.S117867.

[32] E. Merinopoulou, M. Raluy-Callado, S. Ramagopalan, S. Maclachlan, J.M. Khalid, COPD exacerbations by disease severity in England, Int. J. COPD 11 (2016) 697–709, https://doi.org/10.2147/COPD.S100250.

[33] J.D. Chalmers, A. Tebboth, A. Gayle, A. Ternouth, N. Ramscar, Determinants of initial inhaled corticosteroid use in patients with GOLD A/B COPD: a retrospective study of UK general practice, NPJ Prim. Care. Respir. Med. 27 (2017) 43, https://doi.org/10.1038/s41533-017-0040-z.

[34] D. Price, D. West, G. Brusselle, K. Gruffydd-Jones, R. Jones, M. Miravitlles, et al., Management of COPD in the UK primary-care setting: an analysis of real life prescribing patterns, Int. J. COPD 9 (2014) 889–905, https://doi.org/10.2147/COPD.S62750.

[35] D. Wisniewski, M. Porzezinska, M. Gruchala-Niedoszytko, M. Niedoszytko, J.M. Slominski, E. Jassem, Factors influencing adherence to treatment in COPD patients and its relationship with disease exacerbations, Pneumonol. Alergol. Pol. 82 (2014) 96–104, https://doi.org/10.5603/PiAP.2014.0015.

[36] P. Hardelid, G. Rait, R. Gilbert, I. Petersen, Recording of influenza-like illness in UK primary care 1995-2013: cohort study, PLoS One 10 (2015), https://doi.org/10.1371/journal.pone.0138659.

[37] J.K. Quint, H. Müllerova, R.L. DiSantostefano, H. Forbes, S. Eaton, J.R. Hurst, et al., Validation of chronic obstructive pulmonary disease recording in the Clinical Practice Research Datalink (CPRD-GOLD), BMJ Open 4 (2014), https://doi.org/10.1136/bmjopen-2014-005540.

[38] K. Gorska, R. Krenke, P. Korczynski, J. Kosciuch, J. Domagala-Kulawik, R. Chazan, Eosinophilic airway inflammation in chronic obstructive pulmonary disease and asthma, J. Physiol. Pharmacol. 59 (Suppl 6) (2008) 261–270.

[39] L.J. Forbes, C. Marchand, T. Doran, S. Peckham, The role of the Quality and Outcomes Framework in the care of long-term conditions: a systematic review, Br. J. Gen. Pract. 67 (2017) e775–e784, https://doi.org/10.3399/bjgp17X693077.

[40] M.K. Han, P.M. Quibrera, E.E. Carretta, R.G. Barr, E.R. Bleecker, R.P. Bowler, et al., Frequency of exacerbations in patients with chronic obstructive pulmonary disease: an analysis of the SPIROMICS cohort, Lancet Respir. Med. 5 (2017) 619–626, https://doi.org/10.1016/S2213-2600(17)30207-2.