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Myocardial infarction and ischaemic stroke following exacerbations of chronic obstructive pulmonary disease

Running title: Exacerbations of COPD and vascular events

Authors: Kieran J Rothnie[1,2], Olivia Connell[1], Hana Müllerová[3], LiamSmeeth[2], Neil Pearce[2], Ian Douglas[2], Jennifer K Quint[1,2]

Affiliations

1 Respiratory Epidemiology, Occupational Medicine and Public Health, National Heart and Lung Institute, Imperial College London, London

2 Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London

3 Respiratory Epidemiology, GlaxoSmithKline R&D, Uxbridge

Corresponding author
Kieran J Rothnie
Respiratory Epidemiology, Occupational Medicine and Public Health
National Heart and Lung Institute
Emmanuel Kaye Building
Imperial College London
London
SW3 6LR

Email: k.rothnie@imperial.ac.uk
Tel: +44 20 7594 8824

9.6 COPD: Epidemiology

Funding

This work was funded by GSK and the MRC as part of an MRC Industry Collaboration Agreement [G0902135].

Author contributions: Conception and design: KJR, JKQ, HM, LS, ID, NP; Analysis and interpretation: KJR, OC, JKQ, HM, LS, ID, NP; Drafting the manuscript for important intellectual content: KJR, OC, JKQ, HM, LS, ID, NP. KJR is the guarantor of the paper, taking responsibility for the integrity of the work as a whole, from inception to published article.

Abstract

Rationale

Previous studies have suggested that acute exacerbations of COPD may be associated with increased risk of myocardial infarction and ischaemic stroke.

Objective

We aimed to quantify the increased risks of myocardial infarction and ischemic stroke risk associated with both moderate and severe acute exacerbation, and to investigate factors which may modify these risks.

Methods

We performed a self-controlled case-series to investigate the rates of myocardial infarction and ischemic stroke following acute exacerbation compared to stable time, within individuals. The participants were 5,696 adults with COPD with a first myocardial infarction (n = 2,850) or ischemic stroke (n = 3,010) and at least one acute exacerbation from the UK Clinical Practice Research Datalink with linked Hospital Episodes Statistics data.

Results

The risks of both myocardial infarction and ischemic stroke were increased in the 91 days following a acute exacerbation. The risks were greater following a severe exacerbation (incidence rate ratio (IRR) of 2.58 (95% CI 2.26 to 2.95) for myocardial infarction; and IRR 1.97 (95% CI 1.66-2.33) for ischemic stroke) than after a moderate exacerbation (IRR 1.58 (95% CI 1.46-1.71) for myocardial infarction; and IRR 1.45 (95% CI 1.33-1.57) for ischemic stroke. The relative risks of myocardial infarction and ischemic stroke associated with acute exacerbation were lower among those with more frequent exacerbations (IRR 1.42 (95% CI 1.24-1.62) vs 1.69 (95% CI 1.50-1.91) for myocardial infarction; and IRR 1.30 (95% CI 1.15-1.48) vs 1.68 (95% CI 1.50-1.89) for ischemic stroke). Higher GOLD stage associated with a lower rate of myocardial infarction (IRR 1.98 (95% CI 1.61-2.05) vs 1.69 (95% CI 1.45-1.98)) but not for ischemic stroke. Aspirin use at baseline was associated with a lower risk of ischemic stroke (IRR 1.28 (95% CI 1.10-1.50) vs 1.63 (95% CI 1.47-1.80)), but not with myocardial infarction.

Conclusions

Acute exacerbations of COPD are associated with an increased risk of myocardial infarction and ischemic stroke within 28 days of their onset. Several patient characteristics were identified which are associated with these events.

Introduction

People with chronic obstructive pulmonary disease (COPD) are at increased risk of myocardial infarction (myocardial infarction)[1] and stroke[2], and up to one third of COPD patients die from cardiovascular disease[3]. This increased risk cannot be completely explained by smoking[4] and has been attributed to increased systemic inflammation[5].

Acute exacerbations of COPD normally last several days; most are thought to be triggered by bacterial or viral infection[6, 7] and are associated with increased systemic inflammation[8, 9]. Previous work has shown that lower respiratory tract infections (LRTI) are associated with an increased risk of myocardial infarction in the general population[10](10). In addition, two small studies have suggested that there may be an increased risk of myocardial infarction following periods of acute exacerbation compared to stable periods[11, 12]. Frequent exacerbators (people who have two or more treated exacerbations per year), also seem to have a higher long term risk of myocardial infarction than infrequent exacerbators[11]. The relationship between acute exacerbation and stroke is less clear. A previous study found an increased risk of stroke following acute exacerbation, but this risk was delayed until 49 days after an acute exacerbation[11]. Another study found a slightly increased risk of stroke over a 10 year follow-up when comparing exacerbating to non-exacerbating COPD patients[13].

The risk factors for myocardial infarction and ischemic stroke following acute exacerbation are not known, limiting the strategies or interventions that might mitigate this risk. Recent improvements in methods to identify acute exacerbation in electronic health records (EHR) mean that acute exacerbation can now be identified with greater sensitivity and precision[14]. Additionally, with linkage to secondary care records, the severity of acute exacerbations in COPD patients can be stratified using a health-care utilisation definition into moderate (general practitioner treated; primary care managed) and severe (hospitalised) events.

The aims of this study were therefore to: 1) characterise the magnitude and duration of myocardial infarction and ischemic stroke risks following acute exacerbation; 2) investigate the relationship between severity of acute exacerbation and myocardial infarction and ischemic stroke risk, and; 3) investigate whether the associations between exacerbation and both myocardial infarction and ischemic stroke are modified by COPD severity, prior acute exacerbation frequency, myocardial infarction type (STEMI or non-STEMI), comorbid cardiovascular disease, use of cardiovascular medicines, use of inhaled COPD maintenance therapy, or influenza vaccination at baseline.

Methods

Data Sources

We used data from the Clinical Practice Research Datalink (CPRD) linked with Hospital Episodes Statistics (HES) data. The CPRD is a large database of primary-care data. It contains details on more than 11 million patients in the UK, with over four million of these being active patients (around 7% of the UK population)[15]. The available data includes details on symptoms, diagnoses, tests, prescriptions, details on patient demographics and health behaviours, and referrals to secondary care. The diagnostic data in CPRD are mainly recorded using a system of Read codes, which is a hierarchical classification system. HES is an administrative database containing details of all episodes of admitted patient care in England and Wales. Data are structured into episodes of care by single consultants ("finished consultant episodes"), such that each hospitalisation may be involve several finished consultant episodes. Data are recorded using ICD-10 codes. Each finished consultant episode may be associated with up to 20 ICD-10 codes, with the first code generally representing the reason for hospitalisation. The remaining codes may represent other acute problems, or co-morbidities. Data for about 60% of CPRD patients are linked to HES. CPRD-HES data were also linked to Office of National Statistics (ONS) data to determine exact date of death.

Study design

The self-controlled case-series is a within-person design developed to reduce confounding in observational studies. The incidence rate of an outcome following an exposure is compared to unexposed periods of time in the same individual, using only data for those who experience the outcome[16]. This method been used widely to investigate the risk of acute cardiovascular events associated with episodes of infection and inflammation[17, 18]. We used this design to estimate the incidences of myocardial infarction or ischemic stroke following the onset of acute exacerbation compared to stable periods. As well as being able to estimate the transient effect of an exposure, the major advantage of this design is that within-individual inferences are made since each subject

acts as their own control. This means that the design implicitly controls for the effects of fixed confounders such as sex, socioeconomic status and genetic factors, as well as other unknown/unmeasured fixed confounders. Follow-up time is accumulated in various age-bands to account for confounding by age.

The self-controlled case-series method relies on three assumptions:

1) That events do not change the probability of future exposures. This assumption should be met in our analysis, as it is not likely that having an myocardial infarction or ischemic stroke changes the future risk of acute exacerbation.
2) That recurrent events are independent. As recurrent myocardial infarctions and strokes are not likely to be independent, we restricted the analysis to first myocardial infarction or stroke only.
3) That the occurrence of the event does not censor or alter observation periods. This assumption may not be met as myocardial infarction and ischemic stroke are associated with considerable mortality. In order to assess the impact of this assumption, we conducted a sensitivity analysis described in the statistical methods section. In addition, we also stratified the 91 day risk period into smaller time segments to address this potential issue.

Following a previous study[10] we made an *a priori* decision to include the maximum of 91 days following the onset of acute exacerbation as the exposure period. Additionally, we segmented this period into smaller periods of 1-3, 4-7, 8-14, 15-28, and 29-91 days, to determine how the relative risk changes over the exposure period. To reduce misclassification of acute exacerbation with myocardial infarction (or ischemic stroke), we created a 14-day window of pre-exposure time including the first day of the acute exacerbation, which was not included in either baseline or exposed time. The study design is shown in Figure 1.

Study participants were followed from January 1, 2004, date of COPD diagnosis, 35th birthdate, or CPRD practice "up to standard" date, whichever was later; follow-up finished on March 31, 2015, date of death, transfer out of practice or practice last collection date, whichever was earlier; the first year of follow up served as the baseline year.

Study sample, exposure, co-variates, and outcomes

The study sample was comprised of COPD patients who had at least one acute exacerbation and a first myocardial infarction or ischemic stroke during the study period. COPD patients were identified using a previously validated algorithm[19], and had a diagnostic Read code for COPD, a smoking history (ex or current smoker), and were age 35 or older. Patients were excluded if their CPRD records could not be linked to HES or ONS.

We characterised acute exacerbation severity according to health care utilisation, with those requiring treatment from their general practitioner (GP) as "moderate" events, and those requiring hospitalisation as "severe" events using previously validated algorithms[14, 20]. Acute exacerbations that occurred within two weeks of the onset of a previous acute exacerbation were taken to be a continuing event.

Apart from age, sex, and type of myocardial infarction, all potential effect modifiers were defined during the year prior to start of follow-up using CPRD data. Cardiovascular drug use (β-blocker, aspirin, and statins), inhaled COPD therapy use (long-acting β-agonists, long-acting muscarinic antagonists, and inhaled corticosteroids), and influenza vaccination status were defined by the presence of at least one prescription during the one year period prior to the start of follow-up.

Previous cardiovascular disease (stroke, heart failure, and angina for the myocardial infarction analysis; and atrial fibrillation, angina and previous myocardial infarction for the stroke analysis) was defined as any code suggesting one of these conditions was diagnosed at any time prior to follow up start. GOLD grade of airflow limitation was defined using spirometry results from the year prior to the start of follow-up. Study participants were dichotomised into exacerbation frequency phenotype categories depending on the number of exacerbations in the one year prior to follow-up start, we also expressed exacerbation frequency during this time in terms of actual number of events (0, 1, 2, ≥3). The main analyses of the associations between acute exacerbation and the risks of myocardial infarction or ischemic stroke within 91 days were stratified by potential effect modifiers.

Myocardial infarction and stroke events were defined using both primary care (CPRD) and hospital data (HES). Read codes were used to define myocardial infarction and ischemic stroke in CPRD (supplementary material). In HES, myocardial infarctions and ischemic stroke were defined as an ICD-10 code for myocardial infarction or ischemic stroke in the first position of a finished consultant episode. The date of myocardial infarction or ischemic stroke was taken as the date of the start of the finished consultant episode containing the myocardial infarction or ischemic stroke code, rather than the date of admission to hospital. ICD-10 codes I21.0-I21.4 were used to identify myocardial infarction in HES. ICD-10 codes I63.0-I63.9 were used to identify ischemic stroke in HES.

Statistical analysis

We used conditional Poisson regression to estimate the incidence rate ratio (IRR) of first myocardial infarction or stroke in the 91 days following acute exacerbation compared to stable periods.

We adjusted for age in one year age bands. In addition, as weather may be associated with both acute exacerbation[21] and myocardial infarction[22] or stroke[23], we adjusted for season (split into October-March and April-September).

In addition to the main self-controlled case series analysis, we also used a non-parametric spline based self-controlled case series method[24]. The advantages of this method are that the time segments within the total risk period (91 days after an acute exacerbation) do not have to be pre-specified, and that this method allows an easier visualisation of the evolution of the relative risk across the total 91 day risk period.

Secondary analyses

One of the assumptions of the self-controlled case series analysis is that the outcomes do not alter the probability of future exposure or result in censoring of the observation time. As myocardial infarction and stroke are associated with death, which would decrease the probability of further acute exacerbation and result in informative censoring, we conducted a sensitivity analysis similar to previous studies[15, 16] to assess the potential impact of breaking this assumption. To do this, we repeated the main analysis in those whose follow up was not censored due to death first for at least 6 months following myocardial infarction or ischemic stroke, and also in those whose follow up was not censored due to death for at least 12 months following myocardial infarction or ischemic stroke.

The analysis was conducted using Stata 14.1MP and R 3.2.4.

Ethics

The protocol for this research was approved by the Independent Scientific Advisory Committee (ISAC) for the Medicines & Healthcare Products Regulatory Agency (MHRA) Database Research (protocol numbers 15_226A and 17_060). Generic ethical approval for observational research using the CPRD with approval from ISAC has been granted by a Health Research Authority (HRA) Research Ethics Committee (East Midlands – Derby, REC reference number 05/MRE04/87). The protocol is available on request.

Results

In total, we included 5,696 participants in the study: 2,850 individuals who had a first myocardial infarction and at least one acute exacerbation, during the study period, and 3,466 with a first ischemic stroke and at least one acute exacerbation during the study period (Figure 2). 164 COPD participants were included in both analyses. The characteristics of the study participants are summarised in Table 1.

Compared to stable periods, the 91 days following the onset of acute exacerbation were associated with a 65% increased risk of myocardial infarction (IRR 1.65, 95% CI 1.50-1.81) and a 51% increased risk of ischemic stroke (IRR 1.51, 95% CI 1.39-1.65). The increased risk peaked in the first 3 days post-acute exacerbation onset for myocardial infarction and appeared to peak in the 4-7 days post onset for ischemic stroke (Figure 3). The risk gradually fell back to stable period level after 28 days for myocardial infarction, however appeared to remain elevated longer for ischemic stroke (Figure 3).

The associations of acute exacerbation and both myocardial infarction and ischemic stroke were modified by the severity of acute exacerbation (p-value for interaction <0.001 for both myocardial infarction and ischemic stroke), with the risk of myocardial infarction being over 2.5 times that of stable periods in the 91 days following a severe acute exacerbation, compared to 1.6 times that of stable periods for moderate events. The risk of ischemic stroke was 1.7 times that of stable periods following severe acute exacerbation, and 1.4 times that of stable periods following moderate acute exacerbation. The results of the non-parametric self-controlled case series analysis using spline regression are displayed in Figure 4 and confirm the patterns observed in the segmented analysis (Figure 3).

The association of acute exacerbation with myocardial infarction was stronger among infrequent exacerbators compared to frequent exacerbators, with infrequent exacerbators having a 69% higher rate of myocardial infarction in the 91 days following onset of acute exacerbation compared to their stable periods, and frequent exacerbators having a 42% higher rate of myocardial infarction compared to their stable periods (p=0.009); and infrequent exacerbators having a 68% higher risk of ischemic stroke following acute exacerbation compared to 30% increase for frequent exacerbators (p<0.001) (Figures 5-6). This pattern was also apparent when using number of baseline acute exacerbation rather than the dichotomous phenotype, although more so for myocardial infarction than ischemic stroke.

The association of acute exacerbation with myocardial infarction was also stronger for those with severe as compared to mild-to-moderate airflow limitation (GOLD grade 1-2 IRR 1.69, 95% CI 1.45-1.98; GOLD grade 3-4 IRR 1.98, 95% CI 1.61-2.05; p=0.007). However, the association of acute exacerbation with ischaemic stroke was not modified by severity of airflow limitation (p=0.74).

We found that the association of acute exacerbation with myocardial infarction in the 91 days following acute exacerbation was higher for non-STEMIs (IRR 1.80, 95% CI 1.56-2.06) than for STEMIs (IRR 1.39, 95% CI 1.16-1.68)).

Those with previous heart failure had a lower relative risk of myocardial infarction associated with acute exacerbation (IRR 1.06, 95% CI 0.76-1.47, compared to IRR 1.62, 95% CI 1.48-1.78, p=0.01), and those with previous angina had a lower risk of ischaemic stroke associated with acute exacerbation (IRR 1.55, 95% CI 1.41-1.70, compared to 1.37, 95% CI 1.12-1.67, p=0.01). There was some evidence that the association between acute exacerbation and ischemic stroke was lower among those using aspirin (IRR 1.28, 95% CI 1.10-1.50) compared to non-aspirin users (IRR 1.63, 95% CI 1.47-1.80, p=0.04). There was no modification of the associations between acute exacerbation and either myocardial infarction or stroke by other previous cardiovascular disease, cardiovascular drugs, COPD medicines, or influenza vaccine in the baseline period, or by age or sex (data for age and sex not shown).

In the sensitivity analysis among individuals whose observation time was not censored by death following myocardial infarction or ischemic stroke, relative risks were slightly smaller than the main analysis (supplementary material).

Discussion

We found that the increased risks of myocardial infarction and ischemic stroke in the weeks following acute exacerbation were of greater magnitude and longer duration than previously estimated[11]. These associations were also stronger among those with a severe exacerbation requiring hospitalization. suggesting possible modifiers of the associations between acute exacerbation and both myocardial infarction and ischemic stroke risk. Our data suggest that those

with a history of more frequent exacerbations may be at lower risk of myocardial infarction and ischemic stroke following an acute exacerbation, and that the association between acute exacerbation and myocardial infarction may be stronger among those with more severe airflow obstruction. The association between acute exacerbation and ischemic stroke was weaker among aspirin users compared to non-aspirin users.

We found an eight-fold risk of myocardial infarction in the first three days following hospitalised acute exacerbation, compared to a two-fold risk for moderate events, suggesting a dose-response relationship by severity of acute exacerbation. Additionally, our findings suggest that risk of myocardial infarction increases again at around 8-14 days after falling for the first 7 days following moderate but not severe acute exacerbation. This could be a chance finding, but the timing may correspond to secondary bacterial infection in those with a viral exacerbation[25].

For ischemic stroke, we found a 43% increased risk of ischemic stroke in the first three days and a two-fold risk for severe acute exacerbation compared to stable periods, again suggesting a dose-response relationship. The peak risk of ischemic stroke was in the 4-7 days following acute exacerbation onset at an 80% increased risk of ischemic stroke following GP treated acute exacerbation and almost a four-fold increased risk of ischemic stroke following hospitalised acute exacerbation.

Previous studies have suggested that frequent exacerbators have a higher risk of myocardial infarction[11]. Our study found that the associations of acute exacerbation with the risks of myocardial infarction and ischemic stroke were lower for frequent exacerbators. Crucially, our study compared the relative risk of a myocardial infarction during acute exacerbation to a participant's own stable period, not risk of myocardial infarction and ischemic stroke between individuals. One

explanation could be that frequent exacerbators have a higher risk of myocardial infarction and ischemic stroke during stable periods (due to perhaps increased baseline inflammation[26]), and thus there is less of a relative difference between stable and exacerbation periods for them. Because the self-controlled case series design includes only people who have the outcome of interest, we were not able to measure absolute rates of myocardial infarction or ischemic stroke.

Others have found that increased airflow limitation is associated with increased risk of myocardial infarction.[27] This is reflected in our finding that COPD patients with worse airflow limitation are more susceptible to the effects of acute exacerbation on risk of myocardial infarction than those with lesser limitation. There was no modification of the effect of acute exacerbation on risk of ischemic stroke by severity of airflow limitation, despite increased airflow limitation being associated with stroke. [28] Although there may be other differences between these patients, this finding points to the possibility that acutely worsening airflow limitation during acute exacerbation may be involved in the increased risk of myocardial infarction associated with acute exacerbation. This finding lends support to the idea that acute exacerbation may be a risk factor for type-2 myocardial infarction; which is the result of mismatch of myocardial supply and demand of oxygen, but not due to plaque rupture[29]. Coupled with our finding that the association between acute exacerbation and ischemic stroke (but not myocardial infarction) was stronger among aspirin non-users is also suggestive of different mechanisms driving risk of ischemic stroke and myocardial infarction following acute exacerbation.

We found that those with a previous heart failure diagnosis had a lower relative risk of myocardial infarction associated with acute exacerbation. However, this is based on a small number of events in the at risk period and may be due to misclassification of episodes of breathlessness due to acute heart failure being misclassified as acute exacerbation in these patients thereby misclassifying

episodes of stable time as exposed time. Interestingly we also found a weaker association between acute exacerbation and ischemic stroke among those with prior angina, which is potentially due to an effect of treatment for angina.

We have previously reported that people with COPD and acute myocardial infarction are more likely to have a non-STEMI than a STEMI, compared to people without COPD with acute myocardial infarction [30]. Our finding that the associations of acute exacerbation with myocardial infarction was greater for non-STEMIs may help explain these excess non-STEMIs in those with COPD.

Our finding that acute exacerbation is associated with a transient increased risk of myocardial infarction confirms suggestions from previous work that acute exacerbation are associated with myocardial infarction[11, 12] and myocardial injury[31]. Our study also supports previous findings that exacerbating COPD patients have a higher risk of stroke compared to non-exacerbating patients over a 10 year follow up[13], and our results extend these findings by precisely identifying the timing and duration of increased risk. In a within-individual analysis of 426 COPD patients and using prescription of antibiotics and oral steroids as a definition of acute exacerbation, Donaldson et al. [11] also found an increased risk of myocardial infarction associated with acute exacerbation, but this was limited to the first 5 days following acute exacerbation onset. Donaldson et al. also investigated the risk of stroke following acute exacerbation and found a small increase risk after 49 days following acute exacerbation. We found a significantly higher risk than that previously estimated in previous studies. Our large sample size and validated exposure measures may have allowed us to estimate a more precise effect size and duration of increased risk.

Broadly, our results are comparable with those from Smeeth et al.[10], who investigated the relationship between lower respiratory tract infection (LRTI) and risks of myocardial infarction and

stroke in 20,921 people from the general population. Smeeth et al. reported an IRR of 4.95 (95% CI 4.43-5.53) for myocardial infarction and IRR of 3.19 (95% CI 2.81-3.62) for stroke in the three days following LRTI, which declined towards baseline over time, but lasted more than 4 weeks. The higher relative risk of myocardial infarction and ischemic stroke following LRTI in the general population compared to acute exacerbation may be due to a smaller relative difference in inflammation between acute exacerbation/LRTI and stable periods for those with COPD. Alternatively, those with COPD may attend their general practitioner with milder LRTI (in terms of inflammatory burden) than would those from the general population.

We did not find that beta-blockers, or statins modified the effect of acute exacerbation on risk of first myocardial infarction or ischemic stroke. These findings are is not evidence that these medicines do not prevent myocardial infarction or ischemic stroke associated with acute exacerbation, but suggest that the particular risk of myocardial infarction and ischemic stroke associated with acute exacerbation may not be mitigated by use of these medicine. Our findings do not suggest that beta blockers and statins do not attenuate risk overall, since we investigated the relative risk between periods of stability (baseline) and exacerbation. A COPD patient who has been vaccinated against influenza will have some protection from influenza, but an acute exacerbation can still occur and will still increase the risk of cardiovascular events in the short term. Similarly, while statins or aspirin will reduce the absolute risk of a cardiovascular event in an individual, they will not remove all risk, and a period of increased risk following an acute exacerbation will still occur. However, this finding might also be explained by the definition of medicine use. We defined medicine use at baseline rather than as a time-varying effect modifier as prescription of these drugs are very much more likely after acute myocardial infarction or ischemic stroke. Since we only included first myocardial infarctions in the analysis, this period would be associated with an apparent rate of myocardial infarction or ischemic stroke of zero, and as such would have resulted in bias had we used a time-varying definition of cardiovascular medicines. This approach, however, may have resulted in underestimation of any effect modification by these medicines. It is worth noting that those patients in whom primary

prevention with these medicines was completely effective would have not been included in the study due to the case only nature of the design.

Clinicians should be aware that their COPD patients will be at higher risk of myocardial infarction and ischemic stroke in the weeks following acute exacerbation, and that this risk is much higher for those hospitalised with acute exacerbation. Acute exacerbations are known to be associated with mortality in those with COPD, and our findings are another reason that clinicians should focus on preventing acute exacerbation. We speculate that those patients with higher exacerbation frequency are at lower risk of stroke/myocardial infarction following an exacerbation for two reasons; 1) as they have more frequent medical care and are more likely to have relevant co-morbidities diagnosed and therefore be on more robust risk reduction strategies and 2) because frequent exacerbators have a heightened inflammatory response even in the stable state, their change in inflammation is less from baseline to exacerbation. This increased response to inflammatory stimuli among infrequent exacerbators may contribute to the increased risk of myocardial infarction and stroke. Such a hypothesis would only apply to relative risk increase between baseline and exacerbation periods, but will not be associated with an overall absolute risk of myocardial infarction and stroke which is higher among frequent exacerbators.

Our findings suggest that acute exacerbation may explain some of the increased cardiovascular risk in those with COPD. However, the recently reported SUMMIT trial[32], which investigated the effects of vilanterol and fluticasone furoate, did not find a reduction in cardiovascular events despite a reduction in acute exacerbation. However, most of the SUMMIT population had previous coronary artery disease. It is difficult to disentangle the effects of treatment of acute exacerbation on myocardial infarction from the effects of acute exacerbation itself.

Our study had several strengths. Firstly, the within-individual nature of the study design minimizes confounding by factors such as sex, genetics, long term medicine use and socioeconomic status. Our study also used data from the CPRD which is broadly generalizable to the UK population. In addition, compared to previous studies, we used a validated definition of acute exacerbation in electronic health records which enabled us to accurately identify acute exacerbation and we used linked secondary care HES data to categorise them as moderate or severe. In addition, we obtained data on myocardial infarction and ischemic stroke events from both primary and linked HES data which allowed us to identify more myocardial infarction[33] and ischemic stroke. Another strength of our study was that, compared to previous work in similar populations, our sample size was significantly larger.

Our study also has some weaknesses. In order to deal with time-varying confounders, we split time up into one year age bands and adjusted for these. In addition, we specifically adjusted for the effects of season. However, our study could still be susceptible to time-varying confounders if these correlated very closely in time with acute exacerbation, such as the use of treatments for acute exacerbation. Additionally, our study may have been susceptible to misclassification of acute exacerbation and myocardial infarction. We have previously demonstrated that people with COPD have delayed diagnosis of myocardial infarction[30], if these events are originally diagnosed as acute exacerbation, this may result in a spurious association between acute exacerbation and myocardial infarction. However, to reduce the impact of this bias we excluded the first day of acute exacerbation from the analysis, and used a validated algorithm for identifying acute exacerbation[14]. We are aware we may not have eliminated this bias completely, however; such a bias is very unlikely to explain a substantial proportion of the effect however, as the effect of acute exacerbation in the risk of myocardial infarction lasted for several weeks. We find it unlikely that stroke would be misclassified as acute exacerbation. Whilst there is evidence that troponin may rise at the time of an acute exacerbation, we are also aware that people with COPD do not have as great a troponin rise at myocardial infarction as people without COPD. Thus, the misclassification may

occur in both directions. We have used validated definitions for acute exacerbation and validated myocardial infarction codes based on the work of others and so what we have defined as “events” are likely to be true exacerbations or myocardial infarction/stroke events.

Conclusions

Compared to stable periods, we found associations between acute exacerbation and increased risks of myocardial infarction and ischemic stroke in the four weeks following the exacerbation. The increased risk of acute vascular events following acute exacerbation was significantly higher for severe compared to moderate acute exacerbation. The association of acute exacerbation with myocardial infarction risk was higher for infrequent exacerbators, and for those with more severe airflow limitation, and was more strongly associated with non-STEMIs. The association of acute exacerbation with ischemic stroke risk was higher for infrequent exacerbators and weaker among aspirin non-users.

References

1 Rothnie KJ, Yan R, Smeeth L, et al. Risk of myocardial infarction (MI) and death following MI in people with chronic obstructive pulmonary disease (COPD): a systematic review and meta-analysis. *BMJ Open* 2015;**5**.

2 Morgan AD, Sharma C, Rothnie KJ, et al. Chronic Obstructive Pulmonary Disease and the Risk of Stroke. *Annals of the American Thoracic Society* 2017;**14**:754-65.

3 Sin DD, Anthonisen NR, Soriano JB, et al. Mortality in COPD: role of comorbidities. *European Respiratory Journal* 2006;**28**:1245-57.

4 Feary JR, Rodrigues LC, Smith CJ, et al. Prevalence of major comorbidities in subjects with COPD and incidence of myocardial infarction and stroke: a comprehensive analysis using data from primary care. *Thorax* 2010;**65**:956-62.

5 Barnes PJ. Chronic Obstructive Pulmonary Disease: Effects beyond the Lungs. *PLoS Med* 2010;**7**:e1000220.

6 Sethi S. Bacteria in Exacerbations of Chronic Obstructive Pulmonary Disease. *Proceedings of the American Thoracic Society* 2004;**1**:109-14.

7 Wedzicha JA. Role of Viruses in Exacerbations of Chronic Obstructive Pulmonary Disease. *Proceedings of the American Thoracic Society* 2004;**1**:115-20.

8 Wedzicha JA, Seemungal TAR, MacCallum PK, et al. Acute Exacerbations of Chronic Obstructive Pulmonary Disease Are Accompanied by Elevations of Plasma Fibrinogen and Serum IL-6 Levels. *Thrombosis and Haemostasis* 2000;**84**:210-5.

9 Dev D, Wallace E, Sankaran R, et al. Value of C-reactive protein measurements in exacerbations of chronic obstructive pulmonary disease. *Respiratory Medicine* 1998;**92**:664-7.

10 Smeeth L, Thomas SL, Hall AJ, et al. Risk of Myocardial Infarction and Stroke after Acute Infection or Vaccination. *New England Journal of Medicine* 2004;**351**:2611-8.

11 Donaldson GC, Hurst JR, Smith CJ, et al. Increased Risk of Myocardial Infarction and Stroke Following Exacerbation of COPD. *Chest* 2010;**137**:1091-7.

12 Halpin DMG, Decramer M, Celli B, et al. Risk of Nonlower Respiratory Serious Adverse Events Following COPD Exacerbations in the 4-year UPLIFT(®) Trial. *Lung* 2011;**189**:261-8.

13 Lin C-S, Shih C-C, Yeh C-C, et al. Risk of Stroke and Post-Stroke Adverse Events in Patients with Exacerbations of Chronic Obstructive Pulmonary Disease. *PLOS ONE* 2017;**12**:e0169429.

14 Rothnie KJ, Müllerová H, Hurst JR, et al. Validation of the Recording of Acute Exacerbations of COPD in UK Primary Care Electronic Healthcare Records. *PLOS ONE* 2016;**11**:e0151357.

15 Herrett E, Gallagher AM, Bhaskaran K, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). *International Journal of Epidemiology* 2015.

16 Whitaker HJ, Paddy Farrington C, Spiessens B, et al. Tutorial in biostatistics: the self-controlled case series method. *Statistics in Medicine* 2006;**25**:1768-97.

17 Minassian C, Thomas SL, Smeeth L, et al. Acute Cardiovascular Events after Herpes Zoster: A Self-Controlled Case Series Analysis in Vaccinated and Unvaccinated Older Residents of the United States. *PLOS Medicine* 2015;**12**:e1001919.

18 Thomas SL, Minassian C, Ganesan V, et al. Chickenpox and Risk of Stroke: A Self-controlled Case Series Analysis. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America* 2014;**58**:61-8.

19 Quint JK, Müllerova H, DiSantostefano RL, et al. Validation of chronic obstructive pulmonary disease recording in the Clinical Practice Research Datalink (CPRD-GOLD). *BMJ Open* 2014;**4**.

20 Rothnie KJ, Müllerová H, Thomas SL, et al. Recording of hospitalizations for acute exacerbations of COPD in UK electronic health care records. *Clinical Epidemiology* 2016;**8**:771-82.

21 Tseng C-M, Chen Y-T, Ou S-M, et al. The Effect of Cold Temperature on Increased Exacerbation of Chronic Obstructive Pulmonary Disease: A Nationwide Study. *PLoS ONE* 2013;**8**:e57066.

22 Bhaskaran K, Hajat S, Haines A, et al. Short term effects of temperature on risk of myocardial infarction in England and Wales: time series regression analysis of the Myocardial Ischaemia National Audit Project (MINAP) registry. *BMJ* 2010;**341**.
23 Kyobutungi C, Grau A, Stieglbauer G, et al. Absolute Temperature, Temperature Changes and Stroke Risk: A Case-Crossover Study. *European Journal of Epidemiology* 2005;**20**:693-8.
24 Ghebremichael-Weldeselassie Y WH, Farrington C. Spline-based self-controlled case series method. 2015.
25 George SN, Garcha DS, Mackay AJ, et al. Human rhinovirus infection during naturally occurring COPD exacerbations. *European Respiratory Journal* 2014;**44**:87-96.
26 Wedzicha JA, Brill SE, Allinson JP, et al. Mechanisms and impact of the frequent exacerbator phenotype in chronic obstructive pulmonary disease. *BMC Medicine* 2013;**11**:1-10.
27 Sin DD, Wu L, Man SFP. The Relationship Between Reduced Lung Function and Cardiovascular Mortality: A Population-Based Study and a Systematic Review of the Literature. *Chest* 2005;**127**:1952-9.
28 Truelsen T, Prescott E, Lange P, et al. Lung function and risk of fatal and non-fatal stroke. The Copenhagen City Heart Study. *Int J Epidemiol* 2001;**30**:145-51.
29 Saaby L, Poulsen TS, Hosbond S, et al. Classification of Myocardial Infarction: Frequency and Features of Type 2 Myocardial Infarction. *The American Journal of Medicine* 2013;**126**:789-97.
30 Rothnie KJ, Smeeth L, Herrett E, et al. Closing the mortality gap after a myocardial infarction in people with and without chronic obstructive pulmonary disease. *Heart* 2015;**101**:1103-10.
31 McAllister DA, Maclay JD, Mills NL, et al. Diagnosis of myocardial infarction following hospitalisation for exacerbation of COPD. *European Respiratory Journal* 2012;**39**:1097-103.
32 Vestbo J, Anderson JA, Brook RD, et al. Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk (SUMMIT): a double-blind randomised controlled trial. *The Lancet*;**387**:1817-26.
33 Herrett E, Shah AD, Boggon R, et al. Completeness and diagnostic validity of recording acute myocardial infarction events in primary care, hospital care, disease registry, and national mortality records: cohort study. *BMJ* 2013;**346**.

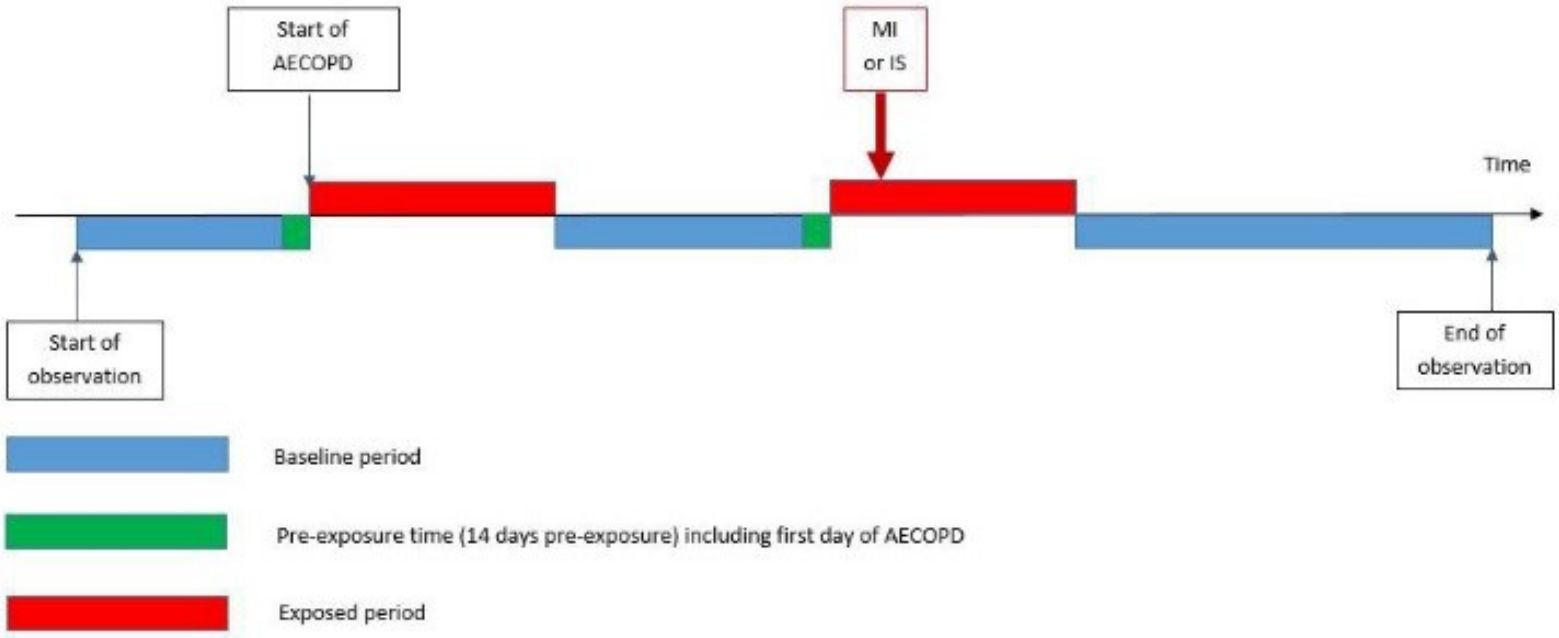

Figure 1. Diagram representing the study design. In this hypothetical example the patient has two exposed periods (acute exacerbation) during follow up and a first myocardial infarction within 91 days of the start of the second exposed period (acute exacerbation).

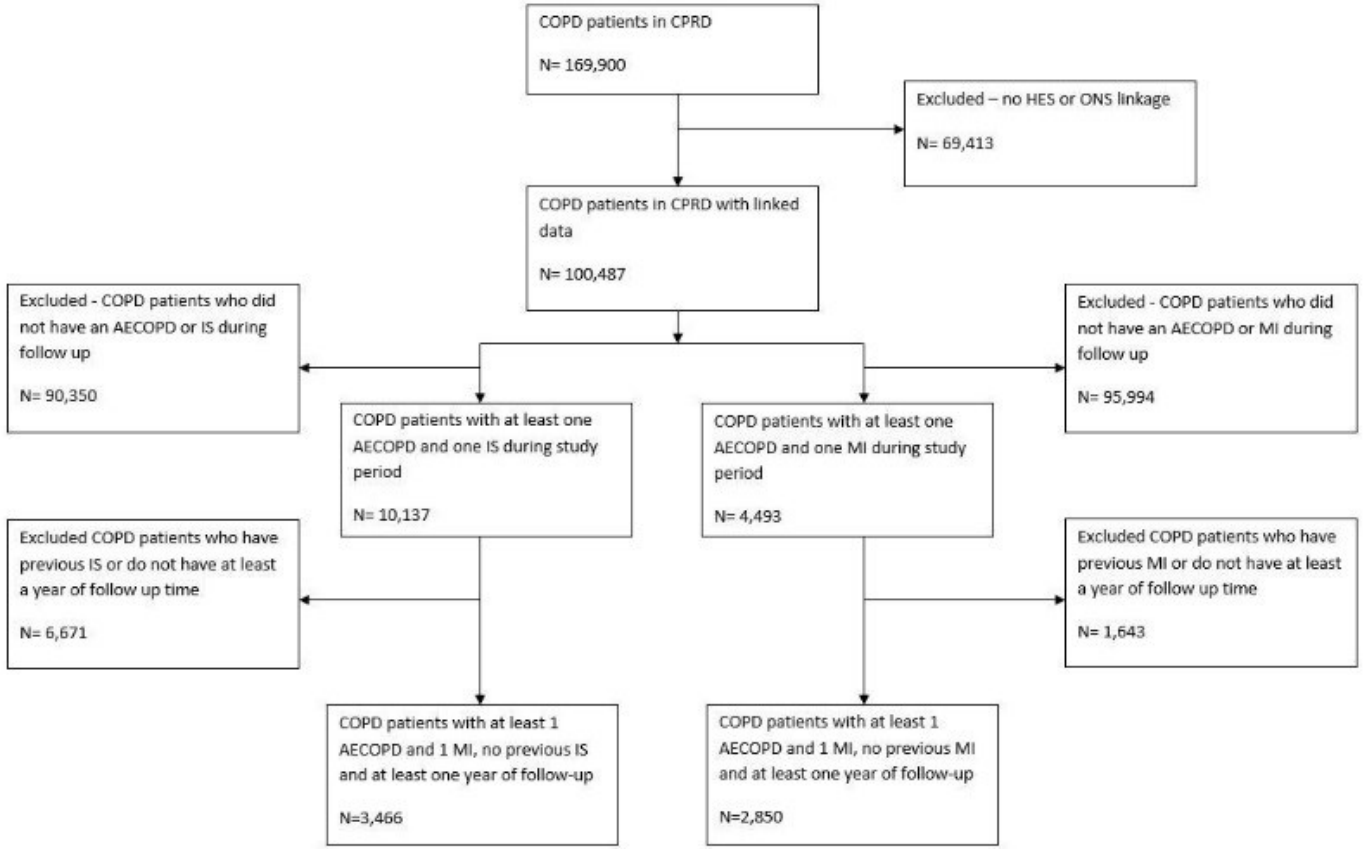

Figure 2. Patient flow in the study.

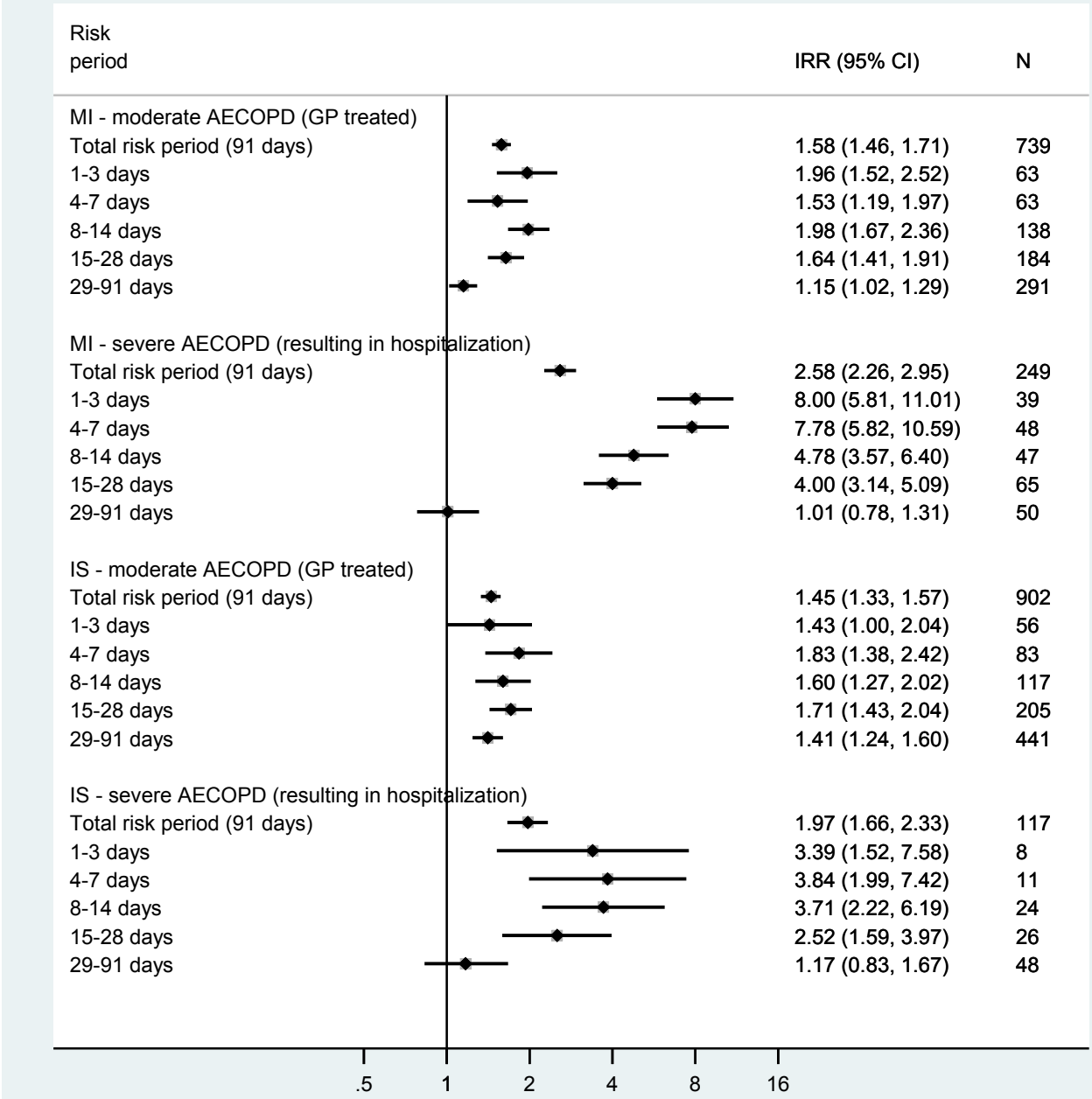

Figure 3. Incidence rate ratios of first myocardial infarction or ischaemic stroke in risk periods after an acute exacerbation of COPD relative to stable periods and stratified by acute exacerbation severity

p-value for interaction between moderate and severe acute exacerbation for risk of myocardial infarction <0.001
p-value for interaction between moderate and severe acute exacerbation for risk of ischemic stroke <0.001
IRR – incidence rate ratio.

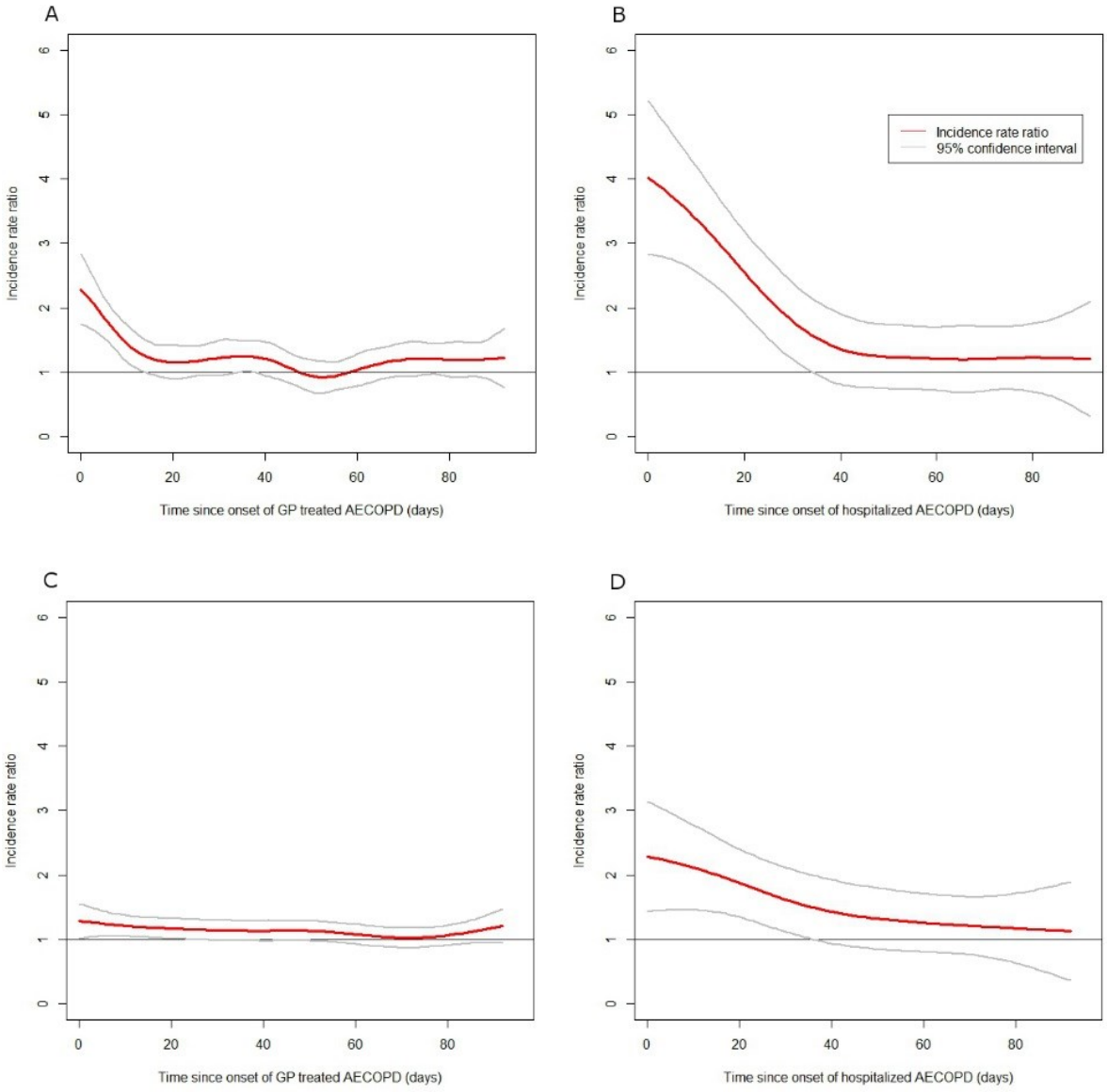

Figure 4. **A** Risk of myocardial infarction associated with moderate (general practitioner treated) acute exacerbation; **B** Risk of myocardial infarction associated with severe (hospitalized) acute exacerbation; **C** Risk of ischaemic stroke associated with moderate (general practitioner treated) acute exacerbation; and **D** Risk of ischaemic stroke associated with severe (hospitalized) acute exacerbation

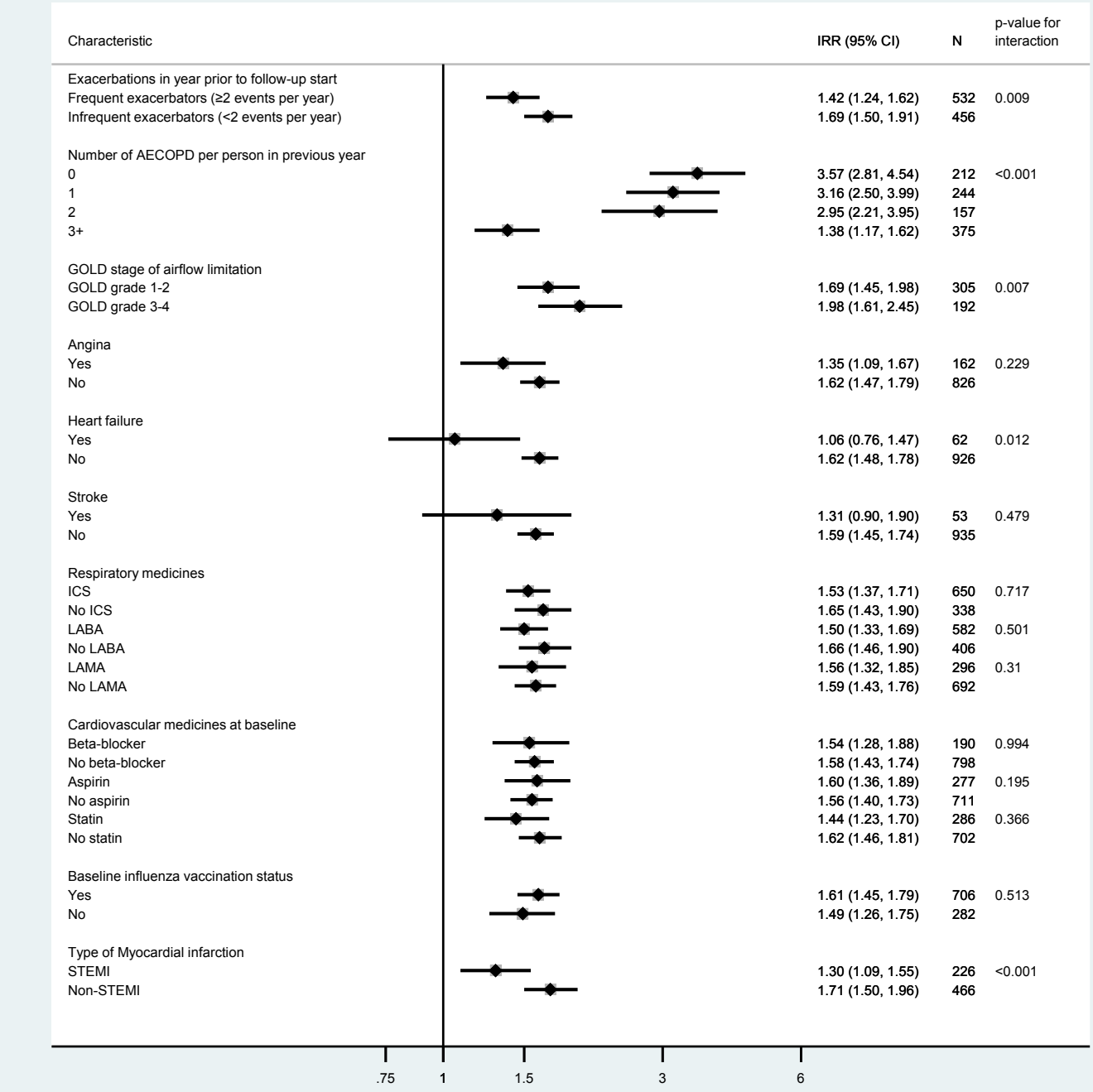

Figure 5: Incidence rate ratios of first myocardial infarction in risk period (91 days) after an acute exacerbation of COPD relative to stable periods stratified by COPD patient characteristics

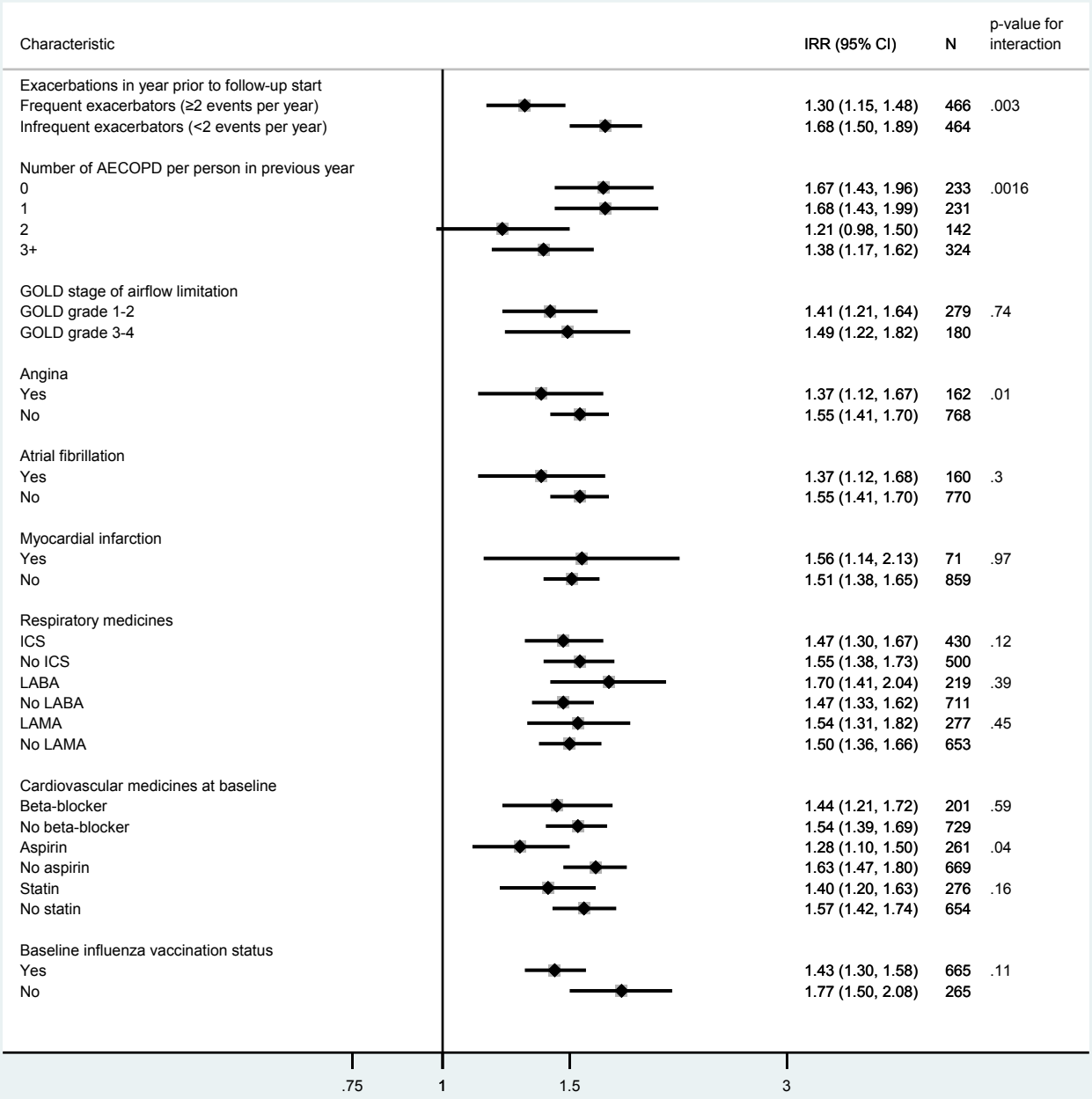

Figure 6: Incidence rate ratios of first ischaemic stroke in risk period (91 days) after an acute exacerbation of COPD (relative to stable periods stratified by COPD patient characteristics

Table 1. Characteristics of study participants with myocardial infarction or ischemic stroke and acute exacerbation of COPD during the study period

Characteristic	Myocardial infarction	Ischaemic stroke
No. of participants	2,850	3,466
Age at index myocardial infarction/ischemic stroke, years	73.3 (66.0-80.3)	75.8 (68.8-81.8)
Average observation time from follow-up start, years	8.2 (6.0-10.3)	6.3 (3.9-9.0)
Male sex	59.5%	55.1%
Number with at least one severe event (acute exacerbation requiring hospitalisation)	51.0%	36.1%
Frequent exacerbators, 12mo prior to follow-up start	42.9%	39.5%
Cardiovascular comorbid disease at any time prior to the start of follow up		
Angina	17.9%	17.2%
Heart failure	7.7%	-
Stroke	5.7%	-
Atrial fibrillation	-	19.0%
Myocardial infarction	-	7.2%
Prescribed cardiovascular drug within 12 months prior to the start of follow-up		
Statin	29.4%	30.5%
Aspirin	28.6%	30.6%
Beta-blocker	20.7%	23.7%
GOLD stage of airflow limitation at start of follow-up (N=1476)		
Grade 1-2, n (%)	976 (64.1)	978 (65.3)
Grade 3-4, n (%)	547 (35.9)	519 (34.7)
Missing, n	1,374	1,513

Prescribed respiratory drug, 12 months prior to the start of follow up		
ICS users	60.8%	42.1%
- Concomitant LABA	79.8%	72.4%
- Concomitant LAMA	34.5%	29.0%
Non ICS users	39.2%	57.9%
- LABA	14.1%	34.8%
- LAMA	16.0%	22.8%
Baseline influenza vaccination status	69.3%	72.6%
Type of myocardial infarction (N=1872)		
STEMI, n (%)	734 (37.2)	-
Non-STEMI, n (%)	1,242 (62.9)	-
Missing, n	978	-

Data are median (interquartile range) or percentage

Supplementary online material

Table S1 Medical codes used to identify myocardial infarction in CPRD.

Table S2. Medical codes used to identify ischaemic stroke in CPRD.

Table S3. Incidence rate ratios of first myocardial infarction in risk periods after an acute exacerbation of COPD relative to stable periods sensitivity analysis censoring within 6 months of myocardial infarction

Table S4 Incidence rate ratios of first myocardial infarction in risk periods after an acute exacerbation of COPD relative to stable periods sensitivity analysis censoring within 12 months of myocardial infarction

Table S5. Incidence rate ratios of first myocardial infarction in risk periods after an acute exacerbation of COPD relative to stable periods sensitivity analysis censoring within 6 months of ischemic stroke

Table S6 Incidence rate ratios of first myocardial infarction in risk periods after an acute exacerbation of COPD relative to stable periods sensitivity analysis censoring within 12 months of ischemic stroke

Table S1 Medical codes used to identify myocardial infarction in CPRD.

Medical code	Read term
241	acute myocardial infarction
1204	heart attack
1677	mi - acute myocardial infarction
1678	inferior myocardial infarction nos
5387	other specified anterior myocardial infarction
10562	acute non-st segment elevation myocardial infarction
12229	acute st segment elevation myocardial infarction
14658	acute myocardial infarction nos
14897	anterior myocardial infarction nos
14898	lateral myocardial infarction nos
23892	posterior myocardial infarction nos
29758	acute transmural myocardial infarction of unspecif site
32854	acute posterolateral myocardial infarction
34803	other acute myocardial infarction
46017	other acute myocardial infarction nos
63467	true posterior myocardial infarction
96838	[x]acute transmural myocardial infarction of unspecif site

Table S2 Medical codes used to identify ischaemic stroke in CPRD.

Medical code	Read term
94482	[x]cereb infarct due unsp occlus/stenos precerebr arteries
91627	[x]cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs
92036	[x]occlusion and stenosis of other cerebral arteries
90572	[x]occlusion and stenosis of other precerebral arteries
53745	[x]other cerebral infarction
19280	anterior cerebral artery syndrome
32447	basilar artery occlusion
8443	brain stem stroke syndrome
25615	brainstem infarction
15252	brainstem infarction nos
4240	carotid artery occlusion
39344	cereb infarct due cerebral venous thrombosis, nonpyogenic
40758	cereb infarct due unsp occlus/stenos precerebr arteries
5602	cerebellar infarction
17322	cerebellar stroke syndrome
8837	cerebral arterial occlusion
15019	cerebral embolism
34758	cerebral embolus
23671	cerebral infarct due to thrombosis of precerebral arteries
27975	cerebral infarction due to embolism of cerebral arteries
24446	cerebral infarction due to embolism of precerebral arteries
36717	cerebral infarction due to thrombosis of cerebral arteries
3149	cerebral infarction nos
16517	cerebral thrombosis
33543	cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs
5363	cva - cerebral artery occlusion
40053	generalised ischaemic cerebrovascular disease nos
12555	generalised ischaemic cerebrovascular disease nos
569	infarction - cerebral
57495	infarction - precerebral
26424	infarction of basal ganglia
9985	left sided cerebral infarction
18689	middle cerebral artery syndrome
98642	multiple and bilateral precerebral arterial occlusion
57527	occlusion and stenosis of anterior cerebral artery
55602	occlusion and stenosis of cerebellar arteries
51759	occlusion and stenosis of middle cerebral artery
65770	occlusion and stenosis of posterior cerebral artery
71274	occlusion+stenosis of multiple and bilat cerebral arteries
51326	other precerebral artery occlusion
19260	posterior cerebral artery syndrome
45781	precerebral arterial occlusion
71585	precerebral artery occlusion nos

33499	pure motor lacunar syndrome
51767	pure sensory lacunar syndrome
10504	right sided cerebral infarction
6155	stroke due to cerebral arterial occlusion
4152	thrombosis, carotid artery
40847	vertebral artery occlusion
73901	[x]cerebrovascular diseases
70536	acute cerebrovascular insufficiency nos
10062	cerebrovascular disease nos
47607	cva - cerebrovascular accident in the puerperium
6116	cva - cerebrovascular accident unspecified
1298	cva unspecified
7780	left sided cva
37493	other cerebrovascular disease nos
34117	other cerebrovascular disease os
51311	other specified cerebrovascular disease
12833	right sided cva
98188	small vessel cerebrovascular disease
1469	stroke and cerebrovascular accident unspecified
56279	stroke in the puerperium
6253	stroke unspecified

Table S3 Incidence rate ratios of first myocardial infarction in risk periods after an acute exacerbation of COPD relative to stable periods sensitivity analysis censoring within six months of myocardial infarction

Risk period	N outcome events (myocardial infarction)	IRR (95% CI)
Total risk period (91 days)	695	1.53 (1.38-1.68)
1-3 days	73	2.68 (2.11-3.41)
4-7 days	66	1.91 (1.48-2.45)
8-14 days	121	2.11 (1.74-2.56)
15-28 days	172	1.80 (1.52-2.12)
29-91 days	263	1.12 (0.97-1.29)

Table S4 Incidence rate ratios of first myocardial infarction in risk periods after an acute exacerbation of COPD relative to stable periods sensitivity analysis censoring within 12 months of myocardial infarction

Risk period	N outcome events (myocardial infarction)	IRR (95% CI)
Total risk period (91 days)	586	1.49 (1.34-1.67)
1-3 days	59	2.48 (1.90-3.25)
4-7 days	56	1.85 (1.41-2.44)
8-14 days	104	2.08 (1.69-2.56)
15-28 days	138	1.67 (1.39-2.01)
29-91 days	229	1.14 (0.98-1.32)

Table S5. Incidence rate ratios of first ischaemic stroke in risk periods after an acute exacerbation of COPD relative to stable periods sensitivity analysis censoring within 6 months of ischemic stroke

Risk period	N outcome events (myocardial infarction)	IRR (95% CI)
Total risk period (91 days)	804	1. (1.-1.)
1-3 days	47	1.54 (1.15-2.07)
4-7 days	70	1.79 (1.40-2.28)
8-14 days	119	1.80 (1.40-2.28)
15-28 days	185	1.65 (1.41-1.93)
29-91 days	383	1.35 (1.20-1.52)

Table S6. Incidence rate ratios of first ischaemic stroke in risk periods after an acute exacerbation of COPD relative to stable periods sensitivity analysis censoring within 12 months of ischemic stroke

Risk period	N outcome events (myocardial infarction)	IRR (95% CI)
Total risk period (91 days)	749	1.52 (1.38-1.68)
1-3 days	43	1.53 (1.13-2.08)
4-7 days	61	1.69 (1.31-2.20)
8-14 days	112	1.84 (1.51-2.24)
15-28 days	170	1.64 (1.39-1.94)
29-91 days	363	1.39 (1.24-1.57)