PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Risk factors for acute exacerbations in primary care COPD patients: a retrospective observational cohort study
AUTHORS	Müllerová, Hana; Shukla, Amit; Hawkins, Adam; Quint, Jennifer

VERSION 1 - REVIEW

REVIEWER	Arne Didrik Høiseth Division of Medicine, Akershus University Hospital, Lørenskog, Norway and Institute of Clinical Medicine, University of Oslo, Norway
REVIEW RETURNED	22-Aug-2014

GENERAL COMMENTS	Based on data from an English and Welsh primary care database, the authors have investigated risk factors for exacerbations of COPD. From the database that includes 8% of the inhabitants in these two countries, a very large number of COPD patients (58 589) have been investigated. The authors find that a history of prior exacerbations, increased COPD severity (measured either by airflow limitation or burden of symptoms), gender, and important comorbidites all predict future exacerbation. They found a “dose-response” relationship between some risk factors and number of future exacerbations (none vs. one vs. two or more). This study confirms the findings of the ECLIPSE cohort study, which concluded that exacerbations best may be predicted by history of prior exacerbations. This study adds to this by identifying COPD severity and comorbidites as predictors, which ECLIPSE did not. ---------- Major comments I really have no major comments, at least I think not. One may of course point out the inevitable draw-backs of retrospective register studies like this. With regard to the present paper, one might argue that two of the most important variables in the analysis, moderate exacerbations and airflow limitation, are subject to uncertainty. The working diagnosis of an exacerbation is not standardized, duly stated by the authors in the article summary. GP diagnosis of moderate exacerbation and the prescription of steroid and/or antibiotics may not always be correct. Less than 10% of the patients were reported to have congestive heart failure. Several papers on comorbidity in COPD report a significantly higher prevalence. Mistreating decompensating heart failure with steroids may cause water retention, aggravating the symptoms, and you may have yourself a frequent exacerbator. Spirometry recordings were not standardized (with or without bronchodilation, in stable phase or not?), which may lead to

	misclassification of patients. There are other examples that could be mentioned. However, I am not sure whether these potential errors may be systematic and may introduce bias. I trust the authors have given this a lot of thought, and ask them kindly to briefly share their insight. Minor comments Methods: Page 6, line 3: "… within 5 days of each other." To this reader, it is unclear what should happen within 5 days of what to qualify for an exacerbation. Statistical analyses/table 1: It is not mentioned, but I suppose that in table 1 only the associations that are listed on page 8, lines 23-35, were statistically significant? For the sake of clarity, this could be written somewhere. P-values in the table? Perhaps even a test for trend? You use half of page 15 to write about inflammation and COPD exacerbations. You start by writing that the factors you have observed to be associated with exacerbations are suggestive of a shared inflammatory mechanisms. Even though I support that idea, I find that initial statement to be a little far fetched. Still, being a believer of the inflammation theory, I have heard that Statins may have anti-inflammatory properties. Since you have medication data, would you consider performing a post hoc analysis of a potential protective effect of statins?

REVIEWER	Charlotte Bolton University of Nottingham UK
REVIEW RETURNED	02-Oct-2014

GENERAL COMMENTS	This is a well written manusript utilising the CPRD-GOLD. I have minor questions that I am grateful for the authors considering. - If I understand correctly, this was not just NEW diagnoses but"A" diagnosis of COPD within the timeframe. The QOF does recommend post bronchodilator confirmation of COPD at diagnosis. However, the spirometry that was within 3 months of the "mention" need not necessarily be the diagnostic one (just needs to show obstruction) and therefore may well have been pre-bronchodilator, especially as in the UK, recommendation of postbronchodilator spirometry on each occasion did not come in till 2010 and then required adoption into practice. It is acceptable that it might not be possible to determine if pre or post BD, however the phrasing in methods requires altering. - There may well be under-representation in that everyone had to survive at least a year after entry. Exacerbations are associated with significant mortality. Therefore, some patients who had frequent exacerbations / very severe disease are not included here. - NEW COPD diagnoses would have been made and therefore in

	the 12 months prior would not have referred to "exacerbation of COPD" (and if they had that would have been the reference date) but perhaps classed as LRTI / alternative? - If a patients first reference to COPD from 2009 was in reference to an exacerbation - was that included and if so, a "prior" or "in follow-up"? - Patients may have received antibiotics and steroids as "standby" for future exacerbation. Usually these would be replenished when they had used the previous for an exacerbation and hence does reflect an exacerbation. However, perhaps need discussion in brief?

VERSION 1 – AUTHOR RESPONSE

Reviewer Name Arne Didrik Høiseth

Major comments
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Spirometry recordings were not standardized (with or without bronchodilation, in stable phase or not?), which may lead to misclassification of patients.

There are other examples that could be mentioned. However, I am not sure whether these potential errors may be systematic and may introduce bias. I trust the authors have given this a lot of thought, and ask them kindly to briefly share their insight.

R1: We accept the outlined drawbacks in the definition of exacerbations and spirometric procedure. As with any disease definition in the CPRD-GOLD, we analyze what has been recorded by general practitioners in the electronic medical record used for patient care. Overall, CPRD has been shown as a reliable source of information for diagnoses (Khan NF: Br J Gen Pract. 2010 Mar;60(572):e128-36; Herrett E: Br J Clin Pharmacol. 2010 Jan;69(1):4-14). For example, our estimate of about 10% of patients being diagnosed with heart failure corresponds with an earlier estimate reported by Garcia-Rodriguez and colleagues from the same database (J COPD 2009; 6:369–379)

Authors have used various definitions of exacerbations of COPD. We derived our definition based on experience working with the CPRD-GOLD (and former GPRD) and clinical experience working with COPD patients. The exacerbation definition was tested in ten randomly selected profiles of COPD patients from the CPRD-GOLD with excellent specificity. We have little information on sensitivity other than using results from external cohorts as a reference point. Compared to randomized clinical trials and longitudinal observational studies like the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE), the exacerbation frequency reported in our study is somewhat lower than expected in this general practice population exhibiting lower disease severity than the one

recruited into trials.
Regarding the spirometry recordings, the UK Quality Outcomes Framework specifies that postbronchodilator spirometry should be conducted and recorded. Further, the Primary Care Respiratory Society is educating general practice staff in conducting high quality spirometry. However, we understand this recommendation may not translate in real-life situation and certain misclassification will be present. From the available data, we are unable to quantify the extent of misclassification based on spirometry. The level of misclassification reported by Strong (Prim Care Respir J. 2014 Mar;23(1):67-73), which was reported prior to the introduction of programs to improve practice spirometry, was not observed by a recent validation of COPD diagnosis in the CPRD-GOLD (Quint: BMJ Open. 2014 Jul 23;4(7):e005540).

Minor comments

Methods:
Page 6, line 3: "… within 5 days of each other." To this reader, it is unclear what should happen within 5 days of what to qualify for an exacerbation.

R2: We required ATB and OCS prescriptions to be recorded with a maximum interval of 5 days from each other. This means that if OCS was prescribed first, the ATB had to be prescribed on the same day (as it happened in most instances) or up to 5 days later. If ATB was prescribed first, then again, the OCS had to be prescribed on the same day or up to 5 days later.
We edited the Methods text for better clarity.

Statistical analyses/table 1: It is not mentioned, but I suppose that in table 1 only the associations that are listed on page 8, lines 23-35, were statistically significant? For the sake of clarity, this could be written somewhere. P-values in the table? Perhaps even a test for trend?

R3: In the study of this sample size (~60,000 patients), we experienced issues with formal testing of statistical significance whereby even minor numerical differences are returned as highly significant, e.g, differences in smoking status. Therefore, we decided against statistical significance testing and applied clinical judgment when interpreting the data.

You use half of page 15 to write about inflammation and COPD exacerbations. You start by writing that the factors you have observed to be associated with exacerbations are suggestive of a shared inflammatory mechanisms. Even though I support that idea, I find that initial statement to be a little far fetched. Still, being a believer of the inflammation theory, I have heard that Statins may have anti-inflammatory properties. Since you have medication data, would you consider performing a post hoc analysis of a potential protective effect of statins?

R4: We edited this discussion section making the text more concise. Regarding the idea of exploring the statin use, we appreciate this suggestion; however, it appears that statins, especially prevalent users of statins, tend to show associations with most of the endpoints tested for reasons possibly not mechanistically related to the statin's effectiveness (Danaei: Bias in Observational Studies of Prevalent Users: Lessons for Comparative Effectiveness Research From a Meta-Analysis of Statins Am J Epidemiol. 2012 Feb 15;175(4):250-62). Therefore, we would need to limit the analysis to incident statin users, which would have required additional effort beyond 2 weeks given to us for a response back to the journal.

Reviewer Name Charlotte Bolton

This is a well written manusript utilising the CPRD-GOLD.

I have minor questions that I am grateful for the authors considering.

HM: Thank you!

- If I understand correctly, this was not just NEW diagnoses but"A" diagnosis of COPD within the timeframe. The QOF does recommend post bronchodilator confirmation of COPD at diagnosis. However, the spirometry that was within 3 months of the "mention" need not necessarily be the diagnostic one (just needs to show obstruction) and therefore may well have been pre-bronchodilator, especially as in the UK, recommendation of postbronchodilator spirometry on each occasion did not come in till 2010 and then required adoption into practice. It is acceptable that it might not be possible to determine if pre or post BD, however the phrasing in methods requires altering.

R1: We agree that we cannot discriminate spirometry recordings as being pre- or postbronchodilator. As you pointed out the recommendations for quality of spirometry were being implemented since 2010. This is partly why we limited the COPD cohort definition between 1 April 2009 and 30 September 2012. We changed the sentence in the Methods section to: “COPD diagnosis was required to be accompanied by spirometry....”.

- There may well be under-representation in that everyone had to survive at least a year after entry. Exacerbations are associated with significant mortality. Therefore, some patients who had frequent exacerbations / very severe disease are not included here.

R2: We agree with your notion of a possible survival bias due to fixed observation period time. We expect this bias will be of limited importance during the 12 months period, but would increase if the period was further extended. We added this limitation to the discussion section.

- NEW COPD diagnoses would have been made and therefore in the 12 months prior would not have referred to "exacerbation of COPD" (and if they had that would have been the reference date) but perhaps classed as LRTI / alternative?

R3: We agree that patients who would have been first diagnosed with COPD during 12 months prior to observation period start would not be considered as having past exacerbations of COPD. However, COPD as a chronic disease is usually diagnosed only when fully clinically manifesting. As such, events in the past history can be considered as prior events of exacerbations of COPD. Further, the incidence of COPD in the CPRD-GOLD is relatively low, about 2.6 per 1000 person-years as per Garcia-Rodriguez and colleagues (J COPD; 6:369–379) and, therefore, we expect only about 152 patients in this analysis being impacted. We placed further explanation into the Methods section.

- If a patients first reference to COPD from 2009 was in reference to an exacerbation - was that included and if so, a "prior" or "in follow-up"?

R3: Patients could qualify into COPD cohort based on set of codes that had been recently validated by Quint (BMJ Open. 2014 Jul 23;4(7):e005540). These codes mainly imply stable state of COPD. We counted events of exacerbation episodes. If such an episode started prior to the patient’s observation period start, it would count into the “prior” time period, even though the patient qualified into the cohort on the first possible day of the cohort identification period (between 1 April 2009 and 30 September 2012) or, even when the exacerbation overlapped from the “prior” into “in follow-up” period. If the episode started on or after of the patient’s observation period start, it was counted as “in follow-up”.

- Patients may have received antibiotics and steroids as "standby" for future exacerbation. Usually these would be replenished when they had used the previous for an exacerbation and hence does

reflect an exacerbation. However, perhaps need discussion in brief?

R4: We agree with your observation and mentioned this limitation in the Discussion section.

VERSION 2 – REVIEW

REVIEWER	Charlotte Bolton University of Nottingham, UK
REVIEW RETURNED	27-Nov-2014

GENERAL COMMENTS	I am happy the authors have addressed my comments.