PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The Impact of Exacerbation Frequency on Mortality Following Acute Exacerbations of COPD: A Registry-Based Cohort Study
AUTHORS	Schmidt, Sigrun Alba; Johansen, Martin; Olsen, Morten; Xu, Xiao; Parker, Joseph; Molfino, Nestor; Lash, Timothy; Sørensen, Henrik T.; Christiansen, Christian

VERSION 1 - REVIEW

REVIEWER	Nicolas Roche Université Paris Descartes, France
REVIEW RETURNED	13-Oct-2014

GENERAL COMMENTS	This paper reports a well-described database analysis aimed at assessing whether past exacerbations are predictive of short-term and long-term survival. Major comments 1. My main concern is that, although the analyzes were properly performed considering the question addressed, it is difficult to determine what this study adds to current knowledge. 2. Many studies already addressed this question with variable results, essentially depending on the study population and available variables, as appropriately acknowledged by the authors. Results of the present study are similarly influenced by these study characteristics, so that the difference in setting and databases structure is the only new component, not the results per se… 3. The initial question is very focused on a specific potential predictor, i.e., exacerbations. Why didn't the authors begin with a wider approach using univariate followed by multivariate analyzes to identify independent predictors of mortality? The results would have been quite the same but with less a priori hypotheses… 4. It would have been interesting to use age at first prescription of inhaled treatment and duration of inhaled treatment as possible predictors of mortality. 5. Classifying patients according to "GOLD A B C D treatment categories" does not appear to be adequate since it suggests that these correspond to severity categories. But many studies found poor correlations between treatment and actual severity or phenotype. Mentioning treatment categories without referring to GOLD A B C D classification would be more appropriate.

REVIEWER	Cat Chang Waikato Hospital New Zealand
REVIEW RETURNED	15-Oct-2014

GENERAL COMMENTS	Thank you for the opportunity to review the study from Schmidt and colleagues. This is a registry-based retrospective cohort study examining the relationship between COPD exacerbations and subsequent outcome. The study is based on data extracted from three Danish registries with information pertaining to emergency department presentations, hospital admissions, outpatient specialist clinic visits, prescription and drug redemption details and mortality information. The study methods are well described and the results are presented clearly and systematically. The study methods are similar to the landmark study by Suissa et al (Thorax 2012) which demonstrated the cumulative detrimental effect of acute COPD exacerbations requiring hospitalisations. Schmidt and colleagues incepted a similar cohort based on coding and prescription data with standard exclusions (e.g. patients under the age of 40, history of asthma etc). The main difference in data is that while Suissa et al only included patients following the first severe COPD exacerbation requiring hospitalisations, the current study also included exacerbations treated in the community (using prescription data). Surprisingly, the current study found that the number of preceding exacerbations within the last 12 months were not associated with increased risk within 30 days following the next COPD exacerbation (but were associated with increased risk from 30-365 days). My main issue with the current study is that this surprising primary outcome is not adequately discussed and explored. As the authors mention in their discussion, there is fairly extensive literature supporting the negative impact of previous exacerbations in patients with AECOPD. Although the authors postulate several potential confounders in their cohort which may have biased their study results and washed out the effects of exacerbations, I get no clear sense on how the authors propose their study results should be viewed in light of these. What we are then left with is a negative study providing conflicting evidence to the current literature with no clear suggestion on how this may be re-examined or validated and then incorporated into the existing knowledge paradigm. Further subgroup analyses examining the effect of severe exacerbations (e.g. hospitalisation, use of non-invasive or invasive ventilation) and first severe exacerbations may be helpful. Is there any lung function data at all? Other comments: 1. The authors chose to use the newly proposed GOLD treatment groups to stratify disease severity. This approach is problematic because the treatment groups had to be extrapolated retrospectively using prescription data and a large proportion of patients (29%) were unable to be classified in this way. Further, the GOLD ABCD pharmacological approach model was proposed in the 2011 update while the patients included in this study were diagnosed with COPD prior to 2004. As such I would expect the prescription practice to reflect guidelines current to the cohort rather than the newest update. Not surprisingly, the study analysis showed no significant difference in outcome between the groups. This is a reflection of the

	study methods rather than a lack of effect. 2. The study concluded that a history of COPD exacerbations indicate a higher risk during 31-365 days after the COPD exacerbations. Again, this finding is in conflict with existing literature – I would expect some discussion regarding potential mechanisms. 3. All the results are presented in the form of adjusted hazard ratios in tables. I would suggest presenting some data in a graphical format may be helpful to the reader to interpret the findings. Of particular interest are the adjusted rates of death following an exacerbation over time. Essentially I feel that this study deserves publication in some form but further work is needed clarifying the significance and interpretation of results.

REVIEWER	Anne Hildur Henriksen Department of Occupational and Thoracic Medicine, Trondheim University Hospital, Norway
REVIEW RETURNED	15-Oct-2014

GENERAL COMMENTS	This is a well written and interesting manuscript addressing important questions. The grouping of patients according to prescription data ought to be reconsidered, and the authors should consider whether a more simple approach (i.e. patients on combination therapy versus those only receiving LABA and/or muscarine antagonists) would be more useful? -The abstract reflects the content of the manuscript. -In the introduction section actual previous studies are described and an introduction to the research questions is presented. It is pointed out that no previous studies on the present topic have included information on preadmission therapy. However, there is no mention on the impact of COPD severity versus exacerbation rate and mortality. Various definitions of severity of COPD and impact of severity versus exacerbation rate on mortality ought to be mentioned in the introduction section. -The methods section describes properly how the patients are selected for the study. However, it is unclear how participants and AECOPD admittances are handled in the analyses, and the number of admittances that are included in the analyses. The definition of less severe AECOPD as an episode where the patients are not submitted to hospital, but receive a combination of systemic steroids plus antibiotics is adequate, but this approach ought to be further discussed in the discussion section and references to previous studies using this method are needed. - Covariates: COPD severity groups are defined according to prescriptions of medication for COPD using the GOLD A, B, C and D treatment group recommendations. The four groups are defined in a detailed, but complicated way. The authors assume that these treatment groups reflect COPD severity, but no references to previous papers using this approach are listed. The authors need to reflect on the implication of the amount of unclassified participants and the relevance of this way to group COPD patients. Results: Table 4 and 5 presenting data on MMR according to GOLD treatments group contain no interesting results and should be simplified or left out. -Discussion: See the previous sections. The main limitation of the study is the definition of severity by using

	the ABCD treatment groups. It is a not validated method, and the findings of no substantial variation in mortality with the ABCD treatment groups are an indication that the treatments groups do not reflect the COPD severity in this population. The authors need to use the data on medication subscription to make a simpler categorization procedure.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1: Nicolas Roche, Université Paris Descartes, France

This paper reports a well-described database analysis aimed at assessing whether past exacerbations are predictive of short-term and long-term survival.

Major comments

1. My main concern is that, although the analyses were properly performed considering the question addressed, it is difficult to determine what this study adds to current knowledge.

Reply: We thank the reviewer for the appreciation of our analyses. In our view, we report several new and important findings. First, we included exacerbations treated in different types of settings including hospitals, outpatient clinics, and general practice. Thus, we were able to examine if the association depended on treatment level (i.e., hospitalized or not, as proxy for exacerbation severity). Second, we included COPD treatment and examined how the association depended on this variable. Third, we designed our study as a prognostic study focusing on the association between exacerbation frequency and mortality specifically, whereas some of the previous studies were prediction studies including prior exacerbation as a potential predictor without in-depth confounder-adjusted analyses to the association. Finally, our medical registries provide virtually complete and accurate follow-up data. We have adjusted the introduction to express these advantages more clearly to the reader. In the introduction, we now write:

“We conducted a cohort study to examine how the exacerbation frequency impacts one-year mortality following an AECOPD. Specifically, we addressed the limitations of previous studies by including exacerbations treated in the hospital, outpatient clinics and in general practice, and by using Danish registries with detailed data on comorbidity, COPD treatment and with complete follow-up.”

2. Many studies already addressed this question with variable results, essentially depending on the study population and available variables, as appropriately acknowledged by the authors. Results of the present study are similarly influenced by these study characteristics, so that the difference in setting and databases structure is the only new component, not the results per se…

Reply: Please see previous comment about the advantages of the current study. In particular, we have conducted a truly prognostic study, whereas earlier studies with limited data could only use exacerbation frequency as a predictor because of incomplete data on potential confounders.

3. The initial question is very focused on a specific potential predictor, i.e., exacerbations. Why didn’t the authors begin with a wider approach using univariate followed by multivariate analyzes to identify independent predictors of mortality? The results would have been quite the same but with less a priori hypotheses…

Reply: As mentioned in comment 1, the aim of our study was to examine specifically the association between exacerbation frequency and mortality following AECOPD. Thus, we were interested in examining causation not prediction. To answer this aim, we designed the study as a prognostic study.

Indeed, previous prediction studies for death following AECOPD have identified prior AECOPD as a predictor of mortality. However, as the purpose of the previous studies was to build strong prediction models, they did not focus specifically on confounders and effect modifiers of the association between exacerbation frequency and AECOPD mortality.

4. It would have been interesting to use age at first prescription of inhaled treatment and duration of inhaled treatment as possible predictors of mortality.

Reply: We agree that inclusion of such information would have been interesting. However, because we included data on both age and COPD treatment within prior 12 months, we took into account the major variation due to duration of disease. Furthermore, registry-based studies in general can suffer from left censoring; our prescription database was not complete until 1998. We would therefore expect some misclassification due to left censoring for variables such as age at first prescription of inhaled treatment and duration could. Based on these considerations, we would prefer to avoid including the suggested variables.

5. Classifying patients according to “GOLD A B C D treatment categories” does not appear to be adequate since it suggests that these correspond to severity categories. But many studies found poor correlations between treatment and actual severity or phenotype. Mentioning treatment categories without referring to GOLD A B C D classification would be more appropriate.

Reply: We thank the reviewer for this observation, which we agree with. Our original intention with the treatment categorisation was not to use it as a proxy for severity; we acknowledge that this may have been misinterpreted as such by using the term “GOLD A B C D treatment categories”. To avoid confusion, we now use the term “COPD treatment” and label the categories according to the drugs included. The definition is now described in “Covariates” (page 8, paragraph 2, lines 2-9):
“From the Prescription Database, we retrieved information on COPD treatment within 12 months before study start. Following the latest Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, we then grouped patients into the following five mutually exclusive groups of escalating treatment: (1) non-treated/unclassified, (2) short-acting bronchodilators, (3) monotherapy with a long-acting bronchodilator (beta2-agonists or long-acting muscarinic antagonists), (4) double therapy with any possible combination of long-acting beta2-agonists, inhaled corticosteroids, and/or long-acting muscarinic antagonists, (5) triple therapy with long-acting beta2-agonists, inhaled corticosteroids, and/or long-acting muscarinic antagonists, as defined in the Supplementary File (eTable 1).”

We still believe that inclusion of COPD treatment is an advantage of the study because appropriate pharmacological therapy can reduce the frequency of exacerbations (Decramer M et al. Chronic obstructive pulmonary disease. Lancet 2012;379:1341–1351; Seemungal TAR et al. Exacerbation rate, health status and mortality in COPD--a review of potential interventions. COPD 2009;4:203–223). We have therefore kept the original coding of the variable, which also reflects the frequent treatment combinations used in Denmark.

In total, 29% of COPD patients eligible for study were untreated/classified according to this categorisation. We believe that this represents patients with poor adherence or possibly patients with mild COPD. This had been added to the discussion (“Strengths and limitations”, page 14, paragraph 2, lines 15-16).

Reviewer 2: Cat Chang, Waikato Hospital, New Zealand

Thank you for the opportunity to review the study from Schmidt and colleagues. This is a registry-based retrospective cohort study examining the relationship between COPD exacerbations and

subsequent outcome. The study is based on data extracted from three Danish registries with information pertaining to emergency department presentations, hospital admissions, outpatient specialist clinic visits, prescription and drug redemption details and mortality information. The study methods are well described and the results are presented clearly and systematically.

The study methods are similar to the landmark study by Suissa et al (Thorax 2012), which demonstrated the cumulative detrimental effect of acute COPD exacerbations requiring hospitalisations. Schmidt and colleagues incepted a similar cohort based on coding and prescription data with standard exclusions (e.g. patients under the age of 40, history of asthma etc). The main difference in data is that while Suissa et al only included patients following the first severe COPD exacerbation requiring hospitalisations, the current study also included exacerbations treated in the community (using prescription data). Surprisingly, the current study found that the number of preceding exacerbations within the last 12 months were not associated with increased risk within 30 days following the next COPD exacerbation (but were associated with increased risk from 30-365 days).

My main issue with the current study is that this surprising primary outcome is not adequately discussed and explored. As the authors mention in their discussion, there is fairly extensive literature supporting the negative impact of previous exacerbations in patients with AECOPD. Although the authors postulate several potential confounders in their cohort, which may have biased their study results, and washed out the effects of exacerbations, I get no clear sense on how the authors propose their study results should be viewed in light of these. What we are then left with is a negative study providing conflicting evidence to the current literature with no clear suggestion on how this may be re-examined or validated and then incorporated into the existing knowledge paradigm. Further subgroup analyses examining the effect of severe exacerbations (e.g. hospitalisation, use of non-invasive or invasive ventilation) and first severe exacerbations may be helpful. Is there any lung function data at all?

Reply: We thank the reviewer for the thorough comments. Regarding the discussion of the primary outcome, there may be several explanations for the higher risk observed during 31–365 days of follow-up and the discrepancy with further studies (please see “Comparison with other studies”, page 15, paragraph 2, lines 11 to page 16, paragraph 1, line 11). Our study was not based on an inception cohort. Also, it is possible that patients experiencing few exacerbations and those experiencing several exacerbations (“frequent exacerbation phenotype”) are two very distinct patient populations. We have previously shown that patients with no AECOPD in the year before an AECOPD are younger and have less comorbidity (Johannesdottir et al. Hospitalization with acute exacerbation of chronic obstructive pulmonary disease and associated health resource utilization: A population-based Danish cohort study. J Med Econ 2013;16:897–906). Even though these patients may have had more newly diagnosed, and thus less severe, COPD, it is possible that some of these patients have more severe exacerbations because they postpone seeking medical attention due to unfamiliarity with the symptoms hereof. On the other hand, an older patient with higher comorbidity and a recent history of AECOPD may be more aware of the threatening situation and act more quickly, resulting in a lower mortality than expected in the acute phase. Thus, frequent exacerbation phenotype may be more “tough”, having survived many exacerbations already. The situation may then reverse after day 30 when the relative impact of frequent exacerbations on severity of COPD, complication rate, and relapse rate becomes clearer, as well as death from other causes than COPD. Finally, differences in baseline mortality rates for the short-term and longer-term follow-up may have made the association seem more pronounced in the longer-term analysis.

The potential confounders included in our study were chosen a priori because they may be associated both with exacerbation frequency and mortality. We do not believe that inclusion of these confounders washed out the effects of exacerbation. In fact, when comparing the crude mortality rates

with the adjusted hazard ratio, it can be seen that the adjusted estimates are similar or higher. Although potential unmeasured confounding cannot be ruled out, we note that the lack of information on clinical variables mentioned in the discussion is not regarded as unmeasured confounders. Rather, we believe that clinical variables, e.g. lung function, could be on the causal pathway acting as mediators of the association between exacerbation and mortality (please see “Strengths and limitations”, page 14, paragraph 2). We had no data on lung function, which we do acknowledge as a limitation in disentangling the association between exacerbation frequency and mortality (see “Strengths and limitations”, page 14, paragraph 2). Future studies should focus on including such information to clarify the potential association between AECOPD and mortality and also if the association varies with time as suggested by our results.

Regarding subgroup analyses, we did examine if the association depended on severity of exacerbation defined as hospitalization or not (Table 3, page 12), as suggested by Dr. Chang. Data on non-invasive or invasive ventilation could have been obtained from our databases. However, ventilation treatment could potentially be on the causal pathway linking exacerbation frequency with mortality (i.e., frequent exacerbations cause declining lung function resulting in need for ventilation support). Furthermore, inclusion of treatment data during follow-up period after the exacerbation would be challenging, as potential immortal-time bias would have to be circumvented somehow (i.e., the most sick patients would die before ever having the opportunity to receive respiratory support). Thus, we performed the appropriate subgroup analyses with the data available.

Other comments:
1. The authors chose to use the newly proposed GOLD treatment groups to stratify disease severity. This approach is problematic because the treatment groups had to be extrapolated retrospectively using prescription data and a large proportion of patients (29%) were unable to be classified in this way. Further, the GOLD ABCD pharmacological approach model was proposed in the 2011 update while the patients included in this study were diagnosed with COPD prior to 2004. As such I would expect the prescription practice to reflect guidelines current to the cohort rather than the newest update. Not surprisingly, the study analysis showed no significant difference in outcome between the groups. This is a reflection of the study methods rather than a lack of effect.

Reply: We have answered a similar comment from a reviewer above (reviewer #1, comment #5). We have inserted the reply here for completeness:

We thank the reviewer for this observation, which we agree with. Our original intention with the treatment categorisation was not to use it as a proxy for severity; we acknowledge that this may have been misinterpreted as such by using the term “GOLD A B C D treatment categories”. To avoid confusion, we now use the term “COPD treatment” and label the categories according to the drugs included. The definition is now described in “Covariates” (page 8, paragraph 2, lines 2-9):
“From the Prescription Database, we retrieved information on COPD treatment within 12 months before study start. Following the latest Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, we then grouped patients into the following five mutually exclusive groups of escalating treatment: (1) non-treated/unclassified, (2) short-acting bronchodilators, (3) monotherapy with a long-acting bronchodilator (beta2-agonists or long-acting muscarinic antagonists), (4) double therapy with any possible combination of long-acting beta2-agonists, inhaled corticosteroids, and/or long-acting muscarinic antagonists, (5) triple therapy with long-acting beta2-agonists, inhaled corticosteroids, and/or long-acting muscarinic antagonists, as defined in the Supplementary File (eTable 1).”

We still believe that inclusion of COPD treatment is an advantage of the study because appropriate pharmacological therapy can reduce the frequency of exacerbations (Decramer M et al. Chronic obstructive pulmonary disease. Lancet 2012;379:1341–1351; Seemungal TAR et al. Exacerbation rate, health status and mortality in COPD--a review of potential interventions. COPD 2009;4:203–

223). We have therefore kept the original coding of the variable, which also reflects the frequent treatment combinations used in Denmark.

In total, 29% of COPD patients eligible for study were untreated/classified according to this categorisation. We believe that this represents patients with poor adherence or possibly patients with mild COPD. This had been added to the discussion ("Strengths and limitations", page 14, paragraph 2, lines 15-16).

2. The study concluded that a history of COPD exacerbations indicate a higher risk during 31-365 days after the COPD exacerbations. Again, this finding is in conflict with existing literature – I would expect some discussion regarding potential mechanisms.

Reply: Please see our reply to the major comment (first paragraph).

3. All the results are presented in the form of adjusted hazard ratios in tables. I would suggest presenting some data in a graphical format may be helpful to the reader to interpret the findings. Of particular interest are the adjusted rates of death following an exacerbation over time.

Reply: We agree with the reviewer that some graphical illustration of the data could be appropriate. However, according to comments by another reviewer (reviewer #3, comment #6), we have now moved Tables 4 and 5 to the supplementary appendix. Because the data load presented in the paper has been reduced substantially by this change, we have kept the results presented in the paper in a table format. If the Editor wishes so, we are willing to present the data from the subgroup analyses (Tables 4 and 5, now in the Appendix) in a forest plot instead.

Essentially I feel that this study deserves publication in some form but further work is needed clarifying the significance and interpretation of results.

We thank Dr. Chang for expressing this view and for the interesting comments to our paper. We hope that our response is satisfactory.

Reviewer 3: Anne Hildur Henriksen, Department of Occupational and Thoracic Medicine, Trondheim University Hospital, Norway.

1. This is a well written and interesting manuscript addressing important questions. The grouping of patients according to prescription data ought to be reconsidered, and the authors should consider whether a more simple approach (i.e. patients on combination therapy versus those only receiving LABA and/or muscarine antagonists) would be more useful?

Reply: In fact, the original variable categorises treatment as single, double or triple therapy. If we understand correctly, this categorisation is similar to that proposed by Dr. Henriksen. We have therefore kept the categorisation as in the original submission, but labelled it more clearly. We have also answered a similar comment from a reviewer above (reviewer #1, comment #5). We have inserted the reply here for completeness:

We thank the reviewer for this observation, which we agree with. Our original intention with the treatment categorisation was not to use it as a proxy for severity; we acknowledge that this may have been misinterpreted as such by using the term "GOLD A B C D treatment categories". To avoid confusion, we now use the term "COPD treatment" and label the categories according to the drugs included. The definition is now described in "Covariates" (page 8, paragraph 2, lines 2-9):
"From the Prescription Database, we retrieved information on COPD treatment within 12 months before study start. Following the latest Global Initiative for Chronic Obstructive Lung Disease (GOLD)

guidelines, we then grouped patients into the following five mutually exclusive groups of escalating treatment: (1) non-treated/unclassified, (2) short-acting bronchodilators, (3) monotherapy with a long-acting bronchodilator (beta2-agonists or long-acting muscarinic antagonists), (4) double therapy with any possible combination of long-acting beta2-agonists, inhaled corticosteroids, and/or long-acting muscarinic antagonists, (5) triple therapy with long-acting beta2-agonists, inhaled corticosteroids, and/or long-acting muscarinic antagonists, as defined in the Supplementary File (eTable 1)."

We still believe that inclusion of COPD treatment is an advantage of the study because appropriate pharmacological therapy can reduce the frequency of exacerbations (Decramer M et al. Chronic obstructive pulmonary disease. Lancet 2012;379:1341–1351; Seemungal TAR et al. Exacerbation rate, health status and mortality in COPD--a review of potential interventions. COPD 2009;4:203–223). We have therefore kept the original coding of the variable, which also reflects the frequent treatment combinations used in Denmark.

In total, 29% of COPD patients eligible for study were untreated/classified according to this categorisation. We believe that this represents patients with poor adherence or possibly patients with mild COPD. This had been added to the discussion ("Strengths and limitations", page 14, paragraph 2, lines 15-16).

2. The abstract reflects the content of the manuscript.

3. In the introduction section actual previous studies are described and an introduction to the research questions is presented. It is pointed out that no previous studies on the present topic have included information on preadmission therapy. However, there is no mention on the impact of COPD severity versus exacerbation rate and mortality. Various definitions of severity of COPD and impact of severity versus exacerbation rate on mortality ought to be mentioned in the introduction section.

Reply: We agree that it would improve the introduction also to mention both the impact of COPD severity and COPD treatment on mortality. We have therefore changed the 2nd paragraph of the previous version of the introduction. The introduction now reads:

"COPD is frequently complicated by acute exacerbations (AECOPD), defined as "an acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to change in medication".5 The annual number of exacerbations in COPD patients is estimated at between 0.82 and 2.01, increasing with disease severity6 and history of frequent exacerbations.7 The mortality following AECOPD is high especially in patients with severe COPD.8 Thus, severity of disease is associated with both increased risk and mortality of AECOPD.8 However, the relationship is complex because frequent exacerbations may themselves also result in decreased lung function and thereby increase mortality.1,2,8,9 Indeed, several epidemiological studies have demonstrated an impact of AECOPD frequency on mortality following AECOPD overall showing that a history of AECOPD may be associated with worse prognosis. Comparison of these studies is, however, hampered by differences in the exposure windows used for assessing previous AECOPD hospitalisations, in the length of follow-up, and in the patient populations included.10-19 Although current therapies for COPD may decrease the exacerbations frequency and mortality,2,8 only one study examined if the association depended on preadmission therapy. However, authors did not provide the results for the analysis except for an insignificant interaction term,11 which limits the interpretation to statistical significance only. Finally, none of the studies included AECOPDs treated outside the hospital."

4. The methods section describes properly how the patients are selected for the study. However, it is unclear how participants and AECOPD admittances are handled in the analyses, and the number of admittances that are included in the analyses. The definition of less severe AECOPD as an episode

where the patients are not submitted to hospital, but receive a combination of systemic steroids plus antibiotics is adequate, but this approach ought to be further discussed in the discussion section and references to previous studies using this method are needed.

Reply: The design of the study is complicated because we used time-varying covariates. We classified each AECOPD during follow-up according to whether it was preceded by 0, 1, 2, or 3+ AECOPDs in the prior 12 months (Study population, page 7, 2nd paragraph, lines 7-16). We then entered this value as a time-varying exposure in the analysis. Therefore, each time a patient had an AECOPD during follow-up, we assessed the number of AECOPDs in the 12 months before the event and assigned the patient to the corresponding exposure group (0, 1, 2, or 3+ AECOPDs). One patient could thus have multiple AECOPDs during follow-up and contribute person-time in several exposure groups depending on the rate of AECOPD. With AECOPD frequency within the last year, we then computed the number of deaths, person-time, and mortality rates in each exposure group (Statistical analysis, page 8, last paragraph, line 22 to page 9, 1st paragraph, line 6). We used Cox regression analysis to compute crude hazard ratios as a measure of mortality rate ratios (MRRs) and associated 95% confidence intervals (CIs) for AECOPD patients with 1, 2, or 3+ AECOPDs in the 12 months preceding an AECOPD, compared with patients with no exacerbations in the preceding 12-month period. We then computed the MRRs adjusted for sex, age (as a continuous variable), and comorbidities.

5. Covariates: COPD severity groups are defined according to prescriptions of medication for COPD using the GOLD A, B, C and D treatment group recommendations. The four groups are defined in a detailed, but complicated way. The authors assume that these treatment groups reflect COPD severity, but no references to previous papers using this approach are listed. The authors need to reflect on the implication of the amount of unclassified participants and the relevance of this way to group COPD patients.

Reply: Please see our reply to the previous comment on treatment (comment #3).

6. Results: Table 4 and 5 presenting data on MMR according to GOLD treatments group contain no interesting results and should be simplified or left out.

Reply: We agree that the subgroup analysis in Table 4 and 5 generally demonstrated no substantial pattern of variation. We have thus moved the tables to the supplementary appendix and mention only the important results in the results section of the paper (Results, page 13, 1st paragraph).

7. Discussion: See the previous sections.

8. The main limitation of the study is the definition of severity by using the ABCD treatment groups. It is a not validated method, and the findings of no substantial variation in mortality with the ABCD treatment groups are an indication that the treatments groups do not reflect the COPD severity in this population. The authors need to use the data on medication subscription to make a simpler categorization procedure.

Please see previous comments regarding this limitation. We that hope that our response is satisfactory for Dr. Henriksen.

VERSION 2 – REVIEW

REVIEWER	Nicolas Roche Cochin Hospital group, University Paris Descartes, France
REVIEW RETURNED	23-Nov-2014

GENERAL COMMENTS	The authors delt satisfactorily with the comments.

REVIEWER	Anne Hildur Henriksen Department of Circulation and Medical Imaging, NTNU and Department of Thoracic and Occupational Medicine, Trondheim University Hospital, Norway
REVIEW RETURNED	23-Nov-2014

GENERAL COMMENTS	The content of the manuscript is now acceptable for publication, but the languish in the introduction must be improved. Moreover, in the discussion, in the part “comparison with other studies” first paragraph has one much too long sentence containing too many details. This section of the discussion ought to be rewritten.

VERSION 2 – AUTHOR RESPONSE

Reviewer 1: Nicolas Roche, Université Paris Descartes, France
The authors delt satisfactorily with the comments.

Reviewer 3: Anne Hildur Henriksen, Department of Occupational and Thoracic Medicine, Trondheim University Hospital, Norway.
The content of the manuscript is now acceptable for publication, but the language in the introduction must be improved. Moreover, in the discussion, in the part “comparison with other studies” first paragraph has one much too long sentence containing too many details. This section of the discussion ought to be rewritten.

Reply: We thank the reviewer for giving us the opportunity to revise the introduction of our manuscript. We have now revised as follows:

“Chronic obstructive pulmonary disease (COPD) is characterized by a progressive decline in pulmonary function due to airway inflammation in response to noxious particles and gases.1,2 In Denmark, the standardised incidence rate of hospitalisation for COPD was 231 per 100,000 person-years in 2006.3 The 0-180-day and 181-day to 5-year standardised mortality rates in COPD patients were 389 per 1,000 person-years and 164 per 1,000 person-years, respectively,3 making it one of the leading causes of death among the elderly.4
COPD is frequently complicated by acute exacerbations (AECOPD), defined as “an acute event characterized by a worsening of the patient’s respiratory symptoms that is beyond normal day-to-day variations and leads to change in medication”.5 The annual number of exacerbations in COPD patients is estimated at between 0.82 and 2.01.6,7 Exacerbation frequency6 and mortality8 increases with increasing COPD severity. On the other hand, frequent AECOPDs may themselves result in decreased lung function and could thereby increase disease severity and AECOPD mortality.1,2,8,9 Several epidemiological studies support this by demonstrating an impact of exacerbation history on mortality in patients admitted with AECOPD. Comparison of previous studies is, however, hampered by differences in the definitions of AECOPD frequency, in the length of follow-up, and in the patient populations included.10-19 Furthermore, none of the studies included AECOPDs treated outside the hospital. Finally, only one of the studies examined if the association depended on preadmission therapy.11 Unfortunately, authors provided only an insignificant interaction term for the analysis,11 which limits the interpretation to statistical significance only.
We conducted a cohort study to examine how the exacerbation frequency impacts one-year mortality following an AECOPD. Specifically, we addressed the limitations of previous studies by including exacerbations treated in the hospital, outpatient clinics and in general practice, and by using Danish

registries with detailed data on comorbidity, COPD treatment, and with complete follow-up."

It is not entirely clear to us, which sentence in the discussion that the reviewer is referring to. We have revised the first paragraph as follows, which we hope satisfies the request:
"In a Canadian inception cohort of 73,106 COPD patients, Suissa et al.17 showed that the AECOPD mortality rate increased with each exacerbation, as compared with the mortality rate following the first AECOPD. The adjusted MRR was 1.9 (95% CI: 1.8, 1.9) for the second AECOPD increasing to 5.2 (95% CI: 4.9, 5.5) after the 10th or later events. Mortality peaked within the first week after admission. Several other studies have also found an association between a history of AECOPD and mortality.10-16,18,19 However, definitions of exposure have varied greatly, including a history of hospitalisation for AECOPD within 6 months,16 1 year,10,11,14,18,19 and up to 7 years12 before current AECOPD hospitalisation, within 2 years before inclusion period,15 or admission with respiratory failure within 2 years before current admission.13 Similarly, various definitions of AECOPD mortality were applied, including mortality in-hospital,12,13,16 at 30 days13 and at longer term (median 3.1 years)14 following admission, and at 3 months,10 6 months,11 1 year,11 2 years,11,19 and at longer-term mortality (3 or more years)15,18 following discharge. Besides these differences in assessment of prior AECOPD hospitalisations and in follow-up periods, populations included also varied substantially (e.g., inclusion of primarily men,11,15,18 emergency room patients only,14,16 and discharged patients only10,15,18,19)."