Author's response to reviews

**Title:** Psychosocial risk factors for hospital readmission in COPD patients on early discharge schemes: a cohort study

**Authors:**

Peter A Coventry (peter.a.coventry@manchester.ac.uk)
Isla Gemmell (isla.gemmell@manchester.ac.uk)
Chris J Todd (chris.todd@manchester.ac.uk)

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**Author's response to reviews:** see over

Dear Dr Shipley

Thank you for sending reviewers’ comments about the revisions made to the above manuscript.

We thank the reviewers for taking the time to read the revised version and for offering further comments that can strengthen the manuscript. We have now amended the manuscript where possible and where appropriate and all changes are highlighted using tracked changes.

We especially thank Dr Kim Lavoie for her considered and comprehensive review. Below is a point-by-point response to Dr Lavoie’s comments:

1) Dr Lavoie wrote: The additional information about the ESSI is appreciated. However, the 2nd part of the authors’ response suggests they may not have understood Dr. Gruffydd-Jones’s comment. In the absence of a validation study of the psychometric properties of the ESSI in the population under study (ie, COPD patients), we could expect a different factorial structure of the ESSI in the disease area under study. In others words, it is possible that higher scores on the ESSI observed here would be not due to higher levels on the construct of interest (i.e., perceived social support) but rather (i) to the instrument measuring a
different construct, or (ii) measuring it differently in the current sample. In sum, the authors should indicate it in the limitation section.

Author’s response: We have now included in the discussion section on social support a methodological note that addresses Dr Lavoie’s comments about the potential for the ESSI to have a different factorial structure when used with COPD patients as opposed to heart disease patients.

2) Dr Lavoie wrote: Both Dr. Gruffydd-Jones and myself requested justification for powering the study based on a secondary endpoint (SGRQ). The authors’ response: “We have edited the paragraph in the methods on sample size so that it relates to our primary outcome” and edits made to the paper: “Logistic and survival models produce stable estimates if the limiting sample size allows for a ratio of 10–15 observations per predictor variable [38]. Based on previous data [2] it was estimated that a sample of 150 would yield 100 events for a regression model” on page 7 unfortunately, do not directly address our question and raise additional concerns. Did the authors make a mistake when writing this section the 1st time? Their response does not clarify why they had originally powered the study based on a secondary outcome, nor does it clearly state that the study was ACTUALLY AND ORIGINALLY powered based on their primary outcome (admission/death), which is what the paper edits suggest (but again, it is not clear). The concern here is that there was no acknowledgement of making a mistake (if indeed that was the case in the original version), and I wonder about whether the study was originally powered appropriately.

Author’s response: Yes, we did make a mistake when writing this the first time. The original sample size calculation was based on obtaining a sample size to accommodate a range of predictor variables in a regression model with estimates for readmission rate, and attrition rate due to death obtained from a paper by Groenewegen (Chest 2003). We have changed the section on sample size to make this clearer. It was not based on SGRQ which is why we removed this sentence. The study was originally powered on the primary outcome (re-admission). In the discussion we acknowledge that the study would have benefited from increased power (pages 10 & 13).

3) Dr Lavoie wrote: I had originally requested information about how many patients were excluded for each of the exclusion criteria, and the authors’ response: “We do not have access to data related to patients excluded from enrolment on an EDS service – this is data used to determine eligibility for EDS at each of the hospital sites. However we have stated in the first paragraph of the results that one patient was excluded from the cohort study because of newly diagnosed lung cancer” was a bit confusing. Study exclusion versus EDS exclusion are not necessarily the same, but this response would suggest there were no specific study exclusion, and that the authors excluded patients who were not eligible for EDS at each hospital site. Is this the case? If so, could the authors clarify? Also, if data on the number of patients excluded for each reason is not available, could they at least provide the total number of patients excluded for these reasons? Ideally, the authors would present the total number of COPD admitted for acute exacerbation across the three study hospitals (if 43 refused + 1 cancer patient, and the final sample size was 79, were only 123 patients
referred to EDS over the study period? This seems low?), and then the total number of patients referred for EDS (across the three sites) that ended up in the study (which appears to be 79). In sum, please clarify the patient flow through the study, which is important to determine generalizability of results.

**Author’s response:** We have now included data that shows the total numbers of patients admitted for AECOPD during the recruitment period across north, south and central Manchester (which covers the areas used for recruitment). We have then reported the total number of patients who were referred onto EDS across the 3 sites - it equates to about 30% of all patients admitted to AECOPD which is in-keeping with other EDS for the UK. We have rewritten this paragraph to make clear that 123 patients were invited to participate in the study by the nurse teams and that 43 refused. That left 80 recruits to the study and we subsequently excluded one patient because mid-way through the study they were diagnosed with lung cancer. We did not exclude any other patients, leaving 79 in total.

We have also amended the methods section where we discuss the inclusion/exclusion criteria to both EDS across the 3 sites and then into the study. This makes it clear that we only accepted patients into the study referred onto EDS because this was a prospective study of risk factors for readmission among patients receiving nurse led support on EDS. We applied additional exclusion criteria where patients were diagnosed with severe mental health problems or were not English language speaking as all participants had to be able to use the English language self-report instruments.

4) **Dr Lavoie wrote:** Regarding the modest participation rate of 65%, I suggested that one possible explanation might have been that patients felt the home visits were intrusive. The authors’ response that: “most patients in our study anecdotally reported that they valued the EDS nurses and were comforted by their presence. Furthermore, again, anecdotally, patients that were enrolled in this cohort study were very enthusiastic about being involved in the study” suggests another possibility, that there was some self-selection bias towards inclusion (or participation) of the most positive and enthusiastic patients, which also potentially limits generalizability of results. Could the authors comment on this?

**Author’s response:** We have now added a further statement in the discussion of limitations to flag up the notion that those who participated in this study may have been untypical of wider populations of COPD patients because they may have been the most willing to take part. However our broader point still stands. Whilst there may be a trend towards self-selection bias among observational studies of this kind there is evidence that patients’ willingness to participate in psychosocial research is possibility under estimated and that participation can be high even in studies that demand weekly assessments (e.g. see Altmaier EM. Rehabilitation Psychology, 1989; 34:185-189.)

5) **Dr Lavoie wrote:** Regarding who collected the data at baseline and follow-up, the authors clarified that indeed it was the study PI and primary author (PC) who undertook both baseline and follow-up assessments, who was not blind to patients’ baseline psychosocial status (see page 5 of paper). While the clarification is appreciated, it does raise some important methodological concerns. How can you exclude the possibility of bias in
assessment and recording outcome data when it was not only the same person who conducted baseline and f-up assessments, but the study PI (and first author) who has the greatest stake in the study findings? This is problematic and a major source of potential bias that may be difficult (if not impossible) to exclude, and is a major study limitation that at least be noted in the limitations section. What, if any measures were taken to ensure impartiality? Nothing in the authors’ response to reviews suggests that any measures were taken, or that they understand the potential seriousness of this potential source of bias. Could they comment?

**Author’s response:** We fully appreciate the potential for assessments to be biased during the conduct of observational studies. The PI was funded by a MRC Training Fellowship which did not allow for the employment of a researcher who could have remained blind to all outcomes during the course of the study. In the limitations section of the discussion we have acknowledged the potential for bias to have occurred but made it clear that the PI did not score follow-up assessments until the end of the follow-up period and was therefore not aware of the psychological status of patients during the follow-up period. Furthermore, the PI did not score the questionnaires. This task was done by a research administrator (Mrs Kim Hunter) who was separate to the study team. We have also stated that we used patient reported outcomes, as opposed to interview led outcomes, which may have minimised measurement bias on the part of the PI.

6) **Dr Lavoie wrote:** Regarding the statistical analysis approach, there are two remaining concerns. First, there is some confusion (perhaps only related to ensuring consistency and clarity across the different sections of the paper) regarding the primary outcomes(s). The authors wrote in the abstract introduction and methods (see page 2) and paper introduction (see page 4) that the primary outcome was “readmission for AECOPD” and that “This study aimed to identify psychosocial risk factors for readmission,” respectively, which is fine. Yet in the methods/outcomes section (see page 5), the authors write: “The primary outcomes were readmission to hospital for AECOPD or death within 365 days of index admission”, which is inconsistent with both the abstract and introduction, and which adds confusion. Was the primary outcome readmissions only or readmissions and death? The sample size estimate section, which does not actually refer to any primary outcome(s) specifically (see page 7), did not help clarify these inconsistencies. This is important to clarify as this affects the sample size estimate and power calculation.

**Author’s response:** The primary outcome for this study was readmission for AECAOPD. We have removed ‘or death’ from the methods/outcomes section. The sample size estimate was based on the primary outcome, readmission and we feel we have made this clearer in paper and in our response to point 2).

7) **Dr Lavoie wrote:** Second, I disagree with the author’s position on the appropriate way to determine covariates. They write in their response: “We do not agree with the reviewers suggestion that ‘a number of a-priori determined covariates should have been selected, based on known of theoretical links with the primary outcome and/or predictors (e.g., age, some measure of COPD severity such as lung function or number of previous exacerbations’. We believe that the methodology of assessing each individual covariate in a univariate model and then entering those covariates that were statistically associated with
the outcome into a multivariate model is the correct method of conducting statistical analyses. It would be very difficult to defend the selection of variables into the model if we had just used a-priori determined covariates; in fact we do not believe that this would constitute a valid research protocol for this study." In fact, one of (if not the most) highly respected journal in the field of behavioural medicine and psychosocial research, Psychosomatic Medicine (as well as the CONSORT guidelines for clinical trial reporting) has clear and published guidelines on several aspects of statistical practice, including covariate selection and adjustment that been available for several years. The authors are encouraged to consult this link for details: http://www.psychosomaticmedicine.org/site/misc/stat.xhtml#number5, but here is the except regarding covariate selection that is supported by several noteworthy references.

So the authors are encouraged to re-consider this aspect of their statistical approach, and to re-consider their choice of covariates, which should include smoking for example, as current smoking is theoretically likely to influence the primary outcome, even though it did not emerge as significant in univariate analyses. As the authors correctly point out, "It is not unusual for variables to be found not significant at p<0.05 in a univariate analysis but then to be found to be significant in a multivariate model", which is an additional reason for determining covariates a-priori.

**Author's response:** We have added smoking in the multivariate analysis even though it was not significant in the univariate – the new analysis is in Table 2 and we have adjusted the text of the results in the abstract to reflect this new adjusted analysis. The results in the table indicate that current smokers are less likely to be re-admitted than ex/never smokers. We used a combination of a priori variables and variables based on a threshold for significance. For example we included gender in the model even though it was not significant. However, we needed to restrict the number of variables in our model due to the small sample size so we could not include many a priori non significant variables. This line in the discussion refers to this strategy: “The final regression models included a set of a priori predictors (age and sex) and measured the effects of as many known confounders within sample size limits”

8) **Dr Lavoie wrote:** As no measure of gender was used, all references to gender (a complex psychosocial construct related to sex-role identity, masculinity/femininity, among others) should be replaced with sex (which refers to one being male or female).

**Author’s response:** Agreed. We have changed sex to gender to denote differences between men and women.
Below are the responses to Dr Judith Garcia-Aymerich.

**Dr Judith Garcia-Aymerich wrote:** “The authors have not answered satisfactorily the comments from reviewers (mine or others’). The paper has not improved and still keeps all its limitations.

**Author’s response:** We accept that there are limitations to this study and we have made these clearer in the limitations section of the discussion. We have worked diligently to address where possible the original (and new) comments of all the referees and we respectfully disagree that the manuscript has kept all of its limitations and has not improved.

1) **Dr Judith Garcia-Aymerich wrote:** Major compulsory revision #1. “Relapse vs readmission” Authors have not answered at all.

**Authors response:** This query has prompted us to be more specific about the focus of our study and has given us an opportunity to update the introduction. We have rewritten the opening section of the introduction to highlight recent research that has shown that there is a high risk of recurrent exacerbation in the 8 weeks after an initial exacerbation (Hurst et al. Am J Resp Crit Care Med 2009;179:369-374) and that this is consistent with the finding from a UK audit that 30% of patients with AECOPD have a readmission within 3 months (Price et al, Thorax 2006). The purpose of these introductory remarks is to emphasise that readmissions are common and important events in the natural history of COPD patients and that many patients suffer these events often.

Hurst et al. also make it clear that recurrent exacerbations are best described as a second, discrete event after successful treatment of a first episode. Whereas they define a relapse as an exacerbation associated with treatment failure of a first exacerbation.

Following this definition, we did not set out to investigate risk factors for relapse associated with treatment failure of an initial exacerbation. That would demand a different question and a different data collection strategy. We did not distinguish between exacerbations that were initial, isolated, or recurrent events but consistent with the definition and classification used by Hurst et al., all exacerbations were discrete events separated by at least a week during which no additional symptoms were recorded. This point has now been made in the methods section.

However, we accept that the reasons for relapse owing to treatment failure of an initial event may well be different than for readmission for another event that was successfully treated and we have highlighted this point in the discussion. The question raised by Dr Garcia-Aymerich is clearly an important one that should be addressed in further work as interventions designed to prevent readmission may need to take into account whether readmissions are due to relapse or recurrent events.
2) Dr Judith Garcia-Aymerich wrote: Major compulsory revision #2. "Temporality. (...) the authors do not include time as a factor and some interpretations are misleading, e.g., in the abstract" Authors answer: "we do not think the last sentence of the abstract is misleading". The sentence alluded to is "Depressive symptoms and socioeconomic status (...) predict readmissions for AECOPD". Actually, readmissions are measured before depression questionnaire, and there is no way depression can "predict" something that happened before. The authors are certainly confused with temporality thorough the whole manuscript.

Author's response: We have taken time into the analysis by conducting a survival analyses. In a survival analysis the dependent variable is 'time to readmission'. We did this analysis and demonstrated that 'only FEV1% adjusted for sex and age was a significant predictor of time to readmission or death (HR 0.97, 95% CI 0.95 to 0.99, p=0.003).'

The results of the study show that depression measured at baseline is predictive of readmission over 365 days. This is what the abstract, Table 2 and the conclusion in the discussion refer to – we have made this clearer in the results of the abstract and the discussion section. We have never suggested that depression scores measured at 3 or 12 months can predict events in the past. Furthermore, in the discussion we have already stated that we cannot make claims about whether changes in depression caused readmissions or whether readmissions caused changes in depression.

3) Dr Judith Garcia-Aymerich wrote: Minor essential revision #7 "When was COPD defined? Stability should be ensured". Authors answer "COPD diagnosis was made at the time of referral to the early discharge service. Stability was also checked at this time". Authors should know that COPD is not stable during an exacerbation, it takes some weeks or months to recover. Patients were NOT in clinical stability when COPD diagnosis was assessed and so the diagnosis may be wrong. 

Author's response: Specialist respiratory nurses were responsible for checking diagnosis of COPD at time of referral to EDS. The same nurses made sure patients were stable enough to be discharged home and it was then that they invited patients to take part in the study. We have amended the methods to make this clearer.

We thank the reviewers for their additional input and comments to improve the manuscript and we believe the responses outlined in this letter address their major concerns and queries.

We look forward to your response following submission of this revised manuscript.

Yours sincerely

Peter A Coventry (PhD)