PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Primary Sjögren's Syndrome 1976-2005 and Associated Interstitial Lung Disease: A Population Based- Study of Incidence and Mortality
AUTHORS	Nannini, Carlotta; Jebakumar, Adlene; Crowson, Cindy; Ryu, Jay; MATTESON, Eric

VERSION 1 - REVIEW

REVIEWER	Stephen Shiboski Professor Dept. of Epidemiology and Biostatistics University of California, San Francisco USA
REVIEW RETURNED	22-Aug-2013

GENERAL COMMENTS	**General comments**: This manuscript presents results of a cohort study of interstitial lung disease (ILD) incidence among patients with primary Sjögren's Syndrome (pSS). Patients were recruited via retrospective review of medical records. Diagnosis of pSS was based on 2012 ACR consensus group criteria; ILD was defined using validated composite criteria. The methodology and results are clearly presented, and the text generally well written. Although the title and abstract prominently feature ILD incidence and mortality among pSS patients as a primary objective, all figures and tables presented address pSS findings. Further, 2/3 of the results section is dedicated to pSS. The main results provided specific to ILD take up two sentences in the results section (the hazard ratio reported is for any lung involvement and is not specific to ILD). Although these findings provide useful information, neither is very surprising. A revision should emphasize the pSS incidence objectives more strongly to reflect this. Finally, due to the clear chronological variation in the tests used to classify pSS cases evident from Table 2 of the paper, the possibility that the observed time trend in incidence is an artifact of changes in classification procedure (e.g. later classifications may have relied more on serology). This possibility should be acknowledged in the limitations and discussion/conclusions. **Specific comments**: 1. Abstract (page 2): There is an apparent error in the first sentence of the conclusion:

	“Patients with and ILD have increased premature mortality detrimental survival experience”. The statement that the diagnosis of pSS was based on the recent ACR criteria is apparently false (see comment 3 below). 2. Article summary (page 3): The first item in the “Article focus” is to “estimate the trends in incidence of pSS”, yet this objective is not mentioned in the abstract which focuses on ILD incidence. The meaning of the last sentence in this section is unclear: "Despite these difficulties, the relevance of information coming to clinical attention will provide a strong resource to address the study aims". 3. Patients and Methods (page 6, last paragraph): It is stated here: "all cases fulfilled the 2002 American-European Consensus Group (AECG) criteria for pSS", and “accordingly the 2012 published expert consensus approach for pSS classification Criteria”. The latter phrase is referenced to the recently published preliminary ACR criteria, and the sentence seems to imply that these are equivalent to the 2002 AECG criteria. This implication is incorrect for the following reasons: First, the ACR criteria are based on objective tests only (including focus scores based on salivary gland biopsy), and do not rely on symptoms. It’s clear from Table 2a of the manuscript that pSS case definitions (especially from the earlier chronological period) relied heavily on symptoms, making the correspondence with the ACR criteria questionable for at least half of the pSS cases considered here. Second, the ACR criteria are not targeted specifically at pSS. In fact, in the conclusion of the cited paper defining the ACR criteria the authors state: “the distinction between primary and secondary forms of SS is based on an early definition of the disease and may now be obsolete”. In a revision, the authors should make it clear throughout that there pSS case definition is based on the American-European Consensus Group criteria, and not the recent ACR criteria. Presumably, the correspondence with the ACR definition may be reasonably close (at least for SS diagnosed in the later time period), but this is impossible to assess in the entire cohort. 4. Patients and Methods (page 7): The assumed incidence date (first paragraph) could also represent prevalent pSS. It would be useful to know how many of the “incident” cases were determined based on multiple clinic observations with complete observation of relevant defining characteristics, and thus could be reasonably defined as new rather than prevalent cases. The Data Collection subsection mentions smoking

	status variables, but these don't appear in either analysis descriptions or results. 5. Patients and Methods (page 8): The definition of the time dependent covariate for respiratory involvement should be clarified. Was this a binary indicator for current involvement, or a cumulative indicator (i.e. once lung disease was detected, the indicator was set to "on" for the remainder of follow-up)? The interpretation of the resulting relative hazard estimate depends critically on this definition. 6. Results (page 9): The interpretation of the hazard ratio for mortality among pSS patients developing lung disease is a bit unclear since the definition of the covariate for the latter is incomplete (see comment 5). 7. Discussion, page10: The following sentence is incomplete: "Comparison to existing epidemiologic studies is complicated by differences in the definition and application of diagnostic." 8. The claim that pSS was diagnosed "evaluated using the new ACR classification criteria for pSS" is false, as noted above. 9. The title could be simplified to omit the double use of the word "based": Interstitial Lung Disease in Primary Sjögren's Syndrome: A Population-Based Study.

REVIEWER	Rekha Vij, MD Instructor University of Chicago, Department of Internal Medicine, Section of Pulmonary / Critical Care Medicine USA
REVIEW RETURNED	17-Sep-2013

THE STUDY	Authors reports that the development of lung disease in pSS is associated with poor survival with a hazard ratio of 2.16, however the confidence interval crosses zero. The authors have to address and clarify how the reader should interpret this finding. Also, the last sentence of the abstract is misleading and/or an overstatement. This study doesn't address whether the identification and/or treatment of pSS-ILD improves the survival experience.
RESULTS & CONCLUSIONS	Authors reports that the development of lung disease in pSS is associated with poor survival with a hazard ratio of 2.16, however the confidence interval crosses zero. The authors have to address and clarify how the reader should interpret this finding.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

Specific comments:
1. Abstract (page 2): There is an apparent error in the first sentence of the conclusion: “Patients with and ILD have increased premature mortality detrimental survival experience”. The statement that the diagnosis of pSS was based on the recent ACR criteria is apparently false (see comment 3 below).

We confirm the sentence in abstract conclusion section considering the 2002 AECG criteria revision (see answer the comment 3 below). We abide by our conclusion that these patients likely have an increased premature mortality expectation. We believe the reviewer is concerned by the lower CI of .99, which indicates the statistical test did not achieve the arbitrary cut-off of $p<0.05$ used conventionally. However, this result approaches statistical significance and this sizeable twofold risk is unlikely to be due to chance alone, and is therefore in a range that is compelling for our conclusion, all the more of interest when one realizes that a difference of a single case pushes the estimate well into the higher range. We use the term “likely”, which we hope is helpful in interpreting the estimate. We appreciate the lesson of the reviewer.

2. Article summary (page 3): The first item in the “Article focus” is to “estimate the trends in incidence of pSS”, yet this objective is not mentioned in the abstract which focuses on ILD incidence. The meaning of the last sentence in this section is unclear: "Despite these difficulties, the relevance of information coming to clinical attention will provide a strong resource to address the study aims".

We appreciate this comment and have included this verbiage and have enriched the methods and the results sections in the abstract with relevant summary data.

3. Patients and Methods (page 6, last paragraph): It is stated here: "all cases fulfilled the 2002 American-European Consensus Group (AECG) criteria for pSS", and “accordingly the 2012 published expert consensus approach for pSS classification Criteria”. The latter phrase is referenced to the recently published preliminary ACR criteria, and the sentence seems to imply that these are equivalent to the 2002 AECG criteria. This implication is incorrect for the following reasons: First, the ACR criteria are based on objective tests only (including focus scores based on salivary gland biopsy), and do not rely on symptoms. It’s clear from Table 2a of the manuscript that pSS case definitions (especially from the earlier chronological period) relied heavily on symptoms, making the correspondence with the ACR criteria questionable for at least half of the pSS cases considered here. Second, the ACR criteria are not targeted specifically at pSS. In fact, in the conclusion of the cited paper defining the ACR criteria the authors state: “the distinction between primary and secondary forms of SS is based on an early definition of the disease and may now be obsolete”. In a revision, the authors should make it clear throughout that there pSS case definition is based on the American-European Consensus Group criteria, and not the recent ACR criteria. Presumably, the correspondence with the ACR definition may be reasonably close (at least for SS diagnosed in the later time period), but this is impossible to assess in the entire cohort.

At the suggestion of the reviewer we use data develped with the 2002 AECG criteria only since the new criteria have some differences to these. For reader reference, in the discussion we point out that the effect of using the different sets is likely minimal, as the two sets of criteria are pretty close even if

they could not be applied to the entire cohort.

4. Patients and Methods (page 7): The assumed incidence date (first paragraph) could also represent prevalent pSS. It would be useful to know how many of the “incident” cases were determined based on multiple clinic observations with complete observation of relevant defining characteristics, and thus could be reasonably defined as new rather than prevalent cases. The Data Collection subsection mentions smoking status variables, but these don’t appear in either analysis descriptions or results.

The medical linkeage system of Rochester Epidemiology project allows to have a complete access to patients records of Olmsted County therefore it is possible to evaluate the presence of new diagnosis looking at the medical charts of patients where new symptoms, new laboratories evalution or radiologic study are reported. It is the standard in all studies of incidence of rheumatic diseases we have published over the past decades to use the date at which the patietns fulfilled the classification criteria for a disease as the incident date, which avoids misclassification of disease. Patients included in the study were incident cases. We appreciate the suggestion regarding smoking data reporting which appear in Table 2.

5. Patients and Methods (page 8): The definition of the time dependent covariate for respiratory involvement should be clarified. Was this a binary indicator for current involvement, or a cumulative indicator (i.e. once lung disease was detected, the indicator was set to “on” for the remainder of follow-up)? The interpretation of the resulting relative hazard estimate depends critically on this definition.

The statistical methods section has been modified to clarify that the time-dependent covariate for respiratory system involvement was modeled as an exposure variable which was set to “on” for the remainder of follow-up once lung disease was detected.

6. Results (page 9): The interpretation of the hazard ratio for mortality among pSS patients developing lung disease is a bit unclear since the definition of the covariate for the latter is incomplete (see comment 5).

This issue has been clarified in the statistical methods section (see response to comment 5).

7. Discussion, page10: The following sentence is incomplete: “Comparison to existing epidemiologic studies is complicated by differences in the definition and application of diagnostic.”
Thank you for pointing this out. We have clarified with “..differences in disease definition and classification criteria.”

8. The claim that pSS was diagnosed “evaluated using the new ACR classification criteria for pSS” is false, as noted above.

See answer to comment 3

9. The title could be simplified to omit the double use of the word “based”: Interstitial Lung Disease in Primary Sjögren’s Syndrome: A Population-Based Study.

The reviewer has helped us realize that our title should be modified to better reflect the study purpose, which we have done.

Reviewer 2

Authors reports that the development of lung disease in pSS is associated with poor survival with a hazard ratio of 2.16, however the confidence interval crosses zero. The authors have to address and clarify how the reader should interpret this finding.
Also, the last sentence of the abstract is misleading and/or an overstatement. This study doesn't address whether the identification and/or treatment of pSS-ILD improves the survival experience.

Thank you for this comment. We addressed the issue of the interpretation of the hazard ratio in reponse to query one of reviewer one. Likely reviewer 2 means a confidence interval crossing 1, as it is mathematically impossible to have a CI which crosses 0 into a negative direction. We take the point regarding the conclusions, and have modified this to read: “Attention to the occurrence of, and improved management of ILD in patients with pSS, may contribute to reduction of the disease burden of the disease.”