**Author’s response to reviews**

**Title:** Trends in incidence, mortality, and causes of death associated with systemic sclerosis in Denmark between 1995 and 2015: A nationwide cohort study

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Point-by-point response letter


Reviewer #1:

This study provides contemporary epidemiology in Denmark. In general, the paper is well-written. I have some minor comments.

1. The source data seem to contain hospitalization data. I'm not familiar with Danish medical system. Will you hospitalize all patients with systemic sclerosis and make diagnosis during hospitalization? Is it possible for a patient being diagnosed at GP? Are there any
discrepancies in time between initial suspicion (or diagnosis) to first record of hospitalization?

Our response:

First, we would like to thank the reviewer for taking the valuable time to read our paper and to provide some very insightful comments.

It could indeed represent a source of selection bias if the full spectrum of patients with SSc were not included in our study. However, as mentioned in the article (validation section, p.6, l. 6-8) SSc patients in Denmark are almost exclusively treated in specialized departments of Rheumatology and Dermatology i.e. seen at a hospital level. Of note, the Danish National Patient Registry includes diagnoses on both hospitalized patients (i.e. “in hospital” diagnoses) and outpatient visits (i.e. non-hospitalized patients).

Patients with SSc are most often seen in out-patient clinics, but can be hospitalized e.g. due to severe organ involvement or other need for in-patient care. It is theoretically possible for a patient to be diagnosed at a General Practitioner, but under normal circumstances the patient would hereafter be referred to a specialized department of Dermatology or Rheumatology for further work-up and treatment. The diagnosis would then be made/confirmed and registered in the Danish National Patient Registry. The discrepancy in time would be assumed to be short amounting to the time from initial referral from e.g. a GP to an initial out-patient visit and diagnosis (including registration in the Danish National Health Registry).

Added sentence, validation section, p. 6, l.9-10:

“Patients with SSc are usually seen at outpatient clinics where a diagnosis is typically made and registered in the DNPR.”

2. About mortality, how do you define the starting and end date for 1-year mortality? For patients with SSc, I assume they started their follow-up when they had first record of diagnosis and were censored at death or one year plus diagnosis date. For background mortality, I assume they were estimated per calendar year. This may cause a slight difference in follow-up definition for cases and background population but I think the effect is trivial.

Our response:

We thank the reviewer for pointing this out. One year mortality for SSc-cases was defined with first registration of diagnosis and censored at death or at 365 days follow-up. For the background population the 1-year mortality is defined per calendar year.
This could indeed result in selection bias due to differences in completeness of follow-up between the comparison groups. We also considered the difference on outcome due to the slightly different follow-up definitions to be negligible. We therefore concur with the reviewer in that the effect of a slightly different follow-up definition is trivial.

Added sentence, Statistics section, p. 7, l. 1-3:

“One year mortality for SSc-cases was defined with first registration of diagnosis and censored at death or at 365 days follow-up. For the background population the 1-year mortality was defined per calendar year.”

3. I’m not sure whether it is suitable to use Cox regression to assess trends. Please explain the reason or use other methods such as joinpoint regression.

Our response:

Our choice was based partly on traditions, but was considered as reasonable because the crude rates were decreasing in a slight, but overall more or less linear way (see Figure 2 in manuscript). We agree with the reviewer that joinpoint regression may have some advantages over Cox regression, especially if the aim is to look at changes in rates at various time-points over a period of time. However, joinpoint regression may also overfit the data and for our purpose we considered Cox models to be a more straightforward choice than joinpoint regression. However, if either the reviewer or Editor feel strongly about it, we would be happy to explore our data by additional methods.

4. Some information in the tables and figures overlaps. At least part of them should be moved to supplement.

Our response:

Thank you for your comment. We have provided a few figures to ease the readers understanding of the data. Some information in tables and figures is as noted overlapping.

It is stated under Biomed Central/BMC Rheumatology “Submission Guidelines” that there is not a restriction on the length and quantity of data. Furthermore guidelines on how to use supplementary information are mentioned under the “Additional Files” section. Here authors are required only to upload ‘figure files and tables as additional files if they are too large’. As this is not the case for our files or tables we have followed the guidelines. However, upon the reviewers request, we have removed Table 2 to the additional file information.

Added paragraph, Additional Material, p. 17, l.7-11.
Additional Material. Additional file 1.docx. Title: Overall incidence rates, mean age at diagnosis and proportion of women in 1995-2015. Description: The table depicts data from 1995-2015 including number of cases per year, observation time (total person years), incidence rate per million, mean age at onset, and proportion of women (%).

Table 2 has been replaced by Additional file 1 (reference: p. 8, l 19).

Table 3 has replaced Table 2 (reference: p. 9, l. 6, 8, 12).

Table 4 has replaced Table 3 (reference: p. 9, l. 10).

Table 5 has replaced Table 4 (reference: p.9, l. 16)

Table 6 has replaced Table 5 (reference: Table 1).

Reviewer #2:

Good manuscript with interesting subject matter. A few queries:

Based on the manuscript the authors describe that data was collected after 1994, based on ICD-10 codes. Were ICD-9 codes ever used in Denmark or did the country transition from ICD-8 straight to ICD 10 codes? Please clarify this.

Our response:

We want to thank the reviewer for the thorough review and for the great comments. In the methods section we have mentioned that the diagnostic codes have been based on the international classification of diseases (ICD) 10th version system since 1994. Between 1978 (when the hospitalization registry was established) and 1993 the codes were based on the ICD 8th version. The ICD-9 codes were never implemented in Denmark.

Added sentence, methods section, p.5, line 16:

“The ICD-9 coding system was never implemented in Denmark.”

Do we have data on how many of the SSc patients are seen at specialized centers and how many are not? Validating just based on the highly skilled SSC centers would as expected correlate well with the DNPR. Why wasn't validation also done with patients not seen at these highly specialized centers?

Our response:
Thank you for your comment. In short, validation was also done in patients not seen at highly specialized centers. In brief, only one of the three departments was “highly specialized”, while the other two departments of rheumatology and dermatology were “ordinary” hospital departments. As Denmark is a small homogeneous country with a uniform referral process and hospital system, we consider the validation process reflecting the common referral process in Denmark.

Added sentence, validation section, p.6, l. 14-16:

“The chosen departments were chosen to represent one highly specialized and two ordinary referral centers for connective tissue diseases reflecting the common referral process in Denmark.”

What is the explanation for more renal, disease, diabetes, HTN and cancer in the late study period? Other than the fact that patients who started in the early stage are now older with more comorbidities, was there any change in access or utilization of health care during this time period in Denmark?

Our response:

Thank you for your comment. As the reviewer notes, we observed changes in the comorbidity patterns of patients with SSc across the 3 timespans from 1995-2001, 2002-2008 and 2009-2015. Renal disease, diabetes and hypertension are closely linked and have also been shown to having an increasing prevalence in the general population just as e.g. lung cancer. We are not sure about the exact reasons underlying our observations, but each timespan only included newly-diagnosed patients. Thus, people included in 2009-2015 were not the same patients as those included in the 1995-2001 cohort. We want to thank the reviewer for the opportunity to broaden the discussion a bit:

Added sentence, “Discussion, incidence” section, p.11, l.12-15:

“The etiology behind this may be multifactorial and in part due to an ageing population, more adverse lifestyle manifestations, earlier diagnosis, lower threshold for treatment, better access to screening programs and specialized care.”

What is the typical Danish SSc population? If this was previously described in other studies would make a quick reference to this so that the reader can understand what sort of SSc patient population is seen in Denmark.

Our response:
Thank you for your comment. The literature on SSc in Denmark is scarce. We have added a reference to a prior study depicting a previous cohort in Denmark.

Added sentence, background section, p.4, l. 18-19:

“The SSc population in Denmark has been scarcely depicted (10).”

What is the though of why between the 1st and the 2nd 5 years the cases when up by 47 but between the 2nd 5 years and the 3rd 5 years the cases when up by 174? Related to the new SSc classification scheme of 2013 or something else?

Our response:

We thank the reviewer for pointing out the relatively higher increase in incidence proportions during the latter timespan compared to the first. As the reviewer notes the classification criteria of SSc have changed over time. The criteria were altered in 1980, 1988, 2001, and 2013. Changes in classification criteria could translate into a more sensitive diagnosis with e.g. the use of serological markers and capillaroscopy, which may identify more patients with early or milder disease.

Added sentence, “Discussion, incidence” section, p.11, l.12-15:

“Our study found an overall substantially smaller increase over the time period than those prior estimates albeit an increased incidence proportion in the latter timespan from 2008-2015 compared to the first from 1995-2002. The latter could perhaps also be explained by e.g. increasing use of serological markers or capillaroscopy leading to a diagnosis of early and mild disease.”