PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Sex differences in the 1-year risk of dying following all-cause and cause-specific hospital admission after age 50 in comparison with a general and non-hospitalized population: A register-based cohort study of the Danish population.
AUTHORS	Höhn, Andreas; Larsen, Lisbeth; Schneider, Daniel Christoph; Jacobsen, Rune; Rau, Roland; Christensen, Kaare; Oksuzyan, Anna

VERSION 1 – REVIEW

REVIEWER	Daniel Avdic University of Duisburg-Essen, Germany None declared
REVIEW RETURNED	13-Feb-2018

GENERAL COMMENTS	This is a nice interesting study of the underlying causes for the observed gender difference in mortality. The authors focus on the 1-year mortality risk of death of men and women after a hospitalization and find substantial excess mortality of men, compared to a non-hospitalized sample and the general population. They conclude that one potential major cause for the gender difference in life expectancy might be due to higher survivability of women after an adverse health condition sets in. I have four main comments that the authors might want to address: (i.) Some results seem to me a bit obvious. The different population samples could be ordered as healthy (non-hospitalized), unhealthy (hospitalized), and a weighted average of the healthy and unhealthy population (randomsample from the entire population) so it is hardly a surprise that the hospitalized are more likely to die than the non-hospitalized. The authors might want to reduce the emphasis on these not too surprising findings and concentrate more on the objective of the study, the gender differences. (ii.) If the results by gender would be presented in relative terms, the interpretation would be quite different. The authors argue that it can lead to distorted conclusions when the baseline risk is very different. In my view, one could give the same argument for why the absolute difference should be interpreted with caution. I advise the authors to provide a more convicing discussion on the virtues of using relative vs. absolute measures of the sex difference. (iii.) The paper has one main result, that men are (absolutely) more likely to die one year after a hospital admission compared to women and that this risk is higher for an unhealthy population. Following this result is a speculative discussion on the potential mechanisms for this finding, reinforced by previous related findings.

	To me it seems like some of these mechanisms are possible to study in more detail with the data at hand. Why not study whether men have more co-morbidities when they are hospitalized (to evaluate the hypothesis than bad health behavior and late help-seeking). The findings provide an excellent way of studying the, in my opinion, much more interesting question of whether the excess male mortality is due to differences in health awareness (the morbidity-mortality paradox). (iv.) Can the results be put into a context on how much the "hospitalization" effect can explain of the overall gender difference in survival? As of now, the numbers are not related to anything so it is difficult to say if the effects are large or small. The anaylsis need not be very rigorous, but a back-of-the-envelope would certainly bring more context into the findings.

REVIEWER	Alexandre Stephens, PhD Northern NSW Local Health District and The University of Sydney (Adjunct), Australia
REVIEW RETURNED	19-Mar-2018

GENERAL COMMENTS	The authors present a study on the estimated absolute sex differences in 1-year mortality following hospitalisation with comparison to 1-year mortality of matched individuals (matched by age and sex) in the general population and the non-hospitalised population. The main findings of the study are that the absolute sex differentials in 1-year mortality are markedly higher following hospitalisation compared to the sex differences observed in the general population and the non-hospitalised population. While the results do appear to provide some insight into the higher mortality in males across three populations (hospitalised, general and non-hospitalised), it is somewhat unclear what this information can be used for. For example, can this data be used to monitor any initiatives or interventions aimed at reducing the male disadvantage in mortality (many such reasons were actually well described in the discussion)? There are also some other aspects of the manuscript that require clarification as follows: Abstract: The objectives, which is to compare whether the sex difference in mortality following hospitalisation is different to the differences observed in the general or non-hospitalised populations, is not consistent with the title. According to the title, it just seems like the paper is on estimating the sex-differences in mortality following hospitalisation (i.e. not comparing the estimates to sex-differences observed in general and non-hospitalised populations). In the conclusions, I'm not sure the use of "onset of adverse health" is accurate. Hospitalisation is just a manifestation of poor health to such an extent, or acute stage, that it prompts individuals to seek treatment in a hospital setting. This doesn't mean that the general or non-hospitalised population doesn't have adverse (or poor) health. Health is a continuous measure with certain "trigger" points prompting an individual to seek treatment or health care to a certain level (e.g. self-management, primary care, other health care, hospital care).

	Introduction: Paragraph 2, sentence 1 (“A number of previous studies…”): I find this to be a strange sentence. Wouldn't most admissions to hospital above age 50 be for adverse health? Is there any data showing the proportion of admissions after age 50 that are not related to some health problem? Paragraph 2: I struggle, somewhat, to see how paragraph 2 of the introduction relates to the study. I think it's fairly well understood and accepted, internationally, that the majority of hospital admissions, with perhaps the exception of injuries and poisonings, are due to an adverse health condition or disease. How does this paragraph relate to the aims of the study? Perhaps you need to better link the content (of paragraph 2) to the aims of the study – e.g. all this literature confirms that hospitalisation is a proxy/marker of poor health, and we estimated the sex-differences in 1-year mortality following hospitalisation as a way to estimate the sex-differences in mortality during illness/poor health. Paragraph 3, sentence 1: I'm not sure this language is correct. Hospitalisation for poor health can be seen as the manifestation of a health condition to such an acute degree that it requires some sort of treatment or intervention. I'm not sure this actually accurately defines the onset of poor/adverse health; some conditions develop over many months/years before requiring hospitalisation. What I think you are doing in this study is estimating 1-year risk of mortality following an acute episode of adverse health, not the onset of adverse health, and comparing estimates to those observed in the general and non-hospitalised populations. Materials and methods: Data: Does the 5% sample refer to a 5% sample of the CPR? Study population: I may have missed it, but why was age 79 used as the upper limit? This means that those born in 1898 can only contribute to mortality risk information at age 79; those born in 1899 can only potentially contribute to mortality risk at age 78 and 79.... thus individuals born in late 19th and early 20th centuries will be overrepresented in older age hospitalisations. Conversely, those born between 1898 and <1927 cannot contribute to mortality data at age 50 as all would be aged greater than 50 years at the earliest time that hospitalisation data was available in 1977. Is this likely to impact the results in any way? In the last sentence of paragraph 2 (of the study population section), you note that the same person may appear in different matching scenarios. What is the likely impact of the same person matching to multiple cases? Does this reduce the amount of (statistical) information? Does this impact the results/inferences? Is there any other way that "matches" could have been obtained without replacement to avoid people matching to multiple cases (e.g. increasing the pool of general and non-hospitalised individuals?)

	Statistical analysis: Near the middle of the first paragraph (line 22, page 8), you make reference to “right-censored”. Is this survival analysis terminology? How does this relate to the GAM analysis for binary outcomes? Were these individuals simply excluded from the analysis? Results: Lines 55 and 57, page 10: Are the estimates (30.2 and 37.2 per 1,000) direct estimates (as in calculated from the observed data as marginal estimates) or are they modelled? If modelled, what age do they refer to (or are conditional on)? Also, you clearly show that the absolute sex-differences in mortality are larger following hospitalisation. However, how do they compare in a relative sense? I.e. what is the relative risk of mortality in men (vs women) across the 3 different populations? I know this is not the main aim of the work but it might reveal some useful information.

REVIEWER	Dr. Christel Renoux McGill University, Canada None declared
REVIEW RETURNED	19-Mar-2018

GENERAL COMMENTS	The authors used a 5% random sample of the Danish population, using data from the National patients Register and the Central Population Registry. They examined absolute sex-differences in 1-year mortality in patients aged 50-70 following a first hospitalisation, as well in 2 reference populations (general and non-hospitalized population). The question is relevant to the description and understanding of sex-differences in mortality. Major comments -For each of the two comparison groups (general population) please clarify how many non-hospitalized patients were selected for each hospitalized patient. From the methods section, it seems that 1 patient with first hospital admission during the study period was matched on age, sex and calendar time to 1 patient from each reference group, and this process was repeated 100 times. However In table 2, some age groups in the matched reference groups contain slightly more patients that the cohort of patients with first hospital admission. Please clarify -The selection process of the second comparison group (non-hospitalised population) also needs a bit of clarification. It is written that individuals in this non-hospitalized population had not been hospitalised within a concordant year before and after the corresponding case was admitted to the hospital which I understand meaning that they were not hospitalized in the year before the date of matching with the corresponding case but could also not being hospitalized in the year following cohort entry. Please clarify. While it is correct to define these reference patients as not have been hospitalized in the year before cohort entry, the patients with a hospitalisation during follow-up in the year after cohort entry should have been censored, not excluded to avoid potential selection bias. It may not necessarily have a great impact on the results but it should at least be discussed. -In the results, some results of absolute sex differences are reported in the text with a few numbers and in a figure.

	As this is the main focus of the paper, it would be informative to report more results with 95% CI, by age bands for instance, in a table for the hospitalized population and the reference populations. -Results, page 10 lines 53-56, please give more details about the risk differences estimated leading to “an additional 30.2 male deaths per 1,000 individuals when compared with the general population, and in an additional 37.2 male deaths per 1,000 individuals in comparison with the non-hospitalized population”. -The authors chose to focus on the risk differences in 1-year mortality between men and women, and to not also examine risk ratios. In the discussion section, they explain that it ‘could have led to distorted conclusions’. There is nothing wrong with their choice to focus on risk differences because risk differences are very informative. However their justification for not also estimating risk ratios in the discussion section is questionable; Risk ratios convey a different type of information and are interpreted differently but they would not lead to wrong conclusions as suggested in the discussion if they are interpreted correctly. I suggest that the authors develop further on the advantages and relevant information conveyed by risk differences rather than implying the risk ratios would be problematic. - The overall conclusion stating ‘this study indicates a larger male disadvantage in mortality following hsopitalisation, pointing towards the fact that women’s advantage in mortality is due to better survival in the first year after the onset of adverse health condition’ is a bit confusing and not very informative. When the authors refer to women’s advantage in mortality, do they refer to mortality after hospitalisation? If this is the case, then the second part of the sentence is simply a repetition of the fact stated in the first part (a male disadvantage necessarily implies a women advantage and hospitalisation is simply replaced in the second part of the sentence by adverse health condition). If the authors refer to women’s advantage in overall mortality, then this is an overstatement because the women’ advantage in mortality may be, in part, related to better survival in the year following a hospitalisation as seen in the study where the risk differences were more pronounced, but the same was observed in the two comparison cohorts, although the absolute differences were smaller. I strongly suggest that the authors rephrase their conclusion. Also in the abstract, I would use only the term hospital admission or specify that an adverse health condition was measured as a hospital admission to avoid misinterpretation of the meaning of the term ‘adverse health condition’. Minor comments -In the abstract, the results section contains very few numbers. I suggest reporting some actual estimates of sex-differences in mortality (second sentence). -Study population, page 6 first paragraph: The authors write that they ‘selected all individuals.’ but they used a 5% random sample (Data section). Please specify. Idem in the abstract (section setting) -Page 4, the first 3 sentences in the summary of strengths and limitations do not point to some strengths and limitations of the study but they summarize objectives, findings and interpretation. Please modify. -Page 9, lines 49-56: the same idea seems to be repeated in the two sentences. Please check -Page 9, line 53: the risk for dying increased (not increases). Please correct -Page 10, line 11-12: the authors state they found the absolute increase in mortality with age to be smaller in the general population than in the hospitalized population.

	However, in the following sentences they provide risk estimates but not any estimate of the absolute increase. -Discussion, page 12 Although the authors examined patterns by cause-specific admission, these were very broad categories and this limitation should be given more emphasis along with the lack of any medical information on severity of diseases etc. discussed in the second paragraph page 12. -Table 2: the last row represents 'all other diseases' and is one of the most frequent group. What types of diseases are included in this group? Maybe a footnote with the most frequent diseases in this group could be informative for the readers. -Please check reference 12. It seems incomplete.

VERSION 1 – AUTHOR RESPONSE

III. Reviewer 1: Daniel Avdic

Comment R1.1: "The different population samples could be ordered as healthy (non-hospitalized), unhealthy (hospitalized), and a weighted average of the healthy and unhealthy population (random sample from the entire population) so it is hardly a surprise that the hospitalized are more likely to die than the non-hospitalized. The authors might want to reduce the emphasis on these not too surprising findings and concentrate more on the objective of the study, the gender differences."

 Response: Throughout the whole manuscript we focus explicitly on the raised research target: the investigation of the sex differentials in mortality in the three sub-populations. To lead the reader smoothly though our paper, we introduce the three populations and the observed differences in their mortality levels in a first step. In a second step, we elaborate on the sex differentials in the three populations. While we tried to give the first step as less space as possible -- i.e. results of this first step are not mentioned in the abstract -- we aimed for devoting as much space as possible to our findings regarding the sex differences in the three populations and their implications.

Comment R1.2: "If the results would be presented in relative terms, the interpretation would be quite different. (…) I advise the authors to provide a more convincing discussion on the virtues of using relative vs. absolute measures of the sex differences."

 Response: We revised the discussion of manuscript and included a) an indication that risk rations can be used as an alternative way to examine sex differences in mortality, b) a brief overview on findings when using a relative scale, and c) an elaboration on the reasons of the choice of the scale with additional references (see page 12). A figure showing results on a relative scale, was added to the submission as a supplementary figure (see supplementary figure 1-S).

Comment R1.3: "The paper has one main result, that men are (absolutely) more likely to die one year after a hospital admission compared to women and that this risk is higher for an unhealthy population. Following this result is a speculative discussion on the potential mechanisms for this finding, reinforced by previous related findings. To me it seems like some of these mechanisms are possible to study in more detail with the data at hand. Why not study whether men have more co-morbidities when they are hospitalized (to evaluate the hypothesis than bad health behavior and late help-seeking). The findings provide an excellent way of studying the, in my opinion, much more interesting question of whether the excess male mortality is due to differences in health awareness (the morbidity-mortality paradox)."

 Response: The present paper can be seen as a first exploratory approach of whether men experience excess mortality compared with women short-term after the first hospitalization. We agree

with the reviewer on the relevance of the new research question that can be raised based on our findings. However, we are not able to provide any further analysis in this paper due to the different focus of this question and the fact that investigating this phenomenon would require a different research design. It needs to be taken into account that register data offer only limited possibilities to operationalize the health status of individuals as the data were created for administrative reasons and not for research purposes. We state in the discussion section that, in principle, it might be possible to use certain information, such as the number of prescribed medications, the number of GP contacts or the lengths of stay in hospital as additional health indicators. However, the addition of more administrative information raises questions about the validity of these potential proxy indicators of individual's health status that are beyond the scope of this study. We agree with the reviewer that it is a limitation of our study that we do not investigate co-morbidities and health care use around hospital admission. We now point out this limitation in the article summary of the revised manuscript (see page 4) and in the discussion section (see page 12).

We have moreover started working on the question of why the sex differences increase after hospital admission. We hypothesize that the sex differences in treatment seeking behaviors, i.e. the tendency of men to postpone help seeking, to be important factors in explaining the male excess mortality after hospital admission.

Comment R1.4: "Can the results be put into a context on how much the "hospitalization" effect can explain of the overall gender difference in survival? As of now, the numbers are not related to anything so it is difficult to say if the effects are large or small. The analysis need not be very rigorous, but a back-of-the-envelope would certainly bring more context into the findings."

 Response: We assume that it is not hospitalization that is the factor that increases mortality, but that hospitalization indicates a worsening of the health status. Within this process – the manifestation of a health decline, which we measure as a hospital admission – we identified an increase of the absolute mortality disadvantage of men To our knowledge, there is no method to quantify this "hospitalization" effect in terms of estimating it's contribution to the widening of mortality differentials in general populations, which would have been applicable within the framework of this study. As it was shown by previous studies, the prevailing majority of the population is admitted to hospital at a certain point in life and as they age [1,2]. We have now revised the conclusion of the abstract and the discussion section in response to this comment (see page 3 and page 15).

IV. Reviewer 2: Alexandre Stephens

General Comments
Comment R2.1: "While the results do appear to provide some insight into the higher mortality in males across three populations (hospitalized, general and non- hospitalized), it is somewhat unclear what this information can be used for. For example, can this data be used to monitor any initiatives or interventions aimed at reducing the male disadvantage in mortality (many such reasons were actually well described in the discussion)?"

 Response: In the discussion section of our manuscript we elaborate on biological and behavioral mechanisms, including treatment-seeking behaviors, which may help to explain our findings. We fully agree with the reviewer that questions of how to reduce the larger mortality disadvantage of men after hospital admission are of significant importance. Our findings are important for future research aiming to identify mechanisms, which underlie the male excess mortality short-term after the first hospitalization. This evidence can further be used to prevent or delay hospital admissions and to design interventions which can reduce mortality after hospitalization, if – for example – future research suggests that male excess mortality is due to delayed treatment-seeking. Post-

hospitalization mortality can be one of the indicators to evaluate the effectiveness of these interventions. We agree with the reviewer on the importance of the raised issue.
In response, we have revised the abstract and the concluding section of the discussion to underline the overall importance of our findings (see page 3 and pages 11-15).

Abstract
Comment R2.2: “The objectives, which is to compare whether the sex difference in mortality following hospitalization is different to the differences observed in the general or non-hospitalized populations, is not consistent with the title. According to the title, it just seems like the paper is on estimating the sex-differences in mortality following hospitalization (i.e. not comparing the estimates to sex-differences observed in general and non-hospitalized populations).“

 Response: We agree with the reviewer that the title needs to reflect the comparison of the sex differences observed in the three population. We therefore decided to change the title of the paper (see page 1).

Comment R2.3: “In the conclusions, I’m not sure the use of “onset of adverse health” is accurate. Hospitalization is just a manifestation of poor health to such an extent, or acute stage, that prompts individuals to seek treatment in a hospital setting. This doesn't mean that the general or non-hospitalized population doesn't have adverse (or poor) health. Health is a continuous measure with certain "trigger" points prompting an individual to seek treatment or health to a certain level (e.g. self-management, primary care, other health care, hospital care). “

 Response: We fully agree with the reviewer that individuals of the general and the non-hospitalized population may have adverse health conditions or poor health as well. Nevertheless, their lower mortality suggests that the level of their health is generally better than those of the hospitalized population. We also agree with the reviewer that hospitalization is an indicator of the manifestation of poor health, which is closely related to some sort of trigger, which may range from need-driven help-seeking to the sudden onset of severe symptoms. To be more accurate we have elaborated on the concept of hospitalization in different parts of the manuscript, including the introduction and the discussion (pages 5-6 and pages 11-15).

Introduction
Comment R2.4: “Paragraph 2, sentence 1 (“A number of previous studies…”): I find this to be a strange sentence. Wouldn't most admissions to hospital above age 50 be for adverse health? Is there any data showing the proportion of admissions after age 50 that are not related to some health problem? “

 Response: We agree with reviewer that the prevailing majority of admissions after the age of 50 can be seen as the manifestation of an adverse health condition. We point out in the discussion that due to the strong gate-keeping function of GPs in Denmark most hospitalization after age 50 are likely to be due to adverse health. Despite this, it is possible that an inpatient admission occurs for preventive measures or (minor) accidents, implying that the underlying worsening of the health status is of short duration and low severity.

Unfortunately, it is difficult to provide a measure of severity as neither the duration of stay nor the cause of admission are unambiguous enough to rank causes of admission with respect to their severity. We give a descriptive overview on the causes of admission to hospital in table 1.

Comment R2.5: “I struggle, somewhat, to see how paragraph 2 of the introduction relates to the study. I think it's fairly well understood and accepted, internationally, that the majority of hospital admissions, with perhaps the exception of injuries and poisonings, are due to an adverse health

condition or disease. How does this paragraph relate to the aims of the study? Perhaps you need to better link the content (of paragraph 2) to the aims of the study
– e.g. all this literature confirms that hospitalization is a proxy/marker of poor health, and we estimated the sex-differences in 1-year mortality following hospitalization as a way to estimate the sex-differences in mortality during illness/poor health. “

 Response: We previously submitted the manuscript to The BMJ and the reviewers asked us to prove our assumption that an admission to hospital may serve as an indicator of health at an early point in the study. In the second paragraph of the introduction we therefore claim that a hospital admission can be used as an indicator of health and continue with a summary of research findings to prove that our assumption holds. In the first sentence of the next paragraph we immediately come back to our initial aim by arguing that we use an admission to hospital as a proxy for bad health and that we investigate whether women’s advantage in mortality changes after the manifestation of bad health, which we measured as a hospital admission.

Comment R2.6: “Paragraph 3, sentence 1: I'm not sure this language is correct. Hospitalization for poor health can be seen as the manifestation of a health condition to such an acute degree that it requires some sort of treatment or intervention. I'm not sure this actually accurately defines the onset of poor/adverse health; some conditions develop over many months/years before requiring hospitalization. What I think you are doing in this study is estimating 1-year risk of mortality following an acute episode of adverse health, not the onset of adverse health, and comparing estimates to those observed in the general and non-hospitalized populations.”

 Response: We agree with the reviewer that the language at this point is not precise enough. An admission to hospital may represent the onset of a decline of the health status, i.e. in cases of accidents or sudden cardiovascular events. However, hospitalization might also reflect an acute episode of a health decline that might have started long before the date of admission. We therefore reworked the phrasing in the introduction and the discussion to be more precise (pages 3-4 and pages 11-15).

Materials and Methods: Data
Comment R2.7: “Does the 5% sample refer to a 5% sample of the CPR?”

 Response: Yes, we work with a 5% random sample of the population alive and residing in Denmark after 1968, which we were able to follow through a variety of registers, such as the National Patient Register (NPR). The random selection of the unique personal identification numbers (CPR-numbers), which is the basis for the extraction of information from the other registers, was carried out by Statistics Denmark. The identification of the study population is based on this 5% random sample.

Methods and Materials: Study Population
Comment R2.8: “I may have missed it, but why was age 79 used as the upper limit? This means that those born in 1898 can only contribute to mortality risk information at age 79; those born in 1899 can only potentially contribute to mortality risk at age 78 and 79.... thus individuals born in late 19th and early 20th centuries will be overrepresented in older age hospitalizations. Conversely, those born between 1898 and <1927 cannot contribute to mortality data at age 50 as all would be aged greater than 50 years at the earliest time that hospitalization data was available in 1977. Is this likely to impact the results in any way? “

 Response: Age 79 was used as the upper limit because the number of cases and events would have been too small to have reliable estimates for older ages using 1-year age groups and separating by causes of admission to hospital due to fluctuating patterns of mortality among the three

populations. In this regard we found that an additional open-ended age group “80+” would have not solved this issue.
The reviewer is right about the fact that only certain cohorts can contribute to certain age groups and the example he gives is correct. Due to the cohort study design we are unfortunately not able to estimate the impact of this issue. However, we discuss these limitations in more detail in the revised version of the manuscript, specifically in relation to the Danish female smoking phenomenon – an example of a national cohort effect.
It needs to be taken into account that, due to the matching criteria, the structure of the investigated populations with respect to age and cohort are identical. As a result, period, age and cohort effects are therefore very likely to have an impact on all populations. We now specify this issue in the discussion section of the revised manuscript (see pages 13).

Comment R2.9: “In the last sentence of paragraph 2 (of the study population section), you note that the same person may appear in different matching scenarios. What is the likely impact of the same person matching to multiple cases? Does this reduce the amount of (statistical) information? Does this impact the results/inferences? Is there any other way that "matches" could have been obtained without replacement to avoid people matching to multiple cases (e.g. increasing the pool of general and non-hospitalized individuals?)”

 Response: Within the observed period, a large proportion of the studied cohort were admitted to a hospital. As cases and matches should be drawn from the same source population [3], the number of potential matches per case is too low when using matching without replacement. Unfortunately, using available data there was no way to increase the pool of potential matches, and we decided not to draw a sample from the hospitalized population to ensure the highest possible number of cases and events. In a first step, we checked the results for a matching scenario without replacement. Because a substantial number of cases remained without a match, we decided to use matching with replacement. It is very likely that this decision corrects the previously observed bias emerging from the matching without replacement, because controls that look similar to many treated individuals in terms of their demographic characteristics can be used multiple times [4].
The feature that a person might appear in different matching scenarios is simply the result that the matching with replacement was carried out 100 times. We chose this strategy to bypass the need to choose a single matching scenario, leading to an increase of the robustness of the matching results. We do not assume that this decision reduces the amount of (statistical) information in this case. We added extended the section on the study population to give more insights into our decision to use a matching with replacement and how this influenced our results (see page 7).

Methods and Materials: Statistical Analysis
Comment R2.10: “Near the middle of the first paragraph (line 22, page 8), you make reference to “right-censored”. Is this survival analysis terminology? How does this relate to the GAM analysis for binary outcomes? Were these individuals simply excluded from the analysis?”

 Response: In a preparatory step, a Kaplan-Meier survival model, we used right-censoring to account for the fact that not all individuals experience the event (in our case: mortality) within the first year after the survival time has started, but contribute to the population at risk until they are censored no matter whether they experienced an event or not within the follow-up period [5]. These individuals were not simply excluded from all following analyses as this would have led to a serious bias due to the exclusion of all survivors.
We agree with the reviewer that a more precise description was needed in this phrase, because the fact that their survival time is censored is not of importance for the estimation of the risk in the model we used. In the model – and following the definition of a “risk” (or: “probability) – these individuals contribute to the population at risk (they were alive at the beginning), but they had no event (they did

not die within the period they were followed-up). We therefore specified this phrase in the section on the statistical analysis (see page 8).

Results

Comment R2.11: “Lines 55 and 57, page 10: Are the estimates (30.2 and 37.2 per 1,000) direct estimates (as in calculated from the observed data as marginal estimates) or are they modelled? If modelled, what age do they refer to (or are conditional on)? Also, you clearly show that the absolute sex-differences in mortality are larger following hospitalization. However, how do they compare in a relative sense? I.e. what is the relative risk of mortality in men (vs women) across the 3 different populations? I know this is not the main aim of the work but it might reveal some useful information.”

 Response: The excess male mortality was not estimated directly. It was calculated based on the estimated (modelled) mortality trajectories as: “(Risk_Men – Risk_Women) * 1,000”. To ensure the most intuitive interpretation for the reader and according to what is most common in demography and epidemiology, we refer to the risk of dying as an unconditional measure, which value does not depend directly on surviving previous ages. This risk can be interpreted as the probability to die at age x taking into account only those who survived to the beginning of age x (or in other words: the relative frequency (“q(x)”) of those who died at age x (“d(x)”) in relation to those who were alive at the beginning of age x (“l(x)”), while this implies that only those individuals are at risk, who survived to the beginning of age x.

 “q(x) = d(x) : l(x)”

The number of the additional male deaths after admission to hospital in comparison with the number of excess male deaths in the two reference populations (30.21 in comparison with the general population and 37.16 in comparison with the non-hospitalized population) were gained by comparing the average (average within the age range 50—79) number of excess male deaths in the three populations (43.75 in the hospitalized population, 13.53 in the general population and 6.59 in the non-hospitalized population). We think that it is more intuitive and easier to understand for the reader if we would have had presented the average number of excess male deaths in the three populations instead of a relational number. We therefore revised this paragraph in the results section and the abstract (see page 3 and pages 10—11).

It is not wrong to use risk ratios for our purpose to compare the mortality differentials among the three populations since both measures, the risk difference and the risk ratio, can be used to compare mortality differentials. We revised the discussion and included a) a brief overview on findings when using a relative scale b) an indication that it would not have been generally wrong to use relative differences, and c) an elaboration on the reasons of the choice of the scale with additional references (see page 12). A figure showing results on a relative scale, was added to the submission as a supplementary figure (see supplementary figure 1-S).

V. Reviewer 3: Christel Renoux

Major Comments

Comment R3.1: “For each of the two comparison groups (general population) please clarify how many non-hospitalized patients were selected for each hospitalized patient. From the methods section, it seems that 1 patient with first hospital admission during the study period was matched on age, sex and calendar time to 1 patient from each reference group, and this process was repeated 100 times. However In table 2, some age groups in the matched reference groups contain slightly more patients that the cohort of patients with first hospital admission. Please clarify “

 Response: Yes, each patient with first hospital admission during the study period was matched on age, sex and calendar time to one patient from each reference group. This process was repeated 100 times. We agree that the description of this process in the manuscript required more elaboration and revised the section on the study population (see page 7).

The slightly different numbers in table 2 emerge from the fact that the age of matches can deviate from the age of admitted people by + / - 30 days.

Comment R3.2: “The selection process of the second comparison group (non-hospitalized population) also needs a bit of clarification. It is written that individuals in this non-hospitalized population had not been hospitalized within a concordant year before and after the corresponding case was admitted to the hospital which I understand meaning that they were not hospitalized in the year before the date of matching with the corresponding case but could also not being hospitalized in the year following cohort entry. Please clarify. While it is correct to define these reference patients as not have been hospitalized in the year before cohort entry, the patients with a hospitalization during follow-up in the year after cohort entry should have been censored, not excluded to avoid potential selection bias. It may not necessarily have a great impact on the results but it should at least be discussed. “

 Response: Yes, the reviewer is right: individuals of the second comparison group (non-hospitalized population) had to fulfill the criteria that they were not admitted to hospital in the year before and after the exact date the corresponding case was hospitalized. Each hospitalized individual is assigned to one match from a specifically tailored pool of potential matches, or in other words: each hospitalized individual gets one match assigned as a result of an individual-level and individual-specific selection process. For example: person X who does not serve as potential match for hospitalized individual A is excluded for the selection process for A. However, this individual might serve as a match for hospitalized individuals C and B -- if case X matches their criteria. We have elaborated on the matching process in the section on the study population. We do not think that censoring applies in this case since,

Comment R3.3: ”In the results, some results of absolute sex differences are reported in the text with a few numbers and in a figure. As this is the main focus of the paper, it would be informative to report more results with 95% CI, by age bands for instance, in a table for the hospitalized population and the reference populations.”

 Response: To our knowledge there is no valid approach to give confidence intervals when using the measure of excess male mortality, which we calculated based on the absolute risk differences and as: “(Risk_Men – Risk_Women) * 1,000”. The risk differences were calculated based on the estimated mortality trajectories and by single years of age, which makes it questionable whether a grouping would be more informative. Since the model is a non-linear GAM and without coefficients in a classical sense, we decided that plotting results rather than tabulating them is the most intuitive way to catch the reader’s attention. To get the chance to provide as much information and as succinct as possible, we decided to present results graphically in two figures, and to provide readers with the most relevant and interesting general information in the main text.

Comment R3.4: “Results, page 10 lines 53-56, please give more details about the risk differences estimated leading to ‘an additional 30.2 male deaths per 1,000 individuals when compared with the general population, and in an additional 37.2 male deaths per 1,000 individuals in comparison with the non-hospitalized population.’”

 Response: The risk differences, presented in figure 2, were calculated based on the modelled mortality trajectories, which we present in figure 1. All findings described in the manuscript refer to the numbers presented in the two figures. The number of additional male deaths after admission to hospital in comparison with the number of excess male deaths in the two reference populations (30.21 in comparison with the general population and 37.16 in comparison with the non-hospitalized population) were gained by comparing the average (average within the age range 50—79) number of excess male deaths in the three populations (43.75 in the hospitalized population, 13.53 in the general population and 6.59 in the non-hospitalized population). We think that it is more intuitive and

easier to understand the average number of excess male deaths in the three populations instead of a relational number. We therefore revised this paragraph in the results section and the abstract (see page 3 and pages 10—11). See also response to comment R2.11 for more information.
Comment R3.5: "The authors chose to focus on the risk differences in 1-year mortality between men and women, and to not also examine risk ratios. In the discussion section, they explain that it 'could have led to distorted conclusions'. There is nothing wrong with their choice to focus on risk differences because risk differences are very informative. However their justification for not also estimating risk ratios in the discussion section is questionable; Risk ratios convey a different type of information and are interpreted differently but they would not lead to wrong conclusions as suggested in the discussion if they are interpreted correctly. I suggest that the authors develop further on the advantages and relevant information conveyed by risk differences rather than implying the risk ratios would be problematic."

 Response: We agree with the reviewer that it would not have been wrong to use risk ratios for our purpose to compare the mortality differentials among the three populations. Both measures, the risk difference and the risk ratio, can be used to compare mortality differentials. We agree with the reviewer that the discussion of the manuscript will benefit from an elaboration on this issue in general. We therefore revised the discussion and included a) a brief overview on findings when using a relative scale b) an indication that it would not have been generally wrong to use relative differences, and c) an elaboration on the reasons of the choice of the scale and added additional references (see page 12). A figure showing results on a relative scale, was added to the submission as a supplementary figure (see supplementary figure 1-S).

Comment R3.6: "The overall conclusion stating 'this study indicates a larger male disadvantage in mortality following hospitalization, pointing towards the fact that women's advantage in mortality is due to better survival in the first year after the onset of adverse health condition' is a bit confusing and not very informative. When the authors refer to women's advantage in mortality, do they refer to mortality after hospitalization? If this is the case, then the second part of the sentence is simply a repetition of the fact stated in the first part (a male disadvantage necessarily implies a women advantage and hospitalization is simply replaced in the second part of the sentence by adverse health condition). If the authors refer to women's advantage in overall mortality, then this is an overstatement because the women' advantage in mortality may be, in part, related to better survival in the year following a hospitalization as seen in the study where the risk differences were more pronounced, but the same was observed in the two comparison cohorts, although the absolute differences were smaller. I strongly suggest that the authors rephrase their conclusion. Also in the abstract, I would use only the term hospital admission or specify that an adverse health condition was measured as a hospital admission to avoid misinterpretation of the meaning of the term 'adverse health condition'."

 Response: We rephrased the conclusion of the abstract and the manuscript and believe this is now a more precise on the main interpretation and implication of our findings (see page 3 and 15). We agree with the reviewer that the term 'adverse health condition' in the abstract is too vague and we revised this issue throughout the whole manuscript.

Minor Comments
Comment R3.7: "In the abstract, the results section contains very few numbers. I suggest reporting some actual estimates of sex-differences in mortality (second sentence). "

 Response: Due to the word limitation of the abstracts for The BMJ open (300 words), we decided to present results for all-cause hospital admission only and to briefly describe the patterns we observed for cause-specific admissions.

Comment R3.8: “Page 4, the first 3 sentences in the summary of strengths and limitations do not point to some strengths and limitations of the study but they summarize objectives, findings and interpretation. Please modify.“

 Response: We revised the ‘Strengths and Limitations’ section of the manuscript by relating this section specifically to the methods of the study (see page 4).

Comment R3.9: “Study population, page 6 first paragraph: The authors write that they ‘selected all individuals.’ but they used a 5% random sample (Data section). Please specify.”

 Response: We work with a 5% random sample of the population alive and residing in Denmark after 1968, which we were able to follow through a range of registers. The identification of the study population is based on this 5% random sample. We specify this in the very beginning of the section on the study population (see page 6). See also comment R2.7.

Comment R3.10: “Page 9, lines 49-56: the same idea seems to be repeated in the two sentences. Please check.”

 Response: While the first sentence states our finding that we observed an excess mortality of men with respect to all populations and causes of admission, the second sentence is on the finding that mortality increases with age for all sub-groups. We did not change the sentences as they focus on two different findings.

Comment R3.11: “Page 9, line 53: the risk for dying increased (not increases). Please correct.”

 Response: We corrected this typo in the revised version (see page 9).

Comment R3.12: “Page 10, line 11-12: the authors state they found the absolute increase in mortality with age to be smaller in the general population than in the hospitalized population. However, in the following sentences they provide risk estimates but not any estimate of the absolute increase.”

 Response: We kept the description of the mortality patterns in the three populations as short and concise as possible, since the focus of the paper is on the comparison of the sex differences and other reviewers asked us not to put too much emphasize on a description of the mortality trajectories in the three populations (see i.e. R1.1). To ensure also a good readability of this section, which includes a lot of numbers and parenthesis, we therefore decided that it is a good compromise to give the levels of the risk of dying at age 50 and 79 with 95% confidence intervals in all populations and not to provide any further numbers on the absolute increase.

Comment R3.13: “Discussion, page 12 : Although the authors examined patterns by cause-specific admission, these were very broad categories and this limitation should be given more emphasis along with the lack of any medical information on severity of diseases etc. discussed in the second paragraph page 12.”

 Response: Due to the long observation period and the change in the classification system (1977-1993: ICD-8, 1994-2011: ICD-10) we decided to use broad categories to classify the causes of admission. We agree with the reviewer that using broad categories is clearly a limitation of this study. In the study we use the ICD main chapters to minimize misspecification errors due to changes in ICD codes over observation period. We agree with the reviewer that the lack of medical information, i.e. on the severity of the underlying condition leading to the admission, is a limitation of our data (see third paragraph on page 12 and page 4).

Comment R3.14: “Table 2: the last row represents ‘all other diseases’ and is one of the most frequent group. What types of diseases are included in this group? Maybe a footnote with the most frequent diseases in this group could be informative for the readers.”

 Response: The majority of causes among the group of all other diseases are symptoms, signs and abnormal clinical and laboratory findings not elsewhere classified (ICD-10: R00-R99, ICD-8: 780-796), which accounted for 57.57% among men and 58.42% among women. The second largest group among the group of all other diseases are factors influencing health status and contact with health services (ICD-10: Z00-Z99), which accounted for 37.47% among men and for 36.99% among women. Together these two groups account for approximately 95% of all other diseases. The revised manuscript contains a footnote with on overview on the most frequent causes among this category (see page 25).

Comment R3.15: “Please check reference 12. It seems incomplete.

 Response: We revised reference 12 by adding the missing information on the working paper (see page 12).

VERSION 2 – REVIEW

REVIEWER	Daniel Avdic University of Duisburg-Essen, Germany None declared
REVIEW RETURNED	22-May-2018

GENERAL COMMENTS	My concerns have been satisfactorily addressed and I have no further comments on the manuscript.

REVIEWER	Alexandre Stephens Northern NSW Local Health District, Australia, and School of Public Health, The University of Sydney, Australia None declared
REVIEW RETURNED	10-May-2018

GENERAL COMMENTS	Thank you for thoroughly revising the manuscript. The authors' responses and revisions made to the manuscript have addressed all of my comments.

REVIEWER	Christel Renoux McGill University, Canada None declared
REVIEW RETURNED	19-May-2018

GENERAL COMMENTS	The authors have answered and clarified all the points raised and modified their manuscript accordingly.