BMJ Open

# Sex differences in the 1-year risk of dying following all-cause and cause-specific hospital admission after age 50. A register-based cohort study of the Danish population.



| | |
|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2018-021813 |
| Article Type: | Research |
| Date Submitted by the Author: | 23-Jan-2018 |
| Complete List of Authors: | Höhn, Andreas; Max-Planck-Institut fur Demografische Forschung, Gender Gaps in Health and Survival ; Syddansk Universitet Det Sundhedsvidenskabelige Fakultet, Department of Epidemiology, Biostatistics and Biodemography<br>Larsen, Lisbeth; Syddansk Universitet Det Sundhedsvidenskabelige Fakultet, Department of Epidemiology, Biostatistics and Biodemography<br>Schneider, Daniel Christoph; Max-Planck-Institut fur Demografische Forschung, Laboratory of Population Health<br>Jacobsen, Rune; Syddansk Universitet Det Sundhedsvidenskabelige Fakultet, Department of Epidemiology, Biostatistics and Biodemography; Max-Planck Odense Center on the Biodemography of Aging<br>Rau, Roland; Max Planck Institute for Demographic Research, Mathematical and Actuarial Demography ; Universitat Rostock Wirtschafts und Sozialwissenschaftliche Fakultat<br>Christensen, Kaare; University of Southern Denmark, Department of Epidemiology, Biostatistics and Biodemography; Max-Planck Odense Center on the Biodemography of Aging<br>Oksuzyan, Anna; Max-Planck-Institut fur Demografische Forschung, Gender Gaps in Health and Survival |
| Keywords: | EPIDEMIOLOGY, SEX DIFFERENCES, HOSPITALIZATION, MORTALITY |
| | |

# Sex differences in the 1-year risk of dying following all-cause and cause-specific hospital admission after age 50. A register-based cohort study of the Danish population.

**Authors:**

[1,2] **Andreas Höhn***, PhD Student

[2] **Lisbeth Aagaard Larsen**, Research Scientist

[1] **Daniel Christoph Schneider**, Statistical Programmer and Research Scientist

[2,3] **Rune Lindahl-Jacobsen**, Associate Professor

[1,4] **Roland Rau**, Professor

[2,3,5] **Kaare Christensen**, Professor

[1] **Anna Oksuzyan**, Head of Independent Research Group

**Affiliations:**

[1] Max Planck Institute for Demographic Research Konrad-Zuse-Straße 1 18057 Rostock, Germany

[2] Department of Epidemiology, Biostatistics and Biodemography University of Southern Denmark J.B. Winsløws Vej 9B 5000 Odense C, Denmark

[3] Max-Planck Odense Center on the Biodemography of Aging University of Southern Denmark J.B. Winsløws Vej 9B 5000 Odense C, Denmark

[4] Department of Sociology & Demography University of Rostock Ulmenstraße 69 18057 Rostock, Germany

[5] Danish Aging Research Center J.B. Winsløws Vej 9B 5000 Odense C, Denmark

* Correspondence to:
Andreas Höhn
Max Planck Institute for Demographic Research
Konrad-Zuse-Straße 1
18057 Rostock, Germany
Phone: +49 (0)381 2081-177
Email: hoehn@demogr.mpg.de

# Abstract


## Objectives

We examine the mortality of men and women within the first year after all-cause and cause-specific hospital admission to investigate whether the sex differences in mortality after hospitalization are higher than in the corresponding general and non-hospitalized population.

## Design

This is a population-based, longitudinal study with nationwide coverage. The study population was identified by linking the National Patient Register with the Central Population Register using a 5% random sample of the Danish population.

## Setting

The population born between 1898 and 1961, who was alive and residing in Denmark after 1977, was followed up between 1977 and 2012 with respect to hospital admissions and mortality while aged 50 – 79.

## Primary Outcome Measures

The absolute sex differences in the 1-year risk of dying after all-cause and cause-specific hospital admission. The hospitalized population sex differentials were then compared with the sex differences for a general and a non-hospitalized population, randomly matched by age, sex and hospitalization status.

## Results

The risk of dying was consistently higher for hospitalized men and women. At all ages, the absolute sex differences in mortality were largest in the hospitalized population, were smaller in the general population, and were smallest in the non-hospitalized population. This pattern was consistent across all-cause admissions, as well as with respect to admissions for neoplasms, circulatory diseases and respiratory diseases. For all-cause hospital admissions, the larger absolute sex differences in the 1-year risk following hospital admission resulted in an additional 30.2 male deaths per 1,000 individuals compared with the general population, and an additional 37.2 male deaths per 1,000 individuals compared with the non-hospitalized population.

## Conclusions

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 conditions.

# Article Summary

## Strengths and limitations of this study:

- We examine the mortality of men and women after all-cause and cause-specific hospitalization and investigate whether the absolute sex differences in mortality increases following hospital admission.
- Our findings show an increasing male disadvantage after admission to hospital, suggesting that women's advantage in mortality is due to better survival in the first year after the onset of adverse health conditions.
- We assume a higher severity of diseases in men and different attitudes towards illness between men and women to be among the likely explanations of our results.
- This study utilizes high-quality Danish register data with nationwide coverage that leaves little room for selection bias due to non-response or loss to follow-up.

# 1 Background

Empirical studies have consistently reported that women have a mortality advantage at all ages, starting at infancy and extending over the entire life course.[1] Women have lower rates of mortality than men for nearly all causes of death, including most cancers,[2-4] respiratory diseases,[5;6] and accidents.[7] Moreover, the female advantage in mortality persists even after stressful events during the life course, such as bereavement[8;9] or famines and epidemics.[10] While the relative sex differences in mortality peak at around age 25 and tend to become smaller with age,[11] the absolute sex differences grow almost exponentially between ages 40 and 90, as general levels of mortality increase.[12] Thus, in recent decades, the largest share of the sex differences in life expectancy has been attributed to mortality differentials after the age of 50[13] – when individuals start to accumulate disease and disabilities, and the incidence of most adverse health conditions increases.[14]

A number of previous studies have argued that a hospital admission may serve as a quasi-objective indicator of adverse health conditions, since it marks the onset of an acute worsening of the health status that requires extensive medical interventions.[15-17] The use of hospitalization as a proxy for health is also supported by previous research findings suggesting that adults of all ages who rate their health and their quality of life as poor are at an increased risk of hospital admission.[18-21] Furthermore, the well-established associations between major risk factors and the increased risk of dying from certain causes, such as smoking and lung cancer; have also been found for the relationship between risk factors and cause-specific reasons of admission.[22-24] Empirical findings have demonstrated that smoking,[22] hazardous drinking,[25] being overweight,[26] having high cholesterol levels,[27] and a lack of physical activity[28] are related to an increased risk of hospital admission. The presence of multiple risk factors has been found to be especially strongly associated with a high risk of admission.[29]

Although it has been well established that women have a mortality advantage across all ages and all causes of death, it is not yet known whether this advantage changes after the onset of an adverse health condition, measured as a hospital admission. To answer this question, we estimate the absolute sex differences in the 1-year risk of dying after all-cause and

cause-specific hospital admission as an inpatient. We compare these sex differentials with the corresponding differences we would have observed in the general and the non-hospitalized population.

## 2 Methods and materials

### Data

This study uses a 5% random sample of the Danish population. Using the unique personal identification number that is assigned to all individuals residing in Denmark,[30] we linked records from the National Patient Register (NPR) with data of the Central Population Registry (CPR). The CPR, which covers the entire population alive and residing in Denmark since 1968 and in Greenland since 1972, contains information on each resident's vital status, sex, and place and date of birth.[31] The NPR is a population-based register with nationwide coverage that contains information on all admissions to hospitals since 1977.[32] As reports to the administration are compulsory, the NPR data have high levels of completeness and reliability, making these data an excellent tool for research.[33] Whereas data on hospitalizations are available for the period 1977–2011, the vital status of individuals was traceable up to the year 2013. In the NPR, diagnoses were classified in accordance with the ICD-8 until 1993 and the ICD-10 starting in 1994.[34] We classified the causes of admission to hospital according to the main chapters and using broad groups to reduce the potential bias, which may emerge from combining two systems of classification. An overview of the coding is given in supplementary table 1 – S.

### Study population

We identified all individuals who were born between January 1, 1898, and December 31, 1961, who were alive, and who resided in Denmark after 1968 (n = 214,613). Of those, we then selected all individuals who survived up to age 50 and resided in Denmark after January 1, 1977 (n = 198,580). Out of all remaining individuals, 64.3% (n = 127,642) of the sample

had been admitted to the hospital at least once between January 1, 1977, and December 31, 2011. Hospitalization was defined as the first time an individual was admitted to the hospital while aged 50 – 79 as an inpatient, for at least one night, and for any reason between the years 1977 and 2011. Subsequent admissions and admissions that occurred among these individuals before the age of 50, after age 79, and before 1977 – for the same or other causes – were not taken into account.

To examine whether the sex differences in mortality increase following an admission to hospital, we compared the sex differentials after hospitalization with the corresponding differences measure among two healthier references. For this purpose two matched populations aged 50 – 79 were selected randomly from the study sample: one group to represent the general population, and the other group to represent the non-hospitalized population. The matched individuals, forming the two reference populations had to be the same age (+/- 30 days), the same sex, and alive on the day the corresponding case was hospitalized. Whereas the individuals representing the general population were selected irrespective of hospitalization status, the individuals representing the non-hospitalized population had not been hospitalized within a concordant year before and after the corresponding case was admitted to hospital, irrespective of the case's cause of admission. The matching with replacement was carried out 100 times to increase the robustness of the matching results, and to bypass the need to choose a single matching scenario. Consequently, the same person may appear in different matching scenarios.

## Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

## Statistical analysis

While the data preparation and the merging of registries was carried out with STATA (Version 15), all statistical analyses were performed in R (Version 3.3.2). The survival time of the hospitalized individuals starts immediately with the day of the first all-cause hospital admission after age 50, which was recorded in the registers. No lag-time or wash-out period was used for the purpose to capture the immediate impact on the risk of dying, implying that deaths during the index hospital stay are included in the mortality calculations. Analogously, the process time of the individuals of both reference populations starts on the day the corresponding case was hospitalized. The survival status of all individuals was followed up within 1 year. If a person was alive by the end of the follow-up period or had migrated, the survival time was right-censored. We used a generalized additive (GAM) for binary data with a logit link. Unlike in generalized linear models (GLM), the linear predictor in the GAM is replaced by a sum of smoothing functions.[35;36] We used penalized B-splines – so called P-splines – as basis functions in the regression to smooth over age.[37;38] We modeled the age-specific 1-year risk of dying separately for the men and the women of each population by single years of age. For the hospitalized population, we further estimated separate models by cause of admission to hospital to investigate whether the female advantage in survival following hospitalization varies across different causes of admission.

# 3 Results

Of the 127,642 individuals who were hospitalized, 49.9% (n = 63,649) were men and 50.1% (n = 63,993) were women. The mean age at hospitalization was slightly lower among the men (61.7; SD = 8.5) than among the women (62.0; SD = 9.0). An overview on the causes of admission to hospital is provided in table 1. We found the distribution of causes of hospital admission to be different in men than in women. In comparison with men, women were more likely to be hospitalized due to neoplasms, diseases of the blood and blood-forming organs, endocrine, nutritional and metabolic diseases, diseases of the eye and adnexa, musculosceletal disorders, and diseases of the genitourinary system. In contrast to this, more

men were admitted due to ischaemic heart diseases, cerebrovascular diseases and other circulatory diseases, as well as due to respiratory and digestive diseases than women. We found only small sex differences in the distribution with respect to infectious and parasitic diseases, mental and behavioral disorders, diseases of the nervous system, diseases of the ear and mastoid process, diseases of the skin and subcutaneous tissue as well as injuries, poisonings and accidents.

[Table 1]

An overview of the three populations is given in table 2. While the data for the hospitalized population represent the exact number of observed cases, the numbers for the general and the non-hospitalized population refer to the mean of 100 matched samples. Because the matched individuals were of the same age and the same sex as the corresponding cases, the three populations had identical age structures (mean = 61.9, SD = 8.9) and sex ratios. We found that the risk of dying was highest among the men and the women of the hospitalized population at the level of 9.42% (95% CI 9.26% to 9.58%). The risk of dying was substantially lower and at the level of 1.98% (95% CI 1.90% to 2.05%) in the corresponding general population, and lowest among the non-hospitalized population at a level of 0.80% (95% CI 0.75% to 0.85%), respectively. As it is shown in table 2, men had consistently higher mortality than women in all of the three populations. In all populations, we found the mortality of both sexes to increase consistently with age.

[Table 2]

We further estimated the risk of dying and the trajectory of this risk by single years of age for men and women in each population and corresponding 95% confidence intervals using a non-parametric GAM. As shown in figure 1, we found that men had consistently higher mortality than their female counterparts in each population, at all ages, and for admissions due to all causes, neoplasms, circulatory and respiratory diseases. The risk of dying increases consistently with age among the men and the women of each population, and with respect to all causes of admission to hospital At the age of 50, the 1-year risk of dying for all-cause

admissions in the hospitalized population was 5.17% (95% CI 4.60% to 5.73%) for men and 2.97% (95% CI 2.66% to 3.29%) for women. With age, the risk of dying increased and reached a level of 26.61% (95% CI 24.08% to 29.13%) and 19.12% (95% CI 17.65% to 20.60%) among 79-year old men and women of the hospitalized population, respectively. We found the absolute increase in mortality with age to be smaller in the general population than in the hospitalized population. Starting with levels of 0.47% (95% CI 0.46% to 0.49%) among men and 0.39% (95% CI 0.38% to 0.41%) among women at age 50, the risk of dying was 9.30% (95% CI 9.12% to 9.47%) and 5.61% (95% CI 5.49% to 5.73%) at the age 79 in the general population, respectively. We found the non-hospitalized population to have the lowest absolute increase in mortality with age: at age 50 the risk of dying was 0.25% (95% CI 0.24% to 0.26%) for men and 0.12% (95% CI 0.11% to 0.13%) for women, and it increased to 4.54% (95% CI 4.42% to 4.67%) and 2.52% (95% CI 2.43% to 2.60%) at age 79, respectively.

[Figure 1]

In a next, step we calculated the absolute sex differences in the 1-year risk of dying and the the male excess mortality per 1,000 persons. Figure 2 shows the age trajectory of the male excess mortality in each of the three populations and by cause of admission to hospital. At all ages and regarding admissions for all causes, neoplasms, circulatory and respiratory diseases,the absolute sex differences were largest in the hospitalized population, were smaller in the general population, and were smallest in the non-hospitalized population. At age 50 and for all-cause admissions, the sex differences in survival resulted in 22.0 excess male deaths per 1,000 individuals in the hospitalized population, while there were 0.8 excess male deaths in the general population, and 1.3 excess male deaths in the non-hospitalized population. Within the observed age range the excess male mortality increased almost steadily among all three populations, resulting at levels of 42.0, 9.8 and 4.8 excess male per 1,000 individuals at age 65, and levels of 74.8, 36.9 and 20.3 at age 79, respectively. The larger absolute sex differences in 1-year survival after all-cause hospital admission resulted, on average, in 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. While the male excess mortality after all-cause hospital admission increases steadily with age, the pattern differs when broken down by specific causes of admission. Whereas for admissions due to circulatory and respiratory diseases the male excess mortality shows a similar increasing pattern, the male excess mortality is highest at younger ages for admissions due to neoplasms and decreases with age.

[Figure 2]

# 4 Discussion

In this study we investigated whether women's mortality advantage changes after the onset of an adverse health condition, measured as a hospital admission. We estimated the absolute sex differences in the 1-year risk of dying after an all-cause and cause-specific hospitalization among the population aged 50 – 79, and compared these patterns with those observed in a matched general and non-hospitalized population. As expected, women had consistently lower mortality than men in all three populations. In addition, we found that the absolute sex differences in mortality were highest for the hospitalized population, were lower in the general population and were lowest in the non-hospitalized population. The excess of male mortality always remained larger in the hospitalized population also when differentiating by cause of admission to hospital. Our results show an increasing absolute female mortality advantage following hospital admission, suggesting that women's additional years of life are due to lower mortality in bad health.

## Strengths and weaknesses of the study

In this study, we used Danish register data, which provide nationwide coverage and are representative of the total Danish population. In contrast to longitudinal survey data, these register data suffer less in terms of non-response and loss to follow-up – issues that that could have biased the analyses and led to skewed results.[39] Another strength is that we were able to examine mortality for the over arching all-cause hospital admissions as well as the mortality

patterns for cause-specific hospital admissions. This allowed us to establish if the larger male excess mortality following hospitalization was present across different causes of hospital admission, representing admissions for the major causes of death in Denmark. Similar patterns of sex differences in all-cause and cause-specific admissions suggest that the larger sex differences in mortality after hospital admission cannot be fully explained by differences in the distribution of causes of admission among men and women. We calculated the absolute sex differences in the 1-year risk of dying after an admission to hospital. This allowed us to directly compare the male excess mortality in the hospitalized, the general and the non-hospitalized population. The relative differentials would have also allowed us to compare mortality differences. However, it could have led to distorted conclusions which may emerge when sex differentials in mortality are compared across populations which differ significantly in their mortality regime.[12] This may lead to the impression that the sex differences were lowest among the hospitalized individuals when focusing on relative differentials only.

Our study does not address the underlying reasons for the greater excess male mortality in the 1-year period after admission to hospital. In this regard, the register data did not allow us to examine the severity of the underlying causes of hospital admission or account for the potential biological and behavioral mechanism that may explain the sex differences in mortality following hospitalization. The study further did not allow us to examine the question of whether the observed gaps in survival after hospital admission changed over time or by cohorts. This issue may be particularly relevant for Denmark where the sex differentials in mortality are known to have been affected by a stagnation of female life expectancy during the 1977 – 1995 period, which was a consequence of smoking among women born between the two World Wars.[40-42] The increased prevalence of smoking among women within this period may have an impact on our findings by leading to higher levels of mortality among women in general, as well as to higher rates of admissions for smoking-related diseases among women. This demonstrates that factors which determine the distribution of causes of admission to hospital and the levels of disease-specific mortality after hospitalization within a population are complex. Both factors may be influenced by changes in the organization and the performance of the health care system, including shifts in the admission strategies and the quality of medical treatment; or they could depend on a range of demographic characteristics,

such as the prevalence of diseases or the distribution of risk factors in a population.[22] It is important to highlight that our analysis compares men and women of the same age and does not control for the health status of individuals. However, we recognize that men tend to develop adverse health conditions at earlier ages than women,[43;44] and that studies on strokes and myocardial infarctions have shown that, on average, men are eight years younger than women at the onset of these conditions.[45-48] To gain a deeper understanding of the sex differences in mortality after hospital admission, future research should aim to identify the underlying reasons for these differences, and investigate how these sex disparities have developed over time, by cohort, and how they vary by socioeconomic status. Also the length of follow up we used needs to be taken into account. It could be that that the increased level of mortality during the first year after admission is temporary and that the duration of the follow-up period has an impact on the mortality levels of the hospitalized men and women due to selective mortality and cure. As we wanted to capture the immediate impact of an adverse health condition in the period following hospital admission, we decided to use a relatively short follow-up period of 1-year length.

## Interpretation and implications in light of previous findings

The existing literature focusing on the female mortality advantage has pointed towards the effects and the interactions of biological, behavioral, and social factors.[39] The most widely cited biological factors are hormonal, based on the observation that the female hormone estrogen has favorable effects on serum lipid levels, as well as vasoprotective and immune-enhancing effects; and genetic, based on the assumption that women's second X chromosome helps to ameliorate the harmful effects of gene mutations on the X chromosome.[49-52] Moreover, women may have stronger immune systems than men which could help women to recover more quickly,[53] and may play a fundamental role in women's better survival of harsh conditions, including famines and epidemics.[10] In addition to these biological factors, researchers have attributed a portion of the male disadvantage in mortality to behavioral and social factors.[54] For example, it has been argued that men have higher rates than women of smoking, excessive drinking, drug use, and violence, and that they are more likely than women to postpone help seeking.[55]

A large body of previous research, including research for Denmark, has shown that men tend to seek medical help later than women, which can lead to delays in diagnosis and treatment.[56-62] It is possible that compared to their female counterparts, men who are admitted to the hospital have more severe conditions and diseases at more advanced stages, and may therefore require more complex medical interventions. Previous studies have shown that men who are hospitalized tend to have conditions that are more severe than those of the women who are hospitalized; although the reasons for this pattern are not yet been fully understood.[63]

In Denmark, hospital care is financed through taxes, and is thus available to all residents, regardless of their sex and socioeconomic characteristics.[64] Although our results may have been affected by changes in policies related to hospital admission, treatment, and discharge; it is likely that such changes would have affected men and women in similar ways. Although access to health care services is free and universal in Denmark, individuals may encounter hurdles in accessing health care services for a variety of reasons, including social, economic, demographic, and geographic factors.[65] In Denmark, general practitioners (GPs) typically serve not just as gatekeepers for the use of secondary health care, but also as care providers who can help patients avoid or postpone an admission to the hospital. For example, GPs assist patients in monitoring their health and in preventing the progress of many chronic conditions through regular medical check-ups, health consultations, the prescription of medications, and other preventive measures.[66] It is therefore possible that the higher excess mortality after hospital admission among men, found in our study, can be partially explained by sex differences in health awareness and help-seeking long before the onset of an adverse health condition, underlining the importance of an efficient primary health care system, as well as individuals awareness of diseases, risk factors and compliance with preventive measures. Thus, the female advantage in survival after hospital admission is likely to be due to multiple factors, including biological advantages underpinned by sex differences in health behavior.

## Conclusion

In this study we found that the risk of dying was highest for the hospitalized men and women in the 1-year period after admission to hospital, was lower among their counterparts in the general population, and was lowest among those individuals who were not admitted to hospital. Our findings show that the male disadvantage in mortality increased substantially after admission to hospital, 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 conditions.

# 5 References


[1] Drevenstedt GL, Crimmins EM, Vasunilashorn S, Finch CE. The rise and fall of excess male infant mortality. PNAS. 2008;105:5016–5021.

[2] Najari BB, Rink M, Li PS, Karakiewicz PI, Scherr DS, Shabsigh R, et al. Sex disparities in cancer mortality: the risks of being a man in the United States. J Urol. 2013;189:1470–1474.

[3] Edgren G, Liang L, Adami HO, Chang ET. Enigmatic sex disparities in cancer incidence. Eur J Epidemiol. 2012;3:187–196.

[4] Cook MB, McGlynn KA, Devesa SS, Freedman ND, Anderson WF. Sex Disparities in Cancer Mortality and Survival. Cancer Epidemiol Biomarkers Prev. 2011;20:1629–1637.

[5] De Torres J, Cote C, Lopez M, Casanova C, Diaz O, Marin JM, et al. Sex differences in mortality in patients with COPD. Eur Respir J. 2009;33:528–535.

[6] Dransfield MT, Washko GR, Foreman MG, Estepar RSJ, Reilly J, Bailey WC. Gender differences in the severity of CT emphysema in COPD. Chest. 2007;132:464–470.

[7] Waldron I, McCloskey C, Earle I. Trends in gender differences in accidents mortality: Relationships to changing gender roles and other societal trends. Demogr Res. 2005;13:415–454.

[8] Stroebe M, Schut H, Stroebe W. Health outcomes of bereavement. Lancet. 2007;370:1960–1973.

[9] Moon JR, Kondo N, Glymour MM, Subramanian S. Widowhood and mortality: a meta-analysis. PLoS One. 2011;6:e23465.

[10] Zarulli V, Jones JAB, Oksuzyan A, Lindahl-Jacobsen R, Christensen K, Vaupel JW. Women live longer than men even during severe famines and epidemics. PNAS. 2018;201701535.

[11] Gjonça A, Tommassini C, Toson B, Smallwood S. Sex differences in mortality, a comparison of the United Kingdom and other developed countries. Health Stat Q. 2005;26&27:6–16.

[12] Wisser O, Vaupel JW. The sex differential in mortality: a historical comparison of the adult-age pattern of the ratio and the difference. MPIDR Working Paper. 2014.

[13] Beltrán-Sánchez H, Finch CE, Crimmins EM. Twentieth century surge of excess adult male mortality. PNAS. 2015;112:8993–8998.

[14] Christensen K, Doblhammer G, Rau R, Vaupel JW. Ageing populations: the challenges ahead. Lancet. 2009;374:1196–1208.

[15] Karampampa K, Andersson T, Drefahl S, Ahlbom A, Modig K. Does Improved Survival Lead to a More Fragile Population: Time Trends in Second and Third Hospital Admissions among Men and Women above the Age of 60 in Sweden. PloS one. 2014;9:e99034.

[16] Karampampa K, Drefahl S, Andersson T, Ahlbom A, Modig K. Trends in age at first hospital admission in relation to trends in life expectancy in Swedish men and women above the age of 60. BMJ Open. 2013;3:439–454.

[17] Case A, Paxson C. Sex differences in morbidity and mortality. Demography. 2005;42:189–214.

[18] Fleury MJ, Ngui AN, Bamvita JM, Grenier G, Caron J. Predictors of healthcare service utilization for mental health reasons. Int J Environ Res Public Health. 2014;11:10559–10586.

[19] Farkas J, Kosnik M, Flezar M, Suskovic S, Lainscak M. Self-rated health predicts acute exacerbations and hospitalizations in patients with COPD. Chest. 2010;138:323–330.

[20] DeSalvo KB, Fan VS, McDonell MB, Fihn SD. Predicting mortality and healthcare utilization with a single question. Health Serv Res. 2005;40:1234–1246.

[21] Kennedy BS, Kasl SV, Vaccarino V. Repeated hospitalizations and self-rated health among the elderly: a multivariate failure time analysis. Am J Epidemiol. 2001;153:232–241.

[22] Hanlon P, Lawder R, Elders A, Clark D, Walsh D, Whyte B, et al. An analysis of the link between behavioural, biological and social risk factors and subsequent hospital admission in Scotland. J Public Health. 2007;29:405–412.

[23] Hanlon P, Walsh D, Whyte BW, Scott SN, Lightfoot P, Gilhooly ML. The link between major risk factors and important categories of admission in an ageing cohort. J Public Health. 2000;22:81–89.

[24] Hanlon P, Walsh D, Whyte BW, Scott SN, Lightbody P, Gilhooly MLM. Hospital use by an ageing cohort: an investigation into the association between biological, behavioural and social risk markers and subsequent hospital utilization. J Public Health. 1998;20:467–476.

[25] Smyth A, Teo KK, Rangarajan S, O'Donnell M, Zhang X, Rana P, et al. Alcohol consumption and cardiovascular disease, cancer, injury, admission to hospital, and mortality: a prospective cohort study. Lancet. 2015;386:1945–1954.

[26] Reeves GK, Balkwill A, Cairns BJ, Green J, Beral V. Hospital admissions in relation to body mass index in UK women: a prospective cohort study. BMC Med. 2014;12:45.

[27] Crowe FL, Appleby PN, Travis RC, Key TJ. Risk of hospitalization or death from ischemic heart disease among British vegetarians and nonvegetarians: results from the EPIC-Oxford cohort study. Am J Clin Nutr. 2013;97:597–603.

[28] Garcia-Aymerich J, Lange P, Benet M, Schnohr P, Antó JM. Regular physical activity reduces hospital admission and mortality in chronic obstructive pulmonary disease: a population based cohort study. Thorax. 2006;61:772–778.

[29] Syddall HE, Westbury LD, Simmonds SJ, Robinson S, Cooper C, Sayer AA. Understanding poor health behaviours as predictors of different types of hospital admission in older people: findings from the Hertfordshire Cohort Study. J Epidemiol Community Health. 2016;70:292–298.

[30] Thygesen LC, Daasnes C, Thaulow I, Brønnum-Hansen H. Introduction to Danish (nationwide) registers on health and social issues: structure, access, legislation, and archiving. Scand J Public Health. 2011;7:12–16.

[31] Pedersen CB. The Danish Civil Registration System. Scand J Public Health. 2011;7:22–25.

[32] Lynge E, Lynge Sandegaard J, Rebolj M. The Danish National Patient Register. Scand J Public Health. 2011;7:30–33.

[33] Andersen TF, Madsen M, Jørgensen J, Mellemkjaer L, Olsen JH. The Danish National Hospital Register. A valuable source of data for modern health sciences. Dan Med Bull. 1999;46:263–268.

[34] Schmidt M, Pedersen L, Sorensen HT. The Danish Civil Registration System as a tool in epidemiology. Eur J Epidemiol. 2014;8:541–549.

[35] Hastie T, Tibshirani R. Generalized additive models. Stat Sci. 1986;1:297–310.

[36] Hastie T, Tibshirani R. Generalized additive models for medical research. Stat Methods Med Res. 1995;4:187–196.

[37] Wood S. Generalized additive models: an introduction with R. CRC press; 2006.

[38] Eilers PH, Marx BD. Flexible smoothing with B-splines and penalties. Stat Sci. 1996;11:89–102.

[39] Oksuzyan A, Juel K, Vaupel JW, Christensen K. Men: good health and high mortality. Sex differences in health and aging. Aging Clin Exp Res. 2008;2:91–102.

[40] Lindahl-Jacobsen R, Rau R, Jeune B, Canudas-Romo V, Lenart A, Christensen K, et al. Rise, stagnation, and rise of Danish women's life expectancy. PNAS. 2016;113:4015–4020.

[41] Lindahl-Jacobsen R, Oeppen J, Rizzi S, Möller S, Zarulli V, Christensen K, et al. Why did Danish women's life expectancy stagnate? The influence of interwar generation's smoking behaviour. Eur J Epidemiol. 2016;31:1207–1211.

[42] Jacobsen R, Oksuzyan A, Engberg H, Jeune B, Vaupel JW, Christensen K. Sex differential in mortality trends of old-aged Danes: a nation wide study of age, period and cohort effects. Eur J Epidemiol. 2008;23:723–730.

[43] Hubbard RE, Rockwood K. Frailty in older women. Maturitas. 2011;69:203–207.

[44] Eskes T, Haanen C. Why do women live longer than men? Eur J Obstet Gynecol Reprod Biol. 2007;133:126–133.

[45] Zhang Z, Fang J, Gillespie C, Wang G, Hong Y, Yoon PW. Age-specific gender differences in in-hospital mortality by type of acute myocardial infarction. Am J Cardiol. 2012;109:1097–1103.

[46] Berger JS, Elliott L, Gallup D, Roe M, Granger CB, Armstrong PW, et al. Sex differences in mortality following acute coronary syndromes. JAMA. 2009;302:874–882.

[47] Appelros P, Stegmayr B, Terént A. A review on sex differences in stroke treatment and outcome. Acta Neurol Scand. 2010;121:359–369.

[48] Appelros P, Stegmayr B, Terént A. Sex differences in stroke epidemiology a systematic review. Stroke. 2009;40:1082–1090.

[49] Seifarth JE, McGowan CL, Milne KJ. Sex and life expectancy. Gend Med. 2012;9:390–401.

[50] Bouman A, Heineman MJ, Faas MM. Sex hormones and the immune response in humans. Hum Reprod Update. 2005;11:411–423.

[51] Stindl R. Typing it all together: telomeres, sexual size dimorphism and the gender gap in life expectancy. Med Hypotheses. 2004;62:151–154.

[52] Christensen K, Ørstavik KH, Vaupel JW. The X chromosome and the female survival advantage. Annals of the New York Academy of Sciences. 2001;954:175–183.

[53] Oertelt-Prigione S. The influence of sex and gender on the immune response. Autoimmun Rev. 2012;11:479–485.

[54] Rieker PP, Bird CE. Rethinking gender differences in health: why we need to integrate social and biological perspectives. J Gerontol B Psychol Sci Soc Sci. 2005;60:40–47.

[55] Rogers RG, Everett BG, Saint Onge JM, Krueger PM. Social, behavioral, and biological factors, and sex differences in mortality. Demography. 2010;47:555–578.

[56] Farrimond H. Beyond the caveman: Rethinking masculinity in relation to men's help-seeking. Health. 2012;16:208–225.

[57] Chan RK, Hayashi K. Gender roles and help-seeking behaviour promoting professional help among Japanese men. J Soc Work. 2010;10:243–262.

[58] Juel K, Christensen K. Are men seeking medical advice too late? Contacts to general practitioners and hospital admissions in Denmark 2005. J Public Health. 2008;30:111–113.

[59] Noone JH, Stephens C. Men, masculine identities, and health care utilisation. Sociol Health Illn. 2008;30:711–725.

[60] Adeyemi SA. Men's health help-seeking and implications for practice. Am J Health Stud. 2007;22:88–95.

[61] Smith JA, Braunack-Mayer A, Wittert G. What do we know about men's help-seeking and health service use? Med J Aust. 2006;184:81–83.

[62] Smith LK, Pope C, Botha JL. Patients' help-seeking experiences and delay in cancer presentation: a qualitative synthesis. Lancet. 2005;366:825–831.

[63] Simmonds SJ, Syddall HE, Walsh B, Evandrou M, Dennison EM, Cooper C, et al. Understanding NHS hospital admissions in England: linkage of Hospital episode statistics to the Hertfordshire cohort study. Age Ageing. 2014;43:653–660.

[64] Olesen F, Hansen RP, Vedsted P. Delay in diagnosis: the experience in Denmark. Br J Cancer. 2009;101:5–8.

[65] Starfield B, Gérvas J, Mangin D. Clinical care and health disparities. Annu Rev Public Health. 2012;33:89–106.

[66] Gérvas J, Starfield B, Heath I. Is clinical prevention better than cure? Lancet. 2008;372:1997–1999.

## Exclusive License



## Contributors

AH, RLJ, RR, KC and AO designed the study. AH, LAL analyzed the data. AH, LAL, DCS and provided support to optimize the program code. AH, RLJ, RR, KC, AO interpreted and discusses the results and implications. AH wrote the paper. All authors contributed to the revision of the paper and have approved the final version.

## Funding

The work was supported by the US National Institute of Health [P01AG031719, R01AG026786, and 2P01AG031719], the VELUX Foundation, and the Max Planck Society within the framework of the project *"On the edge of societies: New vulnerable populations, emerging challenges for social policies and future demands for social innovation. The experience of the Baltic Sea States (2016-2021)"*. The funders had no role in the design of the study or in the collection, analysis, and interpretation of data and results.

## Competing Interests

All authors have completed the ICMJE uniform disclosure and declare: no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work. The disclosure can be found at: (http://www.icmje.org/coi_disclosure.pdf)

## Ethics Approval

The study involves secondary data analysis of existing register data. The project was approved by the ethical committee assigned through the Danish National Committee on Biomedical Research and the Danish Data Protection Agency.

## Data Sharing

No additional data are available.

## Transparency Declaration

The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

# Supplementary Material

Supplementary table 1 – S: Classification of causes of hospital admission.

| Cause of hospital admission | ICD-8 | ICD-10 |
|---|---|---|
| Infectious & parasitic diseases | 000 - 136 | A00 - B99 |
| Neoplasms | 140 - 239 | C00 - D48 |
| Diseases of the blood & blood-forming organs | 280 - 289 | D50 - D89 |
| Endocrine, nutritional & metabolic diseases | 240 - 279 | E00 - E90 |
| Mental & behavioral disorders | 290 - 315 | F00 - F99 |
| Diseases of the nervous system | 320 - 358 | G00 - G99 |
| Diseases of the eye & adnexa | 360 - 379 | H00 - H59 |
| Diseases of the ear & mastoid process | 380 - 389 | H60 - H95 |
| Ischemic heart diseases* | 410 - 414 | I20 - I25 |
| Cerebrovascular diseases* | 430 - 438 | I60 - I69 |
| Other circulatory diseases* | remaining 390 - 458 | remaining I00 - I99 |
| Respiratory diseases | 460 - 519 | J00 - J99 |
| Digestive diseases | 520 - 577 | K00 - K93 |
| Diseases of the skin & subcutaneous tissue | 680 - 709 | L00 - L99 |
| Musculoskeletal disorders | 710 - 738 | M00 - M99 |
| Diseases of the genitourinary system | 580 - 629 | N00 - N99 |
| Injuries, poisonings & accidents | 800 - 999 | S00 - T98 & V01-Y98 |
| All other diseases | - all other - | - all other - |

** the three causes were further grouped and referred to as circulatory diseases*

# Tables

Table 1: Overview on causes of admission to hospital by sex.

| Cause of Hospital Admission | Men | | Women | |
|---|---|---|---|---|
| | Number | Share in % | Number | Share in % |
| Infectious & parasitic diseases | 980 | 1.54 | 1,012 | 1.58 |
| Neoplasms | 6,625 | 10.41 | 9,310 | 14.55 |
| Diseases of the blood & blood-forming organs | 266 | 0.42 | 401 | 0.63 |
| Endocrine, nutritional & metabolic diseases | 1,368 | 2.15 | 2,220 | 3.47 |
| Mental & behavioral disorders | 1,000 | 1.57 | 883 | 1.38 |
| Diseases of the nervous system | 1,434 | 2.25 | 1,382 | 2.16 |
| Diseases of the eye & adnexa | 1,026 | 1.61 | 1,464 | 2.29 |
| Diseases of the ear & mastoid process | 461 | 0.72 | 496 | 0.78 |
| Ischemic heart diseases | 5,899 | 9.27 | 2,601 | 4.06 |
| Cerebrovascular diseases | 2,386 | 3.75 | 1,756 | 2.74 |
| Other circulatory diseases | 6,324 | 9.94 | 5,368 | 8.39 |
| Respiratory Diseases | 3,785 | 5.95 | 3,233 | 5.05 |
| Digestive diseases | 8,368 | 13.15 | 6,166 | 9.64 |
| Diseases of the skin & subcutaneous tissue | 786 | 1.23 | 700 | 1.09 |
| Musculoskeletal disorders | 4,737 | 7.44 | 5,858 | 9.15 |
| Diseases of the genitourinary system | 4,680 | 7.35 | 6,968 | 10.89 |
| Injuries, poisonings & accidents | 6,466 | 10.16 | 7,228 | 11.29 |
| All other diseases | 7,058 | 11.09 | 6,947 | 10.86 |
| **Total** | **63,649** | **100.00** | **63,993** | **100.00** |

Table 2: Number of individuals, number of deaths, and the risk of dying within 1 year of follow-up by sex and age in the hospitalized, general, and non-hospitalized population.

| Age at Hospital Admission / Age of Matches | Men | | | | Women | | | |
|---|---|---|---|---|---|---|---|---|
| | Individuals | | Deaths | | Individuals | | Deaths | |
| | No. | Share in % | No. | Risk in % | No. | Share in % | No. | Risk in % |
| **Hospitalized Population** | | | | | | | | |
| 50–54 | 18,397 | 28.90 | 906 | 4.92 | 19,569 | 30.58 | 622 | 3.18 |
| 55–59 | 12,392 | 19.47 | 898 | 7.25 | 11,432 | 17.86 | 514 | 4.50 |
| 60–64 | 10,493 | 16.49 | 1,074 | 10.24 | 9,244 | 14.45 | 655 | 7.09 |
| 65–69 | 9,030 | 14.19 | 1,320 | 14.62 | 8,508 | 13.30 | 844 | 9.92 |
| 70–74 | 7,623 | 11.98 | 1,432 | 18.79 | 7,967 | 12.45 | 1,046 | 13.13 |
| 75–79 | 5,714 | 8.98 | 1,457 | 25.50 | 7,273 | 11.37 | 1,261 | 17.34 |
| **Total** | **63,649** | **100.00** | **7,087** | **11.13** | **63,993** | **100.00** | **4,942** | **7.72** |
| **General Population*** | | | | | | | | |
| 50–54 | 18,400 | 28.91 | 124 | 0.68 | 19,558 | 30.56 | 88 | 0.45 |
| 55–59 | 12,394 | 19.47 | 145 | 1.17 | 11,452 | 17.90 | 80 | 0.70 |
| 60–64 | 10,486 | 16.47 | 195 | 1.86 | 9,231 | 14.43 | 100 | 1.08 |
| 65–69 | 9,042 | 14.21 | 268 | 2.97 | 8,520 | 13.31 | 153 | 1.80 |
| 70–74 | 7,612 | 11.96 | 369 | 4.85 | 7,961 | 12.44 | 218 | 2.74 |
| 75–79 | 5,714 | 8.98 | 449 | 7.85 | 7,270 | 11.36 | 334 | 4.60 |
| **Total** | **63,649** | **100.00** | **1,551** | **2.44** | **63,993** | **100.00** | **974** | **1.52** |
| **Non-Hospitalized Population*** | | | | | | | | |
| 50–54 | 18,400 | 28.91 | 57 | 0.31 | 19,558 | 30.56 | 27 | 0.14 |
| 55–59 | 12,393 | 19.47 | 53 | 0.43 | 11,452 | 17.90 | 21 | 0.18 |
| 60–64 | 10,488 | 16.48 | 76 | 0.72 | 9,232 | 14.43 | 32 | 0.34 |
| 65–69 | 9,042 | 14.21 | 108 | 1.20 | 8,521 | 13.32 | 52 | 0.61 |
| 70–74 | 7,612 | 11.96 | 150 | 1.97 | 7,958 | 12.44 | 83 | 1.05 |
| 75–79 | 5,713 | 8.98 | 150 | 2.63 | 7,271 | 11.36 | 154 | 2.12 |
| **Total** | **63,649** | **100.00** | **656** | **1.03** | **63,993** | **100.00** | **369** | **0.58** |

* the number of deaths and the risk of dying refers to the average of 100 matching results

# Figure Legends

Figure 1: Estimated age trajectories in the risk of dying within 1 year of follow-up by cause of admission to hospital.

Figure 2: Male excess mortality within 1 year of follow-up by cause of admission to hospital.

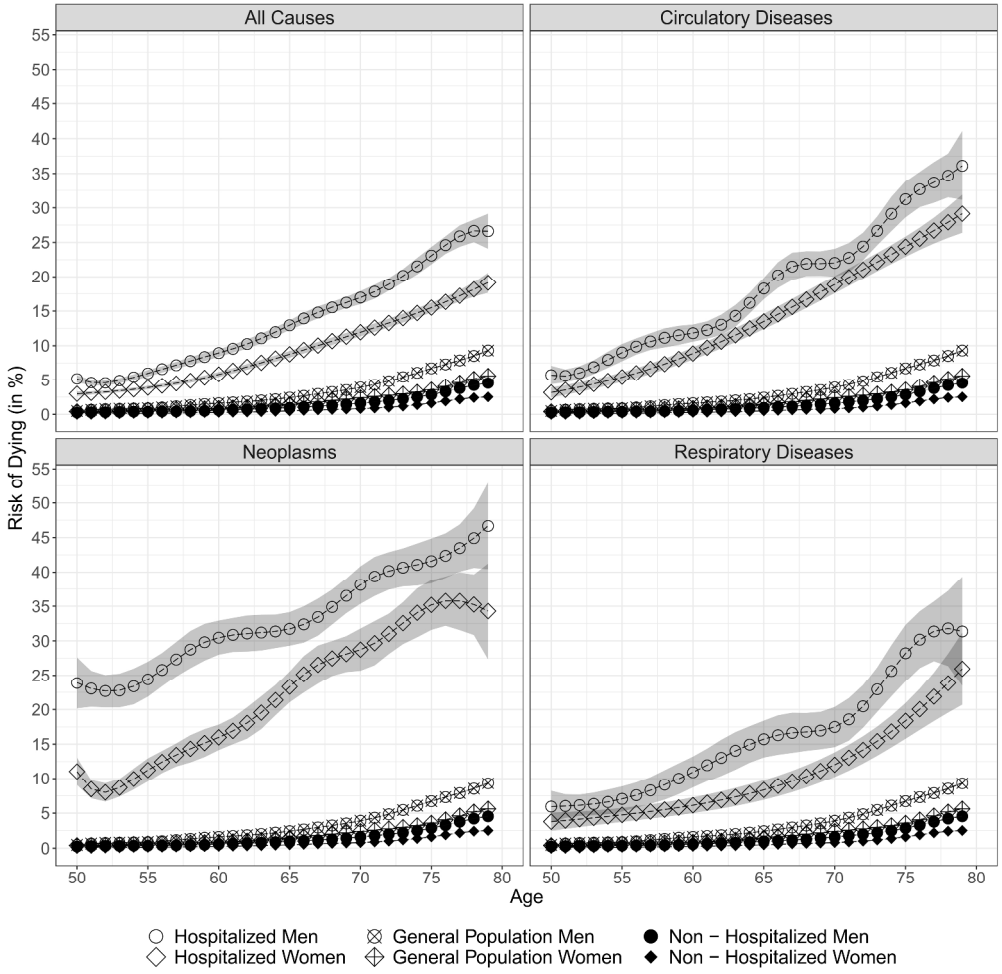



Figure 1: Estimated age trajectories in the risk of dying within 1 year of follow-up by cause of admission to hospital.

299x299mm (300 x 300 DPI)

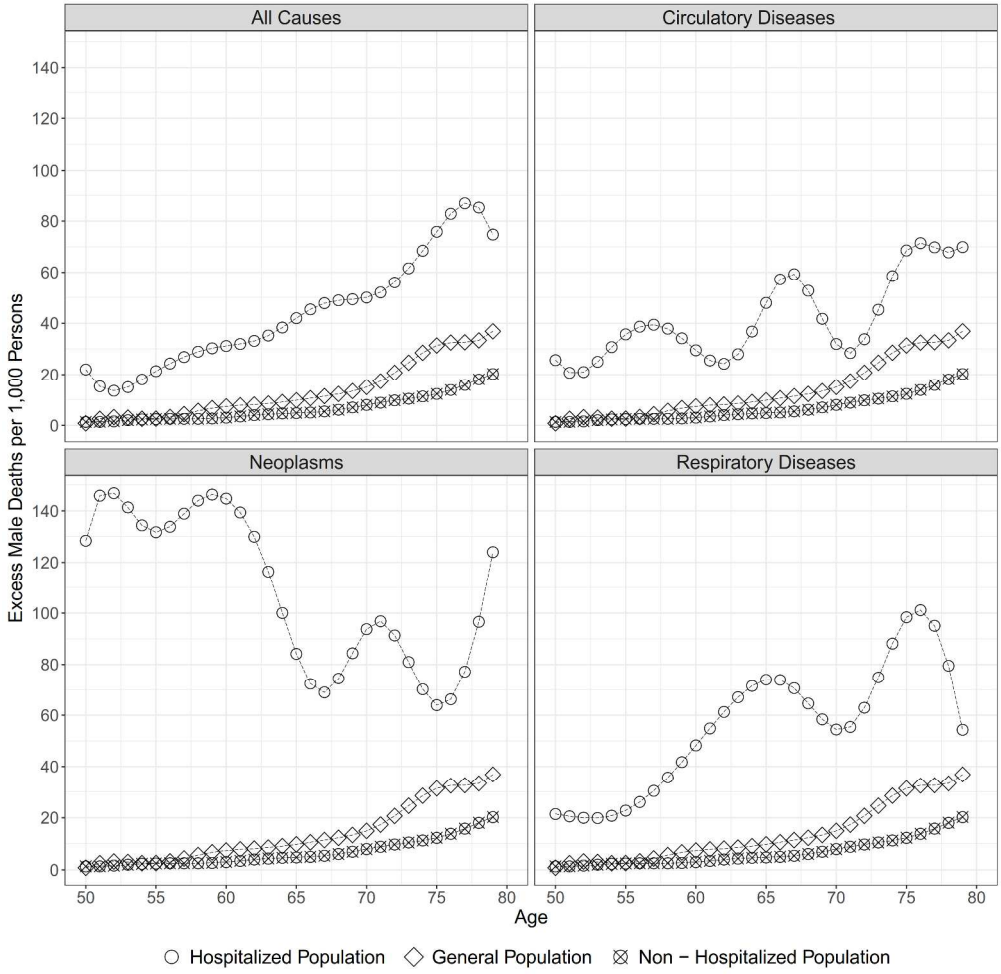



Figure 2: Male excess mortality within 1 year of follow-up by cause of admission to hospital.

299x299mm (300 x 300 DPI)

BMJ Open

# 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.



| | |
|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2018-021813.R1 |
| Article Type: | Research |
| Date Submitted by the Author: | 03-May-2018 |
| Complete List of Authors: | Höhn, Andreas; Max-Planck-Institut fur Demografische Forschung, Gender Gaps in Health and Survival ; Syddansk Universitet Det Sundhedsvidenskabelige Fakultet, Department of Epidemiology, Biostatistics and Biodemography<br>Larsen, Lisbeth; Syddansk Universitet Det Sundhedsvidenskabelige Fakultet, Department of Epidemiology, Biostatistics and Biodemography<br>Schneider, Daniel Christoph; Max-Planck-Institut fur Demografische Forschung, Laboratory of Population Health<br>Jacobsen, Rune; Syddansk Universitet Det Sundhedsvidenskabelige Fakultet, Department of Epidemiology, Biostatistics and Biodemography<br>Rau, Roland; Max Planck Institute for Demographic Research, Mathematical and Actuarial Demography ; Universitat Rostock Wirtschafts und Sozialwissenschaftliche Fakultat<br>Christensen, Kaare; University of Southern Denmark, Department of Epidemiology, Biostatistics and Biodemography; Danish Aging Research Center<br>Oksuzyan, Anna; Max-Planck-Institut fur Demografische Forschung, Gender Gaps in Health and Survival |
| Primary Subject Heading: | Epidemiology |
| Secondary Subject Heading: | Public health |
| Keywords: | EPIDEMIOLOGY, SEX DIFFERENCES, HOSPITALIZATION, MORTALITY |
| | |

# 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:**

[1,2] **Andreas Höhn***, PhD Student

[2] **Lisbeth Aagaard Larsen**, Research Scientist

[1] **Daniel Christoph Schneider**, Statistical Programmer and Research Scientist

[2] **Rune Lindahl-Jacobsen**, Associate Professor

[1,3] **Roland Rau**, Professor

[2,4] **Kaare Christensen**, Professor

[1] **Anna Oksuzyan**, Head of Independent Research Group

**Affiliations:**

[1] Max Planck Institute for Demographic Research Konrad-Zuse-Straße 1 18057 Rostock, Germany

[2] Department of Epidemiology, Biostatistics and Biodemography University of Southern Denmark J.B. Winsløws Vej 9B 5000 Odense C, Denmark

[3] Department of Sociology & Demography University of Rostock Ulmenstraße 69 18057 Rostock, Germany

[4] Danish Aging Research Center J.B. Winsløws Vej 9B 5000 Odense C, Denmark

* Correspondence to:
Andreas Höhn
Max Planck Institute for Demographic Research
Konrad-Zuse-Straße 1
18057 Rostock, Germany
Phone: +49 (0)381 2081-177
Email: hoehn@demogr.mpg.de

# Abstract


## Objectives

We examine the mortality of men and women within the first year after all-cause and cause-specific hospital admission to investigate whether the sex differences in mortality after hospitalization are higher than in the corresponding general and non-hospitalized population.

## Design

This is a population-based, longitudinal study with nationwide coverage. The study population was identified by linking the National Patient Register with the Central Population Register using a 5% random sample of the Danish population.

## Setting

The population born between 1898 and 1961, who was alive and residing in Denmark after 1977, was followed up between 1977 and 20111 with respect to hospital admissions and mortality while aged 50 – 79.

## Primary Outcome Measures

The absolute sex differences in the 1-year risk of dying after all-cause and cause-specific hospital admission. The hospitalized population sex differentials were then compared with the sex differences in a general and a non-hospitalized population, randomly matched by age, sex and hospitalization status.

## Results

The risk of dying was consistently higher for hospitalized men and women. At all ages, the absolute sex differences in mortality were largest in the hospitalized population, were smaller in the general population, and were smallest in the non-hospitalized population. This pattern was consistent across all-cause admissions, and with respect to admissions for neoplasms, circulatory diseases and respiratory diseases. For all-cause hospital admissions, absolute sex differences in the 1-year risk of dying resulted in 43.8 excess male deaths per 1,000 individuals within the age range 50 – 79, while the levels were lower in the general and the non-hospitalized population, at levels of 13.5 and 6.6 respectively.

## Conclusions

This study indicates a larger male disadvantage in mortality following hospitalization, pointing towards an association between the health status of a population and the magnitude of the female advantage in mortality.

# Article Summary

## Strengths and limitations of this study:

- This study utilizes high-quality Danish register data, with nationwide coverage, that leaves little room for selection bias due to non-response or loss to follow-up.
- Our findings of excess male mortality within the first year after all-cause hospitalization compared with their female counterparts remain robust when stratifying by the main causes of admission to hospital in Denmark.
- Due to a lack of further medical data on the admissions, including information on risk factors and severity of diseases, we were not able to disentangle the potential behavioral and biological mechanisms behind widening sex differences after hospitalization.

# 1 Background

Empirical studies have consistently reported that women have a mortality advantage at all ages, starting at infancy and extending over the entire life course[1]. Women have lower rates of mortality than men for nearly all causes of death, including most cancers [2–4], respiratory diseases[5,6], and accidents [7]. Moreover, the female advantage in mortality persists even after stressful events during the life course, such as bereavement [8,9] or famines and epidemics [10]. While the relative sex differences in mortality peak at around age 25 and tend to become smaller with age [11], the absolute sex differences grow almost exponentially between ages 40 and 90, as general levels of mortality increase [12]. Thus, in recent decades, the largest share of the sex differences in life expectancy has been attributed to mortality differentials after the age of 50 [13] – when individuals start to accumulate disease and disabilities, and the incidence of most adverse health conditions increases [14].

A number of previous studies have argued that a hospital admission may serve as a quasi-objective indicator of health. An admission to hospital may indicate the onset of a health decline or the manifestation of a heallh decline that started long ago that now requires extensive medical interventions [15–17]. The use of hospitalization as a proxy for health is supported by previous research findings showing that adults of all ages who rate their health and their quality of life as poor are at an increased risk of hospital admission [18–21]. Furthermore, the well-established associations between major risk factors and the increased risk of dying from certain causes, such as smoking and lung cancer; have also been found for the relationship between risk factors and cause-specific reasons of admission [22–24]. Empirical findings have demonstrated that smoking [22], hazardous drinking [25], being overweight [26], having high cholesterol levels [27], and a lack of physical activity [28] are related to an increased risk of hospital admission. The presence of multiple risk factors has been found to be especially strongly associated with a high risk of admission [29].

Although it has been well established that women have a mortality advantage across all ages and all causes of death, it is not yet known whether this advantage changes after the manifestation of bad health, which we measure as a hospital admission. To answer this question, we estimate the absolute sex differences in the 1-year risk of dying after all-cause

and cause-specific hospital admission as an inpatient. We compare these absolute sex differentials with the corresponding differences we would have observed in the general and the non-hospitalized population.

# 2 Methods and materials

## Data

This study uses a 5% random sample of the Danish population. Using the unique personal identification number that is assigned to all individuals residing in Denmark [30], we linked records from the National Patient Register (NPR) with data of the Central Population Registry (CPR). The CPR, which covers the entire population alive and residing in Denmark since 1968, contains information on each resident's vital status, sex, and place and date of birth [31]. The NPR is a population-based register with nationwide coverage that contains information on all admissions to hospitals since 1977 [32]. As reports to the administration are compulsory, the NPR data have high levels of completeness and reliability, making these data an excellent tool for research [33]. Whereas data on hospitalizations are available for the period 1977–2011, the vital status of individuals was traceable up to the year 2013. In the NPR, diagnoses were classified in accordance with the ICD-8 until 1993 and the ICD-10 starting in 1994 [34]. We classified the causes of admission to hospital according to the main chapters and using broad groups to reduce the potential bias, which may emerge from combining two systems of classification. An overview of the coding is given in supplementary table 1 – S.

## Study population

We identified all individuals who were born between January 1, 1898, and December 31, 1961, who were alive, and who resided in Denmark after 1968 in the 5% random sample (n = 214,613). Of those, we then selected all individuals who survived up to age 50 and resided in Denmark after January 1, 1977 (n = 198,580). Out of all remaining individuals, 64.3% (n = 127,642) of the sample had been admitted to the hospital at least once between January 1,

1977, and December 31, 2011. Hospitalization was defined as the first time an individual was admitted to the hospital while aged 50 – 79 as an inpatient, for at least one night, and for any reason between the years 1977 and 2011. Subsequent admissions and admissions that occurred among these individuals before the age of 50, after age 79, and before 1977 – for the same or other causes – were not taken into account.

To examine whether the sex differences in mortality increase following an admission to hospital, we compared the sex differentials after hospitalization with the corresponding differences measure among two healthier references. For this purpose two matched populations aged 50 – 79 were selected randomly from the study sample: one group to represent the general population, and the other group to represent the non-hospitalized population. Each hospitalized individual was matched to one individual from each reference group. The matched individuals, forming the two reference populations had to be the same age (+/- 30 days), the same sex, and alive on the day the corresponding case was hospitalized. Whereas the individuals representing the general population were selected irrespective of hospitalization status, the individuals representing the non-hospitalized population had not been hospitalized within a concordant year before and after the exact date the corresponding case was admitted to hospital, irrespective of the case's cause of admission. Cases and matches were drawn from the same source population. We used matching with replacement to correct the observed distortion that a certain proportion of the hospitalized population would have remained without a match, which emerged when matching without replacement was tested.The matching was carried out 100 times to increase the robustness of the matching results, and to bypass the need to choose a single matching scenario. Consequently, the same person may appear more than once in each of the 100 matching scenarios.

## Patient and public involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. No patients were involved in the recruitment to and conduct of the study. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

## Statistical analysis

The survival time of the hospitalized individuals starts immediately with the day of the first all-cause hospital admission after age 50, which was recorded in the registers. No lag-time or wash-out period was used to ensure that the immediate impact of the manifestation of bad health on the risk of dying was captured, implying that deaths during the index hospital stay are included in the mortality calculations. Analogously, the process time of the individuals of both reference populations starts on the day the corresponding case was hospitalized. The survival status of all individuals was followed up within 1 year. If a person was alive by the end of the follow-up period or had migrated, this individual was considered as having no event. We used a generalized additive (GAM) for binary data with a logit link. Unlike in generalized linear models (GLM), the linear predictor in the GAM is replaced by a sum of smoothing functions [35,36]. We used penalized B-splines – so called P-splines – as basis functions in the regression to smooth over age [37,38]. We modeled the age-specific 1-year risk of dying separately for the men and the women of each population by single years of age. For the hospitalized population, we further estimated separate models by cause of admission to hospital to investigate whether the female advantage in survival following hospitalization varies across different causes of admission. While the data preparation and the merging of registries was carried out with STATA (Version 15), all statistical analyses were performed in R (Version 3.3.2).

# 3 Results

Of the 127,642 individuals who were hospitalized, 49.9% (n = 63,649) were men and 50.1% (n = 63,993) were women. The mean age at hospitalization was slightly lower among the men (61.7; SD = 8.5) than among the women (62.0; SD = 9.0). An overview on the causes of admission to hospital is provided in table 1. We found the distribution of causes of hospital admission to be different in men and in women. In comparison with men, women were more likely to be hospitalized due to neoplasms, diseases of the blood and blood-forming organs, endocrine, nutritional and metabolic diseases, diseases of the eye and adnexa,

musculosceletal disorders, and diseases of the genitourinary system. In contrast, more men were admitted due to ischaemic heart diseases, cerebrovascular diseases and other circulatory diseases, as well as due to respiratory and digestive diseases than women. We found only small sex differences in the distribution with respect to infectious and parasitic diseases, mental and behavioral disorders, diseases of the nervous system, diseases of the ear and mastoid process, diseases of the skin and subcutaneous tissue as well as injuries, poisonings and accidents.

[Table 1]

An overview of the three populations is given in table 2. While the data for the hospitalized population represent the exact number of observed cases, the numbers for the general and the non-hospitalized population refer to the mean of 100 matched samples. Because the matched individuals were of the same age and the same sex as the corresponding cases, the three populations had identical age structures (mean = 61.9, SD = 8.9) and sex ratios. We found that the risk of dying was highest among the men and the women of the hospitalized population at the level of 9.42% (95% Confidence Interval (CI) 9.26% to 9.58%). The risk of dying was substantially lower and at the level of 1.98% (95% CI 1.90% to 2.05%) in the corresponding general population, and lowest among the non-hospitalized population at a level of 0.80% (95% CI 0.75% to 0.85%), respectively. As it is shown in table 2, men had consistently higher mortality than women in all of the three populations. In all populations, we found the mortality of both sexes to increase consistently with age.

[Table 2]

We further estimated the risk of dying and the trajectory of this risk by single years of age for men and women in each population and corresponding 95% confidence intervals using a non-parametric GAM. As shown in figure 1, we found that men had consistently higher mortality than their female counterparts in each population, at all ages, and for admissions due to all causes, neoplasms, circulatory and respiratory diseases. The risk of dying increased

consistently with age among the men and the women in each population, and with respect to all causes of admission to hospital

At the age of 50, the 1-year risk of dying for all-cause admissions in the hospitalized population was 5.17% (95% CI 4.60% to 5.73%) for men and 2.97% (95% CI 2.66% to 3.29%) for women. With age, the risk of dying increased and reached a level of 26.61% (95% CI 24.08% to 29.13%) and 19.12% (95% CI 17.65% to 20.60%) among 79-year old men and women of the hospitalized population, respectively.

We found the absolute increase in mortality with age to be smaller in the general population than in the hospitalized population. Starting with levels of 0.47% (95% CI 0.46% to 0.49%) among men and 0.39% (95% CI 0.38% to 0.41%) among women at age 50, the risk of dying was 9.30% (95% CI 9.12% to 9.47%) and 5.61% (95% CI 5.49% to 5.73%) at the age 79 in the general population, respectively.

We found the non-hospitalized population to have the lowest absolute increase in mortality with age: at age 50 the risk of dying was 0.25% (95% CI 0.24% to 0.26%) for men and 0.12% (95% CI 0.11% to 0.13%) for women, and it increased to 4.54% (95% CI 4.42% to 4.67%) and 2.52% (95% CI 2.43% to 2.60%) at age 79, respectively.

[Figure 1]

In a next step we calculated the absolute sex differences in the 1-year risk of dying and the the male excess mortality per 1,000 persons. Figure 2 shows the age trajectory of the male excess mortality in each of the three populations and by cause of admission to hospital. At all ages and regarding admissions for all causes, neoplasms, circulatory and respiratory diseases,the absolute sex differences were largest in the hospitalized population, were smaller in the general population, and were smallest in the non-hospitalized population. At age 50 and for all-cause admissions, the sex differences in survival resulted in 22.0 excess male deaths per 1,000 individuals in the hospitalized population, while there were 0.8 excess male deaths in the general population, and 1.3 excess male deaths in the non-hospitalized population. Within the observed age range the excess male mortality increased almost steadily among all three populations, resulting at levels of 42.0, 9.8 and 4.8 excess male deaths per 1,000 individuals at age 65, and levels of 74.8, 36.9 and 20.3 at age 79, respectively. For all-cause hospital

admissions, the larger absolute sex differences in the 1-year risk of dying resulted, on average, in 43.8 excess male deaths per 1,000 individuals within the age range 50 – 79, while the levels were lower in the general and the non-hospitalized poulation, and at levels of 13.5 and 6.6 respectively. While the male excess mortality after all-cause hospital admission increases steadily with age, the pattern differs when broken down by specific causes of admission. Whereas for admissions due to circulatory and respiratory diseases the male excess mortality shows a similar increasing pattern, the male excess mortality is highest at younger ages for admissions due to neoplasms and decreases with age.

[Figure 2]

# 4 Discussion

In this study we investigated how women's mortality advantage changes after the manifestation of an adverse health condition, which we measured as a hospital admission. We estimated the absolute sex differences in the 1-year risk of dying after an all-cause and cause-specific hospitalization among the population aged 50 – 79, and compared these patterns with those observed in a matched general and non-hospitalized population. As expected, women had consistently lower mortality than men in all three populations. In addition, we found that the absolute sex differences in mortality were highest for the hospitalized population, were lower in the general population and were lowest in the non-hospitalized population. The excess of male mortality always remained larger in the hospitalized population also when differentiating by cause of admission to hospital.

## Strengths and weaknesses of the study

In this study, we used Danish register data, which provide nationwide coverage and are representative of the total Danish population. In contrast to longitudinal survey data, these register data suffer less in terms of non-response and loss to follow-up – issues that that could have biased the analyses and led to skewed results [39]. Another strength is that we were able to examine mortality for the over arching all-cause hospital admissions as well as the

mortality patterns for cause-specific hospital admissions. This allowed us to establish if the larger male excess mortality following hospitalization was present across different causes of hospital admission, representing admissions for the major causes of death in Denmark. Similar patterns of sex differences in all-cause and cause-specific admissions suggest that the larger sex differences in mortality after hospital admission cannot be fully explained by differences in the distribution of causes of admission among men and women. In order to minimize the bias due to changes in ICD coding over the study period, we used broad categories to group causes of hospital admission.

We calculated the absolute sex differences in the 1-year risk of dying after an admission to hospital. This allowed us to directly compare the male excess mortality in the hospitalized, the general and the non-hospitalized population. It has been shown that different conclusions about health inequalities might be the result of the effect measure used. This has been shown in relation to mortality differences between socioeconomic groups, across countries, over time [40] and in respect to sex differences [12,41]. We therefore replicated the analysis using risk ratios (see supplementary figure 1 – s). Using risk ratios leads to a different interpretation, that the sex differences were lowest among the hospitalized individuals and highest for the non hospitalized population where the overall risk of mortality was lowest. Both, absolute and relative measures are context dependent and their use needs to be justified [40]. Problems surrounding the interpretation of risk ratios often appear when populations under investigation differ in their overall risks of mortality [12]. In our case, the discrepancy between absolute and relative measures is driven by the fact that the three populations differ significantly in their initial levels of mortality. As we are interested in quantifying the burden of the male excess mortality across the three populations, an absolute measure appears to be most suitable as it takes into account the underlying risks of mortality [42].

Our study does not address the underlying reasons for the greater excess male mortality in the 1-year period after admission to hospital. The register data did not allow us to examine the severity of the underlying causes of hospital admission and to control for differences in health behaviors. Furthermore, the study design did not allow us to examine the question of whether the observed gaps in survival after hospital admission changed over time or across cohorts. This issue may be particularly relevant for Denmark where the sex differentials in mortality are known to have been affected by a stagnation of female life expectancy during the 1977 –

1995 period, which was a consequence of smoking among women born between the two World Wars [43–45]. The increased prevalence of smoking among Danish women, when compared to countries where the prevalence of female smokers remained low throughout the 20th century, may have an impact on our findings in two ways. First, by leading to higher levels of mortality among women of all three populations. Second, by leading to higher rates of admissions for smoking-related diseases among women. Likely, the male excess mortality would have been higher in all three populations in the absence of higher smoking rates among Danish women.The data do not allow us to quantify the impact of the Danish smoking phenomenon on our findings. All in all, this demonstrates that factors which determine the distribution of causes of admission to hospital and the levels of disease-specific mortality after hospitalization within a population are complex. Both factors may be influenced by changes in the organization and the performance of the health care system, including shifts in the admission strategies and the quality of medical treatment; or they could depend on a range of demographic characteristics, such as the prevalence of diseases or the distribution of risk factors in a population [22].

It is important to highlight that our analysis compares men and women of the same age and does not control for the health status of individuals. However, we recognize that men tend to develop adverse health conditions at earlier ages than women [46,47], and that studies on strokes and myocardial infarctions have shown that, on average, men are eight years younger than women at the onset of these conditions [48–51].

To gain a deeper understanding of the sex differences in mortality after hospital admission, future research should aim to identify the underlying reasons for these differences, and investigate how these sex disparities have developed over time, by cohort, and how they vary by socioeconomic status. Also the length of follow up we used needs to be taken into account. It could be that that the increased level of mortality during the first year after admission is temporary and that the duration of the follow-up period has an impact on the mortality levels of the hospitalized men and women due to selective mortality and cure. As we wanted to capture the immediate mortality development following hospital admission, we decided to use a relatively short follow-up period of 1-year length.

## Interpretation and implications in light of previous findings

The existing literature focusing on the female mortality advantage has pointed towards the effects and the interactions of biological, behavioral, and social factors [39]. The most widely cited biological factors are hormonal, based on the observation that the female hormone estrogen has favorable effects on serum lipid levels, as well as vasoprotective and immune-enhancing effects; and genetic, based on the assumption that women's second X chromosome helps to ameliorate the harmful effects of gene mutations on the X chromosome [52–55]. Moreover, women may have stronger immune systems than men which could help women to recover more quickly [56], and may play a fundamental role in women's better survival of harsh conditions, including famines and epidemics [10]. In addition to these biological factors, researchers have attributed a portion of the male disadvantage in mortality to behavioral and social factors [57]. For example, it has been argued that men have higher rates than women of smoking, excessive drinking, drug use, and violence [58].In addition to this, a large body of previous research, including research for Denmark, has shown that men tend to seek medical help later than women, which can lead to delays in diagnosis and treatment [59–65]. Previous studies have shown that men who are hospitalized tend to have conditions that are more severe and diseases are at more advanced stages than those of the women who are hospitalized; although the reasons for this pattern are not yet been fully understood [66].

In Denmark, hospital care is financed through taxes, and is thus available to all residents, regardless of their sex and socioeconomic characteristics [67]. Although our results may have been affected by changes in policies related to hospital admission, treatment, and discharge; it is likely that such changes would have affected men and women in similar ways. Although access to health care services is free and universal in Denmark, individuals may encounter hurdles in accessing health care services for a variety of reasons, including social, economic, demographic, and geographic factors [68]. In Denmark, general practitioners (GPs) typically serve not just as gatekeepers for the use of secondary health care, but also as care providers who can help patients avoid or postpone an admission to the hospital. For example, GPs assist patients in monitoring their health and in preventing the progress of many chronic conditions through regular medical check-ups, health consultations, the prescription of medications, and other preventive measures [69]. It is possible that the higher excess mortality after hospital

admission among men, found in our study, may be partially explained by sex differences in health awareness and help-seeking long before an adverse health condition becomes visible. Thus, the female advantage in survival after hospital admission is likely to be due to multiple factors, including biological advantages underpinned by sex differences in health behaviors. Our findings point towards the importance of further research on the possibilities of an efficient primary health care system, as well as individuals awareness of diseases, risk factors and compliance with preventive measures to reduce the male excess mortality following the manifestation of bad health.

## Conclusion

In this study we found that the risk of dying was highest for the hospitalized men and women in the 1-year period after admission to hospital, was lower among their counterparts in the general population, and was lowest among those individuals who were not admitted to hospital. We found the male excess mortality to be larger after the manifestation of bad health, which we measured as a hospital admission. Our findings point towards an association between the health status of a population and the magnitude of the absolute female advantage in mortality.

# 5 References


1 Drevenstedt GL, Crimmins EM, Vasunilashorn S, *et al.* The rise and fall of excess male infant mortality. *Proc Natl Acad Sci U S A* 2008;**105**:5016–21.

2 Najari BB, Rink M, Li PS, *et al.* Sex disparities in cancer mortality: the risks of being a man in the United States. *J Urol* 2013;**189**:1470–4.

3 Edgren G, Liang L, Adami HO, *et al.* Enigmatic sex disparities in cancer incidence. *Eur J Epidemiol* 2012;**3**:187–96.

4 Cook MB, McGlynn KA, Devesa SS, *et al.* Sex Disparities in Cancer Mortality and Survival. *Cancer Epidemiol Biomarkers Prev* 2011;**20**:1629–37.

5 De Torres JP, Cote CG, Lopez M V, *et al.* Sex differences in mortality in patients with COPD. *Eur Respir J* 2009;**33**:528–35.

6 Dransfield MT, Washko GR, Foreman MG, *et al.* Gender differences in the severity of CT emphysema in COPD. *Chest* 2007;**132**:464–70.

7 Waldron I, McCloskey C, Earle I. Trends in gender differences in accidents mortality: Relationships to changing gender roles and other societal trends. *Demogr Res* 2005;**13**:415–54.

8 Stroebe M, Schut H, Stroebe W. Health outcomes of bereavement. *Lancet* 2007;**370**:1960–73.

9 Moon JR, Kondo N, Glymour MM, *et al.* Widowhood and mortality: a meta-analysis. *PLoS One* 2011;**6**:e23465.

10 Zarulli V, Jones JAB, Oksuzyan A, *et al.* Women live longer than men even during severe famines and epidemics. *PNAS* 2018;201701535.

11 Gjonça A, Tommassini C, Toson B, *et al.* Sex differences in mortality, a comparison of the United Kingdom and other developed countries. *Heal Stat Q* 2005;**26&27**:6–16.

12 Wisser O, Vaupel JW. The sex differential in mortality: a historical comparison of the adult-age pattern of the ratio and the difference. *MPIDR Work Pap* 2014;**005**.

13 Beltrán-Sánchez H, Finch CE, Crimmins EM. Twentieth century surge of excess adult

male mortality. *Proc Natl Acad Sci U S A* 2015;**112**:8993–8.

14 Christensen K, Doblhammer G, Rau R, *et al.* Ageing populations: the challenges ahead. *Lancet* 2009;**374**:1196–208.

15 Karampampa K, Andersson T, Drefahl S, *et al.* Does Improved Survival Lead to a More Fragile Population: Time Trends in Second and Third Hospital Admissions among Men and Women above the Age of 60 in Sweden. *PLoS One* 2014;**9**.

16 Karampampa K, Drefahl S, Andersson T, *et al.* Trends in age at first hospital admission in relation to trends in life expectancy in Swedish men and women above the age of 60. *BMJ Open* 2013;**3**:439–54.

17 Case A, Paxson C. Sex differences in morbidity and mortality. *Demography* 2005;**42**:189–214.

18 Fleury M-J, Ngui AN, Bamvita J-M, *et al.* Predictors of healthcare service utilization for mental health reasons. *Int J Env Res Public Heal* 2014;**11**:10559–86.

19 Farkas J, Kosnik M, Flezar M, *et al.* Self-rated health predicts acute exacerbations and hospitalizations in patients with COPD. *Chest* 2010;**138**:323–30.

20 DeSalvo KB, Fan VS, McDonell MB, *et al.* Predicting mortality and healthcare utilization with a single question. *Heal Serv Res* 2005;**40**:1234–46.

21 Kennedy BS, Kasl S V, Vaccarino V. Repeated hospitalizations and self-rated health among the elderly: a multivariate failure time analysis. *Am J Epidemiol* 2001;**153**:232–41.

22 Hanlon P, Lawder R, Elders A, *et al.* An analysis of the link between behavioural, biological and social risk factors and subsequent hospital admission in Scotland. *J Public Heal* 2007;**29**:405–12.

23 Hanlon P, Walsh D, Whyte BW, *et al.* The link between major risk factors and important categories of admission in an ageing cohort. *J Public Heal* 2000;**22**:81–9.

24 Hanlon P, Walsh D, Whyte BW, *et al.* Hospital use by an ageing cohort: an investigation into the association between biological, behavioural and social risk markers and subsequent hospital utilization. *J Public Heal* 1998;**20**:467–76.

25 Smyth A, Teo KK, Rangarajan S, *et al.* Alcohol consumption and cardiovascular disease, cancer, injury, admission to hospital, and mortality: a prospective cohort study. *Lancet* 2015;**386**:1945–54.

26 Reeves GK, Balkwill A, Cairns BJ, *et al.* Hospital admissions in relation to body mass index in UK women: a prospective cohort study. *BMC Med* 2014;**12**:45.

27 Crowe FL, Appleby PN, Travis RC, *et al.* Risk of hospitalization or death from ischemic heart disease among British vegetarians and nonvegetarians: results from the EPIC-Oxford cohort study. *Am J Clin Nutr* 2013;**97**:597–603.

28 Garcia-Aymerich J, Lange P, Benet M, *et al.* Regular physical activity reduces hospital admission and mortality in chronic obstructive pulmonary disease: a population based cohort study. *Thorax* 2006;**61**:772–8.

29 Syddall HE, Westbury LD, Simmonds SJ, *et al.* Understanding poor health behaviours as predictors of different types of hospital admission in older people: findings from the Hertfordshire Cohort Study. *J Epidemiol Community Heal* 2016;**70**:292–8.

30 Thygesen LC, Daasnes C, Thaulow I, *et al.* Introduction to Danish (nationwide) registers on health and social issues: structure, access, legislation, and archiving. *Scand J Public Heal* 2011;**7**:12–6.

31 Pedersen CB. The Danish Civil Registration System. *Scand J Public Heal* 2011;**7**:22–5.

32 Lynge E, Lynge Sandegaard J, Rebolj M. The Danish National Patient Register. *Scand J Public Heal* 2011;**7**:30–3.

33 Andersen TF, Madsen M, Jørgensen J, *et al.* The Danish National Hospital Register. A valuable source of data for modern health sciences. *Dan Med Bull* 1999;**46**:263–8.

34 Schmidt M, Pedersen L, Sorensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol* 2014;**8**:541–9.

35 Hastie T, Tibshirani R. Generalized additive models. *Stat Sci* 1986;297–310.

36 Hastie T, Tibshirani R. Generalized additive models for medical research. *Stat Methods Med Res* 1995;**4**:187–96.

37 Wood S. *Generalized additive models: an introduction with R*. CRC press 2006.

38 Eilers PHC, Marx BD. Flexible smoothing with B-splines and penalties. *Stat Sci* 1996;89–102.

39 Oksuzyan A, Juel K, Vaupel JW, *et al.* Men: good health and high mortality. Sex differences in health and aging. *Aging Clin Exp Res* 2008;**2**:91–102.

40 Moser K, Frost C, Leon D. Comparing health inequalities across timeand place - rate

rtios and rste differences lead to different conclusions: analysis of cross-sectional data from 22 countries 1991. *Int J Epidemiol* 2007;**36**:1285–91.

41 Harper S, Lynch J. Methods for measuring cancer disparities: a review using data relevant to Healthy People 2010 cancer related objectives. SurveilanceMonograph Series 6. 2006.

42 Tramér M, Walder B. Number needed to treat (or harm). *World J Surg* 2005;**29**:576–81.

43 Lindahl-Jacobsen R, Rau R, Jeune B, *et al.* Rise, stagnation, and rise of Danish women's life expectancy. *Proc Natl Acad Sci U S A* 2016;201602783.

44 Lindahl-Jacobsen R, Oeppen J, Rizzi S, *et al.* Why did Danish women's life expectancy stagnate? The influence of interwar generations' smoking behaviour. *Eur J Epidemiol* 2016;1–5.

45 Jacobsen R, Oksuzyan A, Engberg H, *et al.* Sex differential in mortality trends of old-aged Danes: a nation wide study of age, period and cohort effects. *Eur J Epidemiol* 2008;**23**:723–30.

46 Hubbard RE, Rockwood K. Frailty in older women. *Maturitas* 2011;**69**:203–7.

47 Eskes T, Haanen C. Why do women live longer than men? *Eur J Obs Gynecol Reprod Biol* 2007;**133**:126–33.

48 Zhang Z, Fang J, Gillespie C, *et al.* Age-specific gender differences in in-hospital mortality by type of acute myocardial infarction. *Am J Cardiol* 2012;**109**:1097–103.

49 Berger JS, Elliott L, Gallup D, *et al.* Sex differences in mortality following acute coronary syndromes. *JAMA* 2009;**302**:874–82.

50 Appelros P, Stegmayr B, Terént A. A review on sex differences in stroke treatment and outcome. *Acta Neurol Scand* 2010;**121**:359–69.

51 Appelros P, Stegmayr B, Terént A. Sex differences in stroke epidemiology a systematic review. *Stroke* 2009;**40**:1082–90.

52 Seifarth JE, McGowan CL, Milne KJ. Sex and life expectancy. *Gend Med* 2012;**9**:390–401.

53 Bouman A, Heineman MJ, Faas MM. Sex hormones and the immune response in humans. *Hum Reprod Updat* 2005;**11**:411–23.

54 Stindl R. Typing it all together: telomeres, sexual size dimorphism and the gender gap

in life expectancy. *Med Hypotheses* 2004;151–4.

55 Christensen K, Ørstavik KH, Vaupel JW. The X chromosome and the female survival advantage. *Ann N Y Acad Sci* 2001;**954**:175–83.

56 Oertelt-Prigione S. The influence of sex and gender on the immune response. *Autoimmun Rev* 2012;**11**:A479--A485.

57 Rieker PP, Bird CE. Rethinking gender differences in health: why we need to integrate social and biological perspectives. *J Gerontol B Psychol Sci Soc Sci* 2005;**60**:S40--S47.

58 Rogers RG, Everett BG, Saint Onge JM, *et al.* Social, behavioral, and biological factors, and sex differences in mortality. *Demography* 2010;**47**:555–78.

59 Farrimond H. Beyond the caveman: Rethinking masculinity in relation to men's help-seeking. *Health (Irvine Calif)* 2012;**16**:208–25.

60 Chan RKH, Hayashi K. Gender roles and help-seeking behaviour promoting professional help among Japanese men. *J Soc Work* 2010;**10**:243–62.

61 Juel K, Christensen K. Are men seeking medical advice too late? Contacts to general practitioners and hospital admissions in Denmark 2005. *J Public Heal* 2008;**30**:111–3.

62 Noone JH, Stephens C. Men, masculine identities, and health care utilisation. *Sociol Heal Illn* 2008;**30**:711–25.

63 Adeyemi SA. Men's health help-seeking and implications for practice. *Am J Heal Stud* 2007;**22**:88.

64 Smith JA, Braunack-Mayer A, Wittert G. What do we know about men's help-seeking and health service use? *Med J Aust* 2006;**184**:81.

65 Smith LK, Pope C, Botha JL. Patients' help-seeking experiences and delay in cancer presentation: a qualitative synthesis. *Lancet* 2005;**366**:825–31.

66 Simmonds SJ, Syddall HE, Walsh B, *et al.* Understanding NHS hospital admissions in England: linkage of Hospital episode statistics to the Hertfordshire cohort study. *Age Ageing* 2014;afu020.

67 Olesen F, Hansen RP, Vedsted P. Delay in diagnosis: the experience in Denmark. *Br J Cancer* 2009;**101**:S5--S8.

68 Starfield B, Gérvas J, Mangin D. Clinical care and health disparities. *Annu Rev Public Heal* 2012;**33**:89–106.

69 Gérvas J, Starfield B, Heath I. Is clinical prevention better than cure? *Lancet* 2008;**372**:1997.

## Exclusive License



## Contributors

AH, RLJ, RR, KC and AO designed the study. AH, LAL analyzed the data. AH, LAL, DCS and provided support to optimize the program code. AH, RLJ, RR, KC, AO interpreted and discusses the results and implications. AH wrote the paper. All authors contributed to the revision of the paper and have approved the final version.

## Funding

The work was supported by the US National Institute of Health [P01AG031719, R01AG026786, and 2P01AG031719], the VELUX Foundation, and the Max Planck Society within the framework of the project *"On the edge of societies: New vulnerable populations, emerging challenges for social policies and future demands for social innovation. The experience of the Baltic Sea States (2016-2021)"*. The funders had no role in the design of the study or in the collection, analysis, and interpretation of data and results.

## Competing Interests

All authors have completed the ICMJE uniform disclosure and declare: no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work. The disclosure can be found at: (http://www.icmje.org/coi_disclosure.pdf)

## Ethics Approval

The study involves secondary data analysis of existing register data. The project was approved by the ethical committee assigned through the Danish National Committee on Biomedical Research and the Danish Data Protection Agency.

## Data Sharing

No additional data are available.

## Transparency Declaration

The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

# Tables

Table 1: Overview on causes of admission to hospital by sex.

| Cause of Hospital Admission | Men | | Women | |
|---|---|---|---|---|
| | Number | Share in % | Number | Share in % |
| Infectious & parasitic diseases | 980 | 1.54 | 1,012 | 1.58 |
| Neoplasms | 6,625 | 10.41 | 9,310 | 14.55 |
| Diseases of the blood & blood-forming organs | 266 | 0.42 | 401 | 0.63 |
| Endocrine, nutritional & metabolic diseases | 1,368 | 2.15 | 2,220 | 3.47 |
| Mental & behavioral disorders | 1,000 | 1.57 | 883 | 1.38 |
| Diseases of the nervous system | 1,434 | 2.25 | 1,382 | 2.16 |
| Diseases of the eye & adnexa | 1,026 | 1.61 | 1,464 | 2.29 |
| Diseases of the ear & mastoid process | 461 | 0.72 | 496 | 0.78 |
| Ischemic heart diseases | 5,899 | 9.27 | 2,601 | 4.06 |
| Cerebrovascular diseases | 2,386 | 3.75 | 1,756 | 2.74 |
| Other circulatory diseases | 6,324 | 9.94 | 5,368 | 8.39 |
| Respiratory Diseases | 3,785 | 5.95 | 3,233 | 5.05 |
| Digestive diseases | 8,368 | 13.15 | 6,166 | 9.64 |
| Diseases of the skin & subcutaneous tissue | 786 | 1.23 | 700 | 1.09 |
| Musculoskeletal disorders | 4,737 | 7.44 | 5,858 | 9.15 |
| Diseases of the genitourinary system | 4,680 | 7.35 | 6,968 | 10.89 |
| Injuries, poisonings & accidents | 6,466 | 10.16 | 7,228 | 11.29 |
| All other diseases[†] | 7,058 | 11.09 | 6,947 | 10.86 |
| **Total** | **63,649** | **100.00** | **63,993** | **100.00** |

[†] The largest groups among the category of all other diseases are symptoms, signs and abnormal clinical and laboratory findings (men: 57.57%, women: 58.42%) and factors influencing the health status and contact with health services (men: 37.47%, women: 36.99% ).

Table 2: Number of individuals, number of deaths, and the risk of dying within 1 year of follow-up by sex and age in the hospitalized, general, and non-hospitalized population.

| Age at Hospital Admission / Age of Matches | Men | | | | Women | | | |
|---|---|---|---|---|---|---|---|---|
| | Individuals | | Deaths | | Individuals | | Deaths | |
| | No. | Share in % | No. | Risk in % | No. | Share in % | No. | Risk in % |
| **Hospitalized Population** | | | | | | | | |
| 50–54 | 18,397 | 28.90 | 906 | 4.92 | 19,569 | 30.58 | 622 | 3.18 |
| 55–59 | 12,392 | 19.47 | 898 | 7.25 | 11,432 | 17.86 | 514 | 4.50 |
| 60–64 | 10,493 | 16.49 | 1,074 | 10.24 | 9,244 | 14.45 | 655 | 7.09 |
| 65–69 | 9,030 | 14.19 | 1,320 | 14.62 | 8,508 | 13.30 | 844 | 9.92 |
| 70–74 | 7,623 | 11.98 | 1,432 | 18.79 | 7,967 | 12.45 | 1,046 | 13.13 |
| 75–79 | 5,714 | 8.98 | 1,457 | 25.50 | 7,273 | 11.37 | 1,261 | 17.34 |
| **Total** | **63,649** | **100.00** | **7,087** | **11.13** | **63,993** | **100.00** | **4,942** | **7.72** |
| **General Population*** | | | | | | | | |
| 50–54 | 18,400 | 28.91 | 124 | 0.68 | 19,558 | 30.56 | 88 | 0.45 |
| 55–59 | 12,394 | 19.47 | 145 | 1.17 | 11,452 | 17.90 | 80 | 0.70 |
| 60–64 | 10,486 | 16.47 | 195 | 1.86 | 9,231 | 14.43 | 100 | 1.08 |
| 65–69 | 9,042 | 14.21 | 268 | 2.97 | 8,520 | 13.31 | 153 | 1.80 |
| 70–74 | 7,612 | 11.96 | 369 | 4.85 | 7,961 | 12.44 | 218 | 2.74 |
| 75–79 | 5,714 | 8.98 | 449 | 7.85 | 7,270 | 11.36 | 334 | 4.60 |
| **Total** | **63,649** | **100.00** | **1,551** | **2.44** | **63,993** | **100.00** | **974** | **1.52** |
| **Non-Hospitalized Population*** | | | | | | | | |
| 50–54 | 18,400 | 28.91 | 57 | 0.31 | 19,558 | 30.56 | 27 | 0.14 |
| 55–59 | 12,393 | 19.47 | 53 | 0.43 | 11,452 | 17.90 | 21 | 0.18 |
| 60–64 | 10,488 | 16.48 | 76 | 0.72 | 9,232 | 14.43 | 32 | 0.34 |
| 65–69 | 9,042 | 14.21 | 108 | 1.20 | 8,521 | 13.32 | 52 | 0.61 |
| 70–74 | 7,612 | 11.96 | 150 | 1.97 | 7,958 | 12.44 | 83 | 1.05 |
| 75–79 | 5,713 | 8.98 | 150 | 2.63 | 7,271 | 11.36 | 154 | 2.12 |
| **Total** | **63,649** | **100.00** | **656** | **1.03** | **63,993** | **100.00** | **369** | **0.58** |

* the number of deaths and the risk of dying refers to the average of 100 matching results

# Figure Legends

Figure 1: Estimated age trajectories in the risk of dying within 1 year of follow-up by cause of admission to hospital.

Figure 2: Male excess mortality within 1 year of follow-up by cause of admission to hospital.

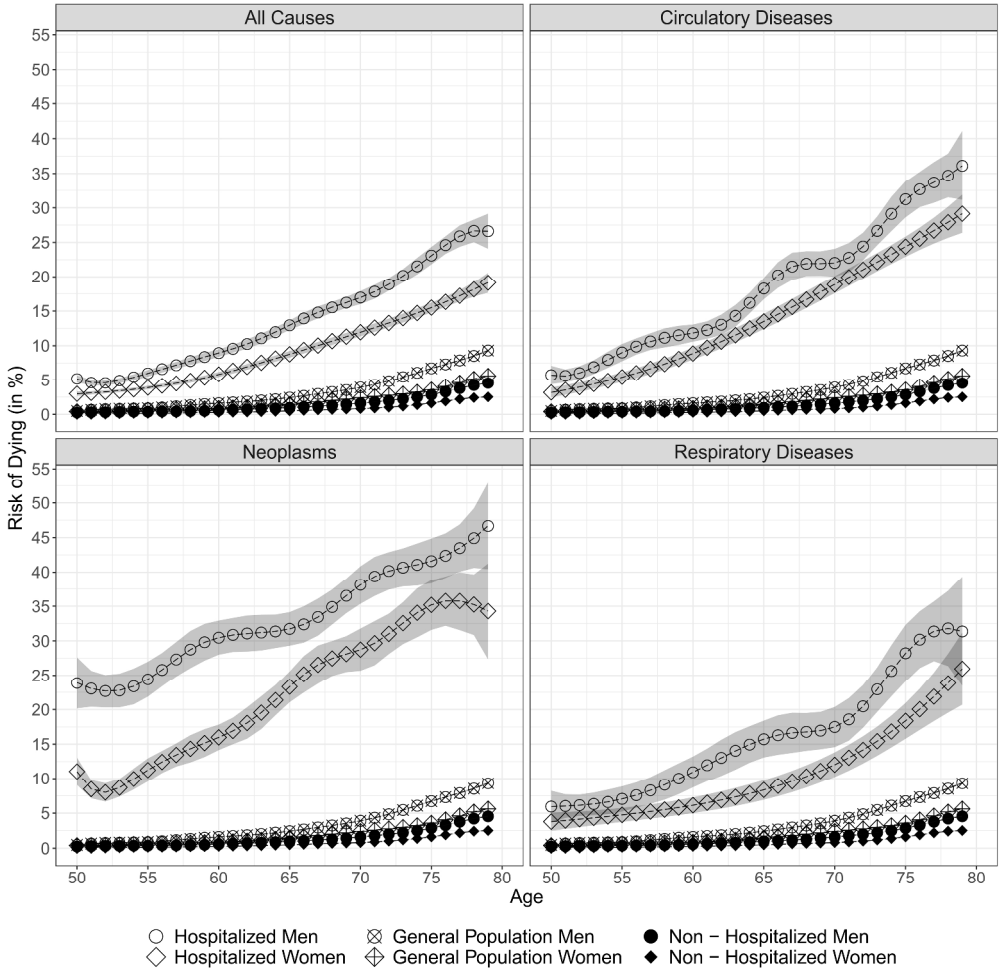



Figure 1: Estimated age trajectories in the risk of dying within 1 year of follow-up by cause of admission to hospital.

299x299mm (300 x 300 DPI)

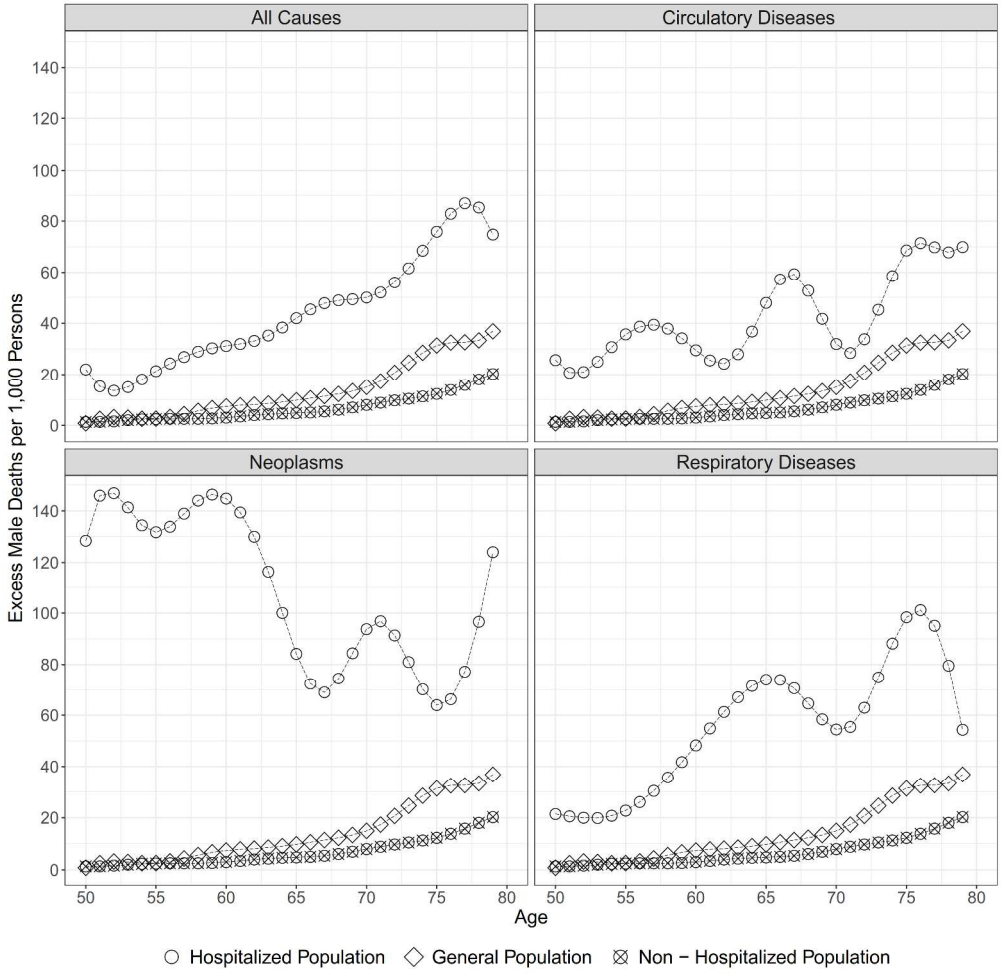
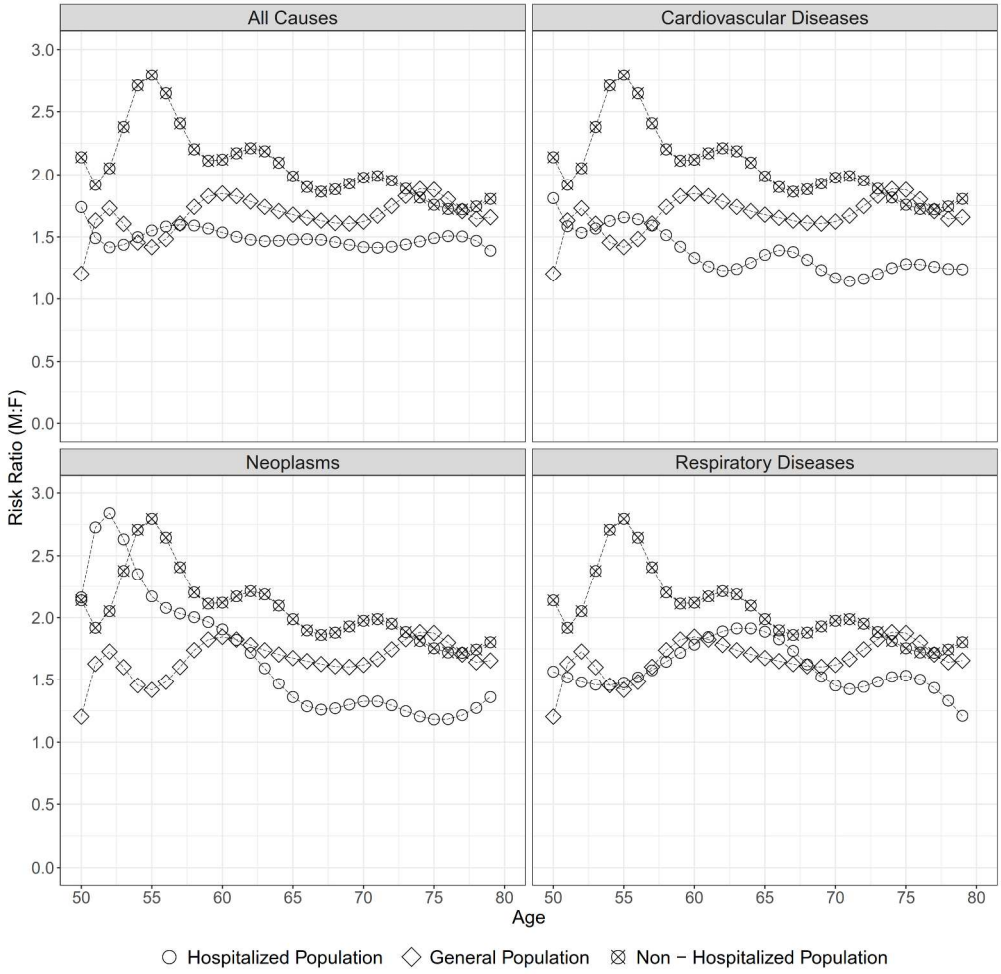



Figure 2: Male excess mortality within 1 year of follow-up by cause of admission to hospital.

299x299mm (300 x 300 DPI)




257x257mm (300 x 300 DPI)

# Supplementary Material

Supplementary table 1 – S: Classification of causes of hospital admission.

| Cause of hospital admission | ICD-8 | ICD-10 |
|---|---|---|
| Infectious & parasitic diseases | 000 - 136 | A00 - B99 |
| Neoplasms | 140 - 239 | C00 - D48 |
| Diseases of the blood & blood-forming organs | 280 - 289 | D50 - D89 |
| Endocrine, nutritional & metabolic diseases | 240 - 279 | E00 - E90 |
| Mental & behavioral disorders | 290 - 315 | F00 - F99 |
| Diseases of the nervous system | 320 - 358 | G00 - G99 |
| Diseases of the eye & adnexa | 360 - 379 | H00 - H59 |
| Diseases of the ear & mastoid process | 380 - 389 | H60 - H95 |
| Ischemic heart diseases* | 410 - 414 | I20 - I25 |
| Cerebrovascular diseases* | 430 - 438 | I60 - I69 |
| Other circulatory diseases* | remaining 390 - 458 | remaining I00 - I99 |
| Respiratory diseases | 460 - 519 | J00 - J99 |
| Digestive diseases | 520 - 577 | K00 - K93 |
| Diseases of the skin & subcutaneous tissue | 680 - 709 | L00 - L99 |
| Musculoskeletal disorders | 710 - 738 | M00 - M99 |
| Diseases of the genitourinary system | 580 - 629 | N00 - N99 |
| Injuries, poisonings & accidents | 800 - 999 | S00 - T98 & V01-Y98 |
| All other diseases | - all other - | - all other - |

** the three causes were further grouped and referred to as circulatory diseases*

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

| | Item No | Recommendation |
|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract **[within the title and the design section of the abstract on page 2]** |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **[within the abstract on pages 2-3]** |
| **Introduction** | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported **[within the background section on page 5]** |
| Objectives | 3 | State specific objectives, including any pre-specified hypotheses **[within the background section on pages 5-6]** |
| **Methods** | | |
| Study design | 4 | Present key elements of study design early in the paper **[within the methods and materials section on pages 6-7]** |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **[within the methods and materials section on pages 6-7]** |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **[within the methods and materials section on pages 6-7]** |
| | | (*b*) For matched studies, give matching criteria and number of exposed and unexposed **[within the methods and materials section on pages 6-7]** |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **[within the methods and materials section on pages 6-8]** |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **[within the methods and materials section on pages 6-8]** |
| Bias | 9 | Describe any efforts to address potential sources of bias **[within the methods and materials section on pages 6-8]** |
| Study size | 10 | Explain how the study size was arrived at **[within the methods and materials section on pages 6-7]** |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **[within the methods and materials section on pages 6-8]** |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding **[within the methods and materials on pages 6-8]** |
| | | (*b*) Describe any methods used to examine subgroups and interactions **[within the methods and materials section on page 6-8]** |
| | | (*c*) Explain how missing data were addressed **[properties of the data are described within the methods and materials section on pages 6-8 and in the discussion on pages 11-13]** |
| | | (*d*) If applicable, explain how loss to follow-up was addressed **[properties of the data are described within the methods and materials section on page 6-8 and in the discussion on pages 11-13]** |

| | | |
|---|---|---|
| | | (*e*) Describe any sensitivity analyses<br>**[The investigation of mortality differentials after cause-specific admission was used as a sensitivity analysis and robustness check and is part of the manuscript. Results are presented in the results section on pages 8-11. Moreover, a discussion of the findings can be found in the discussion section on pages 13-15.]** |
| **Results** | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed<br>**[identification of individuals is described within the methods and materials section on pages 6-7; an overview is given in table 1 and table 2]** |
| | | (b) Give reasons for non-participation at each stage<br>**[properties of the data are described within the methods and materials section on page 6 and in the discussion on pages 11-13]** |
| | | (c) Consider use of a flow diagram<br>**[NA, but identification of individuals is described within the methods and materials section on pages 6-8]** |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders<br>**[within the methods and materials section on pages 6-8 and in more detail in the results section on pages 8-10; potentially unobserved characteristics of the participants are described in the discussion on pages 11-13]** |
| | | (b) Indicate number of participants with missing data for each variable of interest<br>**[NA, but properties of the data are described within the methods and materials section on page 6 and in the discussion on pages 11-13]** |
| | | (c) Summarise follow-up time (eg, average and total amount)<br>**[within the methods and materials section on pages 6-8]** |
| Outcome data | 15* | Report numbers of outcome events or summary measures over time<br>**[within the results section on pages 8-11; table 1, table 2, figure 1, figure 2]** |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included<br>**[within the results section on pages 8-11; table 1, table 2, figure 1, figure 2]** |
| | | (*b*) Report category boundaries when continuous variables were categorized<br>**[NA]** |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period<br>**[NA]** |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses<br>**[the main analysis contains already an analysis of subgroups to check for sensitivity and robustness of our results; findings are presented in the results section on pages 8-11]** |
| **Discussion** | | |
| Key results | 18 | Summarise key results with reference to study objectives<br>**[within the discussion section on pages 11 and 15]** |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias<br>**[within the discussion section on pages 11-12]** |

| | | |
|---|---|---|
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **[within the discussion section on pages 13-15]** |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results **[within the discussion section on pages 13-15]** |
| **Other information** | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **[within the funding section on page 22]** |

*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.