PhD Thesis

Gender, Hospitalization, and Mortality

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December 2019

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Acknowledgments

At this point, I would like to thank my supervisors Rune Lindahl-Jacobsen, Roland Rau, Anna Oksuzyan, and Kaare Christensen. Throughout my PhD, I was always well supervised and guided by this multidisciplinary team. Thank you very much for sharing your ideas and thoughts honestly with me. I would like to thank Anna for hiring me as your first PhD student. Anna's encouragement has been a valuable source of motivation throughout my entire PhD. I would like to thank Kaare and Rune for encouraging me to become a PhD student in Denmark while giving me the freedom to keep my close connections with Rostock and the MPIDR.

With some years of delay, I would like to thank Roland. In 2011, Roland spontaneously called his friend Domas at the MPIDR in Rostock to arrange a meeting for me on the very same day to discuss my BA thesis ideas. Since then, the MPIDR has always been an amazing place for me to learn and develop as a researcher.

An outstanding and very special thanks goes to Ute for your patience and excellent conversations. I hope we have not caused too many administrative problems within our institute – although we should be proud of causing at least one or two.

I would like to thank my colleague, office mate, and good friend Jen for being such a great mentor, adviser, and critical reviewer of my papers and this thesis. I am very thankful for all of your help and feedback during the last months of my PhD.

I also thank my co-authors for their great contributions throughout the four papers of my PhD: Lisbeth Aagaard Larsen, Daniel Schneider, Jutta Gampe, Alyson van Raalte, and Pekka Martikainen.

Very warm thanks go to my mother Nadja and my sister Lena for their help and understanding. Although I have not been very good (or patient enough) in explaining what my actual research is about, you have never questioned my enthusiasm and enjoyment. I think this thesis marks the point of no return; I won't become a dentist anymore.

I also want to thank my friends Mathias and Laura, who were my flatmates throughout the preparatory year of my PhD – the EDSD 2015/2016 in Rome. Thank you very much for sharing and discussing thoughts, hopes, fears, project ideas, wines, memes, as well as Rcode and solutions for the pending assignments. This is also the place to say thank you to my friends from the 'Saturday Group': June, Karen, Stefan, Kieron, Tim, Ainhoa, Aitor, and Jen. Thank you very much for letting me win so many rounds of board games, particularly 'Seven Wonders'. Another very special thanks goes to my friends from Rostock, of which most I have known for more than 10 years now. Your outstanding company made my amazing days feel even greater and the difficult days a little more bearable.

And, finally, a last and very big thanks goes to Rosie. It is my biggest pleasure to say thank you for an infinite number of things, but in particular, for constantly reminding me of all the big and little things in life that matter. Thank you very much for teaching me that compromises are acceptable up to a certain point – except when it's about compromising on happiness in life.

Funding

This thesis was primarily funded by the grant to establish the Max Planck Research Group 'Gender Gaps in Health and Survival' at the Max Planck Institute for Demographic Research, Rostock. Furthermore, the thesis received funding from the Max Planck Odense Center on the Biodemography of Aging (MaxO), the Interdisciplinary Center on Population Dynamics at the University of Southern Denmark, Odense (CPop), 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 and the experience of the Baltic Sea States (2016-2021)'.

In addition, the papers of the thesis were supported by the US National Institute of Health (P01AG031719, R01AG026786, and 2P01AG031719), the VELUX Foundation, the European Research Council (Grant Number 716323), the Academy of Finland, and the Odense University Hospital within the Framework of the AgeCare Program (Academy of Geriatric Cancer Research).

Summary – English

Although women tend to have poorer health than men, they have a mortality advantage. This finding has been documented across different countries and contexts. However, the generalizability of this paradox is contested – particularly among individuals of post-reproductive ages, when health deteriorates and aging accelerates. Routinely-collected hospital records may provide a unique framework for studying gender differences in mortality and health. These data cover information on medically diagnosed conditions, can often be linked with mortality data, and exist for a variety of countries, including Denmark.

Using Danish register data, four papers were developed to analyze particular features of gender differences in mortality and health surrounding hospital admissions. In the first paper, male excess mortality following the first all-cause and cause-specific hospitalization after age 50 was estimated. Results from the first paper indicate that part of the female mortality advantage at post-reproductive ages can be attributed to their lower risk of dying following the deterioration of health.

The second paper examined how gender patterns in treatment-seeking behavior changed around a major health shock, measured as the first admission to hospital after age 60 for either stroke, myocardial infarction, chronic obstructive pulmonary disease, or gastrointestinal cancers. Findings point towards the fact that women's higher levels of primary healthcare use are attributable to a combination of both, a lower threshold to seek medical advice, and a health disadvantage resulting from lower mortality in bad health.

The third paper studied whether the mean age at first hospital admission after age 60 has increased among Danish men and women over time, and whether

this trend has been accompanied by increasing or decreasing variation in the mean age. Results show that morbidity has been shifted towards older ages. However, increasing variation in the age at first admission indicates that this average increase has not been experienced by everyone.

In the fourth paper, the current demographic profile of hospital care use in Denmark was described, and changes up to 2050 were projected. Increasing longevity among men and women, in combination with men's higher risk to be hospitalized at post-reproductive ages, mean men aged 70+ are projected to be the fastest-growing patient group.

Regarding hospital admissions, women at post-reproductive ages have multiple advantages in comparison to men: Women have a lower risk of being admitted to hospital, and have lower mortality following hospitalization. One potential explanation for these patterns could be that women seek advice earlier in the disease course. Healthcare systems preparing for population aging should be aware of these gender patterns to ensure that hospitals meet the needs of future patients.

Summary – Danish

Selvom kvinder gennemgående har et dårligere helbred end mænd, har de mindre dødsrisiko. Dette er vist i studier på tværs af lande og tidsperioder. Alligevel anfægtes generaliserbarheden af dette paradoks – især for mennesker som er ovre den reproduktive alder, hvor helbredet bliver dårligere og aldringsprocesserne accelererer. Rutinemæssigt indsamlede hospitalsregistreringer giver værdifuld, objektiv information og skaber et godt grundlag for at studere kønsforskelle i dødelighed og helbred. Disse oplysninger omfatter medicinsk diagnosticerede lidelser, som ofte kan kobles til data vedrørende dødelighed, og som er tilgængelige i en lang række lande, heriblandt Danmark.

Hospitalsregistreringer for hele den danske befolkning dannede grundlag for fire studier, der analyserede kønsforskelle i helbred og dødelighed i forbindelse med hospitalsindlæggelser. Det første studie estimerede den mandlige overdødelighed, både samlet og årsagsspecifik, efter den første hospitalsindlæggelse efter det fyldte 50 år. Resultaterne fra det første studie tyder på at kvinders mindre dødsrisiko efter den reproduktive alder kan tilskrives det forhold at kvinder har lavere risiko for at dø i forbindelse med helbredsforværring.

Det andet studie undersøgte hvordan den kønsspecifikke behandlingssøgende adfærd ændrede sig i forbindelse med et større helbredsmæssigt chok defineret som første hospitalsindlæggelse efter det fyldte 60 år på grund af enten slagtilfælde, hjerteinfarkt, kronisk obstruktiv lungesygdom eller mave-tarmkræft. Resultaterne indikerer at kvinders større brug af det primære sundhedsvæsen kan skyldes en kombination af at kvinder oftere søger lægehjælp og det forhold at de har mindre risiko for at dø i forbindelse med helbredsforværring.

Det tredje studie undersøgte om gennemsnitsalderen ved første hospitalsindlæggelse efter det fyldte 60 år var steget med tiden blandt danske mænd og kvinder, og om denne tendens var ledsaget af en stigende eller faldende variation i gennemsnitsalderen. Resultaterne viser at sygdomme indtræffer senere i livet. Alligevel viser den stigende variation i alder ved første indlæggelse, at det ikke er alle, der oplever denne sygdomsudskydelse.

Det fjerde studie omhandlede den nuværende demografiske profil for hospitaliseringer i Danmark samt en fremskrivning til år 2050. Stigende levetid for mænd og kvinder sammenholdt med mænds højere risiko for at blive indlagt efter den reproduktive alder betyder at mænd på 70+ forventes at blive den hurtigst voksende patientgruppe.

Med hensyn til hospitalsindlæggelser har kvinder efter den reproduktive alder en række fordele sammenlignet med mænd: Kvinder har mindre risiko for at blive indlagt på et hospital og de har lavere dødelighed efter hospitalisering sammenlignet med mæ nd. En mulig forklaring på dette kan være at kvinder søger læge tidligere i sygdomsforløbet. De forskellige landes sundhedssystemer arbejder hen mod at kunne rumme en aldrende befolkning, og de må derfor være opmærksomme på disse kønsforskelle for at sikre at hospitalerne kan imødekomme fremtidige patienters behov.

Papers of the Thesis

The main body of the thesis consists of the following four papers:

<u>Andreas Höhn</u>, Lisbeth Aagaard Larsen, Daniel Christoph Schneider, Rune Lindahl-Jacobsen, Roland Rau, Kaare Christensen, and Anna Oksuzyan: 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. **BMJ open** 2018;8(7),e021813. *doi:10.1136/bmjopen-2018-021813*

<u>Andreas Höhn</u>, Jutta Gampe, Rune Lindahl Jacobsen, Kaare Christensen, and Anna Oksuzyan: Do men avoid seeking medical advice? A register-based study of gender-specific changes in primary healthcare use after first hospitalization at ages 60+ in Denmark. ***Submitted to a peer-reviewed journal***

Rosie Seaman, <u>Andreas Höhn</u>, Rune Lindahl Jacobsen, Pekka Martikainen, Alyson van Raalte, and Kaare Christensen: Rethinking Morbidity Compression: Increasing Inequality in Age at Morbidity Onset. ***Submitted to a peer-reviewed journal***

<u>Andreas Höhn</u>, Anna Oksuzyan, Rune Lindahl-Jacobsen, Roland Rau, and Kaare Christensen: Preparing for the future: The changing demographic composition of hospital patients in Denmark between 2014 and 2050. ***Submitted to a peer-reviewed journal***

Co-Authored Papers

In addition to the four papers of the thesis, I co-authored the following papers during my time as a PhD student. These papers are not directly linked with the thesis and are therefore not included in the main body.

Anna Oksuzyan, Torsten Sauer, Jutta Gampe, Andreas Höhn, Mette Wod, Kaare Christensen, and Jonas W. Wastesson: Is whom you ask important? Concordance between survey and registry data on medication use among self- and proxy-respondents in the Longitudinal Study of Aging Danish Twins and the Danish 1905-Cohort Study. **J Gerontol A Biol Sci Med Sci** 2019;74(5),742–747. *doi:10.1093/gerona/gly104*

Adriana Santacroce, Jonas W. Wastesson, Andreas Höhn, Kaare Christensen, and Anna Oksuzyan: Gender differences in the use of anti-infective medications before and after widowhood: A register-based study. **J Epidemiol Community Health** 2018;72(6),526–531. *doi:10.1136/jech-2017-210114*

Abbreviations

Some abbreviations were used in the thesis, of which each is spelled out at first appearance in every chapter. The following abbreviations were used:

AIC:	Akaike Information Criterion
CI:	Confidence Interval
CoefV:	Coefficient of Variation
COPD:	Chronic Obstructive Pulmonary Disease
CPR:	Central Population Register
DFLE:	Disability-Free Life Expectancy
GAM:	Generalized Additive Model
GLM:	Generalized Linear Model
GIC:	Gastrointestinal Cancers
GP:	General Practitioner
HLE:	Healthy Life Expectancy
HMD:	Human Mortality Database
ICD:	International Classification of Diseases
MI:	Myocardial Infarction
NPR:	National Patient Register
NHSR:	National Health Service Register
OR:	Odds Ratio
SD:	Standard Deviation

Preface: Sex and/or Gender?

Sex is a biological concept – based on chromosomal, cellular, hormonal, and molecular characteristics.[1] In contrast to this, gender is a social concept – the reflection of behavioral and cultural factors which contribute to both a person's self-identity and societal structures by defining norms, roles, expectations, and power relations.[1] Since being introduced nearly half a century ago, this distinction has become widely accepted in the medical sciences and is now visible within journals editorial policies on how sex and gender should be reported, for example in The Lancet.[2] Although sex is a key variable in most studies and models of the health sciences, it seems that there is still no clear standard for how gender can be measured and followed throughout all stages of research.[3] This issue was ever-present while working on the thesis, and I discovered that even the most contemporary research often uses sex and gender inconsistently, interchangeably, or inappropriately. Sex and gender are distinct concepts and should not be considered synonyms.

The question of whether the term sex and/or gender should be used in a research project is an important empirical question – rather than a matter of belief – as both concepts, one, or neither concept may play a key role.[4] For example: Sex differences in hormonal levels have an impact on the age at onset of cardiovascular diseases.[5] In addition, gender-patterned health behaviors such as smoking, drinking, or nutrition are at least of equal importance for explaining why men experience cardiovascular diseases earlier in life than women.[6] However, factors not related to sex or gender, such as high levels of air pollution, may also be important for explaining increased population-level incidence rates.[7]

The title of the thesis contains the phrase gender – not sex. However, some sections of the thesis refer to the term sex. The Scandinavian languages, including Danish, do not force a distinction between sex and gender but use *køn*, *kön*, or *kjønn* for both concepts.[8] Underlining this, the journal articles describing the Danish registries translate the dichotomous-coded variable *køn* interchangeably as sex and gender – even within the same publication.[9,10] Additionally, official data and material provided by Statistics Denmark often refer to both sex and gender.

Another important feature emerges from the binary coding of the sex/gender variable in the utilized Danish registers. Given such a dichotomous concept, it is impossible to study individuals which may identify themselves outside the binary framework of "men" and "women". The literature has found that the likelihood of certain health outcomes, and the pathways to these health outcomes, may differ among individuals who do not identify as either "men" or "women".[11–13] In this regard, the majority of national agencies and data providers have not yet accounted for the diversity of gender identities.

Throughout the thesis, I decided to follow the rule of Clayton and Tannenbaum (2016) who argued that, in order to avoid misleading conclusions, what should be reported is what has been studied or recorded.[1] In practice, this meant I chose to use the term "gender" in applications which primarily targeted or incorporated behavioral features – and preferred to use the term "sex" when no information on behavioral features were available or when studies being referenced explicitly used this terminology.

1 Introduction

1.1 Sex Differences in Mortality and Health

1.1.1 Gaps in Life Expectancy Between Men and Women

A female advantage in life expectancy has been reported for most historic populations, even when levels of maternal mortality were high.[14–16] Before the 19th century, sex differences in life expectancy were generally small as poor living conditions, inadequate sanitation, epidemics, and famines resulted in high levels of mortality among both men and women.[17] Throughout the 19th and 20th centuries, the impact of these external hazards diminished. At the same time, the impact of infectious diseases rapidly decreased and non-communicable diseases became the major causes of death, including cardiovascular diseases and neoplasms. This process is known as the epidemiological transition.[18,19]

Key features of the epidemiological transition were sustained improvements in life expectancy for men and women in most developed countries.[20] Following this modern mortality decline, but with a lag of about half a century, sex differences in life expectancy started to widen. While differences in life expectancy between men and women widened slowly during the 19th century, they increased more rapidly throughout the 20th century as mortality became increasingly patterned by behavioral factors.[21,22] In nearly all developed countries, sex differences in life expectancy peaked in the 1970s and 1980s and declined thereafter.[23,24] Today, women outlive men in all countries of the world.[25,26]

Figure 1 illustrates the magnitude of sex differences in life expectancy at birth. Women's advantage in life expectancy is shown for Denmark and all other countries covered in the Human Mortality Database (HMD).[27] An important feature to highlight is that the magnitude of women's advantage in life expectancy has varied over time, and even differs in developed countries today. For example, in 2016, women had an advantage of 3.6 years in Iceland and 10.1 years in Belarus.[27]

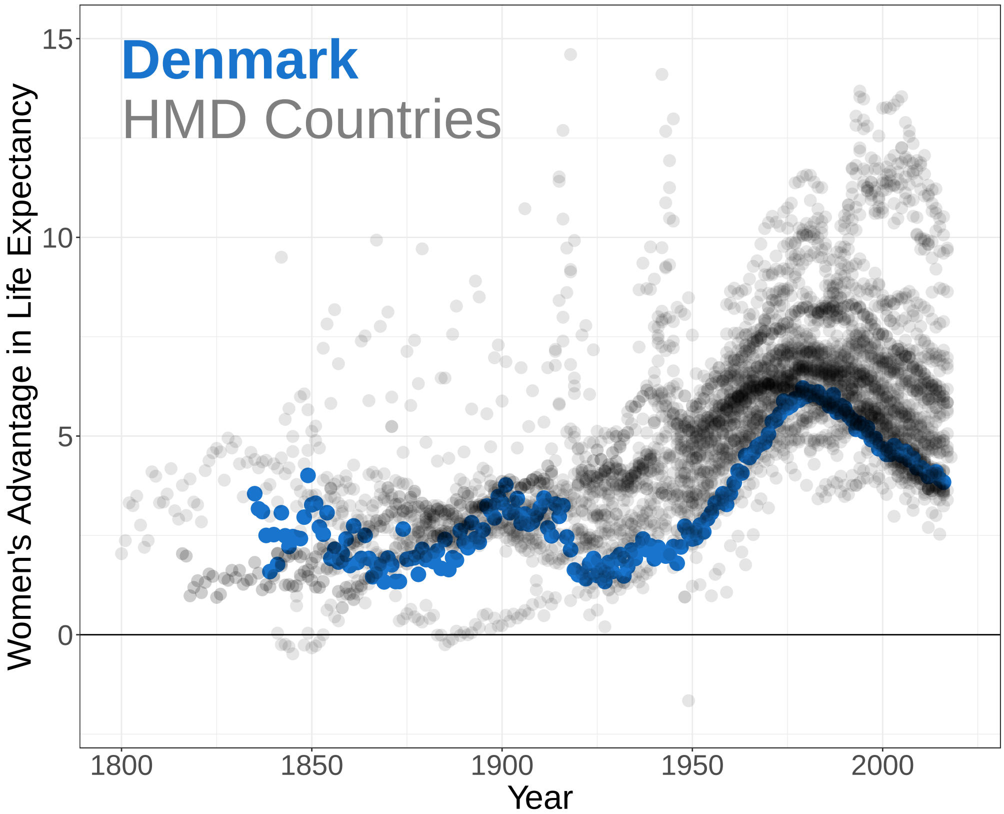


Figure 1: Women's absolute advantage in life expectancy at birth in Denmark and all other HMD countries. *Source: Own calculations based on HMD data.*

1.1.2 The Contribution of Behavior and Biology

In order to explain the rapid divergence and convergence of sex differences in life expectancy across developed countries throughout the 19th and 20th centuries, as well as cross-country differences in the timing of these trends, studies have drawn attention to behavioral aspects. In addition, studies have highlighted that mortality patterns at post-reproductive ages are an important part of the explanation for these patterns of divergence and convergence.[17,28]

It has been shown that the widening sex gap in life expectancy throughout the 20th century was caused by the cohorts of men born in the late 19th century.[28] Throughout the 20th century, men aged 50 to 70 years old experienced slower mortality declines than women at these ages, which has been widely attributed to smoking.[23] During the 20th century, men had higher rates of smoking than women, and the prevalence of smoking among men increased at an earlier point in time.[28] Women picked up smoking, but with a delay of some decades.[29] During the peak of the gender gap in life expectancy, studies have estimated that differences in smoking accounted for up to 40% of the gap in life expectancy in some countries.[30] Alongside the lagged effect of smoking on mortality, men's higher propensity of hazardous drinking, poor nutrition, risk-taking behavior, higher levels of aggression and violence, and their reluctance to seek medical advice are assumed to have significantly contributed to sex differences in mortality.[31,32]

Substantial changes in gender roles have reduced behavioral differences and, as a result, sex differences in life expectancy started to narrow since the 1970s.[30] Support for this hypothesis comes from the observation that the prevalence of smoking increased among women born around the mid of the 20th century, while smoking rates had already started to drop among men of the same cohorts within most developed countries.[33]

Although behavioral factors are the largest drivers of cross-country differences in the magnitude of the gender gap when comparing Eastern and Western European countries, not all features of women's mortality advantage can be attributed to behavioral factors.[34]

One pattern that does not reflect behavioral causes is the fact that female infants have lower levels of mortality than male infants.[35] A consistent female advantage in mortality has also been found across historic populations who experienced extreme mortality conditions due to severe famines and epidemics – an observation which has been interpreted as biologically-rooted.[16] Quasi-natural experiments which have examined long-term trends in mortality among men and women in societies with strict behavioral rules and who have nearly identical lifestyles have also found a mortality advantage among women. Study populations included Mormons,[36] Israeli Jews,[37] and cloistered populations in Bavaria.[38,39]

The two most plausible biological explanations for the female mortality advantage are differences in genes and endocrinology.[40] Differences in the set of chromosomes are major genetic features that distinguish males and females. While males have one active X and one active Y chromosome in each cell, females have two X chromosomes, of which only one is active.[41] Studies have argued that the ability of the female organism to inactivate the disadvantageous X chromosome helps to prevent X-linked diseases and mutations, and weakens the effects of physiological stress on women compared to men.[42]

With regard to endocrinology, hormonal differences between the sexes, and in particular the strong sex-patterning of the steroid hormones estrogen, progesterone and testosterone, have been pointed out to have an impact on the female mortality advantage.[43] For example, higher estrogen levels in females were shown to have beneficial effects on serum lipid levels – a major risk factor for the age at onset of cardiovascular diseases.[5] In addition, estrogen was shown to have immune-enhancing effects which may make females more resistant to certain infectious processes but more likely to suffer from autoimmune diseases.[44]

Despite all biological evidence, it needs to be taken into account that neither the exact impact of a single nor the sum of all biological factors can be estimated. In addition, not all species with sexual dimorphism show a general mortality advantage of females.[45,46]

Studies have increasingly argued that for human populations, gender is an important modifier of sex.[47] For example, immune responses are strongly affected by social and environmental conditions, such as nutrition or the exposure to biologicals and chemicals.[48] To understand the origins of women's mortality advantage, a holistic, but the same time detailed perspective, is necessary that simultaneously explores mortality and health.

1.1.3 The Paradox of Health and Survival

Women's higher life expectancy at birth is the result of a universal mortality advantage. This advantage starts at infancy and can be found even at the highest ages, as absolute sex differences in mortality exponentially increase with age.[22,49,50] Women have lower rates of mortality with respect to most causes of death, as well as following most adverse life course events such as bereavement or job loss.[51,52] However, women's mortality advantage does not translate into a universal health advantage – a phenomenon known as the male-female health-survival paradox.[32,40]

Health is a multifaceted concept which incorporates various dimensions of physical, mental, and social well-being.[53] The recognized complexity of this concept has led to various approaches for measuring health and it's dimensions.[54] Although conclusions about the health status of individuals and populations depend on how health has been measured,[55,56] poor and declining health should be associated with lower levels of life expectancy.[57,58] However, this is not consistently the case when comparing men and women.

Empirical evidence for the existence of a male-female health-survival paradox has been reported widely over the past decades, and across a large number of countries.[59–62] With respect to the physical dimensions of health, studies have shown that men have better physical performance and less functional limitations than same-aged women.[32,60,63] Furthermore, men were shown to be less likely than women to report symptoms of depression, anxiety, and fear.[64]

Another observation which has been interpreted as evidence for the paradox is that women, on average, use primary health care services more often than same aged men – even when controlling for obstetrics-related treatments.[65] However, it has remained unanswered whether higher levels of primary healthcare use among women are due to a lower threshold to seek medical treatment or a reflection of a true health disadvantage.[31,66] As it will be shown in the next section, lower levels of primary healthcare use among men are in contrast to their higher levels of hospital care use.

A growing number of studies have begun to assess whether the health disadvantage of women is generalizable across all measures of health. These studies have shown that gender differences in health might be small or even reversed with regards to bio-markers and objective health measures.[67,68] Even studies using survey data have shown that gender differentials in self-reported health substantially decrease or even flip when comparing men and women who have similar socioeconomic backgrounds, who engage in similar health behaviors, or when data for total populations are used.[69–74]

Overall, it is not yet fully understood whether gender differences in health reflect real differences or are likely to be explained by a number of distorting factors, such as gender-patterned survey participation rates or reporting styles.[75,76] As it will be shown in the next section, patterns reported in existing studies using hospital admission data may question the generalizability of the health-survival paradox.

1.2 Gender and Hospitalization

1.2.1 Hospitalization as a Health Indicator

Routinely-collected hospital records are available for a variety of countries, such as the UK, Finland, Sweden, Norway, and Denmark. These data offer the potential to derive powerful indicators of health. In addition, hospital records may provide a unique framework for studying gender differences in mortality and health as these data cover information on medically diagnosed conditions and can often be linked with mortality data.

While contacts with primary healthcare services can be postponed or avoided, an admission to hospital is usually the consequence of a health deterioration that requires a needs-driven medical intervention.[31,69,74] Irrespective of whether an admission to hospital occurred due to a planned surgery or due to a sudden, life-threatening health shock, this contact with the healthcare system reflects a medical necessity. In both cases, a timely and medically more invasive intervention is required to prevent the worsening of health in the short or the long term, or even death.

A large number of previous studies have shown that the risk of hospitalization is strongly associated with a variety of well-established individual- and population-level health measures. With respect to individual-level health, poor self-rated health is a powerful predictor of an increased risk of hospital admission.[77,78] A large number of studies have pointed out that certain behavioral factors are strongly associated with the risk of all-cause, as well as cause-specific hospital admissions. For example, smoking was shown to increase the risk of all-cause admissions, as well as the risk of hospitalization for neoplasms, through it's association with lung cancer.[79] In addition, studies reported that hazardous drinking, being overweight, a poor diet, and a lack of physical activity are associated with an increased risk of all-cause and cause-specific hospital admissions.[80–85]

In line with these observations at the individual level, studies have pointed out that the distribution of risk factors within populations is closely linked to population-level hospitalization patterns.[80] For example, it has been argued that health behaviors and the health status of the underlying background population are closely associated with dimensions of population health, such as number of hospital admissions, bed days, cause-specific admission rates as well as rates of emergency admissions.[85–89] Therefore, measures obtained from all-cause and cause-specific hospital admission data offer a pragmatic approach to monitor both population-level and individual-level health within a proxy framework. The potential of using routinely-collected, large-scale hospitalization records to study gender differences in mortality and health has not been fully realized.

1.2.2 Gender Patterns in Admission and Mortality

The risk of hospitalization is strongly patterned by health conditions and increases with age as most non-communicable diseases become more prevalent.[79,80,90–93] Generally, men and women at post-reproductive ages share a similar spectrum of diseases and disease co-occurrences when a life course perspective is taken.[73,74] However, when controlling for conditions and socio-demographic characteristics, the risk of all-cause and cause-specific admission to hospital consistently differs between men and women. For example, for most conditions, men are more likely to be admitted to hospital and get admitted at younger ages in comparison to women.[31,72,74,79,88]

Figure 2 provides an overview of the average number of hospital days per person, across age, for Danish men and women using four different settings: (A) all patient types - all causes (B) all patient types - excluding obstetrics (C) excluding outpatients - all causes (D) excluding outpatients - excluding obstetrics.[a]

As shown in Figure 2, irrespective of the specified setting, men spend more days in hospital than women during infancy and childhood. With the start of puberty, this pattern starts to change and women have higher levels of hospital bed days throughout the reproductive ages. At post-reproductive ages, the lines for men and women cross over in all settings and men, on average, spend more days in hospital than same-aged women. This male disadvantage in the risk of admission to hospital has also been reported for the oldest-old population in Denmark above the age of 90.[94,95] When comparing the panels in the left column with the panels in the right column, it becomes evident that the higher level of hospital bed days among women across reproductive ages is directly linked with obstetrics-related admissions.

[a] Obstetrics-related admissions were defined as O.00-O.99 and Z.30-Z.39 according to the 10th Revision of the International Classification of Diseases (ICD-10)

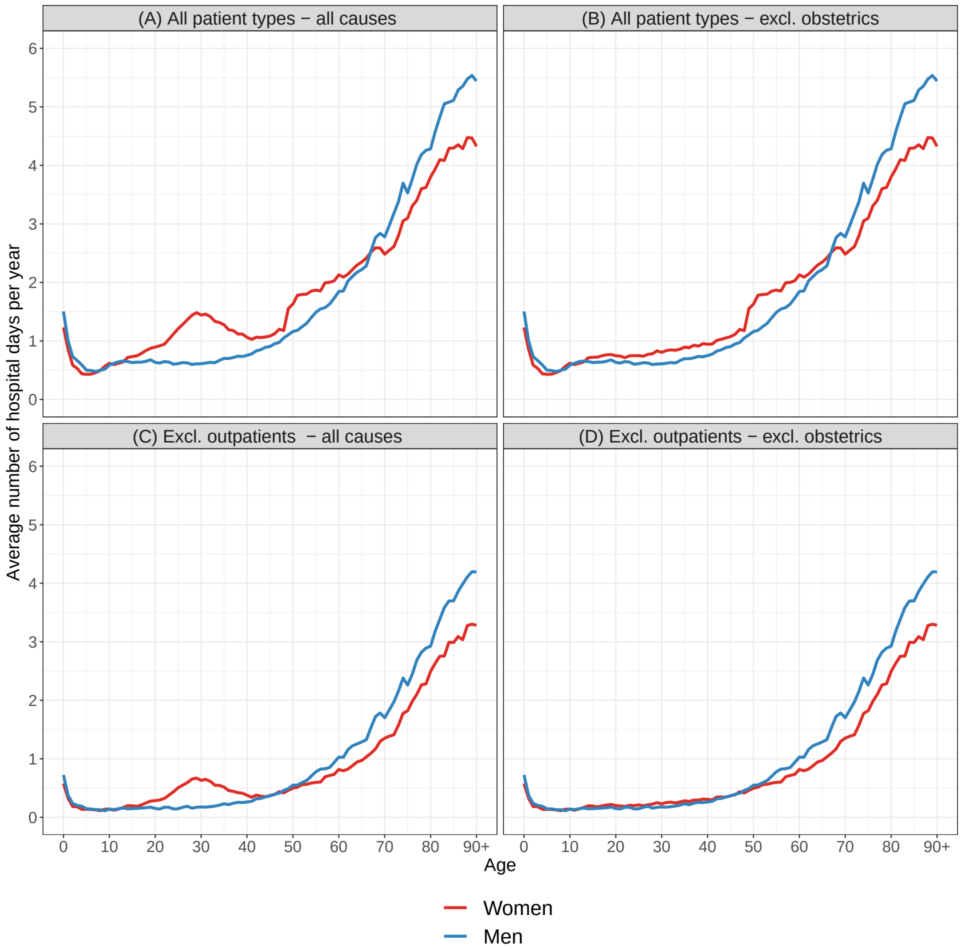


Figure 2: Sex differences in hospital care use in Denmark, 2014. *Source: Own calculations based on register data for the total Danish population.*

A cause-specific perspective is needed to further understand why men have higher levels of hospital care use at post-reproductive ages in comparison to women. Women have a higher risk of admission to hospital for a number of less life-threatening conditions, such as diseases of the eye or musculoskeletal disorders,[74,96,97] as well as conditions which can be treated in outpatient settings.[73] In contrast, men at post-reproductive ages have a higher risk of being admitted to hospital for the majority of other diseases, including cardiovascular diseases, neoplasms, respiratory diseases, and diseases of the digestive system.[74,96] Even when controlling for age, health behaviors, and co-morbidity, men have a higher risk of being admitted to hospital and to die following admission than women with the same conditions.[31]

Women experience lower mortality following most causes of admission to hospital than same-aged men. This is the case for most neoplasms,[98–100] chronic obstructive pulmonary disease (COPD),[101,102] Pneumonia,[103,104] or hip fractures.[105,106] In contrast, findings for myocardial infarction (MI) and stroke were ambiguous. Some studies report no gender differences or even a mortality disadvantage among women following an admission for stroke[107–110] and MI[111,112]. However, women tend to be significantly older than their male counterparts at disease onset, and age-specific incidence rates for these causes are usually higher in men than in women.[107,109]

Previous studies have provided valuable insights into gender differences in the risk of hospitalization and mortality following admissions. However, important gender-patterns surrounding hospital admissions are not yet fully understood – for example whether the magnitude of gender differentials in mortality changes following an admission to hospital when compared with the differential in the general population. The next section provides an overview of specific research gaps, which have been addressed in the thesis.

1.2.3 Research Gaps

The mortality advantage of women is well explored in general populations and following most causes of admission to hospital. It is also well-established that men are more likely to die following hospitalization, suggesting that the implications of deteriorating health are stronger in men than in women.[31,40,79] However, it is not yet known whether the magnitude of women's mortality advantage increases or decreases following all-cause and cause-specific hospital admissions when compared with women's mortality advantage in the general population.

One important observation among previous studies is that women, on average, engage with primary healthcare services more often in comparison with same-aged men.[31,32,65,113–115] On the one hand side, these studies interpreted this pattern as an indicator of women's poorer health. On the other hand side, these studies have argued that this may be the reason why women are less likely to be admitted to hospital and have lower levels of mortality. Therefore it remains unclear whether women's higher levels of primary healthcare use are due to a potential health disadvantage or whether they reflect a lower threshold to seek medical advice.[66] Looking at changes in treatment-seeking behavior surrounding hospital admissions may provide valuable insights into this debate.

Research has shown that increases in the age at first admission to hospital for men and women at post-reproductive ages have kept pace with increases in average life expectancy.[72] This was considered as evidence of morbidity compression. Studies of morbidity compression typically measure progress in health and life expectancy in terms of averages.[116–120] Despite the rapidly improving quantity, quality and availability of health data, for example provided by the Global Burden of Disease Study,[121] variation in age at morbidity onset has largely been overlooked. One part of the explanation is that it is challenging to estimate long-term trends in morbidity incidence reliably for total populations.[122–124] Routinely-collected hospital admission data, collected for an entire population and consistently over a long period of time, provide a unique framework for identifying changes in the first incidence of a medically diagnosed condition.[69,72–74] From these data, measures of variation in age at morbidity onset can be estimated. This is particularly important for understanding the extend of gender differences in health beyond average measures. The amount of variation indicates the level of uncertainty individuals can expect in the timing of health deterioration.[125] At the population level, welfare states will have to adapt to the heterogeneous needs of aging populations.[125–127]

The demographic structure of the population has important implications for the provision of healthcare, including hospital settings.[20,128] On average, older individuals have higher levels of hospital care use than younger individuals.[129] Furthermore, the incidence of most non-communicable diseases, such as cardiovascular diseases,[92] cancers,[91] and dementia[93] are strongly patterned by sex and age. Therefore, one important consequence of population aging is that the demographic composition of patients in need of hospital care is likely to change. An adequate supply and mix of well-trained health workers will be necessary to meet the needs of future patients.[130] In addition, forecasting the structure of future hospital patients with respect to both, age and sex, is particularly important for the education of the future medical workforce.[131–133] Part of the reason is that the medical workforce in training, including medical doctors and student nurses, tends to have negative attitudes towards older patients – factors which were shown to have a significant impact on career choices as well as the quality of care and treatment.[132,134–136]

1.3 Denmark – The Context of the Thesis

Denmark, the geographical focus of the thesis, has similar gender patterns in mortality and health to those observed in most developed countries.[27,62,137,138] In addition, Denmark is an example country which clearly illustrates that the magnitude of gender differences in mortality is affected by modifiable factors.

In Denmark, the difference in life expectancy between men and women was 3.6 years in 1835, and this gap reached a peak in 1979 at 6.2 years.[27] In between these years, and as previously illustrated in Figure 1, the magnitude of gender differentials in life expectancy has been relatively low in Denmark when compared to other HMD countries. In 2016, Danish women outlived Danish men by 3.8 years.

Denmark provides a unique framework for studying gender differences in mortality, as improvements in life expectancy among Danish women stagnated between the 1970s and 1990s.[137–140] Studies have identified that this stagnation was driven by the cohorts of Danish women born between the two world wars and is closely related to the the emergence of smoking in these cohorts.[141,142]

More specifically, Danish women born between 1915 and 1945 had a high prevalence of smoking throughout their entire lives, resulting in high death rates from smoking-attributable diseases relative to most other European countries.[143] The effect of smoking on population-level mortality is not immediate, and subject to a lag effect.[33] Therefore, it took multiple decades for this pattern to become visible in Denmark. As these cohorts of Danish women are now dying out, the phenomenon of stagnating life expectancy is diminishing.[144] Within the past two decades, the life expectancy of women in Denmark has increased faster than for women in Sweden and Norway.[144] Nevertheless, the life expectancy of Danish women is still lower than in most Western European countries today.[27,27]

In pragmatic terms, Danish register data provide a unique tool for studying differentials in mortality and health.[145–147] These data have a similar structure, validity, and coverage as the registers in the other Nordic Countries.[147–149] The data utilized in the thesis include information on contacts with different sectors of the Danish healthcare system and basic demographic information covering the entire population alive and residing in Denmark.

A universal healthcare system is a particular feature of the Danish welfare state. This system is the outcome of a long path of political decision-making, which traditionally focused on public welfare services in order to reduce socioeconomic inequalities.[150] In Denmark, healthcare is financed through taxes and access to healthcare services is free for all residents.[151,152] This means that this healthcare system should reduce systematic exclusions and hurdles in accessing healthcare services among men and women of post-reproductive ages. Within this framework, general practitioners (GPs) have an essential gate-keeping role regarding the use of hospital care.[10,151,152] Therefore, an admission to hospital in Denmark represents a needs-driven interaction with the healthcare system.

1.4 Aims and Objectives

The thesis aims to study gender differences in mortality and health using hospitalization records for the Danish population at post-reproductive ages. The following research objectives were chosen to achieve this aim:

1. Measure changes in the magnitude of women's mortality advantage following

the deterioration of health (Paper 1).

2. Compare gender differences in treatment-seeking behavior before and after a major health shock (Paper 2).

3. Quantify the mean age, and variation in the mean age, at disease onset among men and women (Paper 3).

4. Forecast changes in the demographic structure of hospital patients due to population aging (Paper 4).

1.5 Methods and Materials

1.5.1 Data

A major similarity among all five Nordic Countries – Norway, Iceland, Finland, Sweden, and Denmark – is the structure of their population-based register systems.[149] Despite the relatively small population sizes of these countries, their registers can ensure large sample sizes as the total population is covered.[148,149] Since the introduction of the personal identification numbers in the 1960s, individuals in the Nordic Countries can be followed throughout different registers. This unique structure enables complex life course perspectives in epidemiological studies.[147]

In the thesis, three different Danish registers were used: the Central Population Register (CPR), The National Patient Register (NPR), and The National Health Service Register (NHSR). Figure 3 illustrates the different time periods for which data were available from each register.

Although these registers were created primarily for administrative reasons, they can be accessed for research purposes.[146,147,153] A 5% sample was used for the first paper. In all subsequent papers, the data covered the total Danish population. The following section provides an overview of the three registers. A more detailed and tailored description of how these data were handled is provided in each paper.

The strengths and limitations of these data are critically evaluated in the discussion section at the end of this chapter.

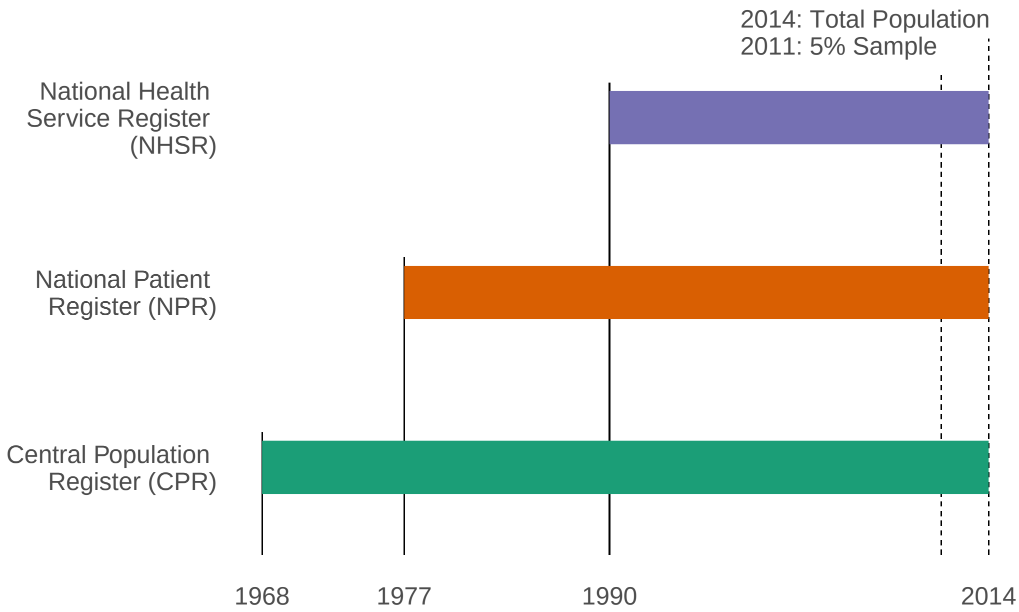


Figure 3: Overview of the utilized data sources.

Central Population Register (CPR)

In 1875, a register on causes of death was established in Denmark.[154] Since 1924, information on all Danish residents have been collected and continuously updated within municipal registers for administrative and planning purposes.[155] In 1968, this system was replaced by a centralized civil registration system.[156] Since then, demographic information on each resident's vital status, sex, and date of birth have been electronically recorded in the CPR. A unique personal identification number (CPR-Number) has been assigned to all individuals residing in Denmark.[9] Information in other Danish registries are collected and saved using the CPR-Number. This enables deterministic linkage of different population-based registers.

National Patient Register (NPR)

Data on hospital admissions were accessed via the NPR. The NPR was established in 1977 and covers administrative and medical information on hospital care provided in Danish hospitals.[157] While inpatient treatments have been recorded since 1977, outpatient treatments, information from psychiatric wards, and emergency admissions have only been included since 1995.[158] Despite this increase of covered information as well as the introduction of new classification systems, for example the change from ICD-8 to ICD-10 in 1994,[159] individuals can be followed consistently over the entire range of time. This makes the hospitalization register a high-quality source of data for epidemiological research.[158]

National Health Service Register (NHSR)

Data on the primary healthcare use of the Danish population is recorded in the National Health Service Register (NHSR). The NHSR was established in 1990 and contains data from health contractors in primary healthcare settings on the service provided and the citizen who received treatment.[154] Treatment of children under age 16 was reported under the CPR-Number of one parent until the end of 1995.[10] To avoid potential bias emerging from this feature, papers in the thesis which utilized data from the NHSR, excluded information prior 1996. A summary of the data sources used for each paper is given in Table 1.

Table 1: Overview of utilized data sources, sample sizes, and study periods covered in the papers of the thesis.

Paper	Sample Size	Register	Period
1: Mortality	5% Sample	CPR, NPR	1977 – 2011
2: Treatment-Seeking	Total Pop.	CPR, NPR, NHSR	1992 – 2014
3: Variation	Total Pop.	CPR, NPR	1977 – 2014
4: Forecasting	Total Pop.	CPR, NPR, NHSR	2014

1.5.2 Methods

The thesis focuses on studying health and mortality using hospital admission data. As the population of post-reproductive ages was focused, a potential sex bias, caused by admissions for reproduction and child birth, is substantially reduced. However, when necessary, the impact of obstetrics-related admissions was controlled for.

Particularly at post-reproductive ages, contacts with the healthcare system, including hospitals, are frequent events. In all papers of the thesis, sample sizes were large – even when stratifying study populations by age, sex, and cause of admission. The properties of the register data provide a unique opportunity to utilize both individual-level and aggregate-level methods, as well as to incorporate cross-sectional and longitudinal perspectives.

This section provides a brief description of the methods applied in each paper, and a justification for why they were used. A summary of the methods used in each paper is provided in Table 2. Details of the modeling processes and results of sensitivity analyses are presented within each paper.

Table 2: Overview of methods and perspectives in the papers of the thesis.

Paper	Perspective	Utilized Methodology
1: Mortality	Ind. Level	GAMs, Splines
2: Treatment-Seeking	Ind. Level	Hurdle Models, Splines
3: Variation	Pop. Level	Life Tables and Variation Measures
4: Forecasting	Pop. Level	Deterministic Forecasting

Generalized Additive Models (GAMs)

The first paper explored levels of mortality among men and women following the first all-cause and cause-specific admission to hospital after age 50. Levels of mortality, and in particular the absolute sex differences in mortality, were compared with the levels observed in two matched reference populations: a general and a temporarily non-hospitalized population. Matching based on sex and day of birth was used to ensure that populations share an identical demographic structure.[160] For hospitalized individuals, the survival time started on the first day of hospitalization and ended either due to death within 1 year following admission or censoring. The survival time of matched individuals in each reference population started the day the corresponding case was admitted to hospital and ended either due to death within 1 year or censoring. GAMs with a binary link[161] and penalized b-splines ('p-splines')[162] were used to estimate the levels of mortality. Mortality was estimated separately for the men and and the women of each population.

In contrast to generalized linear models (GLMs), the linear predictor in a GAM is replaced by a sum of smoothing functions.[161,163] This non-parametric approach allowed the risk of mortality to follow non-linear trajectories over age as the estimated mortality trajectories are not predefined by the functional form of a GLM.

Hurdle Models

The second paper examined whether patterns of treatment-seeking behavior surrounding a major health shock differed between men and women. For this paper, a hurdle model was used.[164–166] The application of a hurdle model matched the full potential of the data as individuals who did not consult with primary healthcare services could be identified. This approach allowed for a distinction between two stochastic processes: the risk of being a non-user of primary healthcare, and the rate of healthcare use among those who engage with primary healthcare.[167] This distinction is important as there might be no difference between men and women who did engage with healthcare services – a feature an aggregate-level approach would have overlooked. Applying a hurdle model enabled the research question to be answered from a longitudinal perspective, as changes in the magnitude of gender differences in primary healthcare use following hospitalization could be studied.

The hurdle model estimated the levels of non-use of primary healthcare as well as the number of contacts with primary healthcare among users surrounding the first inpatient admission to hospital after age 60 for four conditions: stroke, MI, COPD, and gastrointestinal cancers (GIC). Hurdle models combine a logistic model for the probability of zero-counts with a regression model for the positive counts.[164] In order to account for repeated observations, hurdle models allow for the incorporation of individual random effects.[164]

Life Tables and Life Span Variation Measures

In the third paper, time-to-admission life spans were estimated in order to quantify the mean age at morbidity onset and variation in the mean age. For each year, all individuals aged 60+ who were at risk of experiencing a first admission to hospital, as well as those who were actually admitted, were identified. A 7-year washout period was applied in order to ensure that the first admission to hospital was not a re-admission or a follow-up treatment. Time-to-admission life spans started on the 60th birthday and ended the day of the first inpatient admission to hospital for all-causes. This setting enabled the estimation of age-specific risks of first admission for men and women for each year of the study period. Age-specific risks were then used to construct period life tables and calculate lifespan variation measures for each year, and for men and women separately.[168] Variation in the mean age was measured using the coefficient of variation – a relative measure, which accounts for changes in the mean. 95% confidence intervals (CI) for life table parameters were estimated using the approach provided by Chiang (1984).[169]

Deterministic Baseline Forecasting

In the fourth paper, a deterministic baseline forecast was used to examine how the current demographic structure of hospital care use may change due to population aging.[170,171] In a first step, the total Danish population was followed up for inpatient and emergency admissions recorded in Danish hospitals in 2014. This enabled the estimation of the baseline year levels: the age- and sex-specific patterns of hospital care use in 2014. The baseline-year levels were estimated by dividing the number of hospital days by the corresponding population at risk. The baseline levels were kept constant throughout the entire projection period and multiplied with the most recent population estimates provided by Statistics Denmark.[172,173] This enabled a deterministic quantification of hospital care use on the national level up to the year 2050. As patterns observed in the baseline year 2014 were kept constant throughout the entire study period, changes in the age- and sex-specific patterns of hospital days were driven entirely by changes in the demographic structure of the Danish population, and in particular population aging.

1.6 Results and Discussion

1.6.1 Main Findings and Contribution to Existing Knowledge

Sex Differences in Mortality Following Hospitalization

The first paper estimated the magnitude of male excess mortality in the 1-year risk of dying following a deterioration of health, measured as the first all-cause and cause-specific hospital admission after age 50. A comparison was made with the corresponding male excess mortality observed in a matched general and temporary non-hospitalized population. In all populations, women had consistently lower mortality than men. Furthermore, absolute sex differences in mortality were always highest in the hospitalized population, followed by the general population, and the temporary non-hospitalized population. This gradient was consistent across all-cause as well as selected cause-specific hospital admissions.

Findings of the first paper indicate that part of women's mortality advantage after age 50 can be attributed to their lower risk of dying following health deterioration. While it is likely that behavioral and biological aspects have contributed to the mortality differentials following hospitalization, for example differences in treatment-seeking behavior and immune response,[31,48,113,115] the exact causes for the observed patterns could not be disentangled. Nevertheless, findings of the first paper provide valuable insights into the underlying mechanisms of women's mortality advantage at post-reproductive ages: Women have lower mortality after the onset of health deterioration while likely remaining alive in bad health. The finding that women had lower mortality following all studied causes of admission indicates that sex differences in the distribution of the causes of admission do not explain sex differences in mortality after all-cause hospital admission.

Gender-Specific Changes in Treatment-Seeking Around Admission

The second paper examined a potential factor contributing to women's mortality advantage following hospital admission: their higher propensity to seek medical advice before health deterioration.[32,113,114,174] In the paper, gender patterns in treatment-seeking around the first inpatient hospitalization after age 60 were studied. Using a hurdle model, levels of primary healthcare use and levels of non-use before and after hospitalization for stroke, MI, COPD, and GIC were estimated. Before hospitalization, men were substantially more likely to be non-users and had fewer contacts with primary healthcare given that they were users. The use of primary healthcare services increased substantially among men and women following hospitalization. However, levels of non-use dropped more sharply among men and increases in the level of healthcare use were more pronounced among men users. Although the magnitude of absolute gender differences in primary healthcare use decreased sharply following hospitalization, differences between men and women never fully vanished.

The second paper contributed to the question of whether women utilize primary healthcare services more often – and if yes, why.[31,65,66,113,115] Studying these questions within a longitudinal, individual-level framework is a valuable contribution as the majority of quantitative studies have utilized cross-sectional data on the aggregate level.[65,113,114] In addition, a major contribution is that the application of hurdle models allowed two features to be distinguished: non-use and levels of use among the user group. This is important as gender differences in mean levels might be due to differences in the share of users and non-users among men and women. The findings of the paper show that women's higher levels of primary health care use are likely to be due to both a lower threshold for treatment-seeking and a health disadvantage at older ages, emerging from women's lower mortality following hospitalization. It is known that repeatedly missing appointments is associated with an increased risk of mortality.[175] However, future research should examine the association between gender-patterned treatment-seeking behavior and gender-patterned mortality following hospital admissions.

Inequalities in Mean Age at First Hospital Admission

The third paper addressed two questions. First, whether the average age at first admission has increased among Danish men and women over time, and second, whether this trend has been accompanied by increasing or decreasing variation in age at first admission. To answer both questions, individual-level time-to-admission life spans were constructed for all Danish men and women aged 60+ between 1987 and 2014. From these time-to-admission lifespans, annual period life tables were constructed. Results of this paper show that the mean age at first hospital admission has increased for both men and women. This indicates that morbidity, on average, has been postponed towards older ages. However, increasing variation in mean age indicates that this increase has not been experienced by everyone and the age at morbidity onset has become increasingly heterogeneous.

A large number of prior studies have addressed the question of how men and women spend the extra years of life expectancy. This question is typically explored by comparing the average proportion of life expectancy spent in an unhealthy state.[117–120,176–178] One likely scenario is morbidity compression: A scenario in which the extra years of life are spend predominantly in good health.[179–181] Fries (1980) underlined the need to account for the impact of variation between individuals.[179] However, research on morbidity compression has focused primarily on trends in average prevalence-based health measures.[118] The third paper of the thesis thus makes an important contribution by using routinely-collected, administrative hospital data in order to estimate incidence-based measures of disease onset. The paper illustrates that variation, an important dimension of morbidity compression, has been largely overlooked. Incorporating measures of variation has important benefits as it not only quantifies the uncertainty individuals face, but also the uncertainty societies and welfare states are exposed to with respect to the provision of health care, pensions and insurances.[125] Consequently, also gender gaps in morbidity should be measured beyond averages.

In addition, findings of this paper challenge the generalizability of the health-survival paradox beyond self-reported measures of health. This is in line with existing studies which reported a higher mean age at disease onset among women using objective measures of health in total populations, obtained from hospital admission data.[69,72,74] Future research may consider gender differences in the variation of age at disease onset among men and women across different disease groups and explore the causes accounting for the within-gender differences.

Changes in the Demographic Profile of Hospital Patients

In the fourth paper, the current demographic profile of hospital care use in Denmark was described, and changes up to 2050 were projected. In a first step, the Danish population in 2014 was followed up for inpatient and emergency admissions recorded in Danish hospitals in 2014 using individual-level register data. In a second step, the age- and sex-specific patterns of hospital care use in 2014 were combined with Statistics Denmark's population forecasts to estimate the profile of hospital days up to 2050 by age and sex. Results revealed that the total number of hospital days per year will increase by nearly 50% between 2014 and 2050. Already today, the population aged 70+ accounts for nearly half of all hospital days. By 2050, this will increase: Men and women aged 70+ are set to account for nearly two thirds of all hospital days as their absolute contribution is forecast to double.

While a large number of studies have forecast healthcare expenditures or the prevalence of diseases, little is known about the demographic structure of the population to be treated in hospital settings. The paper makes an important contribution by highlighting that the absolute and relative contribution of the population aged 70 and older will rapidly increase. Furthermore, results of the paper underline that population aging, in combination with men's higher levels of hospital care use at older ages, will make men aged 70+ the fastest growing group to be treated in Danish hospital within the next decades. This has important implications for the provision of hospital care as the major non-communicable diseases show age- and sex-patterned incidence rates.[91–93] In addition, the paper draws attention to the fact that a well-balanced mix of health workers will be needed to ensure a high quality of care and treatment.[130,134,182,183] In the future, studies on forecasting hospital care use levels should devote more attention to modeling scenarios of compression and expansion of morbidity as patterns of morbidity postponement might differ between men and women.[180]

1.6.2 Strengths and Limitations

Danish registers were used throughout all papers of the thesis, which provide nationwide coverage. The 5% sample data used in the first paper were representative of the Danish population. All hospitals and primary healthcare facilities in Denmark are obliged to collect and transmit data to the central Danish administration, which results in high levels of completeness, reliability, and validity of the data.[10,147,157] Furthermore, the mandatory collection and transmission of these data eliminate common limitations of surveys such as recall-bias, loss to follow-up, and non-response[147] – features that may systematically vary between men and women.[66,184] All health measures obtained from the registers were based on routinely-collected, administrative information. Therefore, the findings were not affected by gender-patterns in self-reports; features which were shown to have a significant impact on the generalizability of studies addressing gender differences in mortality and health.[76]

In the thesis, hospital records were used to measure health at both the individual- and the population-level. The measures derived were based on the assumption that an admission to hospital, particularly at post-reproductive ages, reflects a health deterioration. This approach has been applied and validated in previous studies.[31,72,74,79,80,85,87–89,185] Within Denmark, GPs have a gate-keeping role regarding the use of hospital care.[10,151,152] Therefore an admission to hospital, at least in this context, captures a needs-driven medical intervention due to an objectively diagnosed health condition.

It was possible to derive detailed information on different health conditions from individual-level ICD-codes. The ICD is a standardized diagnostic tool used in medical administration, epidemiology, and health services research.[186] Bridge coding was used to harmonize ICD-8 and ICD-10 codes – a procedure used to ensure that causes of admission were assigned to the same categories over time as consistently as possible.[187,188]

An issue that the thesis could not account for was shifts in admission and treatment strategies. Changes in these strategies may affect the thresholds of hospitalization for a specific condition as well as the routine treatment for this condition. The minimum data required to understand these strategy changes are consistent and detailed information on inpatient, outpatient, and primary healthcare attendances by cause of admission, provided treatment as well as length of treatment. Even in Denmark, a country with a large number of comprehensive, population-based health registers, this is extremely challenging. Where possible, the thesis included analyses to explore potential changes in admission and treatment strategies. For example, in the third paper, all-cause admissions were broken down into detailed cause-specific categories which, in theory, would be more susceptible to changing admission and treatment strategies. In addition, changing the criteria for defining a first hospital admission and it's impact on the results were explored by altering the minimum length of stay in hospital. Reassuringly, the direction of main results was consistent in the sensitivity analyses when varying the minimum length of stay from 2 days to 1 day, 3 days, 5 days, and 7 days. Nevertheless, these approaches for identifying the impact of shifts in treatment and admission strategies over time was rudimentary. However, it highlighted how complex it is to quantify the impact potential shifts may have on research results.

One further feature that could not be identified from any of the data was the severity of the underlying health condition. Data on primary healthcare in Denmark include information on the patient that received treatment and the type of treatment received – but no further information on health condition or the outcome of examinations.[10] Hospital records did include information on the cause of admission in the form of ICD codes. However, there was no opportunity to compare severity across different causes of admission, or to compare differences in severity across individuals admitted for the same cause.

In addition, the data used for the thesis did not contain bio-medical information on the patients treated. This is a limitation, as it is likely that biological differences between men and women, for example differences in immune functioning and immune responses, are important for explaining sex differentials in mortality following hospitalization as well as differences in the mean age at disease onset.[31,44,48] Given the utilized data, it could have been one option to focus on re-admissions or complications as proxy indicators for biological mechanisms.[189–192] To explore the impact of biological factors more directly, future research may utilize other data sources. Within the past years, more and more population-based data were linked with either disease-specific or general bio-medical information in various European countries,[193–195] for example on healthcare use and complications in diabetes patients.[196]

A further limitation was the absence of information on health behaviors and risk factors. This is important as the prevalence of smoking and alcohol consumption is patterned by gender, and strongly associated with the risk of admission to hospital.[79,80,85,185] Data on health behaviors would have added a valuable dimension to all four papers. One example is whether changes in treatment-seeking behavior around hospital admission were accompanied by major changes in life style, such as smoking cessation. To overcome these limitations, future research could use more detailed survey-linked register data.

A designated cohort perspective could have been beneficial for the aims of the thesis. Changes in behavior, including health behavior, and cohort identification are strongly linked with each other.[197] Cohort phenomena might overlap, multiply, add to each other, or only become visible after a lag effect of several decades.[198] In Denmark, female life expectancy stagnated between the mid-1970s and the mid-1990s due to the high prevalence of smoking among Danish women born between the two world wars.[141,142] This phenomenon is well-explored in terms of mortality. However, no quantification of this cohort phenomenon on hospitalization is presented in the thesis. It is likely that the higher prevalence of smoking among women in Denmark has lead to higher levels of healthcare use among women for smoking-related causes. Whenever this was considered relevant for the interpretation and explanation of findings, a cohort perspective has been discussed.

Findings of the thesis may not apply to other welfare-state regimes, particularly to those that do not have universal access to healthcare and where out-of-pocket payments for healthcare are high. It is likely that the tax-financed healthcare system in Denmark substantially reduces inequalities in access to healthcare, and substantially reduces the systematic exclusion of any population sub-groups.[150,151] Despite this, and despite generally high levels of equality in Denmark, socioeconomic and educational gradients in mortality and health have been reported for the middle- and old-aged population.[199–203] In addition, potential hurdles and delays in accessing healthcare services are likely to exist in Denmark, and there is evidence that groups who need healthcare most access it least[204–207] – the inverse care law.[208–210]

A limitation of the thesis is that the impact of socioeconomic inequalities on gender differences in mortality and health surrounding hospital admissions was not analyzed. Common indicators of socioeconomic status include income, occupation, or education.[211,212] In Denmark, information on the highest achieved education have been systematically recorded in population-based registers since the 1970s.[213] These data are generally considered to be of high validity and coverage.[154,213,214] However, information on the population born before 1945 can be inconsistent while information on the population born before 1930 are hardly recorded at all – a common and well-known data limitation.[215,216] As the study populations in the papers of the thesis often included individuals from these cohorts and covered long study periods, it was not possible to have a consistent indicator of socioeconomic status.

While the papers of this thesis provide both an individual- and population-level perspective, a meso-level perspective is missing. For example, in the second paper, changes in treatment-seeking behavior were modeled on the individual level and the potential impact and interaction with partners, siblings, children, and other social networks was not explored. This is an important limitation as a number of meso-level factors were shown to have a gender-patterned impact on a variety of positive and negative health outcomes.[217–219] Marriage, in particular, might have a protective effect on health, but might also be the result of a health selection process throughout the life course.[220–223] In this regard, future projects could contribute to the existing body of literature by examining the gender-patterned impact of meso-level factors within the context of treatment-seeking behavior surrounding hospital admissions.

Throughout all papers of the thesis, special attention was given to assessing the sensitivity of all main findings to the assumptions being made. This was achieved by looking at patterns across different causes of admission, examining the impact of case fatalities, changing the minimum length of stay, and altering the inclusion criteria for different types of hospital care. In the first paper, different causes of admission showed that women's lower mortality following admissions was a universal advantage, reflected across four broad causes of admission. In the second paper, gender-specific changes in treatment-seeking behavior were similar across four causes of admission – each with a distinct disease profile. In the third paper, the general direction of trends did not change when varying the length of stay in hospital, and a stepwise increase in levels was found when excluding fatal cases. In the fourth paper, changes in the age and sex composition of hospital care use were not affected by the inclusion of outpatient and obstetrics-related admissions. The consistency of the results in all papers of the thesis is a strong indication that routinely-collected hospitalization data can be used to derive valuable indicators of health for examining gender differences in mortality and health at the individual and the population level.

1.6.3 Conclusion

Using Danish register data, the thesis studied gender differences in mortality and health surrounding hospital admissions. Four papers were developed which focused on: mortality following hospitalization, treatment-seeking behavior before and after hospital admission, age patterns of first admissions to hospital after age 60, and the demographic composition of hospital patients today and in the future. The thesis applied a range of individual- and aggregate-level methods, as well as cross-sectional and longitudinal study designs.

Irrespective of an individual's gender, an admission to hospital can be a major life event – particularly when aging processes accelerate and health deteriorates. Nevertheless, the risk of admission to hospital and levels of mortality following hospitalization are gender patterned. Women at post-reproductive ages have a lower risk of being admitted to hospital for most causes, and have lower mortality following hospitalization when compared with men. One potential explanation for these patterns could be that women seek advice earlier in the disease course. Future research should focus on addressing gender-specific barriers for seeking medical advice as this is key for preventing and postponing health deterioration. Healthcare systems preparing for population aging should take into account gender patterns surrounding hospital admissions in order to meet the needs of future patients.

2 Sex Differences in Mortality Following Hospitalization

Publication: Andreas Höhn, Lisbeth Aagaard Larsen, Daniel Christoph Schneider, Rune Lindahl-Jacobsen, Roland Rau, Kaare Christensen, and Anna Oksuzyan: 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. **BMJ open** 2018;8(7),e021813. *doi:10.1136/bmjopen-2018-021813*

2.1 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 2011 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.

2.2 Strengths and Limitations of this Study

- This study uses high-quality Danish register data, with nationwide coverage, that leave 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.

2.3 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.[35] Women have lower rates of mortality than men for nearly all causes of death, including most cancers,[98,224,225] respiratory diseases[101,226] and accidents.[227] Moreover, the female advantage in mortality persists even after stressful events during the life course, such as bereavement[228,229] or famines and epidemics.[16] While the relative sex differences in mortality peak at around age 25 and tend to become smaller with age,[22] the absolute sex differences grow almost exponentially between ages 40 and 90, as general levels of mortality increase.[50] 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[28] when individuals start to accumulate diseases and disabilities, and the incidence of most adverse health conditions increases.[20]

A number of previous studies have argued that a hospital admission may serve as a quasi-objective indicator of health. An admission to the hospital may indicate the onset of a health decline or the manifestation of a health decline that started long ago that now requires extensive medical interventions.[31,72,230] 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.[77,78,231,232] 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.[79,80,185] Empirical findings have demonstrated that smoking,[80] hazardous drinking,[81] being overweight,[82] having high cholesterol levels[83] and a lack of physical activity[84] 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.[85]

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.

2.4 Methods and Materials

2.4.1 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,[154] 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.[9] The NPR is a population-based register with nationwide coverage that contains information on all admissions to hospitals since 1977.[158] 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.[153] 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 International Classification of Diseases (ICD), 8th Revision until 1993 and the ICD 10th Revision starting in 1994.[146] We classified the causes of admission to hospital according to the main chapters and used 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 S1 at the end of this paper.

2.4.2 Study Population

We identified all individuals who were born between 1 January 1898 and 31 December 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 1 January 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 1 January 1977 and 31 December 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 measured 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 the 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.

2.4.3 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.

2.4.4 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 washout 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 model (GAM) for binary data with a logit link. Unlike in generalized linear models, the linear predictor in the GAM is replaced by a sum of smoothing functions.[161,163] We used penalized B-splines, so-called P-splines, as basis functions in the regression to smooth over age.[162,233] 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 14), all statistical analyses were performed in R (Version 3.3.2).

2.5 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 .

Table 1: Overview of 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 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
Iscaemic 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
Musculosceletal disorders	4,737	7.44	5,858	9.15
Diseases of the genitourinary system	4,680	7.35	6,968	10.89
Injuries, poisionings & 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%)*

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, musculoskeletal 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.

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 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.

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% CI 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.

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 Admission / of Matches	Men				Women			
	Ind.		Deaths		Ind.		Deaths	
	No.	Share (%)	No.	Risk (%)	No.	Share (%)	No.	Risk (%)
				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 refer to the average of 100 matching results*

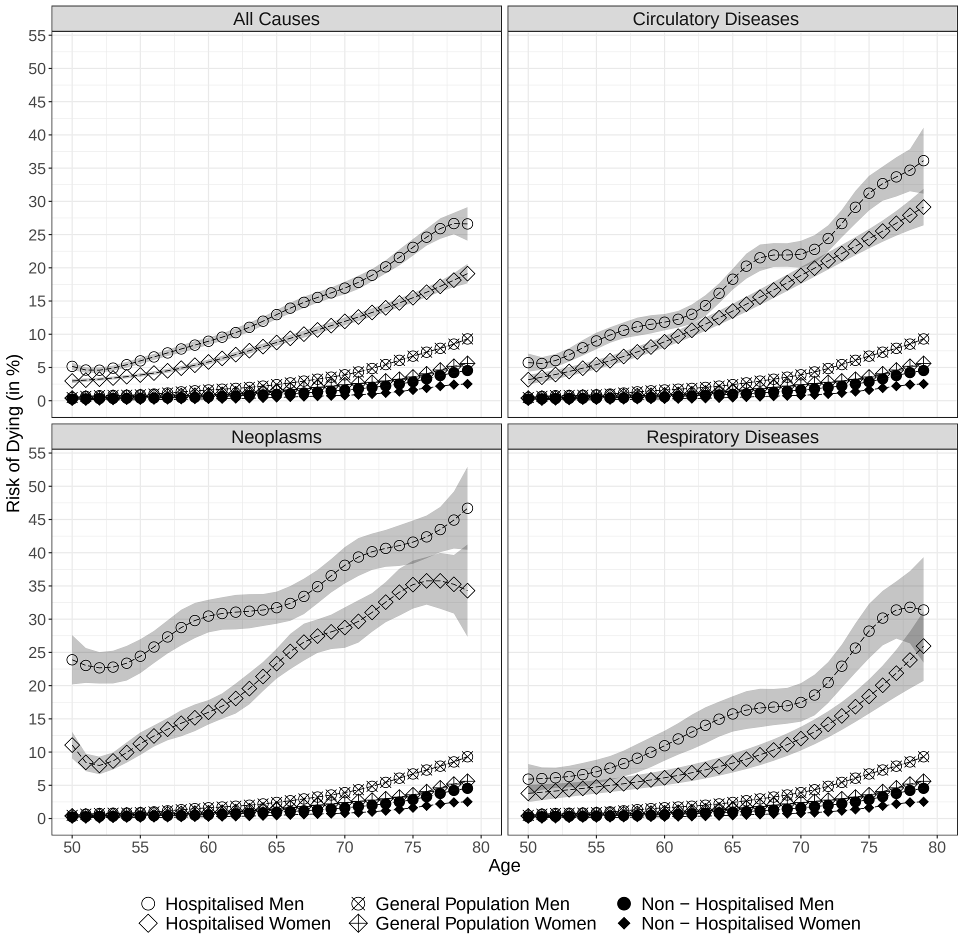


Figure 1: Estimated age trajectories in the risk of dying within 1 year of follow-up by cause of admission to hospital

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, for men and women 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 of 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.

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 1000 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. 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.

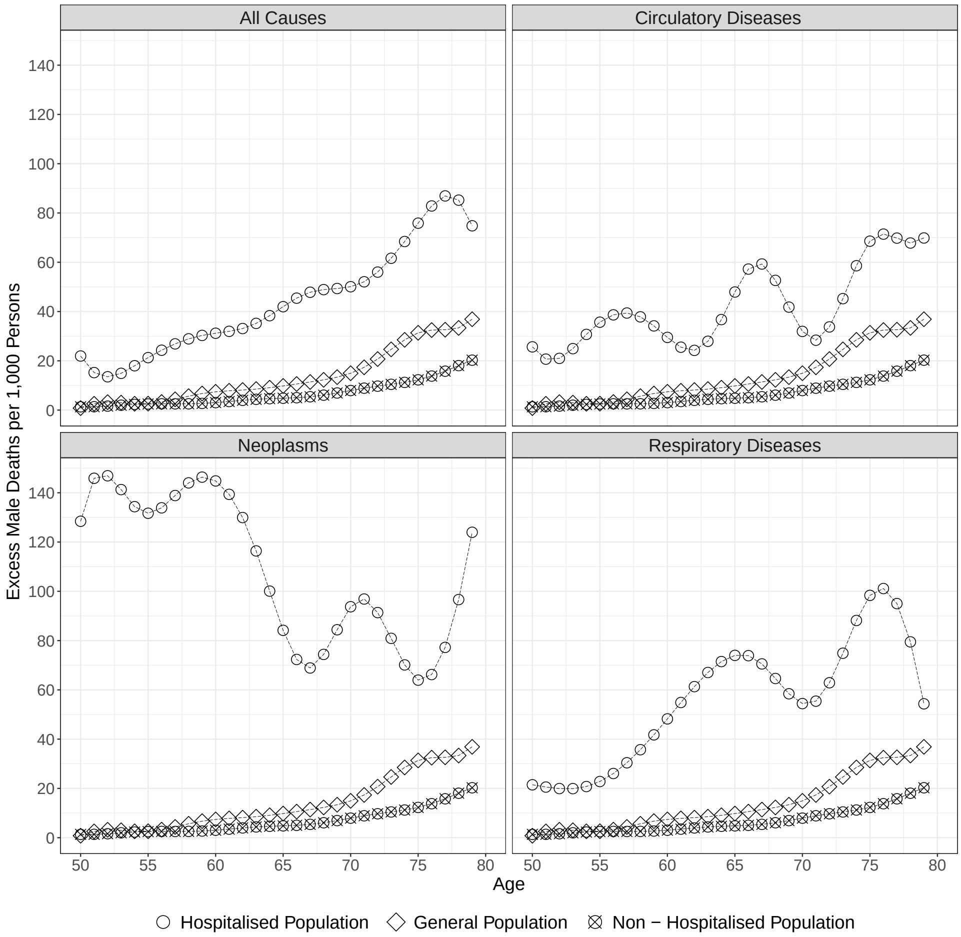


Figure 2 Male excess mortality within 1 year of follow-up by cause of admission to hospital.

2.6 Discussion

2.6.1 Principle Findings

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 male mortality always remained larger in the hospitalized population when differentiating by cause of admission to hospital.

2.6.2 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 could have biased the analyses and led to skewed results.[32] Another strength is that we were able to examine mortality for the overarching 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,[234] and in respect to sex differences.[50,235] We therefore replicated the analysis using risk ratios (see Supplementary Figure S1 at the end of the paper). 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.[234] Problems surrounding the interpretation of risk ratios often appear when populations under investigation differ in their overall risks of mortality.[50] 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.[236]

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 or 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.[142,144,237] The increased prevalence of smoking among Danish women, when compared with 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 healthcare 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.[80]

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,[5,40] and that studies on strokes and myocardial infarctions have shown that, on average, men are 8 years younger than women at the onset of these conditions.[107,108,238,239]

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 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.

2.6.3 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.[32] The most widely cited biological factors are hormonal, based on the observation that the female hormone oestrogen 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.[41,42,44,240] Moreover, women may have stronger immune systems than men, which could help women to recover more quickly,[48] and may play a fundamental role in women's better survival of harsh conditions, including famines and epidemics.[16] In addition to these biological factors, researchers have attributed a substantial part of the male disadvantage in mortality to behavioral and social factors.[47] For example, it has been argued that men have higher rates than women of smoking, excessive drinking, drug use and violence.[241] 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.[113,242–247] 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. However, the reasons for this pattern have not yet been fully understood.[96]

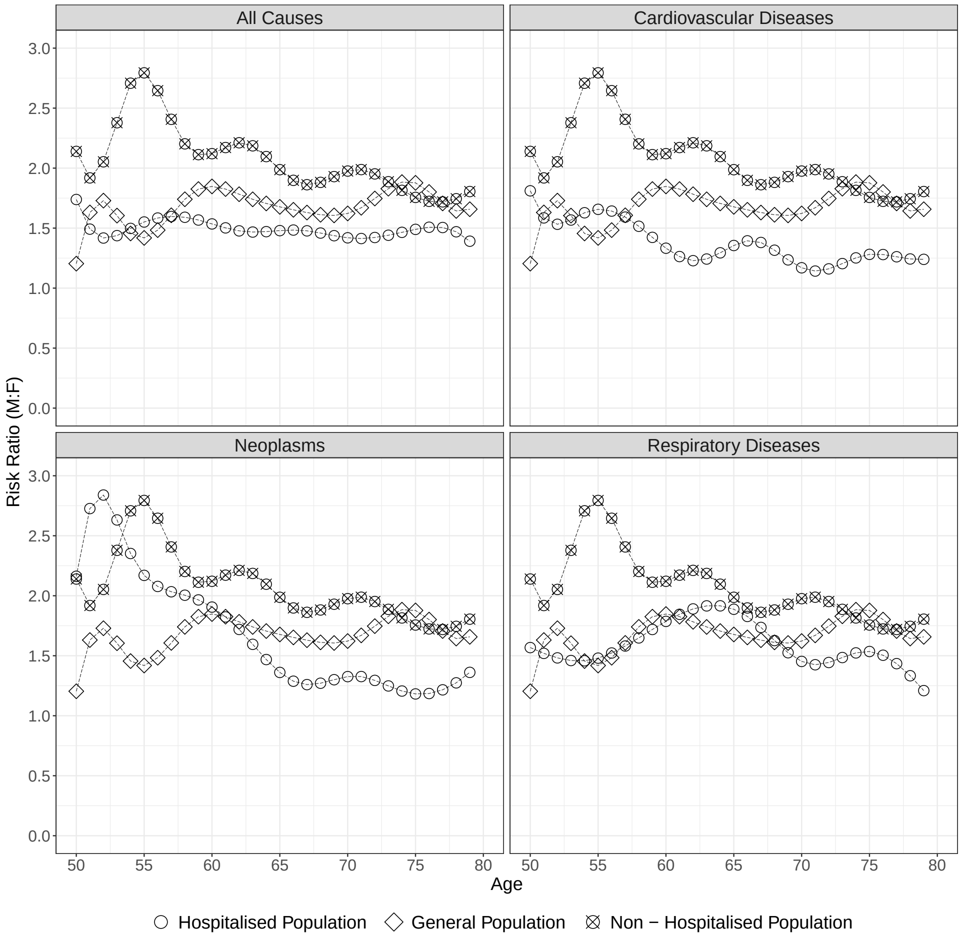
In Denmark, hospital care is financed through taxes, and is thus available to all residents, regardless of their sex and socioeconomic characteristics.[205] Although our results may have been affected by changes in policies related to hospital admission, treatment and discharge, it is likely that such changes would have affected men and women in similar ways. Although access to healthcare services is free and universal in Denmark, individuals may encounter hurdles in accessing healthcare services for a variety of reasons, including social, economic, demographic and geographic factors.[248] In Denmark, general practitioners (GPs) typically serve not just as gatekeepers for the use of secondary healthcare 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.[249] 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 healthcare 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.

2.6.4 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 the 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.

2.7 Supplementary Material

2.7.1 Supplementary Figures



Supplementary Figure S1: Relative sex differences in the 1-year risk of dying.

2.7.2 Supplementary Tables

Supplementary Table S1: 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
Iscaemic 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
Musculosceletal disorders	710 - 738	M00 - M99
Diseases of the genitourinary system	580 - 629	N00 - N99
Injuries, poisionings & 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*

3 Gender-Specific Changes in Treatment-Seeking Around Admission

Paper: ANDREAS HÖHN, JUTTA GAMPE, RUNE LINDAHL-JACOBSEN, KAARE CHRISTENSEN, AND ANNA OKSUZYAN: Do men avoid seeking medical advice? A register-based study of gender-specific changes in primary healthcare use after first hospitalization at ages 60+ in Denmark. ***submitted to a peer-reviewed journal***

3.1 Abstract

Background: It remains unclear whether women's greater primary healthcare use reflects a lower threshold for treatment-seeking or a health disadvantage. We address this question by studying primary healthcare use surrounding a major health shock.

Methods: This cohort study utilized routinely-collected healthcare data covering the total Danish population aged 60+ between 1996 and 2011. Using a hurdle model, we investigated levels of primary healthcare use and levels of non-use before and after the first inpatient hospital admission for stroke, myocardial infarction (MI), chronic obstructive pulmonary disease (COPD), and gastrointestinal cancers (GIC).

Results: Before hospitalization, men were more likely to be non-users (Odds Ratios (ORs) & 95% Confidence Interval (CI); Stroke: 1.802 (1.731-1.872); MI: 1.841 (1.760-1.922); COPD: 2.160 (2.028-2.292); GIC: 1.609 (1.525-1.693)), and had fewer contacts when they were users (Proportional Change (e^{β}) & 95% CI; Stroke: 0.821 (0.806-0.836); MI: 0.796 (0.778-0.814); COPD: 0.855 (0.832-0.878); GIC: 0.859 (0.838-0.881)). Levels of non-use dropped more sharply among men (ORs & 95% CI; Stroke: 0.965 (0.879-1.052); MI: 0.894 (0.789-0.999); COPD: 0.755 (0.609-0.900); GIC: 0.895 (0.801-0.988)), and increases in the level of healthcare use were more pronounced among men users (e^{β} & 95% CI; Stroke: 1.113 (1.102-1.124); MI: 1.112 (1.099-1.124); COPD: 1.078 (1.063-1.093); GIC: 1.097 (1.079-1.114)). Gender differences became more apparent after controlling for survival following hospitalization.

Conclusion: Women's consistently higher levels of primary healthcare use are likely to be explained by a combination of both: a lower threshold for seeking medical advice, and a health disadvantage resulting from better survival in bad health.

3.2 Key Messages

- The use of primary healthcare services increased sharply after an admission to hospital among both men and women, pointing towards a need-driven change in treatment-seeking in response to a health shock.
- Changes in the propensity to seek medical treatment after hospitalization were more pronounced among men when compared to women suggesting that men were more reluctant to engage with primary healthcare before hospitalization. However, gender differences in primary healthcare use did not disappear after admission to hospital.
- Our findings indicate a lower threshold for treatment-seeking among women, which is likely to be underpinned by women's better survival with disabling conditions.
- Attention should be given to increasing the use of primary healthcare services in order to prevent and postpone acute episodes of health deterioration, particularly among men.

3.3 Background

Women have lower mortality rates than men following most adverse health conditions, including hospitalizations.[16,250,251] To explain women's mortality advantage, the literature points towards the interaction of biological and behavioral factors.[32,47] One observation among the behavioral factors is that women, on average, utilize primary healthcare more than men.[113,114] Primary healthcare is among the main means of prevention, and timely diagnosis can be crucial for effective treatment and prolonging an individual's life.[205,209]

Seeking medical help is a complex process, shaped by demographic, structural and individual factors such as age, gender, access to healthcare, socioeconomic inequalities, cultural norms, gender roles, and education.[252–255] Most quantitative research documenting patterns in primary healthcare use is based on cross-sectional analysis of aggregate-level data. These findings have consistently shown that women utilize primary healthcare services more often than same-aged men – even when excluding consultations for child-bearing and birth control.[65,113] In contrast to population-level studies, individual-level studies have yielded mixed findings. Some studies report small or non-significant differences when comparing men and women who face similar conditions, such as headache, back pain, and prior major cancers.[66,115,184] Other studies have found consistently higher female use of primary healthcare when controlling for morbidity levels.[256–259] It therefore remains unclear whether higher rates of primary healthcare use among women are due to a lower threshold for seeking medical help or whether they are due to women's health disadvantage.[31,66] In addition, studies have not distinguished between users and non-users of primary healthcare. This distinction is important because there may be no, or only small, differences in treatment-seeking behavior between women and those men who are willing to engage with healthcare. It may also be the case that gender differences in mean levels of primary healthcare use are primarily driven by gender differences in the share of non-users.

We investigated trajectories of primary healthcare use and levels of non-use surrounding a major health shock, defined as the first hospital admission at age 60 and older. We examined primary healthcare use patterns before and after hospitalization for four major causes of admission: stroke, myocardial infarction (MI), chronic obstructive pulmonary disease (COPD), and gastrointestinal cancers (GIC). We expected the frequency of contacts with primary healthcare to be higher in the period after admission to hospital, and to be generally higher among women. If men are more reluctant to seek medical advice until the occurrence of health shock, we may expect to see a greater change in primary healthcare use among men than among women following hospitalization.

3.4 Methods

3.4.1 Data

We utilized routinely-collected, population-based register data on hospital admissions and contacts with primary healthcare covering the entire Danish population. Using the unique personal identification number (CPR-Number), we linked records from the Central Population Registry (CPR), the National Patient Register (NPR), and the National Health Service Register (NHSR). While the CPR contains information on each resident's vital status, gender, and date of birth,[9,146] the NPR contains information on hospital treatments since 1977, including dates of admission and discharge, and the causes of admission.[158] The NHSR, established in 1990, contains data on primary healthcare use and includes information on the provider and a code for the provided services.[10] Since treatments of under 16-year-olds were reported with the CPR-Number of one parent until 31 December 1995, we restricted our study period to 1996–2014.

3.4.2 Study Population

Over one million men and women were aged 60 or older in Denmark by 1 January, 1999 (N=1,056,733). We focused on healthcare use after age 60 to remove obstetrics-related healthcare use, which would otherwise have introduced a strong gender bias. We applied a 7-year washout-period to increase the likelihood that the observed admission is not a re-admission. Washout-periods of 7 years are recommended by the Swedish National Board of Health and Welfare in order to capture first events of MI,[260] and have been widely used in register-based studies.[72,123] We excluded 433,352 individuals who were admitted to hospital within the previous 7-year period, lasting from 1 January 1992 to 31 December 1998.

Among the remaining individuals (N=623,381), we identified those who were admitted to a Danish hospital between 1 January, 1999 and 31 December, 2011 (N=414,839). We defined an admission to hospital as the first inpatient hospital stay at age 60 or older, lasting three days (equivalent to two overnight stays) or longer, and distinguished whether the underlying cause for the hospitalization was stroke, MI, GIC, and COPD (N=65,622). We linked admissions with data on contacts with primary healthcare, covering the 33 months before and after hospitalization in order to capture changes in treatment-seeking behavior.

To account for a potential bias emerging from an increased healthcare use in close proximity to death,[261] we conducted a sensitivity check by restricting our analysis to those who survived the entire 33-month period following hospitalization.

3.4.3 Study Design and Statistical Modeling

The study design is illustrated in Figure 1. For each individual, we recorded the number of contacts with primary healthcare in five 6-month periods spanning 30 months before and after the hospitalization event. To ensure that all intervals were of 6-month length, and to account for varying lengths of stay in hospital, we specified an additional interval surrounding the period of admission to hospital. This interval covered three months before and after hospitalization. We omitted this period from our analysis, and thus analyzed the frequency of contacts with primary healthcare in the five 6-month intervals preceding and following the 6-month admission period. Consequently, the study period starts 33 months before admission and ends 33 months thereafter.

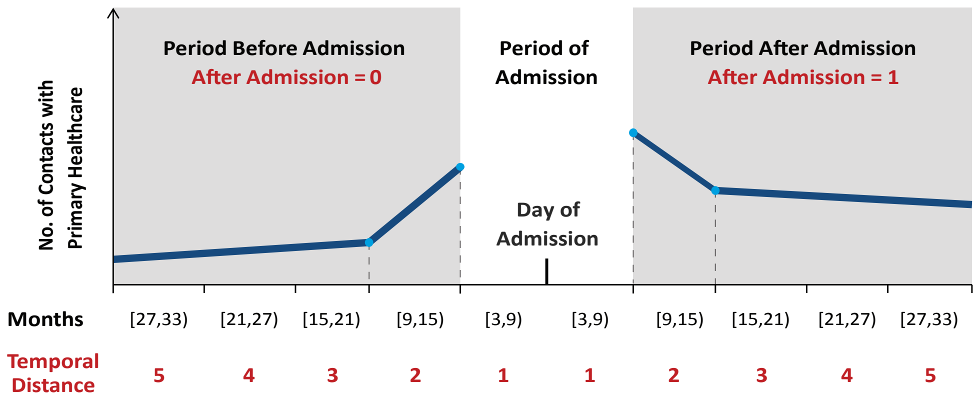


Figure 1: Overview of the study design and the modeling of time before and after hospital admission using a linear spline.

We investigated how the number of contacts with primary healthcare changed with temporal distance to hospital admission (*Temp.Dist.*) and other covariates. We introduced a binary variable (*After*) that could, via interaction with *Temp.Dist.*, capture potential differences in the trajectories of healthcare use before and after hospital admission.

In this longitudinal cohort study, the responses are repeated observations of counts. In addition, as shown in Figure 2, the marked zero-inflation present before hospital admission largely disappears thereafter. We therefore utilized a hurdle model to account for the special properties of our data.[164]

A hurdle model is a two-part model which combines a regression model for the probability of zero-counts with a regression model for the positive counts. The first part is a binomial logistic regression, which captures non-users of primary healthcare. The second part models the frequency of healthcare use for individuals who engage with primary healthcare. An individual random effect was incorporated to account for repeated observations. Positive counts were modeled by a truncated negative binomial regression with a log-link to account for overdispersion not captured by the observed covariates.

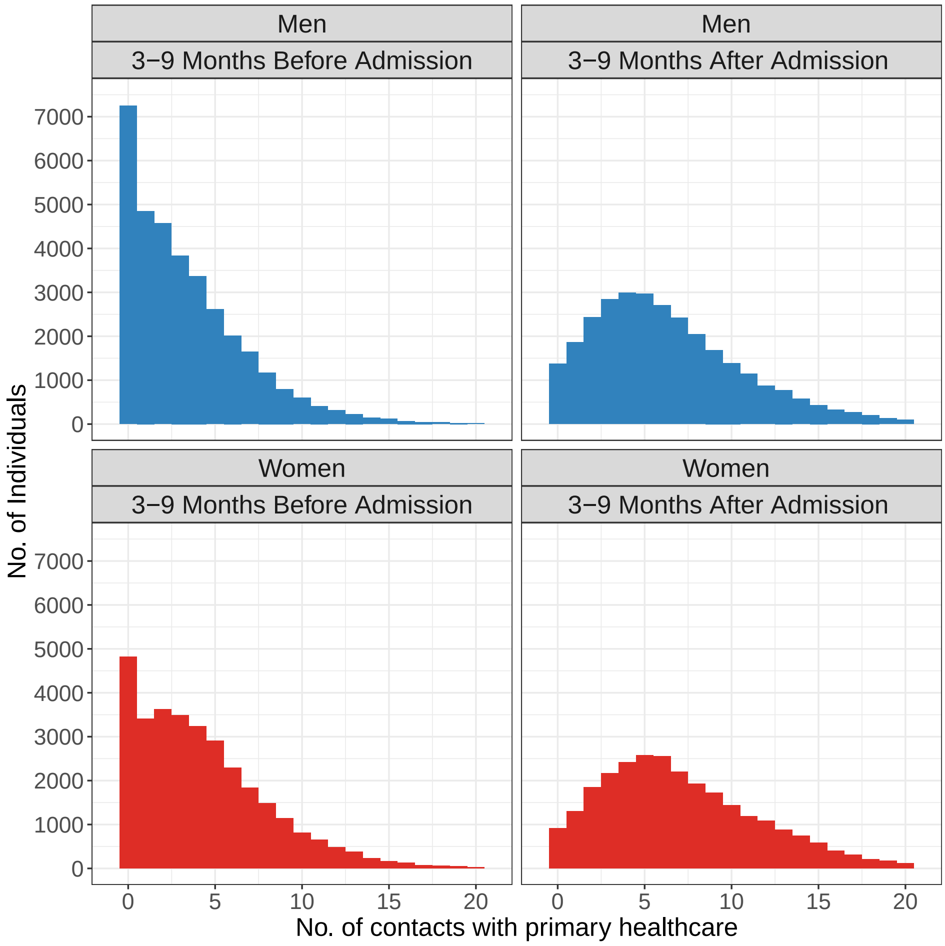


Figure 2: Distribution of contacts with primary healthcare within the 3- to 9-month period before and after admission to hospital.

As shown in Table 1, we performed model selection for both parts of the model step-wise and hierarchically, separately for each cause.[a] Temporal distance to hospitalization was included in two ways: either with a single linear effect (log-scale) or as a linear spline (lin.spl.), a piecewise-linear function, with a knot at *Temp.Dist.* = *2*. The linear spline allowed the slope to be different for the 6-month intervals

[a] *Note:* $(1|ID)$ *stands for individual random effect*

next to the admission period as the healthcare use might change more rapidly close to admission. Using Akaike's Information Criterion (AIC), we selected Model 5 as the final model. Parameter estimates are presented as Odds Ratios (OR) for the logistic model and as Proportional Change (e^{β}) for the count model. Delta method was used to estimate 95% confidence intervals (CI). The merging of registers was carried out with Stata (Version 14). Statistical models were estimated using the glmmTMB package for R (Version 3.5.1).[262]

Table 1: Overview on the stepwise model development process; models were developed separately by cause of admission

Cause	**M**	**Model for zero-counts**	**Model for positive counts**	**AIC**	**dAIC**	**DF**
Stroke	1	After + Gender + Age + $(1 \mid ID)$	Temp.Dist. * After + Gender + Age + $(1 \mid ID)$	1,014,319	753	17
Stroke	2	After + Gender + Age + $(1 \mid ID)$	Temp.Dist. * After + Gender * After + Age + $(1 \mid ID)$	1,013,961	395	18
Stroke	3	After + Gender + Age + $(1 \mid ID)$	lin.spl.(Temp.Dist.) * After + Gender + Age + $(1 \mid ID)$	1,013,925	359	19
Stroke	4	After + Gender + Age + $(1 \mid ID)$	lin.spl.(Temp.Dist.) * After + Gender * After + Age + $(1 \mid ID)$	1,013,566	0	20
Stroke	5	After * Gender + Age + $(1 \mid ID)$	lin.spl.(Temp.Dist.) * After + Gender * After + Age + $(1 \mid ID)$	1,013,567	1	21
MI	1	After + Gender + Age + $(1 \mid ID)$	Temp.Dist. * After + Gender + Age + $(1 \mid ID)$	719,204	468	17
MI	2	After + Gender + Age + $(1 \mid ID)$	Temp.Dist. * After + Gender * After + Age + $(1 \mid ID)$	718,932	195	18
MI	3	After + Gender + Age + $(1 \mid ID)$	lin.spl.(Temp.Dist.) * After + Gender + Age + $(1 \mid ID)$	719,012	275	19
MI	4	After + Gender + Age + $(1 \mid ID)$	lin.spl.(Temp.Dist.) * After + Gender * After + Age + $(1 \mid ID)$	718,739	2	20
MI	5	After * Gender + Age + $(1 \mid ID)$	lin.spl.(Temp.Dist.) * After + Gender * After + Age + $(1 \mid ID)$	718,737	0	21
COPD	1	After + Gender + Age + $(1 \mid ID)$	Temp.Dist. * After + Gender + Age + $(1 \mid ID)$	447,466	176	17
COPD	2	After + Gender + Age + $(1 \mid ID)$	Temp.Dist. * After + Gender * After + Age + $(1 \mid ID)$	447,368	79	18
COPD	3	After + Gender + Age + $(1 \mid ID)$	lin.spl.(Temp.Dist.) * After + Gender + Age + $(1 \mid ID)$	447,399	110	19
COPD	4	After + Gender + Age + $(1 \mid ID)$	lin.spl.(Temp.Dist.) * After + Gender * After + Age + $(1 \mid ID)$	447,302	12	20
COPD	5	After * v + Age + $(1 \mid ID)$	lin.spl.(Temp.Dist.) * After + Gender * After + Age + $(1 \mid ID)$	447,289	0	21
GIC	1	After + Gender + Age + $(1 \mid ID)$	Temp.Dist. * After + Gender + Age + $(1 \mid ID)$	513,393	274	17
GIC	2	After + Gender + Age + $(1 \mid ID)$	Temp.Dist. * After + Gender * After + Age + $(1 \mid ID)$	513,289	169	18
GIC	3	After + Gender + Age + $(1 \mid ID)$	lin.spl.(Temp.Dist.) * After + Gender + Age + $(1 \mid ID)$	513,228	109	19
GIC	4	After + Gender + Age + $(1 \mid ID)$	lin.spl.(Temp.Dist.) * After + Gender * After + Age + $(1 \mid ID)$	513,123	3	20
GIC	5	After * Gender + Age + $(1 \mid ID)$	lin.spl.(Temp.Dist.) * After + Gender * After + Age + $(1 \mid ID)$	513,119	0	21

3.5 Results

3.5.1 Descriptive Statistics

As shown in Table 2, we studied 65,622 individuals, of whom 48% were women and 52% were men. The mean age at first admission was significantly higher (p-Value < 0.001) among women (77.25 years) than men (75.17 years).

Table 2: Number and percentage of hospital admissions by gender and cause of admission to hospital.

Cause of Admission	ICD-10 Chapter	Men		Women	
		No.	in %	No.	in %
Stroke	I.61 – I.64	11,919	34.8	12,227	38.9
MI	I.21 – I.22	10,482	30.6	6,736	21.4
COPD	J.40 – J.47	4,335	12.7	5,530	17.6
GIC	C.15 – C.26	7,465	21.8	6,928	22
Total	**-**	**34,201**	**100**	**31,421**	**100**

3.5.2 Regression Model

The estimated hurdle models are shown in Table 3. The upper section of Table 3 shows the model for being in the non-user group. Before hospitalization, we found that men had higher odds of being in the non-user group than women (ORs & 95% CI; Stroke: 1.802 (1.731-1.872); MI: 1.841 (1.760-1.922); COPD: 2.160 (2.028-2.292); GIC: 1.609 (1.525-1.693); all p-Values < 0.001). For men and women, and across all causes, the odds of being in the non-user group were consistently smaller in the period after admission than in the period before admission (ORs & 95% CI; Stroke: 0.062 (0.000-0.129); MI: 0.074 (0.000-0.163); COPD: 0.190 (0.087-0.293); GIC: 0.230 (0.159-0.301); all p-Values < 0.001). The interaction effect between gender and the period after hospitalization suggests that, after hospital admission, the decline in the probability of being a non-user was larger among men than women for all causes apart from stroke (ORs & 95% CI; Stroke: 0.965 (0.879-1.052), p-Value: 0.420; MI: 0.894 (0.789-0.999), p-Value: 0.036; COPD: 0.755 (0.609-0.900), p-Value: 0.001;

GIC: 0.895 (0.801-0.988), p-Value: 0.020).

Translated into probabilities, this means that levels of non-use were substantially smaller in the period after hospitalization, and that gender differences in the probability of being a non-user were smaller in the period after, than in the period before hospitalization. For example, a man aged 60-69, who was admitted for MI, had a 25% probability of being in the non-user group before admission, while the probability among women was 15%. After admission for MI, the corresponding probabilities of non-use were 2% among men and 1% among women.

The lower section of Table 3 shows the regression results for the positive counts model. Across all causes of admission, we found that the average number of contacts with primary healthcare increased steadily before hospitalization. Within the period before admission, men had less contact when compared to women (e^{β} & 95% CI; Stroke: 0.821 (0.806-0.836); MI: 0.796 (0.778-0.814); COPD: 0.855 (0.832-0.878); GIC: 0.859 (0.838-0.881); all p-Values < 0.001).

The average number of contacts with primary healthcare jumped in level after hospitalization. This increase was higher for the conditions, stroke and MI, when compared with the conditions COPD and GIC (e^{β} & 95% CI; Stroke: 1.727 (1.715-1.739); MI: 1.638 (1.624-1.652); COPD: 1.291 (1.275-1.307); GIC: 1.350 (1.331-1.368); all p-Values < 0.001). However, the post-hospitalization increase in the average number of contacts was larger among men than among women (e^{β} & 95% CI; Stroke: 1.113 (1.102-1.124); MI: 1.112 (1.099-1.124); COPD: 1.078 (1.063-1.093); GIC: 1.097 (1.079-1.114); all p-Values < 0.001). Gender differences among users of primary healthcare were therefore smaller in the period after than in the period before hospital admission. Nevertheless, level differences between men and women of the user group did not fully disappear after hospitalization.

Table 3: Results of hurdle regression models.

Log. Model for Zero Counts	**Stroke Est. (95%CI)**	**p-Value**	**MI Est. (95%CI)**	**p-Value**	**COPD Est. (95%CI)**	**p-Value**	**GIC Est. (95%CI)**	**p-Value**
Intercept	0.173 (0.083-0.262)	<0.001	0.178 (0.084-0.273)	<0.001	0.027 (0.000-0.193)	<0.001	0.217 (0.121-0.314)	<0.001
After	0.062 (0.000-0.129)	<0.001	0.074 (0.000-0.163)	<0.001	0.190 (0.087-0.293)	<0.001	0.230 (0.159-0.301)	<0.001
Men	1.802 (1.731-1.872)	<0.001	1.841 (1.760-1.922)	<0.001	2.160 (2.028-2.292)	<0.001	1.609 (1.525-1.693)	<0.001
Men*After	0.965 (0.879-1.052)	0.42	0.894 (0.789-0.999)	0.036	0.755 (0.609-0.900)	0.001	0.895 (0.801-0.988)	0.02
Age 70-79	0.528 (0.438-0.619)	<0.001	0.465 (0.375-0.555)	<0.001	0.597 (0.444-0.751)	<0.001	0.458 (0.360-0.557)	<0.001
Age 80-89	0.347 (0.247-0.446)	<0.001	0.278 (0.170-0.386)	<0.001	0.435 (0.244-0.626)	<0.001	0.287 (0.168-0.407)	<0.001
Age 90+	0.321 (0.143-0.499)	<0.001	0.265 (0.049-0.480)	<0.001	0.658 (0.134-1.183)	0.118	0.230 (0.000-0.538)	<0.001

NB Model for Positive Counts	**Stroke Est. (95%CI)**	**p-Value**	**MI Est. (95%CI)**	**p-Value**	**COPD Est. (95%CI)**	**p-Value**	**GIC Est. (95%CI)**	**p-Value**
Intercept	3.634 (3.615-3.654)	<0.001	3.535 (3.513-3.558)	<0.001	5.126 (5.101-5.152)	<0.001	3.463 (3.437-3.490)	<0.001
lin.spl.(Temp.Dist.)1	0.944 (0.933-0.955)	<0.001	0.948 (0.935-0.961)	<0.001	0.910 (0.896-0.925)	<0.001	0.871 (0.856-0.887)	<0.001
lin.spl.(Temp.Dist.)2	0.872 (0.861-0.884)	<0.001	0.877 (0.863-0.890)	<0.001	0.801 (0.787-0.816)	<0.001	0.787 (0.771-0.802)	<0.001
After	1.727 (1.715-1.739)	<0.001	1.638 (1.624-1.652)	<0.001	1.291 (1.275-1.307)	<0.001	1.350 (1.331-1.368)	<0.001
lin.spl.(Temp.Dist.)1*After	0.937 (0.922-0.951)	<0.001	0.944 (0.928-0.961)	<0.001	1.056 (1.037-1.075)	<0.001	1.062 (1.040-1.084)	<0.001
lin.spl.(Temp.Dist.)2*After	0.983 (0.968-0.998)	0.023	0.955 (0.938-0.972)	<0.001	1.241 (1.221-1.261)	<0.001	1.166 (1.142-1.189)	<0.001
Men	0.821 (0.806-0.836)	<0.001	0.796 (0.778-0.814)	<0.001	0.855 (0.832-0.878)	<0.001	0.859 (0.838-0.881)	<0.001
Men*After	1.113 (1.102-1.124)	<0.001	1.112 (1.099-1.124)	<0.001	1.078 (1.063-1.093)	<0.001	1.097 (1.079-1.114)	<0.001
Age 70-79	1.116 (1.097-1.135)	<0.001	1.143 (1.123-1.163)	<0.001	1.079 (1.053-1.105)	<0.001	1.132 (1.106-1.157)	<0.001
Age 80-89	1.161 (1.141-1.181)	<0.001	1.240 (1.217-1.263)	<0.001	1.097 (1.066-1.129)	<0.001	1.216 (1.187-1.246)	<0.001
Age 90+	1.129 (1.094-1.164)	<0.001	1.230 (1.186-1.274)	<0.001	1.070 (0.981-1.158)	0.136	1.277 (1.206-1.348)	<0.001
No. of Observations	217,000		157,680		88,712		114,961	
No. of Groups	24,146		17,218		9,865		14,393	
VAR Ind. RE Log. Model	4.6		3.9		6.05		3.87	
VAR Ind. RE NB Model	0.23		0.24		0.25		0.28	
Overdisp. Par. NB Model	11.2		15.5		13.9		8.55	

The trajectories of contacts with primary healthcare before and after hospitalization among men and women admitted for MI are shown in Figure 3. Visualizations for COPD, stroke, and GIC can be found in Supplementary Figure S1, Supplementary Figure S2, and Supplementary Figure S3 at the end of this paper.

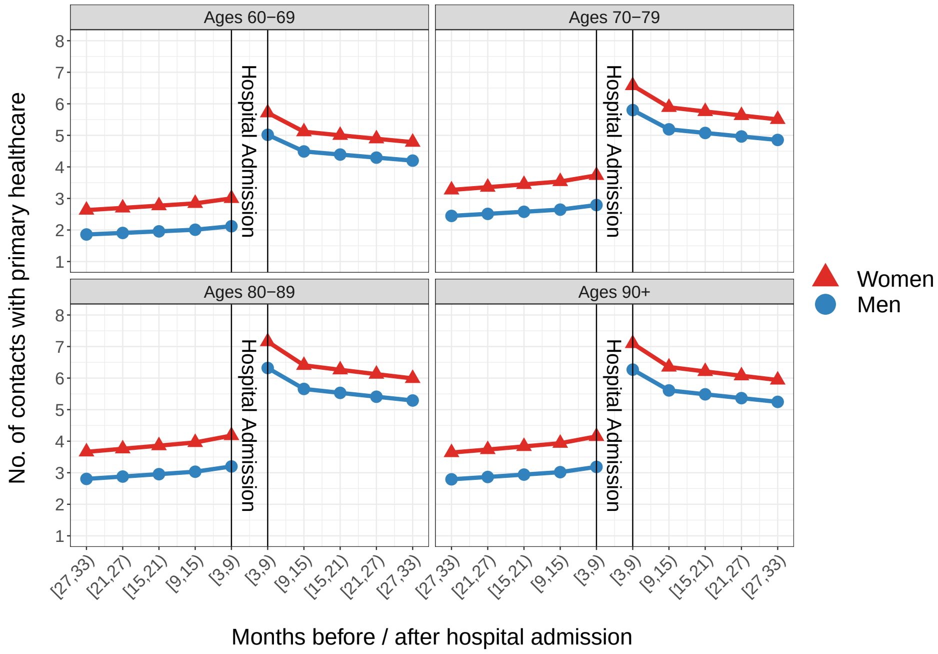


Figure 3: Estimated average number of contacts with primary healthcare before and after admission to hospital for MI.

3.5.3 Sensitivity Analysis

To examine the impact of mortality selection following hospitalization, we restricted the study population to all individuals who survived the 33-month period after admission (N=42,683) and re-ran the analysis. We observed only marginal changes in the parameters of the hurdle models. However, before and after admission, gender differences in non-use and levels of primary healthcare use among users were consistently larger in this setting. This suggests that women's higher primary healthcare use around hospitalization is linked with their longer survival in poorer health when compared to men. Results of sensitivity analyses are shown in Supplementary Table S1, Supplementary Table S2, and Supplementary Table S3 at the end of this paper.

3.6 Discussion

3.6.1 Principal Findings

We investigated patterns of primary healthcare use among men and women around the first hospital admission at ages 60+. Across all studied causes, men had lower levels of primary healthcare use before and after hospitalization. In addition, men had higher probabilities of being non-users – especially before hospitalization. After experiencing a health shock, changes in primary healthcare use patterns, in particular the probability of being a non-user and the primary healthcare use levels, were more marked among men than among women.

3.6.2 Strengths and Limitations

We utilized high-quality register data, which covered the entire Danish Population between 1992 and 2014. Working with population-based registers reduces the challenges of longitudinal surveys: losses to follow-up, recall bias, and non-responses. These often differ systematically between men and women, and may have a significant impact on the generalizability of findings.[66,263]

We used individual-level data on four causes of hospital admission to examine changes in treatment-seeking behavior after a health shock, aiming for a comparison of men and women facing a similar health condition. Unfortunately, our data did not allow us to investigate the severity of the underlying conditions. Furthermore, the data on primary healthcare did not allow us to distinguish whether a contact was directly related to the cause of admission, and whether it was a preventative visit or for continuing treatment. In addition, our findings may be limited to healthcare contexts which are similar to the Danish with nationwide coverage for all residents and no out-of-pocket expenses for GP visits. Despite these limitations, our study makes an important contribution to the literature by examining gender differences in the levels of primary healthcare use in a longitudinal setting, across four major conditions, and by identifying users and non-users of primary healthcare.

3.6.3 Interpretations and Implications

Using a hurdle model enabled us to distinguish between two stochastic processes: first, the probability that individuals do not engage with primary healthcare, and second, the number of contacts for those individuals who are users of primary healthcare. This distinction is important as our analysis showed that, once men and women were users of primary healthcare, their general trajectories of healthcare use do not differ. It is therefore possible that gender differences in non-use might explain a substantial part of gender differences in mean levels of primary healthcare use on the population level.

Differentiating by cause of hospitalization allowed us to investigate whether gender differences in primary healthcare use varied across conditions. We found absolute gender differences in non-use and use levels to be largest across the acute conditions stroke and MI - conditions, for which symptoms might not be present before disease onset, or already-present symptoms might be overlooked. Contrastingly, for example, patients with COPD are likely to have noticeable symptoms long before admission. This is likely to explain why levels of non-use and the magnitude of absolute gender differences in both parts of the hurdle model were generally lowest among patients with COPD.

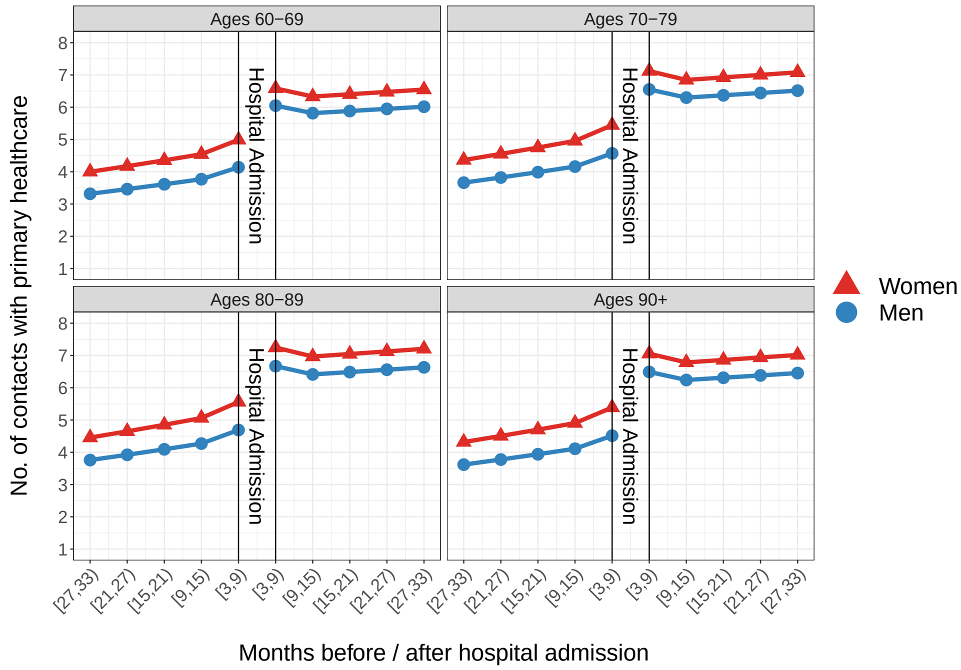
Before admission to hospital, and consistently across all four causes of admission, men were more likely to be non-users of primary healthcare than women. This finding appears to be in line with early qualitative work on differentials in treatment-seeking behavior, which reported that the postponement of treatment-seeking is gender patterned.[174,247,264,265] In the past, the over-generalization of these findings has contributed to over-simplified, stereotypical expectations about gender and treatment-seeking behavior: that men are more reluctant to seek medical advice, while women are over-users of the healthcare system, and are more willing to consult a doctor even with less-serious complaints.[266,267] However, we found a remarkable share of women to be non-users of primary healthcare before admission to hospital. This is consistent with more recent work, which has demonstrated that neglecting symptoms and postponing treatment-seeking exist among women, too.[266] Therefore, treatment-seeking differentials should not be separated into binary gender patterns. Men and women may face similar psycho-social obstacles to using primary healthcare services.[268] For example, both genders may postpone seeing a doctor when no urgency is perceived.[66] At the same time, when experiencing signs of a severe disease, such as lung cancer, fear of the implications of a diagnosis may be a reason for not seeking medical advice.[269–271] In our study, the probabilities of being a non-user of primary healthcare after admission to hospital were equally low among men and women. This may partly reflect the impact of established treatment schemes after hospitalization, which are fixed irrespective of gender. We interpret the higher post-hospitalization increase in primary healthcare use among men, in both parts of the hurdle model, to indicate that men were more reluctant to seek medical advice before experiencing an acute health shock. Nevertheless, gender differences in contacts with primary healthcare did not fully disappear after hospitalization. This may be due to higher mortality selection in men following hospitalization: women are more likely to survive with disabling conditions.[251] Supporting this assumption, we found greater gender differences when restricting the analysis to individuals who survived the entire 33-month period following admission.

3.6.4 Conclusion

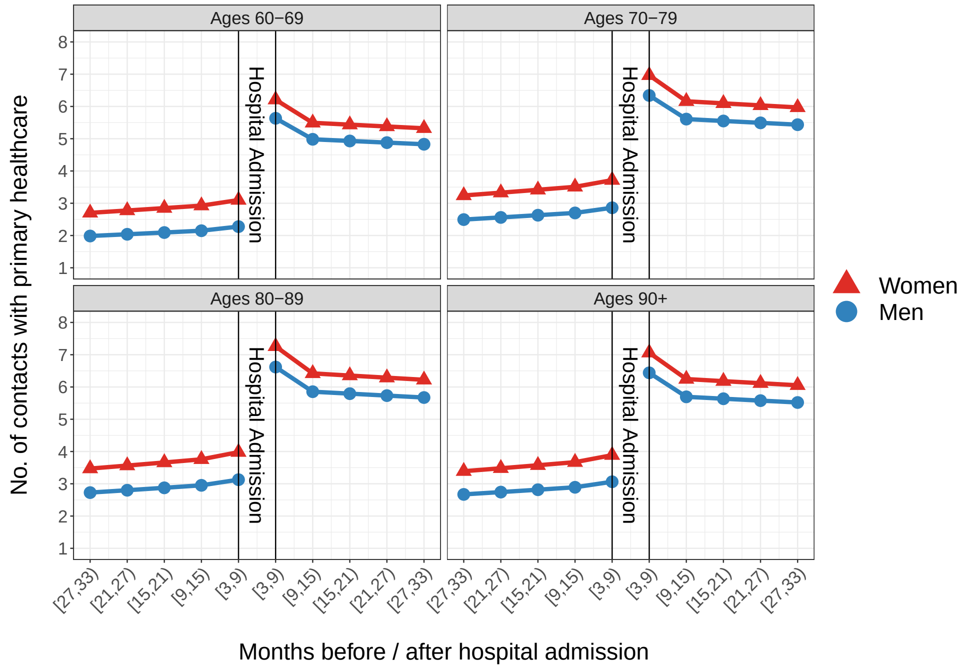
Our findings indicate a lower threshold for treatment-seeking among women. In addition, higher levels of primary healthcare use among women may be underpinned by the fact that women are more likely to survive with disabling conditions following hospitalization. Attention should be given to increasing men's and women's usage of primary healthcare services, long before hospitalization, to prevent or postpone the ultimate health deterioration.

3.7 Supplementary Material

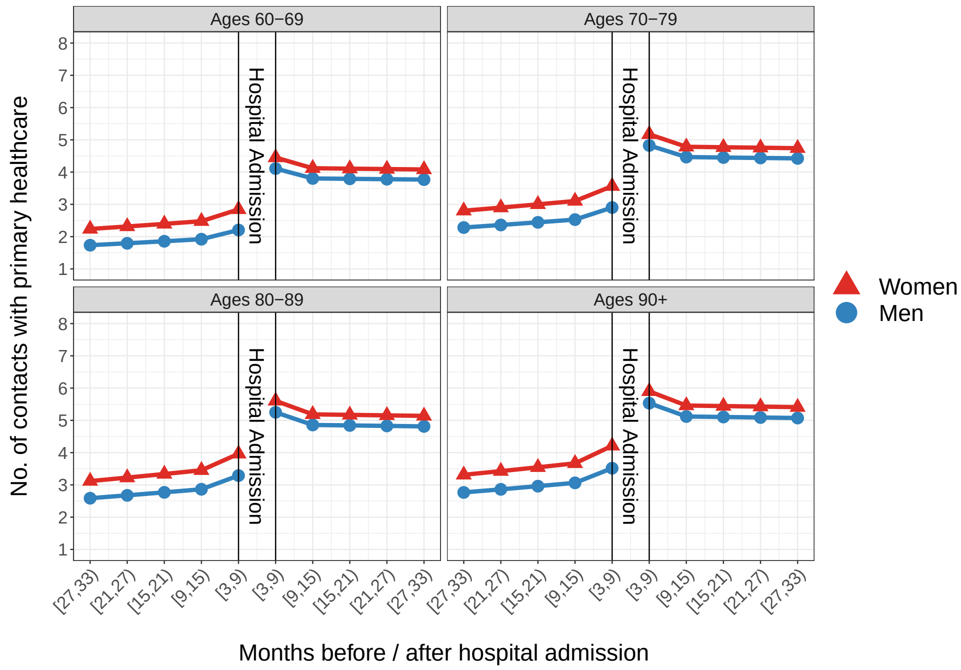
3.7.1 Supplementary Figures



Supplementary Figure S1: Estimated, average number of contacts with primary healthcare before and after admission to hospital for chronic obstructive pulmonary disease (COPD).



Supplementary Figure S2: Estimated, average number of contacts with primary healthcare before and after admission to hospital for stroke.



Supplementary Figure S3: Estimated, average number of contacts with primary healthcare before and after admission to hospital for gastrointestinal cancers (GIC).

3.7.2 Supplementary Tables

Supplementary Table S1: Overview on the stepwise model development process; survivors of the 33-month study period.

Cause	**M**	**Model for zero-counts**	**Model for positive counts**	**AIC**	**dAIC**	**DF**
Stroke	1	After + Gender + Age + $(1 \mid ID)$	Temp.Dist. * After + Gender + Age + $(1 \mid ID)$	783,611	753	17
Stroke	2	After + Gender + Age + $(1 \mid ID)$	Temp.Dist. * After + Gender * After + Age + $(1 \mid ID)$	783,310	395	18
Stroke	3	After + Gender + Age + $(1 \mid ID)$	lin.spl.(Temp.Dist.) * After + Gender + Age + $(1 \mid ID)$	783,224	359	19
Stroke	4	After + Gender + Age + $(1 \mid ID)$	lin.spl.(Temp.Dist.) * After + Gender * After + Age + $(1 \mid ID)$	782,922	0	20
Stroke	5	After * Gender + Age + $(1 \mid ID)$	lin.spl.(Temp.Dist.) * After + Gender * After + Age + $(1 \mid ID)$	782,923	1	21
MI	1	After + Gender + Age + $(1 \mid ID)$	Temp.Dist. * After + Gender + Age + $(1 \mid ID)$	585,568	452	17
MI	2	After + Gender + Age + $(1 \mid ID)$	Temp.Dist. * After + Gender * After + Age + $(1 \mid ID)$	585,347	231	18
MI	3	After + Gender + Age + $(1 \mid ID)$	lin.spl.(Temp.Dist.) * After + Gender + Age + $(1 \mid ID)$	585,342	225	19
MI	4	After + Gender + Age + $(1 \mid ID)$	lin.spl.(Temp.Dist.) * After + Gender * After + Age + $(1 \mid ID)$	585,120	4	20
MI	5	After * Gender + Age + $(1 \mid ID)$	lin.spl.(Temp.Dist.) * After + Gender * After + Age + $(1 \mid ID)$	585,116	0	21
COPD	1	After + Gender + Age + $(1 \mid ID)$	Temp.Dist. * After + Gender + Age + $(1 \mid ID)$	320,473	131	17
COPD	2	After + Gender + Age + $(1 \mid ID)$	Temp.Dist. * After + Gender * After + Age + $(1 \mid ID)$	320,395	53	18
COPD	3	After + Gender + Age + $(1 \mid ID)$	lin.spl.(Temp.Dist.) * After + Gender + Age + $(1 \mid ID)$	320,426	84	19
COPD	4	After + Gender + Age + $(1 \mid ID)$	lin.spl.(Temp.Dist.) * After + Gender * After + Age + $(1 \mid ID)$	320,349	6	20
COPD	5	After * Gender + Age + $(1 \mid ID)$	lin.spl.(Temp.Dist.) * After + Gender * After + Age + $(1 \mid ID)$	320,342	0	21
GIC	1	After + Gender + Age + $(1 \mid ID)$	Temp.Dist. * After + Gender + Age + $(1 \mid ID)$	287,754	171	17
GIC	2	After + Gender + Age + $(1 \mid ID)$	Temp.Dist. * After + Gender * After + Age + $(1 \mid ID)$	287,685	101	18
GIC	3	After + Gender + Age + $(1 \mid ID)$	lin.spl.(Temp.Dist.) * After + Gender + Age + $(1 \mid ID)$	287,656	72	19
GIC	4	After + Gender + Age + $(1 \mid ID)$	lin.spl.(Temp.Dist.) * After + Gender * After + Age + $(1 \mid ID)$	287,586	2	20
GIC	5	After * Gender + Age + $(1 \mid ID)$	lin.spl.(Temp.Dist.) * After + Gender * After + Age + $(1 \mid ID)$	287,584	0	21

Supplementary Table S2: Number and percentage of hospital admissions by gender and cause of admission; survivors of the 33-month study period.

Cause of Admission	**ICD-10 Chapter**	**Men**		**Women**	
		No.	**in %**	**No.**	**in %**
Stroke	I.61 – I.64	8,388	37.4	8,432	41.6
MI	I.21 – I.22	8,065	36	4,873	24.1
COPD	J.40 – J.47	2,651	11.8	3,778	18.6
GIC	C.15 – C.26	3,319	14.8	3,177	15.7
Total	**-**	**22,423**	**100**	**20,260**	**100**

Supplementary Table 3: Results of hurdle regression models; survivors of the 33-month study period.

Log. Model for Zero Counts	**Stroke Est. (95%CI)**	**p-Value**	**MI Est. (95%CI)**	**p-Value**	**COPD Est. (95%CI)**	**p-Value**	**GIC Est. (95%CI)**	**p-Value**
Intercept	0.176 (0.080-0.271)	<0.001	0.176 (0.076-0.276)	<0.001	0.032 (0.000-0.211)	<0.001	0.191 (0.060-0.321)	<0.001
After	0.066 (0.000-0.136)	<0.001	0.076 (0.000-0.169)	<0.001	0.192 (0.081-0.303)	<0.001	0.304 (0.222-0.386)	<0.001
Men	1.870 (1.790-1.951)	<0.001	2.013 (1.923-2.103)	<0.001	2.307 (2.150-2.464)	<0.001	1.863 (1.742-1.984)	<0.001
Men*After	0.942 (0.851-1.033)	0.199	0.868 (0.758-0.978)	0.011	0.793 (0.635-0.951)	0.004	0.894 (0.786-1.001)	0.041
Age 70-79	0.566 (0.470-0.661)	<0.001	0.489 (0.396-0.583)	<0.001	0.609 (0.439-0.779)	<0.001	0.426 (0.294-0.558)	<0.001
Age 80-89	0.390 (0.278-0.502)	<0.001	0.317 (0.192-0.441)	<0.001	0.446 (0.212-0.680)	<0.001	0.272 (0.095-0.449)	<0.001
Age 90+	0.362 (0.076-0.649)	<0.001	0.331 (0.002-0.659)	<0.001	0.921 (0.096-1.746)	0.845	0.153 (0.000-0.837)	<0.001

NB Model for Positive Counts	**Stroke Est. (95%CI)**	**p-Value**	**MI Est. (95%CI)**	**p-Value**	**COPD Est. (95%CI)**	**p-Value**	**GIC Est. (95%CI)**	**p-Value**
Intercept	3.601 (3.579-3.623)	<0.001	3.508 (3.483-3.532)	<0.001	4.875 (4.846-4.904)	<0.001	3.313 (3.276-3.350)	<0.001
lin.spl.(Temp.Dist.)1	0.953 (0.940-0.967)	<0.001	0.957 (0.942-0.972)	<0.001	0.925 (0.908-0.942)	<0.001	0.886 (0.864-0.908)	<0.001
lin.spl.(Temp.Dist.)2	0.887 (0.874-0.901)	<0.001	0.889 (0.874-0.905)	<0.001	0.820 (0.802-0.838)	<0.001	0.804 (0.782-0.827)	<0.001
After	1.731 (1.717-1.745)	<0.001	1.677 (1.661-1.693)	<0.001	1.285 (1.267-1.304)	<0.001	1.221 (1.198-1.245)	<0.001
lin.spl.(Temp.Dist.)1*After	0.924 (0.907-0.941)	<0.001	0.923 (0.905-0.942)	<0.001	1.041 (1.018-1.064)	<0.001	1.042 (1.013-1.071)	0.005
lin.spl.(Temp.Dist.)2*After	0.977 (0.960-0.994)	0.007	0.937 (0.918-0.956)	<0.001	1.246 (1.222-1.269)	<0.001	1.194 (1.164-1.223)	<0.001
Men	0.801 (0.783-0.819)	<0.001	0.781 (0.760-0.801)	<0.001	0.846 (0.818-0.874)	<0.001	0.824 (0.793-0.856)	<0.001
Men*After	1.114 (1.102-1.126)	<0.001	1.109 (1.095-1.122)	<0.001	1.079 (1.062-1.096)	<0.001	1.094 (1.073-1.115)	<0.001
Age 70-79	1.101 (1.081-1.121)	<0.001	1.127 (1.106-1.148)	<0.001	1.080 (1.050-1.110)	<0.001	1.182 (1.147-1.216)	<0.001
Age 80-89	1.127 (1.104-1.150)	<0.001	1.195 (1.169-1.221)	<0.001	1.105 (1.065-1.145)	<0.001	1.267 (1.224-1.311)	<0.001
Age 90+	1.090 (1.034-1.145)	0.002	1.149 (1.082-1.215)	<0.001	0.986 (0.838-1.145)	0.851	1.354 (1.206-1.502)	<0.001
No. of Observations	168,200		129,389		64,290		64,960	
No. of Groups	16,820		12,938		6,429		6,496	
VAR Ind. RE Log. Model	4.19		3.59		5.44		3.56	
VAR Ind. RE NB Model	0.22		0.22		0.25		0.28	
Overdisp. Par. NB Model	12.8		17.5		16.6		11.3	

4 Inequalities in Mean Age at First Hospital Admission

Paper: Rosie Seaman, Andreas Höhn, Rune Lindahl Jacobsen, Pekka Martikainen, Alyson van Raalte, and Kaare Christensen: Rethinking Morbidity Compression: Increasing Inequality in Age at Morbidity Onset. ***Submitted to a peer-reviewed journal***

4.1 Abstract

Background: To evaluate morbidity compression, studies typically report the proportion of life expectancy spent in an unhealthy state. This overlooks variation in age at morbidity onset between individuals, a factor Fries (1980) saw as crucial for determining whether the continuation of disease postponement was possible. We use incidence of first hospitalization after age 60 to study variation in morbidity onset over a 27-year period in Denmark.

Methods: Number of hospitalizations and the population at risk for each year between 1987 and 2014 were identified using nationwide registry data. Sex-specific life tables were constructed, from which the mean and the coefficient of variation in age at first admission were calculated.

Results: Mean age at first admission increased between 1987 and 2014 from 67.8 years (95% CI: 67.7 - 67.9) to 69.5 years (95% CI: 69.4 - 69.6) in men, and 69.1 (95% CI: 69.1 - 69.2) to 70.5 years (95% CI: 70.4 - 70.6) in women. In the same period, the coefficient of variation in age at first admission increased from 9.1% (95% CI: 9.0 - 9.1) to 9.9% (95% CI: 9.8 - 10.0) among men and from 10.3% (95% CI: 10.2 - 10.4) to 10.6% (95% CI: 10.5 - 10.6) among women.

Conclusion: On average, morbidity has been postponed but variation in age at onset has increased. This variation has important implications for individual life planning and population-level welfare. Pensions, social and healthcare services will have to adapt to an increasingly heterogeneous aging population, a phenomenon that trends in the measurement of average morbidity onset cannot identify.

4.2 Key Messages

1. Morbidity compression means that years of bad health should become increasingly concentrated at the end of life. Typically, compression is measured in terms of changes in the proportion of average time spent in an unhealthy state. This approach assumes that the same average gain has been achieved for everyone, or that differences between individuals have stayed constant over time.

2. Inequality in morbidity onset across all individuals has largely been overlooked. Part of the problem is the challenge associated with estimating morbidity incidence.

3. Hospital admissions, among older ages, have been used to measure the onset of individual-level health deterioration. Routinely collected hospital admission data allow estimates of incidence of overall morbidity at the population level, from which variation in age at onset can be calculated.

4. We show that, on average, morbidity has been postponed towards older ages. Alongside this, variation between individuals has increased, suggesting that population health is becoming more heterogeneous.

5. Monitoring variation in age at morbidity onset is important for planning pensions, social care, and health services which will have to adapt to the heterogeneous needs of aging populations, something that average morbidity measures cannot identify.

4.3 Background

Remaining life expectancy at age 60 has rapidly increased across developed countries.[272] Whether the extra years of life are spent in good or bad health remains unclear, and depends in part on how health is measured.[20,118,180,273–275] Fries (1980) proposed a scenario where 'the amount of disability can decrease as morbidity is compressed into the shorter span between the increasing age at onset of disability and death'.[179] Gruenberg (1977) was more pessimistic, arguing that technological advancement would allow people to live for longer but in a prolonged state of poor health.[276] Manton (1982) suggested that falling mortality rates would be associated with a change in the distribution of disease types.[277] Specifically, an increase in the proportion of years spent with moderate health conditions and a decrease in the proportion of years spent with serious health conditions. Monitoring the rate of change in disability-free life expectancy (DFLE) or healthy life expectancy (HLE), compared with the rate of change in mortality, is assumed to be the best way to evaluate which scenario might be emerging as populations are aging.[176,177,278,279] If gains in DFLE or HLE are greater than gains in average life expectancy, morbidity compression is likely. If gains in average life expectancy are greater, it would be considered as evidence of expansion.

Key to Fries (1980) theory of morbidity compression is that alongside increasing age at death, the years spent with bad health or disability would become increasingly concentrated at the end of life. This implies that population age distributions of morbidity would become increasingly homogeneous among individuals. However, this important piece of information for determining whether the continuation of disease postponement is possible, has been overlooked in the morbidity compression debate.[181] Therefore, it is not known whether improving average health has been accompanied by decreasing or increasing variation in the age of morbidity onset between all individuals. Changes in the age distribution of morbidity onset have individual-level and population-level implications beyond theory. For individuals, it represents the amount of uncertainty in the timing of health deterioration. At the macro-level, pensions, social care, and health services will have to adapt to the heterogeneous needs of ageing populations, something that average measures cannot identify.[125]

To estimate the age distribution of morbidity onset across all individuals, we need to distinguish between incidence and prevalence.[180] Estimating incidence is challenging from cross-sectional health surveys.[176] Administrative healthcare data provide an opportunity and are continuously updated. Number of hospital days, number of admissions, and cause of admission have been operationalized to capture health.[85–89,95,96,251] In this paper, we quantify changes in the age distribution of morbidity onset across all individuals aged 60+ between 1987 and 2014, using first hospital admission for all causes among Danish men and women. Denmark is a valuable case study country because the aging population structure is comparable to many other developed countries. Unique to Denmark is that data exist for constructing individual-level hospitalization trajectories for the total population covering a substantial period of time.[74,157]

4.4 Methods and Materials

4.4.1 Data Sources

We used individual-level register data covering the total Danish population aged 60+. We linked records from the National Patient Register (NPR) with data from the Central Population Register (CPR) using the unique personal identification number (CPR-Number). The NPR, a population-based register, contains information on all treatments provided in Danish hospitals since 1977. Reporting of hospital admissions is compulsory, leading to high levels of completeness and reliability. The CPR includes socio-demographic information on the population alive and residing in Denmark since 1968, including sex, place and date of birth, and date of death.[146,157]

4.4.2 Study Population

In an ideal scenario, we would have health information for all individuals, covering the entire life course. This would have allowed us to identify every entry into, and every recovery from, an unhealthy state. As hospitalization data for Denmark began in 1977, we cannot identify admissions before this year. Therefore, we created an identical cohort study population for each calendar year by consistently applying the same method for each year between 1987 (to allow for a washout period) and 2014. This approach means that all estimated values were comparable throughout the study period. Figure 1 summarizes the process of identifying the study population in 1987 as an example year.

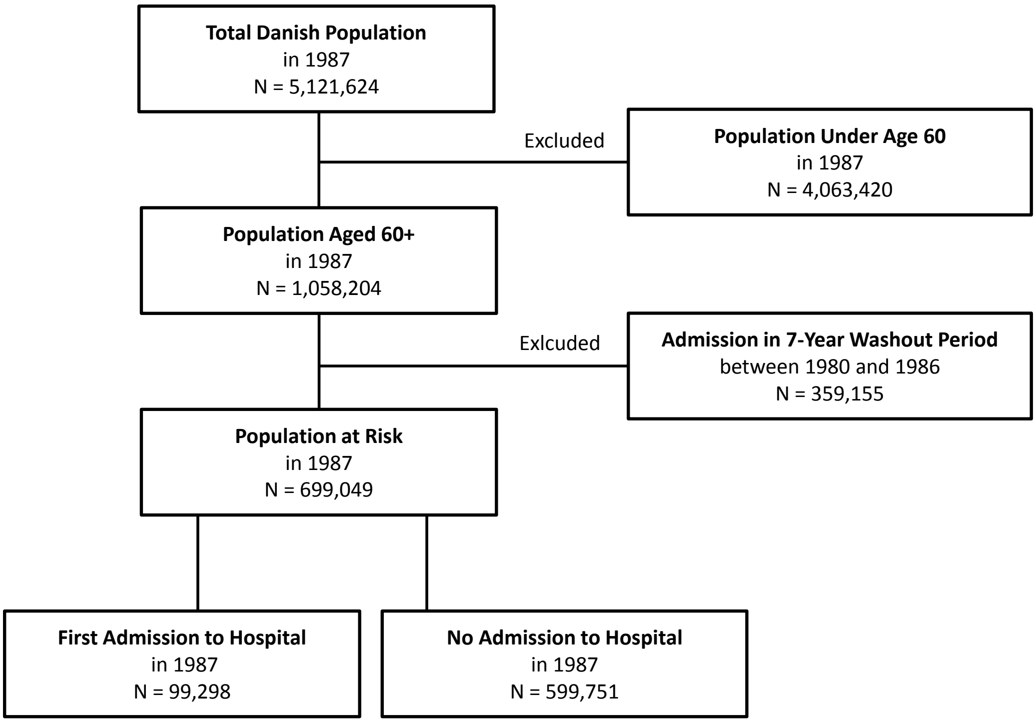


Figure 1: Constructing the Cohort Study Population: Example Year 1987.

First, we linked CPR and NPR information on all inpatient admissions and the population alive and residing in Denmark aged 60+. Second, we identified all individuals hospitalized within the previous 7-year period – irrespective of length of stay, and excluded these individuals from the analyses for the particular year.

Guided by existing literature,[123,280] a 7-year washout period was used to limit the chance that a first event was a readmission or a follow-up treatment. Third, for the remaining Danes, we identified the population at risk and the first events within each calendar year. We defined first events as the first inpatient hospitalization after age 60, from all causes, lasting for at least two days. We included all fatal events regardless of length of admission. This definition is likely to capture hospital admissions that would require inpatient care consistently throughout the study period. Events were included regardless of whether the outcome was death or discharge. Trends over time in the number of individuals at risk, first events, and those excluded in the washout period are given in Appendix 1.

4.4.3 Statistical Analysis

From the number of first hospital admissions and the population at risk, we estimated the age-specific risks of first admission ($q_{x,t}hosp$), for each age x and each calendar year t. Age-specific risks of first admission were calculated for men and women separately. We constructed life tables for each calendar year using standard demographic methodology.[168] Using the age-specific risks to have a first event at age x in year t ($q_{x,t}hosp$), we estimated $e_{x,t}hosp$, which is conditional upon survival to age 60. The definition of $e_{x,t}hosp$ is equivalent to the definition of remaining life expectancy at age x in year t ($e_{x,t}$) in a period life table. It quantifies the remaining average number of years until the event takes place for an individual of exact age x, given hospitalization patterns of year t. In our case, $e_{x,t}hosp$ quantified the expected average number of years until the first hospital admission for a person who is aged x in year t. Adding 60 to the value of $e_{x,t}hosp$ allowed the interpretation to be mean age at first hospital admission lasting for a minimum of 2 days, including cases that ended in death or discharge.

We measured between individual variation in age at first hospital admission using the coefficient of variation (CoefV) and reported values as a percentage. The

CoefV is a standard measure of dispersion and is defined as the ratio of the standard deviation to the mean. Here, the CoefV reflects the variability in age at first hospital admission relative to the mean age at first hospital admission. We calculated 95% Confidence Intervals (95% CIs) for $e_{x,t}hosp$ and CoefV.[169]

4.5 Results

4.5.1 Trends in Mean Age

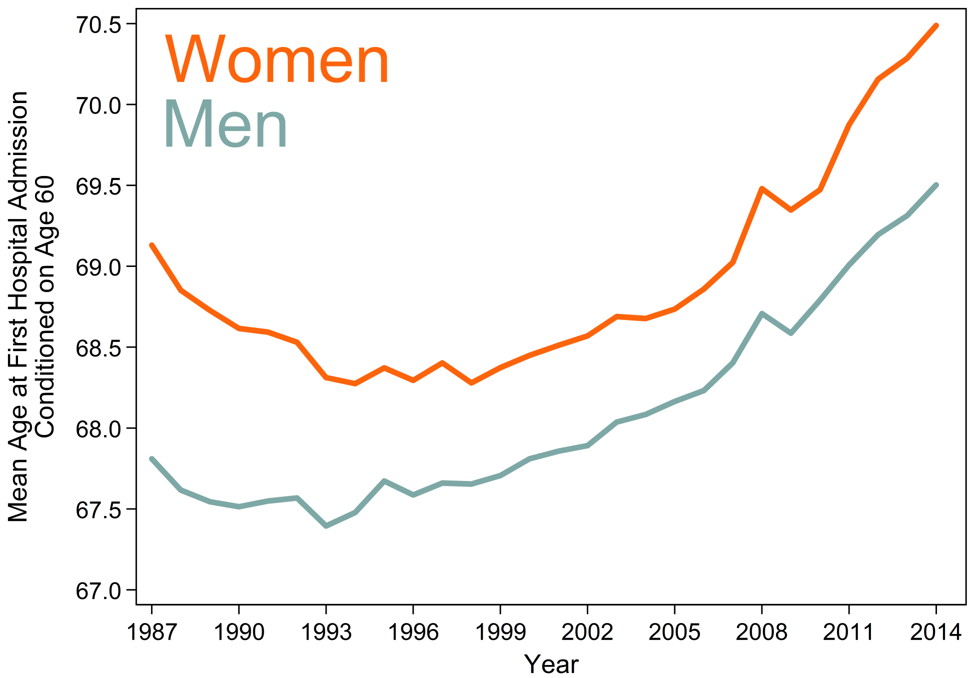


Figure 2: Trends in Mean Age at First Hospital Admission for Men and Women Age 60, 1987 to 2014.

Figure 2 shows trends in mean age at first admission. The trend demonstrates a subtle u-shaped pattern between 1987 and 2014. The trend declined in the 1990s before rebounding in the 2000s. In 1987, the mean age at first admission for men was 67.8 years (95% CI: 67.7 - 67.9). At the midpoint, 2001, mean age had increased onlz slightly to 67.9 years (95% CI: 67.8 - 67.9). By 2014, mean age at first admission had increased to 69.5 years (95% CI: 69.4 - 69.6). For women, the mean age decreased slightly between 1987 and 2001: from 69.1 years (95% CI: 69.1 - 69.2) to 68.5 years (95% CI: 68.4 - 68.6). By 2014, mean age for women had increased to 70.5 years (95% CI: 70.4 - 70.6).

4.5.2 Changes to the Age Distribution

Figure 3 shows the age distribution of first hospital admission in 1987, 2001 and 2014.

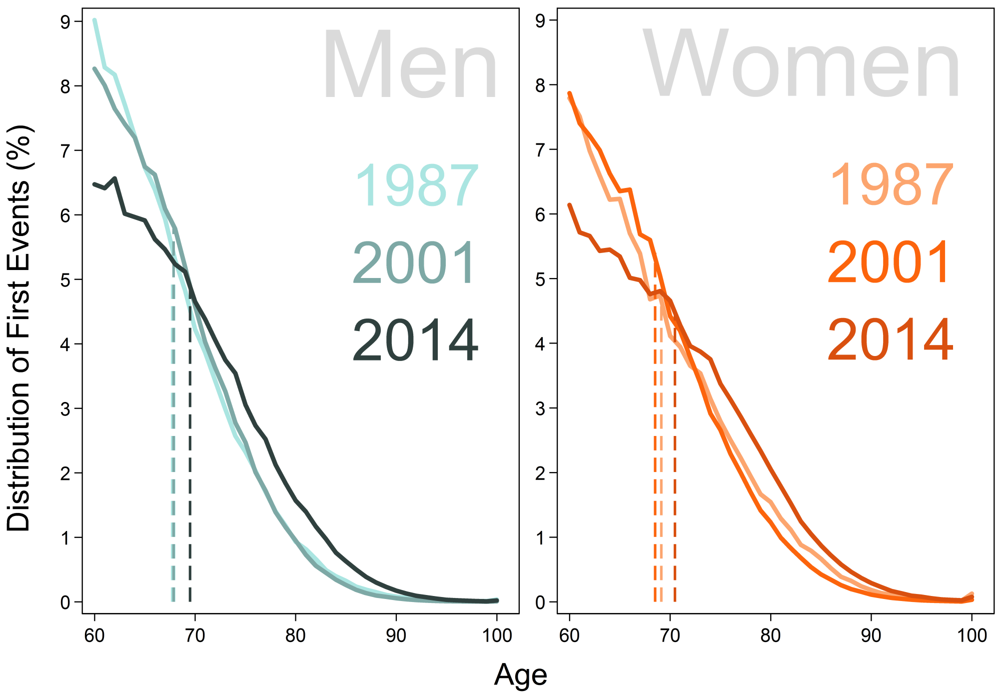


Figure 3: Distribution of Age at First Hospital Admission Across ages 60+ in 1987, 2001 and 2014.

We focus on the change in the distribution of first events from the age groups 60-69 to age 70+, the age groups surrounding the mean age at first admission. In 1987, 69.6% of all men experienced their first admission to hospital between age 60 and 69, while 30.4% of all men had their first admission at ages 70+. By 2001, the proportion among men aged 60 to 69 remained similar at 69.0%, before decreasing to 58.8% in 2014. Among women, the proportion who experienced a first admission at age 60-69 was 61.8% in 1987, while 38.1% experienced a first admission at ages 70+. In contrast to men, the proportion of women aged 60-69 who experienced a first admission in 2001 increased to 65.1%. By 2014, 53.3% of women aged 60 to 69 experienced a first admission and 46.7% experienced a first admission at ages 70+.

4.5.3 Trends in the Coefficient of Variation

To quantify changes in the age distribution, we estimated the CoefV. As shown in Figure 4, we found a u-shaped pattern. Among men, the CoefV in average age at first admission at age 60 decreased from 9.1% (95% CI: 9.0 - 9.1) in 1987 to 8.7% (95% CI: 8.6 - 8.7) in 2001. For women, the corresponding change was from 10.3% (95% CI: 10.2 - 10.4) to 9.4% (95% CI: 9.4 - 9.5). In the early 2000s, the trends in variation changed to increasing. In 2014, the CoefV was 9.9% (95% CI: 9.8 - 10.0) for men and 10.6% (95% CI: 10.5 - 10.6) for women.

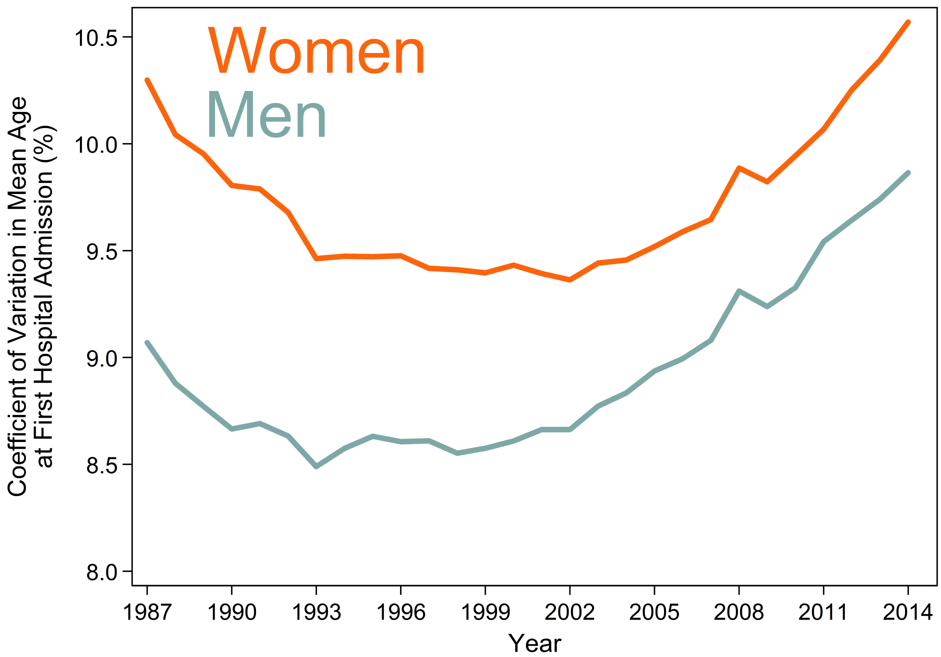


Figure 4: Trends in the CoefV in Mean Age at First Hospital Admission (%) for Men and Women Age 60, 1987 to 2014.

4.5.4 Sensitivity Analyses

Our main results reflect hospital stays lasting a minimum of 2 days, including all fatal events. The direction of the trends were consistent in three sensitivity tests. First, we varied the minimum length of stay from 2 days to 1 day, 3 days, 5 days, and 7 days. Second, we excluded fatal cases that occurred between the 1st day of admission and the minimum length of stay. Third, we changed the washout period length from 7 years to 5 years, and 10 years. Results for sensitivity checks and further details are given in Appendix 2 and Appendix 3.

4.6 Discussion

4.6.1 Summary of Findings

Average age at first admission at age 60 was higher in 2014 than in 1987. The number of first admissions at ages 60-69 reduced during this period. These findings indicate that people became healthier across these ages. However, the shifting of events towards older ages meant that the age distribution of first hospital admission widened over time, causing the coefficient of variation to increase. In pragmatic terms, higher variation in age at first hospital admission after age 60 translates into greater uncertainty for individuals in the timing of the onset of morbidity. At the macro-level, it indicates that population health is becoming increasingly heterogeneous.

4.6.2 Interpretations and Implications

Many people are aging with better health today than in the past. Healthy aging is due to multiple life course factors, including improved health during childhood, reduced exposure to hazardous working conditions, and changes in health behaviors such as smoking or diet.[281,282] Another contributing factor is that technological advancement has enabled more individuals to survive longer in better health. Although some chronic diseases may show increased prevalence over time (e.g. diabetes) they may now lead to a hospital admission later in life. Perhaps the strongest example of this, is the treatment of hypertension and cardiovascular diseases.[19] Treatment has changed dramatically over time and mortality has declined, leading to more people surviving without serious cardiovascular events and only being admitted to hospital later in life. This observation is consistent with our results showing the redistribution of first events from younger to older ages.

At the same time, our results show increasing diversity in healthy aging. The same technological advancements that have postponed major health events, have also enabled individuals to live for longer while managing chronic conditions.[276,283,284] Greater variation between individuals in age at first hospital admission could therefore be due to more heterogeneous health profiles arising from an increased prevalence of chronic conditions. Additionally, some components of increasing health variation could have their roots in the changing epidemiological environment experienced by older adults as infants and children. As infectious diseases became increasingly controlled, weaker individuals that would have died as children in previous decades survived to older ages, making for a more heterogeneous population at older ages.[284] Our results for morbidity echo findings for mortality which have shown that increased survivorship has been accompanied by increasing population-level heterogeneity in age at death at these older ages.[181,284]

4.6.3 Methodological Considerations

Linked hospital admission data have been used to investigate health at older ages and across multiple countries.[86,87,95] Studies clearly demonstrated that these data can be used to derive powerful indicators of health. A particular strength of our study is that we were able to identify individual patient trajectories to derive incidence-based estimates.[74,180] We used the most accurate population denominators for those at risk of admission. Other countries may only be able to identify prevalence-based measures, based on the number of admissions and using an inaccurate total population denominator. Our data allowed us to identify all events during the study period and determine the exact age at event for all individuals. Studies using survey data are often restricted to picking up events retrospectively and may miss out events. While standardized, self-reported measures are powerful, there are limitations in terms of recall bias, selectivity, and subjectivity.

We attempted to exclude re-admissions to hospital by applying a 7-year washout period at each calendar year. While a 7-year washout period will not fully remove all cases of readmission, it was a length of time that reflected established choices in the existing clinical research literature.[123,280]

Accounting for the impact of population-level changes in admission strategies is challenging. To address this issue, we obtained an overview of admissions using 19 causes of admission for the entire study period by utilizing harmonized ICD-8 and ICD-10 codes (Appendix 4). While the relative contribution from some causes decreased over the study period, other causes increased or remained stable. Studying a change in admission strategy requires consistent, detailed information on inpatient, outpatient, and primary healthcare attendances by cause of admission and length of treatment. In Denmark, outpatient data and primary healthcare data do not contain suitable information for carrying out such analyses.

A major aim of current healthcare strategies is to reduce length of stay. This is driven by the assumption that shorter stays are more cost effective. We investigated the potential impact of changing the minimum length of stay on our results by repeating all stages of the analyses for hospital stays lasting for at least 1 day, 3 days, 5 days, and 7 days (Appendix 2). We found a step-wise increase in the mean and the variation in the age at first admission with every increase in minimum length of stay, but no change in the trend direction. Patients in Denmark in 2015 stayed in hospital for an average of 5.5 days, which is one of the shortest average lengths of stay in hospital within Europe.[285] Our main results define an admission as lasting for a minimum of 2 days which is likely to capture conditions that would always require inpatient care over the entire study period and does not bias the trends that are documented.

4.6.4 Concluding Theoretical Reflections

Studies of morbidity compression have consistently calculated the average proportion of time spent in an unhealthy state, relative to average length of life.[116–120,178] This only reflects part of Fries' theory of morbidity compression. To understand whether the continuation of disease postponement is possible 'analysis of variation, not of mean values, becomes crucial'.[179] Although, it has been forty years since Fries linked the measurement of the standard deviation between individuals to the concept of morbidity compression, empirical measurement of variation has been overlooked. In this study, we measure variation in the age of morbidity onset between all individuals, using first hospital admission at ages 60 and older. Measuring the age distribution of morbidity onset across all individuals underlines that the concept of morbidity compression is more nuanced than has previously been conceived. Incorporating a variation perspective into morbidity studies is important for individual life planning and population-level welfare. Pensions, social care and health services will have to adapt to the heterogeneous needs of aging populations, something that average morbidity measures cannot identify.

4.7 Supplementary Material

4.7.1 Appendix 1

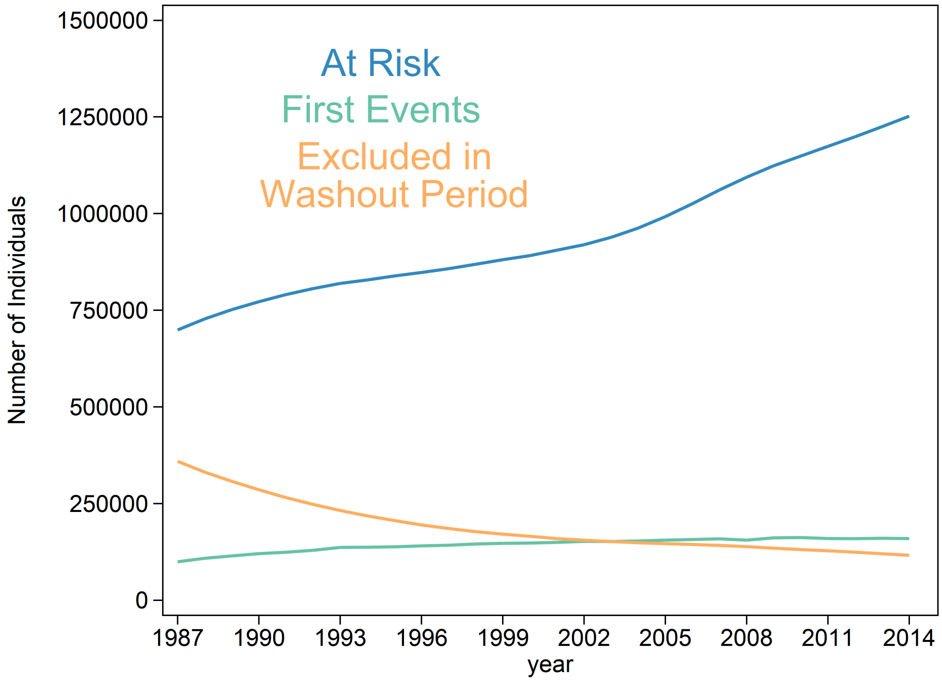


Figure Appendix 1: Absolute number of individuals at risk, first events, and individuals excluded during the washout period for each year in the study period.

4.7.2 Appendix 2

The impact of changing the length of stay in hospital was tested by repeating all stages of the analysis for hospital stays lasting 1 day, 3 days, 5 days and 7 days. We found a stepwise increase in the mean age at first admission and variation with every increase in length of stay. The trends over time followed the same overall patterns, within the context of different absolute levels. Stays lasting 1 day were an exception as mean age at first admission and the variation were slightly decreasing over the entire study period. In 2007, changes in the administrative structuring of healthcare in Denmark resulted in temporary changes in the trends for 1 day. Results for stays lasting for 2 days or longer were not affected.

Removing deaths that occurred during an admission to hospital increased the mean age at first admission and increased variation slightly. This is evidence that removing deaths introduces a selection bias in our study population as individuals who died during an admission to hospital were admitted at slightly younger ages. There was no difference in the trends including and excluding fatal events for lengths of stay lasting only 1 day. Restricting the length of stay to 1 day means that cases could not go on to have a longer length of stay. This is equally true if an admission ended in fatality that occurred on the first day of admission.

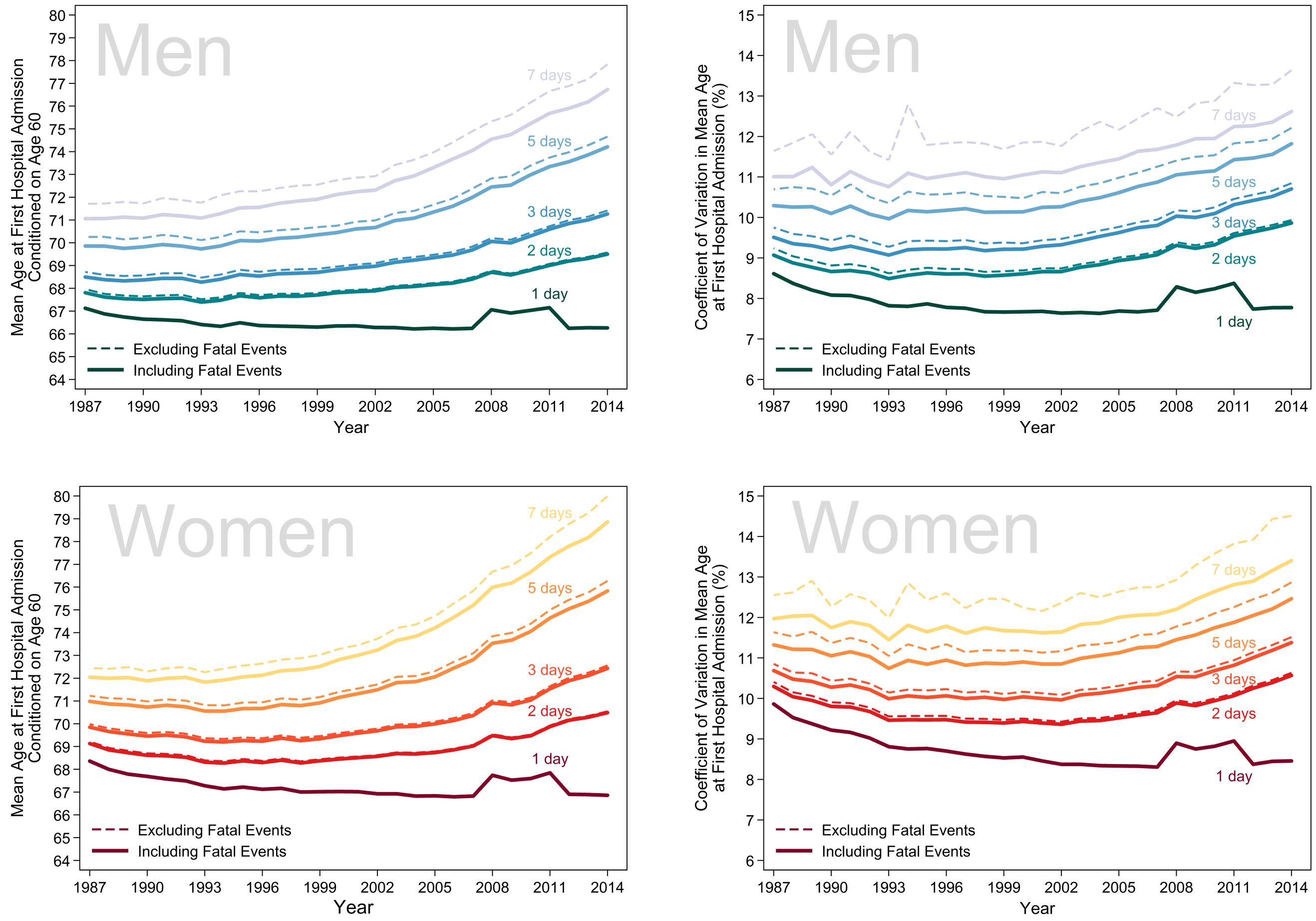


Figure Appendix 2: Trends in Mean Age and CoefV (in %) of First Hospital Admission for Men and Women, 1987 to 2014, for Varying Lengths of Hospital Admission and Comparing the Impact of Fatal Events.

4.7.3 Appendix 3

Our main results used a 7-year washout period. We repeated all of our analyses for hospital admission lasting a minimum of 2 days using a 5-year washout period and a 10-year washout period for comparison. The mean age trends and CoefV trends comparing the different washout period lengths are shown in Appendix Figure 3. The first time point where the data are comparable for all three washout period lengths is 1990. The difference in the trends prior to 1990 are due to the fact that different background data is being used. The trends converge for all three wash-out period lengths over the study period. Therefore the impact of changing the length of wash-out period was minimal.

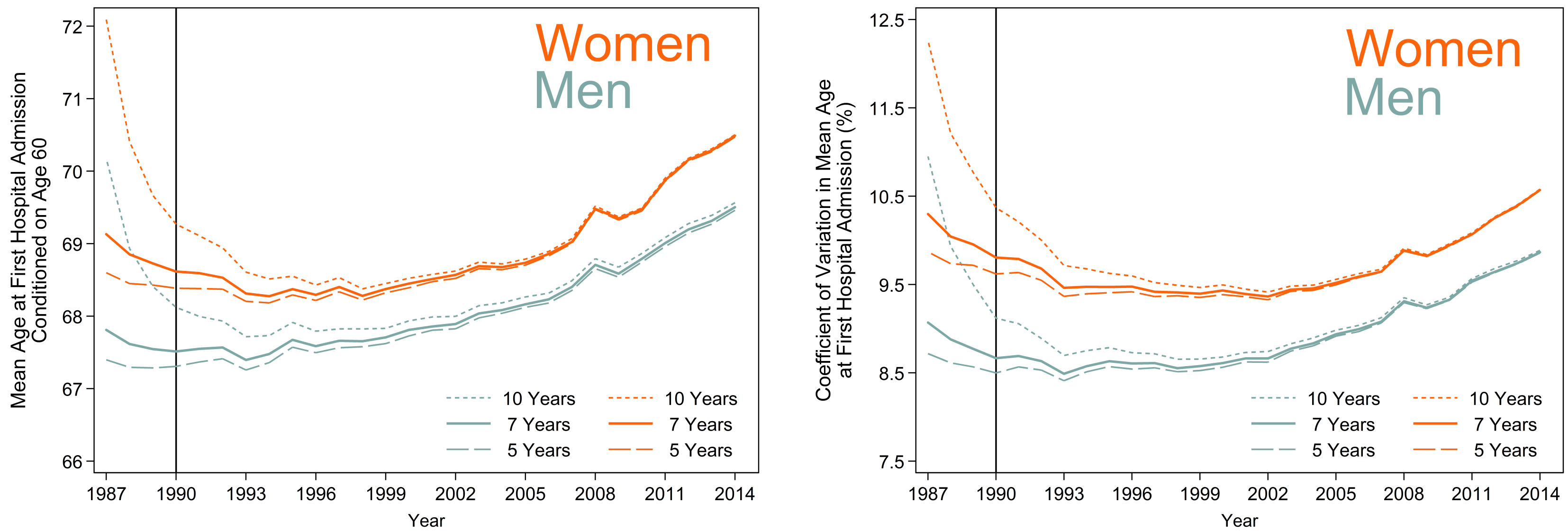


Figure Appendix 3: Trends in Mean Age at First Hospital Admission and CoefV (in %)for Men and Women Age 60, 1987 to 2014, Comparing Different Lengths of Washout Period.

4.7.4 Appendix 4

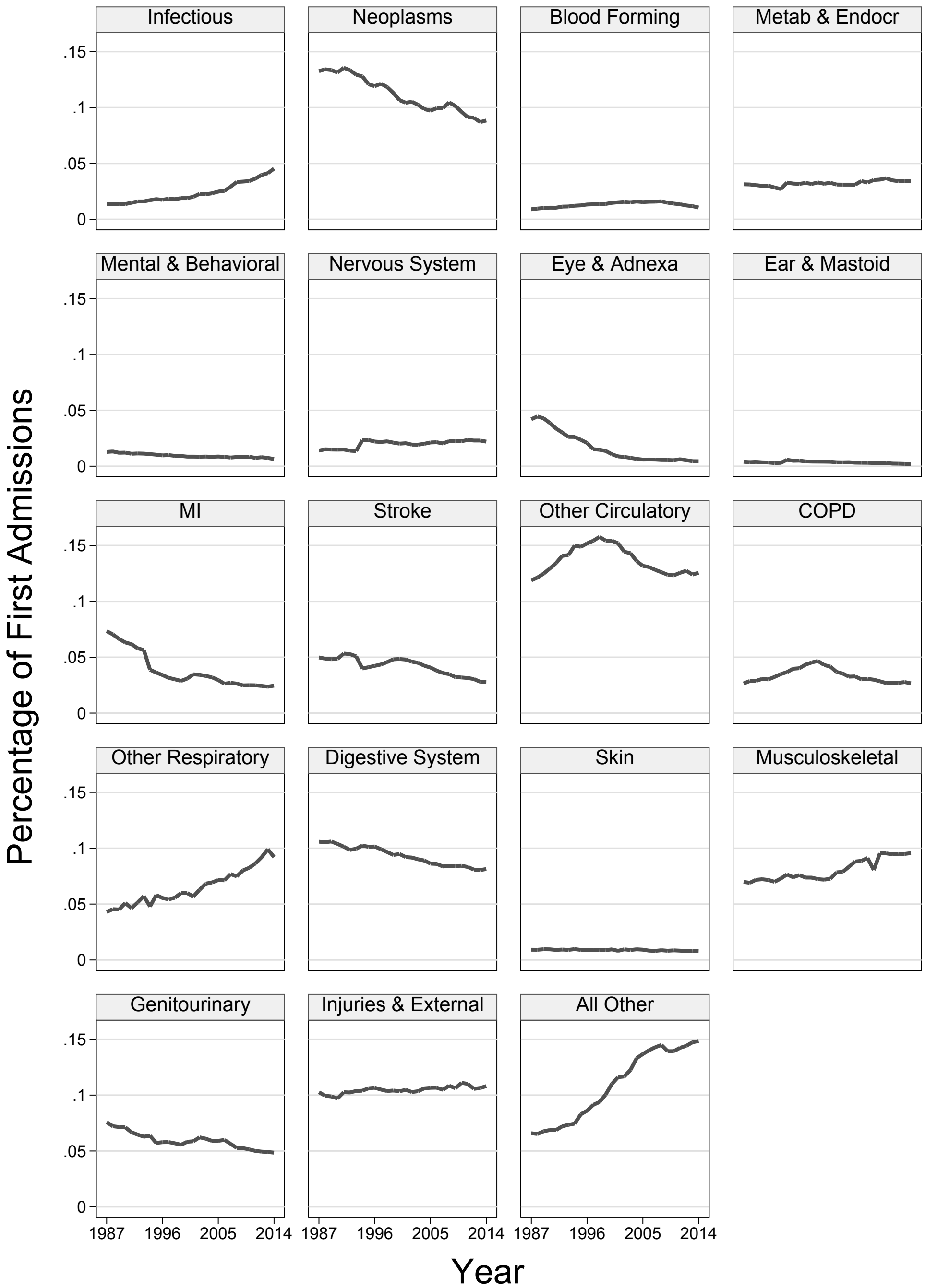


Figure Appendix 4: Percentage of first hospital admission at age 60+ by 19 cause specific groups for yearly study population, 1987 to 2014. Cause specific categories constructed from harmonized ICD-8 and ICD-10 codes (Danish modification).

5 Changes in the Demographic Profile of Hospital Patients

Paper: ANDREAS HÖHN, ANNA OKSUZYAN, RUNE LINDAHL-JACOBSEN, ROLAND RAU, AND KAARE CHRISTENSEN: Preparing for the future: The changing demographic composition of hospital patients in Denmark between 2014 and 2050. ***Submitted to a peer-reviewed journal***

5.1 Abstract

Background: Preparing the healthcare workforce for population aging is a public health challenge, especially as medical students tend to avoid the field of geriatrics. We describe the current demographic profile of hospital care use in Denmark, project changes up to 2050, and interpret this in the light of the attitudes of students in the healthcare workforce.

Methods: The Danish population in 2014 (N=5.63 million) was followed up for inpatient and emergency admissions recorded in Danish hospitals in 2014 using population-based registers. We combined age and sex-specific patterns of hospital care use in 2014 with official population estimates to forecast the profile of hospital days up to 2050 with respect to age and sex.

Results: The total number of hospital days per year is projected to increase by 47% between 2014 and 2050, from 3.75 to 5.51 million days. While small changes are projected among the population aged 0-69, the largest change is projected to occur among the population aged 70+. The 2014 levels were 0.77 and 0.84 million days for men and women aged 70+, respectively. By 2050, these levels are projected to have reached 1.76 and 1.63 million days. Whereas the population aged 70+ accounted for 42.9% of all days in 2014, their contribution is projected to increase to 61.4% by 2050.

Conclusion: Specific attention should be given to the education of the future healthcare workforce, as negative stereotypes and prejudice towards older individuals are important factors discouraging medical students and student nurses from joining the field of geriatrics.

5.2 Introduction

Decreasing mortality trends in high and middle income countries will rapidly increase the population share of older individuals within the next few decades.[286] Currently, in these countries, approximately one person in six is aged 65 or older. By 2050, it is projected that the number of people aged 65+ will have almost doubled within these countries, and that nearly one in three will be 65 or older.[26] As the prevalence of non-communicable diseases increases with age - including cancers,[91] circulatory diseases,[92] and dementia[93] - population aging presents new challenges for healthcare systems, including hospital settings.[128,129] Preparing the medical workforce for the changing demographic profile of patients has been identified as one of these challenges.[287] Efficient delivery of high-quality care requires an adequate supply of well-trained health workers to meet the needs of patients. Already, a number of countries have reported substantial shortfalls in skilled medical workers.[130]

A growing body of literature has reported that medical students and student nurses tend to have negative attitudes towards older individuals.[132,135,136] Working with older patients has often been described as a burden and as less satisfying than working with younger patients. Negative attitudes towards the elderly have been shown to be important predictors for the quality of care and treatment,[183] and are one main reason why young medical professionals tend to avoid the field of geriatrics.[134] Recent studies suggest that medical students are not aware of who their future patients will be.[135] This is problematic, as aging and retirement of the baby-boom generation will accelerate demographic changes, and are likely to leave holes in medical workforces.[288]

Forecasts of future levels of health expenditure are widely available. However, expenditure forecasts tend to be very sensitive to economic shocks and unforeseen changes in costs or new technologies.[289,290] Less research effort has forecast changes in the levels and demographic profile of healthcare use, including hospital care. The profile of future hospital patients depends predominantly on changes in the demographic composition of the population, and is therefore easier to forecast than potential expenditures because a large proportion of future patients have already been born.[182] Previous forecasts of hospital care use have often focused on single causes of admission,[291] or specific services only, such as long-term or palliative care.[292] Only a small body of literature has studied the effect of population aging on hospital care use patterns at the national level. While a small number of studies exist for Australia and the US,[288,293] very little is known about changes in hospital care demand on country-level, and within the European healthcare context.

Here, we examine expected changes in the number of hospital days by age and sex in Denmark up to the year 2050 and interpret this in the light of the attitudes of students in the healthcare workforce.

5.3 Methods and Materials

5.3.1 Linking Register Data

This study utilizes routinely-collected register data, covering the entire Danish population. We used the unique personal identication number (CPR-Number), which is assigned to all individuals residing in Denmark, to link records from the National Patient Register (NPR) with data of the Central Population Registry (CPR). The CPR, established in 1968, contains demographic information, such as information on each resident's vital status, sex, and date of birth.[9] The NPR, a population-based register, covers administrative and medical information on all treatments provided in Danish hospitals since 1977.[157] The NPR data have high levels of completeness and reliability, making them a valuable data source for research.[157]

5.3.2 Estimating Hospital Care Use Patterns from Linked Registers

From the CPR, we identified 5,627,235 men and women alive and residing in Denmark on 1st January 2014, who were at risk of being admitted to hospital in

2014. These individuals were followed up for all inpatient and emergency admissions recorded in Danish hospitals between 1st January 2014 and 31st December 2014. We summed up the number of hospital days as well as the population at risk by age, and separately for men and women. We then divided the number of hospital days by the corresponding population at risk to obtain the average, annual number of hospital days per person by sex and age in 2014.

In contrast to inpatient admissions, information on outpatient treatments include the start date and the end date of the treatment period, but not the number of days an outpatient has received treatment in hospital. This makes it difficult to assign a number of hospital days per admission. In addition, obstetrics-related admissions have the potential to introduce a strong sex bias. We therefore excluded both, obstetric-related admissions and outpatient treatments, from our main analysis but included them in sensitivity analyses.

5.3.3 Statistics Denmark's Population Projection

We then identified the most recent population projection provided by Statistics Denmark, the Danish national statistical office,[294] and utilized its estimates of the Danish population covering the period 2018 to 2050. This is a so-called deterministic projection which makes forecasts on the basis of observed trends in fertility, mortality, and migration – the only parameters that can affect the size and structure of a population – up to the middle of the 21st century. The future trajectories of these parameters are assumed to be a reflection of current trends, and are based on levels which have been observed in Denmark within the last four years.[294] A detailed overview of the projection assumptions is given in Supplementary Table S1.

5.3.4 Forecasting the Hospital Care Use

Lastly, we projected future numbers of hospital days by age and sex using a baseline forecast design.[170] We kept the age- and sex-specific hospital care use patterns of 2014 constant throughout the entire study period and combined them with the population projection provided by Statistics Denmark. We multiplied the average, annual number of hospital days per person observed in 2014 by the corresponding population in each year between 2018 and 2050, for single years of age and separately for men and women. As a result, we obtained the total annual number of hospital days by sex and single years of age, which we aggregated into four age groups, separately for men and women: 0-14, 15-49, 50-69 and 70+. The merging of registers was carried out with Stata (Version 14). Forecasts and Visualizations were produced with R (Version 3.5.1).

5.4 Results

5.4.1 Hospital Care Use Patterns in 2014

Figure 1 shows the average number of hospital days per person in 2014 by age. The age trajectory of hospital care use is consistently J-shaped among men and women. Within the first year of life, the average number of hospital days per year is 0.7 days for men and 0.6 days for women. From age 1 onwards, the levels decline and reach a minimum of 0.1 days at age 9 among men and at age 8 among women. Thereafter, the levels plateau until age 30, at 0.1 to 0.2 days per year for men and women respectively. After age 30, the average number of hospital days per year starts to increase steadily with age, to 4.2 days and 3.3 days among men and women aged 90+, respectively. On average, women spend more days in hospital than men between ages 13 and 43. At age 44, the levels cross over and the annual number of days in hospital become lower among women than among men.

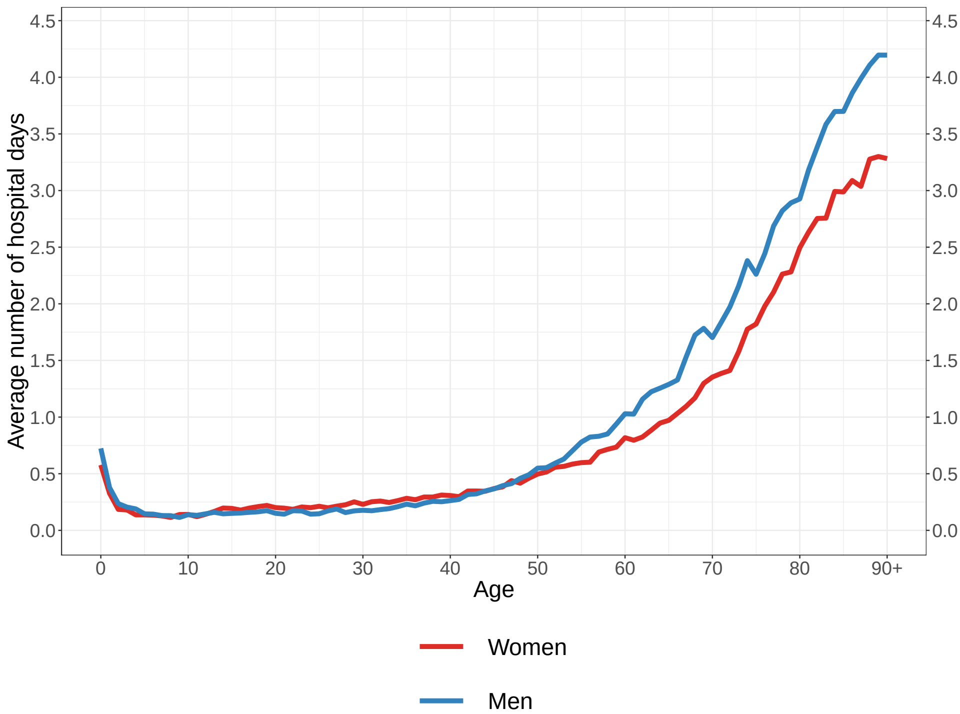


Figure 1: Average number of days spent in hospital per person in 2014

5.4.2 Changes in the Population Structure

In 2014, the size of the Danish population was about 5.62 million. At that time, 0.97 million individuals (17.3%) were aged 0-14. The age group 15-49 consisted of 2.55 million individuals (45.4%), while 1.43 million individuals (25.4%) were aged 50-69. In 2014, 0.67 million Danes (11.9%) were aged 70+, of whom 0.29 million were men and 0.38 million were women.

Within the next decades, it is projected that the structure of the Danish population will change as the size of the population at older ages steadily increases. The projections up to 2050 are given in Figure 2. In 2050, it is forecast that the size of the Danish population will increase to 6.43 million. For the population younger than 70, only small changes in size are anticipated. By 2050, 1.05 million individuals (16.3%) will be aged 0-14, 2.70 million individuals (42.0%) will be aged 15-49, and 1.41 million individuals (21.9%) will be of age 50-69. In contrast, major changes are expected in the older population. By 2050, it is projected that 1.27 million Danes

(19.8%) will be aged 70 or older, of whom 0.59 million will be men and 0.68 million will be women. By this time, the size of the age group 70 is forecast to have almost doubled in absolute terms.

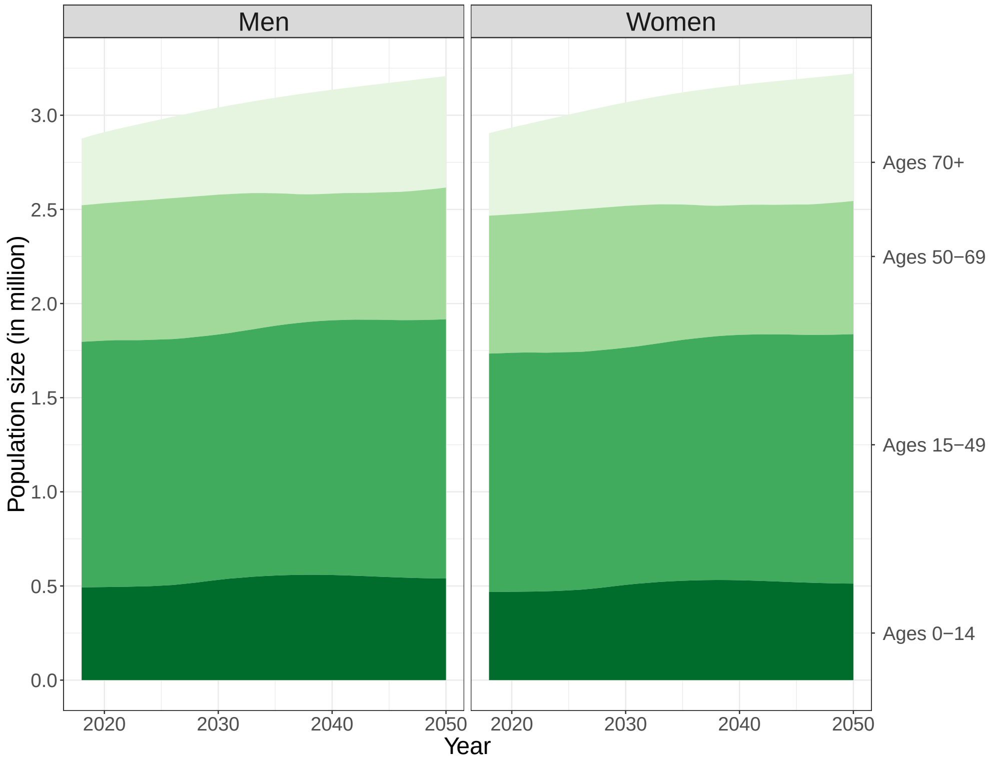


Figure 2: Projected changes in the structure of the Danish population by sex between 2018 and 2050, based on publicly available data provided by Statistics Denmark

5.4.3 Changes in Hospital Days

In 2014, we observed 3.75 million hospital days in the Danish population. The population aged 0-14 accounted for 0.19 million days (5.0%), the population aged 15-49 0.66 million days (17.7%), and the population aged 50-69 accounted for 1.29 million days (34.5%). In 2014, men and women aged 70+ contributed 0.77 and 0.85 million hospital days respectively, together accounting for 42.9% of all hospital days in that year.

We combined the age- and sex-specific hospital care use patterns of 2014 with

Statistics Denmark's population projections to forecast the number of hospital days up to 2050. Results of the forecast are shown in Figure 3. The total number of hospital days per year is set to increase by 47% within the observed period, reaching an overall level of 5.51 million days in 2050. The number of hospital days among the population younger than 70 is forecast to remain relatively stable during the projection period (Levels in 2050; 0-14: 0.21 million days (3.8%) / 15-49: 0.68 million days (12.7%) / 50-69: 1.24 million days (22.5%)). In contrast, the number of days accounted for by the population aged 70+ is projected to increase steadily and to more than double. By 2050, the population aged 70+ is forecast to account for 3.39 million days, or 61.4% of all hospital days. Among the population aged 70+, men are expected to contribute 1.76 million days while women are expected to contribute 1.63 million days. This will correspond to 31.9% and 29.5%, respectively, of all hospital days in 2050.

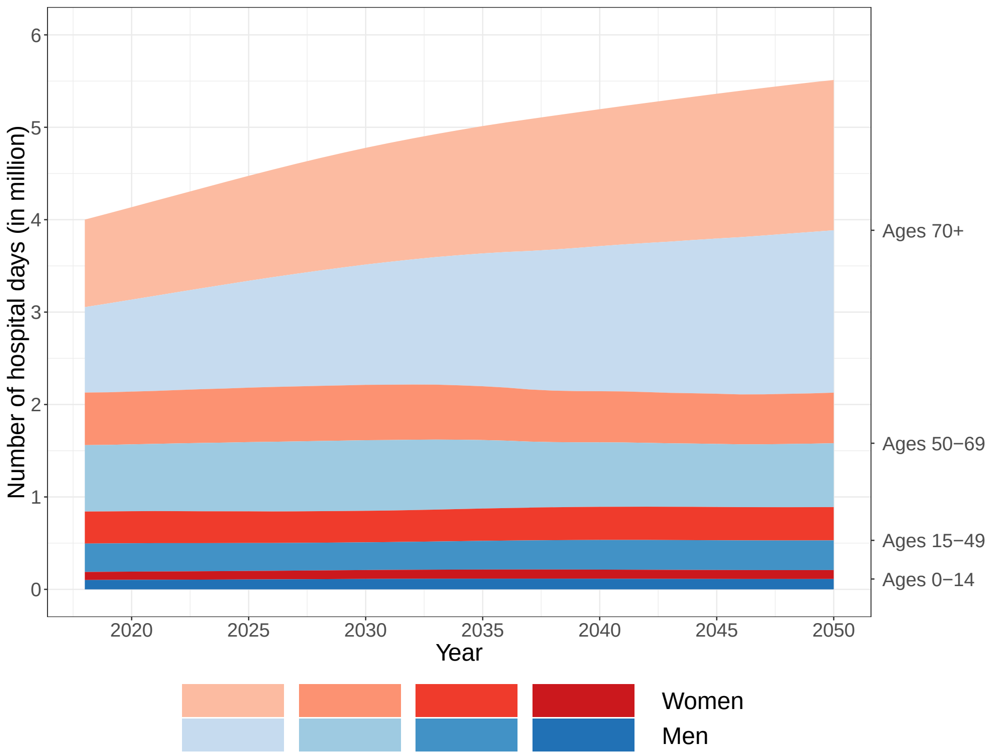


Figure 3: Projected annual number of hospital days until 2050

5.4.4 Sensitivity Analyses

Our main findings do not include outpatient and obstetrics-related admissions. We examined the impact of these admissions on the age- and sex-specific patterns of health care use in 2014 and the projection of annual hospital days up to the year 2050. We controlled separately for the impact of: (i) admissions due to childbearing and birth control, (ii) outpatient admissions, and (iii) a combination of both. Results of this robustness check (further discussed in Supplementary Text S1, and presented in Supplementary Figure S1, Supplementary Figure S2, and Supplementary Table S2 at the end of this paper) show similar trends and do not alter our conclusions. Irrespective of how we estimated the age- and sex-specific hospital care use in the baseline year 2014, the population aged 70+ remained the most important driver for the increasing amount of hospital days. In addition, men aged 70+ were always the fastest growing patient group treated in Danish hospitals in the period up to 2050.

5.5 Discussion

In this study, we show the demographic profile of the demand for hospital care today and in the future. By keeping current age- and sex-specific patterns of hospital care use constant, we studied the changes attributable to population aging. Already today, the population aged 70+ accounts for half of all hospital days. We forecast that the absolute contribution of individuals aged 70+ to total hospital days will more than double and will account for nearly two thirds of all hospital days by 2050. By then, men aged 70+ are projected to be the largest patient group treated in Danish hospitals.

5.5.1 Methodological Considerations

We estimated the age- and sex-specific hospital care use patterns for the baseline year 2014 using routinely collected, individual-level register data. These data cover the total Danish population. Using register data eliminates recall biases, non-response and other problems regarding the under- or overstatement of healthcare use – limitations which often affect studies based on self-reports.[66]

Forecasting is by its nature uncertain. This applies to two components of our projection: first, the structure of the Danish population and, second, patterns of hospital care use in the future. We used the most recent population projection of the Danish national statistical office. This projection is a deterministic projection and based on a continuation of current trends in fertility, mortality, and migration until the mid-21st century.[173] Of all these parameters, future rates of migration are the most uncertain.[295] Statistics Denmark assumes that in-migration will declines rapidly in the next few years, compared to the levels of 2015-2017, and will remain stable thereafter. We acknowledge that other projections do exist for Denmark, such as probabilistic projections by the United Nations.[26] However, we decided to use the projections provided by Statistics Denmark as they are the most recent and detailed for Denmark.

Using a baseline forecast design, we froze the age- and sex-specific levels of hospital care use observed in 2014. Freezing rates assumes that age- and sex-specific patterns of hospital care use will remain constant in the future. Therefore, changes in the annual amounts of hospital days during the projection period are driven exclusively by changes in the demographic profile of the population. Keeping baseline levels constant during the projection period is a pragmatic approach in forecasting and has been applied to detailed projections of hospital care use[296] or fertility.[171] Especially when over-arching trends are difficult to predict, freezing rates has been shown to outperform statistically sophisticated techniques.[171]

5.5.2 Health and Hospital Care Use in Aging Populations

In line with previous findings, our study shows that hospital care use at late- and post-working ages is especially important for the total national hospital care demand. Previous research has shown that two opposite trends may have an impact on future hospital care use levels at these ages. On the one hand, the compression and postponement of morbidity may continue to reduce levels of hospital care use among the elderly.[281] Studies have shown that the incidences of leading causes of death, including stroke and MI, are consistently declining in low-mortality countries at all ages, including Denmark.[297] It has also been shown that cognitive functioning of the old and oldest-old has improved significantly within recent decades.[298] Individuals of post-working age have been found to be increasingly happy and satisfied with their life considering the toll that aging generally takes on well-being, health and physical functioning.[299]

On the other hand, it may be that the time spent with major chronic diseases does not shrink as life expectancy increases, and that frailty among the elderly even increases.[300] In addition, new medical technologies may contribute to increased treatment of this age group in hospitals, leading to higher levels of hospital care use in the future among the old and oldest old.[95] At the same time, these new technologies may enable a shift of treatments from inpatient to outpatient or primary healthcare settings. As both of these changes might have an impact at the same time, the general direction of population-level trends in hospital care use is difficult to predict. We therefore consider our findings to be neither overly optimistic – nor pessimistic – but to reflect a possible scenario.

Irrespective of long-term trends in age patterns and admission strategies, health behaviors impact population health and, as a consequence, future hospital care use. Studies show that smoking, hazardous drinking, obesity, lack of physical activity, and an unhealthy diet are associated with a higher risk of hospitalization at the individual level.[80] In Denmark, the general trend is towards healthier habits: smoking rates are decreasing, diet has improved, and physical inactivity has decreased.[301] Future levels of hospital care use at the population level will be associated with the age pattern of diseases, trends in health behaviors within populations, as well as with the organizational structure and performance of healthcare systems.

5.5.3 Implications of a Changing Patient Profile

We forecast that the number of hospital days for individuals aged 70+ will almost double in the period up to 2050, as an increasing number of individuals reache older ages. The reason for this is rather simple: older individuals, on average, spend more days in hospital than younger individuals. Age is a major risk factor for non-communicable diseases and therefore directly linked with hospital care use levels.

Studies have shown that the prevalence of most leading causes of admission is likely to increase as the population ages, including circulatory diseases and cancers.[20] While more individuals survive to older ages, and better treatment of diseases reduces case fatality, the number of individuals at older ages with chronic conditions, complex diseases and multi-morbidity is increasing.[20] In the light of these findings, inadequacies in geriatric training for the medical workforce have to be addressed in order to meet the complex needs of older patients; this will involve changes in curricula, the role of senior staff, and the organizational structure of hospitals.[132] Addressing these deficiencies may encourage medical students and student nurses to join the field of geriatrics, and contribute to better treatment of the elderly.[136] The education of healthcare workers is a long-term process and requires responsible and careful planning. Preparing healthcare services for changing needs requires an understanding of who the future patients will be. To meet future hospital care needs, reducing prejudice towards the elderly among medical students and student nurses has to be given special emphasis – as soon as possible.[136] Only sufficient numbers, and a well-balanced mix of specialists and sub-specialists, can ensure that the healthcare challenges of aging populations will be met in the coming decades.[182]

5.5.4 Conclusion

Already today, individuals of post-working age are the largest patient group in hospital settings. As populations age, the share of these age groups is projected to steadily increase. To ensure that hospitals meet the needs of future patients, a variety of responses are necessary. Reducing negative stereotypes and creating incentives to work with the elderly has to be one first step in order to ensure that future doctors and nurses are motivated and qualified to join the field of geriatrics. Taking into account the time frame to train medical staff, these issues should be addressed sooner rather than later.

5.6 Supplementary Material

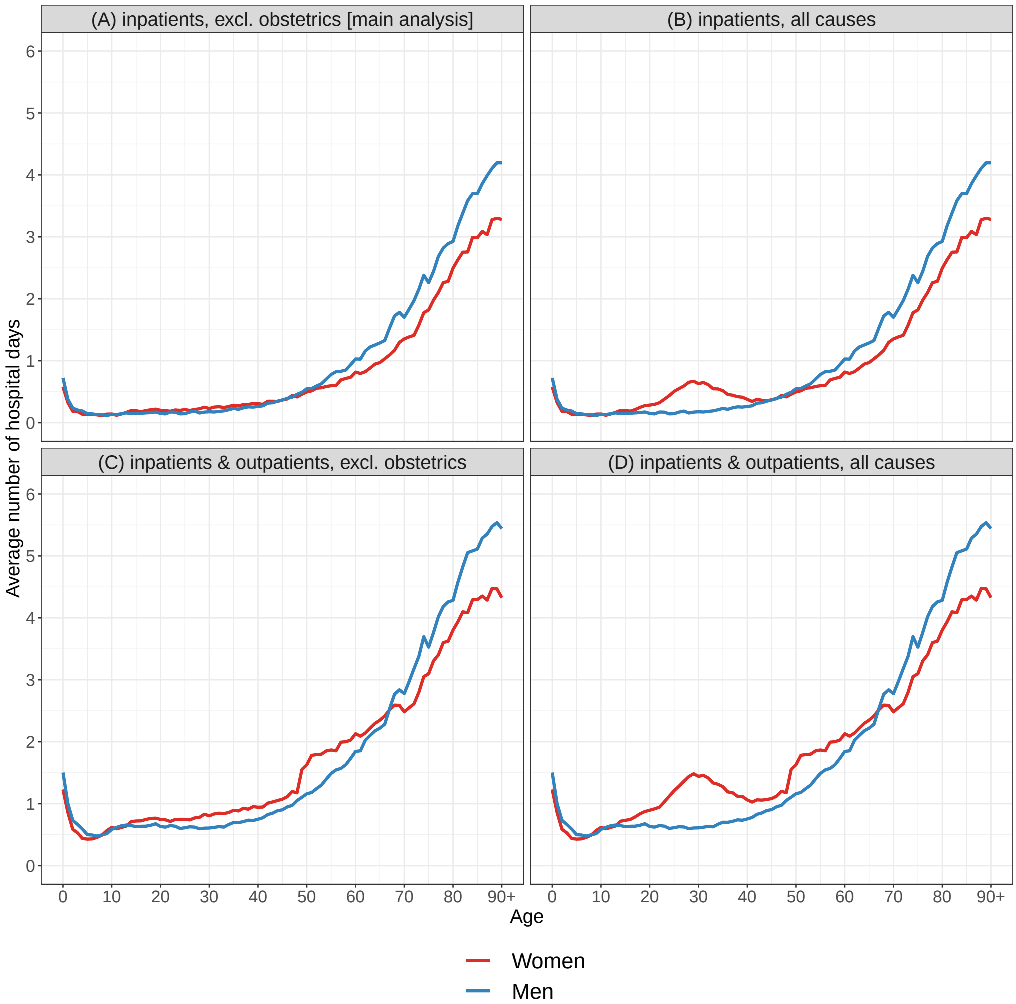
Supplementary Table S1: Overview on projection assumptions.

Process	Parameters	(Sub-) Population	Value
Mortality	e(0) in 2059	Men	87.1 years
	(Lee-Carter Method)	Women	89.5 years
Fertility	Long-Term TFR	Danish Origin - Danish Citizenship	1.91
		Danish Origin - foreign Citizenship	1.91
		Immigrants non-Western countries - Danish citizenship:	1.68
		Immigrants non-Western countries - foreign citizenship:	1.97
		Immigrants Western countries - Danish citizenship:	1.61
		Immigrants Western countries - foreign citizenship:	1.77
		Descendants from non-Western countries - Danish citizenship:	1.91
		Descendants from non-Western countries - foreign citizenship:	1.91
		Descendants from Western countries - Danish citizenship:	1.75
		Descendants from Western countries - foreign citizenship:	1.75
	Origin at birth	Danish origin - Danish citizenship	100.00
	(frequencies of change)	Danish origin - foreign citizenship	100.00
		Immigrants from non-Western countries - Danish citizenship	24.50
		Immigrants from non-Western countries - foreign citizenship	21.80
		Immigrants from Western countries - Danish citizenship	73.10
		Immigrants from Western countries - foreign citizenship	36.40
		Descendants from non-Western countries - Danish citizenship	100.00
		Descendants from non-Western countries - foreign citizenship	41.40
		Descendants from Western countries - Danish citizenship	100.00
		Descendants from Western countries - foreign citizenship	66.30
Out-Migration	Number of out-migrants	entire Danish population and all groups of origin	N/A (not specified as 2015–2017)
In-Migration	Number of in-migrants	Immigrants without Danish citizenship	17,000
		Western immigrants without Danish citizenship	28,100
		Reimmigration: Danish origin and all with Danish citizenship	N/A (not specified, as 2015–2017)

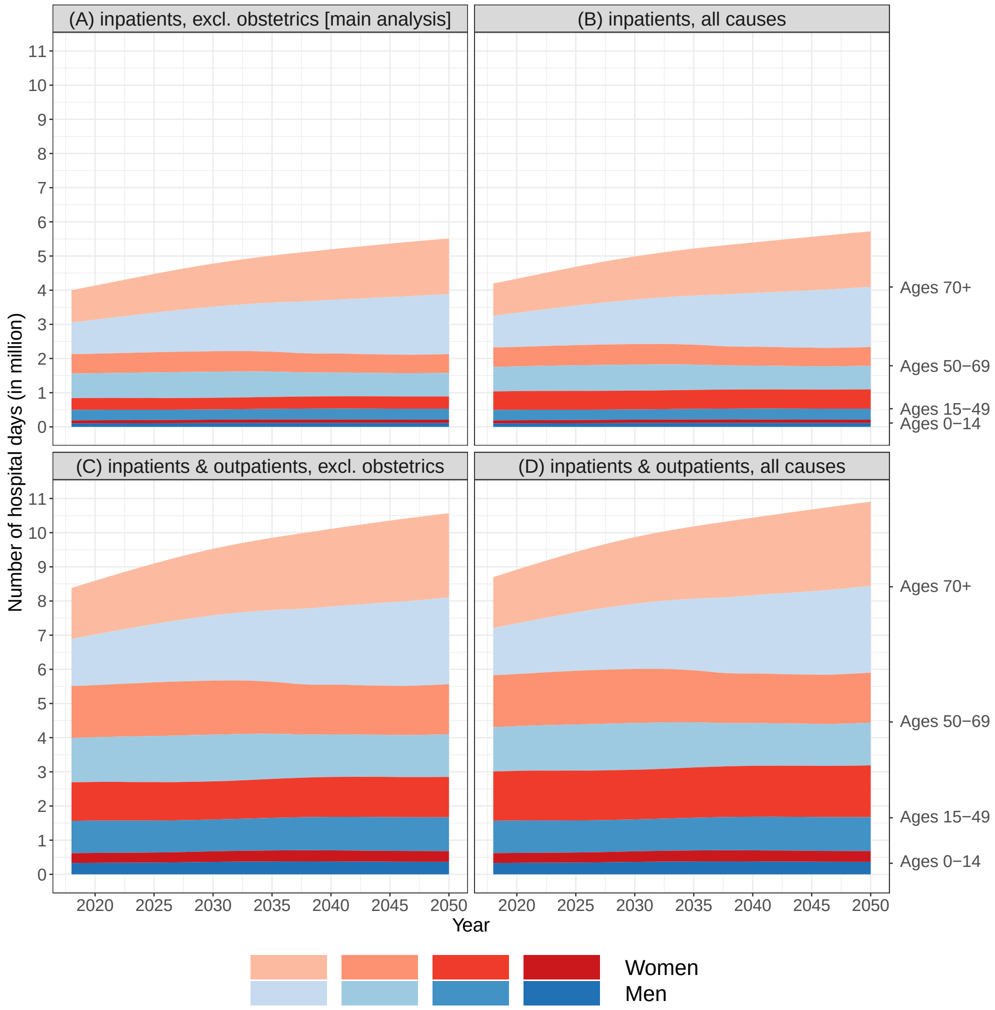
Supplementary Text S1: Further Remarks on Sensitivity Analyses.

Our main findings do not consider outpatient admissions and obstetrics-related admissions **(Setting A)**. We investigated the impact of obstetrics-related admissions **(Setting B)**. We specified this category as O.00 – O.99 and Z.30 – Z.39 using the International Classification of Diseases (ICD), 10th Revision. In addition, we estimated the contribution of those outpatient treatments, which were provided within hospitals **(Setting C)**. Each outpatient treatment was approximated to contribute exactly one day. We used this approximation for outpatient admissions since the registers provide neither the exact number of days an outpatient has spent in the hospital, nor an overview of the provided services. Instead, the information in the registers on outpatient treatments covers the start and the end date of the treatment period for administrative purposes. We further studied the combined impact of outpatient treatments and obstetrics-related admissions **(Setting D)**.

While Supplementary Figure S1 compares age- and sex-specific trajectories for the baseline year 2014 reflecting these four settings, Supplementary Figure S2 compares the results of the corresponding projections. A summary of projection results for all four settings is presented in Supplementary Table S2.



Supplementary Figure S1: Average number of days spend in hospital per person in 2014 by age and for different admission types and causes.



Supplementary Figure S2: Projected annual number of hospital days up to the year 2050 for different admission types and causes.

Supplementary Table S2: Comparing the impact of different specifications of hospital care use for 2014 (baseline year) and 2050 (last year of the projection period).

2014 - Men								
Age Group	**(A) Days in Hospital**		**(B) Days in Hospital**		**(C) Days in Hospital**		**(D) Days in Hospital**	
	N in Mio.	**Share in %**	**N in Mio.**	**Share in %**	**N in Mio.**	**Share in %**	**N in Mio.**	**Share in %**
0-14	0.10	2.66	0.10	2.51	0.33	4.14	0.33	4.03
15-49	0.31	8.31	0.31	7.84	0.95	11.88	0.95	11.48
50-69	0.72	19.30	0.72	18.19	1.30	16.33	1.30	15.73
70+	0.77	20.50	0.77	19.32	1.14	14.34	1.14	13.81
All	**1.90**	**50.77**	**1.90**	**47.86**	**3.72**	**46.69**	**3.72**	**45.05**
2014 - Women								
Age Group	**(A) Days in Hospital**		**(B) Days in Hospital**		**(C) Days in Hospital**		**(D) Days in Hospital**	
	N in Mio.	**Share in %**	**N in Mio.**	**Share in %**	**N in Mio.**	**Share in %**	**N in Mio.**	**Share in %**
0-14	0.09	2.31	0.09	2.18	0.29	3.60	0.29	3.47
15-49	0.35	9.34	0.53	13.42	1.14	14.31	1.44	17.38
50-69	0.57	15.18	0.57	14.31	1.51	18.92	1.51	18.23
70+	0.84	22.41	0.88	22.23	1.31	16.47	1.31	15.87
All	**1.85**	**49.23**	**2.07**	**52.14**	**4.24**	**53.31**	**4.54**	**54.95**
Total	**3.75**	**100**	**3.98**	**100**	**7.96**	**100**	**8.26**	**100**

Supplementary Table S2 - Continued: Comparing the impact of different specifications of hospital care use for 2014 (baseline year) and 2050 (last year of the projection period).

2050 - Men								
Age Group	**(A) Days in Hospital**		**(B) Days in Hospital**		**(C) Days in Hospital**		**(D) Days in Hospital**	
	N in Mio.	**Share in %**	**N in Mio.**	**Share in %**	**N in Mio.**	**Share in %**	**N in Mio.**	**Share in %**
0-14	0.11	2.03	0.11	1.96	0.37	3.45	0.37	3.35
15-49	0.32	5.83	0.32	5.62	0.99	9.38	0.99	9.11
50-69	0.69	12.54	0.69	12.08	1.25	11.83	1.25	11.46
70+	1.76	31.88	1.76	30.72	2.54	23.99	2.54	23.25
All	**2.88**	**52.28**	**2.88**	**50.38**	**5.14**	**48.65**	**5.15**	**47.17**
2050 - Women								
Age Group	**(A) Days in Hospital**		**(B) Days in Hospital**		**(C) Days in Hospital**		**(D) Days in Hospital**	
	N in Mio.	**Share in %**	**N in Mio.**	**Share in %**	**N in Mio.**	**Share in %**	**N in Mio.**	**Share in %**
0-14	0.10	1.75	0.10	1.69	0.32	2.99	0.32	2.90
15-49	0.36	6.53	0.57	9.92	1.18	11.16	1.51	13.88
50-69	0.55	9.93	0.55	9.57	1.47	13.86	1.47	13.43
70+	1.63	29.51	1.63	28.44	2.47	23.35	2.47	22.62
All	**2.63**	**47.72**	**2.84**	**49.62**	**5.43**	**51.35**	**5.76**	**52.83**
Total	**5.51**	**100**	**5.72**	**100**	**10.57**	**100**	**10.91**	**100**

References

[1] Clayton JA, Tannenbaum C. Reporting sex, gender, or both in clinical research? JAMA. 2016;316:1863–1864.

[2] Schiebinger L, Leopold SS, Miller VM. Editorial policies for sex and gender analysis. Lancet. 2016;388:2841–2842.

[3] Schiebinger L, Stefanick M. Gender Matters in Biological Research and Medical Practice. J Am Coll Cardiol. 2016;67:136–138.

[4] Krieger N. Genders, sexes, and health: what are the connections – and why does it matter? Int J Epidemiol. 2003;32:652–657.

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

[6] Mosca L, Barrett-Connor E, Kass Wenger N. Sex/gender differences in cardiovascular disease prevention: what a difference a decade makes. Circulation. 2011;124:2145–2154.

[7] Cosselman KE, Navas-Acien A, Kaufman JD. Environmental factors in cardiovascular disease. Nat Rev Cardiol. 2015;12:627–642.

[8] Widerberg K. Translating Gender. Nordic Journal of Women's Studies. 1998;6:133–138.

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

[10] Sahl Andersen J, De Fine Olivarius N, Krasnik A. The Danish national health service register. Scand J Public Health. 2011;39:34–37.

[11] Richards C, Bouman WP, Seal L, Barker MJ, Nieder TO, TSjoen G. Non-binary or genderqueer genders. Int Rev Psychiatry. 2016;28:95–102.

[12] Koehler A, Eyssel J, Nieder TO. Genders and individual treatment progress in (non-) binary trans individuals. J Sex Med. 2018;15:102–113.

[13] Rider GN, McMorris BJ, Gower AL, Coleman E, Eisenberg ME. Health and care utilization of transgender and gender nonconforming youth: A population-based study. Pediatrics. 2018;141:e20171683.

[14] Klasen S. Marriage, bargaining, and intrahousehold resource allocation: Excess female mortality among adults during early German development, 1740–1860. J Econ Hist. 1998;58:432–467.

[15] McNay K, Humphries J, Klasen S. Excess female mortality in nineteenth-century England and Wales: A regional analysis. Soc Sci His. 2005;29:649–681.

[16] Zarulli V, Jones JAB, Oksuzyan A, Lindahl-Jacobsen R, Christensen K, Vaupel JW. Women live longer than men even during severe famines and epidemics. Proc Natl Acad Sci USA. 2018;115:832–840.

[17] Thorslund M, W WJ, Agahi N, Lagergren M, Parker MG. The rise and fall of womens advantage: a comparison of national trends in life expectancy at ages 65 years. Eur J Ageing. 2013;4:271–277.

[18] Omran AR. The epidemiologic transition: a theory of the epidemiology of population change. Milbank Q. 1971;49:509–538.

[19] Blacher J, Levy BI, Mourad JJ, Safar ME, Bakris G. From epidemiological transition to modern cardiovascular epidemiology: hypertension in the 21st century. Lancet. 2016;388:530–532.

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

[21] Vallin J, Meslé F. Convergences and divergences in mortality: a new approach of health transition. Demogr Res. 2004;2:11–44.

[22] 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.

[23] Glei DA, Horiuchi S. The narrowing sex differential in life expectancy in high-income populations: effects of differences in the age pattern of mortality. Popul Stud. 2007;61:141–159.

[24] Clark R, Peck BM. Examining the Gender Gap in Life Expectancy: A Cross-National Analysis, 1980–2005. Soc Sci Q. 2012;93:820–837.

[25] Barford A, Dorling D, Davey Smith G, Shaw M. Life expectancy: women now on top everywhere. BMJ. 2006;332.

[26] Population Division of the Department of Economic, Social Affairs of the United Nations Secretariat. World Population Prospects: The 2017 Revision. United Nations; 2017.

[27] University of California Berkeley (USA), Max Planck Institute for Demographic Research (GER). Human Mortality Database. Available at www.mortality.org (data downloaded: 2019/07/31); 2019.

[28] Beltrán-Sánchez H, Finch CE, Crimmins EM. Twentieth century surge of excess adult male mortality. Proc Natl Acad Sci USA. 2015;112:8993–8998.

[29] Thun M, Peto R, Boreham J, Lopez AD. Stages of the cigarette epidemic on entering its second century. Tob Control. 2012;21:96–101.

[30] Valkonen T, Van Poppel F. The contribution of smoking to sex differences in life expectancy. Eur J Public Health. 1997;7:302–310.

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

[32] 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.

[33] Lopez AD, Collishaw NE, Piha T. A descriptive model of the cigarette epidemic in developed countries. Tob Control. 1994;3:242–247.

[34] Luy M, Wegner-Siegmundt C. The impact of smoking on gender differences in life expectancy: more heterogeneous than often stated. Eur J Public Health. 2014;25:706–710.

[35] Drevenstedt GL, Crimmins EM, Vasunilashorn S, Finch CE. The rise and fall of excess male infant mortality. Proc Natl Acad Sci USA. 2008;105:5016–5021.

[36] Lindahl-Jacobsen R, Hanson HA, Oksuzyan A, Mineau GP, Christensen K, Smith KR. The male–female health-survival paradox and sex differences in cohort life expectancy in Utah, Denmark, and Sweden 1850–1910. Ann Epidemiol. 2013;23:161–166.

[37] Staetsky LD, Hinde A. Unusually small sex differentials in mortality of Israeli Jews: What does the structure of causes of death tell us? Demogr Res. 2009;20:209–252.

[38] Luy M. Causes of male excess mortality: insights from cloistered populations. Popul Dev Rev. 2003;29:647–676.

[39] Luy M. Unnatural deaths among nuns and monks: is there a biological force behind male external cause mortality? J Biosoc Sci. 2009;41:831–844.

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

[41] Christensen K, Ørstavik KH, Vaupel JW. The X chromosome and the female survival advantage. Ann NY Acad Sci. 2001;954(1):175–183.

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

[43] Regan JC, Partridge L. Gender and longevity: why do men die earlier than women? Comparative and experimental evidence. Best Pract Res Clin Endocrinol Metab. 2013;27:467–479.

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

[45] Austad SN. Why women live longer than men: sex differences in longevity. Gend Med. 2006;3:79–92.

[46] Austad SN, Fischer KE. Sex differences in lifespan. Cell Metab. 2016;23:1022–1033.

[47] 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.

[48] Oertelt-Prigione S. The influence of sex and gender on the immune response. Autoimmun Rev. 2012;11:A479–A485.

[49] Carter LR, Lee RD. Modeling and forecasting US sex differentials in mortality. Int J Forecast. 1992;8:393–411.

[50] 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;.

[51] Martikainen PT, Valkonen T. Excess mortality of unemployed men and women during a period of rapidly increasing unemployment. Lancet. 1996;348:909–912.

[52] Shor E, Roelfs DJ, Curreli M, Clemow L, Burg MM, Schwartz JE. Widowhood and mortality: a meta-analysis and meta-regression. Demography. 2012;49:575–606.

[53] World Health Organization. The preamble of the constitution of the World Health Organization. WHO; 1946.

[54] McDowell I. Measuring health: a guide to rating scales and questionnaires. Oxford Nniversity Press; 2006.

[55] Patrick DL, Deyo RR. Generic and disease-specific measures in assessing health status and quality of life. Med Care. 1989;27(3):S217–S232.

[56] Ware Jr JE. Standards for validating health measures: definition and content. J Chronic Dis. 1987;40(6):473–480.

[57] Lee Y. The predictive value of self assessed general, physical, and mental health on functional decline and mortality in older adults. J Epidemiol Community Health. 2000;54:123–129.

[58] Sasaki H, Kasagi F, Yamada M, Fujita S. Grip strength predicts cause-specific mortality in middle-aged and elderly persons. Am J Med. 2007;120:337–342.

[59] Bambra C, Pope D, Swami V, Stanistreet D, Roskam A, Kunst A, et al. Gender, health inequalities and welfare state regimes: a cross-national study of 13 European countries. J Epidemiol Community Health. 2009;63:38–44.

[60] Oksuzyan A, Crimmins E, Saito Y, ORand A, Vaupel JW, Christensen K. Cross-national comparison of sex differences in health and mortality in Denmark, Japan and the US. Eur J Epidemiol. 2010;7:471–480.

[61] Nusselder W, Looman C, Van Oyen H, Robine JM, Jagger C. Gender differences in health of EU10 and EU15 populations: the double burden of EU10 men. Eur J Ageing. 2010;7:219–227.

[62] Van Oyen H, Nusselder W, Jagger C, Kolip P, Cambois E, Robine JM. Gender differences in healthy life years within the EU: an exploration of the health–survival paradox. Int J Public Health. 2013;58:143–155.

[63] Nybo H, Gaist D, Jeune B, McGue M, Vaupel JW, Christensen K. Functional Status and Self-Rated Health in 2,262 Nonagenarians: The Danish 1905 Cohort Survey. J Am Geriatr Soc. 2001;49:601–609.

[64] McLean CP, Asnaani A, Litz BT, Hofmann SG. Gender differences in anxiety disorders: prevalence, course of illness, comorbidity and burden of illness. J Psychiatr Resh. 2011;45:1027–1035.

[65] Wang Y, Hunt K, Nazareth I, Freemantle N, Petersen I. Do men consult less than women? An analysis of routinely collected UK general practice data. BMJ open. 2013;3:e003320.

[66] Hunt K, Adamson J, Hewitt C, Nazareth I. Do women consult more than men? A review of gender and consultation for back pain and headache. J Health Serv Res Policy. 2011;16:108–117.

[67] Oksuzyan A, Shkolnikova M, Vaupel J, Christensen K, Shkolnikov V. Sex differences in health and mortality in Moscow and Denmark. Eur J Epidemiol. 2014;29:243–252.

[68] Oksuzyan A, Shkolnikova M, Vaupel JW, Christensen K, Shkolnikov VM. Sex Differences in Biological Markers of Health in the Study of Stress, Aging and Health in Russia. PloS one. 2015;6:e0131691.

[69] Lynch C, Holman CDJ, Moorin RE. Use of Western Australian linked hospital morbidity and mortality data to explore theories of compression, expansion and dynamic equilibrium. Aust Health Rev. 2007;31:571–581.

[70] Crimmins EM, Kim JK, Solé-Auró A. Gender differences in health: results from SHARE, ELSA and HRS. Eur J Public Health. 2010;21:81–91.

[71] Dahlin J, Härkönen J. Cross-national differences in the gender gap in subjective health in Europe: Does country-level gender equality matter? Soc Sci Med. 2013;98:24–28.

[72] 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:e003447.

[73] Jensen AB, Moseley PL, Oprea TI, Ellesøe SG, Eriksson R, Schmock H, et al. Temporal disease trajectories condensed from population-wide registry data covering 6.2 million patients. Nat Commun. 2014;5:4022.

[74] Westergaard D, Moseley P, Sørup FKH, Baldi P, Brunak S. Population-wide analysis of differences in disease progression patterns in men and women. Nat Commun. 2019;10:666.

[75] Oksuzyan A, Petersen I, Stovring H, Bingley P, Vaupel JW, Christensen K. The male–female health–survival paradox: a survey and register study of the impact of sex-specific selection and information bias. Ann Epidemiol. 2009;19:504–511.

[76] Oksuzyan A, Dańko MJ, Caputo J, Jasilionis D, Shkolnikov VM. Is the story about sensitive women and stoical men true? Gender differences in health after adjustment for reporting behavior. Soc Sci Med. 2019;228:41–50.

[77] 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.

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

[79] 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.

[80] 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.

[81] 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.

[82] 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;12:1.

[83] 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.

[84] 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.

[85] 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.

[86] Busse R, Krauth C, Schwartz F. Use of acute hospital beds does not increase as the population ages: results from a seven year cohort study in Germany. J Epidemiol Community Health. 2002;56:289–293.

[87] Dixon T, Shaw M, Frankel S, Ebrahim S. Hospital admissions, age, and death: retrospective cohort study. BMJ. 2004;328:1288–1291.

[88] Luben R, Hayat S, Wareham N, Khaw K. Predicting admissions and time spent in hospital over a decade in a population-based record linkage study: the EPIC-Norfolk cohort. BMJ Open. 2016;6:e009461.

[89] Hu Y, Leinonen T, Myrskylä M, Martikainen P. Changes in socioeconomic differences in hospital days with age: cumulative disadvantage, age-as-leveler, or both? J Gerontol B Psychol Sci Soc Sci. 9999;99:99–99.

[90] Hippisley-Cox J, Coupland C. Predicting risk of emergency admission to hospital using primary care data: derivation and validation of QAdmissions score. BMJ Open. 2013;3:e003482.

[91] Campisi J. Aging, cellular senescence, and cancer. Annu Rev Physiol. 2013;75:685–705.

[92] Leening MJ, Ferket BS, Steyerberg EW, Kavousi M, Deckers JW, Nieboer D, et al. Sex differences in lifetime risk and first manifestation of cardiovascular disease: prospective population based cohort study. BMJ. 2014;349:g5992.

[93] Rasmussen KL, Tybjærg-Hansen A, Nordestgaard BG, Frikke-Schmidt R. Absolute 10-year risk of dementia by age, sex and APOE genotype: a population-based cohort study. CMAJ. 2018;190:1033–1041.

[94] Engberg H, Oksuzyan A, Jeune B, Vaupel JW, Christensen K. Centenarians–a useful model for healthy aging? A 29-year follow-up of hospitalizations among 40 000 Danes born in 1905. Aging Cell. 2009;8:270–276.

[95] Oksuzyan A, Jeune B, Juel K, Vaupel JW, Christensen K. Changes in hospitalisation and surgical procedures among the oldest-old: a follow-up study of the entire Danish 1895 and 1905 cohorts from ages 85 to 99 years. Age Ageing. 2013;42:476–481.

[96] 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;p. 653–660.

[97] Rollman GB, Lautenbacher S. Sex differences in musculoskeletal pain. Clin J Pain. 2001;17:20–24.

[98] 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.

[99] Jung KW, Park S, Shin A, Oh CM, Kong HJ, Jun JK, et al. Do female cancer patients display better survival rates compared with males? Analysis of the Korean National Registry data, 2005–2009. PloS one. 2012;7:e52457.

[100] Radkiewicz C, Johansson AL, Dickman PW, Lambe M, Edgren G. Sex differences in cancer risk and survival: A Swedish cohort study. Eur J Cancer. 2017;84:130–140.

[101] 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.

[102] Gonzalez AV, Suissa S, Ernst P. Gender differences in survival following hospitalisation for COPD. Thorax. 2011;66:38–42.

[103] Kaplan V, Angus DC, Griffin MF, Clermont G, Scott Watson R, Linde-Zwirble WT. Hospitalized community-acquired pneumonia in the elderly: age-and sex-related patterns of care and outcome in the United States. Am J Respir Crit Care Med. 2002;165:766–772.

[104] Reade MC, Yende S, DAngelo G, Kong L, Kellum JA, Barnato AE, et al. Differences in immune response may explain lower survival among older men with pneumonia. Crit Care Med. 2009;37:1655–1662.

[105] Kannegaard PN, van der Mark S, Eiken P, Abrahamsen B. Excess mortality in men compared with women following a hip fracture. National analysis of comedications, comorbidity and survival. Age Ageing. 2010;39:203–209.

[106] Katsoulis M, Benetou V, Karapetyan T, Feskanich D, Grodstein F, Pettersson-Kymmer U, et al. Excess mortality after hip fracture in elderly persons from Europe and the USA: the CHANCES project. J Intern Med. 2017;281:300–310.

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

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

[109] Kim JS, Lee KB, Roh H, Ahn MY, Hwang HW. Gender differences in the functional recovery after acute stroke. J Clin Neurol. 2010;6:183–188.

[110] Andersen KK, Andersen ZJ, Olsen TS. Predictors of early and late case-fatality in a nationwide Danish study of 26 818 patients with first-ever ischemic stroke. Stroke. 2011;42:2806–2812.

[111] Simon T, Mary-Krause M, Cambou JP, Hanania G, Guéret P, Lablanche JM, et al. Impact of age and gender on in-hospital and late mortality after acute myocardial infarction: increased early risk in younger women. Eur Heart J. 2006;27:1282–1288.

[112] Nielsen S, Björck L, Berg J, Giang K, Sandström TZ, Falk K, et al. Sex-specific trends in 4-year survival in 37 276 men and women with acute myocardial infarction before the age of 55 years in Sweden, 1987–2006: a register-based cohort study. BMJ Open. 2014;4:e004598.

[113] 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.

[114] Banks I, Baker P. Men and primary care: improving access and outcomes. Trends Urol & Men's Health. 2013;4:39–41.

[115] Wang Y, Freemantle N, Nazareth I, Hunt K. Gender differences in survival and the use of primary care prior to diagnosis of three cancers: an analysis of routinely collected UK general practice data. PLoS One. 2014;9:e101562.

[116] Colvez A, Blanchet M. Potential gains in life expectancy free of disability: a tool for health planning. Int J Epidemiol. 1983;12:224–229.

[117] Robine JM, Romieu I, Cambois E. Health expectancy indicators. Bull World Health Organ. 1999;77:181–185.

[118] Beltrán-Sánchez H, Soneji S, Crimmins EM. Past, present, and future of healthy life expectancy. Cold Spring Harb Perspect Med. 2015;5:a025957.

[119] Salomon JA, Wang H, Freeman MK, Vos T, Flaxman AD, Lopez AD, et al. Healthy life expectancy for 187 countries, 1990–2010: a systematic analysis for the Global Burden Disease Study 2010. Lancet. 2012;380:2144–2162.

[120] Crimmins EM, Zhang Y, Saito Y. Trends over 4 decades in disability-free life expectancy in the United States. Am J Public Health. 2016;106:1287–1293.

[121] Institute for Health Metrics & Evaluation. Global Burden of Disease (GBD). University of Washington; 2019.

[122] Modig K, Andersson T, Drefahl S, Ahlbom A. Age-specific trends in morbidity, mortality and case-fatality from cardiovascular disease, myocardial infarction and stroke in advanced age: evaluation in the Swedish population. PloS one. 2013;8:e64928.

[123] Modig K, Berglund A, Talbäck M, Ljung R, Ahlbom A. Estimating incidence and prevalence from population registers: example from myocardial infarction. Scand J Public Health. 2017;45:5–13.

[124] Modig K, Talbäck M, Ziegler L, Ahlbom A. Temporal trends in incidence, recurrence and prevalence of stroke in an era of ageing populations, a longitudinal study of the total Swedish population. BMC Geriatr. 2019;19:31.

[125] van Raalte AA, Sasson I, Martikainen P. The case for monitoring life-span inequality. Science. 2018;362:1002–1004.

[126] van Raalte AA, Martikainen P, Myrskylä M. Lifespan variation by occupational class: compression or stagnation over time? Demography. 2014;51:73–95.

[127] Sasson I. Trends in life expectancy and lifespan variation by educational attainment: United States, 1990–2010. Demography. 2016;53:269–293.

[128] Beard JR, Bloom DE. Towards a comprehensive public health response to population ageing. Lancet. 2015;385:658–661.

[129] Pallin DJ, Espinola JA, Camargo Jr CA. US population aging and demand for inpatient services. J Hosp Med. 2014;9:193–196.

[130] Darzi A, Evans T. The global shortage of health workers - an opportunity to transform care. Lancet. 2016;388:2576–2577.

[131] Meiboom AA, de Vries H, Hertogh CM, Scheele F. Why medical students do not choose a career in geriatrics: a systematic review. BMC Med Educ. 2015;15:101.

[132] Samra R, Griffiths A, Cox T, Conroy S, Gordon A, Gladman JR. Medical students' and doctors' attitudes towards older patients and their care in hospital settings: a conceptualisation. Age Ageing. 2015;44(5):776–783.

[133] Samra R, Cox T, Gordon AL, Conroy SP, Lucassen MF, Griffiths A. Factors related to medical students and doctors attitudes towards older patients: a systematic review. Age Ageing. 2017;46:911–919.

[134] Hughes NJ, Soiza RL, Chua M, Hoyle GE, MacDonald A, Primrose WR, et al. Medical student attitudes toward older people and willingness to consider a career in geriatric medicine. J Am Geriatr Soc. 2008;56:334–338.

[135] Kusumastuti S, van Fenema E, Polman-van Stratum EC, Achterberg W, Lindenberg J, Westendorp RG. When contact is not enough: Affecting first year medical students image towards older persons. PloS one. 2017;12:e0169977.

[136] Fisher JM, Tullo E, Stewart J. Pejorative phrases or innocent idioms? Exploring terms used by tomorrow's doctors in relation to older people. Educ Gerontol. 2018;44:551–561.

[137] Brønnum-Hansen H. Health expectancy in Denmark, 1987–2000. Eur J Public Health. 2005;15:20–25.

[138] Jeune B, Brønnum-Hansen H. Trends in health expectancy at age 65 for various health indicators, 1987–2005, Denmark. Eur J Ageing. 2008;5:279–285.

[139] Jacobsen R, Keiding N, Lynge E. Long term mortality trends behind low life expectancy of Danish women. J Epidemiol Community Health. 2002;3:205–208.

[140] Aburto JM, Wensink M, van Raalte A, Lindahl-Jacobsen R. Potential gains in life expectancy by reducing inequality of lifespans in Denmark: an international comparison and cause-of-death analysis. BMC Public Health. 2018;18:831.

[141] Jacobsen R, Osler M, Lynge E, Keiding N. Women's death in Scandinavia – what makes Denmark different? Eur J Epidemiol. 2004;19:117–121.

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

[143] Jacobsen R, Keiding N, Lynge E. Causes of death behind low life expectancy of Danish women. Scand J Public Health. 2006;34:432–436.

[144] Lindahl-Jacobsen R, Rau R, Jeune B, Canudas-Romo V, Lenart A, Christensen K, et al. Rise, stagnation, and rise of Danish womens life expectancy. Proc Natl Acad Sci USA. 2016;113:4015–4020.

[145] Frank L. When an entire country is a cohort. Science. 2000;287:2398–2399.

[146] Schmidt M, Pedersen L, Sorensen HT. The Danish Civil Registration System as a tool in epidemiology. Eur J Epidemiol. 2014;344:541–549.

[147] Thygesen LC, Ersbøll AK. When the entire population is the sample: strengths and limitations in register-based epidemiology. Eur J Epidemiol. 2014;29:551–558.

[148] Olsen J, Brønnum-Hansen H, Gissler M, Hakama M, Hjern A, Kamper-Jørgensen F, et al. High-throughput epidemiology: combining existing data from the Nordic countries in health-related collaborative research. Scand J Public Health. 2010;38:777–779.

[149] Maret-Ouda J, Tao W, Wahlin K, Lagergren J. Nordic registry-based cohort studies: Possibilities and pitfalls when combining Nordic registry data. Scand J Public Health. 2017;45:14–19.

[150] Vrangbæk K, Christiansen T. Health policy in Denmark: leaving the decentralized welfare path? J Health Polit Polic. 2005;30:29–52.

[151] Juul A, Krasnik A, Rudkjøbing A, Birk HO, Olejaz M, Hernández-Quevedo C. Denmark: Health System Review. World Health Organization; 2012.

[152] Pedersen KM, Andersen JS, Søndergaard J. General practice and primary health care in Denmark. J Am Board Fam Med. 2012;25:34–38.

[153] 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.

[154] 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.

[155] Malig C. The civil registration system in Denmark. Bethesda Maryland International Institute Technical Papers. 1996;66:1–6.

[156] Pedersen CB, Gøtzsche H, Møller JØ, Mortensen PB. The Danish Civil Registration System. Dan Med Bull. 2006;4:441–449.

[157] Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. Clin Epidemiol. 2015;7:449–490.

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

[159] Munk-Jørgensen P, Bertelsen A, Dahl AA, Lehtinen K, Lindström E, Tomasson K. Implementation of ICD-10 in the Nordic countries. Nord J Psychiatry. 1999;53:5–9.

[160] Rothman KJ, Greenland S, Lash TL. Modern Epidemiology. Wolters Kluwer Health/Lippincott Williams & Wilkins Philadelphia; 2008.

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

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

[163] Hastie T, Tibshirani R. Generalized additive models. Stat Sci. 1986;p. 297–310.

[164] Min Y, Agresti A. Random effect models for repeated measures of zero-inflated count data. Stat Model. 2005;5:1–19.

[165] Rose CE, Martin SW, Wannemuehler KA, Plikaytis BD. On the use of zero-inflated and hurdle models for modeling vaccine adverse event count data. Journal of biopharmaceutical statistics. 2006;16:463–481.

[166] Hu MC, Pavlicova M, Nunes EV. Zero-inflated and hurdle models of count data with extra zeros: examples from an HIV-risk reduction intervention trial. Am J Drug Alcohol Abuse. 2011;37:367–375.

[167] Gerdtham UG. Equity in health care utilization: further tests based on hurdle models and Swedish micro data. Health Econ. 1997;6:303–319.

[168] Preston S, Heuveline P, Guillot M. Demography: measuring and modeling population processes. Wiley-Blackwell; 2000.

[169] Chiang C. The life table and its applications. Krieger Pub. Co.; 1984.

[170] Ganguly A, Nandi S. Using statistical forecasting to optimize staff scheduling in healthcare organizations. J Health Manag. 2016;18:172–181.

[171] Bohk-Ewald C, Li P, Myrskylä M. Forecast accuracy hardly improves with method complexity when completing cohort fertility. Proc Natl Acad Sci USA. 2018;p. 9187–9192.

[172] Education P, Social Statistics Unit. FRDK118: Population Projections 2018 for the Country by Ancestry, Sex, Age and Time. Statistics Denmark; 2018.

[173] Education P, Social Statistics Unit. Documentation of Statistics for Population Projections for Denmark 2018. Statistics Denmark; 2018.

[174] O'Brien R, Hunt K, Hart G. It's caveman stuff, but that is to a certain extent how guys still operate: men's accounts of masculinity and help seeking. Soc Sci Med. 2005;61:503–516.

[175] McQueenie DA Rossand Ellis, McConnachie A, Wilson AE Philipand Williamson. Morbidity, mortality and missed appointments in healthcare: a national retrospective data linkage study. BMC Med. 2019;17.

[176] Robine JM, Ritchie K. Healthy life expectancy: evaluation of global indicator of change in population health. BMJ. 1991;302:457–460.

[177] Robine JM, Mormiche P, Sermet C. Examination of the causes and mechanisms of the increase in disability-free life expectancy. J Aging Health. 1998;10:171–191.

[178] Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380:2197–2223.

[179] Fries JF. Aging, natural death, and the compression of morbidity. New Engl J Med. 1980;303:130–135.

[180] Fries JF, Bruce B, Chakravarty E. Compression of morbidity 1980–2011: a focused review of paradigms and progress. J Aging Res. 2011;2011:261702.

[181] Stallard E. Compression of morbidity and mortality: new perspectives. N Amer Actuarial J. 2016;20:341–354.

[182] Dall TM, Gallo PD, Chakrabarti R, West T, Semilla AP, Storm MV. An aging population and growing disease burden will require alarge and specialized health care workforce by 2025. Health Aff. 2013;32:2013–2020.

[183] Wilson MA, Kurrle S, Wilson I. Medical student attitudes towards older people: a critical review of quantitative measures. BMC Res Notes. 2018;11:71.

[184] Vos HM, Schellevis FG, van den Berkmortel H, van den Heuvel LG, Bor HH, Lagro-Janssen AL. Does prevention of risk behaviour in primary care require a gender-specific approach? A cross-sectional study. Fam Pract. 2012;30:179–184.

[185] 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.

[186] WHO. International Statistical Classification of Diseases and Related Health Problems. Available at www.who.int/classifications/icd/en/; 2016.

[187] Rooney C, Griffiths C, Cook L. The implementation of ICD-10 for cause of death coding-some preliminary results from the bridge coding study. Health Stat Q. 2002;13:31–41.

[188] Janssen F, Kunst AE. ICD coding changes and discontinuities in trends in cause-specific mortality in six European countries, 1950-99. Bull World Health Organ. 2004;82:904–913.

[189] Hahnel J, Burdekin H, Anand S. Re-admissions following hip fracture surgery. Ann R Coll Surg Engl. 2009;91:591–595.

[190] Hannan EL, Zhong Y, Lahey SJ, Culliford AT, Gold JP, Smith CR, et al. 30-day readmissions after coronary artery bypass graft surgery in New York State. JACC Cardiovasc Interv. 2011;4:569–576.

[191] Merkow RP, Ju MH, Chung JW, Hall BL, Cohen ME, Williams MV, et al. Underlying reasons associated with hospital readmission following surgery in the United States. JAMA. 2015;313:483–495.

[192] Ma C, Shang J, Miner S, Lennox L, Squires A. The prevalence, reasons, and risk factors for hospital readmissions among home health care patients: a systematic review. Home Health Care Management & Practice. 2018;30:83–92.

[193] Völzke H, Alte D, Schmidt CO, Radke D, Lorbeer R, Friedrich N, et al. Cohort profile: the study of health in Pomerania. Int J Epidemiol. 2011;40:294–307.

[194] Walldius G, Malmström H, Jungner I, de Faire U, Lambe M, Van Hemelrijck M, et al. Cohort profile: the AMORIS cohort. Int J Epidemiol. 2017;46:1103–1103i.

[195] Borodulin K, Tolonen H, Jousilahti P, Jula A, Juolevi A, Koskinen S, et al. Cohort profile: the national FINRISK Study. Int J Epidemiol. 2017;47:696–696i.

[196] Akbar T, McGurnaghan S, Palmer CN, Livingstone SJ, Petrie J, Chalmers J, et al. Cohort profile: Scottish diabetes research network type 1 bioresource study (SDRNT1BIO). Int J Epidemiol. 2017;46:796–796i.

[197] Ryder NB. The Cohort as a Concept in the Study of Social Change. Am Sociol Rev. 1965;30:843–861.

[198] Hobcraft J, Menken J, Preston S. Age, period, and cohort effects in demography: a review. In: Cohort analysis in social research. Springer; 1985. p. 89–135.

[199] Brønnum-Hansen H. Socioeconomic differences in health expectancy in Denmark. Scand J Public Health. 2000;28:194–199.

[200] Brønnum-Hansen H, Baadsgaard M. Increasing social inequality in life expectancy in Denmark. Eur J Public Health. 2007;17:585–586.

[201] Hoffmann R. Socioeconomic inequalities in old-age mortality: a comparison of Denmark and the USA. Soc Sci Med. 2011;72:1986–1992.

[202] Brønnum-Hansen H, Baadsgaard M. Widening social inequality in life expectancy in Denmark. A register-based study on social composition and mortality trends for the Danish population. BMC Public Health. 2012;12:994.

[203] Christensen U, Krølner R, Nilsson CJ, Lyngbye PW, Hougaard CØ, Nygaard E, et al. Addressing social inequality in aging by the Danish occupational social class measurement. J Aging Health. 2014;26:106–127.

[204] Gundgaard J. Income-related inequality in utilization of health services in Denmark: evidence from Funen County. Scand J Public Health. 2006;34:462–471.

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

[206] Lange P, Marott JL, Vestbo J, Ingebrigtsen TS, Nordestgaard BG. Socioeconomic status and prognosis of COPD in Denmark. COPD. 2014;11:431–437.

[207] Sortsø C, Lauridsen J, Emneus M, Green A, Jensen PB. Socioeconomic inequality of diabetes patients health care utilization in Denmark. Health Econ Rev. 2017;7:21.

[208] Dalton SO, Schüz J, Engholm G, Johansen C, Kjær SK, Steding-Jessen M, et al. Social inequality in incidence of and survival from cancer in a population-based study in Denmark, 1994–2003: summary of findings. Eur J Cancer. 2008;44:2074–2085.

[209] Starfield B, Shi L, Macinko J. Contribution of primary care to health systems and health. Milbank Q. 2005;83:457–502.

[210] Watt G. The inverse care law today. Lancet. 2002;360:252–254.

[211] Næss Ø, Claussen B, Thelle DS, Smith GD. Four indicators of socioeconomic position: relative ranking across causes of death. Scand J Public Health. 2005;33:215–221.

[212] Galobardes B, Lynch J, Smith GD. Measuring socioeconomic position in health research. Br Med Bull. 2007;81:1–17.

[213] Jensen VM, Rasmussen AW. Danish education registers. Scand J Public Health. 2011;39:91–94.

[214] Pallesen PB, Tverborgvik T, Rasmussen HB, Lynge E. Data on education: From population statistics to epidemiological research. Scand J Public Health. 2010;38:177–183.

[215] Koch MB, Diderichsen F, Grønbæk M, Juel K. What is the association of smoking and alcohol use with the increase in social inequality in mortality in Denmark? A nationwide register-based study. BMJ open. 2015;5:e006588.

[216] Brønnum-Hansen H. Socially disparate trends in lifespan variation: a trend study on income and mortality based on nationwide Danish register data. BMJ open. 2017;7:e014489.

[217] Martikainen P, Bartley M, Lahelma E. Psychosocial determinants of health in social epidemiology. Int J Epidemiol. 2002;31:1091–1093.

[218] Avlund K, Lund R, Holstein BE, Due P. Social relations as determinant of onset of disability in aging. Arch Gerontol Geriatr. 2004;38:85–99.

[219] Lund R, Nilsson CJ, Avlund K. Can the higher risk of disability onset among older people who live alone be alleviated by strong social relations? A longitudinal study of non-disabled men and women. Age Ageing. 2010;39:319–326.

[220] Mastekaasa A. Marriage and psychological well-being: Some evidence on selection into marriage. J Marriage Fam. 1992;p. 901–911.

[221] Goldman N. Marriage selection and mortality patterns: Inferences and fallacies. Demography. 1993;30:189–208.

[222] Waldron I, Hughes ME, Brooks TL. Marriage protection and marriage selection – prospective evidence for reciprocal effects of marital status and health. Soc Sci Med. 1996;43:113–123.

[223] Manzoli L, Villari P, Pirone GM, Boccia A. Marital status and mortality in the elderly: a systematic review and meta-analysis. Soc Sci Med. 2007;64:77–94.

[224] 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.

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

[226] 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.

[227] 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.

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

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

[230] 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.

[231] 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.

[232] 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.

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

[234] Moser K, Frost C, Leon DA. Comparing health inequalities across time and placerate ratios and rate differences lead to different conclusions: analysis of cross-sectional data from 22 countries 1991–2001. Int J Epidemiol. 2007;36:1285–1291.

[235] Harper S, Lynch J. Methods for measuring cancer disparities: using data relevant to healthy people 2010 cancer-related objectives. University of Michigan; 2005.

[236] Tramèr MR, Walder B. Number needed to treat (or harm). World J Surg. 2005;29:576–581.

[237] 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.

[238] 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.

[239] 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.

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

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

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

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

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

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

[246] 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.

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

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

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

[250] Wang H, Naghavi M, Allen C, Barber RM, Bhutta ZA, Carter A, et al. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016;388:1459–1544.

[251] Höhn A, Larsen LA, Schneider DC, Lindahl-Jacobsen R, Rau R, Christensen K, et al. 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-hospitalised population: a register-based cohort study of the Danish population. BMJ open. 2018;8:e021813.

[252] Llanwarne N, Newbould J, Burt J, Campbell JL, Roland M. Wasting the doctor's time? A video-elicitation interview study with patients in primary care. Soc Sci Med. 2017;176:113–122.

[253] Koefoed MM, Søndergaard J, dePont Christensen R, Jarbøl DE. Influence of socioeconomic and demographic status on spirometry testing in patients initiating medication targeting obstructive lung disease: a population-based cohort study. BMC Public Health. 2013;13:580.

[254] Gallagher R, Marshall AP, Fisher MJ. Symptoms and treatment-seeking responses in women experiencing acute coronary syndrome for the first time. Heart Lung J Acute Crit Care. 2010;39:477–484.

[255] MacLean A, Sweeting H, Hunt K. Rules for boys,guidelines for girls: Gender differences in symptom reporting during childhood and adolescence. Soc Sci Med. 2010;70:597–604.

[256] Jatrana S, Crampton P. Gender differences in general practice utilisation in New Zealand. Primary Health Care. 2009;1:261–269.

[257] Lyratzopoulos G, Neal RD, Barbiere JM, Rubin GP, Abel GA. Variation in number of general practitioner consultations before hospital referral for cancer: findings from the 2010 National Cancer Patient Experience Survey in England. Lancet Oncol. 2012;13:353–365.

[258] Fridgen GJ, Aston J, Gschwandtner U, Pflueger M, Zimmermann R, Studerus E, et al. Help-seeking and pathways to care in the early stages of psychosis. Soc Psychiatry Psychiatr Epidemiol. 2013;48:1033–1043.

[259] Chang CM, Liao SC, Chiang HC, Chen YY, Tseng KC, Chau YL, et al. Gender differences in healthcare service utilisation 1 year before suicide: national record linkage study. Br J Psychiatry. 2009;195:459–460.

[260] The National Board of Health & Welfare. Myocardial infarctions in Sweden 1987-2010. Report series: Official statistics of Sweden. Statistics – Health and Medical Care. Stockholm, Sweden; 2011.

[261] Werblow A, Felder S, Zweifel P. Population ageing and health care expenditure: a school of red herrings? Health Econ. 2007;16:1109–1126.

[262] Brooks ME, Kristensen K, van Benthem KJ, Magnusson A, Berg CW, Nielsen A, et al. Modeling zero-inflated count data with glmmTMB. bioRxiv. 2017;p. 132753.

[263] Oliver MI, Pearson N, Coe N, Gunnell D. Help-seeking behaviour in men and women with common mental health problems: cross-sectional study. Br J Psychiatry. 2005;186:297–301.

[264] Robertson S. Not living life in too much of an excess: lay men understanding health and well-being. Health. 2006;10:175–189.

[265] Courtenay WH. Constructions of masculinity and their influence on men's well-being: a theory of gender and health. Soc Sci Med. 2000;50:1385–1401.

[266] MacLean A, Hunt K, Smith S, Wyke S. Does gender matter? An analysis of men's and women's accounts of responding to symptoms of lung cancer. Soc Sci Med. 2017;191:134–142.

[267] Annandale E, Harvey J, Cavers D, Dixon-Woods M. Gender and access to healthcare in the UK: a critical interpretive synthesis of the literature. Evid Policy. 2007;3:463–486.

[268] Galdas PM, Johnson JL, Percy ME, Ratner PA. Help seeking for cardiac symptoms: Beyond the masculine–feminine binary. Soc Sci Med. 2010;71:18–24.

[269] Hamann HA, Ostroff JS, Marks EG, Gerber DE, Schiller JH, Lee SJC. Stigma among patients with lung cancer: a patient-reported measurement model. Psycho-Oncol. 2014;23:81–92.

[270] Chambers SK, Dunn J, Occhipinti S, Hughes S, Baade P, Sinclair S, et al. A systematic review of the impact of stigma and nihilism on lung cancer outcomes. BMC Cancer. 2012;12:184.

[271] Scambler G. Health-related stigma. Sociol Health Illn. 2009;31:441–455.

[272] Mathers CD, Stevens GA, Boerma T, White RA, Tobias MI. Causes of international increases in older age life expectancy. Lancet. 2015;385:540–548.

[273] Christensen K, McGue M, Petersen I, Jeune B, Vaupel JW. Exceptional longevity does not result in excessive levels of disability. Proc Natl Acad Sci USA. 2008;105:13274–13279.

[274] Parker MG, Thorslund M. Health trends in the elderly population: getting better and getting worse. Gerontologist. 2007;47:150–158.

[275] Beltrán-Sánchez H, Razak F, Subramanian S. Going beyond the disability-based morbidity definition in the compression of morbidity framework. Glob Health Action. 2014;7:24766.

[276] Gruenberg EM. The failures of success. Milbank Q. 1977;55:3–24.

[277] Manton K. Changing concepts of morbidity and mortality in the elderly population. Milbank Q. 1982;60:183–244.

[278] Sanders BS. Measuring community health levels. Am J Public Health Nations Health. 1964;54:1063–1070.

[279] Sullivan DF. A single index of mortality and morbidity. HSMHA Health Rep. 1971;86:347–354.

[280] Roberts AW, Dusetzina SB, Farley JF. Revisiting the washout period in the incident user study design: why 6–12 months may not be sufficient. J Comp Effect Res. 2015;4:27–35.

[281] Vaupel JW. Biodemography of human ageing. Nature. 2010;464:536–542.

[282] Brandt M, Deindl C, Hank K. Tracing the origins of successful aging: the role of childhood conditions and social inequality in explaining later life health. Soc Sci Med. 2012;74(9):1418–1425.

[283] Reeves D, Pye S, Ashcroft DM, Clegg A, Kontopantelis E, Blakeman T, et al. The challenge of ageing populations and patient frailty: can primary care adapt? BMJ. 2018;362:k3349.

[284] Engelman M, Canudas-Romo V, Agree EM. The implications of increased survivorship for mortality variation in aging populations. Popul Dev Rev. 2010;36:511–539.

[285] OECD. Health at a Glance: OECD Indicators 2017. OECD Publishing, Paris; 2017.

[286] Kontis V, Bennett JE, Mathers CD, Li G, Foreman K, Ezzati M. Future life expectancy in 35 industrialised countries: projections with a Bayesian model ensemble. Lancet. 2017;389:1323–1335.

[287] Bodenheimer T, Chen E, Bennett HD. Confronting the growing burden of chronic disease: can the US health care workforce do the job? Health Aff. 2009;28:64–74.

[288] Schofield DJ, Earnest A. Demographic change and the future demand for public hospital care in Australia, 2005 to 2050. Aust Health Rev. 2006;30:507–515.

[289] Howdon D, Rice N. Health care expenditures, age, proximity to death and morbidity: Implications for an ageing population. J Health Econ. 2018;57:60–74.

[290] Breyer F, Costa-Font J, Felder S. Ageing, health, and health care. Oxford Rev Econ Pol. 2010;26:674–690.

[291] Vogl M, Leidl R. Informing management on the future structure of hospital care: an extrapolation of trends in demand and costs in lung diseases. Eur J Health Econ. 2016;17:505–517.

[292] Etkind S, Bone A, Gomes B, Lovell N, Evans C, Higginson I, et al. How many people will need palliative care in 2040? Past trends, future projections and implications for services. BMC Med. 2017;15:102.

[293] Strunk BC, Ginsburg PB, Banker MI. The Effect Of Population Aging On Future Hospital Demand: A simulation of future spending finds that aging will not be the strongest influence on inpatient hospital use. Health Aff. 2006;25:141–149.

[294] Statistics Denmark. Documentation of Statistics for Population Projections for Denmark 2018. Population Education and Social Statistics Unit; 2018.

[295] De Haas H. Migration and development: A theoretical perspective. Int Migr. 2010;44:227–264.

[296] Vrhovec J, Tajnikar M. Population ageing and healthcare demand: The case of Slovenia. Health Policy. 2016;120:1329–1336.

[297] Schmidt M, Jacobsen JB, Lash TL, Bøtker HE, Sørensen HT. 25 year trends in first time hospitalisation for acute myocardial infarction, subsequent short and long term mortality, and the prognostic impact of sex and comorbidity: a Danish nationwide cohort study. BMJ. 2012;344:e356.

[298] Christensen K, Thinggaard M, Oksuzyan A, Steenstrup T, Andersen-Ranberg K, Jeune B, et al. Physical and cognitive functioning of people older than 90 years: a comparison of two Danish cohorts born 10 years apart. Lancet. 2013;382:1507–1513.

[299] Vestergaard S, Thinggaard M, Jeune B, Vaupel JW, McGue M, Christensen K. Physical and mental decline and yet rather happy? A study of Danes aged 45 and older. Aging Ment Health. 2015;19:400–408.

[300] Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet. 2013;381:752–762.

[301] Groth MV, Sørensen MR, Matthiessen J, Fagt S, Landvad N, Knudsen VK. Disparities in dietary habits and physical activity in Denmark and trends from 1995 to 2008. Scand J Public Health. 2014;42:611–620.