Increasing risk of postoperative infections among hip fracture patients: A nationwide study 2005-2016

Research year report

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Preface

This report is based on a study conducted during my time as a research year student, 2017-2018. I am humble with regard to the opportunities I have been given during this research year. It has been a year full of excitement and erudition, and time has passed by so quickly.

First, I would like to thank my main supervisor, Alma, for always taking time to listen and address all of my questions. You have guided me throughout the year with your knowledge, and I appreciate that you have believed in me, and encouraged me to make the most out of this research year. Furthermore, I would like to thank my co-supervisor Søren, who carefully has given comments and thoughts as well. I would also like to thank my collaborator, Nickolaj, for good help and support. I would express a great thank you to co-supervisor Daniel Prieto-Alhambra, who has been helpful and supportive, and welcomed me at a research stay with him and his obliging research group at NDROMS, University of Oxford, which was truly inspiring.

Further, I will address a warm thank you to my other colleges at the Department of Clinical Epidemiology. You have always addressed my academic and practical questions and assistance when needed. I would also like to thank all the other research year students, who I have shared work office with this year. You have been very helpful, so including and I have really appreciated the times we have shared together during this year.

Last but not least, I would like to thank my family, friends, and especially my boyfriend, for always being so supportive to me.

Kaja Kjørholt, September 2018

Funding

This research year was supported by grants from:

- Danmarks Frie Forskningsfond
- European Medicin Agency
- The Oticon Foundation
- Augustinus Fonden
- Dansk Ortopædisk Selskabs Fond
- ICPE Scholar Stipendium

Abbreviations

aHR	Adjusted Hazard Ratio
ATC	Anatomical Therapeutic Classification
BMI	Body Mass Index
CCI	Charlson Comorbidity Index
CI	Confidence interval
COPD	Chronic Obstructive Pulmonal Disease
DCRS	Danish Civil Registration System
DMHFR	The Danish Multidisciplinary Hip Fracture Registry
DNHSPD	The Danish National Health Service Prescription Database
DNPR	The Danish National Patient Registry
HR	Hazard Ratio
ICD	International Classification of Diseases
IR	Incidence Rate
MR	Mortality Rate
RD	Risk Difference
RR	Risk Ratio
UK	United Kingdom
UTI	Urinary Tract Infection
PPV	Positive Predictive Value
GPs	General Practitioners
SSRI	Selective Serotonin Reuptake Inhibitor
PY	Person-Years

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Abstract

Objective: We aimed to examine trends in the incidence of infections following hip fracture surgery in Denmark from 2005 to 2016.

Methods: We conducted a nationwide cohort study using individual-level linked data from Danish population-based registries. We calculated cumulative incidence considering death as competing risk and, based on the pseudo-observation method, risk ratios (RRs) with 95% confidence interval (CI) using the period 2005-2006 as a reference. RRs were adjusted for age, sex and comorbidity.

Results: A total of 74,771 patients aged 65 years or older with first time hip fracture surgery were included. The risk of post-operative (at 15, 30, 90, and 365 days) infections increased during 2005-2016. The 30 days cumulative incidence of all hospital-treated infections increased from 10.8 % (95 % CI: 10.2-11.3) in 2005-2006 to 14.3% (95 % CI: 13.7-15.0) in 2015-2016 [adjusted RR: 1.32 (95% CI: 1.23-1.42)]. Adjusted RR for 30 days pneumonia was 1.70 (95% CI: 1.49-1.92). The 30 days cumulative incidence of redeeming community-based antibiotic prescriptions increased from 17.5 % (95 % CI: 16.8-18.2) in 2005-2006 to 27.1 % (95 % CI: 26.3-27.9) in 2015-2016 [adjusted RR: 1.54 (95 % CI: 1.47-1.62)]. The largest increase was observed for broad-spectrum antibiotic use [adjusted RR: 1.79 (95 % CI: 1.68-1.90**)]**. During 2005-2016, risk of infections was substantially higher in hip fracture patients than in the general population. The risk of pneumonia and antibiotic prescriptions increased more over time among hip fracture patients.

Conclusion: We found increased risks of infection following hip fracture surgery during the 12-year study period, which could not entirely be explained by increase in risks of infections seen in the general population. Given the high mortality following infections in the elderly, further research is needed to identify patients at increased risk to target preventive treatment and potentially reduce complications and mortality in hip fracture patients.

Dansk Resumé

Formål: At undersøge om forekomsten af infektion efter operation for hoftenære lårbensbrud har ændret sig over tid i Danmark fra i 2005-2016

Metode: Vi sammenkoblede danske landsdækkende registre og udførte et landsdækkende kohortestudie. Vi identificerede postoperative infektioner behandlet på sygehus, eller antibiotika afhentet på apoteket efter operationsdato. Vi udregnede kumulative incidens med død som konkurrerende risiko, og risiko ratio (RR) med 2005-2006 som reference. RR's blev justeret for alder, køn og komorbiditet.

Resultat: Totalt 74,771 patienter ≥ 65 år som for første gang fik udført en operation pga. hoftenært lårbensbrud i perioden 2005-2016 blev inkluderet i studiet. Risikoen for postoperativ infektion (15, 30, 90 og 365 dage efter operation) steg i perioden 2005-2016. 30 dages kumulativ incidens for enhver sygehusbehandlet infektion steg fra 10.8 % (95 % CI: 10.2-11.3) i 2005-2006 til 14.3 % (95 % KI: 13.7-15.0) i 2015-2016 [justeret RR: 1.32 (95% CI: 1.23-1.42)]. Justeret RR for 30-dages lungebetændelse var 1.70 (95% CI: 1.49-1.92). 30-dages kumulative incidens for indløst antibiotika recept steg fra 17.5 % (95 % CI: 16.8-18.2) i 2005-2006 til 27.1 % (95 % CI: 26.3-27.9) in 2015-2016 [justeret RR: 1.54 (95 % CI: 1.47-1.62)]. Bredspektret antibiotika havde den største øgningen over perioden [justeret RR: 1.79 (95 % CI: 1.68-1.90**)]**. I løbet af 2005-2016 var risikoen for infektioner væsentlig højere blandt hoftebrudspatienter fremfor bakgrundsbefolkningen, og forekomsten af antibiotika og lungebetændelse steg mere blandt hoftefrakturpatienter i forhold til baggrundsbefolkningen.

Konklusion: Vi fandt en øget risiko for infektion efter operation for hoftenære lårbensbrud over studiets 12års-periode, og ændringen kan ikke forklares af samme øgning i infektioner blandt baggrundsbefolkningen. Der er et behov for at fremtidige studier identificerer patienter med størst

infektionsrisiko og fokuserer på forebyggende behandling, i håb om at reducere både komplikationer og dødelighed blandt hoftebrudpatienter i fremtiden.

Introduction

Hip fractures constitute a major clinical and financial burden to the health care system [1, 2], and is the most severe outcome of osteoporosis [3]. Scandinavia, and especially Denmark, has the highest incidence rate of hip fracture worldwide[1, 4], with a standardized incidence rate of 4.23 pr. 1000 person-years in 2014 [5]. Due to ageing populations, the burden of osteoporosis is expected to increase [6], and the annual number of hip fracture is estimated to rise to over six million by the year of 2050 worldwide [7]. Although 1-year mortality decreased by 40% from 1980 through 2014 [5], despite increase in the proportion of patients with severe comorbidity, hip fracture is still associated with a 10% mortality within 30 days and up to 30 % within 1 year of surgery [5, 8].

About 9 %-11 % of hip fracture patients has been reported to develop hospital-acquired pneumonia and 4 %-17.9% to develop urinary tract infection [8, 9, 10, 11], within a varying follow-up time window spanning from during admission to six months follow-up. Pneumonia is a leading cause of death among hip fracture patients [12, 13], and is associated with an excess mortality risk among hip fracture patients [8,14,15]. It has been suggested that the decrease in mortality among hip fracture patients over the last 20 years could be explained by improvement in both perioperative and postoperative patient care [5]. Hence, the decrease in mortality in hip fracture patients could be related to a decrease in incidence of infections. We hypothesized that there has been a decrease in the risk of both hospital-treated and community acquired infections over time. No previous studies have examined the change in risk of hospital-treated infections after hip fracture surgery over time in population-based settings; neither have looked at antibiotics use after discharge from the hospital. We therefore conducted a nationwide cohort study to examine temporal trends in the incidence of infections following hip fracture surgery, including hospital-treated infections and community-based antibiotic prescriptions in Denmark from 2005 to 2016. Furthermore, we compared the trends of infections in hip fracture patients with a trend in the general population cohort.

Methods

Setting

We conducted this population-based cohort study within the Danish registers and databases [16]. Denmark is a country of approximately 5.7 million inhabitants with tax-supported universal and free access to healthcare.

The study is reported according to the RECORD guidelines [17].

Data sources

We collected data from The Danish Multidisciplinary Hip Fracture Registry (DMHFR), The Danish National Patient Registry (DNPR), The Danish National Health Service Prescription Database (DNHSPD), and the Danish Civil Registration System (DCRS).

DMHFR is a nationwide clinical-quality database on all hip fracture patients age 65 years or older undergoing surgery for an medial, pertrochanteric or subtrochanteric femoral fracture [18]. The database was established in 2003 with the intention to improve the quality of treatment and care of hip fracture patients.

DNPR was established in 1977, and has registered all non-psychiatric hospital admissions since 1977 and all hospital outpatient and emergency visits since 1995 [19]. It includes dates of admission and discharge, main diagnoses, and up to 20 secondary discharge diagnosis codes according to the *International Classification of Diseases, Eighth Revision* (ICD-8) until the end of 1993 and *Tenth Revision* (ICD-10) thereafter.

DNHSP contains complete data on all reimbursed prescriptions dispensed from community pharmacies and hospital-based outpatient pharmacies in Denmark since 2004 [20]. The drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification system.

The DCRS was established in 1968 and contains electronic records on vital status (date of death or emigration) for the entire Danish population and is updated daily. The DCRS assigns unique civil

register number to every Danish citizen, which goes through all Danish registers allowing for unambiguous linkage between registers on individual level.

Study participants

DMHFR was used to identify all patients aged 65 years and older who sustained a first-time hip fracture surgery between January 1 2005 and December 31 2016. Patients were included if they were coded with hip fracture as either a primary or secondary inpatient diagnosis. In addition, all included patients had undergone surgery including insertion of a primary hip replacement or open reduction and internal fixation. Patients that emigrated (n=19) or disappeared (n=1) were lost to follow-up and therefore excluded. The total cohort included 74,771 hip fracture patients. Hip fracture surgery date was index date. By using DCRS, for each hip fracture patient, we identified up to 5 persons from the general population without hip fracture, alive at the index date, matching on year of birth and sex at the index date. The purpose of the general population comparison cohort was to examine if the infection trends among hip fracture patients differed from infection trends in general. A total of 373,429 persons were included in analysis of the general population comparison cohort.

Outcomes

We examined time to the following outcomes: 1) any hospital-treated infection, and 2) any community-based antibiotic prescriptions in the post-operative period. Using the DNPR, hospital-treated infection was defined as any first time hospital admission or outpatient clinic visit with an infection at a private or a public hospital, after the hip fracture surgery date (ICD-10 codes are listed in Supplemental Tables and Figures). Community-based antibiotic prescription was defined as any redeemed first-time antibiotic prescription recorded in the DNHSPD after the surgery date (ATC-codes are listed in Supplemental Tables and Figures). Data on in-hospital antibiotic treatment was not available. The outcomes were examined 15-, 30-, 90-, and 365 days after the surgery index.

In addition, we examined specific infections, including hospital-treated pneumonia and hospital-treated urinary tract infections (UTIs), as well as specific subgroups of antibiotics, including broad-spectrum and narrow-spectrum antibiotics.

Covariates

We assessed the following covariates at the date of surgery from the DMHFD: age (65-70, 70-74, 75-79, 80-84, 85-90 and ≥ 90), sex, fracture type (femoral neck and per/subtrochanter fracture), operation type (osteosynthesis and total/hemi arthroplasty), and surgery delay (<24, 24-36, >36 hours, and unknown). Further, we obtained information on body weight and height from the DMHFD to calculate body mass index (BMI) [weight in kilograms (kg) divided by the square of height in meters (m)]. Patients were categorized as underweight (BMI was <18.5 kg/m^2), normal weight (BMI was 18.5- 24.9 kg/m^2), overweight (BMI was 25-29.9 kg/m^2), and obese (BMI was ≥30 kg/m^2).

We collected information on the comorbidities from DNPR ten years prior to hip fracture surgery. As a measure of overall comorbidity, we used the Charlson Comorbidity Index (CCI) score [21, 22]. We defined three comorbidity levels: a score of 0 (low), given to individuals with no previous record of diseases included in the CCI; a score of 1-2 (medium); and a score of 3 or more (high) [23]. In addition, information on specific comorbidities related to risk of infection, such as presence of alcoholism-related disorders, was retrieved from DNRP using ICD-10 codes.

Furthermore, we included use of anti-osteoporotic medication, statins and systemic corticosteroids as reflected by at least one redeemed prescription within one year prior surgery date from DNHSPD, due to potential association between these drugs and infection risk.

Statistical analysis

The study population was followed from the hip fracture surgery date (index date for the general population members) until occurrence of the first infection (or first redeemed antibiotic

prescription), death or study end-date. We described characteristics of the hip fracture cohort as the number and percent of patients overall and by calendar period of hip fracture surgery (2005-2006, 2007-2008, 2009-2010, 2011-2012, 2013-2014, 2015-2016).

We computed cumulative incidences by calendar year for the hip fracture cohort, considering death as competing risk [24, 25]. Competing risk analysis was chosen instead of Kaplan-Meier in order to avoid a potential overestimation of infections risk [26]. The overall cumulative incidences were calculated within 15, 30, 90 and 365 days of surgery date. For the hip fracture cohort, we calculated overall 30-days incidence rates (IRs) as the number of hip fracture patients with hospital-treated infection during each calendar year (or biennial) divided by the total of risk-time during the same time period following the hip fracture admission, expressed per 1,000 person-years. The IRs were stratified by sex, age and CCI-score. Based on the pseudo-observation method, 15,30,90 and 365 days cumulative risk ratios (RR) and risk differences (RD) with 95% confidence interval (CI) were calculated using calendar period 2005-2006 as a reference. We estimated both crude and adjusted estimates after accounting for sex, age group and CCI score.

For the general population cohort, we calculated 30-days cumulative incidence of any hospital-treated infection and any community-based antibiotic prescriptions, considering death as competing risk. We used Cox Proportional Hazard Regression to compute 30-days Hazards Ratio (HR) with 95 % CI adjusted for CCI score, comparing the hip fracture cohort to the matched cohort from the general population in each calendar period. Assumptions for proportional hazard were analyzed by log-minus-log plot, and found acceptable.

All analyses were performed using Stata Version 15.0 (Stata Corp, College Station, Texas, USA). The study was approved by the Danish Data Protection Agency (Region of Central Denmark journal number 1-16-02-444-15). Codes for all study variables are listed in the Supplemental Tables and Figures.

Results

Patient characteristics

We identified 74,771 patients with hip fracture surgery from January 1 2005 to December 31 2016. The number of patients per year was stable over the study period. The proportion of females decreased by 4% in 2015-2016 compared to 2005-2006 (Table 1). Age at hip fracture surgery slightly changed over time, and the proportion of patients aged 90 years or older increased from 18 % to 21 % over the study period. The proportion of patients with severe comorbidities (CCI score 3+) increased from 17 % in 2005-2006 to 22 % in 2015-2016. The proportion of patients operated within 24 hours increased from 57 % to 71 % over time. Type of surgery has slightly changed over the study period (Table 1).

Risk of hospital-treated infections

The cumulative incidences of hospital-treated infections increased from 2005-2006 to 2015-2016 (Table 2). The adjusted RRs were 1.28 (95% CI: 1.18-1.39) for 15-day, 1.32 (95% CI: 1.23-1.42) for 30-day, 1.27 (95 % CI: 1.20-1.35) for 90-day, and 1.23 (95% CI: 1.17-1.30) for 365-day post-operative infections in 2015-2016 compared with 2005-2006 (Table 2). The corresponding risk differences were 2.2% (95% CI: 1.4-3.0), 3.3% (95 % CI: 2.4-4.1), 3.8% (95% CI: 2.8-4.7), and 4.8% (95% CI: 3.4-6.1), respectively.

Patients who underwent surgery in 2015-2016 had an adjusted RR for hospital-treated pneumonia of 1.70 (95 % CI: 1.49-1.92) within 30 days compared with period 2005-2006. In contrast, the adjusted RR for hospital treated UTIs within 30 days was 0.99 (95 % CI: 0.89-1.10) comparing the same periods. Cumulative incidences for pneumonia and UTIs are presented in Table 3.

Risk of community-based antibiotic prescriptions

The cumulative incidences and RRs of community-based antibiotic prescriptions increased continuously during the study period (Table 4). The RRs were highest within 15 days follow-up

(Table 4). For patients who underwent surgery in 2015-2016, the adjusted RRs were 2.03 (95% CI: 1.89-2.18) within 15 days, 1.54 (95 % CI: 1.47-62) within 30 days, 1.23 (95 % CI: 1.18-1.28) within 90 days, and 1.06 (95% CI: 1.03-1.09) within 365 days of surgery compared with period 2005-2006. The corresponding adjusted risk differences were 8.7% (95 % CI: 7.9-9.6), 9.6 % (95 % CI: 8.5-10.7), 7.5 % (95 % CI: 6.0-9.0) and 3.1% (95 % CI: 1.5-4.6), respectively. The adjusted RR of broad-spectrum antibiotic prescriptions was 1.79 (95 % CI: 1.68-1.90**)** within 30 days follow up for patients who underwent surgery in 2015-2016 compared with 2005-2006 (Figure 1). The adjusted RR of narrow-spectrum antibiotic prescriptions was 1.25 (95 % CI: 1.14-1.38) over the same study period (Figure 1).

Stratified analyses

The 30-day IRs of hospital-treated infections, stratified by sex, age groups and CCI score are presented in *Supplemental Table 1 A and 1B.* In addition, risk ratios by the same subgroups looking at trends over time are presented in Supplemental *Table 2A and 2B.*

The risk of hospital-treated infections within 30 days increased irrespective of sex, age group, and CCI score during the study period. We observed both the highest absolute and relative increase over time among patients with high CCI score, or patients aged 85 years or older.

Changing the reference group from 2005-2006 to 2007-2008 did not essentially change any of study estimates or study conclusions.

In comparison to the matched general population

The 30-days cumulative incidences of both hospital-treated infections and community-based antibiotics were substantially higher in hip fracture patients than in the background population over the entire study period (Figure 2A and 2B). Hip fracture patients had a 13.70 (95% CI: 12.30-15.27) times higher risk of any hospital-treated infection in 2005-2006 and 13.45 (95% CI: 12.19-14.83) times higher risk in 2015-2016, compared with the matched general population (Figure 3A,

Supplemental Table 3). Similarly, the risk of hospital-treated pneumonia was 11.28 (95% CI: 9.49-13.41) in 2005-2006 increasing to 16.24 (95% CI: 13.89-19.00) in 2015-2016 for hip fracture patients compared with the general population (Figure 3A, Supplemental Table 3). Compared to the background population, hip fracture patients had aHR for community-based antibiotics prescription of 2.70 (95% CI: 2.56-2.85) in 2005-2006 increasing to 4.15 (95% CI: 3.95-4.36) in 2015-2016 (Figure 3B, Supplemental Table 3).

Discussion

In this nationwide cohort study, we found a significant increased risk of both hospital-treated infections and community-based antibiotic prescriptions, following hip fracture surgery during the 12-year study period. The increased risk of treated infections was observed irrespective of patient's age, sex and CCI score. Risk of treated infections in hip fracture patients was substantially higher during the entire study period compared with the risk in the background population.

Methodological considerations

This study is strengthened by its large sample-size with complete follow-up, involving 74,771 patients undergoing hip fracture surgery. Additional strengths include use of a population-based design with nationwide individual-level collected data, eluding potential sampling bias. We identified hospital-treated infections relying on ICD-10 codes from DNPR. Validation studies have indicated a high accuracy, i.e., the positive predictive value (PPV) of any infection diagnosis in the DNPR has been reported to be 98 % among cancer patients between 2006-2010 [27]. Furthermore, the PPV of hospitalized pneumonia was 90 % in 1994-2004 in general [28] , and 93 % in 2006-2010 among cancer patients [27]. However, we do not know if the PPV and sensitivity of the infection diagnoses has changed during the study period among hip fracture patients. Diagnostic tools has presumably improved [19], leading to a higher probability of detecting a hospital-treated infection

over time. An increasing PPV and sensitivity of ICD-10 infection codes among hip fracture patients would potentially lead to differentiated misclassifications and an overestimation of the relative risk estimates. In addition, we cannot eliminate the possibility of residual confounding, and adjustment for CCI might not be sufficient since registration and diagnostic workout for some comorbid conditions included in CCI score most likely improved over time.

Comparison with previous studies

The yearly incidences of pneumonia or UTIs in our study are lower compared to previous studies (in exception of UTI in one study [8],), evaluating the risk after hip fracture surgery [8, 9, 10, 11]. However, these studies have several limitations; including only descriptive analysis and small study populations [8, 9, 10, 11] , measuring outcome as patient-reported [11], or is restricted to patients treated at a single institution or a selected university hospital [8, 9, 11]. We extended the knowledge by including community-based infections, evaluating trends over time, and considered death as competing risk to minimize potential bias.

In the general population, the incidence of common hospital-treated infections, like pneumonia, has increased during 1998-2014 period in UK [29]. The total of pneumonia-related hospitalization increased by 63 % from 1997-2011 in the general population in Denmark, and the proportion of pneumonia after any surgical procedure increased from 5.5-6.6% among first-time pneumonia hospitalization in period 2002-2011[30].This corresponds to our findings of increased risk of hospital-treated infection in both hip fracture patients and general population. However, increased risk of infections has not been observed in all countries, and a decreased risk of pneumonia was reported in U.S general population during 2003-2009, with the largest decrease among patients >85 years old [31]. In contrast, UTIs hospitalization increased by 52 % from 1998 to 2011 in the U.S general population [32], but we observed consistent risk among hip fracture patients in our study. Increase in pneumonia risk was also observed among elective total hip arthroplasty between 2000

and 2013 [33], although the absolute estimates were considerable lower in elective arthroplasty compared with hip fracture patients. The risk of UTIs in elective hip patients remained unchanged over the same period [33]. In addition, some cohort studies reports an increased risk of revision due to prosthetic joint infection after total hip arthroplasty over time (1995-2009 [34], 2003-2015 [35]). However, results are conflicting (2005-2014 [36]), probably related to discrepancy of registration of joint infections in the arthroplasty registers. None of the studies on prosthetic infection was based solely on hip fracture patients.

Possible explanations and underlying mechanisms

The innate and adaptive immune response attenuate with age (immunosenescence) [37], resulting in increased risk of infection. The innate response decreases to an even larger extend after hip fracture surgery [38], leaving hip fracture patients vulnerable to bacterial infections. However, we did not expect increased infections-risk over time because the quality of in-hospital care has increased among hip fracture patients in Denmark, including increase in patients receiving preoperative optimization before surgery by geriatricians and anaesthesiologists, mobilization within 24 hours of surgery, and assessment of nutritional risk, as well as reduction in surgery delay over time [18]. Furthermore, guidelines for pre- and perioperative prophylactic antibiotics has remained unchanged in hip fracture surgery patients over the study period [39, 40]. However, changes in types of surgery and surgical technique, and blood transfusion practice [41] could have explained our results. Further, we do not know much about quality of rehabilitation of hip fracture patients after discharge from the hospital. Finally, survived patients could be more fragile over time and thereby susceptible for infections. Increasing risk of hospital-treated pneumonia in hip fracture patients could not be explained by increase seen in the general population, because we observed a higher increase among hip fracture patients over the study period.

In addition, hospital-treated infections constitute only small part of infections in general, not

capturing infections treated by general practitioners (GPs). Our data suggest that problems with infections in hip fracture patients are even larger than anticipated after including also less serious infections treated by GPs. The total use of antibiotics has generally expanded over the last decades, especially due to an increased use of broad-spectrum antibiotics [(42)]. However, the overall use in primary sector, (representing 90 % of the total use of antibiotics,) has been stabilized in Denmark since 2011 [(43)]. This deviates from the increased risk of antibiotic use among hip fracture patients. As we found higher increase of community-based antibiotic use among hip fracture patients compared to the age-and sex-matched cohort, the increase among hip fracture patients is not explained by similar antibiotics trends in general. If the increase of antibiotic treatment was related to a general higher antibiotic availability or changes in antibiotic prescribing over the study period, we would have expected to see similar patterns in the general population.

Clinical implications

Our observed increasing incidence of infections could potentially raise concern. Inappropriate antibiotic use, and especially use of broad-spectrum antibiotics, contributes to antimicrobial resistance [(44)]. National recommendations (2017) [(43)] highlights the importance of reducing broad-spectrum antibiotic use in general. Hip fracture patients represent a large patient group, and the increase of broad-spectrum antibiotic use should get attention. Given the high mortality following infections in elderly persons, reducing infections will not only improve post-operative care, but potentially reduce mortality as well. It is clinical important that future studies identify patients at higher risk of infections, and that these factors are more than ever considered in individual patient clinical care.

Conclusion

We found evidence of increasing trends in hospital-treated infections and community-based antibiotic use up to one year after hip fracture surgery, from 2005 through 2016. This could not

entirely be explained by increase seen in the background population. Given the high mortality following infections in elderly persons, it is clinically important that future studies identify patients at increased risk to target preventive treatment and reduce the risk of infections in hip fracture patients.

Supplementary

The following section, *Supplementary*, consists of additional methodological considerations of the presented study, including potential bias as well as statistical specifications. However, the very first parts of this section illuminate some results from a second study, conducted in continuation of the presented study. Since we observed increasing trends of postoperative infections, we also aimed to evaluate the association between postoperative infection and 30-days mortality after hip fracture surgery.

Mortality following hospital-treated infection after hip fracture surgery (extract from study nr 2)

Even though postoperative infection is a common complication in hip fracture patients, the association between postoperative infection and mortality after hip fracture surgery remains unclear. We designed a large nationwide cohort study to examine the association between infection and 30-days all-cause mortality following hip fracture surgery.

We used the exactly same hip fracture cohort as presented earlier, consisting of 74,771 hip fracture patients from 2005-2016. We included hospital-treated infection as a time-varying exposure, in order to avoid potential immortal time bias (thus, the patients were classified as unexposed from the date of surgery and up until the exact day of infection, and then classified as exposed throughout the rest of the follow-up period). We followed patients from the date of surgery and up until death or end of follow-up (30 days after surgery date) and calculated 30-days mortality rates (MRs) for each group. To evaluate the association between infection and mortality, we used time-dependent Cox Proportional Hazard Regression to compute crude and multivariable-adjusted hazards ratios (HRs) with 95 % confidence interval (CI). In our multivariate analysis, we adjusted for sex, age, CCI-score, alcohol-related comorbidities, current medication use (systemic corticosteroids, SSRI,

anticoagulantia and antibiotics) and marital status. Furthermore, we stratified according to sex, age CCI-score and calendar year while adjusting for the remaining covariates. Assumptions for proportional hazard were analyzed by log-minus-log plot, and accepted.

A total of 1,443 of 9,592 (15%) infected patients died within 30 days of hip fracture surgery. Unadjusted MR was 8.43 (95 % CI: 8.00-8.88) by 1000 person-years for infected patients, and 3.34 (95 % CI: 3.26-3.43) for non-infected patients, corresponding to aHR of 2.72 (95 % CI: 2.56-2.88) *(Supplemental Table 5).* The 30-day mortality risk was over 4-fold higher for patients who sustained pneumonia compared to non-pneumonia patients [aHR: 4.18 (95 % CI: 3.91-4.48)**]**, with a MR of 14.83 (95 % CI: 13.92-15.79) for pneumonia patients compared to 3.40 (95 % CI: 3.32-3.48) in non-pneumonia patients. The mortality following sepsis, reoperation due to infection and urinary tract infection are presented in Supplemental Table 5. The mortality was higher in infected vs. non-infected patients irrespective of patients' age, sex and comorbidity *(Supplemental Figure 1*). The MR for infected patients increased over the study period, whereas the MR for non-infected patients decreased over the study period, and the infected patients had an aHR of 2.26 (1.92-2.67) 2005-2006 increasing to aHR of 3.35 (2.90-3.87) in 2015-2016 *(Supplemental Figure 1).*

In conclusion, this provides evidence of substantially increased 30-days mortality risk following postoperative infection, after hip fracture surgery. In combination, these two studies suggest that both the incidence of infections, as well as the mortality following infection, has increased over the study period. Research is needed on the prevention of infection/s among hip fracture patients.

Methodological considerations

Study design

We conducted a cohort study using population-based medical registries in order to answer our research question. A cohort study measures an occurrence/outcome during a giving follow-up period, usually comparing the occurrence in an exposed- and unexposed cohort [45]. Hence, a cohort study will first identify exposure, and then identify the outcome. One of the advantages of a cohort study is the ability to measure multiple outcomes of a given exposure [46]. Since we aimed to evaluate different types of infections at different follow-up periods, we chose to design a cohort study instead of other observational designs like a case control design. A case control study will first identify the outcome and categorize in cases (subjects with the outcome) and controls (subjects without the outcome), and then collect information on exposure [45,46].The controls can be sampled in different ways. However, case-control studies are limited as they only provide ratio measures of effect, whereas we got the opportunity to provide absolute risk estimates conducting a cohort study [46]. This means that even though we could compare the incidence of infections by different calendar year, we would not be able to calculate the cumulative incidence in each calendar year. We found it very important to assess absolute risk estimates as well, especially since the incidence of any type of hospital-treated infection, as well as any dispending antibiotic prescriptions, to the best of our knowledge, never had been evaluated among hip fracture patients.

In comparison to observational study design like cohort study and case-control study, a randomized control trial (RCT) is often refereed to as the golden standard regarding study design. A correct execution of a double-blinded RCT will avoid bias due to confounding [46]. However, the presented study could not be designed as a RCT, since exposure is calendar period and we would not be able to predict and randomized the year of hip fracture surgery. This is impossible, and it would be highly unethical to induce a hip fracture among the elderly.

Exposure and outcome

In order to evaluate risk over time, calendar period was our exposure. We combined two and two calendar years to get a more precise estimate with narrow confidence interval. We used the two first years in the study period, 2005 and 2006, as our reference period. However, we also re-analysed the data using another calendar period as reference (Further details are presented later, *Sensitivity-analysis*). Furthermore, when we compared the trends to the general population, the matched cohort was used as reference (calculated in each calendar period).

The overall study outcome was postoperative infection. We included a wide range of hospital-treated infections (sepsis, skin infections, gastrointestinal infections, respiratory infections, miscellaneous bacterial infections, infectious complications of procedures ++), classified as any type of hospital-treated infection. In addition, we further evaluated specific types of infections, but only the two most frequent postoperative infections were included in the study, respectively pneumonia and urinary tract infection. Furthermore, since hospital-treated infections constitute only small part of infections in general, we aimed to include infections treated by general practitioners (GPs) as well. If we only included hospital-treated infections, we would not be able to assess if potential changes could be related to a patient-shift from hospitals to GPs or vice-versa. Infections treated outside the hospital were defined as any type of redeemed community-based antibiotic after the surgery. To obtain more detailed information, antibiotics were further divided into groups of narrow-spectrum and broad-spectrum antibiotics.

We defined four different follow-up periods in order to examine both short-term and long-term risk of postoperative infections. Assessment of different follow-up periods could potentially support and strengthen our conclusion. To exemplify, if the risk of infection increased within 30 days, but decreased within 90 days after surgery, it would rather indicate a change in the time/patterns of the infections, instead of a change in the overall risk of infections.

Matched cohort

We included a comparison cohort in order to evaluate if the increasing trends of hospital-treated infections and antibiotics were related to a general increase among all elderly, instead of hip fracture surgery itself. We matched each hip fracture patient with up to 5 persons randomly sampled from the Danish general population. We matched on age and sex at the date of hip fracture surgery (index date). We matched on age and sex as they are strongly related to the study outcome, and were able to avoid confounding permitted from these variables *(Explanation of confounding can be seen under random and systematic error).*

Time to event analysis: Statistical considerations

We used time to event analysis in order to evaluate the risk of postoperative infections among hip fracture patients, and followed every patient from the date of hip fracture surgery (time zero). We either observed patients with the event before the end of follow-up period, or patients being event free at the end of the follow-up period.

Time to event analysis requires independent censoring, meaning that those being censored at time t should be representative for the population at risk at time t (i.e cencoring is not related to the risk of the outcome) [47].

Cumulative incidence considering death as competing risk

As an absolute risk estimate, we calculated cumulative incidence considering death as competing risk. The cumulative incidence (or the risk) was calculated as the number of new cases during a specific follow-up period, divided by the number of persons initially disease-free [48]. The longer follow-up time, the greater risk (more time for events to occur), as demonstrated in our study. Cumulative incidence is a commonly used estimate, but should not be used in situations with great loss to follow-up [49] .Competing risk analysis was chosen instead of Kaplan-Meier in order to avoid

a potential overestimation of the infection risk [26]. If our outcome of interest was death by any cause, there would not be any competing risk because any death that occurred would represent an outcome accounting in the numerator of the risk measure [45]. But since our outcome was infection, we had to consider that many hip fracture patients would die during the follow-up period, and death was a competing event. The Kaplan Meier would treat death as censoring, assuming that every censored person could develop an infection later on [24, 26]. However, in the competing risk analysis, death is a dependent censoring, and take into account that those who die, not are able to develop an infection later on.

We measured another absolute risk estimate as well, namely incidence rate (IR) *(Stratified analysis - Supplemental Table1)*. This was calculated as the number of events divided by the total person-years during the observation, expressed per 1,000 person-years (rate) [48]. Even though the numerator is the same for both cumulative incidence and IR, the denominators, and hereby the interpretation, is very different [49]. Whereas cumulative incidence measures number of new cases per person over a defined period of time, IR measure number of new cases per unit of time often expressed by person-years-at-risk [48,49] .

Pseudo values and Cox Regression

Among hip fracture patients only, we applied the pseudo value method to calculate the risk of infection in the later years, compared to the first two operation years. The pseudo value approach creates a transformation/pseudo observation of the time to event data, and generates a pseudo value for each patient in the sample [50]. The pseudo values are then used in a generalized linear model, similar to an analysis without censoring [50]. The pseudo value method does not require proportionality [50]. This is in contrast the most common statistical time-to event analysis, Cox Proportional Hazard Regression, were the hazard rates ratio of the different exposure groups must remains constant over time [48]. Assumptions for proportional hazards were not fulfilled at every

follow-up period/outcome in the present study (mainly assessed by log-minus log plots), so we applied the pseudo values observation method instead. Using the pseudo value approach, we were able to compare two cumulative incidences considering death as competing risk, providing a cumulative risk ratio (relative risk) and a cumulative risk difference estimate. In contrast, Cox Regression compares two rates, resulting in a Hazard Ratio estimate. Since we focused on cumulative incidence as the absolute estimate, we found it favourable to calculate relative estimates based on cumulative incidence as well. Furthermore, a hazard ratio can only be interpreted as a relative risk if the event is rare, which was not the case in this study (at least for any infection and any antibiotics). Hence, using the pseudo value approach allowed a more easy interpretation on the relative estimates.

However, when we compared the risk among hip fracture patients to the matched cohort from the general population, we used Cox Proportional Hazard Regression instead of the pseudo value method. To the best of our knowledge, the pseudo value method cannot be assigned to provide results on a matched design. Assumptions for proportional hazards at 30-days follow-up were fulfilled for any infection, any antibiotic as well as pneumonia, and we were able to produce a matched HR instead.

Random errors and systematic errors

There are mainly two types of error in observational studies: Random error and systematic error [(45)]. Random error refers to the variability in the data [(45)]. We added 95 % confidence interval to every point estimate in our analysis in order to assess the statistical variability. We focused on 95 % confidence interval instead of interpretation on p-values. Based on our large sample size, we were able to limit random error and provide estimates with narrow confidence interval and high precision [(45)]. Systematic error, on the other hand, is not affected by increasing size of the study (however, as

random error decrease with sample size, the relative size of systematic error will then increase) [45]. Systematic errors consist of selection bias, information bias and confounding. Given the large size of our study, the potential errors are presumably based on systematic errors.

Selection bias

If the study participants have another association between exposure and outcome than those who not are included in the study, it will introduce selection bias [45,46]. We collected information from nationwide medical registries with high completeness. We used DMHFR to identify our study population, which has had a mandatory registration of every hip fracture surgery in Denmark since 2003, eluding potential sampling bias. Furthermore, as a prospectively collected cohort study, the outcome was unknown at the index date, and could not be related to exposure. Finally, with almost complete follow-up, all this leads to a low risk of selection bias in our study.

Information bias

Information bias can arise from inaccurately information of the study variables, mainly regarding exposure and outcome [45]. A misclassification related to either the exposure, or the outcome, is known as non-differential misclassification [45,46]. Even with a misclassification of both the exposure and the outcome, it will be non-differential as long as it is not depending on the other variable as well [45]. A non-differential misclassification of a dichotomous exposure will mostly never exaggerate a given effect, but lead to bias towards the null [45]. However, a bias towards null cannot be guaranteed only by a non-differential misclassification [51].

We collected information on infections based on ICD-10 codes from DNPR. Since the positive predictive value (PPV) of infections-codes in DNPR was 98 % among cancer patients [27], this indicates a very high accuracy and low risk of erroneous coding. However, both the PPV and the sensitivity of these codes among hip fracture patients are unknown. Infections are probably underreported (reducing the sensitivity), especially since our elderly study population not

necessarily have symptoms or typical signs of infection [52, 53]. On the other hand, it seems likely to expect a high specificity (supported by a high PPV). If the specificity is close to perfect, a low sensitivity will not necessarily bias the rate ratio, but only underestimate the absolute risk estimates [54]. Nevertheless, diagnostic tools have presumably improved over time, and it could be a higher probability of detecting an infection over time (less false negative cases over time). As calendar year is our exposure, the measurement would be dependent of both the exposure and outcome, potentially leading to differential misclassification. Differential misclassification can cause bias in both directions, either against the null, causing and effect (which would be the case in this situation), or towards the null, which will underestimate an effect [45]. Furthermore, potential diagnostic improvements would most likely cause a higher detection of the less severe infections over time. If the proportion of severed infection decreased over time, our results would not necessarily raise concern, but potentially be due to differentiated misclassification. We did not have any information on the severity of infection, but since the mortality following infection increased over the study period (whereas the mortality without infection decreased, *Supplemental Figure 1*), is seems less likely that the proportion of severe infection decreased over time. Furthermore, sever infections like sepsis, also increased over the study period (Results not shown).

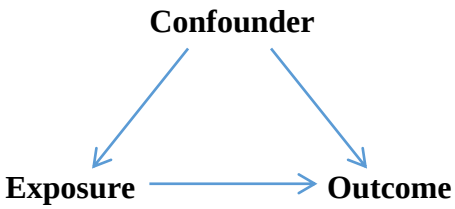
We used antibiotics from DNHSPD as a marker of community-based infections, but antibiotics could potentially be used prophylactic as well. If prophylactic community-based antibiotics prescriptions increased over time, it would indicate that the increasing use of antibiotics not necessarily is related to increasing infections in the community.

Finally, we would like to emphasize that the purpose of the comparison cohort from the general population was to compare changes over time, rather than comparing the risk of infection itself. Since every hip fracture patient is admitted to the hospital at index date, they have a higher probability of being detected with an infection compared to the general population. This type of

information bias is known as surveillance bias [55]. Surveillance bias could potentially be avoided by selecting a more comparable group, for example elective hip replacement surgery. However, since we compared changes over time, we do not think that our conclusion is affected by surveillance bias.

Confounding

Confounding is a central systematic error in epidemiological studies. It can easily be explained as a mixing of effect, where the effect of one variable is attributed to the effect of the exposure [45,46]. If a variable is a confounder, it must fulfil the three following requirements: 1) Be associated with the outcome, 2) Be associated with the exposure and 3) Not be a part of the causal chain between exposure and disease (not an effect of the exposure) [46].



Several approaches can be implemented in order to control for confounding; including statistical analysis like stratification, adjustment in regression models and standardization, or design like restriction or matching [45,46].

We controlled for confounding by adjustment and stratification in the hip fracture cohort, as well as matching the comparison cohort (while adjusting for the remaining confounder variable). It is a rule of thumb that is should be at least 10 observations for every term in a regression model [45] , which was acceptable in this study. If the regression model was overfitted, the results might be strongly biased by random error [45]. An overfitting model can be avoided by using propensity score [45], which would be advantageous in situations with more confounders and less common exposures or outcomes (for example stratified analysis of mortality after some rare postoperative infections).

There are many risk factors for developing a postoperative infection among elderly, however, potential confounders in the presented study was restricted due to association with calendar period (exposure) as well. Even though directed acyclic graphs (DAGs) can be a useful tool for determination of causal interferences and confounders [56], we did not implement one in this study (however, we made a DAG for the association between infection and mortality in the second study). We chose to adjust for the most distinct confounders in this setting: age, comorbidity level and sex. Age was not used as a continuous variable because of some deviations from linearity, but we categorized age into 6 different groups in order to diminish potential residual confounding. We used CCI, a highly implemented index score [57], in order to control for comorbidity. The positive predictive value (PPV) of the comorbidity codes from DNPR has consistently very high accuracy [22]. However, we cannot eliminate the possibility of residual confounding. Adjustment for CCI might not be sufficient since registration and diagnostic workout for some comorbid conditions included in CCI score most likely improved over time (co-variates misclassification). We adjusted for all the 19 comorbidities included in CCI regardless of type of infection, and did not take into account that some comorbidities could be more important than others for some specific infections (for example COPD and pneumonia). In addition, we did not have any information on psychiatric comorbidities or comorbidities treated by general practitioners (GPs). We did not have any information on in-hospital antibiotic use, which could be a potential confounder as well. Furthermore, we did not adjust for socioeconomic status or lifestyle factors. However, even though these factors are related to infection, we cannot with certainty say if these factors changed over time, and if so, in what direction. For example has the proportion of smoking decreased over time, which would underestimate the true increase of postoperative infection, not causing it.

Effect modification and additional results

Effect modification refers to situations where the effect of the exposure changes on presence of some other variable [45, 58]. It is applied as statistical interaction or biological interaction, and it is important to be aware of this ambiguity [45, 58]. We stratified and found increasing risk of infection irrespective of age, sex and comorbidity level; suggesting similar effect of calendar year between these patient groups (no statistical interaction). Furthermore, we included a comparison cohort to evaluate if infection trends among hip fracture patients differed from infection patterns in the general population. Thus, we aimed to investigate if the effect of calendar year differed between the two cohorts, and calculated 30-days HR between the two cohorts at every calendar period. In addition, we included an interaction model between the two cohorts in the Cox Regression (additional results, *Supplemental Table 4*). Over the study period, hip fracture patients had a 1.54 (95 % CI: 1.43-1.65) times higher increase of antibiotics, a 1.43 (95 % CI 1.13-1.80) times higher increase of hospital-treated pneumonia, but aHR was 0.98 (95 % CI 0.85-1.13) for any hospital-treated infection, compared to the general population. This suggest a statistical effect modification of calendar year between the two cohorts with antibiotics and pneumonia as outcome, in contrast to any hospital-treated infection, were we observed approximately similar effect of calendar year between the cohorts. However, it is important to notice that presence of statistical interaction depends on the arbitrary effect measure [45, 58]. If we instead used the absolute risk estimate, the incidence of any hospital-treated infection increased with 3.3 % over the study period among hip fracture patients, and 0.28 % over the study period in the general population, suggesting statistical effect modification in contrast to conclusion from HR as effect measure. Biological interaction, does not have this ambiguous interpretation, but is not discussed further in this setting.

Generalizability

Selection bias, information bias and confounding are systematic errors affecting the internal validation, explaining to what degree the data interpretation is correct [46]. External validation, on the other hand, comprise to what extend the results can be generalized in to other settings [46]. Since we used nationwide registries with mandatory registration of every hip fracture patient in Denmark, these results can be applied within the entire population in Denmark. However, it is previously shown great regional difference in the mortality and in-hospital care after hip fracture surgery in Denmark, and we expect regional variations in the trends of infections as well. We only included patients ≥ 65 years old (average age of a hip fracture is over 80 years), and cannot make any interpretation about infection trends under the age of 65. Furthermore, it is precarious to make a complete and direct generalization into other countries or continents, especially since explanations of increasing infection-trends are unknown. The quality of in-hospital care, the rehabilitation of the patients immediately after discharge, including resources in municipalities, as well as collaboration with GPs, is presumably highly important for the risk of developing a postoperative infection. Different nations might have different changes in these factors, potentially leading to differences in trends as well.

Sensitivity analysis in hip fracture cohort

We reanalysed all data using 2007-2008 as the reference period, which did not change the overall conclusion of increased risk of hospital-treated infections or community-based antibiotics. (The adjusted risk ratios were essentially the same using 2005-2006 or 2007-2008 as reference, results not shown.) However, this could be expected since absolute incidences of infections were quite similar in 05-06 and 07-08.

Overall, we missed 21 % of BMI values, and the proportion of missing BMI values decreased over the study period. We did not handle the missing data by methods like multiple imputation etc, mainly because potential confounding from BMI was dubious in this setting. However, we made some sensitivity analysis to evaluate potential bias from BMI. We stratified the 30-days risk of hospital-treated infection on BMI, and found an increased risk of hospital-treated infection within every BMI group (results not included). Furthermore, we made a complete case analysis with and without BMI as a confounder, where the RR remained exactly the same after adjusting for BMI.

Additional explanations and clinical implications

There are mainly multiple factors contributing to high risk of postoperative infection among hip fracture patients. These patients have high age, and are presented with multimorbidity and polypharmacy. An age-related dysregulation in the immune system, known as immunosenescence [(59)], involves changes like impaired phagocytic ability, and reduction of naïve t-cells, b-cells and antibodies [37]. Furthermore, tissue injury following surgery and trauma, will after the initial systemic inflammatory response syndrome, cause extended depression of cell-mediated immunity, leading to increased risk of infectious complications [(60)].

Our results indicate a strong need of prevention of infections among hip fracture patients. Enhanced focus on early remobilization, respiratory exercises and nutritional support could potentially avert some types of postoperative infections [(61,62,63)]. Systemic prophylactic antibiotics in hip fracture surgery is well-recommended [(64 65)], but doses, durations and combinations might be optimized [(40)]. New implementations of local prophylactic antibiotics may contribute to lower infection-rates [(66)]. Future studies should identify risk factors for developing postoperative infection (both patient-related, surgery-related and quality of care-related), assess potential changes over time, and hopefully we can see reduced risk of infections and mortality after hip fracture surgery in the future.

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TABLE 1: BASELINE CHARACTERISTICS OF THE HIP FRACTURE STUDY POPULATION, DENMARK 2005-2016

	Calendar Period Of hip fracture diagnosis						Total
Patient characteristics	2005-2006	2007-2008	2009-2010	2011-2012	2013-2014	2015-2016	2005-2016
No. of patients	12,453	13,236	12,724	12,706	12,285	11,367	74,771
Age, years							
65-69	884 (7)	895 (7)	986 (8)	1,133 (9)	1,108 (9)	1,045 (9)	6,051 (8)
70-74	1,334 (11)	1,372 (10)	1,426 (11)	1,402 (11)	1,418 (12)	1,399 (12)	8,351 (11)
75-79	2,196 (18)	2,140 (16)	2,027 (16)	2,082 (16)	1,947 (16)	1,793 (16)	12,185 (16)
80-84	3,087(25)	3,163 (24)	2,882 (23)	2,632 (21)	2,507 (20)	2,285 (20)	16,556 (22)
85-89	2,753 (22)	3,205 (24)	3,114 (24)	3,065 (24)	2,827 (23)	2,500 (22)	17,464 (23)
≥90	2,199 (18)	2,461 (19)	2,289 (18)	2,392 (19)	2,478 (20)	2,345 (21)	14,164 (19)
Sex							
Female	9,128(73)	9,628 (73)	9,151(72)	8,919 (70)	8,662 (71)	7,858 (69)	53,346 (71)
Male	3,325 (27)	3,608 (27)	3,573 (28)	3,787 (30)	3,623 (29)	3,509 (31)	21,425 (29)
Charlson Comorbidity Index score							
- 0 (No comorbidity)	5,427 (44)	5,473 (41)	5,140 (40)	5,032 (40)	4,673 (38)	4,354 (38)	30,111 (40)
- 1-2 (Medium)	4,969 (40)	5,383 (41)	5,202 (41)	5,123 (40)	5,006 (41)	4,562 (40)	30,251 (40)
- 3+ (High)	2,057 (17)	2,380 (18)	2,382 (19)	2,551 (20)	2,606 (21)	2,451 (22)	14,429 (19)
Alcohol-related conditions*							
None	12,179 (98)	12,841(97)	12,289 (97)	12,238 (96)	11,766 (96)	10,821 (95)	72,134 (96)
1 or more	274 (2)	395 (3)	435 (3)	468 (4)	519 (4)	546 (5)	2,637 (4)

Body Mass Index, kg/m2							
Underweight <18.5	1,002 (8)	1,274 (10)	1,124 (9)	1,109 (9)	1,088 (9)	857 (8)	6,454 (9)
Normal weight 18.5- 24.9	5,126 (41)	6,179 (47)	5,713 (45)	5,897 (46)	5,926 (48)	5,140 (45)	33,981 (45)
Overweight 25-29.9	1,974 (16)	2,355 (18)	2,328 (18)	2,379 (22)	2,727 (22)	2,568 (23)	14,688 (20)
Obese ≥30	541 (4)	617 (5)	624 (5)	763 (6)	770 (6)	788 (7)	4,103 (5)
Unknown	3,810 (31)	2,811 (21)	2,935 (23)	2,198 (17)	1,777 (14)	2,014 (18)	15,545 (21)
Medication use (yes)							
Anti-Osteoporotic drugs	843 (7)	964 (7)	986 (8)	1,007 (8)	925 (8)	795 (7)	5,520 (7)
Systemic corticosteroids	875 (7)	835 (6)	798 (6)	771 (6)	682 (6)	645 (6)	4,606 (6)
Statins	1,096 (9)	1,825 (18)	2,376 (19)	2,761 (22)	2,832 (23)	2,650 (23)	13,540 (18)
Surgery delay							
<24 hours	7,130 (57)	7,563 (57)	7,614 (60)	8,251 (65)	8,630 (70)	8,097 (71)	47,285 (63)
24-36 hours	1,965 (16)	2,104 (16)	2,035 (16)	1,990 (16)	1,738 (14)	1,547 (14)	11,379 (15)
>36 hours	3,263 (26)	3,496 (26)	3,074 (24)	2,464 (19)	1,917 (16)	1,723(15)	15,937 (21)
Unknown	95 (1)	73 (1)	1 (0)	1 (0)	0 (0)	0 (0)	170 (0)
Fracture type							
Fracture of femoral neck	6,423 (52)	6,736 (51)	6,552 (51)	6,714 (53)	6,821 (56)	6,352 (56)	6,423 (52)
Per and Sub-trochanter fractures	6,030 (48)	6,500 (49)	6,172 (49)	5,992 (47)	5,464 (44)	5,015 (44)	6,030 (48)
Operation type							
Osteosyntheses	9,341 (75)	9,669 (73)	8,830 (69)	8,422 (66)	7,962 (65)	7,312 (64)	51,536 (69)
Total and hemi hip arthroplasty	3,112 (25)	3,567 (27)	3,894 (31)	4,284 (34)	4,323 (35)	4,055 (36)	23,235 (31)

* Not included in the Charlson Comorbidity Index score

TABLE 2*: CUMULATIVE INCIDENCE, CUMULATIVE RISK DIFFERENCE AND CUMULATIVE RISK RATIO FOR HOSPITAL-TREATED INFECTION AFTER HIP FRACTURE SURGERY, DENMARK, 2005-2016

Calendar Period of Diagnosis	No. Of Patients	No. Of Infections	Cumulative Incidence- % (95 % CI)	Cumulative Risk Difference-%** (95 % CI)	Cumulative Risk Ratio (RR) (95 % CI) Crude	Cumulative Risk Ratio (RR) (95 % CI) Adjusted**
0-15 Days of surgery						
2005-2006	12,453	1,043	8.4 (7.9-8.9)	Reference	Reference	Reference
2007-2008	13,236	1,134	8.6 (8.1-9.1)	0.0 (-0.6 -0.7)	1.02 (0.94-1.11)	1.01 (0.93-1.10)
2009-2010	12,724	1,296	10.2 (9.7-10.7)	1.6 (0.9- 2.3)	1.21 (1.12-1.31)	1.21 (1.11-1.31)
2011-2012	12,706	1,242	9.8 (9.3-10.3)	1.2 (0.5-1.9)	1.16 (1.08-1.26)	1.16 (1.07-1.25)
2013-2014	12,285	1,304	10.6 (10.1-11.2)	2.0 (1.3-2.7)	1.27 (1.17-1.36)	1.25 (1.16-1.36)
2015-2016	11,367	1,229	10.8 (10.2-11.4)	2.2 (1.4-3.0)	1.29 (1.19-1.40)	1.28 (1.18-1.39)
0-30 Days of surgery						
2005-2006	12,453	1,339	10,8 (10.2-11.3)	Reference	Reference	Reference
2007-2008	13,236	1,482	11.2 (10.7-11.7)	0.2 (-0.5-0.9)	1.04 (0.97-1.11)	1.03 (0.96-1.10)
2009-2010	12,724	1,679	13.2 (12.6-13.8)	2.2 (1.4-3.0)	1.22 (1.14-1.31)	1.21 (1.13-1.30)
2011-2012	12,706	1,690	13.3 (12.7-13.9)	2.3 (1.5-3.1)	1.23 (1.15-1.32)	1.22 (1.14-1.31)
2013-2014	12,285	1,771	14.4 (13.8-15.0)	3.3 (2.5-4.1)	1.34 (1.25-1.43)	1.32 (1.23-1.41)
2015-2016	11,367	1,631	14.3 (13.7-15.0)	3.3 (2.4-4.1)	1.33 (1.25-1.43)	1.32 (1.23-1.42)
0-90 Days of surgery						
2005-2006	12,453	1,841	14.8 (14.2-15.4)	Reference	Reference	Reference
2007-2008	13,236	2,112	16.0 (15.3-16.6)	0.8 (-0.0-1.7)	1.08 (1.02-1.14)	1.06 (1.00-1.12)
2009-2010	12,724	2,263	17.8 (17.1-18.5)	2.6 (1.7-3.5)	1.20 (1.13-1.27)	1.18 (1.12-1.26)
2011-2012	12,706	2,325	18.3 (17.6-19.0)	3.1 (2.2-4.0)	1.23 (1.17-1.30)	1.22 (1.15-1.29)
2013-2014	12,285	2,387	19.4 (18.7-20.1)	4.1 (3.2-5.1)	1.31 (1.24-1.38)	1.29 (1.22-1.37)
2015-2016	11,367	2,167	19.1 (18.3-19.8)	3.8 (2.8-4.7)	1.29 (1.22-1.36)	1.27 (1.20-1.35)
0-365 Days of surgery						
2005-2006	12,453	2,706	21.8 (21.0-22.4)	Reference	Reference	Reference
2007-2008	13,236	3,112	23.6(22.9-24.3)	1.4 (0.4-2.4)	1.08 (1.04-1.13)	1.07 (1.02-1.12)
2009-2010	12,724	3,212	25.2 (24.5-26.0)	3.0 (2.0-4.0)	1.16 (1.11-1.21)	1.14 (1.09-1.20)
2011-2012	12,706	3,287	25.9(25.1-26.6)	3.5 (2.5-4.6)	1.19 (1.14-1.24)	1.17 (1.12-1.23)
2013-2014	12,285	3,387	27.6 (26.8-28.3)	5.1 (4.0-6.2)	1.27 (1.21-1.32)	1.24 (1.19-1.30)
2015-2016	11,367	1,614 ***	27.2 (26.1-28.3) ***	4.8 (3.4-6.1) ***	1.25 (1.18-1.32) ***	1.23 (1.17-1.30) ***

* Considering death as competing risk, **Adjusted for age, sex and comorbidity (Charlson Comorbidity Index score), ***Only patients operated in 2015 (not 365 days follow-up time in 2016)

TABLE 3*: CUMULATIVE INCIDENCE AND CUMULATIVE RISK RATIO OF SPECIFIC INFECTIONS AFTER HIP FRACTURE SURGERY, DENMARK, 2005-2016

0-30 Days Risk Of Pneumonia and Urinary Tract Infection				
	PNEUMONIA		URINARY TRACT INFECTION (UTI)	
Calendar period of hip fracture diagnosis	Cumulative Incidence- % (95 % CI)	Cumulative Risk Ratio(RR)** (95 % CI)	Cumulative Incidence- % (95 % CI)	Cumulative Risk Ratio(RR)** (95 % CI)
2005-2006	3.7 (3.4-4.0)	Reference	5.7 (5.3-6.1)	Reference
2007-2008	4.2 (3.8-4.5)	1.10 (0.96-1.26)	5.5 (5.1-5.9)	0.94 (0.85-1.04)
2009-2010	5.3 (4.9-5.7)	1.37 (1.20-1.56)	6.0 (5.6-6.4)	1.05 (0.95-1.16)
2011-2012	5.5 (5.1-5.9)	1.42 (1.25-1.61)	5.8 (5.4-6.2)	1.01 (0.91-1.12)
2013-2014	6.5 (6.1-7.0)	1.70 (1.50-1.92)	6.0 (5.5-6.4)	1.02 (0.92-1.13)
2015-2016	6.6 (6.1-7.0)	1.70 (1.49-1.92)	5.7 (5.3-6.1)	0.99 (0.89-1.10)

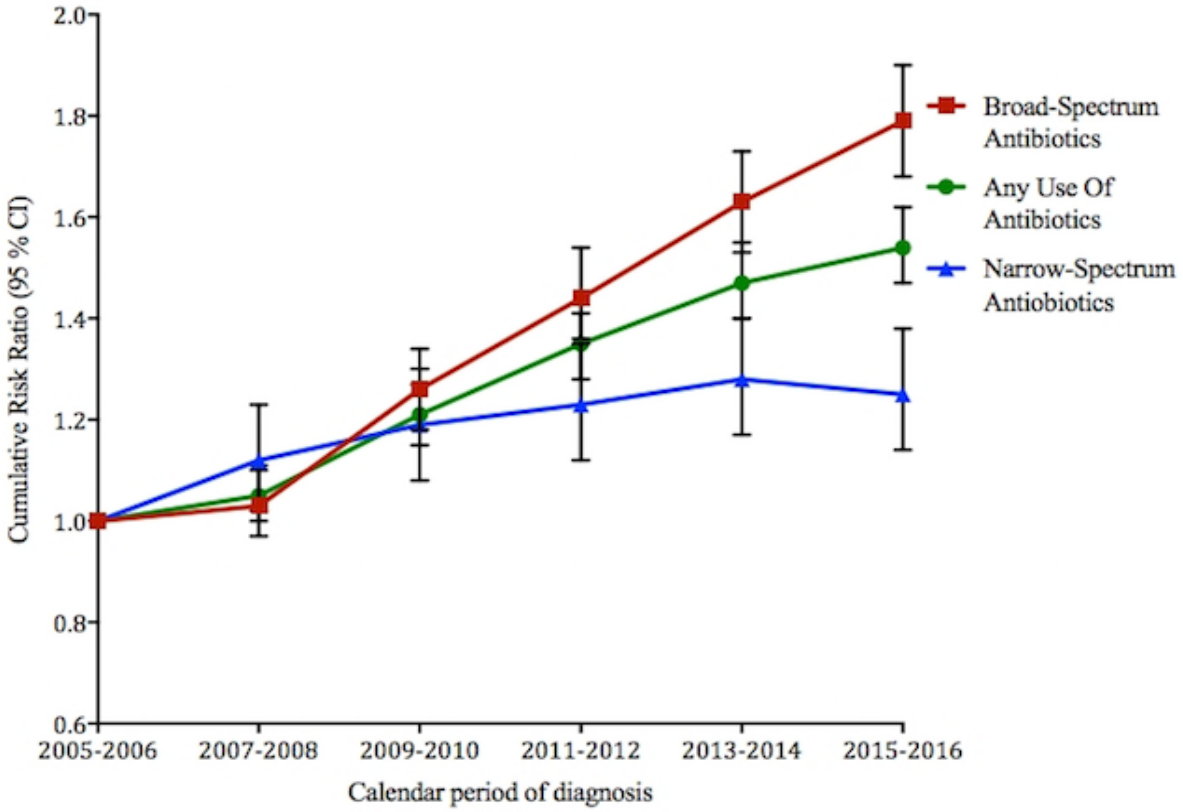
*Considering death as competing risk ** Adjusted for age, sex and comorbidity Charlson Comorbidity Index score)

TABLE 4*: CUMULATIVE INCIDENCE, CUMULATIVE RISK DIFFERENCE AND CUMULATIVE RISK RATIO FOR COMMUNITY-BASED ANTIBIOTIC PRESCIPRTIONS AFTER HIP FRACTURE SURGERY, DENMARK, 2005-2016

		0-15 Days of surgery					**0-30 Days of surgery**				
Calendar Period of Diagnosis	No. Of Patients	No. Of Prescriptions	Cumulative Incidence- % (95 % CI)	Cumulative Risk Difference-%** (95 % CI)	Cumulative Risk Ratio (RR) (95 % CI) Crude	Adjusted**	No. Of Prescriptions	Cumulative Incidence- % (95 % CI)	Cumulative Risk Difference-% ** (95 % CI)	Cumulative Risk Ratio (RR) (95 % CI) Crude	Adjusted**
2005-2006	12,453	1,047	8.4 (7.9-8.3)	Reference	Reference	Reference	2,179	17.5 (16.8-18.2)	Reference	Reference	Reference
2007-2008	13,236	1,244	9.4 (8.9-9.9)	0.8 (0.1-1.4)	1.11 (1.03-1.19)	1.10 (1.02-1.19)	2,472	18.7 (18.0-19.3)	0.8 (-0.0-1.7)	1.06 (1.01-1.12)	1.05 (1.00-1.11)
2009-2010	12,724	1,423	11.2 (10.6-11.7)	2.5 (1.8-3.3)	1.30 (1.21-1.40)	1.32 (1.23-1.43)	2,702	21.2 (20.5-22.0)	3.4 (2.5-4.4)	1.20 (1.14-1.26)	1.21 (1.15-1.27)
2011-2012	12,706	1,719	13.5 (12.9-14.1)	4.9 (4.2-5.7)	1.58 (1.47-1.69)	1.58 (1.47-1.70)	3,023	23.8 (23.1-24.5)	6.1 (5.1-7.1)	1.35 (1.28-1.41)	1.35 (1.28-1.41)
2013-2014	12,285	1,940	15.8 (15.1-16.4)	7.2 (6.4-8.1)	1.85 (1.73-1.98)	1.86 (1.73-2.00)	3,187	25.9 (25.2-26.7)	8.2 (7.2-9.3)	1.47 (1.40-1.54)	1.47 (1.40-1.55)
2015-2016	11,367	1,945	17.1 (16.4-17.8)	8.7 (7.9-9.6)	2.02 (1.89-2.16)	2.03 (1.89-2.18)	3,082	27.1 (26.3-27.9)	9.6 (8.5-10.7)	1.55 (1.47-1.62)	1.54 (1.47-1.62)
		0-90 Days of surgery					**0-365 Days of surgery**				
Calendar Period of Diagnosis	No. Of Patients	No. Of Prescriptions	Cumulative Incidence- % (95 % CI)	Cumulative Risk Difference-%** (95 % CI)	Cumulative Risk Ratio (RR) (95 % CI) Crude	Adjusted**	No. Of Prescriptions	Cumulative Incidence- % (95 % CI)	Cumulative Risk Difference-% ** (95 % CI)	Cumulative Risk Ratio (RR) (95 % CI) Crude	Adjusted**
2005-2006	12,453	4,067	32.7 (31.8-33.5)	Reference	Reference	Reference	6,656	53.4 (52.6-54.3)	Reference	Reference	Reference
2007-2008	13,236	4,484	33.9 (33.07-34.7)	0.7 (-0.0-1.8)	1.03 (1.00-1.07)	1.02 (0.99-1.06)	7,093	53.6 (52.7-54.4)	-0.2 (-1.4- 1.0)	1.00 (0.98-1.02)	0.99 (0.97-1.02)
2009-2010	12,724	4,558	35.8 (35.0-36.7)	2.3 (1.6-3.9)	1.09 (1.06-1.13)	1.09 (1.05-1.12)	6,961	54.7 (53.8-55.6)	1.0 (-0.2-2.3)	1.02 (1.00-1.05)	1.02 (1.00-1.04)
2011-2012	12,706	4,862	38.3 (37.4-39.1)	5.3 (4.2-6.5)	1.17 (1.19-1.21)	1.16 (1.12-1.20)	7,085	55.8 (54.9-56.6)	2.3 (1.0-3.5)	1.04 (1.02-1.07)	1.04 (1.02-1.07)
2013-2014	12,285	4,966	40.4 (39.3-41.2)	7.5 (6.3-8.7)	1.23 (1.19-1.28)	1.23 (1.19-1.27)	7,079	57.6 (56.7-58.5)	4.1 (2.8-5.3)	1.08 (1.05-1.10)	1.08 (1.05-1.10)
2015-2016	11,367	4,576	40.4 (39.2-41.7) ***	7.5 (6.0-9.0) ***	1.23 (1.19-1.28) ***	1.23 (1.18-1.28) ***	3409 ***	56.5 (52.8-54.7) ***	3.1 (1.5-4.6) ***	1.06 (1.03-1.09) ***	1.06 (1.03-1.09) ***

* Considering death as competing risk, **Adjusted for age, sex and comorbidity (Charlson Comorbidity Index score), ***Only patients operated in 2015 (not 365 days follow-up time in 2016

FIGURE 1: Adjusted* cumulative risk ratio of community-based antibiotic prescriptions within 30 days of hip fracture surgery for periods 2007-2008, 2009-2010, 2011-2012, 2013-2014 and 2015-2016 compared with 2005-2006 as reference



*Adjusted for age, sex and comorbidity (Charlson Comorbidity Index Score)

FIGURE 2A: 30-Days Cumulative incidence of any hospital-treated infection in hip fracture patients and general population, 2005-2016

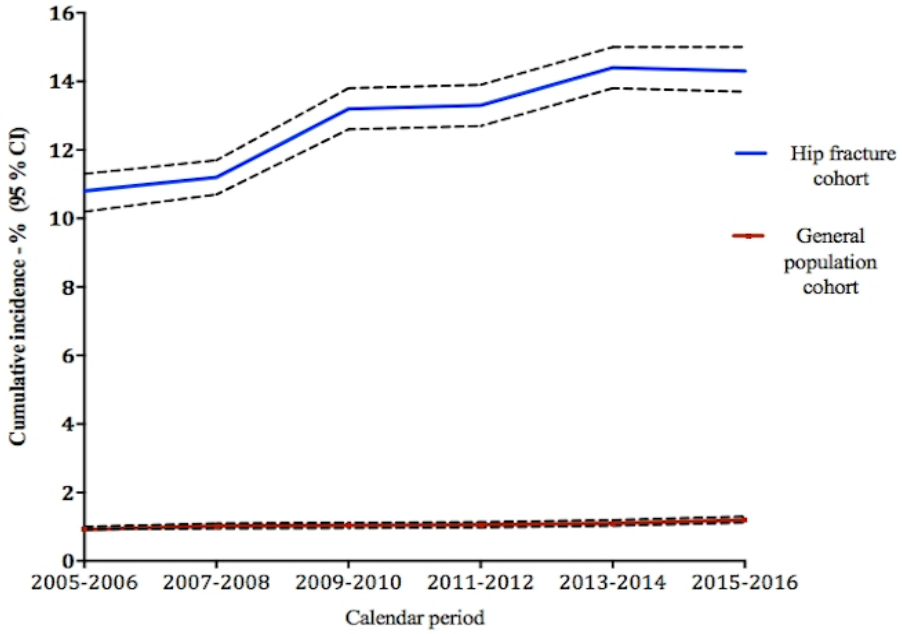


FIGURE 2B: 30-Days Cumulative incidence of any community-based antibiotic prescriptions in hip fracture patients and general population, 2005-2016

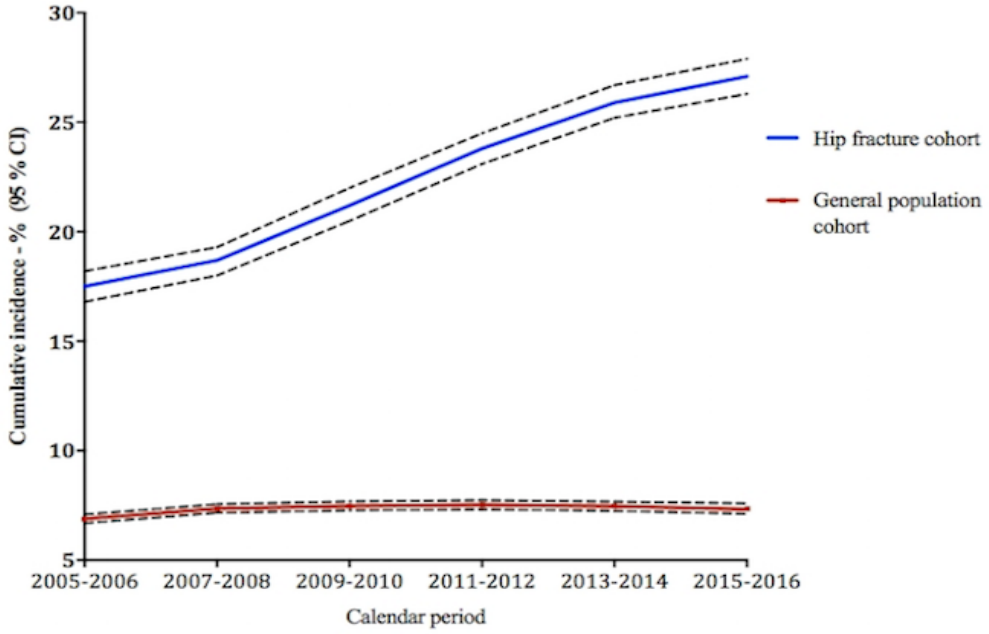
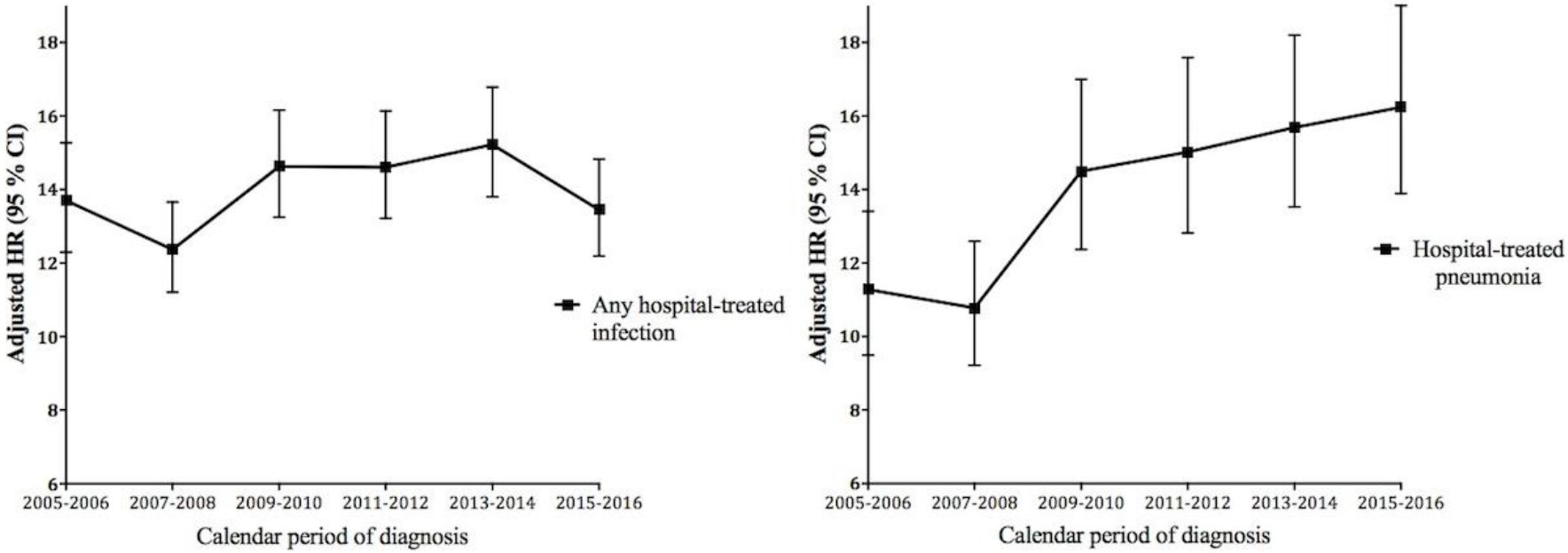
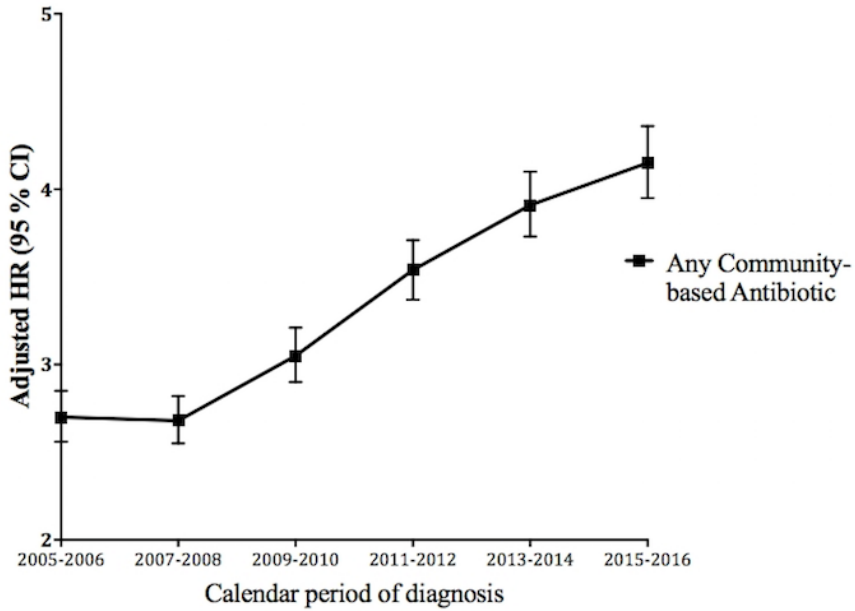


FIGURE 3A: Time trends of 30-Days adjusted hazard ratio (aHR)* of hospital-treated infections in hip fracture patients, compared to a matched cohort from the general population, 2005-2016



*Adjusted for comorbidity (Charlson Comorbidity Index Score)

FIGURE 3B: Time trends of 30-Days adjusted hazard ratio (aHR)* of community-based antibiotics in hip fracture patients, compared to a matched cohort from the general population, 2005-2016



*Adjusted for comorbidity (Charlson Comorbidity Index Score)

Supplemental Tables and Figures

SUPPLEMENTAL TABLE 1A: 0-30 Days Incidence Rates of hospital-treated infections after hip fracture surgery, stratified by sex and comorbidity level (CCI Score)

0-30 Days Incidence rate pr. 1000 person years						
Calendar Period of Diagnosis	Overall Incidence Rate (95 % CI)	Incidence Rate (95 %CI) Stratified by sex		Incidence Rate (95 %CI) Stratified by CCI		
		Female	Male	Low (0)	Medium(1-2)	High(3+)
2005-2006	4.12 (3.91-4.35)	3.86 (2.61-4.11)	4.92 (4.46-5.42)	3.30 (3.02-3.61)	4.43 (4.09-4.81)	5.72 (5.10-6.42)
2007-2008	4.29 (4.08-4.51)	3.87 (3.63-4.11)	5.50 (5.03-6.00)	3.49 (3.20-3.81)	4.56 (4.21-4.93)	5.65 (5.08-6.29)
2009-2010	5.15 (4.91 – 5.40)	4.83 (4.56-5.12)	6.00 (5.51-6.53)	3.98 (3.66-4.32)	5.68 (5.29-6.10)	6.73 (6.09-7.43)
2011-2012	5.20 (4.96-5.45)	4.79 (4.52-5.08)	6.22 (5.73-6.75)	3.90 (3.58-4.25)	5.60 (5.21-6.02)	7.21 (6.56-7.92)
2013-2014	5.62 (5.36-5.89)	5.10 (4.81-5.40)	6.94 (6.41-7.51)	4.41 (4.06-4.79)	5.92 (5.51-6.36)	7.40 (6.76-8.10)
2015-2016	5.57 (5.30-5.85)	5.08 (4.78-5.40)	6.73 (6.20-7.30)	4.23 (3.87-4.62)	5.75 (5.36-6.21)	7.84 (7.16-8.58)

SUPPLEMENTAL TABLE 1B: 0-30 Days Incidence Rates of hospital-treated infections after hip fracture surgery, stratified by age

0-30 Days Incidence rate pr. 1000 person years						
Calendar Period of Diagnosis	Incidence Rate (95 %CI) Stratified by Age					
	65-69 years	70-75 years	75-79 years	80-84 years	85-89 years	>=90 Years
2005-2006	2.49 (1.93-3.20)	3.3**4** (2.79-3.99)	3.60 (3.15-4.12)	4.71 (4.26-5.21)	4.79 (4.30-5.33)	4.24 (3.73-4.83)
2007-2008	2.80 (2.23-3.54)	3.30 (2.77-3.94)	3.96 (3.48-4.51)	4.17 (3.75-4.63)	5.15 (4.68-5.67)	4.85 (4.32-5.44)
2009-2010	3.11 (2.52-3.85)	3.97 (3.39-4.66)	4.81 (4.26-5.44)	5.30 (4.80-5.85)	6.04 (5.52-6.61)	5.83 (5.23-6.50)
2011-2012	3.48 (2.88-4.20)	4.12 (3.52-4.82)	4.47 (3.95-5.06)	5.30 (4.78-5.88)	5.96 (5.43-6.53)	6.46 (5.83-7.16)
2013-2014	3.66 (3.04-4.41)	4.54 (3.91-5.27)	4.71 (5.16-5.34)	5.97 (5.41-6.60)	6.49 (5.93-7.11)	6.79 (6.07-7.93)
2015-2016	3.60 (2.97-4.37)	4.52 (3.89-5.24)	4.58 (4.01-5.23)	6.13 (5.53-6.79)	6.87 (6.25-7.55)	6.10 (5.49-6.78)

SUPPLEMENTAL TABLE 2A: 0-30 Days Cumulative Risk Ratio of hospital-treated infections after hip fracture surgery, stratified by sex and comorbidity level (CCI score)

0-30 Days Cumulative Risk Ratio*						
Calendar Period of Diagnosis	Overall Risk Ratio (95 % CI)	Risk Ratio (95 %CI) Stratified by sex		Risk Ratio (95 %CI) Stratified by CCI		
		Female	Male	Low (0)	Medium(1-2)	High(3+)
2005-2006	Reference	Reference	Reference	Reference	Reference	Reference
2007-2008	1.03 (0.96-1.10)	0.98 (0.90-1.06)	1.13 (0.99-1.29)	1.05 (0.94-1.17)	1.04 (0.93-1.16)	1.00 (0.85-1.18)
2009-2010	1.21 (1.13-1.30)	1.20 (1.11-1.30)	1.22 (1.07-1.39)	1.18 (1.05-1.31)	1.27 (1.14-1.41)	1.17 (1.00-1.37)
2011-2012	1.22 (1.14-1.31)	1.20 (1.10-1.30)	1.26 (1.11-1.44)	1.17 (1.05-1.31)	1.26 (1.13-1.40)	1.24 (1.06-1.44)
2013-2014	1.32 (1.23-1.41)	1.26 (1.17-1.37)	1.42 (1.25-1.61)	1.32 (1.18-1.47)	1.33 (1.20-1.47)	1.32 (1.14-1.54)
2015-2016	1.32 (1.23-1.42)	1.28 (1.18-1.39)	1.42 (1.25-1.61)	1.25 (1.12-1.41)	1.32 (1.18-1.47)	1.42 (1.21-1.63)

*Adjusted for age, sex and CCI-score (without the stratifying variable)

SUPPLEMENTAL TABLE 2B: 0-30 Days Cumulative Risk Ratio of hospital-treated infections after hip fracture surgery, stratified by age

0-30 Days Cumulative Risk Ratio*						
Calendar Period of Diagnosis	Risk Ratio (95 %CI) Stratified by Age					
	65-69 years	70-75 years	75-79 years	80-84 years	85-89 years	≥90 Years
2005-2006	Reference	Reference	Reference	Reference	Reference	Reference
2007-2008	1.12 (0.82-1.52)	0.97 (0.78-1.22)	1.11 (0.93-1.31)	0.89 (0.78-1.02)	1.09 (0.95-1.25)	1.14 (0.95-1.36)
2009-2010	1.18 (0.88-1.59)	1.13 (0.92-1.41)	1.27 (1.07-1.50)	1.07 (0.94-1.23)	1.28 (1.12-1.47)	1.36 (1.14-1.62)
2011-2012	1.35 (1.02-1.79)	1.21 (0.98-1.49)	1.22 (1.03-1.44)	1.07 (0.93-1.22)	1.22 (1.06-1.40)	1.50 (1.26-1.78)
2013-2014	1.40 (1.06-1.85)	1.25 (1.02-1.54)	1.28 (1.08-1.51)	1.20 (1.05-1.37)	1.34 (1.17-1.54)	1.58 (1.33-1.87)
2015-2016	1.24 (0.92-1.66)	1.30 (1.05-1.61)	1.24 (1.04-1.48)	1.25 (1.09-1.43)	1.45 (1.16-1.67)	1.44 (1.21-1.72)

*Adjusted for sex and comorbidity (Charlson Comorbidity Index Score)

SUPPLEMENTAL TABLE 3: 30 Days time trends of infection among hip fracture patients compared to the matched general population cohort, Denmark 2005-2016

30 Days time trends of infection among hip fracture patients compared to the matched general population cohort, Denmark 2005-2016			
Calendar period of hip fracture diagnosis	Any community-based antibiotic aHR* (95 % CI)	Any Hospital-treated infection aHR*(95 % CI)	Hospital-treated pneumonia aHR*(95 % CI)
2005-2006	2.70 (2.56-2.85)	13.70 (12.30-15.27)	11.28 (9.49-13.41)
2007-2008	2.68 (2.55-2.82)	12.37 (11.21-13.66)	10.78 (9.22-12.59)
2009-2010	3.05 (2.90-3.21)	14.63 (13.25-16.16)	14.50 (12.37-17.00)
2011-2012	3.54 (3.37-3.71)	14.61 (13.22-16.14)	15.02 (12.82-17.59)
2013-2014	3.91 (3.73-4.10)	15.22 (13.80-16.79)	15.69 (13.53-18.20)
2015-2016	4.15 (3.95-4.36)	13.45 (12.19-14.83)	16.24 (13.89-19.00)

SUPPLEMENTAL TABLE 4: 30 Days time trends of infection among hip fracture patients compared to the matched general population cohort, using 2005-2006 as reference (Interaction Model) Denmark 2005-2016

30 days Time trends of infections among hip fracture patients compared to the matched general population, using 200-2006 as reference (interaction model), Denmark 2005-2016			
Calendar period of hip fracture diagnosis	Any community-based antibiotic aHR* (95 % CI)	Any Hospital-treated infection aHR*(95 % CI)	Hospital-treated pneumonia aHR*(95 % CI)
2005-2006	Reference	Reference	Reference
2007-2008	0.99 (0.92-1.07)	0.91 (0.78-1.05)	0.95 (0.75-1.20)
2009-2010	1.13 (1.05-1.21)	1.07 (0.92-1.23)	1.25 (0.99-1.57)
2011-2012	1.31 (1.22-1.41)	1.05 (0.91-1.22)	1.29 (1.02-1.62)
2013-2014	1.45 (1.35-1.55)	1.12 (0.97-1.29)	1.39 (1.11-1.75)
2015-2016	1.54 (1.43-1.65)	0.98 (0.85-1.13)	1.43 (1.13-1.80)

*Adjusted for comorbidity (Charlson Comorbidity Index Score)

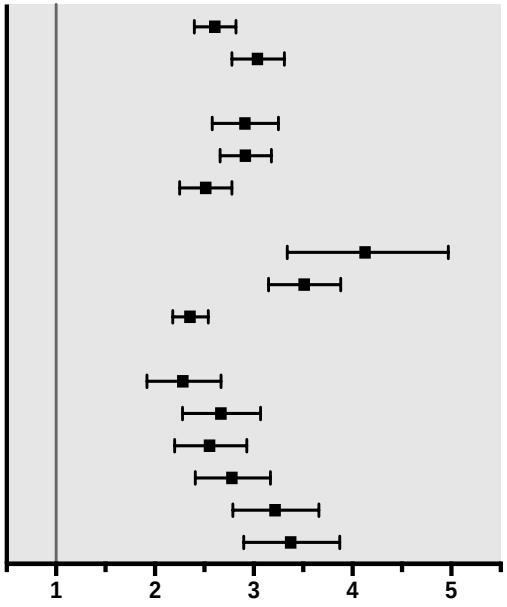
SUPPLEMENTAL TABLE 5: Mortality Rate and Hazard Ratio (HR) following hospital-treated infection* within 30 days after hip fracture surgery, Denmark 2005-2016

	30 Days Mortality					
Postoperative infection within 30 days after surgery	No. Of Patients	No. of Deaths	PY**	Mortality Rate pr. 1000 PY (95 % CI)	Crude HR (95 % CI)	Adjusted HR (95 % CI)***
Any infection						
Yes	9,592	1443	171156	8.43 (8.00-8.88)	3.20 (3.02-3.40)	2.72 (2.56-2.88)
No	74,771	6451	1928987	3.34 (3.26-3.43)	Reference	Reference
Pneumonia						
Yes	3,938	969	65351	14.83 (13.92-15.79)	5.41 (5.05-5.79)	4.18 (3.91-4.48)
No	74,771	6925	2034792	3.40 (3.32-3.48)	Reference	Reference
Sepsis						
Yes	761	300	9052	33.14 (29.60-37.11)	11.29 (10.05-12.68)	8.86 (7.88-9.95)
No	74,771	7594	2091091	3.63 (3.56-3.71)	Reference	Reference
Urinary tract infections	4,328	213	91483	2.44 (2.13-2.79)	0.76 (0.67-0.88)	0.69 (0.60-0.79)
Yes	74,771	7681	2008660	3.82 (3.73-3.90)	Reference	Reference
No						
Reoperation due to Infection						
Yes	261	19	2561	7.50 (4.78-11.76)	3.00 (1.91-4.72)	2.95 (1.88-4.64)
No	74,771	7875	2097582	3.75 (3.67-3.84)	Reference	Reference

* Infection was treated as time-varying covariate. **Person Years PY *** Hazard ratios were adjusted for sex, age, comorbidity level, alcohol-related diseases, marital status and medication use (antibiotics, corticosteroid, anticoagulants and SSRI).

SUPPLEMENTAL FIGURE 1: Association between any hospital-treated infection * and mortality 0-30 days after hip fracture surgery, stratified by sex, Charlson Comorbidity Index Score, age and calendar period, Denmark 2005-2016

	Mortality Rate*		Adjusted HR**
	With infection	Without infection	
Female	6.46 (6.02-6.94)	2.74 (2.66-2.83)	2.60 (2.40-2.82)
Male	12.82 (11.89-13.82)	4.94 (4.75-5.13)	3.03 (2.78-3.31)
CCI Low	6.30 (5.69-6.99)	2.26 (2.16-2.34)	2.90 (2.58-3.25)
CCI Medium	8.77 (8.11-9.47)	3.54 (3.41-3.68)	2.91 (2.66-3.18)
CCI High	10.85 (9.88-11.91)	5.41 (5.17-5.66)	2.51 (2.25-2.78)
Age 65-74	4.98 (4.20-5.90)	1.33 (1.22-1.45)	4.07 (3.34-4.97)
Age 75-84	7.26 (6.64-7.94)	2.37 (2.26-2.48)	3.50 (3.15-3.88)
Age >=85	10.56 (9.86-11.30)	5.30 (5.14-5.46)	2.35 (2.18-2.54)
2005-2006	6.80 (5.86-7.90)	3.46 (3.26-3.67)	2.26 (1.92-2.67)
2007-2008	8.17 (7.16-9.32)	3.29 (3.10-3.49)	2.65 (2.28-3.07)
2009-2010	7.75 (6.82-8.79)	3.43 (3.24-3.64)	2.53 (2.20-2.93)
2011-2012	8.98 (7.96-10.13)	3.64 (3.44-3.85)	2.76 (2.41-3.17)
2013-2014	9.29 (8.27-10.43)	3.20 (3.01-3.41)	3.20 (2.79-3.66)
2015-2016	9.34 (8.31-10.58)	3.02 (2.82-3.22)	3.35 (2.90-3.87)



*Infection was treated as time-varying covariate. [a]: Per 1000 person-years (with corresponding 95 % CI) [b]: Hazard ratios were adjusted for sex, age, and comorbidity level, without the stratifying variable (with corresponding 95 % CI)

INTERNATIONAL CLASSIFICATION OF DISEASES, TENTH REVISION (ICD-10) CODES USED TO IDENTFY HOSPITAL-TREATED INFECTION:

Codes used to identify any hospital-treated infection:

Infections	ICD-10 diagnosis codes
Any hospital-treated (inpatient or outpatient) infection	A20-A38, A42-A44, A48-A49, A65-A79, A3, A49.9, A39.4, A40-A41, B37.7, A32.7, A54.8G, A02.1, A22.7, A26.7, A42.7, A28.2B, A06.5, A54.1, B43, D73.3, E06.0A, E23.6A, E32.1, G06, G07, H00.0A, H05.0A, H44.0A, H60.0, J34.0A, J36, J38.3D, J38.7G, J39.0, J39.1, J39.8A, J85.1, J85.2, J85.3, K04.6, K04.7, K11.3, K12.2, K13.0A, K14.0A, K20.9A, K35.3A, K35.3B, K57.0, K57.2, K57.4, K57.8, K61, K63.0, K65.0, K75.0, K81.0A, K85.8A, L02, L05.0, L05.9, M60.8A, M86.8A, M86.9A, N15.1, N34.0, N41.2, N45.0, N48.2, N49.2A, N61.9A, N61.9B, N70.0A, N70.0B, N71.0A, N73.0A, N73.0B, N73.2A, N73.2B, N73.3A, N73.5A, N73.8A, N73.8C, N75.1, N76.4, N76.8A, Except: A54.1B, B43.0, B43.8, B43.9, K57.0B, K57.0C, K57.2B, K57.2C, K57.4A, K65.0M, K65.0N, K65.0O, K65.0P, A46, H01.0, H03, H60.0, H60.1, H60.2, H60.3, H62, K12.2, K13.0, K61, M72.6, L01, L08, L03, J34.0, L00, L02, L04, L05, L06, L07, L30.3, L73.8, H00, H01.0, H03.0, H03.1, H04.3, H05.0, H06.1, H10, H13.0, H13.1, H15.0, H19.1, H19.2, H22.0, H32.0, H44.0, H44.1, H60, H61.0, H62.0, H62.1, H62.2, H62.3, H65, H66, H67.0, H67.1, H68, H70, H73.0, H75.0, H83.0, H94.0, Except: H60.4, H60.4A, H605, H60.5B, H60.8, H608.A, H65.2, H65.3, H65.4, H65.4C, H66.1, H66.2, H66.3, H68.1, H70.1, H70.8, G00-07, A80-A89, G00, G01, G02, G03, A32.1, A39.0, A17.0, A20.3, A87, A54.8D, A02.2C, B37.5, B00.3, B01.0, B02.1, B05.1, B26.1, B38.4, A00-A09, K35, K37, K57.0, K57.2, K57.4, K57.8, K61, K63.0, K65.0, K65.9, K67, K75.0, K75.1, K80.0, K80.3, K80.4, K81.0, K81.9, K83.0, K85.9, I00-I02, I30.1, I32.0, I33, I38, I40.0, I39.8, B37.6, J00-J06, J36, J39.0, J39.1, J12-J18, J20-J22, J44.0, J85.1, J86, J20-J22, J34.0, J35.0, J38.3C, J38.3D, J38.7B, J38.7F, J38.7G, Except: J34.0E, J34.0F, J34.0G, J34.0H, N10, N11, N12, N15.1, N15.9, N30, N33.0, N34, N39.0, N08.0, N13.6, N16.0, N28.8D, N28.8E, N28.8F, N29.0, N29.1, Except: N30.1, N30.2, N30.4, A50-A64, N41, N45, N48.1, N48.2, N49, N51.1, N51.2, N70-77, O23, O26.4, O41.1, O74.0, O75.3, O85, O86, 088.3, O91, O98, M00, M01, M86, M63.0, M63.2, T80.2, T81.4, T82.6, T82.7, T83.5, T83.6, T84.5, T84.6, T84.7, T85.7, T88.0, T89.9, B90-B99, K04.0, K05.2

Codes for specific hospital-treated infections:

Infections	ICD-10 diagnosis codes
Pneumonia	J12-J18
Urinary tract infections	N10, N11, N12, N15.1, N15.9, N30, N33.0, N34, N39.0, N08.0, N13.6, N16.0, N28.8D, N28.8E, N28.8F, N29.0, N29.1, Except: N30.1, N30.2, N30.4

ANATOMICAL THERAPEUTICAL CHEMICAL CLASSIFICATION SYSTEM (ATC) CODES TO IDENTIFY COMMUNITY-BASED ANTIBIOTIC PRESCRIPTIONS:

Narrow spectrum antibiotics	ATC-code
Beta-lactamase sensitive penicillins, Beta-lactamase resistant penicillins, first-generation cephalosporins,	J01CE, J01CF, J01DB,

Broad-spectrum antibiotics	ATC-code
Cephalosporins (second generation, third-generation, fourth-generation) Carbapenem, Other cephalosporins and penems, Combinations of penicillins, including beta-lactamase inhibitors, penicillins with extended spectrum, macrolides, licosamides and streptogramis, trimethoprim and sulphonamides, Fluoroquinolones, Tetracyclines	J01DC, JO1DD J01DE, J01DH, J01DI, J01CR, J01CA, J01F. J01E, J01MA ,J01AA

CODES TO IDENTYFY CO-VARIATES:

Comorbidites included in Charlton comorbidity index	
Disease	ICD-10 diagnosis codes
Myocardial infarction	I21;I22;I23
Congestive heart failure	I50; I11.0; I13.0; I13.2
Peripheral vascular disease	I70; I71; I72; I73; I74; I77
Cerebrovascular disease	I60-I69; G45; G46
Dementia	F00-F03; F05.1; G30
Chronic pulmonary disease	J40-J47; J60-J67; J68.4; J70.1; J70.3; J84.1; J92.0; J96.1; J98.2; J98.3
Connective tissue disease	M05; M06; M08; M09;M30;M31; M32; M33; M34; M35; M36; D86
Ulcer disease	K22.1; K25-K28
Mild liver disease	B18; K70.0-K70.3; K70.9; K71; K73; K74; K76.0
Diabetes type1 Diabetes type2	E10.0, E10.1; E10.9 E11.0; E11.1; E11.9
Hemiplegia	G81; G82
Moderate to severe renal disease	I12; I13; N00-N05; N07; N11; N14; N17-N19; Q61
Diabetes with end organ damage type1 type2	E10.2-E10.8 E11.2-E11.8
Any tumor	C00-C75
Leukemia	C91-C95
Lymphoma	C81-C85; C88; C90; C96
Moderate to severe liver disease	B15.0; B16.0; B16.2; B19.0; K70.4; K72; K76.6; I85
Metastatic solid tumor	C76-C80
AIDS	B21-B24

Alcoholism-related disorder

Disease	ICD-10
Alcohol related disorder	F10
Alcohol induced chronic pancreatitis	K86.0
Finding of alcohol in blood	R78.0
Toxic effect of alcohol	T51
Alcoholic gastritis without bleeding	K29.2,
Alcoholic polyneuropathy	G62.1
Alcoholic myopathy	G72.1
Degeneration of nervous system due to alcohol	G31.2
Alcoholic cardiomyopathy	I42.6

Systemically absorbed glucocorticoids

ATC-codes	H02BX

Statin use

ATC-codes:	C10AA01, C10AA02, C10AA03 C10AA04, C10AA05, C10AA06,

Anti-osteoporosis medicine

ATC-codes:	M05BA01, B05BB01, M05BA02, M05BA03, M05BA04, M05BB03, M05BB05, M05BA06, M05BA07, M05BB02, M05BB04, M05BX04, M05BX03, G03XC01, H05AA02

CODES USED TO IDENTFY HIP FRACTURE SURGERY

Codes used to identify type of hip fracture:	
ICD-10 diagnosis code	Description
S72.0	Fracture of the femoral neck
S72.1	Pertrochantary fracture
S72.2	Subtrochantary fracture

Codes used to identify fracture type:

Additional codes	Description
ZDS01	Fracture position – shifted
ZDS02	Fracture position – non-shifted
ZDS03	Fracture position – unknown

Codes used to identify type of surgery:	
Operation codes	Description
KNFB.0 - 99	Primary insertion of joint prosthesis in hip joint
KNFJ.4 - 9	Fracture treatments in femur (including osteosynthesis)
Additional codes	
TUL1	Right side
TUL2	Left side

Reports/PhD theses from Department of Clinical Epidemiology

1. Ane Marie Thulstrup: Mortality, infections and operative risk in patients with liver cirrhosis in Denmark. Clinical epidemiological studies. PhD thesis. *2000*.

2. Nana Thrane: Prescription of systemic antibiotics for Danish children. PhD thesis. *2000*.

3. Charlotte Søndergaard. Follow-up studies of prenatal, perinatal and postnatal risk factors in infantile colic. PhD thesis. *2001*.

4. Charlotte Olesen: Use of the North Jutland Prescription Database in epidemiological studies of drug use and drug safety during pregnancy. PhD thesis. *2001*.

5. Yuan Wei: The impact of fetal growth on the subsequent risk of infectious disease and asthma in childhood. PhD thesis. *2001*.

6. Gitte Pedersen. Bacteremia: treatment and prognosis. PhD thesis. *2001*.

7. Henrik Gregersen: The prognosis of Danish patients with monoclonal gammopathy of undertermined significance: register-based studies. PhD thesis. *2002*.

8. Bente Nørgård: Colitis ulcerosa, coeliaki og graviditet; en oversigt med speciel reference til forløb og sikkerhed af medicinsk behandling. PhD thesis. *2002*.

9. Søren Paaske Johnsen: Risk factors for stroke with special reference to diet, Chlamydia pneumoniae, infection, and use of non-steroidal anti-inflammatory drugs. PhD thesis. *2002*.

10. Elise Snitker Jensen: Seasonal variation of meningococcal disease and factors associated with its outcome. PhD thesis. *2003*.

11. Andrea Floyd: Drug-associated acute pancreatitis. Clinical epidemiological studies of selected drugs. PhD thesis. *2004*.

12. Pia Wogelius: Aspects of dental health in children with asthma. Epidemiological studies of dental anxiety and caries among children in North Jutland County, Denmark. PhD thesis. *2004*.

13. Kort-og langtidsoverlevelse efter indlæggelse for udvalgte kræftsygdomme i Nordjyllands, Viborg og Århus amter 1985-2003. *2004*.

14. Reimar W. Thomsen: Diabetes mellitus and community-acquired bacteremia: risk and prognosis. PhD thesis. *2004*.

15. Kronisk obstruktiv lungesygdom i Nordjyllands, Viborg og Århus amter 1994-2004. Forekomst og prognose. Et pilotprojekt. *2005*.

16. Lungebetændelse i Nordjyllands, Viborg og Århus amter 1994-2004. Forekomst og prognose. Et pilotprojekt. *2005*.

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18. Kort- og langtidsoverlevelse efter indlæggelse for udvalgte kræftsygdomme i Nordjyllands, Viborg, Ringkøbing og Århus amter 1995-2005. *2005*.

19. Mette Nørgaard: Haematological malignancies: Risk and prognosis. PhD thesis. *2006*.

20. Alma Becic Pedersen: Studies based on the Danish Hip Arthroplastry Registry. PhD thesis. *2006*.

    Særtryk: Klinisk Epidemiologisk Afdeling - De første 5 år. *2006*.

21. Blindtarmsbetændelse i Vejle, Ringkjøbing, Viborg, Nordjyllands og Århus Amter. *2006*.

22. Andre sygdommes betydning for overlevelse efter indlæggelse for seks kræftsygdomme i Nordjyllands, Viborg, Ringkjøbing og Århus amter 1995-2005. *2006*.

23. Ambulante besøg og indlæggelser for udvalgte kroniske sygdomme på somatiske hospitaler i Århus, Ringkjøbing, Viborg, og Nordjyllands amter. *2006*.

24. Ellen M Mikkelsen: Impact of genetic counseling for hereditary breast and ovarian cancer disposition on psychosocial outcomes and risk perception: A population-based follow-up study. PhD thesis. *2006*.

25. Forbruget af lægemidler mod kroniske sygdomme i Århus, Viborg og Nordjyllands amter 2004-2005. *2006*.

26. Tilbagelægning af kolostomi og ileostomi i Vejle, Ringkjøbing, Viborg, Nordjyllands og Århus Amter. *2006*.

27. Rune Erichsen: Time trend in incidence and prognosis of primary liver cancer and liver cancer of unknown origin in a Danish region, 1985-2004. Research year report. *2007*.

28. Vivian Langagergaard: Birth outcome in Danish women with breast cancer, cutaneous malignant melanoma, and Hodgkin's disease. PhD thesis. *2007*.

29. Cynthia de Luise: The relationship between chronic obstructive pulmonary disease, comorbidity and mortality following hip fracture. PhD thesis. *2007*.

30. Kirstine Kobberøe Søgaard: Risk of venous thromboembolism in patients with liver disease: A nationwide population-based case-control study. Research year report. *2007*.

31. Kort- og langtidsoverlevelse efter indlæggelse for udvalgte kræftsygdomme i Region Midtjylland og Region Nordjylland 1995-2006. *2007*.

32. Mette Skytte Tetsche: Prognosis for ovarian cancer in Denmark 1980-2005: Studies of use of hospital discharge data to monitor and study prognosis and impact of comorbidity and venous thromboembolism on survival. PhD thesis. *2007*.

33. Estrid Muff Munk: Clinical epidemiological studies in patients with unexplained chest and/or epigastric pain. PhD thesis. *2007*.

34. Sygehuskontakter og lægemiddelforbrug for udvalgte kroniske sygdomme i Region Nordjylland. *2007*.

35. Vera Ehrenstein: Association of Apgar score and postterm delivery with neurologic morbidity: Cohort studies using data from Danish population registries. PhD thesis. *2007*.

36. Annette Østergaard Jensen: Chronic diseases and non-melanoma skin cancer. The impact on risk and prognosis. PhD thesis. *2008*.

37. Use of medical databases in clinical epidemiology. *2008*.

38. Majken Karoline Jensen: Genetic variation related to high-density lipoprotein metabolism and risk of coronary heart disease. PhD thesis. *2008*.

39. Blodprop i hjertet - forekomst og prognose. En undersøgelse af førstegangsindlæggelser i Region Nordjylland og Region Midtjylland. *2008*.

40. Asbestose og kræft i lungehinderne. Danmark 1977-2005. *2008*.

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44. Lars Pedersen: Use of Danish health registries to study drug-induced birth defects – A review with special reference to methodological issues and maternal use of non-steroidal anti-inflammatory drugs and Loratadine. PhD thesis. *2009*.

45. Steffen Christensen: Prognosis of Danish patients in intensive care. Clinical epidemiological studies on the impact of preadmission cardiovascular drug use on mortality. PhD thesis. *2009*.

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47. Jette Bromman Kornum: Obesity, diabetes and hospitalization with pneumonia. PhD thesis. *2009*.

48. Theis Thilemann: Medication use and risk of revision after primary total hip arthroplasty. PhD thesis. *2009*.

49. Operativ fjernelse af galdeblæren. Region Midtjylland & Region Nordjylland. 1998-2008. *2009*.

50. Mette Søgaard: Diagnosis and prognosis of patients with community-acquired bacteremia. PhD thesis. *2009*.

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55. Kaare Haurvig Palnum: Implementation of clinical guidelines regarding acute treatment and secondary medical prophylaxis among patients with acute stroke in Denmark. PhD thesis. *2010*.

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62. Anna Lei Lamberg: The use of new and existing data sources in non-melanoma skin cancer research. PhD thesis. *2011*.

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64. Martin Majlund Mikkelsen: Risk prediction and prognosis following cardiac surgery: the EuroSCORE and new potential prognostic factors. PhD thesis. *2011*.

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70. Alkoholisk leversygdom i Region Midtjylland og Region Nordjylland. 2007-2011. *2012*.

71. Lars Jakobsen: Treatment and prognosis after the implementation of primary percutaneous coronary intervention as the standard treatment for ST-elevation myocardial infarction. PhD thesis. *2012*.

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73. Rune Erichsen: Prognosis after Colorectal Cancer - A review of the specific impact of comorbidity, interval cancer, and colonic stent treatment. PhD thesis. *2013*.

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76. Malene Kærslund Hansen: Post-operative acute kidney injury and five-year risk of death, myocardial infarction, and stroke among elective cardiac surgical patients: A cohort study. Research year report. *2013*.

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90. Marie Dam Lauridsen: Impact of dialysis-requiring acute kidney injury on 5-year mortality after myocardial infarction-related cardiogenic shock - A population-based nationwide cohort study. Research year report. *2014*.

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103. Anne Høy Seemann Vestergaard: Geographical Variation in Use of Intensive Care in Denmark: A Nationwide Study. Research year report. *2015*.

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105. Kathrine Dyhr Lycke: Preadmission use of antidepressants and quality of care, intensive care admission and mortality of colorectal cancer surgery – a nationwide population-based cohort study. Research year report. *2015*.

106. Louise Bill: Hyponatremia in acute internal medicine patients: prevalence and prognosis. PhD thesis. *2015*.

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120. Søren Christiansen: Timing of renal replacement therapy and long-term risk of chronic kidney disease and death in intensive care patients with acute kidney injury. Research year report. *2017*.

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