Selective Serotonin Reuptake Inhibitor Use and Mortality, Postoperative Complications, and Quality of Care in Hip Fracture Patients: A population-based cohort study

Research year report

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Preface

In February 2017, I started out my research year the Department of Clinical Epidemiology, Aarhus University Hospital and this report is the result of many hours of studies, frustrations, questions, revelations and laughs.

First, I would like to thank my supervisors Alma Bečić Pedersen, Deirdre Cronin-Fenton and Irene Petersen for their time, encouragement and guidance throughout the year. They developed the project idea, introduced me to clinical epidemiology, and shared their extensive knowledge with me. Despite a tight schedule, they always had time for questions, comments and constructive feedback.

During my research year, I had the privilege to visit Irene at the Department of Primary Care and Population Health, University College London in September. I would like to thank Irene and her PhD students for a warm welcome, pleasant stay and good talks. It was a very interesting and educative stay.

Finally, I would like to thank my colleagues at the Department of Clinical Epidemiology for practical, economical, and statistical help as well as for contributing to the great work environment. A special thanks to my fellow research year students; Cecilie, Hanne, Kaja, Maria, Mette and Sidse for an ever inspiring and supportive work atmosphere. I imagine the “incubation center” will be very quiet in the future.

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Abbreviations

ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
CCI	Charlson comorbidity index
CI	Confidence interval
HR	Hazard ratio
ICD	International Classification of Diseases
MI	Myocardial infarction
RR	Relative risk
SSRI	Selective serotonin reuptake inhibitor
VTE	Venous thromboembolism

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Abstract

Background: Hip fracture is a common and costly condition among elderly and often have adverse outcomes. Many hip fracture patients use several prescription medications including selective serotonin reuptake inhibitors (SSRIs) despite concerns about adverse effects. It is unknown whether SSRI use is associated with adverse outcomes after hip fracture surgery.

Objective: To examine the association between SSRI use and mortality, postoperative complications, and quality of care in hip fracture patients.

Methods: We conducted a nationwide cohort study based on individual-level linked, prospectively-collected data from Danish population-based national registries. Patients with first-time hospitalization due to hip fracture undergoing surgery from 2006 to 2016 were identified. Using Cox regression analysis, hazard ratios (HRs) of 30-day mortality, any readmission, any reoperation, and specific postoperative complications were estimated. Relative risks of quality of in-hospital care were estimated using Poisson regression analysis. All analyses were performed comparing current and former SSRI users with non-users.

Results: In 68,487 hip fracture patients, 13,272 (19%) were current SSRI users, 2,777 (4%) were former SSRI users, and 52,438 (77%) were SSRI non-users. The 30-day mortality risk was 13% in current SSRI users (HR 1.16, 1.10 to 1.21) and 12% in former (HR 1.15, 1.04 to 1.27) compared with 10% in non-users. The HR for any readmission was 1.11 (1.02 to 1.20) in current and 1.13 (1.01 to 1.27) in former SSRI users and for any reoperation 1.21 (1.11 to 1.31) in current and 1.04 (0.84 to 1.28) in former SSRI users compared with non-users. The risk of venous thromboembolism, myocardial infarction, stroke, and bleeding were similar irrespective of SSRI use. No association between current and former SSRI use and quality of in-hospital care was found.

Conclusions: In patients undergoing hip fracture surgery, 30-day mortality and overall readmission risk were elevated in both current and former SSRI users compared with non-users. Those currently using SSRIs had an increased reoperation risk compared with non-users. However, SSRI use was not associated with increased risk of postoperative complications and lower quality of in-hospital care.

Dansk resumé

Baggrund: Hoftefraktur er en almindelig og omkostningsfuld tilstand blandt ældre og har ofte et uhensigtsmæssigt udfald. Mange hoftefrakturpatienter bruger forskellig receptpligtig medicin inklusiv selektive serotoningenoptagelseshæmmere (SSRI) til trods for bekymringer om utilsigtede virkninger. Det er uvist om SSRI er associeret med uhensigtsmæssige udfald efter operation for hoftefraktur.

Formål: At undersøge associationen mellem SSRI-brug og mortalitet, postoperative komplikationer og kvaliteten af hospitalsbehandling hos hoftefrakturpatienter.

Metode: Vi udførte et landsdækkende kohortestudie baseret på prospektive data fra danske befolkningsbaserede nationale registre. Patienter med førstegangshospitalisering på grund af hoftefraktur opereret fra 2006 til 2016 blev identificeret. Ved brug af Cox regressionsanalyse beregnedes hazardratio (HR) for 30-dagesmortalitet, -genindlæggelse, -reoperation og specifikke postoperative komplikationer. Relativ risiko for kvaliteten af hospitalsbehandling beregnedes ved brug af Poisson regressionsanalyse. Alle analyser blev udført under sammenligning af nuværende og tidligere SSRI-brugere med ikke-brugere.

Resultater: Blandt 68.487 hoftefrakturpatienter var 13.272 (19%) nuværende SSRI-brugere, 2.777 (4%) tidligere brugere og 52.438 (77%) ikke-brugere. 30-dagesmortaliteten var 13% hos nuværende SSRI-brugere (HR 1,16; 1,10-1,21) og 12% hos tidligere brugere (HR 1,15; 1,04-1,27) sammenlignet med 10% hos ikke-brugere. HR for alle genindlæggelser var 1,11 (1,02-1,20) hos nuværende og 1,13 (1,01-1,27) hos tidligere SSRI-brugere og HR for alle reoperationer var 1,21 (1,11-1,31) hos nuværende og 1,04 (0,84-1,28) hos tidligere SSRI-brugere sammenlignet med ikke-brugere. Risikoen for venøs tromboemboli, myokardieinfarkt, slagtilfælde og blødning var ens uanset SSRI-brug. Der blev ikke fundet nogen association mellem nuværende og tidligere SSRI-brug og kvaliteten af hospitalsbehandling.

Konklusion: Blandt patienter opereret for hoftefraktur var 30-dagesmortaliteten og genindlæggelsesrisikoen øget hos både nuværende og tidligere SSRI-brugere sammenlignet med ikke-brugere. De patienter, som var nuværende brugere af SSRI'er, havde en øget reoperationsrisiko sammenlignet med ikke-brugere. SSRI-brug var ikke associeret med øget risiko for postoperative komplikationer og lavere behandlingskvalitet.

Manuscript

Introduction

Hip fracture is a frequent surgical procedure among the elderly.[1] It correlates with high medical costs and healthcare utilisation[2] and confers increased risk of mortality.[3] Thirty-day mortality in elderly surgically treated hip fracture patients is 10% and increases to 30% within one year.[4] Patients who receive the recommended pre- and postoperative in-hospital care such as pain assessment, nutritional risk assessment, osteoporosis prophylaxis, and basic mobility assessment at admission and discharge may have a lower mortality risk compared with those who do not.[5] Additionally, high mortality is linked to the occurrence of postoperative complications, which affect approximately 20% of elderly hip fracture patients.[5 6] The most common postoperative complication is infection.[4] However, patients can experience venous thromboembolism (VTE), myocardial infarction (MI), stroke, and gastrointestinal bleeding as well.[4 7]

Elderly hip fracture patients are often multimorbid and receive multiple prescription medication including selective serotonin reuptake inhibitors (SSRIs).[8] SSRIs are prescribed to 8% of Danish elderly aged 65 years or older.[9] In general, SSRI use appears to increase the risk of mortality, new cardiovascular events, and postoperative bleeding.[6 10] Previous studies among patients undergoing major surgery, including orthopedic surgeries reported higher risk of mortality, readmission, and blood transfusion in those using SSRIs perioperatively[11 12] However, a study including orthopedic patients showed no evidence that SSRI use increase the risk of receiving a blood transfusion.[13] Thus, existing literature examining the effect of SSRI use on surgery outcome is somewhat inconclusive. The impact of preadmission SSRI use on mortality, postoperative complications, and quality of in-hospital care among elderly and fragile hip fracture patients, has not been reported previously. Therefore, we conducted a nationwide, prospective cohort study examining whether preadmission SSRI use is associated with adverse outcomes in hip fracture surgery patients.

Methods

Setting and design

The study is a nationwide cohort study using prospectively collected data from Danish medical registries covering all Danish citizens; approximately 5.7 million people.[14] The health care system in Denmark is tax-funded, and all citizens have equal access to health care services.

Data sources

The Danish Multidisciplinary Hip Fracture Registry[15] has routinely registered comprehensive clinical data on all patients aged 65 years or older with first-time hip fracture admitted to any orthopedic department in

Denmark since 2004. Data include detailed pre- and postoperative data, as well as data on quality of in-hospital care represented by process-performance measures. The Danish Civil Registration System[16] established in 1968 holds data on date of birth, vital status, and migration on all individuals in Denmark. Every citizen has a unique civil personal registration number, which allows for individual-level linkage across all Danish registries. The Danish National Patient Registry[17] contains data on civil personal registration number, hospital admission and discharge diagnosis codes, and diagnostic and surgical procedure codes from all Danish somatic hospitals since 1977. Diagnoses were coded using the International Classification of Diseases Eighth Revision (ICD-8) until the end of 1993 and Tenth Revision (ICD-10) thereafter. The Danish National Database of Reimbursed Prescriptions[18] tracks reimbursed medicine dispensing at all community pharmacies and hospital-based outpatient pharmacies in Denmark since 2004. The database holds data on civil personal registration number, Anatomical Therapeutic Chemical code, redemption date, item quantity, pack size, defined daily dose, dose form, and generic substitution done at pharmacy.

Study population

Patients aged 65 years or older undergoing surgical treatment for hip fracture between 2004 and 2016 were identified in the Danish Multidisciplinary Hip Fracture Registry. The study period was subsequently restricted to patients registered between 1 January 2006 and 31 December 2016 to ensure at least two years prescription history. Patients with missing data on operation delay (n=119) were excluded. In total, 68,487 first-time hip fracture patients operated from 2006 to 2016 were available for analyses.

Exposure

All redeemed prescriptions for SSRIs one year before hip fracture surgery were identified in the Danish National Database of Reimbursed Prescriptions. Patients were classified according to SSRI use: Current SSRI users redeemed at least one prescription within 90 days, former users redeemed one prescription between 91 and 365 days, and non-users redeemed no prescriptions within 365 days before hip fracture surgery.

Outcome measures

Several outcomes occurring after hip fracture surgery were examined separately. First, all-cause 30-day mortality was ascertained from the Civil Registration System. Second, postoperative complications were ascertained from the Danish National Patient Registry. The following postoperative complications were examined: 1) any readmission, 2) any reoperation, 3) cardiovascular events including VTE, MI, and stroke, and 4) major bleeding defined as intracranial bleeding, gastrointestinal bleeding, or urinary/lung bleeding within 30 days of surgery. Third, quality of in-hospital care represented by process-performance measures[19] including preoperative optimization, operation delay, mobilization within 24 hours postoperatively, basic

mobility assessment at admission and discharge, nutritional risk assessment, osteoporosis prophylaxis, and future fall prophylaxis were obtained from the Danish Multidisciplinary Hip Fracture Registry.

Covariates

Operation year, housing, body mass index (BMI), fracture type, operation type, and operation delay information were assessed from the Danish Multidisciplinary Hip Fracture Registry. Four categories comprising housing information were created: own accommodation, residential institution, homeless, and unknown. Likewise, four categories based on BMI values were created: underweight (BMI<18.5 kg/m^2), normal weight (BMI≥18.5<25 kg/m^2), overweight or obese (BMI≥25 kg/m^2), and unknown. Age, gender and marital status were obtained from the Danish Civil Registration System. Comorbidities were identified using the Danish National Patient Registry. Overall comorbidity was summarized according to the Charlson Comorbidity Index (CCI) score. The CCI was categorized as low (score 0), medium (score 1-2), and high (score ≥3) comorbidity score.[20] The following medications were assessed from the Danish National Database of Reimbursed Prescriptions: non-steroid anti-inflammatory drugs (NSAIDs), corticosteroids, anticoagulants, statins, non-SSRI antidepressants, and antipsychotics. Use of each medication was defined as follows: current users redeemed one prescription within 90 days, former users redeemed one prescription between 91 and 365 days, and non-users redeemed no prescriptions within 365 days before hip fracture surgery. All codes defining study variables are available in Supplementary table A-C.

Statistical analysis

Patient characteristics were tabulated according to SSRI use. All patients were followed from operation date to death, any readmission, any reoperation, cardiovascular event, bleeding event, or up to 30 days. Kaplan-Meier curves of the three SSRI exposure groups were plotted depicting the absolute mortality risk over time. The cumulative incidence of postoperative complications was estimated treating death as a competing risk. Crude and adjusted hazard ratios (HRs) with 95% confidence intervals of death and postoperative complications within 30 days were estimated using Cox regression analysis comparing current and former SSRI users with non-users. The mortality model was evaluated for effect modification by age and gender. Readmission outcome data were only available for patients operated from 1 January 2011 onwards, thus readmission analyses were restricted to patients operated between 1 January 2011 and 31 December 2016. Relative risks of quality of in-hospital care were estimated using Poisson regression analysis. The process-performance measures representing quality of in-hospital care were introduced in the Danish Multidisciplinary Hip Fracture Registry at various times. Therefore, the analyses regarding the quality of in-hospital care were performed only in hip fracture patients operated between 1 January 2015 and 31 December 2016. Potential confounder assessment was done using a directed acyclic graph (Supplementary

figure A).[21] All adjusted analyses accounted for age, gender, marital status, operation year, comorbidities, other medication, and clustering by unit setting.

Sensitivity analysis

Two sensitivity analyses were performed to test the robustness of the results. First, missing BMI values were imputed using multiple imputation.[22] Missing housing data were not imputed due to lack of predictors. In the multiple imputation model, all variables that were in the subsequent analysis model were included: SSRIs, age, gender, marital status, operation year, body mass index, comorbidities, and other medication. Furthermore, some auxiliary variables such as operation delay, fracture type, operation type, and postoperative complications were included. Imputation of body mass index values was done using truncated regression creating 20 imputed datasets. After imputation, the association between SSRI use and mortality was estimated in each imputed dataset using Cox regression analysis. The measures of association from each imputed dataset were combined using Rubin's rule.[23]

Second, the exposure definition was changed to address potential compliance problems; current SSRI users redeemed two prescriptions within two years, of which one prescription was redeemed within eight months before hip fracture, former users redeemed two prescriptions between eight months and two years, and non-users redeemed one or no prescriptions within two years before hip fracture. The mortality analysis was repeated employing a new exposure definition.

All statistical analyses were performed using Stata 14 for Windows (Stata Corp, College Station, TX, USA) and R for Windows 3.4.2 (The R Foundation for Statistical Computing, Vienna, Austria)

Results

Patient characteristics

We identified 68,487 first-time hip fracture patients between 2006 and 2016. Of these, 13,272 (19%) were current SSRI users, 2,777 (4%) former, and 52,438 (77%) non-users. Table 1 presents the patient characteristics according to SSRI use. The median patient age was 84 years in current users and 83 years in former users and non-users. The current and former SSRI users had higher overall comorbidity than non-users as well as higher prevalence of cerebrovascular disease, dementia, use of non-SSRI antidepressants, and antipsychotics. Current SSRI users had a higher prevalence of anticoagulant use than both former users and non-users (Table 1).

In total, 13,295 patients (19%) were missing BMI data and 30,285 (44%) patients were missing housing data. In the available housing data, we observed that SSRI non-users more often lived in their own accommodation compared with current and former users. However, there was no difference in BMI distribution between the exposure groups (Table 1).

Mortality

Overall, 7,295 hip fracture patients died within the first 30 days following hip fracture surgery. Mortality was higher in current (13%) and former (12%) users compared with non-users (10%) (Figure 1 and Table 2). Compared with non-users, the adjusted HR was 1.16 (1.10 to 1.21) in current users and 1.15 (1.04 to 1.27) in former users (Table 2). We found no effect modification by age and gender of the relation between SSRI use and mortality.

Readmission and reoperation

Table 2 shows cumulative incidences and HRs of any readmission and any reoperation within 30 days postoperatively. In total, 6,208 of 36,356 were readmitted and 2,327 of 68,487 re-operated within 30 days after surgery. Both current (HR 1.11, 1.02 to 1.20) and former users (HR 1.13, 1.01 to 1.27) had a higher readmission risk compared with non-users. Current SSRI users had a higher reoperation risk (HR 1.21, 1.11 to 1.31) compared with non-users while there was no difference between former users (HR 1.04, 0.84 to 1.28) and non-users.

Postoperative complications

During the first 30 days following hip fracture surgery, 573 patients experienced VTE, 546 MI, 863 stroke, and 1,011 major bleeding. Table 2 shows cumulative incidences and HRs of the individual complications. Current SSRI users had a similar risk of VTE (HR 0.89, 0.67 to 1.17), MI (HR 1.03, 0.81 to 1.30), stroke (HR 0.93, 0.80 to 1.09), and bleeding (HR 1.06, 0.89 to 1.28) as non-users. Likewise, former SSRI users had a similar risk of VTE (HR 0.93, 0.64 to 1.35), MI (HR 0.89, 0.57 to 1.40), stroke (HR 0.67, 0.44 to 1.01), and bleeding (HR 1.06, 0.69 to 1.64) as non-users.

Quality of in-hospital care

The analyses included 11,363 patients operated during 2015 to 2016. Figure 2 and Table 3 shows no difference in quality of in-hospital care between the three SSRI exposure groups.

Sensitivity analysis

The HRs of mortality did not materially change after multiple imputation of missing BMI values and adjustment for BMI (Supplementary table E). Changing the exposure definition, we identified 14,530 (21%) current SSRI users, 1,116 (2%) former users, and 52,841 (77%) non-users. Patient characteristics in the new exposure groups were similar to the patient characteristics in the exposure groups used in the main analysis and the HRs of mortality were similar to the main analysis results (Supplementary table F and G).

Discussion

In this nationwide cohort study of hip fracture surgery patients, 30-day mortality and overall readmission were elevated in both current and former SSRI users. Those currently using SSRIs had an increased reoperation risk compared with non-users. However, SSRI use was not associated with increased risk of cardiovascular and bleeding complications and inferior quality of in-hospital care.

Strengths and limitations

The strengths of this study are the use of well-established, well-validated, and prospective-collected data from Danish population-based registries with complete follow-up. The registries originate from a tax-supported and uniformly organized health care system reducing the risk of selection bias. The validity of the hip fracture diagnosis is high,[24 25] and the complete follow-up reduces the risk of differential misclassification. In general, our study included all elderly hip fracture patients aged 65 years or older in Denmark between 2006 and 2016. These patients are similar regarding age and gender to those included in other studies on hip fractures in the elderly.[4 7] To date, this is the largest study examining the association between SSRI use and mortality, postoperative complications, and quality of in-hospital care in hip fracture patients.

We ascertained comprehensive data on potential confounders including complete in-hospital comorbidity history compiled in the Charlson Comorbidity Index (CCI) and history of specific diseases. However, we did not have information on the severity of diseases included in the CCI, on diseases treated in primary care, which were not severe enough to warrant a hospital diagnosis, or information on the underlying disease indication for SSRI prescription. Further, the registries we used did not contain information on socioeconomic status, smoking, alcohol use, and other lifestyle factors. Lack of these data may have resulted in residual confounding. However, in this study we included former SSRI users as a negative control. I.e. we anticipated that they would be more similar to the current users than non-users in many aspects. Thus, if the effect of SSRI exposure on mortality was caused by the medication itself, we would anticipate only seeing an effect in current users and not in former users. However, this was not the case, and the observed association between SSRI use and mortality may rather be caused by underlying risk factors.[26]

We did not have information about compliance. In our study, non-compliance would cause a misclassification of non-users as users, and therefore the observed association between SSRI use and mortality, readmission, or reoperation risk might actually be higher. However, as the patients redeem the prescriptions, our estimates most likely reflect actual drug use. Even considering misclassification, dispensed prescriptions are considered a good measure of medication intake.[27] Furthermore, we had no data on in-hospital medication use. This may not influence the outcome since hip fracture surgery is an acute procedure with short length of hospital stay.

Comparison with other studies

We observed an equally increased mortality risk in current and former SSRI users. This suggests that rather than being a risk factor in itself, SSRI use may be a marker of underlying risk factors such as psychiatric illness, socioeconomic status, and life style factors (smoking, alcohol misuse, and physical inactivity). These results are consistent with those obtained by Auerbach et al. showing an increased mortality in SSRI users compared with non-users after major surgery, including approximately 2% hip fracture surgeries.[11] However, the association found by Auerbach et al. attenuated in patients with depression suggesting that the underlying psychiatric indication for SSRI use may explain the increased risk rather than SSRI in itself.[11] The most common indications for SSRI treatment are depression and anxiety.[28] A systematic review by Eaton et al. showed that depression and anxiety correlate with increased mortality.[29] Mortality in hip fracture patients may also be influenced by socioeconomic status,[30] and Marinacci et al. found an association between lower educational level and mortality.[31] Lower educational level is further associated with increased risk of psychiatric admission due to schizophrenia, alcoholism, drug dependency, affective psychosis, neurosis, and personality disorder.[32] Finally, Seitz et al. found no difference in 30-day mortality between current (9.1%) and former (9.4%) serotonergic antidepressant users undergoing hip fracture surgery.[33] However, they did not include a non-user group, which distorts the association between SSRI use and mortality.

Our findings of an increased overall readmission risk in current and former SSRI users compared with non-users is consistent with findings reported by Auerbach et al. in major surgery patients. In their study, this association persisted in patients receiving SSRI for depression, but not in patients receiving SSRI for other reasons.[11] This also suggests that SSRI use may not be a risk factor in itself but a marker of underlying disease or risk factors.

Another important finding was that current SSRI users had an increased reoperation risk compared with non-users, whereas the risk was not elevated in former users. A possible explanation for this could be that SSRI use may increase the likelihood of complications necessitating reoperation. There are different reasons for performing reoperation for example wound dehiscence, infection, and bleeding,[19] and these complications may be more frequent in SSRI users. Gärtner et al. found an association between SSRI use and reoperation due to bleeding after breast cancer surgery.[34] However, Tully et al. showed no association between serotonergic antidepressant use and reoperation due to infection or bleeding after coronary artery bypass graft surgery.[35] Further research is needed to establish the association between SSRI use and reoperation risk due to different causes in hip fracture patients.

We found little evidence of an association between SSRI and the risk of VTE, MI, stroke, and bleeding. To our knowledge, no other studies investigated the association between SSRI use and the above-mentioned postoperative complications following hip fracture surgery. Auerbach et al. found an association between

SSRI use and postoperative bleeding in major surgery patients. However, they had a broader bleeding definition including bleeding following procedure, and they included both acute and elective operations.[11] Tully et al. showed no association between SSRI use and MI, stroke, or bleeding after coronary artery bypass graft surgery[35] supporting our findings.

The present study did not find any difference between SSRI non-users and users regarding quality of in-hospital care. This is important and in line with efforts of European governments to reduce social inequality in treatment of patients.[36] However, we have no information on quality of patient care outside hospital settings. Previous research suggests lower 30-day mortality in hip fracture patients who received higher quality of care.[5] Quality of in-hospital care may not explain the increased mortality associated with SSRI use in our study.

Implications of findings

One issue emerging from our findings is the question about discontinuation of SSRI treatment after hip fracture surgery. Since hip fracture is an acute condition, it is not possible to stop treatment before surgery. Stopping SSRI treatment after surgery would not change the mortality and overall readmission risk since they were similar in current and former users compared with non-users. The overall reoperation risk was augmented in current users but not in former users compared with non-users. However, pausing SSRI treatment without a complete discussion of the risks and benefits is unwarranted. The increased risk of mortality, readmission, and reoperation calls for increased clinical awareness on hip fracture patients using SSRIs. This patient group may be more prone to adverse outcomes after surgery regardless of the indication for SSRI treatment.

In conclusion, 30-day mortality and overall readmission in hip fracture patients were elevated in both current and former SSRI users compared with non-users. Those currently using SSRIs had an increased overall reoperation risk compared with non-users. However, SSRI use was not associated with increased risk of cardiovascular and bleeding complications and lower quality of in-hospital care.

Supplementary

The following research report section contains general methodological considerations concerning study design, exposure definition, statistical analyses, and missing values. Furthermore, it describes the strengths and limitations including discussion of bias and confounding, and clinical perspectives and future studies related to the present study.

Methodological considerations

Study design

There are several different possibilities when designing a scientific study. First, I will give some examples of different study designs and afterwards justify the choice made in the present study.

Case-control studies start out with a source population, where a limited number of cases and controls are identified. Cases are individuals who had the outcome of interest and controls are individuals who did not have the outcome of interest. Afterwards, information on the exposure is obtained. It is possible to include several exposures, but only one outcome of interest.[37] In traditional case-control studies exposure data are recorded after the outcome occurred leading to an increased risk of recall bias. Recall bias arise as cases may report exposure information different than controls. For example, cases may be more likely to report being exposed than controls because they try to explain the occurrence of the outcome.[37] Recall bias can be eliminated by using prospectively collected register data. Here, exposure information is collected before occurrence of the outcome and thus does not lead to recall bias. Another problem that the case-control study design cannot control is the risk of confounding.[37] One way to eliminate this problem is to use a different study design and conduct a randomized controlled trial.

In the randomized controlled trial, study participants are randomly assigned to different intervention groups. The randomization is intended to balance confounding between intervention groups, but caution must be exercised, as balance is not guaranteed.[37] An issue arises in randomized controlled trials when the patients do not follow the intervention or treatment and e.g. change treatment during the follow-up. This will lead to bias depending on the treatment change.[37] The randomized controlled trial study design can only be used when investigating the effect of an intervention on the outcome occurrence. Therefore, the association between a random event such as hip fracture and an outcome cannot be investigated using the randomized controlled trial study design. If the objective of a study is to investigate this association, another study design such as the cohort study design must be used.

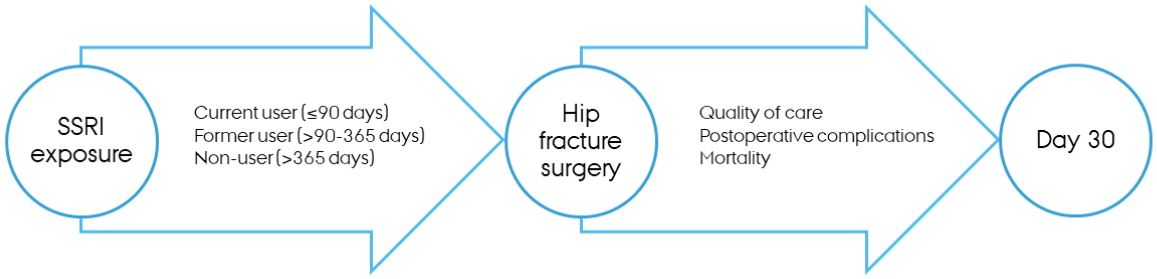
In general, cohort studies measure the disease occurrence within a given cohort.[37] A cohort is defined as a group of individuals who are followed over a time period.[38] Cohort studies present several limitations such as susceptibility to confounding, the need for very large cohorts, the cost and time consuming nature of the

design, and the association assessment relating only to those factors recorded at the outset of the study.[39] On the contrary prospective cohort studies have several strengths such as the ability to establish the absolute risk directly, elimination of recall bias, the ability to examine several outcomes and exposures in one study, and the ability to assess lifestyle factors not available elsewhere.[39]

In the present study, the cohort study design was chosen because the study objective was to examine the association between SSRI use and mortality, postoperative complications, and quality if in-hospital care in hip fracture patients. Thus, there are several outcomes of interest, and hip fracture needs to occur after exposure to SSRI. This favors the conduction of a cohort study. The randomized controlled study design is not possible to apply studying the association between pre-hip fracture SSRI use and adverse outcomes. There are several reasons for this: First, a very large study sample would be necessary. Second, it would be unethical to treat people with medication they may not need. Third, the study would be costly and time-consuming. Finally, a randomized controlled trial is not problem free as loss to follow-up may occur. This is not a problem in the present cohort study as all patients have complete follow-up from hip fracture to outcome occurrence or up to 30 days.

Exposure definition

Exposure is defined as a risk factor that an individual comes in contact with before becoming ill.[39] There are several ways to characterize exposure e.g. ever exposed, current dose, largest dose, cumulative dose, time of exposure, time since first exposure and so on.[39] In the present study, the exposure of interest is SSRI use. SSRI use was characterized as ever use and was categorized as follows: Current SSRI users redeemed at least one prescription within 90 days, former users redeemed at least one prescription between 91 and 365 days, and non-users redeemed no prescriptions within 365 days before hip fracture (Supplementary figure 1).



Supplementary figure 1: Exposure definition and outcomes.

The exposure period was chosen because SSRIs are mainly prescribed in packets for 3 months use. Former users were included as a negative control.[26] This means that if there is a true causal effect of SSRI on

mortality, the association between former SSRI use and mortality is expected to be null, and the association between current SSRI use and mortality not null. If both current and former SSRI use are associated with mortality, there is no causal effect of SSRI, and the association may be due to underlying risk factors.
Patients redeeming a prescription was assumed to have initiated treatment and be compliant. However, compliance seems more likely when patients redeem a second prescription. This was not the case in the present study as a sensitivity analysis with a different exposure definition showed no significant deviation from study results.

Statistical analyses

The time-to-event analyses compare the postoperative outcome rates in the different exposure groups. The survival analysis model is based on two assumptions. First, it assumes that the hazards are proportional. Thus, the ratio of the hazards comparing different exposure groups remains constant over time.[40] This means that the instantaneous risk remains constant in the two exposure groups during the entire follow-up period. Second, it assumes independent censoring meaning that the censoring-probability is not related to the risk of the event occurring.[40] E.g. dependent censoring would occur if those censored were more comorbid and thus at higher risk of dying compared with the uncensored. In other words, an individual censored at a specific time must be representative of those still at risk at that time.[41] In the present study, dependent censoring does not occur, as there was no loss to follow-up. The Kaplan-Meyer estimator was used to compare mortality rates in the different exposure groups. However, caution was exercised when examining outcomes with competing risks.[41] The competing-risk issue arise when the event of interest cannot occur because a competing event happened first. In the present study, it is not possible for patients to experience VTE if death already occurred. The Kaplan-Meyer estimator treats the competing events as independent-censored observations thus overestimating the results.[41] Instead, the Aalen-Johansen estimator was used as it determines the cumulative incidence of an event in a situation with competing risks.[41] Competing risks do not interfere with the Cox regression estimates. The Cox regression model is considering the risk sets of individuals still being followed up at each time an event occurs.[40] If a patient die during follow-up, the patient is no longer at risk and does not contribute to the estimation. However, the patient will contribute with risk time until the occurrence of death.

Poisson regression analyses were used to estimate relative risks comparing the different exposure groups regarding quality of in-hospital care. The model was chosen after careful considerations. First, logistic regression was considered for estimating the associations. Using this model, the model parameters, odds ratios, are used to estimate the relative risks in case-control studies, where the outcome is rare.[37] When the risk is small, the odds are close to the risk. However, in cohort studies, the outcome is often frequent and risks or rates are directly obtainable. In this case, estimating an odds ratio may overestimate the relative risk

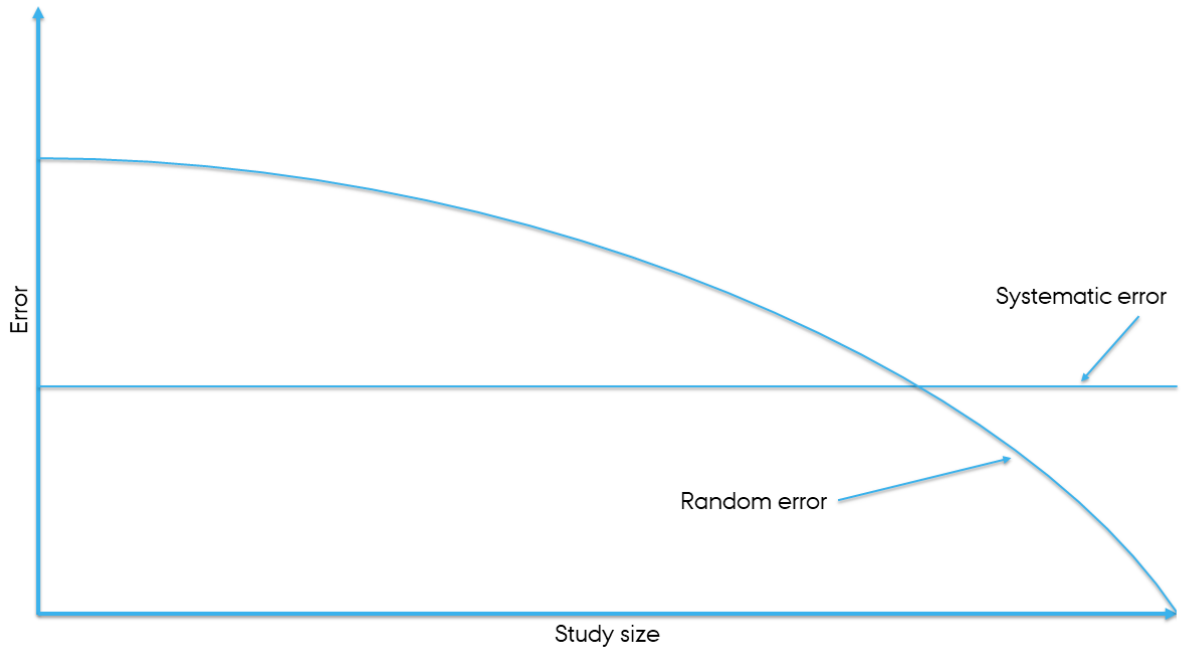
when it is more than 1 and underestimate it when it is less than 1.[42] In this study, more than 10% of exposed patients have an event thus odds ratios would over- or underestimate the relative risk.

Missing data

Missing data are a recurrent issue in registry-based research. It occurs in medical registries for several reasons: loss to follow-up, failure to attend medical appointments, lack of measurements, and inaccurate transfer of data from paper registration to an electronic database.[22] In the present study, data were missing on operation delay (0.2%, n=119), BMI (19%, n=13,329), and housing (44%, n=30,403). There are different types of missing data and they are often categorized in the following three groups: missing completely at random (MCAR), missing at random (MAR), and missing not at random (MNAR).[22] If data are MCAR, it does not depend on observed or unobserved data.[43] For example, in the present study BMI may be missing because the scale broke. However, it is unlikely to be broken 19% of the time, thus the data are probably not MCAR. When the missingness depends on already observed information, data are MAR.[43] In this case, females may be less likely to be weighed and thus having missing data on BMI. Finally, data can be MNAR if they depend on the unobserved data.[43] In the case of missing BMI values, data are MNAR if normal weight individuals are less likely to be weighed than over- or underweight. The missing data in the present study are probably not MCAR, but are more likely to be MAR or MNAR. Missing data can be handled in several ways in data analysis. Three methods were considered during this study. First, the missing indicator method were assessed.[22] Missing values were grouped in an "unknown" category retaining the full dataset. However, the estimates were biased due to residual confounding as the "unknown" category were a mixture of the other categories. Second, complete-case analysis was considered including only individuals with complete data on all variables. This is a simple method to handle missing data, but it assumes that data are MCAR, which is probably not the case.[22] Furthermore, almost half of the observations in this study were excluded reducing statistical power. However, this approach was used regarding operation delay, as there were only 0.2% (n=119) incomplete cases. Finally, multiple imputation was considered aiming to provide unbiased and valid association estimates retaining the full dataset. Multiple imputation assumes that data are MAR, but can handle both data MCAR and MNAR.[22] Some considerations were made before performing the imputation of BMI values. First, auxiliary variables were selected using logistic regression examining the relationship with missingness and value of missing data.[23] Due to lack of predictors, multiple imputation was not performed on housing, but only on BMI. The number of imputed data sets were selected based on the rule of thumb suggested by White et al.: the number of imputations should be similar to the percentage of incomplete cases.[23] In this study, 20 imputations were performed corresponding to 19% (n=13,329) missing BMI values.

Strengths and limitations

The present study aims to obtain measures of the association between SSRI use and mortality, postoperative complications, and quality of in-hospital care in hip fracture patients. However, these measures are only estimates of the true association. If the obtained measure is close to the true association, the study is accurate and has little error. The size of the error can never be determined, as we do not know the true association.[37] Nevertheless, steps are made to reduce error through design and analysis. There are two types of error that should be taken into account; systematic error and random error.[37] Systematic error is also known as bias and are often described as selection bias, information bias, and confounding. Random error is variability in the data that cannot be explained. Random error is decreasing with increasing study size as it is determined by chance.[37] In the present study, the study size is very large and random error plays a relatively small role. However, systematic error is unaffected by study size, and in very large studies the relative role of systematic errors becomes larger (Supplementary figure 2).



Supplementary figure 2: The relation of systematic error and random error to study size.
(After Rothman, KJ, Epidemiology: An Introduction)

Selection bias

Selection bias occurs when the association between exposure and outcome differs for participants and nonparticipants. The bias is introduced through selection of participants at entry or by loss to follow-up.[37] In the present study, participants enter the study on the day of hip fracture. They are identified in the

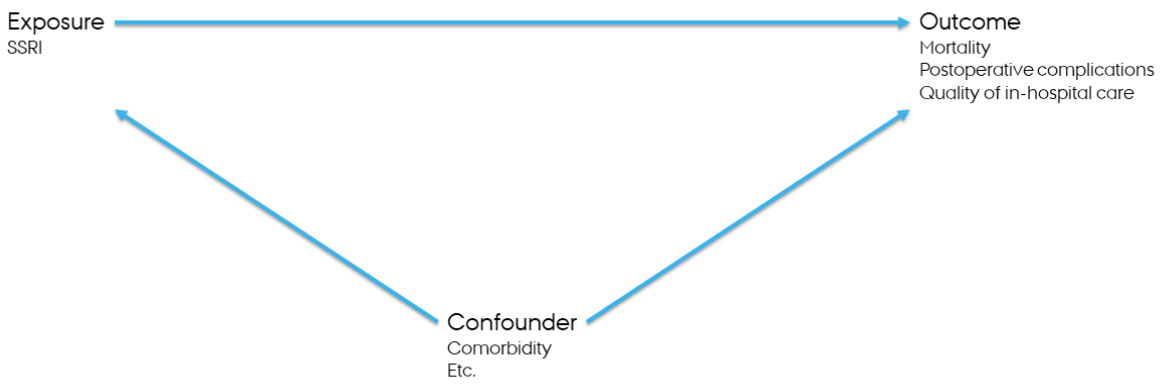
Danish Multidisciplinary Hip Fracture Registry, which contains data on all hip fractures in Denmark from 2003 onwards.[15] As the Danish health care system is tax-funded, all citizens have equal access to health care services. Furthermore, all hip fractures require admission to hospital and are therefore recorded in the Danish medical registries. Therefore, there is no selection of participants at entry. Loss to follow-up is probably nonexistent in this study as the Civil Registration System is virtually complete regarding emigration and death.[16] The combination of complete inclusion of all Danish hip fracture patients and complete follow-up reduces the risk of selection bias.

Information bias

Information bias arises when information about participants are misclassified. Misclassification can be differential or non-differential. Differential misclassification relates to the value of other study variables whereas non-differential misclassification does not.[37] Differential misclassification occurs in cohort studies if unexposed individuals are underdiagnosed more than exposed individuals are. In this study, mortality is unlikely to be underdiagnosed in SSRI non-users. However, postoperative complications may be underdiagnosed in non-users and former users if clinicians are more aware of symptoms in current SSRI users. Non-differential misclassification affects all epidemiological studies to some extent.[37] In the present study, SSRI exposure may be misclassified, as we do not know if people are actually taking the medication after redemption. The misclassification is however non-differential because the misclassification of SSRI exposure does not depend on the outcomes. This means that the associations may be under- or overestimated, but as there is three exposure groups it is not possible to say which way the estimates are biased. However, non-differential misclassification of the exposure will not bias the effect estimate if there is no effect to begin with.[37]

Confounding

Confounding is the confusion of effects. The effect of the exposure is confused with the effect of another variable.[37] Thus, a confounder must influence the outcome and be associated with the exposure.[21] An example from the present study is comorbidity. Comorbidity is a confounder of the association between SSRI and mortality in hip fracture patients as comorbidity increases the risk of developing depression[44] and thus receiving SSRI. Furthermore, mortality after hip fracture surgery increases with increasing comorbidity level.[3 4] Thus, comorbidity is associated with both the exposure and the outcome (Supplementary figure 3). A variable is only a confounder if the distribution of the values differs in the various exposure categories.[37] This is the case for the CCI-score distribution as it differs across SSRI user groups. Finally, a confounder must not be an effect of the exposure.[37] In this study, comorbidity is probably not an effect of SSRI treatment and thus fulfils the confounder properties.



Supplementary figure 3: Correlation of exposure, outcome, and confounder with examples from the present study.

Not all confounders can be identified and controlled. Confounding by indication is often an issue in pharmacoepidemiological research. The issue arises when the medical condition indicating drug use differs between drug users and non-users. Even differences in disease severity or other risk factors between drug users, users of other drug therapies and non-users can introduce confounding by indication.[37] Thus, the indication for drug use may cause the outcome independently of the drug itself. In the present study, the indication for SSRI treatment is unknown as is the severity of disease. Furthermore, psychiatric illness is associated with additional risk factors further complicating the picture.[45] However, the aim was not to investigate the sole pharmacological effect of SSRI treatment, but to investigate differences in mortality, postoperative complications and quality of in-hospital care in the SSRI-treated hip fracture patient subgroup. Thus, both the direct effect of SSRI use and the effect of factors associated with SSRI use was of interest. Therefore, confounding by indication was not a limitation I this study.

Confounding can be prevented in the study design and analysis phases. In the design phase, there are three ways to prevent confounding. The first method is randomization, which can only be done in experimental studies.[37] In the present study, participants cannot be randomly assigned to SSRI treatment before hip fracture. The second method is restriction where the sample is restricted to participants with almost the same value for a potentially confounding variable.[37] This is done to some extent in the present study, as the sample is restricted to patients aged 65 years or older. By restricting the sample to elderly, the confounding effect of age is reduced. The third method is matching where exposed participants are matched with unexposed individuals based on the confounder distribution.[37] This method was not used in this study. However, in the analysis phase, confounding can be controlled in two ways. The first method is to use stratification where data are cross-tabulated on exposure and outcome by categories of potential confounding variables.[37] The other method is to use regression models as done in the present study.

Clinical perspectives and future studies

The population of elderly individuals is increasing.[46] In this population, comorbidity and prescription drug use are frequent and stress the necessity to increase the life quality.[47] Life quality of elderly patients is improved through treatment enhancement, which may further reduce illness burden, prolong the period of adult vigor, and reduce the need for medical care and associated costs.[48] A common and costly disorder in elderly is hip fracture.[1] Therefore, measures to prevent hip fractures as well as to improve the postoperative outcomes are crucial. Many elderly hip fracture patients receive multiple prescription drugs including SSRIs emphasizing the need for improving drug safety.[8]

The results of the present study highlight the need for increased clinical awareness on hip fracture patients currently and formerly treated with SSRIs. These patients may be more prone to adverse outcomes after surgery and therefore requires increased clinical attention. The study adds insight into the issues related to SSRI treatment concerning mortality, readmission, reoperation, postoperative complications, and quality of care in hip fracture surgery patients. However, the study does not elucidate the cause of death, readmission, or reoperation associated with current and former SSRI use. These issues may be subject to future research including data from the Danish Cause of Death Register and the Danish National Patient Registry. Additionally, the long-term prognosis of hip fracture patients using SSRIs may be evaluated.

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Tables and figures

Table 1: Baseline patient characteristics according to pre-hip fracture selective serotonin reuptake inhibitor (SSRI) use 2006-2016

Variable	All patients		SSRI					
			Non-users		Former users		Current users	
	n	%	n	%	n	%	n	%
Total	68,487	100	52,438	76.6	2,777	4.0	13,272	19.4
Median age (years)	83		83		83		84	
Age (years)								
65-74	13,271	19.4	10,571	20.2	533	19.2	2,167	16.3
75-84	26,086	38.1	19,768	37.7	1,159	41.7	5,159	38.9
≥ 85	29,130	42.5	22,099	42.1	1,085	39.1	5,946	44.8
Gender								
Male	19,750	28.8	15,541	29.6	730	26.3	3,479	26.2
Female	48,737	71.2	36,897	70.4	2,047	73.7	9,793	73.8
Marital status								
Married	20,300	29.6	16,105	30.7	842	30.3	3.353	25.3
Unmarried	48,187	70.4	36,333	69.3	1,935	69.7	9,919	74.7
Housing								
Own accommodation	31,075	45.4	25,537	48.7	1,126	40.5	4,412	33.2
Homeless	22	<0.1	20	0.1	0	0.0	2	<0.1
Residential institution	7,105	10.4	4,213	8.0	408	14.7	2,484	18.7
Uknown	30,285	44.2	22,668	43.2	1,243	44.8	6,374	48.0
Fracture type								
Femoral neck fracture	36,341	53.1	27,854	53.1	1,451	52.3	7,036	53.0
Per- and subtrochanteric fracture	32,146	46.9	24,584	46.9	1,326	47.7	6,236	46.9
Operation type								
Alloplastic surgery	46,859	68.4	35,843	68.4	1,902	68.5	9,114	68.7
Osteosynthesis	21,628	31.6	16,595	31.6	875	31.5	4,158	31.3
Operation delay (h)								
<24	41,671	60.8	31,859	60.8	1,721	62.0	8,091	61.0
24-48	12,517	18.3	9,646	18.4	461	16.6	2,410	18.1
>48	14,299	20.9	10,933	20.8	595	21.4	2,771	20.9
Operation year								
2006-2010	32,131	46.9	23,822	45.4	1,342	48.3	6,967	52.5
2011-2016	36,356	53.1	28,616	54.6	1,435	51.7	6,305	47.5
Body mass index (BMI), kg/m^2								
< 18.5: Underweight	5,988	8.8	4,558	8.7	292	10.5	1,138	8.6
≥ 18.5 < 25: Normal weight	31,582	46.1	24,390	46.5	1,254	45.2	5,938	44.7
≥ 25: Overweight or obese	17,622	25.7	13,602	25.9	689	24.8	3,331	25.1
Unknown	13,295	19.4	9,888	18.9	542	19.5	2,865	21.6

Table 1 continued

Variable	All patients		SSRI					
			Non-users		Former users		Current users	
	n	%	n	%	n	%	n	%
Charlson comorbidity index								
Low (0)	27,283	39.8	22,505	42.9	840	30.3	3,938	29.7
Medium (1-2)	27,787	40.6	20,365	38.8	1,244	44.8	6,178	46.5
High (3+)	13,417	19.6	9,568	18.3	693	24.9	3,156	23.8
Comorbidity								
Myocardial infarction	3,762	5.5	2,820	5.4	151	5.4	791	6.0
Congestive heart failure	6,289	9.2	4,632	8.8	291	10.5	1,366	10.3
Peripheral vascular disease	5,511	8.1	4,060	7.7	267	9.6	1,184	8.9
Cerebrovascular disease	12,678	18.5	8,467	16.2	689	24.8	3,522	26.5
Dementia	6,733	9.8	3,859	7.4	433	15.6	2,441	19.4
Chronic pulmonary disease	8,663	12.7	6,191	11.8	496	17.9	1,976	14.9
Connective tissue disease	3,243	4.7	2,480	4.7	139	5.0	624	4.7
Ulcer disease	3,855	5.6	2,673	5.1	224	8.1	958	7.2
Liver disease	870	1.3	646	1.2	46	1.7	178	1.3
Diabetes type 1 and 2	6,689	9.8	5,005	9.5	281	10.1	1,403	10.6
Hemiplegia	175	0.3	111	0.2	12	0.4	52	0.4
Moderate to severe renal disease	2,688	3.9	1,973	3.4	132	4.8	583	4.4
Cancer	10,957	16.0	8,351	15.9	501	18.0	2,105	15.9
Other medication*								
NSAID	7,681	11.2	5,869	11.2	334	12.0	1,478	11.1
Corticosteroids	4,158	6.1	3,068	5.9	186	6.7	904	6.8
Anticoagulants	26,716	39.0	19,323	36.9	1,064	38.3	6,329	47.7
Statins	13,052	19.1	9,581	18.3	505	19.2	2,966	22.4
Non-SSRI antidepressants	7,975	11.6	4,977	9.5	596	21.5	2,402	18.1
Antipsychotics	4,992	7.3	2,899	5.5	319	11.5	1,774	13.4

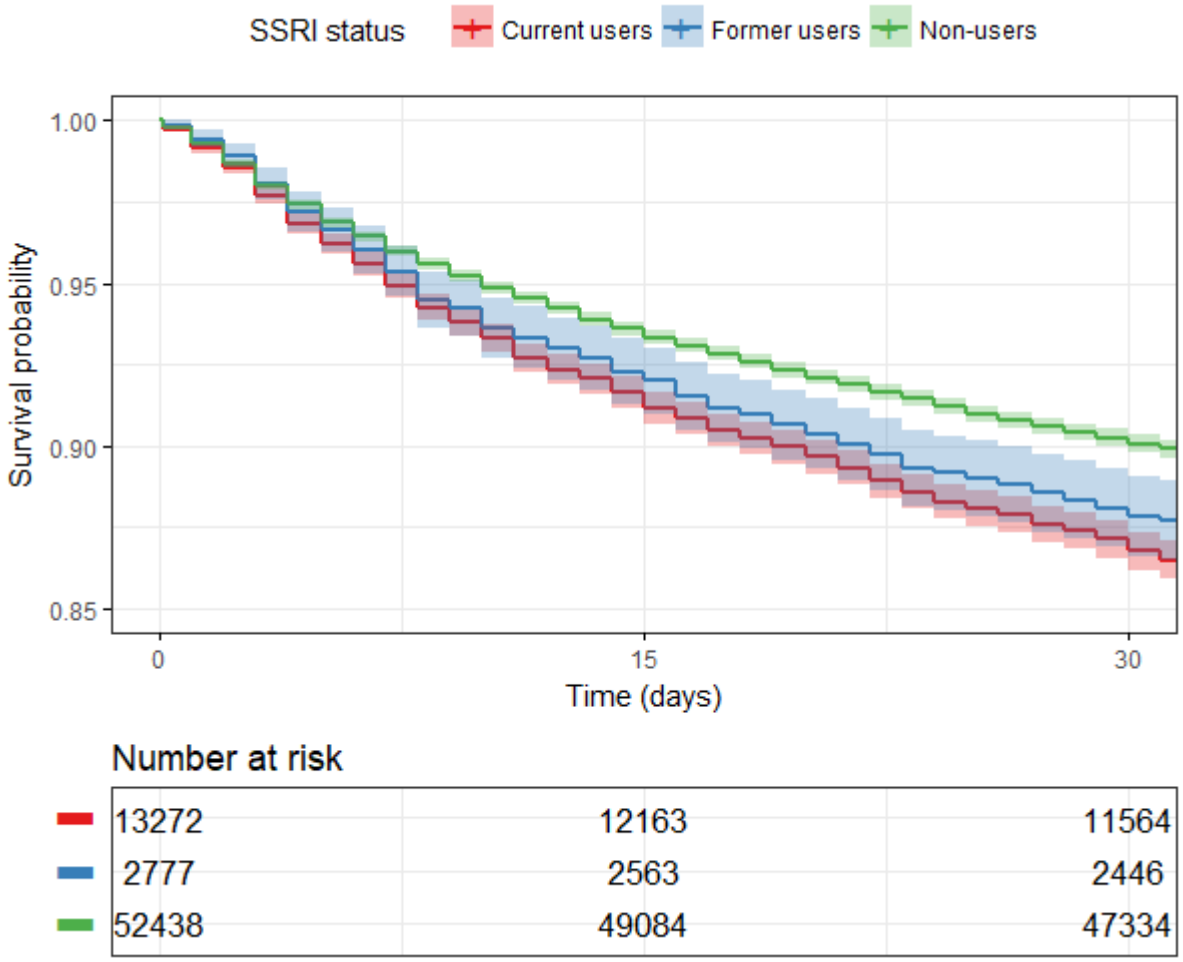


Figure 1: Kaplan-Meyer survival curve showing mortality in hip fracture patients according to selective serotonin reuptake inhibitor (SSRI) use 2006-2016.

Table 2: Cumulative incidences and hazard ratios (HRs) with 95% confidence intervals (CIs) of mortality, readmission, reoperation, and postoperative complications within 30 days of hip fracture surgery according to selective serotonin reuptake inhibitor use 2006-2016 (N=68,487)

	Event/total	Incidence % (95% CI)	Unadjusted HR (95% CI)	Adjusted* HR (95% CI)
Mortality				
Current users	1,755/13,272	13.2 (12.7-12.8)	1.35 (1.28-1.43)	1.16 (1.10-1.21)
Former users	338/2,777	12.2 (11.0-12.5)	1.24 (1.11-1.38)	1.15 (1.04-1.27)
Non-users	5,202/52,438	9.9 (9.7-10.2)	1.00	1.00
Readmission†				
Current users	975/6,305	15.5 (14.6-16.4)	1.30 (1.21-1.39)	1.18 (1.08-1.28)
Former users	215/1,435	15.0 (13.2-16.9)	1.22 (1.06-1.40)	1.12 (0.97-1.28)
Non-users	3,574/28,616	12.5 (12.1-12.9)	1.00	1.00
Reoperation				
Current users	749/13,272	5.6 (5.3-6.0)	1.29 (1.18-1.40)	1.21 (1.11-1.31)
Former users	135/2,777	4.9 (4.1-5.7)	1.10 (0.92-1.30)	1.04 (0.84-1.28)
Non-users	2,353/52,438	4.5 (4.3-4.7)	1.00	1.00
Venous thromboembolism				
Current users	96/13,272	0.7 (0.6-0.9)	0.85 (0.68-1.06)	0.89 (0.67-1.17)
Former users	22/2,777	0.8 (0.5-1.7)	0.92 (0.60-1.42)	0.93 (0.64-1.35)
Non-users	455/52,438	0.9 (0.8-0.9)	1.00	1.00
Myocardial infarction				
Current users	109/13,272	0.8 (0.7-1.0)	1.04 (0.84-1.28)	1.03 (0.81-1.30)
Former users	18/2,777	0.6 (0.4-1.0)	0.82 (0.51-1.31)	0.89 (0.57-1.40)
Non-users	419/52,438	0.8 (0.7-0.9)	1.00	1.00
Stroke				
Current users	176/13,272	1.3 (1.1-1.5)	1.06 (0.90-1.25)	0.93 (0.80-1.09)
Former users	25/2,777	0.9 (0.6-1.3)	0.72 (0.48-1.07)	0.67 (0.44-1.01)
Non-users	662/52,438	1.3 (1.2-1.4)	1.00	1.00
Bleeding				
Current users	218/13,272	1.6 (1.4-1.9)	1.17 (1.01-1.36)	1.06 (0.89-1.28)
Former users	43/2,777	1.5 (1.1-2.1)	1.09 (0.81-1.49)	1.06 (0.69-1.64)
Non-users	750/52,438	1.4 (1.3-1.5)	1.00	1.00

*Adjusted for age, gender, marital status, operation year, myocardial infarction, congestive heart failure, peripheral vascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, liver disease, diabetes type 1 and 2, hemiplegia, moderate to severe renal disease, cancer, non-steroid anti-inflammatory drugs, corticosteroids, anticoagulants, statins, non-SSRI antidepressants, antipsychotics, and clustering by unit setting.

†Restricted to hip fracture patients operated between 2011 and 2016 (n=36,356).

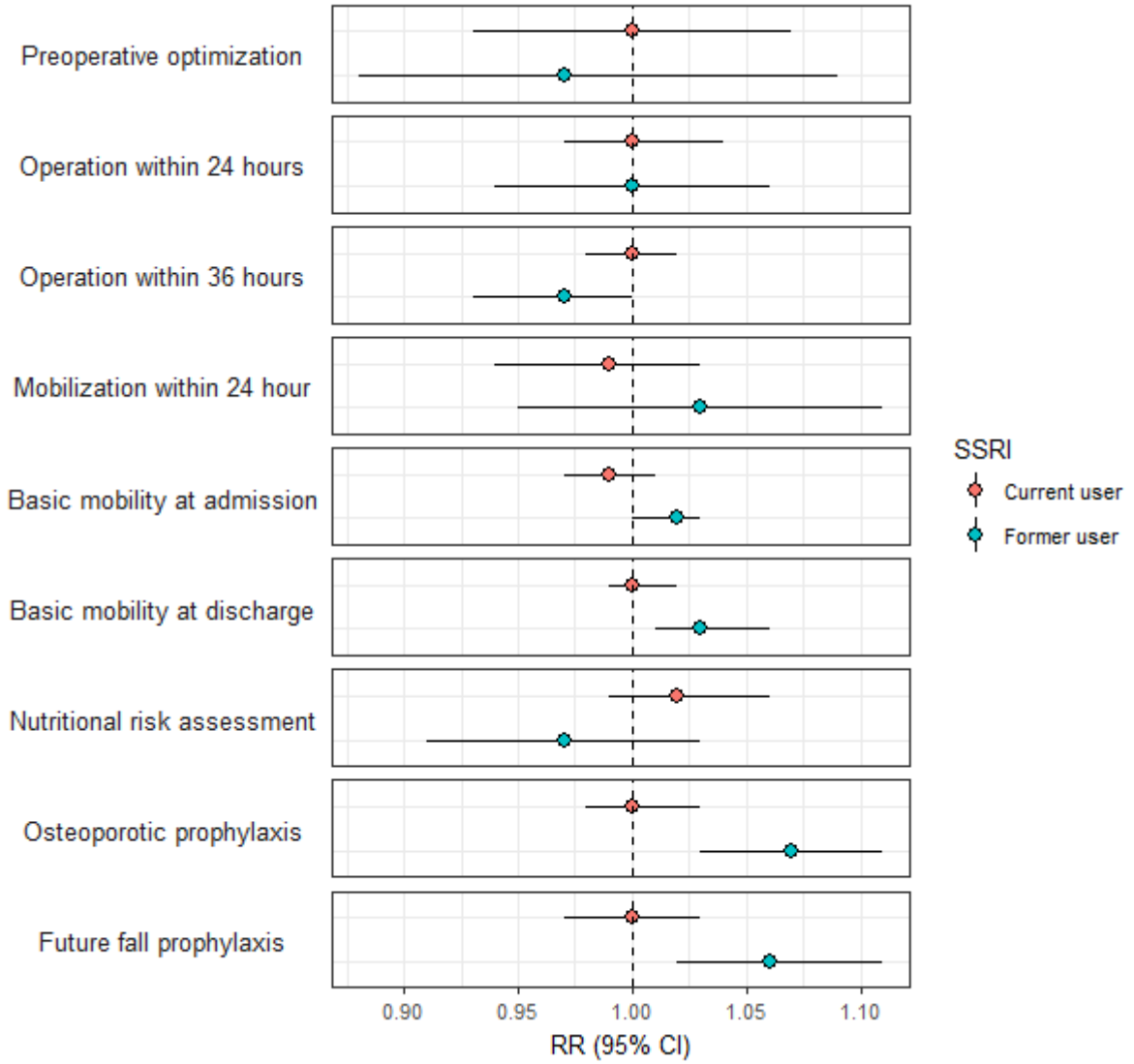


Figure 2: Adjusted relative risks (RRs) with 95% confidence intervals (CIs) of quality of in-hospital care according to selective serotonin reuptake inhibitor (SSRI) use 2015-2016 (N=11,363).

Adjusted for age, gender, marital status, operation year, myocardial infarction, congestive heart failure, peripheral vascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, liver disease, diabetes type 1 and 2, hemiplegia, moderate to severe renal disease, cancer, non-steroid anti-inflammatory drugs, corticosteroids, anticoagulants, statins, non-SSRI antidepressants, antipsychotics, and clustering by unit setting.

Table 3: Unadjusted and adjusted relative risks (RRs) with 95% confidence intervals (CIs) of quality of in-hospital care according to selective serotonin reuptake inhibitor (SSRI) use 2015-2016 (N=11,363)

	Fulfilment (%)	Unadjusted RR (95% CI)	Adjusted* RR (95% CI)
Preoperative optimization	**4,301 (37.9)**		
Non-user	3,491 (38.0)	1.00	1.00
Former user	161 (37.0)	0.97 (0.83-1.14)	0.97 (0.88-1.09)
Current user	649 (37.2)	0.98 (0.90-1.07)	1.00 (0.93-1.07)
Surgery within 24 hours	**7,751 (68.2)**		
Non-user	6,285 (68.4)	1.00	1.00
Former user	291 (66.9)	0.98 (0.87-1.10)	1.00 (0.94-1.06)
Current user	1,175 (67.4)	0.99 (0.93-1.05)	1.00 (0.97-1.04)
Surgery within 36 hours	**9,641 (84.8)**		
Non-user	7,816 (85.1)	1.00	1.00
Former user	354 (81.4)	0.96 (0.86-1.06)	0.97 (0.93-1.00)
Current user	1,471 (84.4)	0.99 (0.94-1.05)	1.00 (0.98-1.02)
Mobilization within 24 hours	**6,483 (57.1)**		
Non-user	5,282 (57.5)	1.00	1.00
Former user	249 (57.2)	1.00 (0.88-1.13)	1.03 (0.95-1.11)
Current user	952 (54.6)	0.95 (0.89-1.02)	0.99 (0.94-1.03)
Basic mobility at admission	**10,383 (91.4)**		
Non-user	8,412 (91.6)	1.00	1.00
Former user	402 (92.4)	1.01 (0.91-1.12)	1.02 (1.00-1.03)
Current user	1,569 (90.0)	0.98 (0.93-1.04)	0.99 (0.97-1.01)
Basic mobility at discharge	**9,945 (87.5)**		
Non-user	8,033 (87.5)	1.00	1.00
Former user	391 (89.9)	1.03 (0.93-1.14)	1.03 (1.01-1.06)
Current user	1,521 (97.3)	1.00 (0.94-1.05)	1.00 (0.99-1.02)
Nutritional status assessment	**9,304 (81.9)**		
Non-user	7,511 (81.8)	1.00	1.00
Former user	344 (79.1)	0.97 (0.87-1.08)	0.97 (0.91-1.03)
Current user	1,449 (83.1)	1.02 (0.96-1.08)	1.02 (0.99-1.06)
Osteoporosis prophylaxis	**9,673 (85.1)**		
Non-user	7,805 (85.0)	1.00	1.00
Former user	392 (90.1)	1.06 (0.96-1.17)	1.07 (1.03-1.11)
Current user	1,476 (84.7)	1.00 (0.94-1.05)	1.00 (0.98-1.03)
Future fall prophylaxis	**9,402 (82.7)**		
Non-user	7,591 (82.7)	1.00	1.00
Former user	380 (87.4)	1.06 (0.95-1.17)	1.06 (1.02-1.11)
Current user	1,431 (82.1)	0.99 (0.94-1.05)	1.00 (0.97-1.03)

*Adjusted for age, gender, marital status, operation year, myocardial infarction, congestive heart failure, peripheral vascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, liver disease, diabetes type 1 and 2, hemiplegia, moderate to severe renal disease, cancer, non-steroid anti-inflammatory drugs, corticosteroids, anticoagulants, statins, non-SSRI antidepressants, antipsychotics, and clustering by unit setting.

Supplementary tables and figures

Supplementary table A: Anatomical Therapeutic Chemical (ATC) codes defining exposure variables

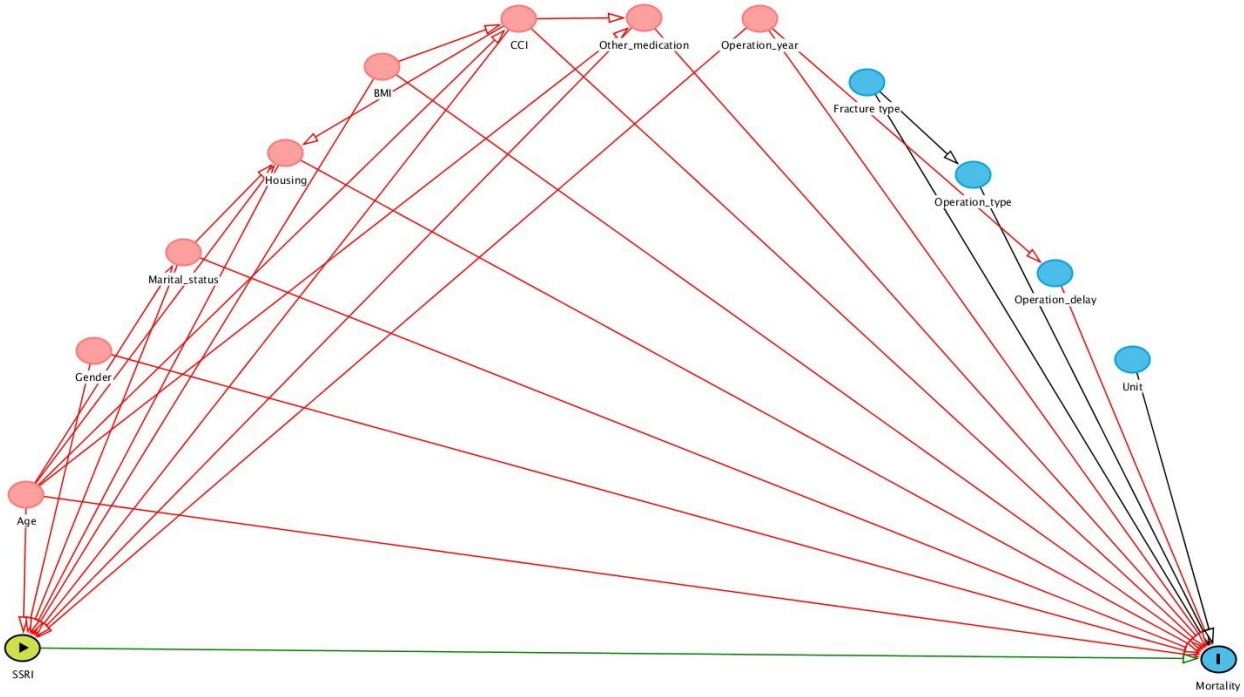
Selective serotonin reuptake inhibitors	**ATC codes**
Fluoxetin	N06AB03
Citalopram	N06AB04
Paroxetin	N06AB05
Sertralin	N06AB06
Fluvoxamin	N06AB08
Escitalopram	N06AB10

Supplementary table B: International Classification of Diseases 10th revision (ICD-10) codes defining outcome variables

Postoperative complications	**ICD-10 codes**
Bleeding	I60-I62, I850, J942, K250, K260, K270, K280, K252, K262, K272, K282, K254, K264, K274, K284, K256, K266, K276, K286, K290, K625, K920-K922, R31, N02, R04
Venous thromboembolism	I801-I803, I26
Myocardial infarction	I21
Ischemic stroke	I63, I64, G459

Supplementary table C: International Classification of Diseases 8th revision (ICD-8), 10th revision (ICD-10) and Anatomical Therapeutic Chemical (ATC) codes defining covariates

Covariates	**Codes**	
Carlson comorbidity index	**ICD-8 codes**	**ICD-10 codes**
Myocardial infarction	410	I21, I22, I23
Congestive heart failure	427.09, 427.10, 427.11, 427.19, 428.99, 782.49	I50, I11.0, I13.0, I13.2
Peripheral vascular disease	440, 441, 442, 443, 444, 445	I70, I71, I72, I73, I74, I77
Cerebrovascular disease	430-438	I60-I69, G45, G46
Dementia	290.09-290.19, 293.09	F00-F03, F05.1, G30
Chronic pulmonary disease	490-493, 515-518	J40-J47, J60-J67, J68.4, J70.1, J70.3, J84.1, J92.0, J96.1, J98.2, J98.3
Connective tissue disease	712, 716, 734, 446, 135.99	M05, M06, M08, M09, M30, M31, M32, M33, M34, M35, M36, D86
Ulcer disease	530.91, 530.98, 531-534	K22.1, K25-K28
Liver disease	571, 573.01, 573.04, 070.00, 070.02, 070.04, 070.06, 070.08, 573.00, 456.00-456.09	B18, K70.0-K70.3, K70.9, K71, K73, K74, K76.0, B15.0, B16.0, B16.2, B19.0, K70.4, K72, K76.6, I85
Diabetes mellitus type 1 and 2	249.00, 249.06, 249.07, 249.09, 250.00, 250.06, 250.07, 250.09, 249.01-249.05, 249.08, 250.01-250.05, 250.08	E10.0, E10.1, E10.9, E11.0, E11.1, E11.9, E10.2-E10.8, E11.2-E11.8
Hemiplegia	344	G81, G82
Moderate to severe renal disease	403, 404, 580-583, 584, 590.09, 593.19, 753.10-753.19, 792	I12, I13, N00-N05, N07, N11, N14, N17-N19, Q61
Cancer	140-194, 204-207, 200-203, 275.59, 195-198, 199	C00-C75, C91-C95, C81-C85, C88, C90, C96, C76-C80
Other medication	**ATC codes**	
NSAIDs	M01A	
Corticosteroids	H02AB	
Anticoagulants	B01A, B01AC06, N02BA	
Statins	C10AA	
Non-SSRI antidepressants	N06AA, N06AF, N06AG, N06AX	
Antipsychotics	N05A	



Supplementary figure A: Directed acyclic graph of the possible relationship between important covariates and mortality in hip fracture patients.

Supplementary table D: Baseline characteristics of hip fracture patients (n=68,487) according to preoperative selective serotonin reuptake inhibitor (SSRI) use 2006-2016 after imputation of body mass index

Variable			SSRIs					
	All patients		Non-users		Former users		Current users	
	n	%	n	%	n	%	n	%
Total	68,487	100	52,438	76.6	2,777	4.0	13,272	19.4
Median age (years)	83		83		83		84	
Age (years)								
65-74	13,271	19.4	10,571	20.2	533	19.2	2,167	16.3
75-84	26,086	38.1	19,768	37.7	1,159	41.7	5,159	38.9
≥ 85	29,130	42.5	22,099	42.1	1,085	39.1	5,946	44.8
Gender								
Male	19,750	28.8	15,541	29.6	730	26.3	3,479	26.2
Female	48,737	71.2	36,897	70.4	2,047	73.7	9,793	73.8
Marital status								
Married	20,300	29.6	16,105	30.7	842	30.3	3.353	25.3
Unmarried	48,187	70.4	36,333	69.3	1,935	69.7	9,919	74.7
Housing								
Own accommodation	31,075	45.4	25,537	48.7	1,126	40.5	4,412	33.2
Homeless	22	<0.1	20	0.1	0	0.0	2	<0.1
Residential institution	7,105	10.4	4,213	8.0	408	14.7	2,484	18.7
Unknown	30,285	44.2	22,668	43.2	1,243	44.8	6,374	48.0
Fracture type								
Fracture of femoral neck	36,341	53.1	27,854	53.1	1,451	52.3	7,036	53.0
Per- and subtrochanteric fracture	32,146	46.9	24,584	46.9	1,326	47.7	6,236	46.9
Operation type								
Alloplastic surgery	46,859	68.4	35,843	68.4	1,902	68.5	9,114	68.7
Osteosynthesis	21,628	31.6	16,595	31.6	875	31.5	4,158	31.3
Operation delay (h)								
<24	41,671	60.8	31,859	60.8	1,721	62.0	8,091	61.0
24-48	12,517	18.3	9,646	18.4	461	16.6	2,410	18.1
>48	14,299	20.9	10,933	20.8	595	21.4	2,771	20.9
Operation year								
2006-2010	32,131	46.9	23,822	45.4	1,342	48.3	6,967	52.5
2011-2016	36,356	53.1	28,616	54.6	1,435	51.7	6,305	47.5
Body mass index (kg/m^2)*								
< 18.5: underweight	7,672	11.2	5,806	11.1	357	12.9	1,509	11.4
≥ 18.5 < 25: normal weight	35,397	51.7	27,163	51.8	1,440	51.8	6,794	51.2
≥ 25: overweight or obese	25,418	37.1	19,469	37.1	980	35.3	4,969	37.4

Supplementary table D continued

Variable			SSRIs					
	All patients		Non-users		Former users		Current users	
	n	%	n	%	n	%	n	%
Charlson comorbidity index								
Low (0)	27,283	39.8	22,505	42.9	840	30.3	3,938	29.7
Medium (1-2)	27,787	40.6	20,365	38.8	1,244	44.8	6,178	46.5
High (3+)	13,417	19.6	9,568	18.3	693	24.9	3,156	23.8
Comorbidity								
Myocardial infarction	3,762	5.5	2,820	5.4	151	5.4	791	6.0
Congestive heart failure	6,289	9.2	4,632	8.8	291	10.5	1,366	10.3
Peripheral vascular disease	5,511	8.1	4,060	7.7	267	9.6	1,184	8.9
Cerebrovascular disease	12,678	18.5	8,467	16.2	689	24.8	3,522	26.5
Dementia	6,733	9.8	3,859	7.4	433	15.6	2,441	19.4
Chronic pulmonary disease	8,663	12.7	6,191	11.8	496	17.9	1,976	14.9
Connective tissue disease	3,243	4.7	2,480	4.7	139	5.0	624	4.7
Ulcer disease	3,855	5.6	2,673	5.1	224	8.1	958	7.2
Liver disease	870	1.3	646	1.2	46	1.7	178	1.3
Diabetes type 1 and 2	6,689	9.8	5,005	9.5	281	10.1	1,403	10.6
Hemiplegia	175	0.3	111	0.2	12	0.4	52	0.4
Moderate to severe renal disease	2,688	3.9	1,973	3.4	132	4.8	583	4.4
Cancer	10,957	16.0	8,351	15.9	501	18.0	2,105	15.9
Other medication								
NSAID	7,681	11.2	5,869	11.2	334	12.0	1,478	11.1
Corticosteroids	4,158	6.1	3,068	5.9	186	6.7	904	6.8
Anticoagulants	26,716	39.0	19,323	36.9	1,064	38.3	6,329	47.7
Statins	13,052	19.1	9,581	18.3	505	19.2	2,966	22.4
Other antidepressants	7,975	11.6	4,977	9.5	596	21.5	2,402	18.1
Antipsychotics	4,992	7.3	2,899	5.5	319	11.5	1,774	13.4

*Body mass index values from m=1 data

Supplementary table E: Incidences and hazard ratios (HRs) with 95% confidence intervals (CIs) of mortality within 30 days of hip fracture surgery according to selective serotonin reuptake inhibitor use 2006-2016 (N=68,487) after imputation of body mass index

	Events	**Incidence (95% CI)**	**Unadjusted HR (95% CI)**	**Adjusted* HR (95% CI)**
Non-user	5,202	9.9 (9.7 to 10.2)	Ref.	Ref.
Former user	338	12.2 (11.0 to 12.5)	1.24 (1.11 to 1.38)	1.12 (1.00 to 1.24)
Current user	1,755	13.2 (12.7 to 12.8)	1.35 (1.28 to 1.43)	1.16 (1.10 to 1.22)

*Adjusted for age, gender, marital status, body mass index, operation year, myocardial infarction, congestive heart failure, peripheral vascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, liver disease, diabetes type 1 and 2, hemiplegia, moderate to severe renal disease, cancer, non-steroid anti-inflammatory drugs, corticosteroids, anticoagulants, statins, non-SSRI antidepressants, antipsychotics, and clustering by unit setting.

Supplementary table F: Baseline characteristics of hip fracture patients (n=68,487) according to preoperative selective serotonin reuptake inhibitor (SSRI) use 2006-2016 after changing the exposure definition

Variable			SSRIs					
	All patients		Non-users		Former users		Current users	
	n	%	n	%	n	%	n	%
Total	68,487	100	52,841	77.2	1,116	1.6	14,530	21.2
Median age (years)	83		83		82		84	
Age (years)								
65-74	13,271	19.4	10,620	20.1	230	20.6	2,421	16.6
75-84	26,086	38.1	19,910	37.7	487	43.6	5,689	39.2
≥ 85	29,130	42.5	22,311	42.2	399	35.8	6,420	44.2
Gender								
Male	19,750	28.8	15,690	29.7	274	24.5	3,786	26.1
Female	48,737	71.2	37,151	70.3	842	75.5	10,744	73.9
Marital status								
Married	20,300	29.6	16,247	30.7	320	28.7	3,733	25.7
Unmarried	48,187	70.4	36,594	69.3	796	71.3	10,797	74.3
Housing								
Own accommodation	31,075	45.4	25,728	48.7	414	37.1	4,933	33.9
Homeless	22	<0.1	17	<0.1	3	0.3	2	<0.1
Residential institution	7,150	10.4	4,232	8.0	190	17.0	2,683	18.5
Unknown	30,285	44.2	22,864	43.3	509	45.6	6,912	47.6
Fracture type								
Fracture of femoral neck	36,341	53.1	28.073	53.1	595	53.3	7.673	52.8
Per- and subtrochanteric fracture	32,146	46.9	24,768	46.9	521	46.7	6,857	47.2
Operation type								
Alloplastic surgery	46,859	68.4	36,122	68.4	761	68.2	9,976	68.7
Osteosynthesis	21,628	31.6	16,719	31.6	355	31.8	4,554	31.3
Operation delay (h)								
<24	41,671	60.8	32,090	60.7	700	62.7	8,881	61.1
24-48	12,517	18.3	9,715	18.4	196	17.6	2,606	17.9
>48	14,299	20.9	11,036	20.9	220	19.7	3,043	21.0
Operation year								
2006-2010	32,131	46.9	24,061	45.5	539	48.3	7,531	51.8
2011-2016	36,356	53.1	28,780	54.5	577	51.7	6,999	48.2
Body mass index (kg/m^2)								
< 18.5: underweight	5,988	8.8	4,623	8.7	104	9.3	1,261	8.7
≥ 18.5 < 25: normal weight	31,582	46.1	24,630	46.6	492	44.1	6,460	44.5
≥ 25: overweight or obese	17,622	25.7	13,616	25.8	292	26.2	3,714	25.5
Unknown	13,295	19.4	9,972	18.9	228	20.4	3,095	21.3

Supplementary table F continued

Variable	All patients		SSRIs					
			Non-users		Former users		Current users	
	n	%	n	%	n	%	n	%
Charlson comorbidity index								
Low (0)	27,283	39.8	22,655	42.9	339	30.4	4,289	29.5
Medium (1-2)	27,787	40.6	20,544	38.9	494	44.3	6,749	46.5
High (3+)	13,417	19.6	9,642	18.2	283	25.3	3,492	24.0
Comorbidity								
Myocardial infarction	3,762	5.5	2,848	5.4	57	5.1	857	5.9
Congestive heart failure	6,289	9.2	4,677	8.9	125	11.2	1,487	10.2
Peripheral vascular disease	5,511	8.1	4,092	7.7	112	10.0	1,307	9.0
Cerebrovascular disease	12,678	18.5	8,549	16.2	278	24.9	3,851	26.5
Dementia	6,733	9.8	3,891	7.4	172	15.4	2,670	18.4
Chronic pulmonary disease	8,663	12.7	6,229	11.8	187	16.8	2,247	15.5
Connective tissue disease	3,243	4.7	2,495	4.7	60	5.4	688	4.7
Ulcer disease	3,855	5.6	2,693	5.1	81	7.3	1,081	7.4
Liver disease	870	1.3	647	1.2	24	2.2	199	1.4
Diabetes type 1 and 2	6,689	9.8	5,041	9.5	131	11.7	1,517	10.4
Hemiplegia	175	0.3	112	0.2	3	0.3	60	0.4
Moderate to severe renal disease	2,688	3.9	1,995	3.8	54	4.8	639	4.4
Cancer	10,957	16.0	8,440	16.0	175	15.7	2,342	16.1
Other medication								
NSAID	7,681	11.2	5,926	11.2	128	11.5	1,627	11.2
Corticosteroids	4,158	6.1	3,100	5.9	86	7.7	972	6.7
Anticoagulants	26,716	39.0	19,520	36.9	425	38.1	6,771	46.6
Statins	13,052	19.1	9,698	18.4	182	16.3	3,172	21.8
Other antidepressants	7,975	11.6	4,905	9.3	372	33.3	2,698	18.6
Antipsychotics	4,992	7.3	2,897	5.5	165	14.8	1,930	13.3

Supplementary table G: Incidences and hazard ratios (HRs) with 95% confidence intervals (CIs) of mortality within 30 days of hip fracture surgery according to selective serotonin reuptake inhibitor use 2006-2016 (N=68,487) after changing the exposure definition

	Events	**Incidence (95% CI)**	**Unadjusted HR (95% CI)**	**Adjusted* HR (95% CI)**
Non-user	5,251	9.9 (9.7 to 10.2)	Ref.	Ref.
Former user	137	12.3 (10.5 to 14.4)	1.25 (1.05 to 1.48)	1.12 (0.97 to 1.30)
Current user	1,907	13.1 (12.6 to 13.7)	1.34 (1.27 to 1.41)	1.16 (1.10 to 1.21)

*Adjusted for age, gender, marital status, operation year, myocardial infarction, congestive heart failure, peripheral vascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, liver disease, diabetes type 1 and 2, hemiplegia, moderate to severe renal disease, cancer, non-steroid anti-inflammatory drugs, corticosteroids, anticoagulants, statins, non-SSRI antidepressants, antipsychotics, and clustering by unit setting.

Reports/PhD theses from Department of Clinical Epidemiology

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

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122. Sara Søndergaard Schwartz: Incidence and mortality of pulmonary hypertension in adults with congenital heart disease. Research year report. *2017*.

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