

Selective serotonin reuptake inhibitor use and mortality, postoperative complications, and quality of care in hip fracture patients: a Danish nationwide cohort study

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Purpose: To examine the association between selective serotonin reuptake inhibitor (SSRI) use and mortality, postoperative complications, and quality of in-hospital care in hip fracture patients.

Patients and methods: The study was a nationwide cohort study based on individual-level linked, prospectively collected data from Danish population-based national registries covering all hospitals in Denmark. The health care system in Denmark is tax-funded, and all citizens have equal access to health care services. We included patients with first-time hospitalization due to hip fracture undergoing surgery from 2006–2016. We estimated the risk of 30-day mortality, any unplanned readmission, any reoperation, specific postoperative complications including cardiovascular events and major bleeding, and quality of in-hospital care using Cox and Poisson regression analyses 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, 1.10–1.21) and 12% in former (HR 1.15, 1.04–1.27) compared with 10% in non-users. The HR for any unplanned readmission was 1.11 (1.02–1.20) in current and 1.13 (1.01–1.27) in former SSRI users and for any reoperation 1.21 (1.11–1.31) in current and 1.04 (0.84–1.28) 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.

Conclusion: 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 SSRI had a 26% increased reoperation risk compared with non-users. However, SSRI use was not associated with increased risk of other postoperative complications and lower quality of in-hospital care. A limitation of this study was the inability to control for potential confounding of social deprivation.

Keywords: cohort studies, hip fracture, mortality, postoperative complications, quality of care, selective serotonin reuptake inhibitors

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Introduction

Hip fracture is a frequent surgical procedure among the elderly.¹ It correlates with high medical costs and health care utilization² and confers increased risk of mortality.³ Thirty-day mortality in elderly surgically treated hip fracture patients is 10% and

increases to 30% within 1 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 ~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 medications including selective serotonin reuptake inhibitors (SSRIs).⁸ SSRIs are prescribed to 10% of Danish elderly aged 65 years or older.⁹ The most common indications for SSRI prescribing are depression and anxiety.¹⁰ In general, SSRI use appears to increase the risk of mortality, new cardiovascular events, and postoperative bleeding.^{6,11} Previous studies among patients undergoing major surgery, including orthopedic surgeries, reported higher risk of mortality, readmission, and blood transfusion in those using SSRIs perioperatively.^{12,13} However, a study including orthopedic patients showed no evidence that SSRI use increased the risk of receiving a blood transfusion.¹⁴ 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.

Ethics approval

Ethical approval was not required according to the Danish Act on Research Ethics Review of Health Research Projects due to the register-based nature of the study. The study was approved by the Danish Data Protection Agency (record number: 1-16-02-467-15).

Patients and 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.¹⁵ 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 Registry¹⁶ 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 System¹⁷ 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 Registry¹⁸ 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 ICD-8 until the end of 1993 and ICD-10 thereafter. The Danish National Database of Reimbursed Prescriptions¹⁹ 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.

Participants

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 January 1, 2006, and December 31, 2016, to ensure at least 2 years prescription history. Patients with missing data on operation delay (n=119) were excluded. In total, 68,487 first-time hip fracture patients who received surgery from 2006–2016 were available for analyses.

Variables

Exposure

All redeemed prescriptions for SSRIs 1 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.

Outcomes

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 unplanned 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 measures²⁰ 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, BMI, fracture type, operation type, and operation delay information was 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/m²), normal weight (BMI ≥18.5 <25 kg/m²), overweight or obese (BMI ≥25 kg/m²), 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 original Charlson Comorbidity Index (CCI) score. The CCI was categorized as low (score 0), medium (score 1–2), and high (score ≥3) comorbidity score, slightly modified compared with the original CCI.²¹ The following medications were assessed from the Danish National Database of Reimbursed Prescriptions: non-steroidal anti-inflammatory drugs, 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 Tables S1–S3.

Statistical methods

Main analyses

Patient characteristics were tabulated according to SSRI use. All patients were followed from operation date to death, any unplanned 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 HRs with 95% CIs 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 on from January 1, 2011 onward, thus readmission analyses were restricted to patients operated on between January 1, 2011 and December 31, 2016. RRs 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 on between January 1, 2015 and December 31, 2016. Potential confounder assessment was done using a directed acyclic graph (Figure S1).²² 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 (Supplementary materials).²³ Missing housing data were not imputed due to lack of predictors. Second, the exposure definition was changed to address potential compliance problems; current SSRI users redeemed two prescriptions within 2 years, of which one prescription was redeemed within 8 months before hip fracture, former users redeemed two prescriptions between 8 months and 2 years, and non-users redeemed one or no prescriptions within 2 years before hip fracture. The mortality analysis was repeated including BMI in the Cox regression model and employing a new exposure definition. Cox and Poisson regression analyses were performed using Stata 14 for Windows (StataCorp LP, College Station, TX, USA). The Kaplan–Meier plot was produced using 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 (IQR 78–89 years) and 83 years in former users (IQR 77–88 years) and non-users (IQR 77–89 years). 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. From the available housing data, we observed that SSRI non-users (25,537 [49%]) more often lived in their own accommodation compared with current (4,412 [33%]) and former (1,126 [41%]) 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 (1.10–1.21) in current users and 1.15 (1.04–1.27) 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 unplanned 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, 1.02–1.20) and former users (HR 1.13, 1.01–1.27) had a higher readmission risk compared with non-users. Current SSRI users had a higher reoperation risk (HR 1.21, 1.11–1.31) compared with non-users while there was no difference between former users (HR 1.04, 0.84–1.28) and non-users.

Other 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, 0.67–1.17), MI (HR 1.03, 0.81–1.30), stroke (HR 0.93, 0.80–1.09), and bleeding (HR 1.06, 0.89–1.28) as non-users. Likewise, former SSRI users had a similar risk of VTE (HR 0.93, 0.64–1.35), MI (HR 0.89, 0.57–1.40), stroke (HR 0.67, 0.44–1.01), and bleeding (HR 1.06, 0.69–1.64) as non-users.

Quality of in-hospital care

The analyses included 11,363 patients operated on during 2015–2016. Figure 2 shows a marginally higher chance of assessment of basic mobility at discharge, osteoporosis prophylaxis, and future fall prophylaxis in former SSRI users compared with non-users. Overall, there was no association between current and former SSRI use and quality of in-hospital care (Table S4).

Sensitivity analysis

The HRs of mortality did not materially change after multiple imputation of missing BMI values and adjustment for BMI (Tables S5 and S6). 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 of the exposure groups used in the main analysis and the HRs of mortality were similar to the main analysis results (Tables S7 and S8).

Discussion

In this nationwide cohort study of hip fracture surgery patients, 30-day mortality and overall readmission were elevated for 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 prospectively collected data from Danish population-based registries with complete follow-up.^{19,24–26} 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,^{27,28} 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

Table 1 Baseline characteristics of hip fracture patients (n=68,487) according to preoperative selective serotonin reuptake inhibitor use 2006–2016

Characteristics	All patients (N=68,487)		SSRI status					
	n	%	Current users (N=13,272)		Former users (N=2,777)		Non-users (N=52,438)	
			n	%	n	%	n	%
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 (hours)								
<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
BMI (kg/m²)								
<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
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

(Continued)

Table 1 (Continued)

Characteristics	All patients (N=68,487)		SSRI status					
			Current users (N=13,272)		Former users (N=2,777)		Non-users (N=52,438)	
	n	%	n	%	n	%	n	%
NSAIDs	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

Abbreviations: SSRI, selective serotonin reuptake inhibitor; NSAIDs, non-steroidal anti-inflammatory drugs.

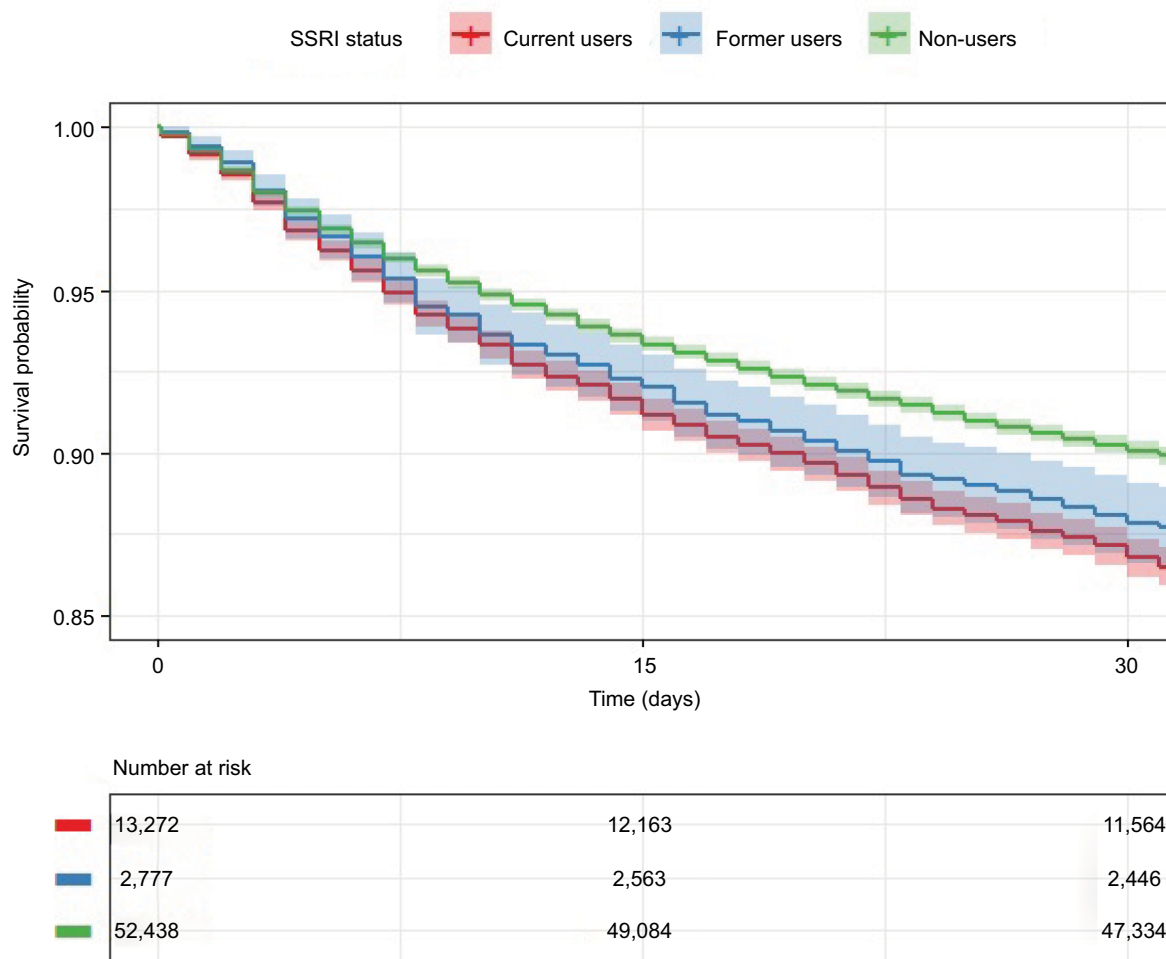


Figure 1 Kaplan–Meyer survival curve showing mortality in hip fracture patients according to selective serotonin reuptake inhibitor (SSRI) use 2006–2016.

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 gathered comprehensive data on potential confounders including complete in-hospital comorbidity history com-

pared in the CCI²⁶ 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. However, we included information on

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

	Event/total	Incidence % (95% CI)	Unadjusted HR (95% CI)	Adjusted ^a 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^b				
Current users	1,192/6,305	19.0 (18.0–19.9)	1.21 (1.14–1.29)	1.11 (1.02–1.20)
Former users	280/1,435	19.6 (17.5–21.6)	1.24 (1.10–1.40)	1.13 (1.01–1.27)
Non-users	4,642/28,616	16.3 (15.8–16.7)	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
VTE				
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
MI				
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

Notes: ^aAdjusted for age, gender, marital status, operation year, MI, 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-steroidal anti-inflammatory drugs, corticosteroids, anticoagulants, statins, non-SSRI antidepressants, antipsychotics, and clustering by unit setting. ^bRestricted to hip fracture patients operated on between 2011 and 2016.

Abbreviations: VTE, venous thromboembolism; MI, myocardial infarction.

other medication, which may indicate treatment of conditions not captured in the CCI. The registries we used did not contain information on socioeconomic status, smoking, alcohol use, and other lifestyle factors. Furthermore, almost half of the patients were missing data on housing, making control of confounding difficult. Thus, we were not able to control for the potential confounding of social deprivation and lack of these data may have resulted in unmeasured and residual confounding. Information on comorbidities, other medication, marital status, and unit setting may contribute to control of confounding, but is not an adequate measure of social deprivation.

We included former SSRI users as a negative control. That is, we anticipated that former users were more similar to current users than non-users regarding potential confounding factors such as socioeconomic status and lifestyle factors.

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.²⁹

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 redeemed the prescriptions, our estimates most likely reflect actual drug use. Even considering misclassification, dispensed prescriptions are considered a good measure of medication intake.³⁰ Furthermore, we had no data on in-hospital medication use. This may not have influenced the outcome

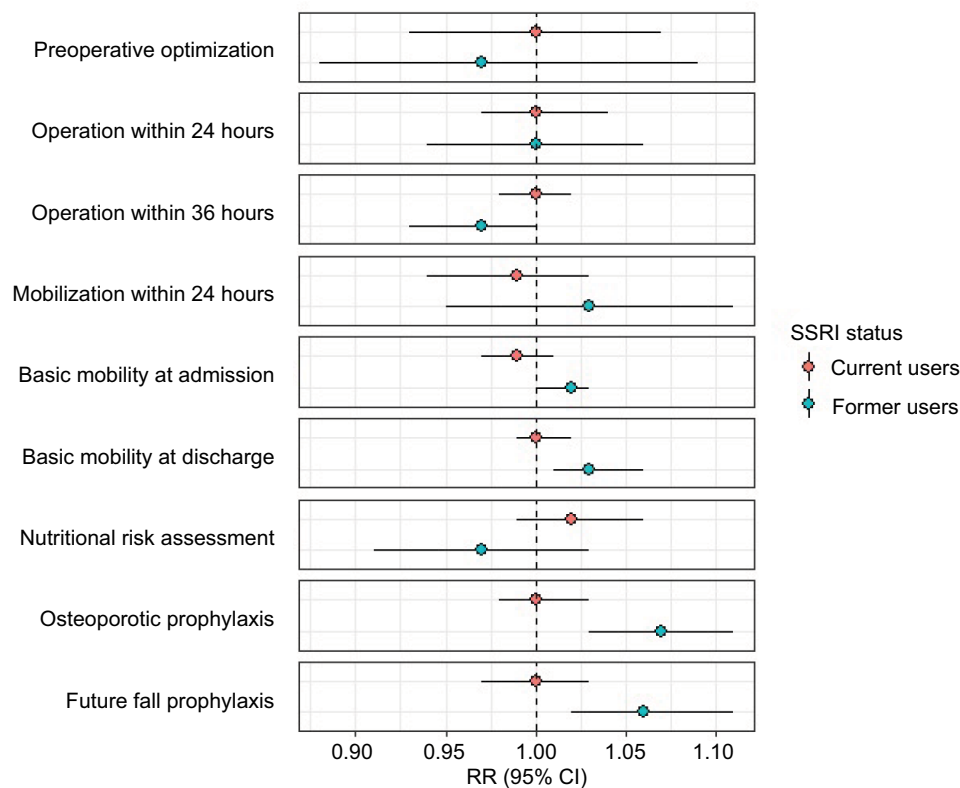


Figure 2 Adjusted RRs with 95% CIs of quality of in-hospital care comparing current and former selective serotonin reuptake inhibitor (SSRI) users with non-users (reference) 2015–2016 (N=11,363).

Notes: 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-steroidal anti-inflammatory drugs, corticosteroids, anticoagulants, statins, non-SSRI antidepressants, antipsychotics, and clustering by unit setting.

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 lifestyle 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.¹² However, the association found by Auerbach et al was attenuated in patients with depression suggesting that the underlying psychiatric indication for SSRI use may explain the increased risk rather than SSRIs in itself.¹² A meta-analysis by Maslej et al found an increased mortality in antidepressant users compared to non-users in the general population independent of treatment indication.³¹ The most common indications for SSRI treat-

ment are depression and anxiety¹⁰ and a systematic review by Eaton et al showed that depression and anxiety correlate with increased mortality.³² Mortality in hip fracture patients may also be influenced by socioeconomic status,³³ and Marinacci et al found an association between lower education level and mortality.³⁴ Lower education level is further associated with increased risk of psychiatric admission due to schizophrenia, alcoholism, drug dependency, affective psychosis, neurosis, and personality disorder.³⁵ 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.³⁶ 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 the findings reported by Auerbach et al in major surgery patients. In their study, this association persisted in patients receiving SSRIs for depression, but not in patients receiving SSRIs for other reasons.¹² This

also suggests that SSRI use may not be a risk factor in itself but a marker of underlying disease or risk factors. A meta-analysis by Pizzi et al found no association between SSRI use and readmission in patients with coronary heart disease and depression, further supporting our results that SSRI use may not be a risk factor in itself.³⁷

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, eg, wound dehiscence, infection, and bleeding,²⁰ 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.³⁸ However, Tully et al showed no association between serotonergic antidepressant use and reoperation due to infection or bleeding after coronary artery bypass graft surgery.³⁹ 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 have investigated the association between SSRI use and the previously 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.¹² Tully et al showed no association between SSRI use and MI, stroke, or bleeding after coronary artery bypass graft surgery,³⁹ 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.⁴⁰ 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. Our analysis suggests that stopping

SSRI treatment after surgery would not change the mortality and overall readmission since these were similar in current and former users compared with non-users. We found that overall reoperation 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. Our findings call for increased clinical awareness of hip fracture patients using SSRIs as they may have an increased risk of mortality, unplanned readmission, and reoperation. This patient group may be more prone to adverse outcomes after surgery regardless of the indication for SSRI treatment and may benefit from improved models of care. The follow-up care in Denmark is carried out by the municipality. Our findings suggest that hip fracture patients currently or formerly using SSRIs may benefit from closer follow-up and better communication between hospital, municipality, and general practitioner. However, the content and implementation of such improvements are beyond the scope of this paper. In future studies, it may be relevant to investigate how social deprivation influences surgical outcomes for these patients.

Conclusion

Thirty-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.

Data availability

The authors are not authorized to share the data as it were assessed via the data custodian, ie, the Danish National Data Board.

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Author contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

Table SI ICD-8 and ICD-10 diagnosis codes from the Danish National Patient Registry

Variable	Codes	
Disease	ICD-8 diagnosis codes	ICD-10 diagnosis 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 type 1 and type 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
Intracranial bleeding		I60–I62
Esophagus varices with bleeding		I850
Hemothorax		J942
Acute ulcer with bleeding		K250, K260, K270, K280
Acute ulcer with bleeding and perforation		K252, K262, K272, K282
Chronic or non-specified ulcer with bleeding		K254, K264, K274, K284
Chronic or non-specified ulcer with bleeding and perforation		K256, K266, K276, K286
Acute bleeding gastritis		K290
Bleeding from anus or rectum		K625
Gastrointestinal bleeding		K920–K922
Hematuria		R31, N02
Airway bleeding		R04
Deep venous thromboembolism		I801–I803
Lung embolism		I26
Acute myocardial infarction		I21
Brain infarction		I63
Apoplexy, unspecified		I64
Transitory cerebral infarction		G459

Table S2 Codes from the Danish Multidisciplinary Hip Fracture Registry

Description	Codes
Housing	
Procedure code specifying housing	ZZ8050
Own accommodation	ZRSB01
Own accommodation in association with an institution	ZRSB01A
Homeless	ZRSB02
Residential institution	ZRSB04
No information on housing	ZRSB09
Fracture type	
Fracture of the femoral neck	S72.0
Pertrochanteric fracture	S72.1
Subtrochanteric fracture	S72.2
Operation type	
Primary insertion of joint prosthesis in hip joint	KNFB.0–99
Fracture treatments in femur (including osteosynthesis)	KNFJ.4–9
BMI	
Procedure code determining BMI	ZZ0242
BMI 10–80	VPH0010 – VPH0080
BMI 10–80	VPK10K00 – VPK80K00
Assessment of the patient's nutritional risk	
Preparation of nutritional plan	ZZ2009C
Assessment: no indication for preparation of nutritional plan	ZZ2009D
Systematic pain assessment during mobilization of the patient	
Systematic assessment of pain using pain scale	ZZV008A
Pain assessment attempted: not possible	ZZV008Z
Early mobilization within 24 hours of surgery	
Early mobilization commenced	ZZP0030A
Assessed, no indication for early mobilization	ZZP0030C
Date of mobilization (eg, ZT20160602)	ZT ^a
Time of mobilization (eg, ZU1430)	ZU ^a
Assessment of basic mobility before admission for hip fracture	
Assessment of the basic mobility prior to fracture	ZZV020G1
Cumulated Ambulation Score (CAS)	ZRRA00 – ZRRA09
Assessment of basic mobility before discharge	
Assessment of basic mobility at discharge	ZZV020G2
CAS	ZRRA00 – ZRRA09
Initiation of rehabilitation program	
Preparation of rehabilitation plan, general rehabilitation	ZZ0175X
Preparation of rehabilitation plan, specialized rehabilitation	ZZ0175Y
Preparation of rehabilitation plan, rehabilitation in the specialized level	ZZ0175V
Assessment of need for rehabilitation, no rehabilitation	ZZ0172W
Osteoporosis prophylaxis	
Treatment with medicine for osteoporosis	BLHM7
Evaluation of the indication for drug therapy for osteoporosis	ZZV010A1A
Pending complete investigation regarding indication for drug therapy for osteoporosis	ZZV010A1X
Fall prophylaxis	
Offer of fall prophylaxis given	ZZ5707B1
Assessment of need for fall prophylaxis: no indication	ZZ5707A
Surgery delay	
Indicates the percentage of patients who are operated on within 24 hours of arrival at hospital	2A
Indicates the percentage of patients who are operated on within 36 hours of arrival at hospital	2B

Note: ^aNumber specifying the date or time of mobilization.

Table S3 Anatomical Therapeutic Chemical (ATC) codes from the Danish National Database of Reimbursed Prescriptions

Selective serotonin reuptake inhibitor (SSRI)	ATC codes
Citalopram	N06AB04
Escitalopram	N06AB10
Fluoxetine	N06AB03
Fluvoxamine	N06AB08
Paroxetine	N06AB05
Sertraline	N06AB06
Other medication	
Non-SSRI antidepressants	N06AA, N06AF, N06AG, N06AX
Antipsychotics	N05A
Antithrombotic medicine	B01A
Non-steroidal anti-inflammatory drugs	M01A
Corticosteroids	H02AB
Statins	C10AA

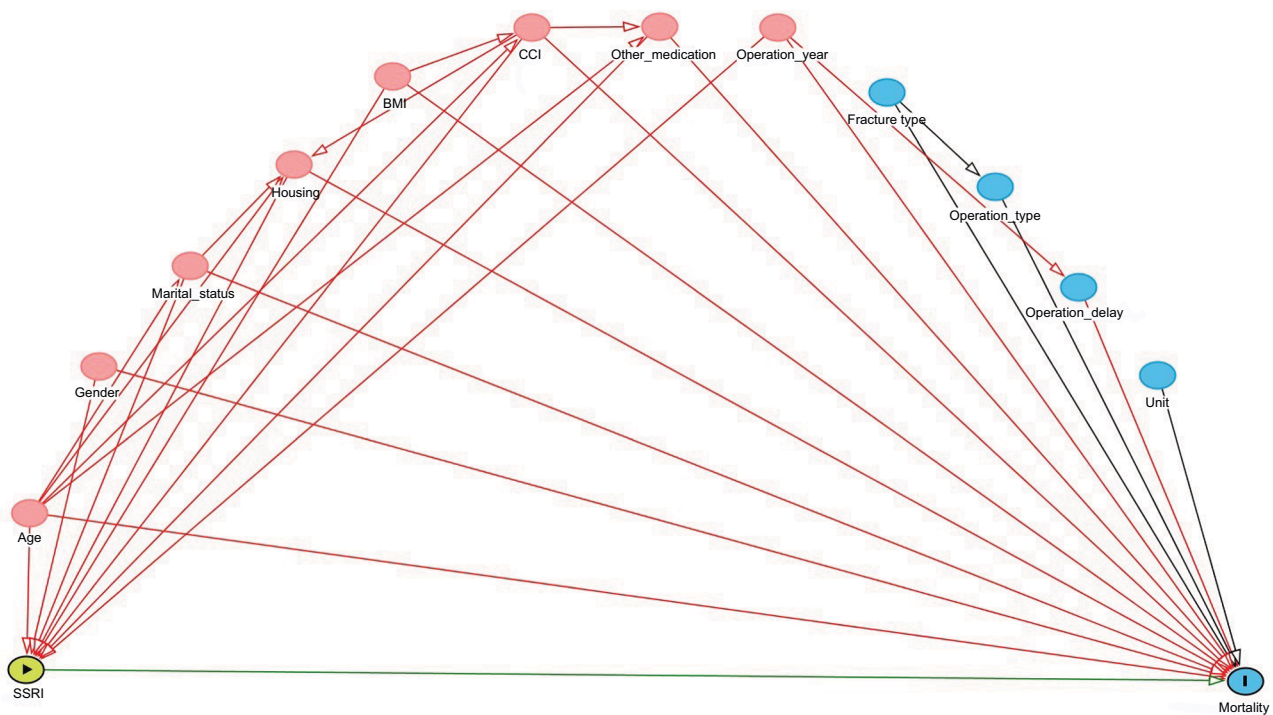


Figure S1 Directed acyclic graph of the possible relationship between important covariates and mortality in hip fracture patients.

Abbreviations: SSRI, selective serotonin reuptake inhibitor; CCI, Charlson Comorbidity Index.

Table S4 Unadjusted and adjusted RRs with 95% 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 ^a RR (95% CI)
Preoperative optimization	4,301 (37.9)		
Current user	649 (37.2)	0.98 (0.90–1.07)	1.00 (0.93–1.07)
Former user	161 (37.0)	0.97 (0.83–1.14)	0.97 (0.88–1.09)
Non-user	3,491 (38.0)	1.00	1.00
Surgery within 24 hours	7,751 (68.2)		
Current user	1,175 (67.4)	0.99 (0.93–1.05)	1.00 (0.97–1.04)
Former user	291 (66.9)	0.98 (0.87–1.10)	1.00 (0.94–1.06)
Non-user	6,285 (68.4)	1.00	1.00
Surgery within 36 hours	9,641 (84.8)		
Current user	1,471 (84.4)	0.99 (0.94–1.05)	1.00 (0.98–1.02)
Former user	354 (81.4)	0.96 (0.86–1.06)	0.97 (0.93–1.00)
Non-user	7,816 (85.1)	1.00	1.00
Mobilization within 24 hours	6,483 (57.1)		
Current user	952 (54.6)	0.95 (0.89–1.02)	0.99 (0.94–1.03)
Former user	249 (57.2)	1.00 (0.88–1.13)	1.03 (0.95–1.11)
Non-user	5,282 (57.5)	1.00	1.00
Basic mobility at admission	10,383 (91.4)		
Current user	1,569 (90.0)	0.98 (0.93–1.04)	0.99 (0.97–1.01)
Former user	402 (92.4)	1.01 (0.91–1.12)	1.02 (1.00–1.03)
Non-user	8,412 (91.6)	1.00	1.00
Basic mobility at discharge	9,945 (87.5)		
Current user	1,521 (97.3)	1.00 (0.94–1.05)	1.00 (0.99–1.02)
Former user	391 (89.9)	1.03 (0.93–1.14)	1.03 (1.01–1.06)
Non-user	8,033 (87.5)	1.00	1.00
Nutritional status assessment	9,304 (81.9)		
Current user	1,449 (83.1)	1.02 (0.96–1.08)	1.02 (0.99–1.06)
Former user	344 (79.1)	0.97 (0.87–1.08)	0.97 (0.91–1.03)
Non-user	7,511 (81.8)	1.00	1.00
Osteoporosis prophylaxis	9,673 (85.1)		
Current user	1,476 (84.7)	1.00 (0.94–1.05)	1.00 (0.98–1.03)
Former user	392 (90.1)	1.06 (0.96–1.17)	1.07 (1.03–1.11)
Non-user	7,805 (85.0)	1.00	1.00
Future fall prophylaxis	9,402 (82.7)		
Current user	1,431 (82.1)	0.99 (0.94–1.05)	1.00 (0.97–1.03)
Former user	380 (87.4)	1.06 (0.95–1.17)	1.06 (1.02–1.11)
Non-user	7,591 (82.7)	1.00	1.00

Notes: ^aAdjusted 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-steroidal anti-inflammatory drugs, corticosteroids, anticoagulants, statins, non-SSRI antidepressants, antipsychotics, and clustering by unit setting. The numbers in bold represent the total number of patients fulfilling each process-performance measure.

Sensitivity analyses

Multiple imputation

Methods

In the multiple imputation model, we included all variables that were in the subsequent analysis model: selective serotonin reuptake inhibitors (SSRIs), age, gender, marital status, operation year, BMI, comorbidities, and other medication. Further-

more, some auxiliary variables such as operation delay, fracture type, operation type, and postoperative complications were included. Imputation of BMI 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. The measures of association from each imputed dataset were combined using Rubin's rule.

Table S5 Baseline characteristics of hip fracture patients (n=68,487) according to preoperative selective serotonin reuptake inhibitor (SSRI) use 2006–2016 after imputation of BMI

Variables	All patients		SSRI					
	n	%	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 (hours)								
<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
BMI (kg/m²)^a								
<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
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

(Continued)

Table S5 (Continued)

Variables	All patients		SSRI					
			Non-users		Former users		Current users	
	n	%	n	%	n	%	n	%
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								
NSAIDs	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

Note: *BMI values from $m = 1$ data.

Abbreviation: NSAIDs, non-steroidal anti-inflammatory drugs.

Table S6 Incidences and HRs with 95% CIs of mortality within 30 days of hip fracture surgery according to selective serotonin reuptake inhibitor (SSRI) use 2006–2016 (N=68,487) after imputation of BMI

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

Notes: *Adjusted for age, gender, marital status, BMI, 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-steroidal anti-inflammatory drugs, corticosteroids, anticoagulants, statins, non-SSRI antidepressants, antipsychotics, and clustering by unit setting.

Table S7 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

Variables	All patients		SSRIs					
			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 (hours)								
<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
BMI (kg/m²)								
<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
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

(Continued)

Table S7 (Continued)

Variables	All patients		SSRIs					
			Non-users		Former users		Current users	
	n	%	n	%	n	%	n	%
Other medication								
NSAIDs	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

Abbreviation: NSAIDs, non-steroidal anti-inflammatory drugs.

Table S8 Incidences and HRs with 95% CIs of mortality within 30 days of hip fracture surgery according to selective serotonin reuptake inhibitor (SSRI) use 2006–2016 (N=68,487) after changing the exposure definition

	Events	Incidence (95% CI)	Unadjusted HR (95% CI)	Adjusted ^a HR (95% CI)
Current user	1,907	13.1 (12.6–13.7)	1.34 (1.27–1.41)	1.16 (1.10–1.21)
Former user	137	12.3 (10.5–14.4)	1.25 (1.05–1.48)	1.12 (0.97–1.30)
Non-user	5,251	9.9 (9.7–10.2)	1.00	1.00

Notes: ^aAdjusted 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-steroidal anti-inflammatory drugs, corticosteroids, anticoagulants, statins, non-SSRI antidepressants, antipsychotics, and clustering by unit setting.

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