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Risk factors for new chronic opioid use after hip fracture surgery: a Danish nationwide cohort study from 2005 to 2016 using the Danish Multidisciplinary Hip Fracture Registry

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Abstract

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Objective

To examine the risk factors for new chronic opioid use in elderly hip fracture surgery patients.

Design

Prospective population-based cohort study.

Setting and participants

Using Danish nationwide health registries, we identified all opioid non-user patients aged ≥65 years who had undergone hip fracture surgery from 2005-2016 and were alive within the first year following surgery.

Main outcome measures

New chronic opioid use defined by the dispensing of at least 2 prescription opioids within 2 of the last 3 quarters during the first year following surgery.

Results

We identified 37,202 opioid non-user patients who underwent hip fracture surgery. Of these, 5,497 (15%) developed new chronic opioid user within 1 year of surgery.

Risk factors for new chronic opioid use were BMI <18.5 (adjusted Odds Ratio (aOR) 1.22 (95% confidence interval (95% CI) 1.09-1.36)), BMI 25-29.9 (aOR 1.12 (95% CI 1.04-1.21)), and BMI ≥30 (aOR 1.57 (95% CI 1.40-1.76)) with BMI 18.6-24.9 as reference, a per-/subtrochanteric fracture (aOR 1.27 (95% CI 1.20-1.34)) with femoral neck fracture as reference, preoperative use (versus no-use) of NSAID (aOR 1.68 (95% CI 1.55-1.83)), SSRI (aOR 1.42 (95% CI 1.32-1.53)), antidepressants (aOR 1.36 (95% CI 1.24-1.49)), antipsychotics (aOR 1.21 (95% CI 1.07-1.35)), corticosteroids (aOR 1.54 (95% CI 1.35-1.76)), statins (aOR 1.09 (95% CI 1.02-1.18)), antibiotics (aOR 1.32 (95% CI 1.22-1.42)), anti-osteoporosis drugs (aOR 1.33 (95% CI 1.19-1.49)), anticoagulantives (aOR 1.24 (95% CI 1.17-1.32)), and antiplatelet drugs (aOR 1.24 (95% CI 1.16-1.32)). Presence of cardiovascular comorbidities, diabetes, gastrointestinal diseases, dementia, COPD, or renal diseases were further identified as risk factors.

Conclusion

In this large nationwide cohort study, we identified several risk factors associated with new chronic opioid use after hip fracture surgery. Although not all factors are modifiable preoperative, this will allow clinicians to appropriately counsel patients preoperatively and tailor postoperative treatment.

Article Summary

Strengths and limitations of this study

- The strengths of this study includes a large prospective population-based cohort design with complete follow-up based on Danish nationwide health registries allowing us to identified 37,202 patients with hip fracture surgery.
- Other strengths were comprehensive high-quality data on medication use and comorbidities prior surgery, detailed clinical data on hip fracture patients, and opioid information based on registry data rather that patient-reported data.
- We identified several risk factors associated with new chronic opioid use after hip fracture surgery.
- Our study has several limitations including a lack of consensus on how to define new chronic opioid use, inability to extract reasons for opioid prescriptions, inability to measure patient compliance with opioid prescriptions, and no information on re-operation.

Word count: 3331

Introduction

The prevalence of hip fractures is estimated to reach 6.3 million people worldwide by 2050 [1]. Hip fracture patients often suffer from comorbidities and polypharmacy, which have been associated with an increased risk of complications and increased mortality. In addition, postsurgical pain can delay mobilization and rehabilitation[2]. These factors make treatment and rehabilitation for hip fracture surgery patients challenging.

Opioids are commonly accepted as standard clinical practice for pain treatment in hip fracture surgery patients. However, initial prescription opioid treatment for acute postsurgical pain still merits caution as it can result in chronic opioid use [3]. Previous studies have shown that a high percentage of hip fracture patients who did not use opioids before their hip fracture were still using opioids several months after surgery [4 5]. This is concerning as chronic prescription opioid use can have a negative impact on quality of life [6], has been associated with increased risk of sustaining new fractures [7] and other adverse events including general medical complications [3].

The risk of chronic opioid use can be influenced by patient-related, surgical and healthcare-related factors, some of which are modifiable (weight, medication, surgery type) whereas others are non-modifiable (age, gender). Only few studies have investigated risk factors for chronic opioid use in orthopedic patients. Moreover, these studies are limited by small sample sizes, study populations that differ from the hip fracture population, varying definitions of opioid use, different follow-up duration, and lack of adjustment for potential confounders [8 9]. No previous studies have investigated risk factors for chronic opioid use after hip fracture surgery. Thus, there is a need for more knowledge on risk factors for new chronic opioid use in hip fracture patients, in particular risk factors that are modifiable during pre-, peri-, and postoperative period.

The aim of this study was to examine patient-related and surgery-related risk factors associated with new chronic opioid use in elderly hip fracture surgery patients using nationwide health registries.

Patients and Methods

Study design and setting

We conducted this population-based cohort study in Denmark using prospectively collected administrative health data from health registries, which cover all contacts to the health sector [10]. The Danish National Health Services provide tax-supported primary and secondary health care for the entire population[10], ensuring that all eligible hip fracture patients undergo surgery at a public hospital. All Danish citizens can be identified using a 10-digit personal identification number, which goes through all Danish health registries allowing for unambiguous individually record linkage of data [11].

Data sources

The Danish Civil Registration System (DCRS) was initiated in 1968. Daily updated information on migration and vital status allows for virtually complete long-term follow-up on emigration and death [11].

The Danish Multidisciplinary Hip Fracture Registry (DMHFR) was initiated in 2003 and contains nationwide population-based data about all patients undergoing primary hip fracture surgery [12]. The positive predictive value of the hip fracture diagnosis is between 90% and 98% depending on fracture type [13].

The Danish National Health Service Prescription Database (DNHSPD) has kept information on all prescriptions for reimbursed drugs dispensed by community pharmacies in Denmark since 2004 according to Anatomical Therapeutic Chemical classification system (ATC codes). Data from the DNHSPH can account for patient's medication [14].

The Danish National Patient Registry (DNPR) is an administrative registry established in 1977 covering all somatic contacts in all Danish hospitals [15]. Information reported to the DNPR includes administrative data, diagnoses, treatments and examinations. Primary and secondary diagnoses are reported to the DNPR according to the International Disease Classification tenth revision (ICD-10) since 1995 [15]. The positive predictive value of the diagnoses included in the medical comorbidities are more than 90% [16].

Study population

We used the DMHFR to identify all patients aged 65 or older who were treated for a fracture of the femoral neck, per-, or sub-trochanteric fracture with osteosynthesis or total/partial hip

replacement surgery between January 1, 2005 and December 31, 2015 (appendix 1). Patients were indexed on their surgery date and followed up for 12 months (to December 31, 2016). Patients who had dispensed an opioid in the 6 months prior to index were excluded to ensure they were opioid non-users at the index date. Patients who died from any cause within 12 months following their index date were also excluded (figure 1).

Opioid prescriptions

Postsurgical opioid prescriptions were identified in the first year following surgery, which we divided into four quarters (4 months per quarter). Prescription opioids dispensed by community pharmacies seven days prior to index and within the first quarter after index were not included in the outcome definition because they are likely to have been associated with the initial opioid treatment to manage acute postoperative pain [4]. Thus, we were only interested in subsequent opioid prescriptions beyond the early perioperative period (quarters 2-4).

Outcome

Our primary outcome was new chronic opioid use after surgery.

New chronic opioid use after surgery was defined as chronic use among previously opioid non-user patients [8]. Our definition of chronic opioid use after surgery was inspired by the definition from the International Association for the Study of Pain, which defines chronic postsurgical pain as pain that develops after a surgical procedure and persists for at least 3 months after surgery [17]. The first year following surgery was therefore divided into quarters. We characterized patients with new chronic opioid use as having dispensed an opioid prescription in at least 2 of the 3 quarters within the first year following surgery (figure 2) [18].

The following prescription opioids were included in the analysis: morphine, hydromorphine, nicomorphine, oxycodone, oxycodone combined with naloxone, pethidine, fentanyl, ketobemidone, methadone, codeine, tramadol, tapentadol, and buprenorphine.

Risk factors

Based on previous literature and clinical experience, the below-mentioned patient- and surgery-related factors were considered and examined as potential risk factors for new chronic opioid use [8 9]. From the DMHFR, we obtained information on age (in categories 65-74, 75-84 and ≥85 years), sex, fracture type (femoral neck and per-/subtrochanteric fracture),

and surgery type (osteosynthesis and total/partial hip replacement). Body mass index (BMI) was calculated using information on height and weight (weight in kilograms divided by height in metres squared) and divided into groups (underweight defined as BMI <18.5, normal as BMI 18.6-24.9, overweight as BMI 25-29.9 and obese as BMI ≥30). We examined several specific medical comorbidities including myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, diabetes, liver disease, peptic ulcer disease, connective tissue disease, dementia, hemiplegia, chronic obstructive pulmonary disease, renal disease and cancer (Table 1). BMI and various comorbidities were in previous studies found to be associated with increased risk of mortality and could be associated with increased risk of chronic opioid use [8 19-21].

We also included data on preoperative dispensing of the following co-medications: nonsteroidal anti-inflammatory drug (NSAID), selective serotonin reuptake inhibitors (SSRI), any antidepressants, antipsychotics, oral corticosteroids, statins, antibiotics, hormone replacement therapy, anti-osteoporosis medication, vitamin K, any anticoagulants, novel oral anticoagulant (NOAC), antiplatelet drugs and heparins (appendix 2). These drugs are included as potential risk factors because they can influence general healthcare utilization and behaviour, or are associated with increased mortality [22]. The preoperative medication for each drug was defined as at least 1 dispensing in the 1 year before surgery.

Statistical analyses

For the presentation of demographic data, descriptive statistics were used and presented for the entire study population at the time of surgery and separately for patients with new chronic use. Odds ratios (ORs) with 95% confidence intervals (CI) were calculated using multiple logistic regression and adjusted for age and sex (aOR). Sensitivity analysis was performed using logistic regression and adjusting for multiple relevant factors. However, these aORs did not differ significantly from the age and sex adjusted ORs and were therefore not presented here. All statistical analyses were performed in STATA version 15 (STATACorp, TX, USA).

The study was approved by the Danish Data Protection Agency's journal number (2015-57-0002) and Aarhus University's journal number (2016-051-000001), record number 880.

This paper was reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [23], and the Reporting of studies Conducted using Observational Routinely-collected Data (RECORD) statement [24].

Results

Description of the study population

In total, 37,202 patients with hip fracture surgery were included in our cohort (figure 1). Overall, 27,133 patients (73%) were female and the mean age at the time of surgery was 81 years (range 65-107). In our study population, 5,497 (15%) developed new chronic opioid use within 1 year of surgery.

The proportion of patients who developed new chronic opioid use in relation to all hip fracture patients was 15% for both females and males, 13% for patients with femoral neck fractures, and 16% for patients with a per- or subtrochanteric fracture (Table 1).

The characteristics of patients with new chronic opioid use were similar to the characteristics of the total population of hip fracture patients with small differences seen in the distribution of BMI, fracture type, surgery type, and preoperative medication use (Table 1).

Risk factors for new chronic opioid use

The risk factors for new chronic opioid use were being underweight (aOR 1.22 (CI 1.09-1.36)), overweight (aOR 1.12 (CI 1.04-1.21)), or obese (aOR 1.57 (CI 1.40-1.76)) with normal weight as reference and sustaining a per-/subtrochanteric fracture (aOR 1.27 (CI 1.20-1.34)) with fracture of the femoral neck as reference. Treatment with total/partial hip replacement was associated with lower risk of new chronic opioid use, with osteosynthesis as reference (aOR 0.65 (CI 0.60-0.69)) (figure 3). A sub-analysis was done, where we analysed the treatment with total/partial hip replacement or osteosynthesis but only including patients, who sustained a fracture of the femoral neck. Here we found the same association, where treatment with total/partial hip replacement was associated with lower risk of new chronic opioid use.

Preoperative use of NSAIDs (aOR 1.68 (CI 1.55-1.83)), SSRIs (aOR 1.42 (CI 1.32-1.53)), antidepressants (aOR 1.36 (CI 1.24-1.49)), antipsychotics (aOR 1.21 (CI 1.07-1.35)), corticosteroids (aOR 1.54 (CI 1.35-1.76)), statins (aOR 1.09 (CI 1.02-1.18)), antibiotics (aOR 1.32 (CI 1.22-1.42)), anti-osteoporosis drugs (aOR 1.33 (CI 1.19-1.49)), anticoagulants (aOR 1.24 (CI 1.17-1.32)), and antiplatelet drugs (aOR 1.24 (CI 1.16-1.32)) were identified as risk factors for new chronic opioid use (figure 3).

The presence of the following preoperative comorbidities were further associated with risk of new chronic opioid use: cardiovascular comorbidity, diabetes, gastrointestinal diseases, dementia, COPD, and renal diseases (figure 3).

Discussion

To our knowledge, this is the first study to examine risk factors for new chronic opioid use following hip fracture surgery. In this large nationwide cohort study of 37,202 hip fracture surgery patients, 15% of the patients had become new chronic opioid users within the first 12 months after surgery of which patients with a femoral neck represented 55%. We identified several patient characteristics, comorbidities and preoperative medications as possible risk factors that could be associated with new chronic opioid use after surgery.

Strength and limitations

The strength of this study is that it is a nationwide population-based cohort study with prospective, validated data and complete follow-up. In addition, we had comprehensive information on medication use and comorbidities prior to surgery, detailed clinical data on hip fracture patients in regards to information on fracture type, surgery type and BMI, and opioid information based on dispensing data rather than patient-reported data.

Our study also has some limitations. First, there is no consensus on how to define chronic opioid use. Previous studies have defined chronic opioid use as postoperative opioid prescription fulfilment between 90 and 180 days [32], or opioid prescriptions for 120 non-consecutive days [8]. The heterogeneity in definitions for chronic opioid use limits the ability to compare our results with previous studies. Moreover, dispensing data provides an imperfect representation of true preoperative medication use, and we were unable to ascertain the intended indications of opioid prescriptions. We know that patients have collected the opioid prescription at the pharmacy, but we have no knowledge regarding the patient's compliance. Even so, using prescription opioid dispensing data is considered a better measure of medication use than most alternative measures [33]. Second, we excluded all deceased patients within the first year following surgery, which might have compromised the external validity of our study. We can only conclude that identified risk factors for new chronic opioid use apply for hip fracture patients that survived one year post-surgery. Third, we were not able to include reoperation as a competing event. This may have overestimated the risk of new

chronic opioid use in younger female patients, since hip fracture patients are at risk of reoperation, which may lead to prolonged or restarted opioid use. We know that 6% of hip fracture patients are reoperated [34], and that individuals aged 80 years or younger and male gender are associated with risk of reoperation [35].

Comparison with previous studies

Only two studies have reported prescription opioid use after hip fracture surgery. Simoni et al. found that 28% of Danish hip fracture patients had dispensed an opioid prescription within the first year after surgery. Moreover, 17% of the patients who were opioid non-users before surgery had dispensed an opioid prescription 1 year after surgery [4]. That study, however, did not examine chronic opioid use, only opioid use in general defined as 1 dispensed opioid prescription. In a similar study, Lindestrand et al. conducted a medical record review from a single institutional with 416 patients and found 2.9% of previous opioid non-user patients were opioid users at 6 months. The study reported further that osteoporosis and opioid use prior to admission were predictors for postoperative opioid use at 6 months. In contrast to our study, they did not define opioid use, and the follow-up period ended at 6 months after hip fracture [5]. We studied the risk factors in a large nationwide setup, whereby we uncover trends across the entire country and not only from a single institution.

In general, there is evidence that younger biological age is a predictor of persistent opioid use in the general surgical population [6 8]. This is explained by a wide variety of factors in the aging population such as a decline in the production of several proteins and neuropeptides, a decline of the immune response and an increase in the inflammatory response [25]. Our study shows the same tendency.

Several studies have shown the prevalence of chronic pain and consumption of opioids tend to be higher in females than males [18 26]. Psychological, biological, cultural, and social factors all play a role in the differences between the sex in pain responses and management [18 27]. Our study demonstrates a weak association between the female sex and new chronic opioid use after hip fracture surgery.

Overweight and obesity have been shown to be associated with a proinflammatory state after surgery inducing hyperalgesia, suggesting an increase in opioid use, which correlates with findings by Westermann et al. of an association between obesity and prolonged postoperative opioid use [19 20 28]. This is in line with our findings of an association between overweight and obesity and developing a new chronic opioid use after surgery.

Our data suggest that fracture type and surgery type is associated with new chronic opioid use. Hip fracture patients with a trochanteric fracture experience more and severe pain than patients with femoral neck fractures [29]. Similarly, patients with osteosynthesis experience more pain than the patients with a stable arthroplasty [30]. The reported mechanisms being shortening of the limb length and range of motion limitations [30]. Another explanation to why surgery type is associated with new chronic opioid use could be that these patients might have a higher rate of reoperation converting to a total hip arthroplasty performed by a more experienced surgeon. However, we do not have data to support this statement.

Several preoperative comorbidities were associated with risk of new chronic opioid use after surgery. Although we excluded all hip fracture patients with prior use of opioids, it is possible that some patients had an unmanaged pain condition prior to surgery. These patients may have continued to use prescription opioids intended for treating postsurgical pain in order to treat their pre-existing chronic pain.[6]. Inacio et al. support this behaviour as they found back pain prior to surgery was associated with chronic opioid use [8]. Comorbidities associated with unrelieved chronic pain conditions are heart failure and COPD. These comorbidities have been associated with chronic opioid use, which concords with our study [6 8]. Diabetes has also been associated with a constant chronic inflammatory state inducing neuropathy, which has also been associated with unrelieved chronic pain. This mechanism is a potential risk factor for chronic pain, which is in accordance with our study [6 8]. Other comorbidities have also been associated with chronic pain and chronic opioid use such as liver disease and depression [8]. By knowing the impact of these comorbidities on the risk of new chronic opioid use, attainment of a greater focus on comorbidity pre- and postoperative may reduce new chronic opioid use after surgery.

Medication use is frequent in hip fracture patients and nearly all of the included medications in our study were identified as a risk factor for chronic opioid use [31]. Medication use is closely related to comorbidities. Treatment of chronic medical conditions is a complex task that require multidisciplinary approach. It is possible that surgeons and patients are preoccupied with attempting to manage chronic pain conditions leaving long-term opioid use as a secondary priority. Some drugs when taken on their own or in combination, might change the level of sensitivity to opioids which could result in patients who continue to take opioids even though their level of pain decreases over time and does not necessarily coincide with the prescribed opioid dose.

Chronic opioid use

There are no standard guidelines in Denmark for post-discharge clinical follow-up of hip fracture patients. However, many orthopaedic and geriatric departments focus on the reduction of prescription opioid exposure after surgery by instituting a plan for opioid tapering. Patients do not receive follow-up appointments in outpatient clinics or at the general practitioner unless they take the initiative themselves. Since hip fracture patients often are characterized as being frail, receiving several medications, and having multimorbidity, they may lack the resources to follow such a tapering plan. Thus, it is important to ensure that patients are well informed and included in the development of a tapering plan, and understand the risks and benefits of prescription opioids for the treatment of postsurgical pain. However, it is important to note that not all hip fracture surgeries are successful and some patients may experience a greater level of postsurgical pain and postsurgical pain treatment.

Conclusion

In this large nationwide cohort study, 15% of the patients who underwent hip fracture surgery developed new chronic opioid use. We identified under- and overweight, obesity, per or subtrochanteric fracture, preoperative use of several medications and presence of several comorbidities as risk factors associated with the risk of new chronic opioid use after hip fracture surgery.

By identifying risk factors, we can reduce the number of new chronic opioid users by developing more effective preventive intervention strategies targeted to the patients with the identified risk factors. In addition, the identified risk factors are also relevant for clinicians in order to advise patients appropriately before surgery about their risk for chronic postsurgical opioid use.

Authors' Contributions

NME, CV, SO, LN, CFC and ABP contributed to the conception or design of the study. NME carried out the analytical aspects of the study. NME, CV, SO, LN, CFC and ABP contributed to the interpretation of data. NME, CV, SO, LN, CFC and ABP drafted the manuscript or revised it critically. All authors gave their final approval and agreement to be accountable for all aspects of the work.

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Competing interests

None declared.

Patient consent for publication

Not required

Data sharing statement

No additional data are available

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Legends

Figure 1: Flowchart of the patients from the Danish Multidisciplinary Hip Fracture Registry to the study population.

Figure 2: New chronic opioid use was defined as patients with at least 2 prescriptions dispensed in 2 of the 3 latter quarters in the first year following surgery

Figure 3: Risk factors for developing new chronic opioid use after hip fracture surgery

Table 1: Patient characteristics for the all hip fracture patients and new chronic users

Appendix 1: Following diagnoses- and procedure codes were used to identify patients undergoing hip fracture surgery.

Appendix 2: ATC codes for all medication in the study

Table 1: Patient characteristics for the all hip fracture patients and new chronic users

	All (n=37,202)	New chronic user (n=5497)	Proportions of new chronic user (%)
	N (%)	N (%)	
Age			
Mean (SD)	*81.4 (7.9)*	*81.3 (7.9)*	
65-74	*8,554 (23)*	*1,302 (24)*	*(15)*
75-84	*15,302 (41)*	*2,268 (41)*	*(15)*
+85	*13,346 (36)*	*1,927 (35)*	*(14)*
Sex			
Female	*27,133 (73)*	*4,021 (73)*	*(15)*
Male	*10,069 (27)*	*1,476 (27)*	*(15)*
BMI group			
Underweight (<18.5)	*2,556 (7)*	*409 (7)*	*(16)*
Normal (18.6-24.9)	*17,129 (46)*	*2,306 (42)*	*(13)*
Overweight (25.-29.9)	*6,783 (18)*	*1,046 (19)*	*(15)*
Obese (+30)	*8,684 (23)*	*1,456 (26)*	*(17)*
Missing	*6,853 (18)*	*1,083 (20)*	*(16)*
Fracture type			
Femoral neck	*20,288 (55)*	*2,724 (50)*	*(13)*
Per-/subtrochanteric	*16,914 (45)*	*2,773 (50)*	*(16)*
Surgery type			
Osteosynthesis	*25,489 (69)*	*4,179 (76)*	*(16)*
Total/partial hip replacement	*11,713 (31)*	*1,318 (24)*	*(11)*
Cardiovascular comorbidities			
Myocardial infarction	*1,629 (4)*	*274 (5)*	*(17)*
Congestive heart failure	*2,340 (6)*	*444 (8)*	*(19)*
Peripheral vascular disease	*2,153 (6)*	*429 (8)*	*(20)*
Cerebrovascular disease	*6,143 (17)*	*1,035 (19)*	*(17)*
Diabetes	*3,055 (8)*	*573 (10)*	*(19)*
Gastrointestinal comorbidities			
Liver disease	*325 (1)*	*88 (2)*	*(27)*
Peptic ulcer disease	*1,526 (4)*	*335 (6)*	*(22)*
Connective tissue disease	*1,387 (4)*	*229 (4)*	*(17)*
Neurological comorbidities			
Dementia	*2,592 (7)*	*434 (8)*	*(17)*
Hemiplegia	*89 (0)*	*16 (0)*	*(18)*
COPD	*3,365 (9)*	*643 (12)*	*(19)*
Renal disease	*828 (2)*	*144 (3)*	*(17)*
Any cancer	*4,623 (12)*	*719 (13)*	*(16)*
Preoperative medication			
NSAID	*3,904 (10)*	*817 (15)*	*(21)*
SSRI	*5,959 (16)*	*1,103 (20)*	*(19)*
Corticosteroid	*1,427 (4)*	*295 (5)*	*(21)*

Anticoagulants	*13,062 (35)*	*2,134 (39)*	*(16)*
Statins	*6,949 (19)*	*1,088 (20)*	*(16)*
Antibiotics	*6,479 (17)*	*1,106 (20)*	*(17)*
Antidepressants	*3,250 (9)*	*601 (11)*	*(18)*
Antipsychotics	*2,150 (6)*	*367 (7)*	*(17)*
HRT	*1,955 (5)*	*312 (6)*	*(16)*
Anti-osteoporosis medicine	*2,143 (6)*	*394 (7)*	*(18)*
Vitamin K	*1,915 (5)*	*311 (6)*	*(16)*
NOAC	*321 (1)*	*32 (1)*	*(10)*
Antiplatelet drugs	*11,247 (30)*	*1,855 (34)*	*(16)*
Heparins	*29 (0)*	*6 (0)*	*(21)*

BMI: Body Mass Index, COPD: Chronic pulmonary disease, NSAID: nonsteroidal anti-inflammatory drug, SSRI: selective serotonin reuptake inhibitors, HRT: Hormone Replacement Therapy, NOAC: novel oral anticoagulant. Odds ratios (ORs) with 95% confidence intervals (CI)

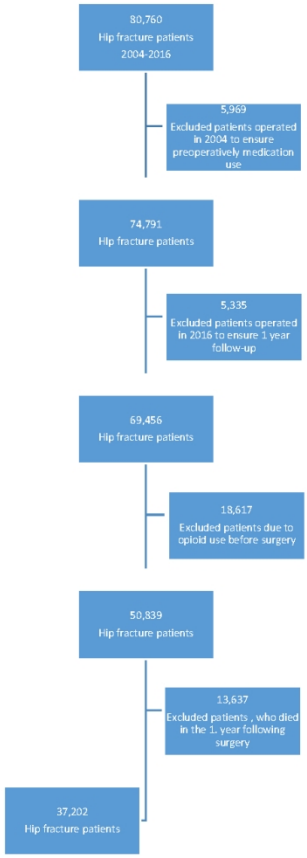

Figure 1: Flowchart of the patients from the Danish Multidisciplinary Hip Fracture Registry to the study population.

Figure 1

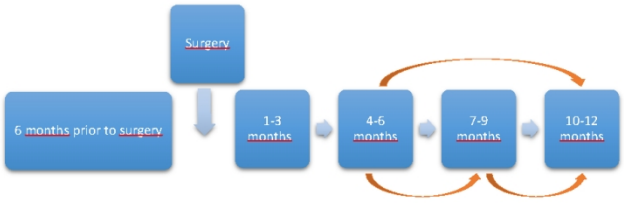

Figure 2: Chronic opioid use was defined as patients with at least 2 prescriptions dispensed in 2 of the 3 latter quarters in the first year following surgery

Figure 2

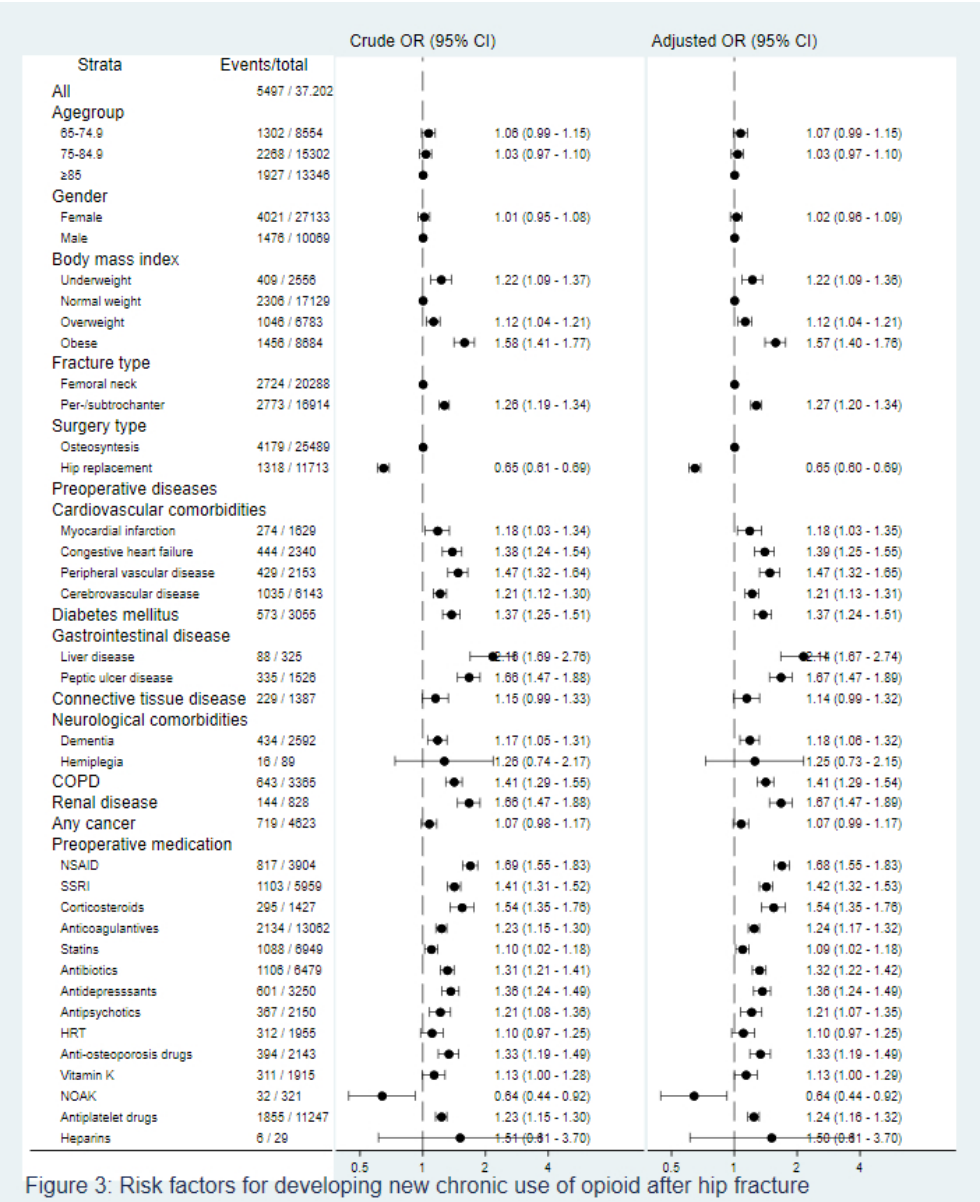

Figure 3: Risk factors for developing new chronic use of opioid after hip fracture

Figure 3

247x302mm (72 x 72 DPI)

Appendix 1: Following diagnoses- and procedure codes were used to identify patients undergoing hip fracture surgery.

ICD-10 code	**Diagnosis code**
Fracture of the femoral neck	DS720
Per-trochanter fracture	DS721
Sub-trochanter fracture	DS722
	Surgery procedure code
Osteosynthesis	KNFJ4-9
Primary hip replacement	KNFB0-99

ICD-10: WHO's International Statistical Classification of Diseases and Related Health Problems, 10th Revision.

Appendix 2: ATC codes for all medication in the study

Categories	**Name**	**ATC code**
Non-steroidal anti-inflammatory drugs (NSAIDs):	Celecoxib	M01AH01
	Rofecoxib	M01AH
	Valdecoxib	M01AH03
	Etoricoxib	M01AH05
	Lornoxicam	M01AC05
	Diclofenac	M01AB05
	Meloxicam	M01AC06
Selective serotonin reuptake inhibitors (SSRIs)	Fluoxetine	N06AB03
	Citalopram	N06AB04
	Paroxetine	N06AB05
	Sertraline	N06AB06
	Fluvoxamine	N06AB08
	Escitalopram	N06AB10
Antidepressants	Non-selective monoamine reuptake inhibitors	N06AA
	Non-selective monoamine-oxidase inhibitors	N06AF
	Monoamine-oxidase type A inhibitors	N06AG
	Other antidepressants	N06AX
Antipsychotics	Antipsychotics	N05A-
Corticosteroids	Systemic hormones	H02AB
		H02BX
Oral anticoagulation therapy	Heparin	B01AB
	Arixtra	B01AX
	Fibrinolytika	A01AD
	Vitamin K antagonister	B01AA
	NOAC	B01AE07
	Rivaroxaban	B01AF01
	Apixaban	B01AF02
	Edoxaban	B01AF03
	Trombocytinhibitors	B01AC
	Aspirin	N02BA01
	Aspirin	N02BA51
Statins	Simvastatin	C10AA01
	Lovastatin	C10AA02
	Fluvastatin	C10AA04
	Cerivastatin	C10AA06
	Atorvastatin	C10AA05
	Pravastatin	C10AA03
	Rosuvastatin	C10AA07
Antibiotics	Oral treatment of bacterial infections	J01x
	viral infections	J05x
Opioids	Morfin	N02AA01
	Fentanyl	N02AB03
	Hydromorphon	N02AA03
	Ketobemidon (ketogan)	N02AG02

	Methadon	N07BC02
	Nicomorphin	N02AA04
	Oxycodon	N02AA05
	Pethidin	N02AB02
	Targin	N02AA55
	Tramadol	N02AX02
	Tapentadol	N02AX06
	Buprenorphin	N02AE01
	Codein	R05DA04
	Codein and paracetamol	N02AJ06
Hormone replacement therapy	Estrogen	G03C
	Estrogen	L02AA
	Progesteron and estrogen in combination	G03F
	Antiandrogen	G03H
	Progesteron	G03D
Anti-osteoporosis medication		
Bisfosfonats	Etidronat	M05BA01
	Clodronate	M05BA02
	Pamidronate	M05BA03
	Alendronat	M05BA04
	Alendronat and colecalciferol	M05BB03
	Alendronat, calcium and colecalciferol	M05BB05
	Tiludronate	M05BA05
	Ibandronat	M05BA06
	Risedronat	M05BA07
	Risedronat and calcium	M05BB02
	Zoledronat	
Other drugs affecting bone structure and mineralization	Denosumab	M05BX04
	Strontiumranelat	M05BX03
Selective estrogen receptor modulators	Raloxifen	G03XC01
Teriparatid	PTH treatment	H05AA02

ATC codes: Anatomical Therapeutic Chemical Classification System

Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1

Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	#3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	#4	Present key elements of study design early in the paper	6
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	6
Eligibility criteria	#6b	For matched studies, give matching criteria and number of exposed and unexposed	6
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than	6

		one group. Give information separately for for exposed and unexposed groups if applicable.	
Bias	#9	Describe any efforts to address potential sources of bias	8
Study size	#10	Explain how the study size was arrived at	6
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	7
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	8
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	8
Statistical methods	#12c	Explain how missing data were addressed	8
Statistical methods	#12d	If applicable, explain how loss to follow-up was addressed	8
Statistical methods	#12e	Describe any sensitivity analyses	8
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-	9

		up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	
Participants	#13b	Give reasons for non-participation at each stage	9
Participants	#13c	Consider use of a flow diagram	9
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	9
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	9
Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	9
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	9
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9
Main results	#16b	Report category boundaries when continuous variables were categorized	9
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9

Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	9
Discussion			
Key results	#18	Summarise key results with reference to study objectives	10
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	10
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	11
Generalisability	#21	Discuss the generalisability (external validity) of the study results	12
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

BMJ Open

Risk factors for new chronic opioid use after hip fracture surgery: a Danish nationwide cohort study from 2005 to 2016 using the Danish multidisciplinary hip fracture registry

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Risk factors for new chronic opioid use after hip fracture surgery: a Danish nationwide cohort study from 2005 to 2016 using the Danish multidisciplinary hip fracture registry

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Risk factors for new chronic opioid use after hip fracture surgery: a Danish nationwide cohort study from 2005 to 2016 using the Danish Multidisciplinary Hip Fracture Registry

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Abstract

Objective

To examine the risk factors for new chronic opioid use in elderly hip fracture surgery patients.

Design

Prospective population-based cohort study.

Setting and participants

Using Danish nationwide health registries, we identified all opioid non-user patients aged ≥65 years who had undergone hip fracture surgery from 2005-2016 and were alive within the first year following surgery.

Main outcome measures

New chronic opioid use defined by the dispensing of at least 2 prescription opioids within 2 of the last 3 quarters during the first year following surgery.

Results

We identified 37,202 opioid non-user patients who underwent hip fracture surgery. Of these, 5,497 (15%) developed new chronic opioid user within 1 year of surgery.

Risk factors for new chronic opioid use were BMI <18.5 (adjusted Odds Ratio (aOR) 1.22 (95% confidence interval (95% CI) 1.09-1.36)), BMI 25-29.9 (aOR 1.12 (95% CI 1.04-1.21)), and BMI ≥30 (aOR 1.57 (95% CI 1.40-1.76)) with BMI 18.6-24.9 as reference, a per-/subtrochanteric fracture (aOR 1.27 (95% CI 1.20-1.34)) with femoral neck fracture as reference, preoperative use (versus no-use) of NSAID (aOR 1.68 (95% CI 1.55-1.83)), SSRI (aOR 1.42 (95% CI 1.32-1.53)), antidepressants (aOR 1.36 (95% CI 1.24-1.49)), antipsychotics (aOR 1.21 (95% CI 1.07-1.35)), corticosteroids (aOR 1.54 (95% CI 1.35-1.76)), statins (aOR 1.09 (95% CI 1.02-1.18)), antibiotics (aOR 1.32 (95% CI 1.22-1.42)), anti-osteoporosis drugs (aOR 1.33 (95% CI 1.19-1.49)), and anticoagulantives (aOR 1.24 (95% CI 1.17-1.32)). Presence of cardiovascular comorbidities, diabetes, gastrointestinal diseases, dementia, COPD, or renal diseases were further identified as risk factors.

Conclusion

In this large nationwide cohort study, we identified several risk factors associated with new chronic opioid use after hip fracture surgery among patients who were alive within the first year following surgery.

Although not all factors are modifiable preoperative, this will allow clinicians to appropriately counsel patients preoperatively and tailor postoperative treatment.

Article Summary

Strengths and limitations of this study

- This study is a prospective population-based cohort study with complete follow-up based on Danish nationwide health registries.
- The study includes comprehensive high-quality data on medication use and comorbidities before surgery, and detailed clinical- and opioid data from registries rather than patient-reported data.
- The definition of new chronic opioid use is inspired by the guidelines from the International Association for the Study of Pain.
- Data on clinical indications for opioid prescriptions and patient compliance with opioid treatment was not available.
- Data on re-operations during follow-up was not available.

Introduction

The prevalence of hip fractures is estimated to reach 6.3 million people worldwide by 2050 [1]. Hip fracture patients often suffer from comorbidities and polypharmacy, which have been associated with an increased risk of complications and increased mortality. In addition, postsurgical pain can delay mobilization and rehabilitation[2]. These factors make treatment and rehabilitation for hip fracture surgery patients challenging.

Opioids are commonly accepted as standard clinical practice for pain treatment in hip fracture surgery patients. However, initial prescription opioid treatment for acute postsurgical pain still merits caution as it can result in chronic opioid use [3]. Previous studies have shown that a high percentage of hip fracture patients who did not use opioids before their hip fracture were still using opioids several months after surgery [4 5]. This is concerning as chronic prescription opioid use can have a negative impact on quality of life [6], has been associated with increased risk of sustaining new fractures [7] and other adverse events including general medical complications [3].

The risk of chronic opioid use can be influenced by patient-related, surgical and healthcare-related factors, some of which are modifiable (weight, medication, surgery type) whereas others are non-modifiable (age, gender). Only few studies have investigated risk factors for chronic opioid use in orthopedic patients. Moreover, these studies are limited by small sample sizes, study populations that differ from the hip fracture population, varying definitions of opioid use, different follow-up duration, and lack of adjustment for potential confounders [8 9]. No previous studies have investigated risk factors for chronic opioid use after hip fracture surgery. Thus, there is a need for more knowledge on risk factors for new chronic opioid use in hip fracture patients, in particular risk factors that are modifiable during pre-, peri-, and postoperative period.

The aim of this study was to examine patient-related and surgery-related risk factors associated with new chronic opioid use in elderly hip fracture surgery patients using nationwide health registries.

Patients and Methods

Study design and setting

We conducted this population-based cohort study in Denmark using prospectively collected administrative health data from health registries, which cover all contacts to the health sector [10]. The Danish National Health Services provide tax-supported primary and secondary health care for the entire population[10], ensuring that all eligible hip fracture patients undergo surgery at a public hospital. All Danish citizens can be identified using a 10-digit personal identification number, which goes through all Danish health registries allowing for unambiguous individually record linkage of data [11].

Data sources

The Danish Civil Registration System (DCRS) was initiated in 1968. Daily updated information on migration and vital status allows for virtually complete long-term follow-up on emigration and death [11].

The Danish Multidisciplinary Hip Fracture Registry (DMHFR) was initiated in 2003 and contains nationwide population-based data about all patients undergoing primary hip fracture surgery [12]. The positive predictive value of the hip fracture diagnosis is between 90% and 98% depending on fracture type [13].

The Danish National Health Service Prescription Database (DNHSPD) has kept information on all prescriptions for reimbursed drugs dispensed by community pharmacies in Denmark since 2004 according to Anatomical Therapeutic Chemical classification system (ATC codes). Data from the DNHSPH can account for patient's medication [14].

The Danish National Patient Registry (DNPR) is an administrative registry established in 1977 covering all somatic contacts in all Danish hospitals [15]. Information reported to the DNPR includes administrative data, diagnoses, treatments and examinations. Primary and secondary diagnoses are reported to the DNPR according to the International Disease Classification tenth revision (ICD-10) since 1995 [15]. The positive predictive value of the diagnoses included in the medical comorbidities are more than 90% [16].

Study population

We used the DMHFR to identify all patients aged 65 or older who were treated for a fracture of the femoral neck, per-, or sub-trochanteric fracture with osteosynthesis or total/partial hip replacement surgery between January 1, 2005 and December 31, 2015 (appendix 1). Patients were indexed on their surgery date and followed up for 12 months (to December 31, 2016). Patients who had dispensed an opioid in the 6 months prior to index were excluded to ensure

they were opioid non-users at the index date. Patients who died from any cause within 12 months following their index date were also excluded (figure 1).

Outcome

We characterized patients with new chronic opioid use as having dispensed an opioid prescription in at least 2 of the 3 last quarters (3-months periods per quarter) within the first year following surgery among previously opioid non-user patients (figure 2) [8 17]. Prescription opioids dispensed by community pharmacies seven days prior to index and within the first quarter after index were not included in the outcome definition because they are likely to have been associated with the initial opioid treatment to manage acute postoperative pain [4]. Thus, we were only interested in subsequent opioid prescriptions beyond the early perioperative period (quarters 2-4). Our definition of chronic opioid use after surgery was aligned with the definition from the International Association for the Study of Pain, which defines chronic postsurgical pain as pain that develops after a surgical procedure and persists for at least 3 months after surgery [18].

The following prescription opioids were included in the analysis: morphine, hydromorphine, nicomorphine, oxycodone, oxycodone combined with naloxone, pethidine, fentanyl, ketobemidone, methadone, codeine, tramadol, tapentadol, and buprenorphine.

Risk factors

Based on previous literature and clinical experience, the below-mentioned patient- and surgery-related factors were considered and examined as potential risk factors for new chronic opioid use [8 9]. From the DMHFR, we obtained information on age (in categories 65-74, 75-84 and ≥85 years), sex, fracture type (femoral neck and per-/subtrochanteric fracture), and surgery type (osteosynthesis and total/partial hip replacement). Body mass index (BMI) was calculated using information on height and weight (weight in kilograms divided by height in metres squared) and divided into groups (underweight defined as BMI <18.5, normal as BMI 18.6-24.9, overweight as BMI 25-29.9 and obese as BMI ≥30). We examined several specific medical comorbidities including myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, diabetes, liver disease, peptic ulcer disease, connective tissue disease, dementia, hemiplegia, chronic obstructive pulmonary disease, renal disease and cancer (Table 1). BMI and various comorbidities were in previous studies found to be associated with increased risk of mortality and could be associated with increased risk of chronic opioid use [8 19-21].

We also included data on preoperative dispensing of the following co-medications: nonsteroidal anti-inflammatory drug (NSAID), selective serotonin reuptake inhibitors (SSRI), any antidepressants, antipsychotics, oral corticosteroids, statins, antibiotics, hormone replacement therapy, anti-osteoporosis medication, vitamin K, any anticoagulants, novel oral anticoagulant (NOAC), antiplatelet drugs and heparins (appendix 2). These drugs are included as potential risk factors because they can influence general healthcare utilization and behaviour, or are associated with increased mortality [22]. The preoperative medication for each drug was defined as at least 1 dispensing in the 1 year before surgery.

Statistical analyses

For the presentation of demographic data, descriptive statistics were used and presented for the entire study population at the time of surgery and separately for patients with new chronic use. Odds ratios (ORs) with 95% confidence intervals (CI) were calculated using multiple logistic regression and adjusted for age and sex (aOR). Several sensitivity analyses were performed: 1. An analysis when using logistic regression and adjusting for multiple relevant factors. 2. An analysis where all patients who died within the first year were included. 3. Landmark analysis at 6 months (only excluding the patients who died in the first and second quarter), and at 9 months (only excluding the patients who died in the first, second, and third quarter). 4. An analysis when only including patients, who sustained a fracture of the femoral neck to analyze the treatment with total/partial hip replacement and osteosynthesis. All statistical analyses were performed in STATA version 15 (STATACorp, TX, USA).

The study was approved by the Danish Data Protection Agency's journal number (2015-57-0002) and Aarhus University's journal number (2016-051-000001), record number 880.

This paper was reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [23], and the Reporting of studies Conducted using Observational Routinely-collected Data (RECORD) statement [24].

Patient and Public Involvement

No patient involved

Results

Description of the study population

In total, 69,456 patients with hip fracture surgery were identified (figure 1). We excluded 18,617 hip fracture patients due to opioid use before surgery, leaving us with 50,839 eligible hip fracture patients. Of these, 13,637 patients died within the first year. The final study population included 37,202 hip fracture patients.

Overall, 27,133 patients (73%) were female and the mean age at the time of surgery was 81 years (range 65-107). In our study population, 5,497 (15%) developed new chronic opioid use within 1 year of surgery.

The proportion of patients who developed new chronic opioid use in relation to all hip fracture patients was 15% for both females and males, 13% for patients with femoral neck fractures, and 16% for patients with a per- or subtrochanteric fracture (Table 1).

The characteristics of patients with new chronic opioid use were similar to the characteristics of the total population of hip fracture patients with small differences seen in the distribution of BMI, fracture type, surgery type, and preoperative medication use (Table 1).

Risk factors for new chronic opioid use

The risk factors for new chronic opioid use were being underweight (aOR 1.22 (CI 1.09-1.36)), overweight (aOR 1.12 (CI 1.04-1.21)), or obese (aOR 1.57 (CI 1.40-1.76)) with normal weight as reference and sustaining a per-/subtrochanteric fracture (aOR 1.27 (CI 1.20-1.34)) with fracture of the femoral neck as reference. Treatment with total/partial hip replacement was associated with lower risk of new chronic opioid use, with osteosynthesis as reference (aOR 0.65 (CI 0.60-0.69)) (figure 3 and appendix figure 1).

Preoperative use of NSAIDs (aOR 1.68 (CI 1.55-1.83)), SSRIs (aOR 1.42 (CI 1.32-1.53)), antidepressants (aOR 1.36 (CI 1.24-1.49)), antipsychotics (aOR 1.21 (CI 1.07-1.35)), corticosteroids (aOR 1.54 (CI 1.35-1.76)), statins (aOR 1.09 (CI 1.02-1.18)), antibiotics (aOR 1.32 (CI 1.22-1.42)), anti-osteoporosis drugs (aOR 1.33 (CI 1.19-1.49)), anticoagulants (aOR 1.24 (CI 1.17-1.32)), and antiplatelet drugs (aOR 1.24 (CI 1.16-1.32)) were identified as risk factors for new chronic opioid use (figure 3 and appendix figure 1).

The presence of the following preoperative comorbidities were further associated with risk of new chronic opioid use: cardiovascular comorbidity, diabetes, gastrointestinal diseases, dementia, COPD, and renal diseases (figure 3 and appendix figure 1).

Several sensitivity analyses were performed. Results of the landmark analyses were similar to the results presented in the primary analyses, where we excluded all patients who died within 12 months of surgery (please see appendix figure 2 and 3). Likewise, analyses adjusting for multiple relevant factors and those based on patients with only a fracture of the femoral neck showed results similar to the primary analysis (data not shown). However, the results based on all population including also all patients who deceased within the first year of surgery showed an overestimation of the estimates, in particular those related to age and gender (please see appendix figure 4)

Discussion

To our knowledge, this is the first study to examine risk factors for new chronic opioid use following hip fracture surgery among patients who were alive within the first year following surgery. In this large nationwide cohort study of 37,202 hip fracture surgery patients, 15% of the patients had become new chronic opioid users within the first 12 months after surgery of which patients with a femoral neck represented 55%. We identified several patient characteristics, comorbidities and preoperative medications as possible risk factors that could be associated with new chronic opioid use after surgery.

Strength and limitations

The strength of this study is that it is a nationwide population-based cohort study with prospective, validated data and complete follow-up. In addition, we had comprehensive information on medication use and comorbidities prior to surgery, detailed clinical data on hip fracture patients in regards to information on fracture type, surgery type and BMI, and opioid information based on dispensing data rather than patient-reported data.

Our study also has some limitations. First, there is no consensus on how to define chronic opioid use. Previous studies have defined chronic opioid use as postoperative opioid prescription fulfilment between 90 and 180 days [25], or opioid prescriptions for 120 non-consecutive days [8]. The heterogeneity in definitions for chronic opioid use limits the ability to compare our results with previous studies. Moreover, dispensing data provides an imperfect representation of true preoperative medication use, and we were unable to ascertain the intended indications of opioid prescriptions. We know that patients have collected the opioid prescription at the pharmacy, but we have no knowledge regarding the patient's compliance.

Even so, using prescription opioid dispensing data is considered a better measure of medication use than most alternative measures [26]. Second, we excluded all deceased patients within the first year following surgery, which might have compromised the external validity of our study. Thus, we can only conclude that identified risk factors for new chronic opioid use apply for hip fracture patients that survived one year after surgery. The number of deceased patients was substantial. A total of 13,637 of the 50,839 hip fracture patients died within the first year (please see appendix figure 5). Including these in the study population would lead to an overestimation of our results, compromising our internal validity (please see appendix figure 4). A total of 751 of the 13,637 deceased hip fracture patients were potentially eligible to be included in our study as new chronic opioid users. These patients had redeemed two opioid prescriptions in either the second, third or fourth quarter cf. our definition (please see appendix figure 5). The performed landmark analyses illustrated, that including the deceased patients from the third and fourth quarter in our primary analysis would not affect our results substantially (please see appendix figure 2 and 3). Third, we were not able to include reoperation as a competing event. This may have overestimated the risk of new chronic opioid use in younger female patients, since hip fracture patients are at risk of reoperation, which may lead to prolonged or restarted opioid use. We know that 6% of hip fracture patients are reoperated [27]iduals aged 80 years or younger and male gender are associated with risk of reoperation [28].

Comparison with previous studies

Only two studies have reported prescription opioid use after hip fracture surgery. Simoni et al. found that 28% of Danish hip fracture patients had dispensed an opioid prescription within the first year after surgery. Moreover, 17% of the patients who were opioid non-users before surgery had dispensed an opioid prescription 1 year after surgery [4]. That study, however, did not examine chronic opioid use, only opioid use in general defined as 1 dispensed opioid prescription. In a similar study, Lindestrand et al. conducted a medical record review from a single institutional with 416 patients and found 2.9% of previous opioid non-user patients were opioid users at 6 months. The study reported further that osteoporosis and opioid use prior to admission were predictors for postoperative opioid use at 6 months. In contrast to our study, they did not define opioid use, and the follow-up period ended at 6 months after hip fracture [5]. We studied the risk factors in a large nationwide setup, whereby we uncover trends across the entire country and not only from a single institution.

In general, there is evidence that younger biological age is a predictor of persistent opioid use in the general surgical population [6 8]. This is explained by a wide variety of factors in the aging population such as a decline in the production of several proteins and neuropeptides, a decline of the immune response and an increase in the inflammatory response [29]. Our study shows the same tendency.

Several studies have shown the prevalence of chronic pain and consumption of opioids tend to be higher in females than males [17 30]. Psychological, biological, cultural, and social factors all play a role in the differences between the sex in pain responses and management [17 31]. Our study demonstrates a weak association between the female sex and new chronic opioid use after hip fracture surgery.

Overweight and obesity have been shown to be associated with a proinflammatory state after surgery inducing hyperalgesia, suggesting an increase in opioid use, which correlates with findings by Westermann et al. of an association between obesity and prolonged postoperative opioid use [19 20 32]. This is in line with our findings of an association between overweight and obesity and developing a new chronic opioid use after surgery.

Our data suggest that fracture type and surgery type is associated with new chronic opioid use. Hip fracture patients with a trochanteric fracture experience more and severe pain than patients with femoral neck fractures [33]. Similarly, patients with osteosynthesis experience more pain than the patients with a stable arthroplasty [34]. The reported mechanisms being shortening of the limb length and range of motion limitations [34]. Another explanation to why surgery type is associated with new chronic opioid use could be that these patients might have a higher rate of reoperation converting to a total hip arthroplasty performed by a more experienced surgeon. However, we do not have data to support this statement.

Several preoperative comorbidities were associated with risk of new chronic opioid use after surgery. Although we excluded all hip fracture patients with prior use of opioids, it is possible that some patients had an unmanaged pain condition prior to surgery. These patients may have continued to use prescription opioids intended for treating postsurgical pain in order to treat their pre-existing chronic pain.[6]. Inacio et al. support this behaviour as they found back pain prior to surgery was associated with chronic opioid use [8]. Comorbidities associated with unrelieved chronic pain conditions are heart failure and COPD. These comorbidities have been associated with chronic opioid use, which concords with our study [6 8]. Diabetes has also been associated with a constant chronic inflammatory state inducing

neuropathy, which has also been associated with unrelieved chronic pain. This mechanism is a potential risk factor for chronic pain, which is in accordance with our study [6 8]. Other comorbidities have also been associated with chronic pain and chronic opioid use such as liver disease and depression [8]. By knowing the impact of these comorbidities on the risk of new chronic opioid use, attainment of a greater focus on comorbidity pre- and postoperative may reduce new chronic opioid use after surgery.

Medication use is frequent in hip fracture patients and nearly all of the included medications in our study were identified as a risk factor for chronic opioid use [35]. Medication use is closely related to comorbidities. Treatment of chronic medical conditions is a complex task that require multidisciplinary approach. It is possible that surgeons and patients are preoccupied with attempting to manage chronic pain conditions leaving long-term opioid use as a secondary priority. Some drugs when taken on their own or in combination, might change the level of sensitivity to opioids which could result in patients who continue to take opioids even though their level of pain decreases over time and does not necessarily coincide with the prescribed opioid dose.

Chronic opioid use

There are no standard guidelines in Denmark for post-discharge clinical follow-up of hip fracture patients. However, many orthopaedic and geriatric departments focus on the reduction of prescription opioid exposure after surgery by instituting a plan for opioid tapering. Patients do not receive follow-up appointments in outpatient clinics or at the general practitioner unless they take the initiative themselves. Since hip fracture patients often are characterized as being frail, receiving several medications, and having multimorbidity, they may lack the resources to follow such a tapering plan. Thus, it is important to ensure that patients are well informed and included in the development of a tapering plan, and understand the risks and benefits of prescription opioids for the treatment of postsurgical pain. However, it is important to note that not all hip fracture surgeries are successful and some patients may experience a greater level of postsurgical pain and postsurgical pain treatment.

Conclusion

In this large nationwide cohort study, 15% of the patients who underwent hip fracture surgery developed new chronic opioid use. We identified under- and overweight, obesity, per or subtrochanteric fracture, preoperative use of several medications and presence of several

comorbidities as risk factors associated with the risk of new chronic opioid use after hip fracture surgery.

By identifying risk factors, we can reduce the number of new chronic opioid users by developing more effective preventive intervention strategies targeted to the patients with the identified risk factors. In addition, the identified risk factors are also relevant for clinicians in order to advise patients appropriately before surgery about their risk for chronic postsurgical opioid use.

Authors' Contributions

NME, CV, SO, LN, CFC and ABP contributed to the conception or design of the study. NME carried out the analytical aspects of the study. NME, CV, SO, LN, CFC and ABP contributed to the interpretation of data. NME, CV, SO, LN, CFC and ABP drafted the manuscript or revised it critically. All authors gave their final approval and agreement to be accountable for all aspects of the work.

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Competing interests

None declared.

Patient consent for publication

Not required

Data sharing statement

No additional data are available

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Legends

Legends

Figure 1: Flowchart of the patients from the Danish Multidisciplinary Hip Fracture Registry to the study population.

Figure 2: New chronic opioid use was defined as patients with at least 2 prescriptions dispensed in 2 of the 3 latter quarters in the first year following surgery.

Figure 3: Risk factors for developing new chronic opioid use after hip fracture surgery among patient with no opioid use before surgery and those who were alive 12 months after surgery, odds ratios adjusted for age and sex.
COPD: Chronic pulmonary disease, NSAID: nonsteroidal anti-inflammatory drug, SSRI: selective serotonin reuptake inhibitors, HRT: Hormone Replacement Therapy, NOAC: novel oral anticoagulant. Odds ratios (ORs) with 95% confidence intervals (CI)

Appendix figure 1: Risk factors for developing new chronic opioid use after hip fracture surgery among patient with no opioid use before surgery and those who were alive 12 months after surgery, crude odds ratios.
COPD: Chronic pulmonary disease, NSAID: nonsteroidal anti-inflammatory drug, SSRI: selective serotonin reuptake inhibitors, HRT: Hormone Replacement Therapy, NOAC: novel oral anticoagulant. Odds ratios (ORs) with 95% confidence intervals (CI)

Appendix figure 2: Landmark analyses at 6 months: Risk factors for developing new chronic opioid use after hip fracture surgery among patients with no opioid use before surgery, when excluding the patients who died in the first and second quarter of surgery, odds ratios adjusted for age and sex.
COPD: Chronic pulmonary disease, NSAID: nonsteroidal anti-inflammatory drug, SSRI: selective serotonin reuptake inhibitors, HRT: Hormone Replacement Therapy, NOAC: novel oral anticoagulant. Odds ratios (ORs) with 95% confidence intervals (CI)

Appendix figure 3: Landmark analyses at 9 months: Risk factors for developing new chronic opioid use after hip fracture surgery among patients with no opioid use before surgery, when excluding the patients who died in the first, second, and third quarter of surgery, odds ratios adjusted for age and sex.
COPD: Chronic pulmonary disease, NSAID: nonsteroidal anti-inflammatory drug, SSRI: selective serotonin reuptake inhibitors, HRT: Hormone Replacement Therapy, NOAC: novel oral anticoagulant. Odds ratios (ORs) with 95% confidence intervals (CI)

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Appendix figure 5: Number of hip fracture patients identified at the time of hip fracture and during the first year following surgery. Patients who were opioid users before surgery were not included in our analyses (number of deceased in this group in each of the 4 quarters of surgery is presented with green color). Our analyses were based on patients with no opioid use before surgery. We presented the number of opioid non-users alive in each of the 4 quarters of surgery with purple color. We presented the number of opioid non-users who dead in each of the 4 quartets of surgery with blue color. Number of eligible new chronic users are patients, who have redeemed two opioid prescriptions, but have died in the first year following surgery, and are therefore not included in our primary analyses (red color).

Table 1: Patient characteristics for the all hip fracture patients and new chronic users

Appendix 1: Following diagnoses- and procedure codes were used to identify patients undergoing hip fracture surgery.

Appendix 2: ATC codes for all medication in the study

Table 1: Patient characteristics for the all hip fracture patients and new chronic users

	All (n=37,202)	New chronic user (n=5497)	Proportions of new chronic user (%)
	N (%)	N (%)	
Age			
Mean (SD)	81.4 (7.9)	81.3 (7.9)	
65-74	8,554 (23)	1,302 (24)	(15)
75-84	15,302 (41)	2,268 (41)	(15)
+85	13,346 (36)	1,927 (35)	(14)
Sex			
Female	27,133 (73)	4,021 (73)	(15)
Male	10,069 (27)	1,476 (27)	(15)
BMI group			
Underweight (<18.5)	2,556 (7)	409 (7)	(16)
Normal (18.6-24.9)	17,129 (46)	2,306 (42)	(13)
Overweight (25.-29.9)	6,783 (18)	1,046 (19)	(15)
Obese (+30)	8,684 (23)	1,456 (26)	(17)
Missing	6,853 (18)	1,083 (20)	(16)
Fracture type			
Femoral neck	20,288 (55)	2,724 (50)	(13)
Per-/subtrochanteric	16,914 (45)	2,773 (50)	(16)
Surgery type			
Osteosynthesis	25,489 (69)	4,179 (76)	(16)
Total/partial hip replacement	11,713 (31)	1,318 (24)	(11)
Cardiovascular comorbidities			
Myocardial infarction	1,629 (4)	274 (5)	(17)
Congestive heart failure	2,340 (6)	444 (8)	(19)
Peripheral vascular disease	2,153 (6)	429 (8)	(20)
Cerebrovascular disease	6,143 (17)	1,035 (19)	(17)
Diabetes	3,055 (8)	573 (10)	(19)
Gastrointestinal comorbidities			
Liver disease	325 (1)	88 (2)	(27)
Peptic ulcer disease	1,526 (4)	335 (6)	(22)
Connective tissue disease	1,387 (4)	229 (4)	(17)
Neurological comorbidities			
Dementia	2,592 (7)	434 (8)	(17)
Hemiplegia	89 (0)	16 (0)	(18)
COPD	3,365 (9)	643 (12)	(19)
Renal disease	828 (2)	144 (3)	(17)
Any cancer	4,623 (12)	719 (13)	(16)
Preoperative medication			
NSAID	3,904 (10)	817 (15)	(21)
SSRI	5,959 (16)	1,103 (20)	(19)
Corticosteroid	1,427 (4)	295 (5)	(21)

Anticoagulants	*13,062 (35)*	*2,134 (39)*	*(16)*
Statins	*6,949 (19)*	*1,088 (20)*	*(16)*
Antibiotics	*6,479 (17)*	*1,106 (20)*	*(17)*
Antidepressants	*3,250 (9)*	*601 (11)*	*(18)*
Antipsychotics	*2,150 (6)*	*367 (7)*	*(17)*
HRT	*1,955 (5)*	*312 (6)*	*(16)*
Anti-osteoporosis medicine	*2,143 (6)*	*394 (7)*	*(18)*
Vitamin K	*1,915 (5)*	*311 (6)*	*(16)*
NOAC	*321 (1)*	*32 (1)*	*(10)*
Antiplatelet drugs	*11,247 (30)*	*1,855 (34)*	*(16)*
Heparins	*29 (0)*	*6 (0)*	*(21)*

BMI: Body Mass Index, COPD: Chronic pulmonary disease, NSAID: nonsteroidal anti-inflammatory drug, SSRI: selective serotonin reuptake inhibitors, HRT: Hormone Replacement Therapy, NOAC: novel oral anticoagulant. Odds ratios (ORs) with 95% confidence intervals (CI)

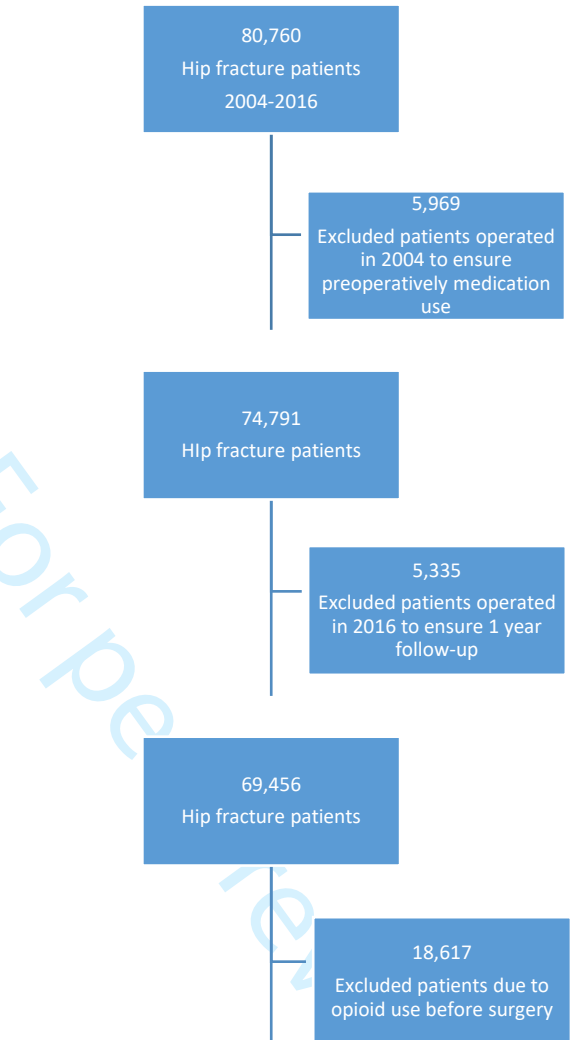


Figure 1: Flowchart of the patients from the Danish Multidisciplinary Hip Fracture Registry to the study population.

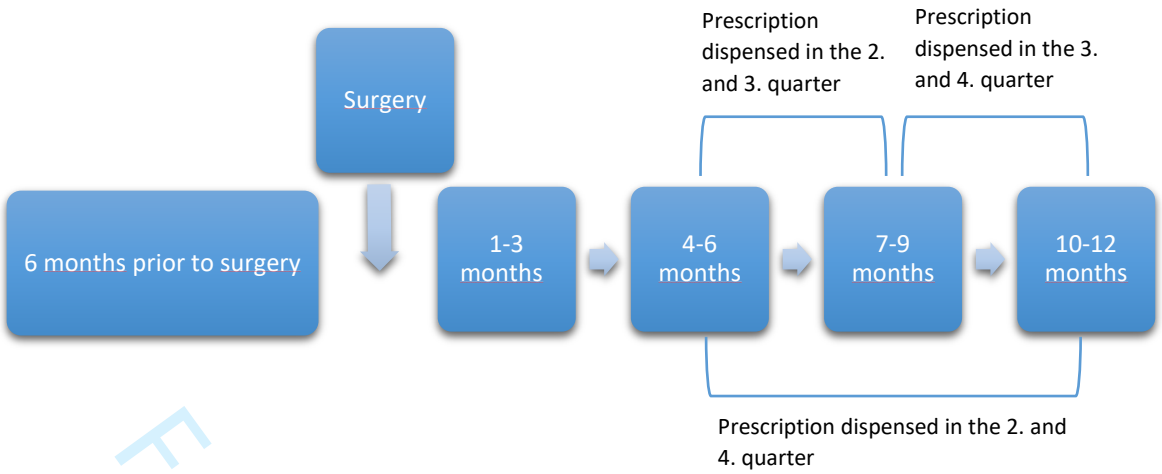


Figure 2: Chronic opioid use was defined as patients with at least 2 prescriptions dispensed in 2 of the 3 latter quarters in the first year following surgery

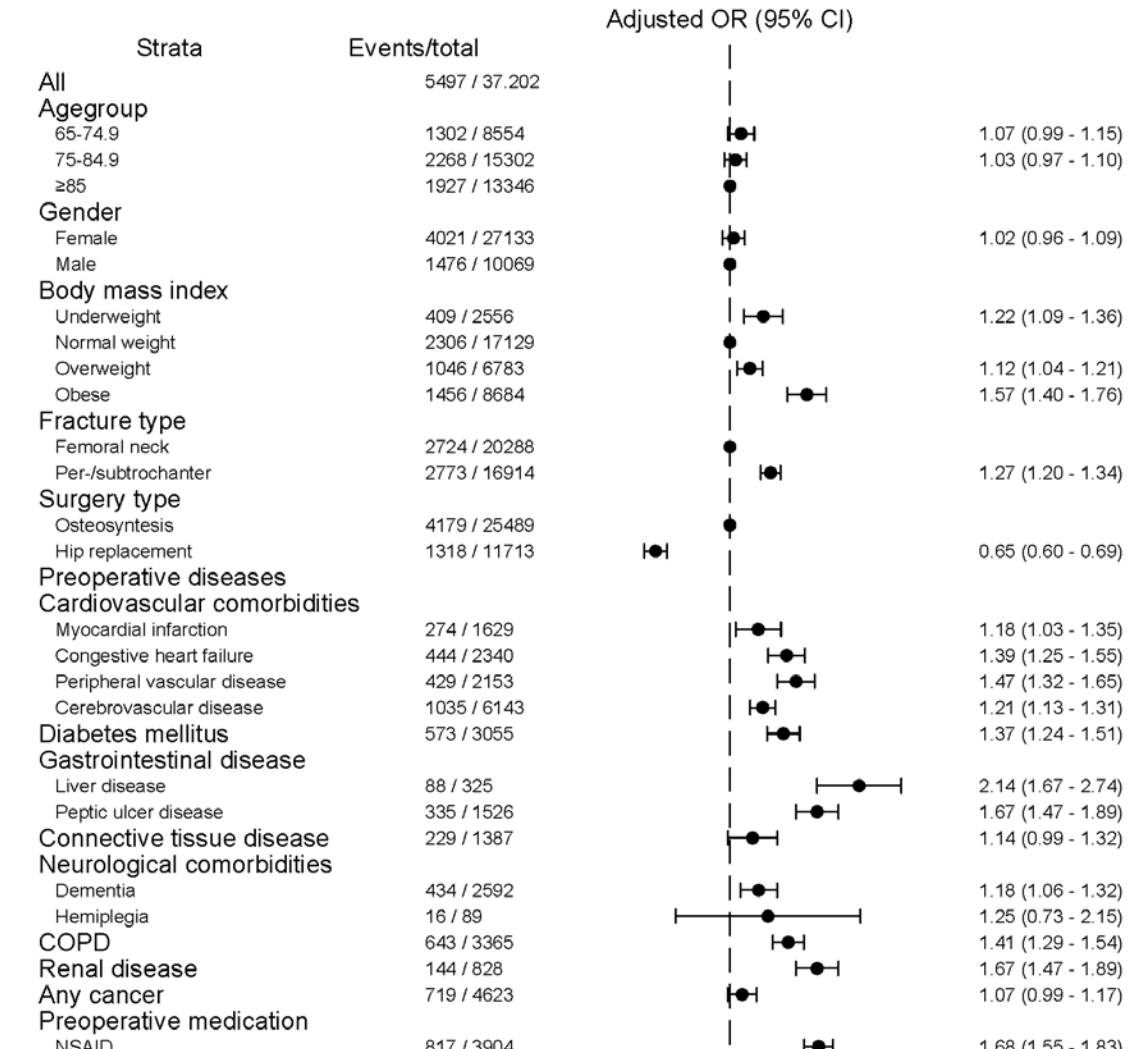


Figure 3: Risk factors for developing new chronic opioid use after hip fracture surgery among patient with no opioid use before surgery and those who were alive 12 months after surgery, odds ratios adjusted for age and sex.

COPD: Chronic pulmonary disease, NSAID: nonsteroidal anti-inflammatory drug, SSRI: selective serotonin reuptake inhibitors, HRT: Hormone Replacement Therapy, NOAC: novel oral anticoagulant. Odds ratios (ORs) with 95% confidence intervals (CI)

Appendix 1: Following diagnoses- and procedure codes were used to identify patients undergoing hip fracture surgery.

ICD-10 code	**Diagnosis code**
Fracture of the femoral neck	DS720
Per-trochanter fracture	DS721
Sub-trochanter fracture	DS722
	Surgery procedure code
Osteosynthesis	KNFJ4-9
Primary hip replacement	KNFB0-99

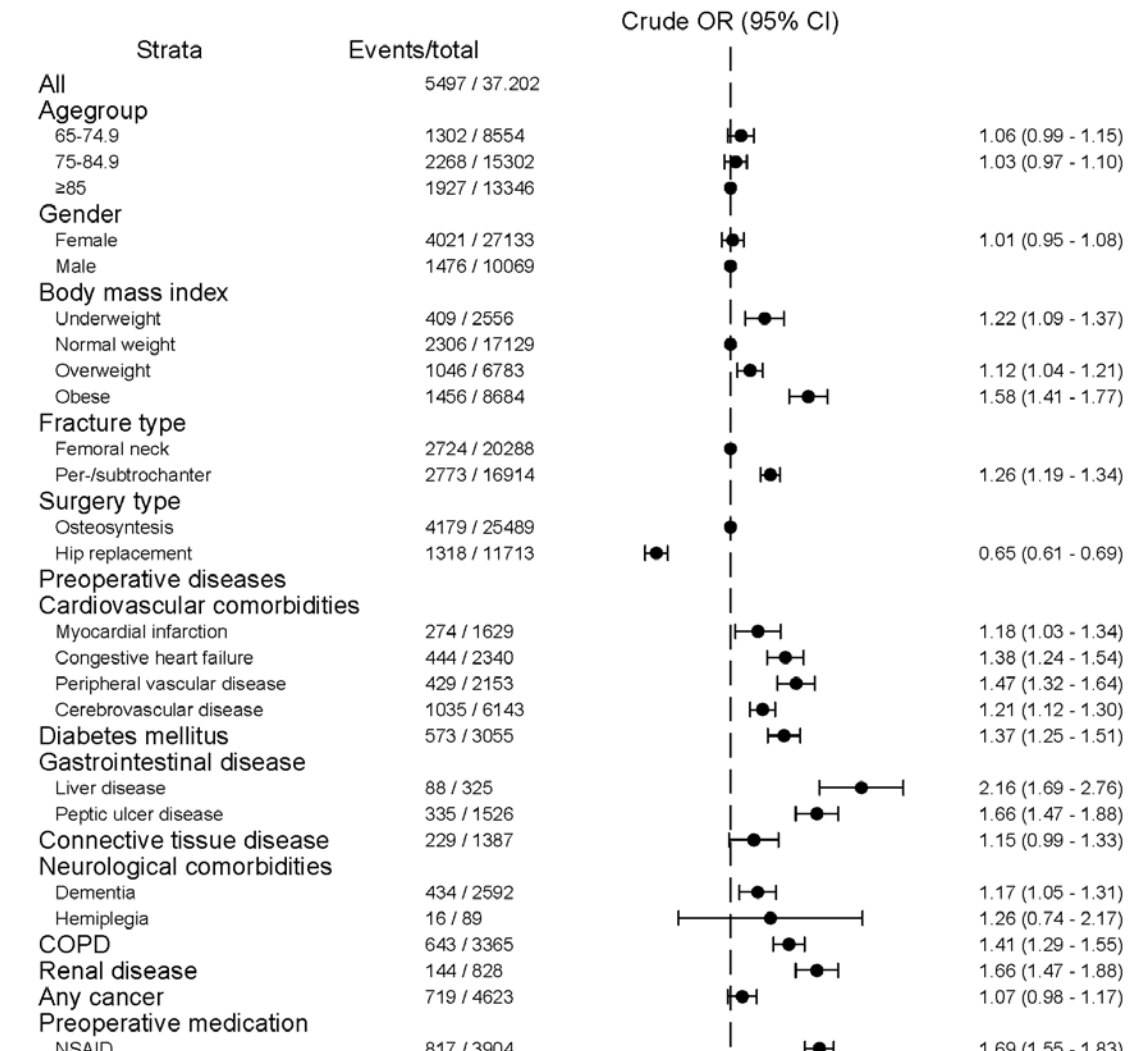
ICD-10: WHO's International Statistical Classification of Diseases and Related Health Problems, 10th Revision.

Appendix 2: ATC codes for all medication in the study

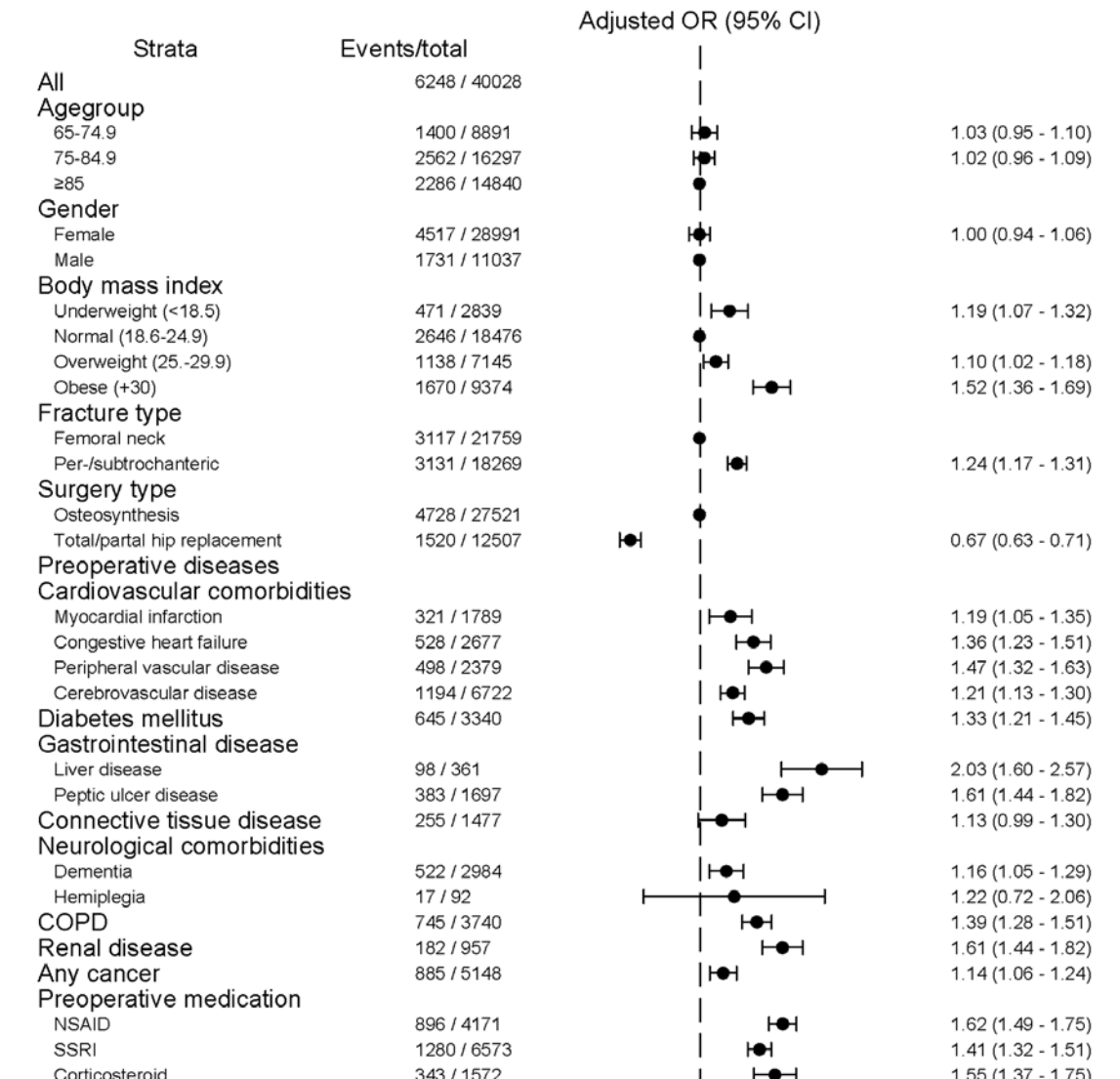
Categories	**Name**	**ATC code**
Non-steroidal anti-inflammatory drugs (NSAIDs):	Celecoxib	M01AH01
	Rofecoxib	M01AH
	Valdecoxib	M01AH03
	Etoricoxib	M01AH05
	Lornoxicam	M01AC05
	Diclofenac	M01AB05
	Meloxicam	M01AC06
Selective serotonin reuptake inhibitors (SSRIs)	Fluoxetine	N06AB03
	Citalopram	N06AB04
	Paroxetine	N06AB05
	Sertraline	N06AB06
	Fluvoxamine	N06AB08
	Escitalopram	N06AB10
Antidepressants	Non-selective monoamine reuptake inhibitors	N06AA
	Non-selective monoamine-oxidase inhibitors	N06AF
	Monoamine-oxidase type A inhibitors	N06AG
	Other antidepressants	N06AX
Antipsychotics	Antipsychotics	N05A-
Corticosteroids	Systemic hormones	H02AB
		H02BX
Oral anticoagulation therapy	Heparin	B01AB
	Arixtra	B01AX
	Fibrinolytika	A01AD
	Vitamin K antagonister	B01AA
	NOAC	B01AE07
	Rivaroxaban	B01AF01
	Apixaban	B01AF02
	Edoxaban	B01AF03
	Trombocytinhibitors	B01AC
	Aspirin	N02BA01
	Aspirin	N02BA51
Statins	Simvastatin	C10AA01
	Lovastatin	C10AA02
	Fluvastatin	C10AA04
	Cerivastatin	C10AA06
	Atorvastatin	C10AA05
	Pravastatin	C10AA03
	Rosuvastatin	C10AA07
Antibiotics	Oral treatment of bacterial infections	J01x
	viral infections	J05x
Opioids	Morfin	N02AA01
	Fentanyl	N02AB03
	Hydromorphon	N02AA03
	Ketobemidon (ketogan)	N02AG02
	Methadon	N07BC02
	Nicomorphin	N02AA04
	Oxycodon	N02AA05
	Pethidin	N02AB02
	Targin	N02AA55

	Tramadol	N02AX02
	Tapentadol	N02AX06
	Buprenorphin	N02AE01
	Codein	R05DA04
	Codein and paracetamol	N02AJ06
Hormone replacement therapy	Estrogen	G03C
	Estrogen	L02AA
	Progesteron and estrogen in combination	G03F
	Antiandrogen	G03H
	Progesteron	G03D
Anti-osteoporosis medication		
Bisfosfonats	Etidronat	M05BA01
	Clodronate	M05BA02
	Pamidronate	M05BA03
	Alendronat	M05BA04
	Alendronat and colecalciferol	M05BB03
	Alendronat, calcium and colecalciferol	M05BB05
	Tiludronate	M05BA05
	Ibandronat	M05BA06
	Risedronat	M05BA07
	Risedronat and calcium	M05BB02
	Risedronat, calcium and colecalciferol	M05BB04
	Zoledronat	
Other drugs affecting bone structure and mineralization	Denosumab	M05BX04
	Strontiumranelat	M05BX03

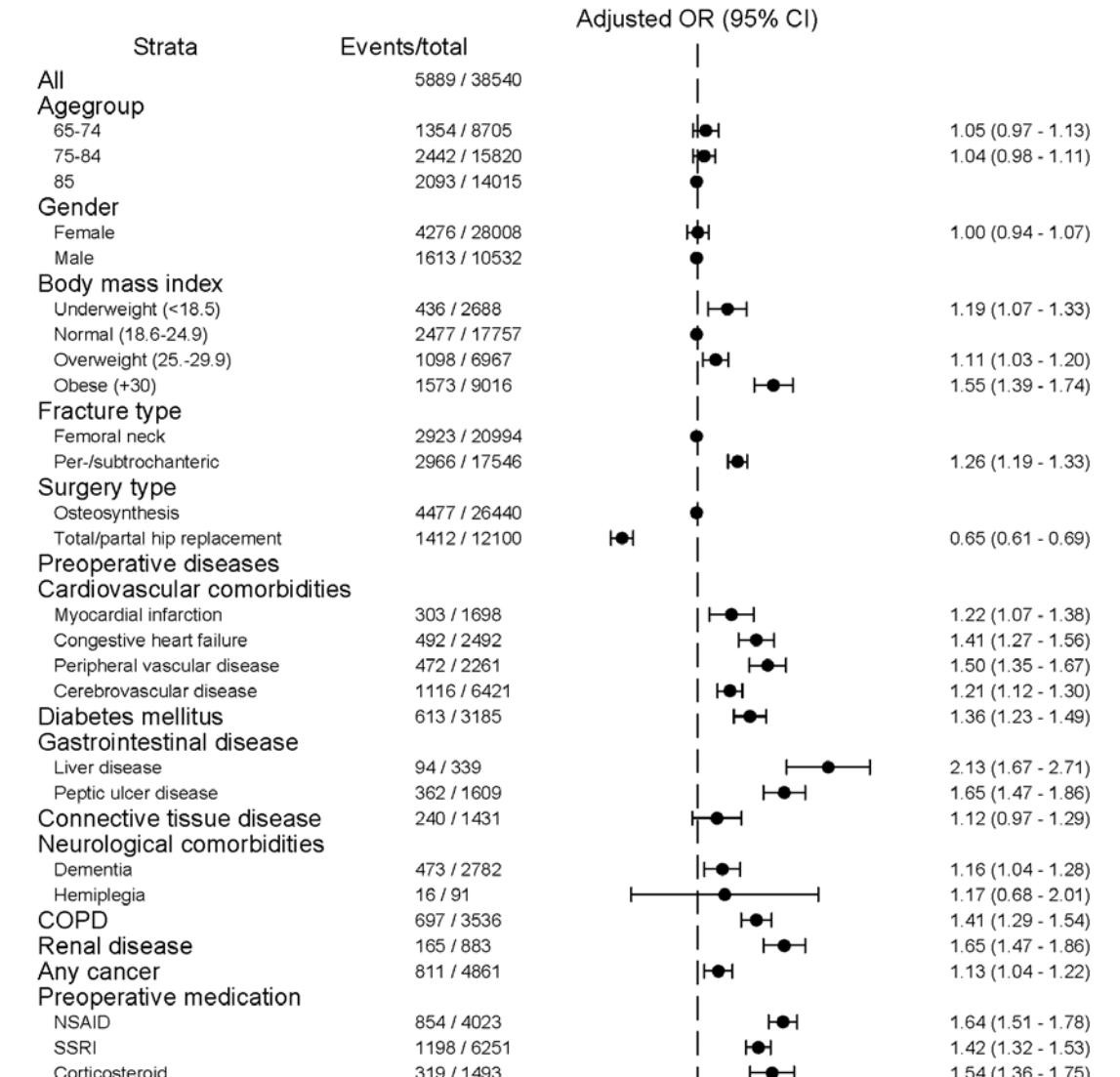
ATC codes: Anatomical Therapeutic Chemical Classification System



Appendix figure 1: Risk factors for developing new chronic opioid use after hip fracture surgery among patient with no opioid use before surgery and those who were alive 12 months after surgery, crude odds ratios. COPD: Chronic pulmonary disease, NSAID: nonsteroidal anti-inflammatory drug, SSRI: selective serotonin reuptake inhibitors, HRT: Hormone Replacement Therapy, NOAC: novel oral anticoagulant. Odds ratios (ORs) with 95% confidence intervals (CI)



Appendix figure 2: Landmark analyses at 6 months: Risk factors for developing new chronic opioid use after hip fracture surgery among patients with no opioid use before surgery, when excluding the patients who died in the first and second quarter of surgery, odds ratios adjusted for age and sex.
COPD: Chronic pulmonary disease, NSAID: nonsteroidal anti-inflammatory drug, SSRI: selective serotonin reuptake inhibitors, HRT: Hormone Replacement Therapy, NOAC: novel oral anticoagulant. Odds ratios (ORs) with 95% confidence intervals (CI)



Appendix figure 3: Landmark analyses at 9 months: Risk factors for developing new chronic opioid use after hip fracture surgery among patients with no opioid use before surgery, when excluding the patients who died in the first, second, and third quarter of surgery, odds ratios adjusted for age and sex.
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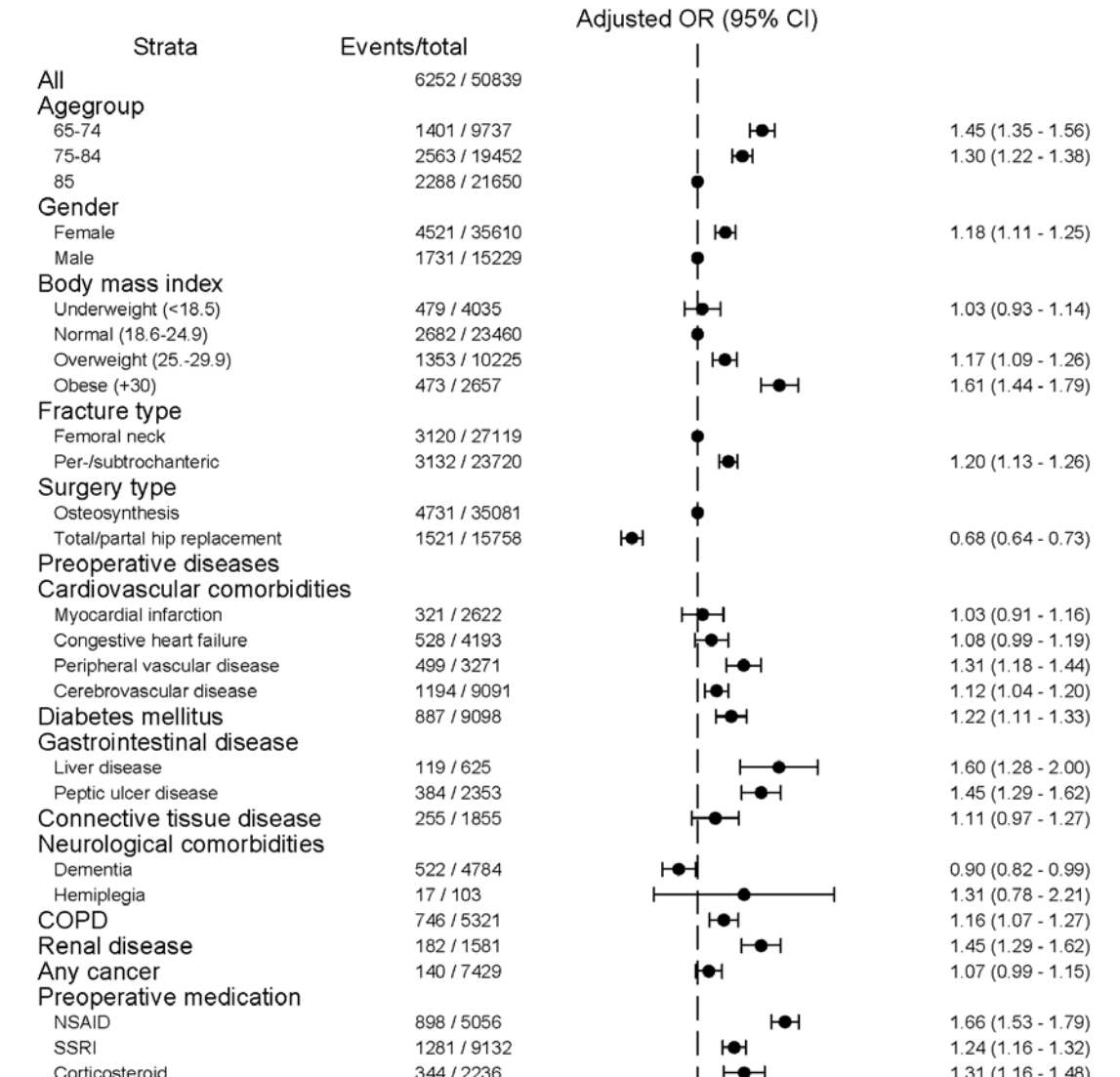

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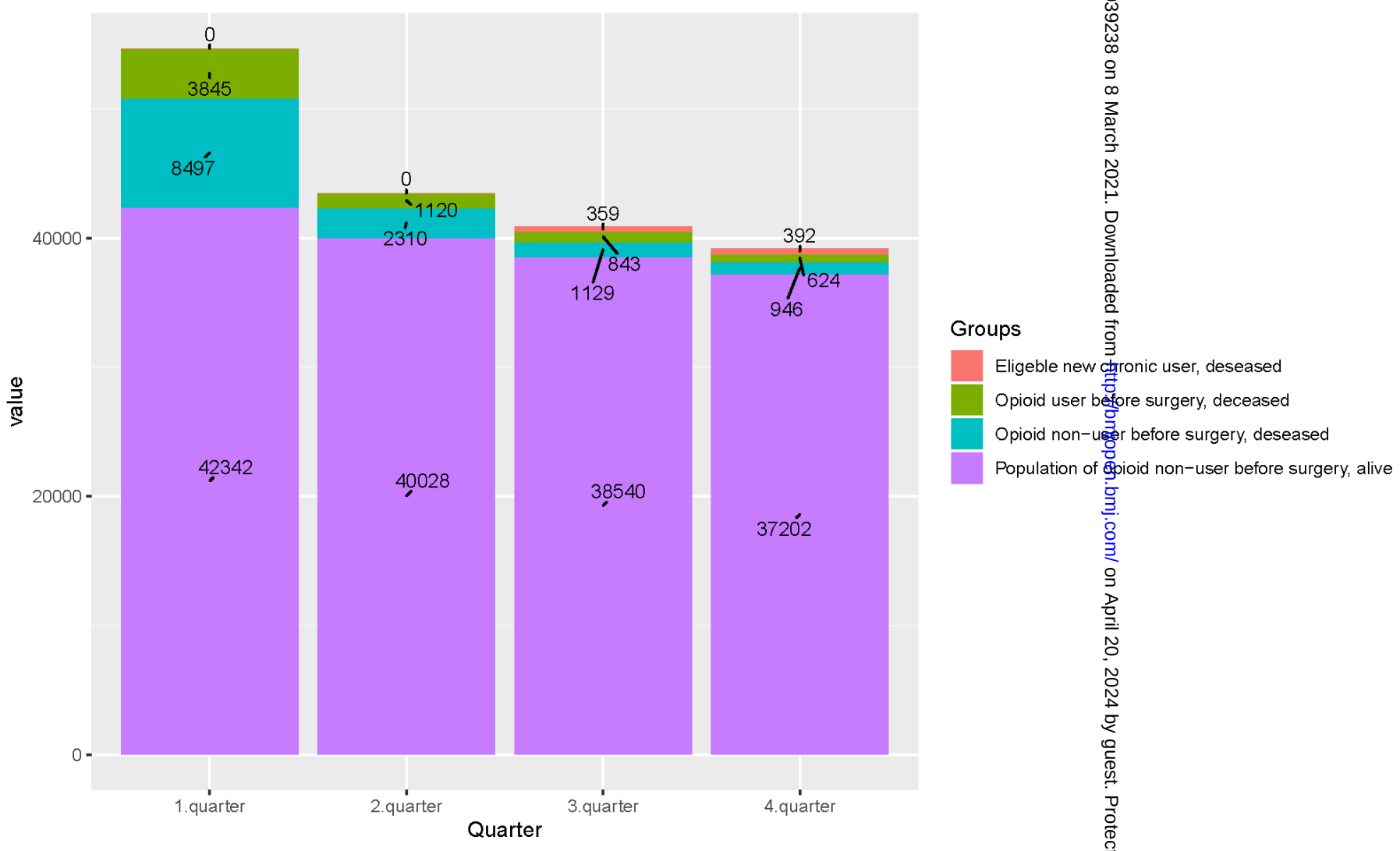

Appendix figure 5: Number of hip fracture patients identified at the time of hip fracture and during the first year following surgery. Patients who were opioid users before surgery were not included in our analyses (number of deceased in this group in each of the 4 quarters of surgery is presented with green color). Our analyses were based on patients with no opioid use before surgery. We presented the number of opioid non-users alive in each of the 4 quarters of surgery with purple color. We presented the number of opioid non-users who dead in each of the 4 quartets of surgery with blue color. Number of eligible new chronic users are patients, who have redeemed two opioid prescriptions, but have died in the first year following surgery, and are therefore not included in our primary analyses (red color).

Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cohortreporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1

Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	#3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	#4	Present key elements of study design early in the paper	6
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	6
Eligibility criteria	#6b	For matched studies, give matching criteria and number of exposed and unexposed	6
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than	6

		one group. Give information separately for for exposed and unexposed groups if applicable.	
Bias	#9	Describe any efforts to address potential sources of bias	8
Study size	#10	Explain how the study size was arrived at	6
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	7
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	8
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	8
Statistical methods	#12c	Explain how missing data were addressed	8
Statistical methods	#12d	If applicable, explain how loss to follow-up was addressed	8
Statistical methods	#12e	Describe any sensitivity analyses	8
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-	9

		up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	
Participants	#13b	Give reasons for non-participation at each stage	9
Participants	#13c	Consider use of a flow diagram	9
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	9
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	9
Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	9
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	9
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9
Main results	#16b	Report category boundaries when continuous variables were categorized	9
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9

Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	9
Discussion			
Key results	#18	Summarise key results with reference to study objectives	10
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	10
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	11
Generalisability	#21	Discuss the generalisability (external validity) of the study results	12
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

BMJ Open

Risk factors for new chronic opioid use after hip fracture surgery: a Danish nationwide cohort study from 2005 to 2016 using the Danish multidisciplinary hip fracture registry

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Keywords:	EPIDEMIOLOGY, Hip < ORTHOPAEDIC & TRAUMA SURGERY, PAIN MANAGEMENT

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Risk factors for new chronic opioid use after hip fracture surgery: a Danish nationwide cohort study from 2005 to 2016 using the Danish Multidisciplinary Hip Fracture Registry

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Abstract

Objective

To examine the risk factors for new chronic opioid use in elderly hip fracture surgery patients.

Design

Prospective population-based cohort study.

Setting and participants

Using Danish nationwide health registries, we identified all opioid non-user patients aged ≥65 years who had undergone hip fracture surgery from 2005-2016 and were alive within the first year following surgery.

Main outcome measures

New chronic opioid use defined by the dispensing of at least 2 prescription opioids within 2 of the last 3 quarters during the first year following surgery.

Results

We identified 37,202 opioid non-user patients who underwent hip fracture surgery. Of these, 5,497 (15%) developed new chronic opioid user within 1 year of surgery.

Risk factors for new chronic opioid use were BMI <18.5 (adjusted Odds Ratio (aOR) 1.22 (95% confidence interval (95% CI) 1.09-1.36)), BMI 25-29.9 (aOR 1.12 (95% CI 1.04-1.21)), and BMI ≥30 (aOR 1.57 (95% CI 1.40-1.76)) with BMI 18.6-24.9 as reference, a per-/subtrochanteric fracture (aOR 1.27 (95% CI 1.20-1.34)) with femoral neck fracture as reference, preoperative use (versus no-use) of NSAID (aOR 1.68 (95% CI 1.55-1.83)), SSRI (aOR 1.42 (95% CI 1.32-1.53)), antidepressants (aOR 1.36 (95% CI 1.24-1.49)), antipsychotics (aOR 1.21 (95% CI 1.07-1.35)), corticosteroids (aOR 1.54 (95% CI 1.35-1.76)), statins (aOR 1.09 (95% CI 1.02-1.18)), antibiotics (aOR 1.32 (95% CI 1.22-1.42)), anti-osteoporosis drugs (aOR 1.33 (95% CI 1.19-1.49)), and anticoagulantives (aOR 1.24 (95% CI 1.17-1.32)). Presence of cardiovascular comorbidities, diabetes, gastrointestinal diseases, dementia, COPD, or renal diseases were further identified as risk factors.

Conclusion

In this large nationwide cohort study, we identified several risk factors associated with new chronic opioid use after hip fracture surgery among patients who were alive within the first year following surgery.

Although not all factors are modifiable preoperative, this will allow clinicians to appropriately counsel patients preoperatively and tailor postoperative treatment.

Article Summary

Strengths and limitations of this study

- This study is a prospective population-based cohort study with complete follow-up based on Danish nationwide health registries.
- The study includes comprehensive high-quality data on medication use and comorbidities before surgery, and detailed clinical- and opioid data from registries rather than patient-reported data.
- The definition of new chronic opioid use is inspired by the guidelines from the International Association for the Study of Pain.
- Data on clinical indications for opioid prescriptions and patient compliance with opioid treatment was not available. Nor was data on reoperations during follow-up available.
- In our primary analysis, we excluded all deceased patients within the first year following surgery. This might have compromised the external validity of our study, and potentially introduced immortal time. We used a number of sensitivity analyses, including landmark analysis to test the robustness of our estimates. Thus, we can only conclude that the identified risk factors for new chronic opioid use apply for hip fracture patients who survived one year after surgery.

Introduction

The prevalence of hip fractures is estimated to reach 6.3 million people worldwide by 2050 [1]. Hip fracture patients often suffer from comorbidities and polypharmacy, which have been associated with an increased risk of complications and increased mortality. In addition, postsurgical pain can delay mobilization and rehabilitation[2]. These factors make treatment and rehabilitation for hip fracture surgery patients challenging.

Opioids are commonly accepted as standard clinical practice for pain treatment in hip fracture surgery patients. However, initial prescription opioid treatment for acute postsurgical pain still merits caution as it can result in chronic opioid use [3]. Previous studies have shown that a high percentage of hip fracture patients who did not use opioids before their hip fracture were still using opioids several months after surgery [4 5]. This is concerning as chronic prescription opioid use can have a negative impact on quality of life [6], has been associated with increased risk of sustaining new fractures [7] and other adverse events including general medical complications [3].

The risk of chronic opioid use can be influenced by patient-related, surgical and healthcare-related factors, some of which are modifiable (weight, medication, surgery type) whereas others are non-modifiable (age, gender). Only few studies have investigated risk factors for chronic opioid use in orthopedic patients. Moreover, these studies are limited by small sample sizes, study populations that differ from the hip fracture population, varying definitions of opioid use, different follow-up duration, and lack of adjustment for potential confounders [8 9]. No previous studies have investigated risk factors for chronic opioid use after hip fracture surgery. Thus, there is a need for more knowledge on risk factors for new chronic opioid use in hip fracture patients, in particular risk factors that are modifiable during pre-, peri-, and postoperative period.

The aim of this study was to examine patient-related and surgery-related risk factors associated with new chronic opioid use in elderly hip fracture surgery patients using nationwide health registries.

Patients and Methods

Study design and setting

We conducted this population-based cohort study in Denmark using prospectively collected administrative health data from health registries, which cover all contacts to the health sector [10]. The Danish National Health Services provide tax-supported primary and secondary health care for the entire population[10], ensuring that all eligible hip fracture patients undergo surgery at a public hospital. All Danish citizens can be identified using a 10-digit personal identification number, which goes through all Danish health registries allowing for unambiguous individually record linkage of data [11].

Data sources

The Danish Civil Registration System (DCRS) was initiated in 1968. Daily updated information on migration and vital status allows for virtually complete long-term follow-up on emigration and death [11].

The Danish Multidisciplinary Hip Fracture Registry (DMHFR) was initiated in 2003 and contains nationwide population-based data about all patients undergoing primary hip fracture surgery [12]. The positive predictive value of the hip fracture diagnosis is between 90% and 98% depending on fracture type [13].

The Danish National Health Service Prescription Database (DNHSPD) has kept information on all prescriptions for reimbursed drugs dispensed by community pharmacies in Denmark since 2004 according to Anatomical Therapeutic Chemical classification system (ATC codes). Data from the DNHSPH can account for patient's medication [14].

The Danish National Patient Registry (DNPR) is an administrative registry established in 1977 covering all somatic contacts in all Danish hospitals [15]. Information reported to the DNPR includes administrative data, diagnoses, treatments and examinations. Primary and secondary diagnoses are reported to the DNPR according to the International Disease Classification tenth revision (ICD-10) since 1995 [15]. The positive predictive value of the diagnoses included in the medical comorbidities are more than 90% [16].

Study population

We used the DMHFR to identify all patients aged 65 or older who were treated for a fracture of the femoral neck, per-, or sub-trochanteric fracture with osteosynthesis or total/partial hip replacement surgery between January 1, 2005 and December 31, 2015 (appendix 1). Patients were indexed on their surgery date and followed up for 12 months (to December 31, 2016). Patients who had dispensed an opioid in the 6 months prior to index were excluded to ensure

they were opioid non-users at the index date. Patients who died from any cause within 12 months following their index date were also excluded (figure 1).

Outcome

We characterized patients with new chronic opioid use as having dispensed an opioid prescription in at least 2 of the 3 last quarters (3-months periods per quarter) within the first year following surgery among previously opioid non-user patients (figure 2) [8 17]. Prescription opioids dispensed by community pharmacies seven days prior to index and within the first quarter after index were not included in the outcome definition because they are likely to have been associated with the initial opioid treatment to manage acute postoperative pain [4]. Thus, we were only interested in subsequent opioid prescriptions beyond the early perioperative period (quarters 2-4). Our definition of chronic opioid use after surgery was aligned with the definition from the International Association for the Study of Pain, which defines chronic postsurgical pain as pain that develops after a surgical procedure and persists for at least 3 months after surgery [18].

The following prescription opioids were included in the analysis: morphine, hydromorphine, nicomorphine, oxycodone, oxycodone combined with naloxone, pethidine, fentanyl, ketobemidone, methadone, codeine, tramadol, tapentadol, and buprenorphine.

Risk factors

Based on previous literature and clinical experience, the below-mentioned patient- and surgery-related factors were considered and examined as potential risk factors for new chronic opioid use [8 9]. From the DMHFR, we obtained information on age (in categories 65-74, 75-84 and ≥85 years), sex, fracture type (femoral neck and per-/subtrochanteric fracture), and surgery type (osteosynthesis and total/partial hip replacement). Body mass index (BMI) was calculated using information on height and weight (weight in kilograms divided by height in metres squared) and divided into groups (underweight defined as BMI <18.5, normal as BMI 18.6-24.9, overweight as BMI 25-29.9 and obese as BMI ≥30). We examined several specific medical comorbidities including myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, diabetes, liver disease, peptic ulcer disease, connective tissue disease, dementia, hemiplegia, chronic obstructive pulmonary disease, renal disease and cancer (Table 1). BMI and various comorbidities were in previous studies found to be associated with increased risk of mortality and could be associated with increased risk of chronic opioid use [8 19-21].

We also included data on preoperative dispensing of the following co-medications: nonsteroidal anti-inflammatory drug (NSAID), selective serotonin reuptake inhibitors (SSRI), any antidepressants, antipsychotics, oral corticosteroids, statins, antibiotics, hormone replacement therapy, anti-osteoporosis medication, vitamin K, any anticoagulants, novel oral anticoagulant (NOAC), antiplatelet drugs and heparins (appendix 2). These drugs are included as potential risk factors because they can influence general healthcare utilization and behaviour, or are associated with increased mortality [22]. The preoperative medication for each drug was defined as at least 1 dispensing in the 1 year before surgery.

Statistical analyses

For the presentation of demographic data, descriptive statistics were used and presented for the entire study population at the time of surgery and separately for patients with new chronic use. Odds ratios (ORs) with 95% confidence intervals (CI) were calculated using multiple logistic regression and adjusted for age and sex (aOR). Several sensitivity analyses were performed: 1. An analysis when using logistic regression and adjusting for multiple relevant factors. 2. An analysis where all patients who died within the first year were included. 3. Landmark analysis at 6 months (only excluding the patients who died in the first and second quarter), and at 9 months (only excluding the patients who died in the first, second, and third quarter) [23 24]. 4. An analysis when only including patients, who sustained a fracture of the femoral neck to analyze the treatment with total/partial hip replacement and osteosynthesis. All statistical analyses were performed in STATA version 15 (STATACorp, TX, USA).

The study was approved by the Danish Data Protection Agency's journal number (2015-57-0002) and Aarhus University's journal number (2016-051-000001), record number 880.

This paper was reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [25], and the Reporting of studies Conducted using Observational Routinely-collected Data (RECORD) statement [26].

Patient and Public Involvement

No patient involved

Results

Description of the study population

In total, 69,456 patients with hip fracture surgery were identified (figure 1). We excluded 18,617 hip fracture patients due to opioid use before surgery, leaving us with 50,839 eligible hip fracture patients. Of these, 13,637 patients died within the first year. The final study population included 37,202 hip fracture patients.

Overall, 27,133 patients (73%) were female and the mean age at the time of surgery was 81 years (range 65-107). In our study population, 5,497 (15%) developed new chronic opioid use within 1 year of surgery.

The proportion of patients who developed new chronic opioid use in relation to all hip fracture patients was 15% for both females and males, 13% for patients with femoral neck fractures, and 16% for patients with a per- or subtrochanteric fracture (Table 1).

The characteristics of patients with new chronic opioid use were similar to the characteristics of the total population of hip fracture patients with small differences seen in the distribution of BMI, fracture type, surgery type, and preoperative medication use (Table 1).

Risk factors for new chronic opioid use

The risk factors for new chronic opioid use were being underweight (aOR 1.22 (CI 1.09-1.36)), overweight (aOR 1.12 (CI 1.04-1.21)), or obese (aOR 1.57 (CI 1.40-1.76)) with normal weight as reference and sustaining a per-/subtrochanteric fracture (aOR 1.27 (CI 1.20-1.34)) with fracture of the femoral neck as reference. Treatment with total/partial hip replacement was associated with lower risk of new chronic opioid use, with osteosynthesis as reference (aOR 0.65 (CI 0.60-0.69)) (figure 3 and appendix figure 1).

Preoperative use of NSAIDs (aOR 1.68 (CI 1.55-1.83)), SSRIs (aOR 1.42 (CI 1.32-1.53)), antidepressants (aOR 1.36 (CI 1.24-1.49)), antipsychotics (aOR 1.21 (CI 1.07-1.35)), corticosteroids (aOR 1.54 (CI 1.35-1.76)), statins (aOR 1.09 (CI 1.02-1.18)), antibiotics (aOR 1.32 (CI 1.22-1.42)), anti-osteoporosis drugs (aOR 1.33 (CI 1.19-1.49)), anticoagulants (aOR 1.24 (CI 1.17-1.32)), and antiplatelet drugs (aOR 1.24 (CI 1.16-1.32)) were identified as risk factors for new chronic opioid use (figure 3 and appendix figure 1).

The presence of the following preoperative comorbidities were further associated with risk of new chronic opioid use: cardiovascular comorbidity, diabetes, gastrointestinal diseases, dementia, COPD, and renal diseases (figure 3 and appendix figure 1).

Several sensitivity analyses were performed. Several sensitivity analyses were performed. The estimates from the sensitivity analysis including patients who deceased within the first year of surgery differed slightly from the primary analysis; e.g. the OR for new chronic opioid use among the youngest patients was 1.07 (CI 0.99-1.15) in the primary analysis changing to 1.45 (CI 1.35-1.56) in this sensitivity analysis (please see figure 4). Results of the landmark analyses were similar to the results presented in the primary analyses, where we excluded all patients who died within 12 months of surgery (please see appendix figure 2 and 3). Likewise, analyses adjusting for multiple relevant factors and those based on patients with only a fracture of the femoral neck showed results similar to the primary analysis (data not shown).

Discussion

To our knowledge, this is the first study to examine risk factors for new chronic opioid use following hip fracture surgery among patients who were alive within the first year following surgery. In this large nationwide cohort study of 37,202 hip fracture surgery patients, 15% of the patients had become new chronic opioid users within the first 12 months after surgery of which patients with a femoral neck represented 55%. We identified several patient characteristics, comorbidities and preoperative medications as possible risk factors that could be associated with new chronic opioid use after surgery.

Strength and limitations

The strength of this study is that it is a nationwide population-based cohort study with prospective, validated data and complete follow-up. In addition, we had comprehensive information on medication use and comorbidities prior to surgery, detailed clinical data on hip fracture patients in regards to information on fracture type, surgery type and BMI, and opioid information based on dispensing data rather than patient-reported data.

Our study also has some limitations. First, there is no consensus on how to define chronic opioid use. Previous studies have defined chronic opioid use as postoperative opioid prescription fulfilment between 90 and 180 days [27], or opioid prescriptions for 120 non-consecutive days [8]. The heterogeneity in definitions for chronic opioid use limits the ability to compare our results with previous studies. Moreover, dispensing data provides an imperfect representation of true preoperative medication use, and we were unable to ascertain the

intended indications of opioid prescriptions. We know that patients have collected the opioid prescription at the pharmacy, but we have no knowledge regarding the patient's compliance. Even so, using prescription opioid dispensing data is considered a better measure of medication use than most alternative measures [28]. Second, we excluded all deceased patients within the first year following surgery, which might have compromised the external validity of our study. Thus, we can only conclude that identified risk factors for new chronic opioid use apply for hip fracture patients that survived one year after surgery. The number of deceased patients was substantial. A total of 13,637 of the 50,839 hip fracture patients died within the first year (please see appendix figure 4). Including these in the study population would have an impact on our results (please see figure 4). A total of 751 of the 13,637 deceased hip fracture patients were potentially eligible to be included in our study as new chronic opioid users. These patients had redeemed two opioid prescriptions in either the second, third or fourth quarter cf. our definition (please see appendix figure 4). In general, immortal time can bias the effect estimates in pharmaco-epidemiological studies [23]. The landmark approach is one of the methods often used when addressing immortal time bias; however, its simplicity comes at the cost of difficulty in interpreting the results [23 24]. The performed landmark analyses illustrated, that including the deceased patients from the third and fourth quarter in our primary analysis would not affect our results substantially (please see appendix figure 2 and 3). The effect of the different analytical assumptions on the results are summarized in figure 5, showing the changes from analysis to analysis plotted side by side. Third, we were not able to include reoperation in our analysis. This may have overestimated the risk of new chronic opioid use in younger female patients, since hip fracture patients are at risk of reoperation, which may lead to prolonged or restarted opioid use. We know that 6% of hip fracture patients are reoperated [29] and that individuals aged 80 years or younger and male gender are associated with risk of reoperation [30].

Comparison with previous studies

Only two studies have reported prescription opioid use after hip fracture surgery. Simoni et al. found that 28% of Danish hip fracture patients had dispensed an opioid prescription within the first year after surgery. Moreover, 17% of the patients who were opioid non-users before surgery had dispensed an opioid prescription 1 year after surgery [4]. That study, however, did not examine chronic opioid use, only opioid use in general defined as 1 dispensed opioid prescription. In a similar study, Lindestrand et al. conducted a medical record review from a single institutional with 416 patients and found 2.9% of previous opioid non-user patients

were opioid users at 6 months. The study reported further that osteoporosis and opioid use prior to admission were predictors for postoperative opioid use at 6 months. In contrast to our study, they did not define opioid use, and the follow-up period ended at 6 months after hip fracture [5]. We studied the risk factors in a large nationwide setup, whereby we uncover trends across the entire country and not only from a single institution.

In general, there is evidence that younger biological age is a predictor of persistent opioid use in the general surgical population [6 8]. This is explained by a wide variety of factors in the aging population such as a decline in the production of several proteins and neuropeptides, a decline of the immune response and an increase in the inflammatory response [31]. Our study shows the same tendency.

Several studies have shown the prevalence of chronic pain and consumption of opioids tend to be higher in females than males [17 32]. Psychological, biological, cultural, and social factors all play a role in the differences between the sex in pain responses and management [17 33]. Our study demonstrates a weak association between the female sex and new chronic opioid use after hip fracture surgery.

Overweight and obesity have been shown to be associated with a proinflammatory state after surgery inducing hyperalgesia, suggesting an increase in opioid use, which correlates with findings by Westermann et al. of an association between obesity and prolonged postoperative opioid use [19 20 34]. This is in line with our findings of an association between overweight and obesity and developing a new chronic opioid use after surgery.

Our data suggest that fracture type and surgery type is associated with new chronic opioid use. Hip fracture patients with a trochanteric fracture experience more and severe pain than patients with femoral neck fractures [35]. Similarly, patients with osteosynthesis experience more pain than the patients with a stable arthroplasty [36]. The reported mechanisms being shortening of the limb length and range of motion limitations [36]. Another explanation to why surgery type is associated with new chronic opioid use could be that these patients might have a higher rate of reoperation converting to a total hip arthroplasty performed by a more experienced surgeon. However, we do not have data to support this statement.

Several preoperative comorbidities were associated with risk of new chronic opioid use after surgery. Although we excluded all hip fracture patients with prior use of opioids, it is possible that some patients had an unmanaged pain condition prior to surgery. These patients may have continued to use prescription opioids intended for treating postsurgical pain in

order to treat their pre-existing chronic pain.[6]. Inacio et al. support this behaviour as they found back pain prior to surgery was associated with chronic opioid use [8]. Comorbidities associated with unrelieved chronic pain conditions are heart failure and COPD. These comorbidities have been associated with chronic opioid use, which concords with our study [6] [8]. Diabetes has also been associated with a constant chronic inflammatory state inducing neuropathy, which has also been associated with unrelieved chronic pain. This mechanism is a potential risk factor for chronic pain, which is in accordance with our study [6 8]. Other comorbidities have also been associated with chronic pain and chronic opioid use such as liver disease and depression [8]. By knowing the impact of these comorbidities on the risk of new chronic opioid use, attainment of a greater focus on comorbidity pre- and postoperative may reduce new chronic opioid use after surgery.

Medication use is frequent in hip fracture patients and nearly all of the included medications in our study were identified as a risk factor for chronic opioid use [37]. Medication use is closely related to comorbidities. Treatment of chronic medical conditions is a complex task that require multidisciplinary approach. It is possible that surgeons and patients are preoccupied with attempting to manage chronic pain conditions leaving long-term opioid use as a secondary priority. Some drugs when taken on their own or in combination, might change the level of sensitivity to opioids which could result in patients who continue to take opioids even though their level of pain decreases over time and does not necessarily coincide with the prescribed opioid dose.

Chronic opioid use

There are no standard guidelines in Denmark for post-discharge clinical follow-up of hip fracture patients. However, many orthopaedic and geriatric departments focus on the reduction of prescription opioid exposure after surgery by instituting a plan for opioid tapering. Patients do not receive follow-up appointments in outpatient clinics or at the general practitioner unless they take the initiative themselves. Since hip fracture patients often are characterized as being frail, receiving several medications, and having multimorbidity, they may lack the resources to follow such a tapering plan. Thus, it is important to ensure that patients are well informed and included in the development of a tapering plan, and understand the risks and benefits of prescription opioids for the treatment of postsurgical pain. However, it is important to note that not all hip fracture surgeries are successful and

some patients may experience a greater level of postsurgical pain and postsurgical pain treatment.

Conclusion

In this large nationwide cohort study, 15% of the patients who underwent hip fracture surgery developed new chronic opioid use. We identified under- and overweight, obesity, per or subtrochanteric fracture, preoperative use of several medications and presence of several comorbidities as risk factors associated with the risk of new chronic opioid use after hip fracture surgery.

By identifying risk factors, we can reduce the number of new chronic opioid users by developing more effective preventive intervention strategies targeted to the patients with the identified risk factors. In addition, the identified risk factors are also relevant for clinicians in order to advise patients appropriately before surgery about their risk for chronic postsurgical opioid use.

Authors' Contributions

NME, CV, SO, LN, CFC and ABP contributed to the conception or design of the study. NME carried out the analytical aspects of the study. NME, CV, SO, LN, CFC and ABP contributed to the interpretation of data. NME, CV, SO, LN, CFC and ABP drafted the manuscript or revised it critically. All authors gave their final approval and agreement to be accountable for all aspects of the work.

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Competing interests

None declared.

Patient consent for publication

Not required

Data sharing statement

No additional data are available

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Legends

Figure 1: Flowchart of the patients from the Danish Multidisciplinary Hip Fracture Registry to the study population.

Figure 2: New chronic opioid use was defined as patients with at least 2 prescriptions dispensed in 2 of the 3 latter quarters in the first year following surgery.

Figure 3: Risk factors for developing new chronic opioid use after hip fracture surgery among patient with no opioid use before surgery in those who were alive 12 months after surgery, odds ratios adjusted for age and sex.
COPD: Chronic pulmonary disease, NSAID: nonsteroidal anti-inflammatory drug, SSRI: selective serotonin reuptake inhibitors, HRT: Hormone Replacement Therapy, NOAC: novel oral anticoagulant. Odds ratios (ORs) with 95% confidence intervals (CI)

Figure 4: Risk factors for developing new chronic opioid use after hip fracture surgery among patients with no opioid use before surgery, including patient who were alive and those who died within 12 months of surgery, odds ratios adjusted for age and sex.
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Table 1: Patient characteristics for the all hip fracture patients and new chronic users

Appendix 1: Following diagnoses- and procedure codes were used to identify patients undergoing hip fracture surgery.

Appendix 2: ATC codes for all medication in the study

Table 1: Patient characteristics for the all hip fracture patients and new chronic users

	All (n=37,202)	New chronic user (n=5497)	Proportions of new chronic user (%)
	N (%)	N (%)	
Age			
Mean (SD)	*81.4 (7.9)*	*81.3 (7.9)*	
65-74	*8,554 (23)*	*1,302 (24)*	*(15)*
75-84	*15,302 (41)*	*2,268 (41)*	*(15)*
+85	*13,346 (36)*	*1,927 (35)*	*(14)*
Sex			
Female	*27,133 (73)*	*4,021 (73)*	*(15)*
Male	*10,069 (27)*	*1,476 (27)*	*(15)*
BMI group			
Underweight (<18.5)	*2,556 (7)*	*409 (7)*	*(16)*
Normal (18.6-24.9)	*17,129 (46)*	*2,306 (42)*	*(13)*
Overweight (25.-29.9)	*6,783 (18)*	*1,046 (19)*	*(15)*
Obese (+30)	*8,684 (23)*	*1,456 (26)*	*(17)*
Missing	*6,853 (18)*	*1,083 (20)*	*(16)*
Fracture type			
Femoral neck	*20,288 (55)*	*2,724 (50)*	*(13)*
Per-/subtrochanteric	*16,914 (45)*	*2,773 (50)*	*(16)*
Surgery type			
Osteosynthesis	*25,489 (69)*	*4,179 (76)*	*(16)*
Total/partial hip replacement	*11,713 (31)*	*1,318 (24)*	*(11)*
Cardiovascular comorbidities			
Myocardial infarction	*1,629 (4)*	*274 (5)*	*(17)*
Congestive heart failure	*2,340 (6)*	*444 (8)*	*(19)*
Peripheral vascular disease	*2,153 (6)*	*429 (8)*	*(20)*
Cerebrovascular disease	*6,143 (17)*	*1,035 (19)*	*(17)*
Diabetes	*3,055 (8)*	*573 (10)*	*(19)*
Gastrointestinal comorbidities			
Liver disease	*325 (1)*	*88 (2)*	*(27)*
Peptic ulcer disease	*1,526 (4)*	*335 (6)*	*(22)*
Connective tissue disease	*1,387 (4)*	*229 (4)*	*(17)*
Neurological comorbidities			
Dementia	*2,592 (7)*	*434 (8)*	*(17)*
Hemiplegia	*89 (0)*	*16 (0)*	*(18)*
COPD	*3,365 (9)*	*643 (12)*	*(19)*
Renal disease	*828 (2)*	*144 (3)*	*(17)*
Any cancer	*4,623 (12)*	*719 (13)*	*(16)*
Preoperative medication			
NSAID	*3,904 (10)*	*817 (15)*	*(21)*
SSRI	*5,959 (16)*	*1,103 (20)*	*(19)*
Corticosteroid	*1,427 (4)*	*295 (5)*	*(21)*

Anticoagulants	*13,062 (35)*	*2,134 (39)*	*(16)*
Statins	*6,949 (19)*	*1,088 (20)*	*(16)*
Antibiotics	*6,479 (17)*	*1,106 (20)*	*(17)*
Antidepressants	*3,250 (9)*	*601 (11)*	*(18)*
Antipsychotics	*2,150 (6)*	*367 (7)*	*(17)*
HRT	*1,955 (5)*	*312 (6)*	*(16)*
Anti-osteoporosis medicine	*2,143 (6)*	*394 (7)*	*(18)*
Vitamin K	*1,915 (5)*	*311 (6)*	*(16)*
NOAC	*321 (1)*	*32 (1)*	*(10)*
Antiplatelet drugs	*11,247 (30)*	*1,855 (34)*	*(16)*
Heparins	*29 (0)*	*6 (0)*	*(21)*

BMI: Body Mass Index, COPD: Chronic pulmonary disease, NSAID: nonsteroidal anti-inflammatory drug, SSRI: selective serotonin reuptake inhibitors, HRT: Hormone Replacement Therapy, NOAC: novel oral anticoagulant. Odds ratios (ORs) with 95% confidence intervals (CI)

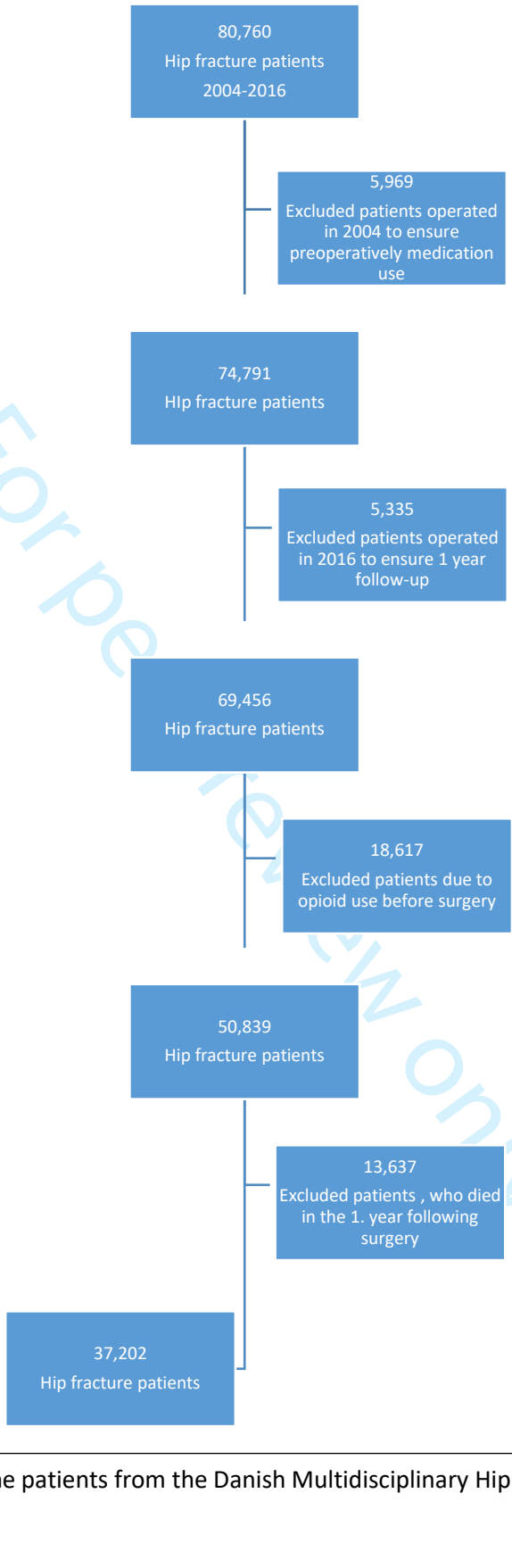

Figure 1: Flowchart of the patients from the Danish Multidisciplinary Hip Fracture Registry to the study population.

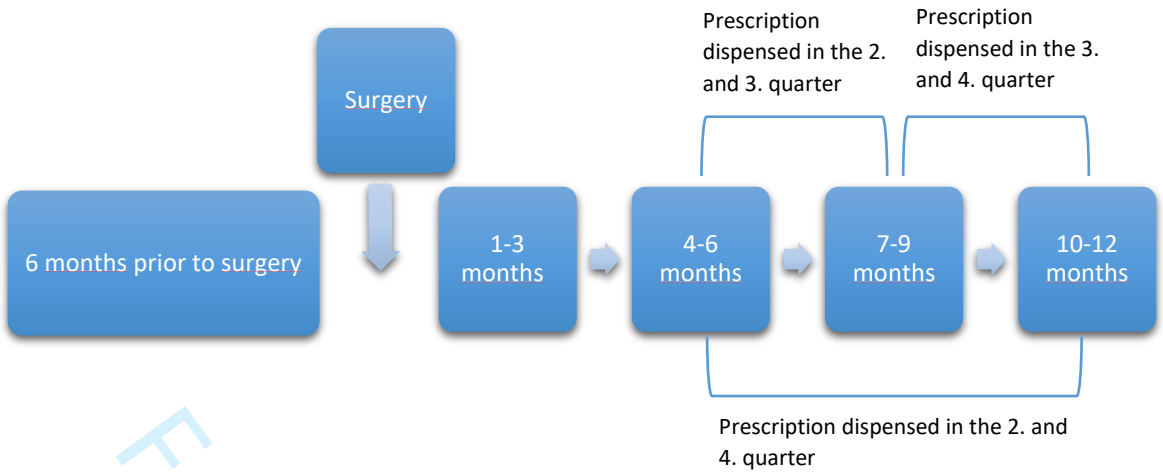

Figure 2: Chronic opioid use was defined as patients with at least 2 prescriptions dispensed in 2 of the 3 latter quarters in the first year following surgery

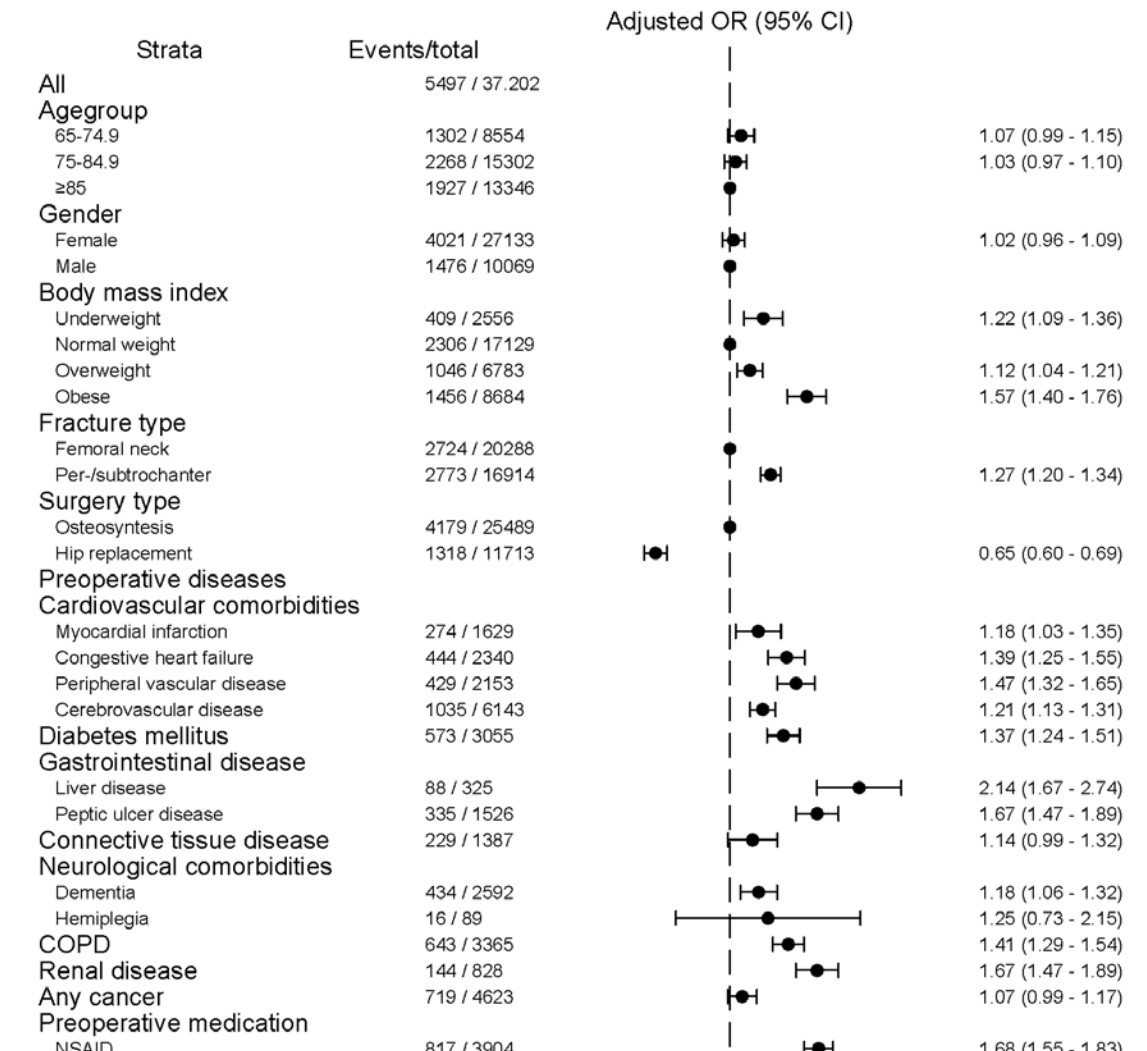

Figure 3: Risk factors for developing new chronic opioid use after hip fracture surgery among patient with no opioid use before surgery and those who were alive 12 months after surgery, odds ratios adjusted for age and sex.

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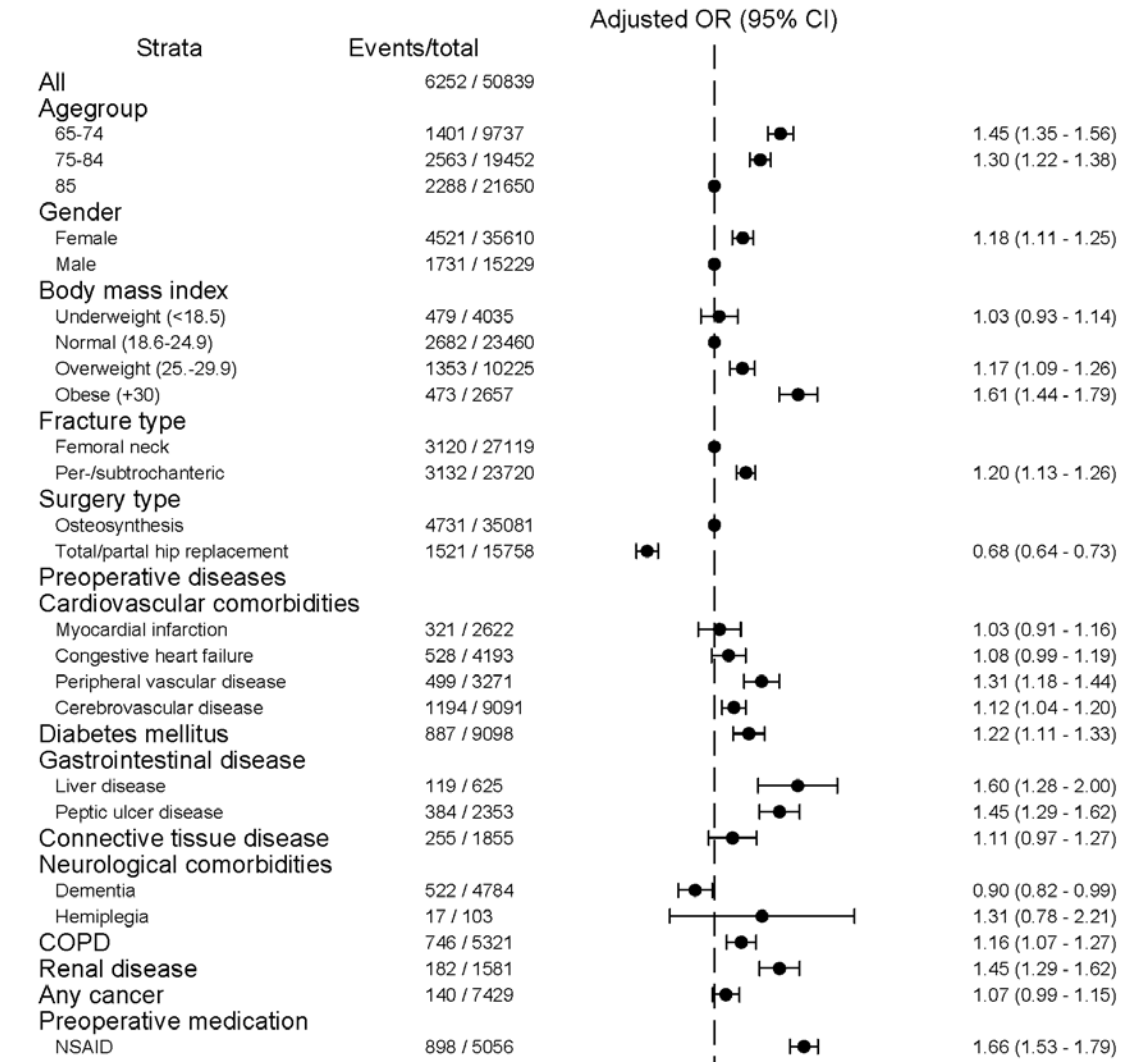

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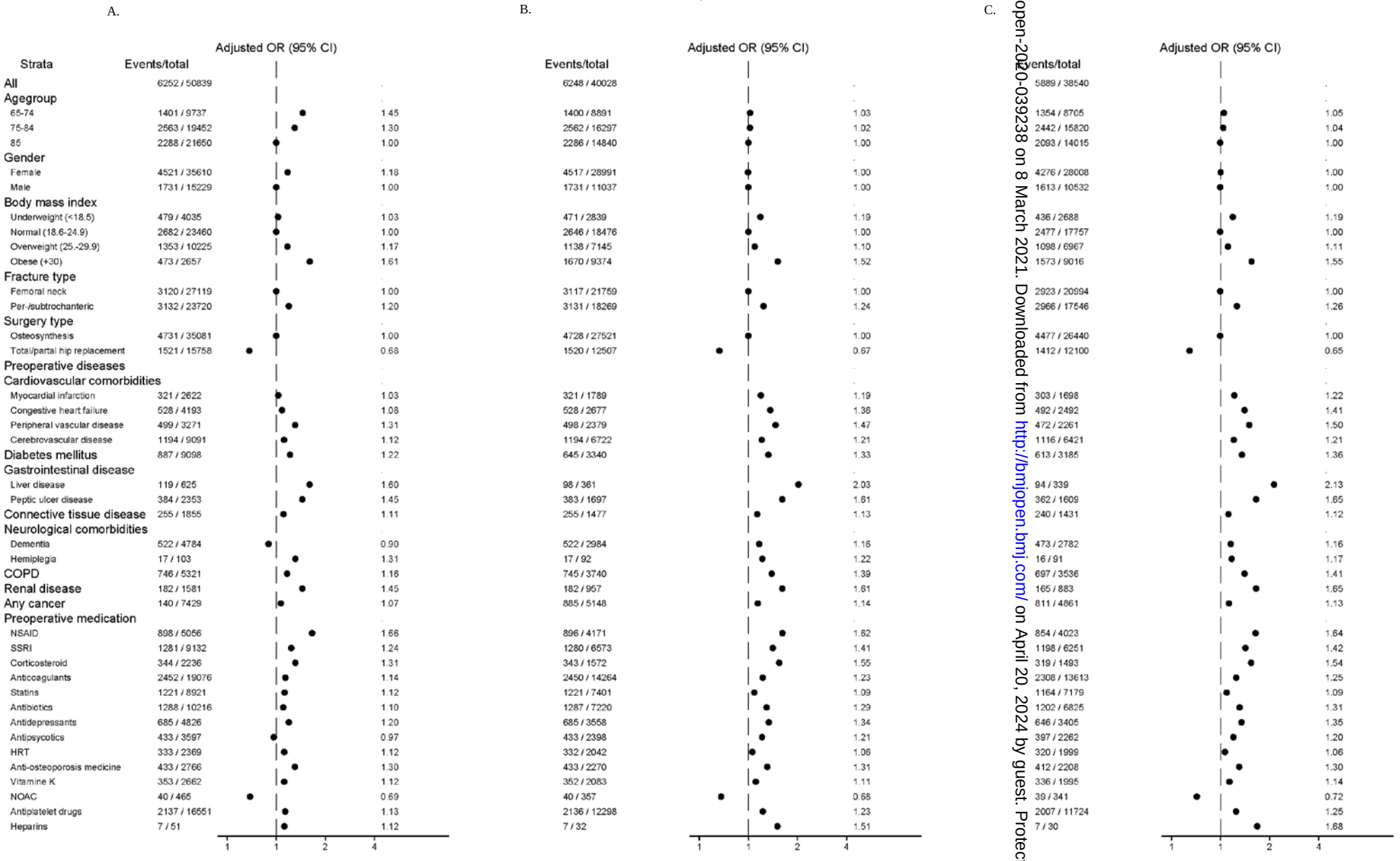

Figure 5: United forest plot. A. Analysis, when including patient who were alive and those who died within 12 months of surgery. B. Landmark analysis at 6 months: Analysis, when including patients with no opioid use before surgery, and excluding the patients who died in the first and second quarter of surgery. C. Landmark analysis at 9 months: Analysis, when including patients with no opioid use before surgery, and excluding the patients who died in the first, second, and third quarter of surgery. Odds ratios adjusted for age and sex.

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Appendix 1: Following diagnoses- and procedure codes were used to identify patients undergoing hip fracture surgery.

ICD-10 code	**Diagnosis code**
Fracture of the femoral neck	DS720
Per-trochanter fracture	DS721
Sub-trochanter fracture	DS722
	Surgery procedure code
Osteosynthesis	KNFJ4-9
Primary hip replacement	KNFB0-99

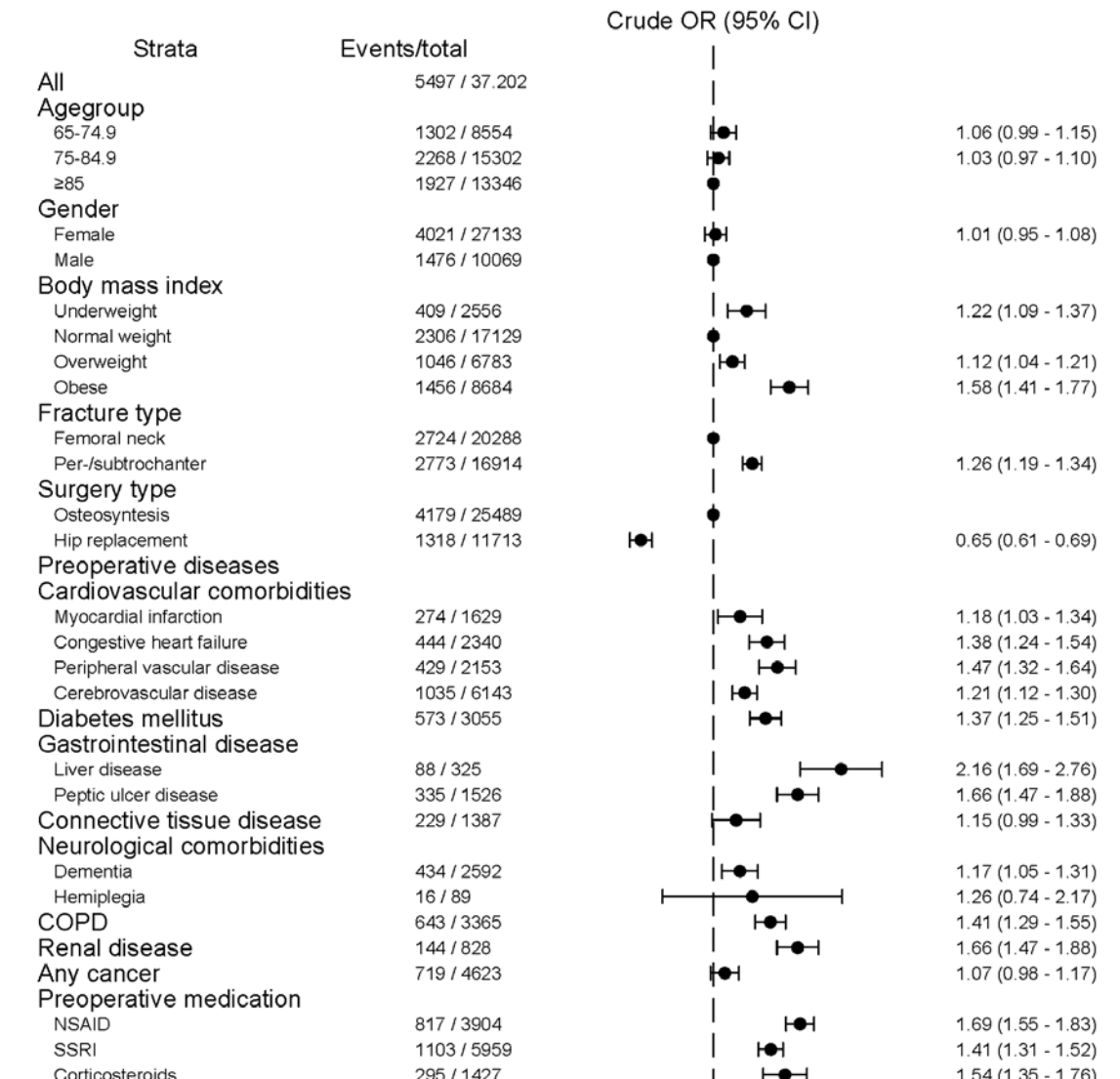
ICD-10: WHO's International Statistical Classification of Diseases and Related Health Problems, 10th Revision.

Appendix 2: ATC codes for all medication in the study

Categories	**Name**	**ATC code**
Non-steroidal anti-inflammatory drugs (NSAIDs):	Celecoxib	M01AH01
	Rofecoxib	M01AH
	Valdecoxib	M01AH03
	Etoricoxib	M01AH05
	Lornoxicam	M01AC05
	Diclofenac	M01AB05
	Meloxicam	M01AC06
Selective serotonin reuptake inhibitors (SSRIs)	Fluoxetine	N06AB03
	Citalopram	N06AB04
	Paroxetine	N06AB05
	Sertraline	N06AB06
	Fluvoxamine	N06AB08
	Escitalopram	N06AB10
Antidepressants	Non-selective monoamine reuptake inhibitors	N06AA
	Non-selective monoamine-oxidase inhibitors	N06AF
	Monoamine-oxidase type A inhibitors	N06AG
	Other antidepressants	N06AX
Antipsychotics	Antipsychotics	N05A-
Corticosteroids	Systemic hormones	H02AB
		H02BX
Oral anticoagulation therapy	Heparin	B01AB
	Arixtra	B01AX
	Fibrinolytika	A01AD
	Vitamin K antagonister	B01AA
	NOAC	B01AE07
	Rivaroxaban	B01AF01
	Apixaban	B01AF02
	Edoxaban	B01AF03
	Trombocytinhibitors	B01AC
	Aspirin	N02BA01
	Aspirin	N02BA51
Statins	Simvastatin	C10AA01
	Lovastatin	C10AA02
	Fluvastatin	C10AA04
	Cerivastatin	C10AA06
	Atorvastatin	C10AA05
	Pravastatin	C10AA03
	Rosuvastatin	C10AA07
Antibiotics	Oral treatment of bacterial infections	J01x
	viral infections	J05x
Opioids	Morfin	N02AA01
	Fentanyl	N02AB03
	Hydromorphon	N02AA03
	Ketobemidon (ketogan)	N02AG02
	Methadon	N07BC02
	Nicomorphin	N02AA04
	Oxycodon	N02AA05
	Pethidin	N02AB02
	Targin	N02AA55

	Tramadol	N02AX02
	Tapentadol	N02AX06
	Buprenorphin	N02AE01
	Codein	R05DA04
	Codein and paracetamol	N02AJ06
Hormone replacement therapy	Estrogen	G03C
	Estrogen	L02AA
	Progesteron and estrogen in combination	G03F
	Antiandrogen	G03H
	Progesteron	G03D
Anti-osteoporosis medication		
Bisfosfonats	Etidronat	M05BA01
	Clodronate	M05BA02
	Pamidronate	M05BA03
	Alendronat	M05BA04
	Alendronat and colecalciferol	M05BB03
	Alendronat, calcium and colecalciferol	M05BB05
	Tiludronate	M05BA05
	Ibandronat	M05BA06
	Risedronat	M05BA07
	Risedronat and calcium	M05BB02
	Risedronat, calcium and colecalciferol	M05BB04
	Zoledronat	
Other drugs affecting bone structure and mineralization	Denosumab	M05BX04
	Strontiumranelat	M05BX03

ATC codes: Anatomical Therapeutic Chemical Classification System



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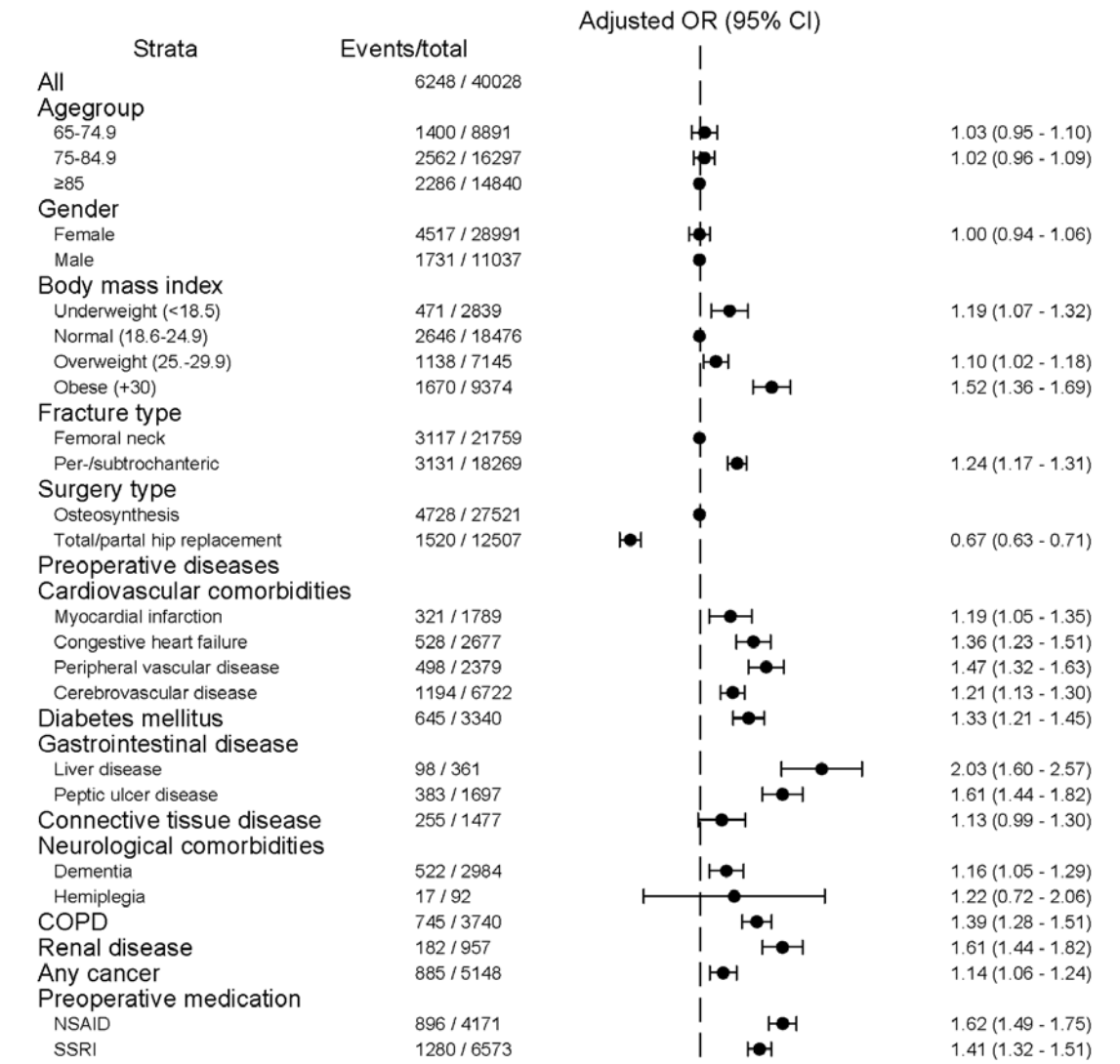

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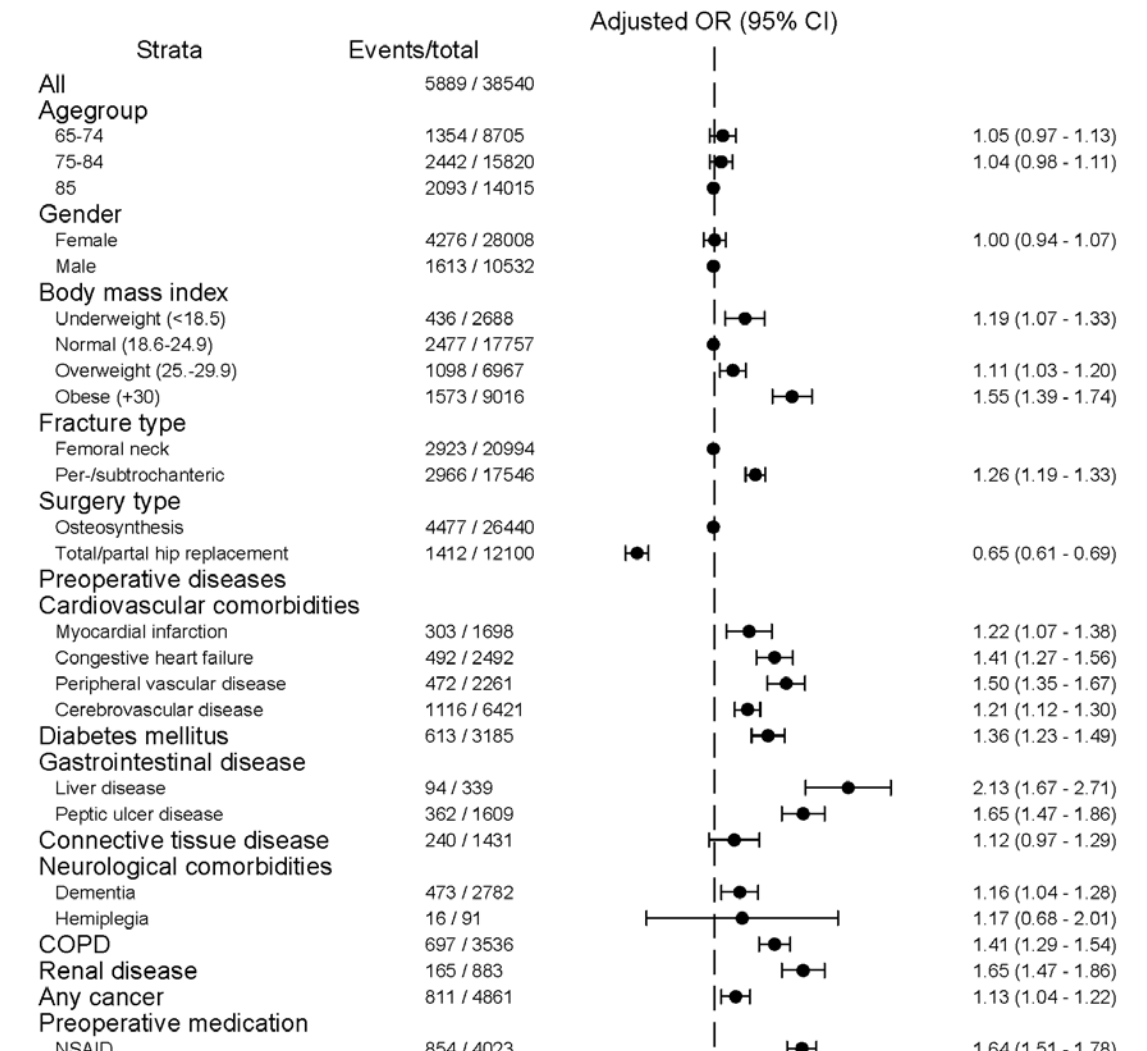

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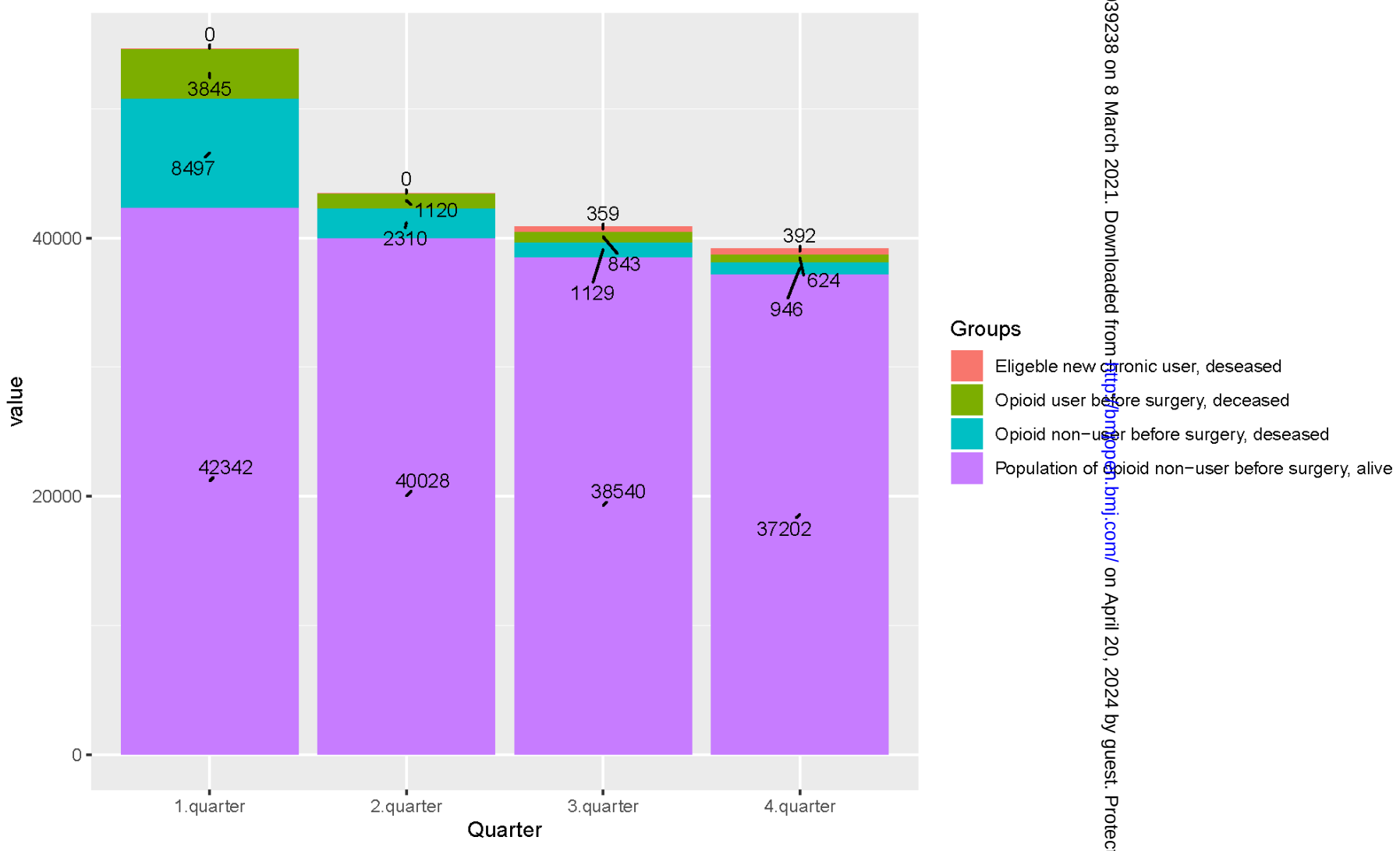

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Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cohortreporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1

Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	#3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	#4	Present key elements of study design early in the paper	6
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	6
Eligibility criteria	#6b	For matched studies, give matching criteria and number of exposed and unexposed	6
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than	6

		one group. Give information separately for for exposed and unexposed groups if applicable.	
Bias	#9	Describe any efforts to address potential sources of bias	8
Study size	#10	Explain how the study size was arrived at	6
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	7
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	8
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	8
Statistical methods	#12c	Explain how missing data were addressed	8
Statistical methods	#12d	If applicable, explain how loss to follow-up was addressed	8
Statistical methods	#12e	Describe any sensitivity analyses	8
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-	9

		up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	
Participants	#13b	Give reasons for non-participation at each stage	9
Participants	#13c	Consider use of a flow diagram	9
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	9
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	9
Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	9
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	9
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9
Main results	#16b	Report category boundaries when continuous variables were categorized	9
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9

Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	9
Discussion			
Key results	#18	Summarise key results with reference to study objectives	10
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	10
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	11
Generalisability	#21	Discuss the generalisability (external validity) of the study results	12
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14