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

**Word count: 295**

### *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  $\geq 65$  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  $\geq 30$  (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)), anticoagulatives (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.

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3 **Word count: 3331**  
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5 **Introduction**  
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8 The prevalence of hip fractures is estimated to reach 6.3 million people worldwide by 2050<sup>1</sup>.  
9 Hip fracture patients often suffer from comorbidities and polypharmacy, which have been  
10 associated with an increased risk of complications and increased mortality. In addition,  
11 postsurgical pain can delay mobilization and rehabilitation<sup>2</sup>. These factors make treatment  
12 and rehabilitation for hip fracture surgery patients challenging.  
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17 Opioids are commonly accepted as standard clinical practice for pain treatment in hip fracture  
18 surgery patients. However, initial prescription opioid treatment for acute postsurgical pain  
19 still merits caution as it can result in chronic opioid use<sup>3</sup>. Previous studies have shown that a  
20 high percentage of hip fracture patients who did not use opioids before their hip fracture were  
21 still using opioids several months after surgery<sup>4,5</sup>. This is concerning as chronic prescription  
22 opioid use can have a negative impact on quality of life<sup>6</sup>, has been associated with increased  
23 risk of sustaining new fractures<sup>7</sup> and other adverse events including general medical  
24 complications<sup>3</sup>.  
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29 The risk of chronic opioid use can be influenced by patient-related, surgical and healthcare-  
30 related factors, some of which are modifiable (weight, medication, surgery type) whereas  
31 others are non-modifiable (age, gender). Only few studies have investigated risk factors for  
32 chronic opioid use in orthopedic patients. Moreover, these studies are limited by small  
33 sample sizes, study populations that differ from the hip fracture population, varying  
34 definitions of opioid use, different follow-up duration, and lack of adjustment for potential  
35 confounders<sup>8,9</sup>. No previous studies have investigated risk factors for chronic opioid use after  
36 hip fracture surgery. Thus, there is a need for more knowledge on risk factors for new chronic  
37 opioid use in hip fracture patients, in particular risk factors that are modifiable during pre-,  
38 peri-, and postoperative period.  
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43 The aim of this study was to examine patient-related and surgery-related risk factors  
44 associated with new chronic opioid use in elderly hip fracture surgery patients using  
45 nationwide health registries.  
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## 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<sup>10</sup>. The Danish National Health Services provide tax-supported primary and secondary health care for the entire population<sup>10</sup>, 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<sup>11</sup>.

### *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<sup>11</sup>.

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<sup>12</sup>. The positive predictive value of the hip fracture diagnosis is between 90% and 98% depending on fracture type<sup>13</sup>.

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<sup>14</sup>.

The Danish National Patient Registry (DNPR) is an administrative registry established in 1977 covering all somatic contacts in all Danish hospitals<sup>15</sup>. 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<sup>15</sup>. The positive predictive value of the diagnoses included in the medical comorbidities are more than 90%<sup>16</sup>.

### *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

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3 replacement surgery between January 1, 2005 and December 31, 2015 (appendix 1). Patients  
4 were indexed on their surgery date and followed up for 12 months (to December 31, 2016).  
5 Patients who had dispensed an opioid in the 6 months prior to index were excluded to ensure  
6 they were opioid non-users at the index date. Patients who died from any cause within 12  
7 months following their index date were also excluded (figure 1).  
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### 10 11 12 *Opioid prescriptions*

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15 Postsurgical opioid prescriptions were identified in the first year following surgery, which we  
16 divided into four quarters (4 months per quarter). Prescription opioids dispensed by  
17 community pharmacies seven days prior to index and within the first quarter after index were  
18 not included in the outcome definition because they are likely to have been associated with  
19 the initial opioid treatment to manage acute postoperative pain<sup>4</sup>. Thus, we were only  
20 interested in subsequent opioid prescriptions beyond the early perioperative period (quarters  
21 2-4).  
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### 27 28 *Outcome*

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30 Our primary outcome was new chronic opioid use after surgery.

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32 New chronic opioid use after surgery was defined as chronic use among previously opioid  
33 non-user patients<sup>8</sup>. Our definition of chronic opioid use after surgery was inspired by the  
34 definition from the International Association for the Study of Pain, which defines chronic  
35 postsurgical pain as pain that develops after a surgical procedure and persists for at least 3  
36 months after surgery<sup>17</sup>. The first year following surgery was therefore divided into quarters.  
37 We characterized patients with new chronic opioid use as having dispensed an opioid  
38 prescription in at least 2 of the 3 quarters within the first year following surgery (figure 2)<sup>18</sup>.  
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45 The following prescription opioids were included in the analysis: morphine, hydromorphone,  
46 nicomorphine, oxycodone, oxycodone combined with naloxone, pethidine, fentanyl,  
47 ketobemidone, methadone, codeine, tramadol, tapentadol, and buprenorphine.  
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### 51 52 *Risk factors*

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54 Based on previous literature and clinical experience, the below-mentioned patient- and  
55 surgery-related factors were considered and examined as potential risk factors for new  
56 chronic opioid use<sup>8,9</sup>. From the DMHFR, we obtained information on age (in categories 65-  
57 74, 75-84 and  $\geq 85$  years), sex, fracture type (femoral neck and per-/subtrochanteric fracture),  
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3 and surgery type (osteosynthesis and total/partial hip replacement). Body mass index (BMI)  
4 was calculated using information on height and weight (weight in kilograms divided by  
5 height in metres squared) and divided into groups (underweight defined as BMI <18.5,  
6 normal as BMI 18.6-24.9, overweight as BMI 25-29.9 and obese as BMI  $\geq$ 30). We examined  
7 several specific medical comorbidities including myocardial infarction, congestive heart  
8 failure, peripheral vascular disease, cerebrovascular disease, diabetes, liver disease, peptic  
9 ulcer disease, connective tissue disease, dementia, hemiplegia, chronic obstructive pulmonary  
10 disease, renal disease and cancer (Table 1). BMI and various comorbidities were in previous  
11 studies found to be associated with increased risk of mortality and could be associated with  
12 increased risk of chronic opioid use<sup>8 19-21</sup>.

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

### 35 *Statistical analyses*

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

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51 The study was approved by the Danish Data Protection Agency's journal number (2015-57-  
52 0002) and Aarhus University's journal number (2016-051-000001), record number 880.

54  
55 This paper was reported following the Strengthening the Reporting of Observational Studies  
56 in Epidemiology (STROBE) statement<sup>23</sup>, and the Reporting of studies Conducted using  
57 Observational Routinely-collected Data (RECORD) statement<sup>24</sup>.

## 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).

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

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

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27 The strength of this study is that it is a nationwide population-based cohort study with  
28 prospective, validated data and complete follow-up. In addition, we had comprehensive  
29 information on medication use and comorbidities prior to surgery, detailed clinical data on  
30 hip fracture patients in regards to information on fracture type, surgery type and BMI, and  
31 opioid information based on dispensing data rather than patient-reported data.  
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37 Our study also has some limitations. First, there is no consensus on how to define chronic  
38 opioid use. Previous studies have defined chronic opioid use as postoperative opioid  
39 prescription fulfilment between 90 and 180 days<sup>32</sup>, or opioid prescriptions for 120 non-  
40 consecutive days<sup>8</sup>. The heterogeneity in definitions for chronic opioid use limits the ability to  
41 compare our results with previous studies. Moreover, dispensing data provides an imperfect  
42 representation of true preoperative medication use, and we were unable to ascertain the  
43 intended indications of opioid prescriptions. We know that patients have collected the opioid  
44 prescription at the pharmacy, but we have no knowledge regarding the patient's compliance.  
45 Even so, using prescription opioid dispensing data is considered a better measure of  
46 medication use than most alternative measures<sup>33</sup>. Second, we excluded all deceased patients  
47 within the first year following surgery, which might have compromised the external validity  
48 of our study. We can only conclude that identified risk factors for new chronic opioid use  
49 apply for hip fracture patients that survived one year post-surgery. Third, we were not able to  
50 include reoperation as a competing event. This may have overestimated the risk of new  
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3 chronic opioid use in younger female patients, since hip fracture patients are at risk of  
4 reoperation, which may lead to prolonged or restarted opioid use. We know that 6% of hip  
5 fracture patients are reoperated <sup>34</sup>, and that individuals aged 80 years or younger and male  
6 gender are associated with risk of reoperation <sup>35</sup>.  
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### 10 *Comparison with previous studies*

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13 Only two studies have reported prescription opioid use after hip fracture surgery. Simoni et  
14 al. found that 28% of Danish hip fracture patients had dispensed an opioid prescription within  
15 the first year after surgery. Moreover, 17% of the patients who were opioid non-users before  
16 surgery had dispensed an opioid prescription 1 year after surgery <sup>4</sup>. That study, however, did  
17 not examine chronic opioid use, only opioid use in general defined as 1 dispensed opioid  
18 prescription. In a similar study, Lindestrand et al. conducted a medical record review from a  
19 single institutional with 416 patients and found 2.9% of previous opioid non-user patients  
20 were opioid users at 6 months. The study reported further that osteoporosis and opioid use  
21 prior to admission were predictors for postoperative opioid use at 6 months. In contrast to our  
22 study, they did not define opioid use, and the follow-up period ended at 6 months after hip  
23 fracture <sup>5</sup>. We studied the risk factors in a large nationwide setup, whereby we uncover trends  
24 across the entire country and not only from a single institution.  
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34 In general, there is evidence that younger biological age is a predictor of persistent opioid use  
35 in the general surgical population <sup>6 8</sup>. This is explained by a wide variety of factors in the  
36 aging population such as a decline in the production of several proteins and neuropeptides, a  
37 decline of the immune response and an increase in the inflammatory response <sup>25</sup>. Our study  
38 shows the same tendency.  
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44 Several studies have shown the prevalence of chronic pain and consumption of opioids tend  
45 to be higher in females than males <sup>18 26</sup>. Psychological, biological, cultural, and social factors  
46 all play a role in the differences between the sex in pain responses and management <sup>18 27</sup>. Our  
47 study demonstrates a weak association between the female sex and new chronic opioid use  
48 after hip fracture surgery.  
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53 Overweight and obesity have been shown to be associated with a proinflammatory state after  
54 surgery inducing hyperalgesia, suggesting an increase in opioid use, which correlates with  
55 findings by Westermann et al. of an association between obesity and prolonged postoperative  
56 opioid use <sup>19 20 28</sup>. This is in line with our findings of an association between overweight and  
57 obesity and developing a new chronic opioid use after surgery.  
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3 Our data suggest that fracture type and surgery type is associated with new chronic opioid  
4 use. Hip fracture patients with a trochanteric fracture experience more and severe pain than  
5 patients with femoral neck fractures <sup>29</sup>. Similarly, patients with osteosynthesis experience  
6 more pain than the patients with a stable arthroplasty <sup>30</sup>. The reported mechanisms being  
7 shortening of the limb length and range of motion limitations <sup>30</sup>. Another explanation to why  
8 surgery type is associated with new chronic opioid use could be that these patients might  
9 have a higher rate of reoperation converting to a total hip arthroplasty performed by a more  
10 experienced surgeon. However, we do not have data to support this statement.  
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18 Several preoperative comorbidities were associated with risk of new chronic opioid use after  
19 surgery. Although we excluded all hip fracture patients with prior use of opioids, it is  
20 possible that some patients had an unmanaged pain condition prior to surgery. These patients  
21 may have continued to use prescription opioids intended for treating postsurgical pain in  
22 order to treat their pre-existing chronic pain.<sup>6</sup> Inacio et al. support this behaviour as they  
23 found back pain prior to surgery was associated with chronic opioid use <sup>8</sup>. Comorbidities  
24 associated with unrelieved chronic pain conditions are heart failure and COPD. These  
25 comorbidities have been associated with chronic opioid use, which concords with our study <sup>6</sup>  
26 <sup>8</sup>. Diabetes has also been associated with a constant chronic inflammatory state inducing  
27 neuropathy, which has also been associated with unrelieved chronic pain. This mechanism is  
28 a potential risk factor for chronic pain, which is in accordance with our study <sup>6,8</sup>. Other  
29 comorbidities have also been associated with chronic pain and chronic opioid use such as  
30 liver disease and depression <sup>8</sup>. By knowing the impact of these comorbidities on the risk of  
31 new chronic opioid use, attainment of a greater focus on comorbidity pre- and postoperative  
32 may reduce new chronic opioid use after surgery.  
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44 Medication use is frequent in hip fracture patients and nearly all of the included medications  
45 in our study were identified as a risk factor for chronic opioid use <sup>31</sup>. Medication use is  
46 closely related to comorbidities. Treatment of chronic medical conditions is a complex task  
47 that require multidisciplinary approach. It is possible that surgeons and patients are  
48 preoccupied with attempting to manage chronic pain conditions leaving long-term opioid use  
49 as a secondary priority. Some drugs when taken on their own or in combination, might  
50 change the level of sensitivity to opioids which could result in patients who continue to take  
51 opioids even though their level of pain decreases over time and does not necessarily coincide  
52 with the prescribed opioid dose.  
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### *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

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

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

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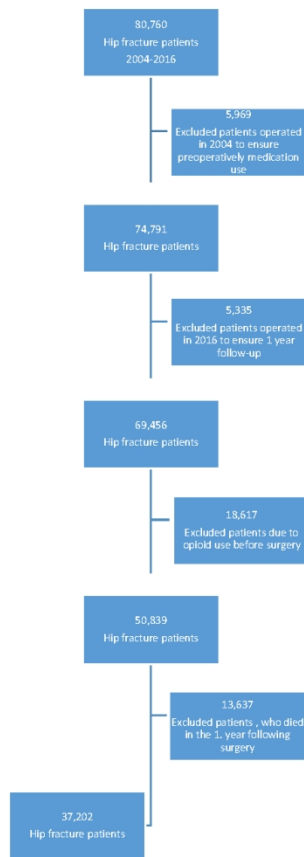


Figure 1: Flowchart of the patients from the Danish Multidisciplinary Hip Fracture Registry to the study population.

Figure 1



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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

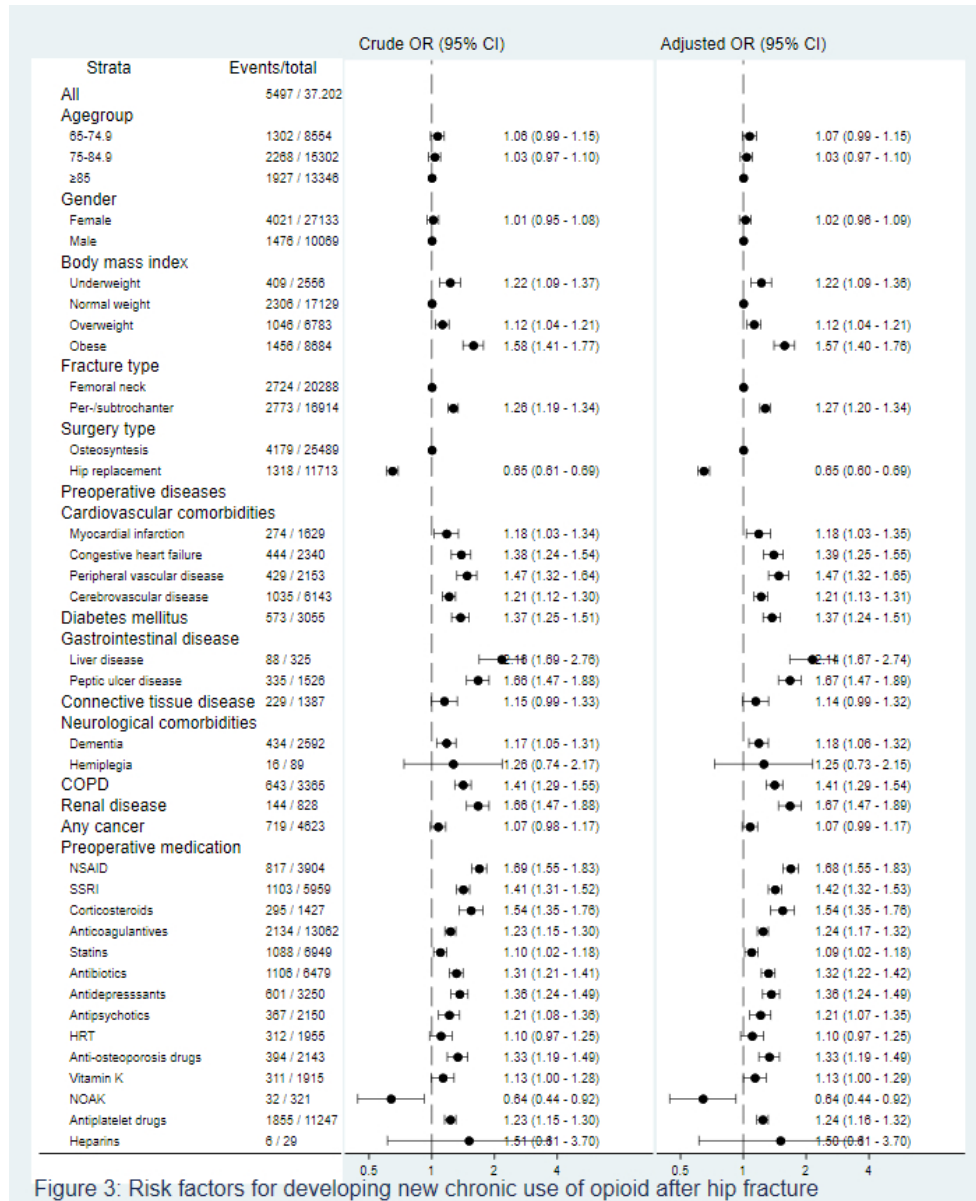


Figure 3: Risk factors for developing new chronic use of opioid after hip fracture

Figure 3

247x302mm (72 x 72 DPI)

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

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

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

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*Appendix 2: ATC codes for all medication in the study*

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

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	Nicomorphin	N02AA04
	Oxycodon	N02AA05
	Pethidin	N02AB02
	Targin	N02AA55
	Tramadol	N02AX02
	Tapentadol	N02AX06
	Buprenorphin	N02AE01
	Codein	R05DA04
	Codein and paracetamol	N02AJ06
	Estrogen	G03C
	Estrogen	L02AA
	Progesteron and estrogen in combination	G03F
	Antiandrogen	G03H
	Progesteron	G03D
	<i>Anti-osteoporosis medication</i>	
	<i>Bisfosfonats</i>	
	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

ATC codes: Anatomical Therapeutic Chemical Classification System

*Other drugs affecting bone structure and mineralization*

	Zoledronat	
	Denosumab	M05BX04
	Strontiumranelat	M05BX03
	<i>Selective estrogen receptor modulators</i>	
	Raloxifen	G03XC01
	<i>Teriparatid</i>	
	PTH treatment	H05AA02

# 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 cohort reporting guidelines, and cite them as:

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

		Page
	Reporting Item	Number
<b>Title and abstract</b>		
Title	<a href="#">#1a</a> Indicate the study's design with a commonly used term in the title or the abstract	1

1	Abstract	<a href="#">#1b</a>	Provide in the abstract an informative and balanced summary	3
2			of what was done and what was found	
3				
4				
5				
6	<b>Introduction</b>			
7				
8				
9	Background /	<a href="#">#2</a>	Explain the scientific background and rationale for the	5
10	rationale		investigation being reported	
11				
12				
13				
14	Objectives	<a href="#">#3</a>	State specific objectives, including any prespecified	5
15			hypotheses	
16				
17				
18				
19				
20	<b>Methods</b>			
21				
22				
23	Study design	<a href="#">#4</a>	Present key elements of study design early in the paper	6
24				
25				
26	Setting	<a href="#">#5</a>	Describe the setting, locations, and relevant dates, including	6
27			periods of recruitment, exposure, follow-up, and data	
28			collection	
29				
30				
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34	Eligibility criteria	<a href="#">#6a</a>	Give the eligibility criteria, and the sources and methods of	6
35			selection of participants. Describe methods of follow-up.	
36				
37				
38				
39	Eligibility criteria	<a href="#">#6b</a>	For matched studies, give matching criteria and number of	6
40			exposed and unexposed	
41				
42				
43				
44				
45	Variables	<a href="#">#7</a>	Clearly define all outcomes, exposures, predictors, potential	7
46			confounders, and effect modifiers. Give diagnostic criteria, if	
47			applicable	
48				
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51				
52	Data sources /	<a href="#">#8</a>	For each variable of interest give sources of data and details	6
53	measurement		of methods of assessment (measurement). Describe	
54			comparability of assessment methods if there is more than	
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one group. Give information separately for for exposed and unexposed groups if applicable.

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6	Bias	<a href="#">#9</a>	Describe any efforts to address potential sources of bias
7			
8			
9	Study size	<a href="#">#10</a>	Explain how the study size was arrived at
10			
11			
12	Quantitative	<a href="#">#11</a>	Explain how quantitative variables were handled in the
13			
14	variables		analyses. If applicable, describe which groupings were
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16			
17			chosen, and why
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19	Statistical	<a href="#">#12a</a>	Describe all statistical methods, including those used to
20			
21	methods		control for confounding
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25	Statistical	<a href="#">#12b</a>	Describe any methods used to examine subgroups and
26			
27	methods		interactions
28			
29			
30	Statistical	<a href="#">#12c</a>	Explain how missing data were addressed
31			
32	methods		
33			
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35			
36	Statistical	<a href="#">#12d</a>	If applicable, explain how loss to follow-up was addressed
37			
38	methods		
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41	Statistical	<a href="#">#12e</a>	Describe any sensitivity analyses
42			
43	methods		
44			
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46	<b>Results</b>		
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49	Participants	<a href="#">#13a</a>	Report numbers of individuals at each stage of study—eg
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51			numbers potentially eligible, examined for eligibility,
52			
53			confirmed eligible, included in the study, completing follow-
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up, and analysed. Give information separately for for  
exposed and unexposed groups if applicable.

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6	Participants	<a href="#">#13b</a>	Give reasons for non-participation at each stage	9
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9	Participants	<a href="#">#13c</a>	Consider use of a flow diagram	9
10				
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12	Descriptive data	<a href="#">#14a</a>	Give characteristics of study participants (eg demographic,	9
13				
14			clinical, social) and information on exposures and potential	
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16			confounders. Give information separately for exposed and	
17				
18			unexposed groups if applicable.	
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22	Descriptive data	<a href="#">#14b</a>	Indicate number of participants with missing data for each	9
23				
24			variable of interest	
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27	Descriptive data	<a href="#">#14c</a>	Summarise follow-up time (eg, average and total amount)	9
28				
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30	Outcome data	<a href="#">#15</a>	Report numbers of outcome events or summary measures	9
31				
32			over time. Give information separately for exposed and	
33				
34			unexposed groups if applicable.	
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38	Main results	<a href="#">#16a</a>	Give unadjusted estimates and, if applicable, confounder-	9
39				
40			adjusted estimates and their precision (eg, 95% confidence	
41				
42			interval). Make clear which confounders were adjusted for	
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44			and why they were included	
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48	Main results	<a href="#">#16b</a>	Report category boundaries when continuous variables were	9
49				
50			categorized	
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53	Main results	<a href="#">#16c</a>	If relevant, consider translating estimates of relative risk into	9
54				
55			absolute risk for a meaningful time period	
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1	Other analyses	<a href="#">#17</a>	Report other analyses done—e.g., analyses of subgroups	9
2			and interactions, and sensitivity analyses	
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6	<b>Discussion</b>			
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10	Key results	<a href="#">#18</a>	Summarise key results with reference to study objectives	10
11				
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13	Limitations	<a href="#">#19</a>	Discuss limitations of the study, taking into account sources	10
14			of potential bias or imprecision. Discuss both direction and	
15			magnitude of any potential bias.	
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20	Interpretation	<a href="#">#20</a>	Give a cautious overall interpretation considering objectives,	11
21			limitations, multiplicity of analyses, results from similar	
22			studies, and other relevant evidence.	
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28	Generalisability	<a href="#">#21</a>	Discuss the generalisability (external validity) of the study	12
29			results	
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33	<b>Other Information</b>			
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36	Funding	<a href="#">#22</a>	Give the source of funding and the role of the funders for the	14
37			present study and, if applicable, for the original study on	
38			which the present article is based	
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# 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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Secondary Subject Heading:	Medical management
Keywords:	EPIDEMIOLOGY, Hip < ORTHOPAEDIC & TRAUMA SURGERY, PAIN MANAGEMENT

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5 Danish nationwide cohort study from 2005 to 2016 using the Danish  
6 multidisciplinary hip fracture registry  
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3 **Risk factors for new chronic opioid use after hip fracture surgery: a Danish nationwide**  
4 **cohort study from 2005 to 2016 using the Danish Multidisciplinary Hip Fracture**  
5 **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  $\geq 65$  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  $\geq 30$  (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 anticoagulatives (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*

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2  
3 In this large nationwide cohort study, we identified several risk factors associated with new  
4 chronic opioid use after hip fracture surgery among patients who were alive within the first  
5 year following surgery.  
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9 Although not all factors are modifiable preoperative, this will allow clinicians to  
10 appropriately counsel patients preoperatively and tailor postoperative treatment.  
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## 14 15 **Article Summary**

### 16 17 *Strengths and limitations of this study*

- 18  
19 • This study is a prospective population-based cohort study with complete follow-up  
20 based on Danish nationwide health registries.
- 21  
22 • The study includes comprehensive high-quality data on medication use and  
23 comorbidities before surgery, and detailed clinical- and opioid data from registries  
24 rather than patient-reported data.
- 25  
26 • The definition of new chronic opioid use is inspired by the guidelines from the  
27 International Association for the Study of Pain.
- 28  
29 • Data on clinical indications for opioid prescriptions and patient compliance with  
30 opioid treatment was not available.
- 31  
32 • Data on re-operations during follow-up was not available.  
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## Introduction

The prevalence of hip fractures is estimated to reach 6.3 million people worldwide by 2050<sup>1</sup>. 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<sup>2</sup>. 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<sup>3</sup>. 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<sup>4,5</sup>. This is concerning as chronic prescription opioid use can have a negative impact on quality of life<sup>6</sup>, has been associated with increased risk of sustaining new fractures<sup>7</sup> and other adverse events including general medical complications<sup>3</sup>.

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<sup>8,9</sup>. 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*

1  
2  
3 We conducted this population-based cohort study in Denmark using prospectively collected  
4 administrative health data from health registries, which cover all contacts to the health sector  
5 <sup>10</sup>. The Danish National Health Services provide tax-supported primary and secondary health  
6 care for the entire population<sup>10</sup>, ensuring that all eligible hip fracture patients undergo surgery  
7 at a public hospital. All Danish citizens can be identified using a 10-digit personal  
8 identification number, which goes through all Danish health registries allowing for  
9 unambiguous individually record linkage of data <sup>11</sup>.

### 16 *Data sources*

17  
18 The Danish Civil Registration System (DCRS) was initiated in 1968. Daily updated  
19 information on migration and vital status allows for virtually complete long-term follow-up  
20 on emigration and death <sup>11</sup>.

21  
22 The Danish Multidisciplinary Hip Fracture Registry (DMHFR) was initiated in 2003 and  
23 contains nationwide population-based data about all patients undergoing primary hip fracture  
24 surgery <sup>12</sup>. The positive predictive value of the hip fracture diagnosis is between 90% and  
25 98% depending on fracture type <sup>13</sup>.

26  
27 The Danish National Health Service Prescription Database (DNHSPD) has kept information  
28 on all prescriptions for reimbursed drugs dispensed by community pharmacies in Denmark  
29 since 2004 according to Anatomical Therapeutic Chemical classification system (ATC  
30 codes). Data from the DNHSPH can account for patient's medication <sup>14</sup>.

31  
32 The Danish National Patient Registry (DNPR) is an administrative registry established in  
33 1977 covering all somatic contacts in all Danish hospitals <sup>15</sup>. Information reported to the  
34 DNPR includes administrative data, diagnoses, treatments and examinations. Primary and  
35 secondary diagnoses are reported to the DNPR according to the International Disease  
36 Classification tenth revision (ICD-10) since 1995 <sup>15</sup>. The positive predictive value of the  
37 diagnoses included in the medical comorbidities are more than 90% <sup>16</sup>.

### 49 *Study population*

50  
51 We used the DMHFR to identify all patients aged 65 or older who were treated for a fracture  
52 of the femoral neck, per-, or sub-trochanteric fracture with osteosynthesis or total/partial hip  
53 replacement surgery between January 1, 2005 and December 31, 2015 (appendix 1). Patients  
54 were indexed on their surgery date and followed up for 12 months (to December 31, 2016).  
55 Patients who had dispensed an opioid in the 6 months prior to index were excluded to ensure  
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1  
2  
3 they were opioid non-users at the index date. Patients who died from any cause within 12  
4 months following their index date were also excluded (figure 1).  
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6

### 7 *Outcome*

8  
9 We characterized patients with new chronic opioid use as having dispensed an opioid  
10 prescription in at least 2 of the 3 last quarters (3-months periods per quarter) within the first  
11 year following surgery among previously opioid non-user patients (figure 2)<sup>8 17</sup>. Prescription  
12 opioids dispensed by community pharmacies seven days prior to index and within the first  
13 quarter after index were not included in the outcome definition because they are likely to  
14 have been associated with the initial opioid treatment to manage acute postoperative pain<sup>4</sup>.  
15 Thus, we were only interested in subsequent opioid prescriptions beyond the early  
16 perioperative period (quarters 2-4). Our definition of chronic opioid use after surgery was  
17 aligned with the definition from the International Association for the Study of Pain, which  
18 defines chronic postsurgical pain as pain that develops after a surgical procedure and persists  
19 for at least 3 months after surgery<sup>18</sup>.  
20  
21

22 The following prescription opioids were included in the analysis: morphine, hydromorphone,  
23 nicomorphine, oxycodone, oxycodone combined with naloxone, pethidine, fentanyl,  
24 ketobemidone, methadone, codeine, tramadol, tapentadol, and buprenorphine.  
25  
26

### 27 *Risk factors*

28  
29 Based on previous literature and clinical experience, the below-mentioned patient- and  
30 surgery-related factors were considered and examined as potential risk factors for new  
31 chronic opioid use<sup>8 9</sup>. From the DMHFR, we obtained information on age (in categories 65-  
32 74, 75-84 and  $\geq 85$  years), sex, fracture type (femoral neck and per-/subtrochanteric fracture),  
33 and surgery type (osteosynthesis and total/partial hip replacement). Body mass index (BMI)  
34 was calculated using information on height and weight (weight in kilograms divided by  
35 height in metres squared) and divided into groups (underweight defined as BMI  $< 18.5$ ,  
36 normal as BMI 18.6-24.9, overweight as BMI 25-29.9 and obese as BMI  $\geq 30$ ). We examined  
37 several specific medical comorbidities including myocardial infarction, congestive heart  
38 failure, peripheral vascular disease, cerebrovascular disease, diabetes, liver disease, peptic  
39 ulcer disease, connective tissue disease, dementia, hemiplegia, chronic obstructive pulmonary  
40 disease, renal disease and cancer (Table 1). BMI and various comorbidities were in previous  
41 studies found to be associated with increased risk of mortality and could be associated with  
42 increased risk of chronic opioid use<sup>8 19-21</sup>.  
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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<sup>22</sup>. 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 (STATA Corp, 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<sup>23</sup>, and the Reporting of studies Conducted using Observational Routinely-collected Data (RECORD) statement<sup>24</sup>.

### *Patient and Public Involvement*

No patient involved

## **Results**

### *Description of the study population*

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3 In total, 69,456 patients with hip fracture surgery were identified (figure 1). We excluded  
4 18,617 hip fracture patients due to opioid use before surgery, leaving us with 50,839 eligible  
5 hip fracture patients. Of these, 13,637 patients died within the first year. The final study  
6 population included 37,202 hip fracture patients.  
7  
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9

10 Overall, 27,133 patients (73%) were female and the mean age at the time of surgery was 81  
11 years (range 65-107). In our study population, 5,497 (15%) developed new chronic opioid use  
12 within 1 year of surgery.  
13  
14  
15

16 The proportion of patients who developed new chronic opioid use in relation to all hip  
17 fracture patients was 15% for both females and males, 13% for patients with femoral neck  
18 fractures, and 16% for patients with a per- or subtrochanteric fracture (Table 1).  
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22 The characteristics of patients with new chronic opioid use were similar to the characteristics  
23 of the total population of hip fracture patients with small differences seen in the distribution  
24 of BMI, fracture type, surgery type, and preoperative medication use (Table 1).  
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#### 28 *Risk factors for new chronic opioid use*

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30 The risk factors for new chronic opioid use were being underweight (aOR 1.22 (CI 1.09-  
31 1.36)), overweight (aOR 1.12 (CI 1.04-1.21)), or obese (aOR 1.57 (CI 1.40-1.76)) with  
32 normal weight as reference and sustaining a per-/subtrochanteric fracture (aOR 1.27 (CI 1.20-  
33 1.34)) with fracture of the femoral neck as reference. Treatment with total/partial hip  
34 replacement was associated with lower risk of new chronic opioid use, with osteosynthesis as  
35 reference (aOR 0.65 (CI 0.60-0.69)) (figure 3 and appendix figure 1).  
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41 Preoperative use of NSAIDs (aOR 1.68 (CI 1.55-1.83)), SSRIs (aOR 1.42 (CI 1.32-1.53)),  
42 antidepressants (aOR 1.36 (CI 1.24-1.49)), antipsychotics (aOR 1.21 (CI 1.07-1.35)),  
43 corticosteroids (aOR 1.54 (CI 1.35-1.76)), statins (aOR 1.09 (CI 1.02-1.18)), antibiotics (aOR  
44 1.32 (CI 1.22-1.42)), anti-osteoporosis drugs (aOR 1.33 (CI 1.19-1.49)), anticoagulants (aOR  
45 1.24 (CI 1.17-1.32)), and antiplatelet drugs (aOR 1.24 (CI 1.16-1.32)) were identified as risk  
46 factors for new chronic opioid use (figure 3 and appendix figure 1).  
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52 The presence of the following preoperative comorbidities were further associated with risk of  
53 new chronic opioid use: cardiovascular comorbidity, diabetes, gastrointestinal diseases,  
54 dementia, COPD, and renal diseases (figure 3 and appendix figure 1).  
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3 Several sensitivity analyses were performed. Results of the landmark analyses were similar to  
4 the results presented in the primary analyses, where we excluded all patients who died within  
5 12 months of surgery (please see appendix figure 2 and 3). Likewise, analyses adjusting for  
6 multiple relevant factors and those based on patients with only a fracture of the femoral neck  
7 showed results similar to the primary analysis (data not shown). However, the results based  
8 on all population including also all patients who deceased within the first year of surgery  
9 showed an overestimation of the estimates, in particular those related to age and gender  
10 (please see appendix figure 4)  
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## 20 **Discussion**

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

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37 The strength of this study is that it is a nationwide population-based cohort study with  
38 prospective, validated data and complete follow-up. In addition, we had comprehensive  
39 information on medication use and comorbidities prior to surgery, detailed clinical data on  
40 hip fracture patients in regards to information on fracture type, surgery type and BMI, and  
41 opioid information based on dispensing data rather than patient-reported data.  
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47 Our study also has some limitations. First, there is no consensus on how to define chronic  
48 opioid use. Previous studies have defined chronic opioid use as postoperative opioid  
49 prescription fulfilment between 90 and 180 days<sup>25</sup>, or opioid prescriptions for 120 non-  
50 consecutive days<sup>8</sup>. The heterogeneity in definitions for chronic opioid use limits the ability to  
51 compare our results with previous studies. Moreover, dispensing data provides an imperfect  
52 representation of true preoperative medication use, and we were unable to ascertain the  
53 intended indications of opioid prescriptions. We know that patients have collected the opioid  
54 prescription at the pharmacy, but we have no knowledge regarding the patient's compliance.  
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3 Even so, using prescription opioid dispensing data is considered a better measure of  
4 medication use than most alternative measures<sup>26</sup>. Second, we excluded all deceased patients  
5 within the first year following surgery, which might have compromised the external validity  
6 of our study. Thus, we can only conclude that identified risk factors for new chronic opioid  
7 use apply for hip fracture patients that survived one year after surgery. The number of  
8 deceased patients was substantial. A total of 13,637 of the 50,839 hip fracture patients died  
9 within the first year (please see appendix figure 5). Including these in the study population  
10 would lead to an overestimation of our results, compromising our internal validity (please see  
11 appendix figure 4). A total of 751 of the 13,637 deceased hip fracture patients were  
12 potentially eligible to be included in our study as new chronic opioid users. These patients  
13 had redeemed two opioid prescriptions in either the second, third or fourth quarter of our  
14 definition (please see appendix figure 5). The performed landmark analyses illustrated, that  
15 including the deceased patients from the third and fourth quarter in our primary analysis  
16 would not affect our results substantially (please see appendix figure 2 and 3). Third, we were  
17 not able to include reoperation as a competing event. This may have overestimated the risk of  
18 new chronic opioid use in younger female patients, since hip fracture patients are at risk of  
19 reoperation, which may lead to prolonged or restarted opioid use. We know that 6% of hip  
20 fracture patients are reoperated<sup>27</sup> individuals aged 80 years or younger and male gender are  
21 associated with risk of reoperation<sup>28</sup>.  
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### 36 *Comparison with previous studies*

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39 Only two studies have reported prescription opioid use after hip fracture surgery. Simoni et  
40 al. found that 28% of Danish hip fracture patients had dispensed an opioid prescription within  
41 the first year after surgery. Moreover, 17% of the patients who were opioid non-users before  
42 surgery had dispensed an opioid prescription 1 year after surgery<sup>4</sup>. That study, however, did  
43 not examine chronic opioid use, only opioid use in general defined as 1 dispensed opioid  
44 prescription. In a similar study, Lindestrand et al. conducted a medical record review from a  
45 single institutional with 416 patients and found 2.9% of previous opioid non-user patients  
46 were opioid users at 6 months. The study reported further that osteoporosis and opioid use  
47 prior to admission were predictors for postoperative opioid use at 6 months. In contrast to our  
48 study, they did not define opioid use, and the follow-up period ended at 6 months after hip  
49 fracture<sup>5</sup>. We studied the risk factors in a large nationwide setup, whereby we uncover trends  
50 across the entire country and not only from a single institution.  
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3 In general, there is evidence that younger biological age is a predictor of persistent opioid use  
4 in the general surgical population <sup>6 8</sup>. This is explained by a wide variety of factors in the  
5 aging population such as a decline in the production of several proteins and neuropeptides, a  
6 decline of the immune response and an increase in the inflammatory response <sup>29</sup>. Our study  
7 shows the same tendency.  
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12 Several studies have shown the prevalence of chronic pain and consumption of opioids tend  
13 to be higher in females than males <sup>17 30</sup>. Psychological, biological, cultural, and social factors  
14 all play a role in the differences between the sex in pain responses and management <sup>17 31</sup>. Our  
15 study demonstrates a weak association between the female sex and new chronic opioid use  
16 after hip fracture surgery.  
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21 Overweight and obesity have been shown to be associated with a proinflammatory state after  
22 surgery inducing hyperalgesia, suggesting an increase in opioid use, which correlates with  
23 findings by Westermann et al. of an association between obesity and prolonged postoperative  
24 opioid use <sup>19 20 32</sup>. This is in line with our findings of an association between overweight and  
25 obesity and developing a new chronic opioid use after surgery.  
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31 Our data suggest that fracture type and surgery type is associated with new chronic opioid  
32 use. Hip fracture patients with a trochanteric fracture experience more and severe pain than  
33 patients with femoral neck fractures <sup>33</sup>. Similarly, patients with osteosynthesis experience  
34 more pain than the patients with a stable arthroplasty <sup>34</sup>. The reported mechanisms being  
35 shortening of the limb length and range of motion limitations <sup>34</sup>. Another explanation to why  
36 surgery type is associated with new chronic opioid use could be that these patients might  
37 have a higher rate of reoperation converting to a total hip arthroplasty performed by a more  
38 experienced surgeon. However, we do not have data to support this statement.  
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46 Several preoperative comorbidities were associated with risk of new chronic opioid use after  
47 surgery. Although we excluded all hip fracture patients with prior use of opioids, it is  
48 possible that some patients had an unmanaged pain condition prior to surgery. These patients  
49 may have continued to use prescription opioids intended for treating postsurgical pain in  
50 order to treat their pre-existing chronic pain.<sup>6</sup> Inacio et al. support this behaviour as they  
51 found back pain prior to surgery was associated with chronic opioid use <sup>8</sup>. Comorbidities  
52 associated with unrelieved chronic pain conditions are heart failure and COPD. These  
53 comorbidities have been associated with chronic opioid use, which concords with our study <sup>6</sup>  
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8. Diabetes has also been associated with a constant chronic inflammatory state inducing



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3 neuropathy, which has also been associated with unrelieved chronic pain. This mechanism is  
4 a potential risk factor for chronic pain, which is in accordance with our study<sup>6,8</sup>. Other  
5 comorbidities have also been associated with chronic pain and chronic opioid use such as  
6 liver disease and depression<sup>8</sup>. By knowing the impact of these comorbidities on the risk of  
7 new chronic opioid use, attainment of a greater focus on comorbidity pre- and postoperative  
8 may reduce new chronic opioid use after surgery.  
9

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

21 There are no standard guidelines in Denmark for post-discharge clinical follow-up of hip  
22 fracture patients. However, many orthopaedic and geriatric departments focus on the  
23 reduction of prescription opioid exposure after surgery by instituting a plan for opioid  
24 tapering. Patients do not receive follow-up appointments in outpatient clinics or at the general  
25 practitioner unless they take the initiative themselves. Since hip fracture patients often are  
26 characterized as being frail, receiving several medications, and having multimorbidity, they  
27 may lack the resources to follow such a tapering plan. Thus, it is important to ensure that  
28 patients are well informed and included in the development of a tapering plan, and  
29 understand the risks and benefits of prescription opioids for the treatment of postsurgical  
30 pain. However, it is important to note that not all hip fracture surgeries are successful and  
31 some patients may experience a greater level of postsurgical pain and postsurgical pain  
32 treatment.  
33

### 34 *Conclusion*

35 In this large nationwide cohort study, 15% of the patients who underwent hip fracture surgery  
36 developed new chronic opioid use. We identified under- and overweight, obesity, per or  
37 subtrochanteric fracture, preoperative use of several medications and presence of several  
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3 comorbidities as risk factors associated with the risk of new chronic opioid use after hip  
4 fracture surgery.  
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7 By identifying risk factors, we can reduce the number of new chronic opioid users by  
8 developing more effective preventive intervention strategies targeted to the patients with the  
9 identified risk factors. In addition, the identified risk factors are also relevant for clinicians in  
10 order to advise patients appropriately before surgery about their risk for chronic postsurgical  
11 opioid use.  
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### 19 **Authors' Contributions**

20  
21 NME, CV, SO, LN, CFC and ABP contributed to the conception or design of the study. NME  
22 carried out the analytical aspects of the study. NME, CV, SO, LN, CFC and ABP contributed  
23 to the interpretation of data. NME, CV, SO, LN, CFC and ABP drafted the manuscript or  
24 revised it critically. All authors gave their final approval and agreement to be accountable for  
25 all aspects of the work.  
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31  
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33 their continuous effort and contribution to acquisition of the data in the Danish  
34 Multidisciplinary Hip Fracture Registry.  
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42 or not-for-profit sectors.  
43  
44

### 45 **Competing interests**

46  
47 None declared.  
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### 50 **Patient consent for publication**

51  
52 Not required  
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### 55 **Data sharing statement**

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57 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)

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3 Appendix figure 3: Landmark analyses at 9 months: Risk factors for developing new chronic  
4 opioid use after hip fracture surgery among patients with no opioid use before surgery, when  
5 excluding the patients who died in the first, second, and third quarter of surgery, odds ratios  
6 adjusted for age and sex.  
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10 COPD: Chronic pulmonary disease, NSAID: nonsteroidal anti-inflammatory drug, SSRI:  
11 selective serotonin reuptake inhibitors, HRT: Hormone Replacement Therapy, NOAC: novel  
12 oral anticoagulant. Odds ratios (ORs) with 95% confidence intervals (CI)  
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18 Appendix figure 4: Risk factors for developing new chronic opioid use after hip fracture  
19 surgery among patients with no opioid use before surgery, including patient who were alive  
20 and those who died within 12 months of surgery, odds ratios adjusted for age and sex.  
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23 COPD: Chronic pulmonary disease, NSAID: nonsteroidal anti-inflammatory drug, SSRI:  
24 selective serotonin reuptake inhibitors, HRT: Hormone Replacement Therapy, NOAC: novel  
25 oral anticoagulant. Odds ratios (ORs) with 95% confidence intervals (CI)  
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30 Appendix figure 5: Number of hip fracture patients identified at the time of hip fracture and  
31 during the first year following surgery. Patients who were opioid users before surgery were  
32 not included in our analyses (number of deceased in this group in each of the 4 quarters of  
33 surgery is presented with green color). Our analyses were based on patients with no opioid  
34 use before surgery. We presented the number of opioid non-users alive in each of the 4  
35 quarters of surgery with purple color. We presented the number of opioid non-users who dead  
36 in each of the 4 quartets of surgery with blue color. Number of eligible new chronic users are  
37 patients, who have redeemed two opioid prescriptions, but have died in the first year  
38 following surgery, and are therefore not included in our primary analyses (red color).  
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49 Table 1: Patient characteristics for the all hip fracture patients and new chronic users

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51 Appendix 1: Following diagnoses- and procedure codes were used to identify patients  
52 undergoing hip fracture surgery.  
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55 Appendix 2: ATC codes for all medication in the study  
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Table 1: Patient characteristics for the all hip fracture patients and new chronic users

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

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

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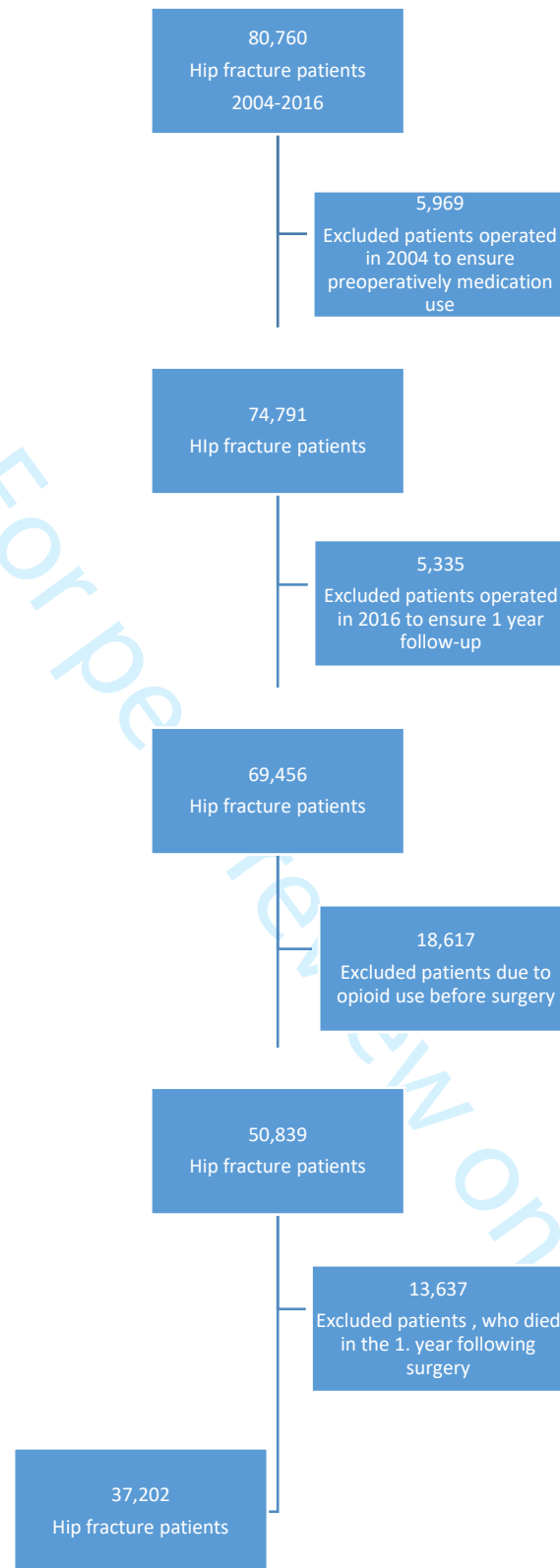


Figure 1: Flowchart of the patients from the Danish Multidisciplinary Hip Fracture Registry to the study population.

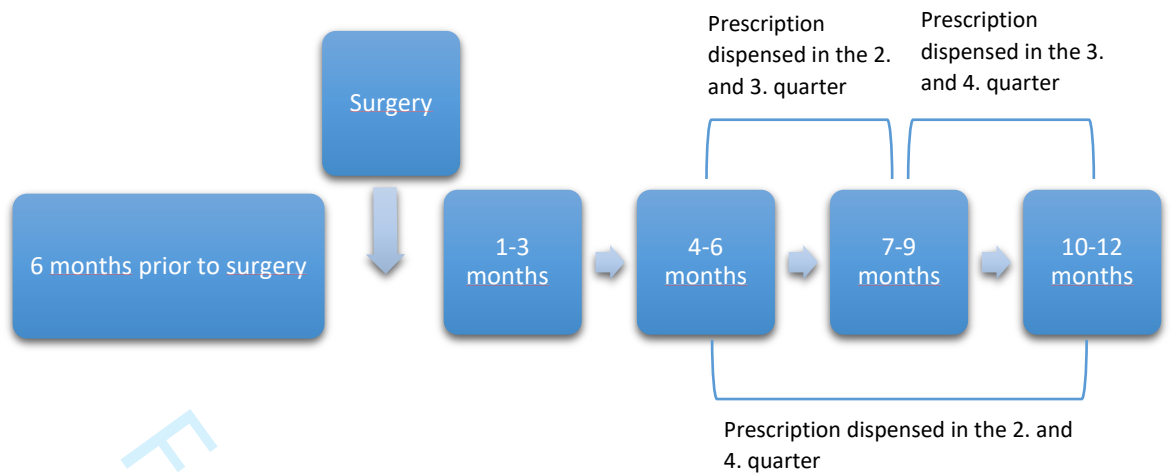


Figure 2: Chronic opioid use was defined as patients with at least 2 prescriptions dispensed in 2 of the 3 latter quarters in the first year following surgery

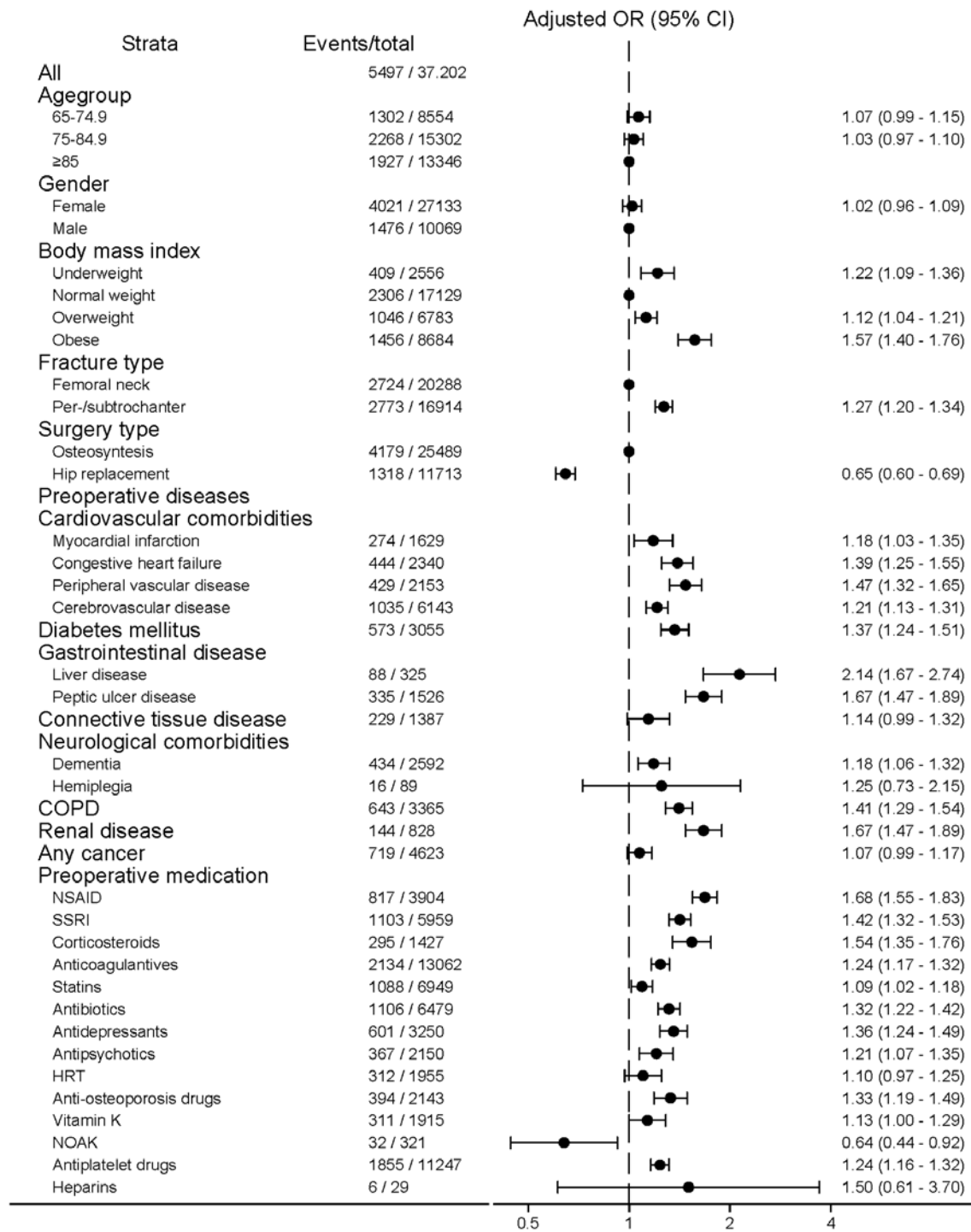


Figure 3: Risk factors for developing new chronic opioid use after hip fracture surgery among patient with no opioid use before surgery and those who were alive 12 months after surgery, odds ratios adjusted for age and sex.

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)

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

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

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15 ICD-10: WHO's International Statistical Classification of Diseases and Related Health Problems, 10<sup>th</sup>  
16 Revision.

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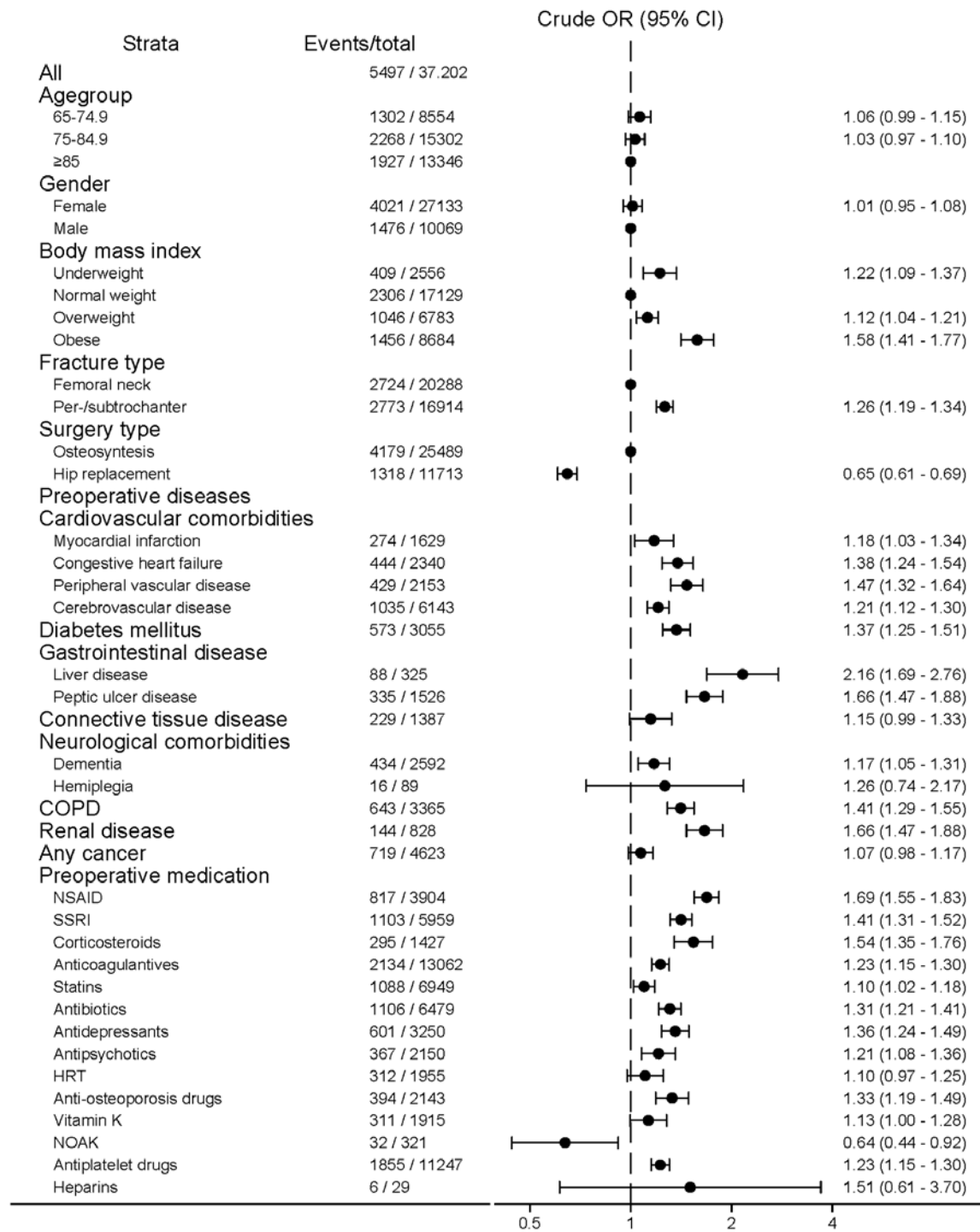
Appendix 2: ATC codes for all medication in the study

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

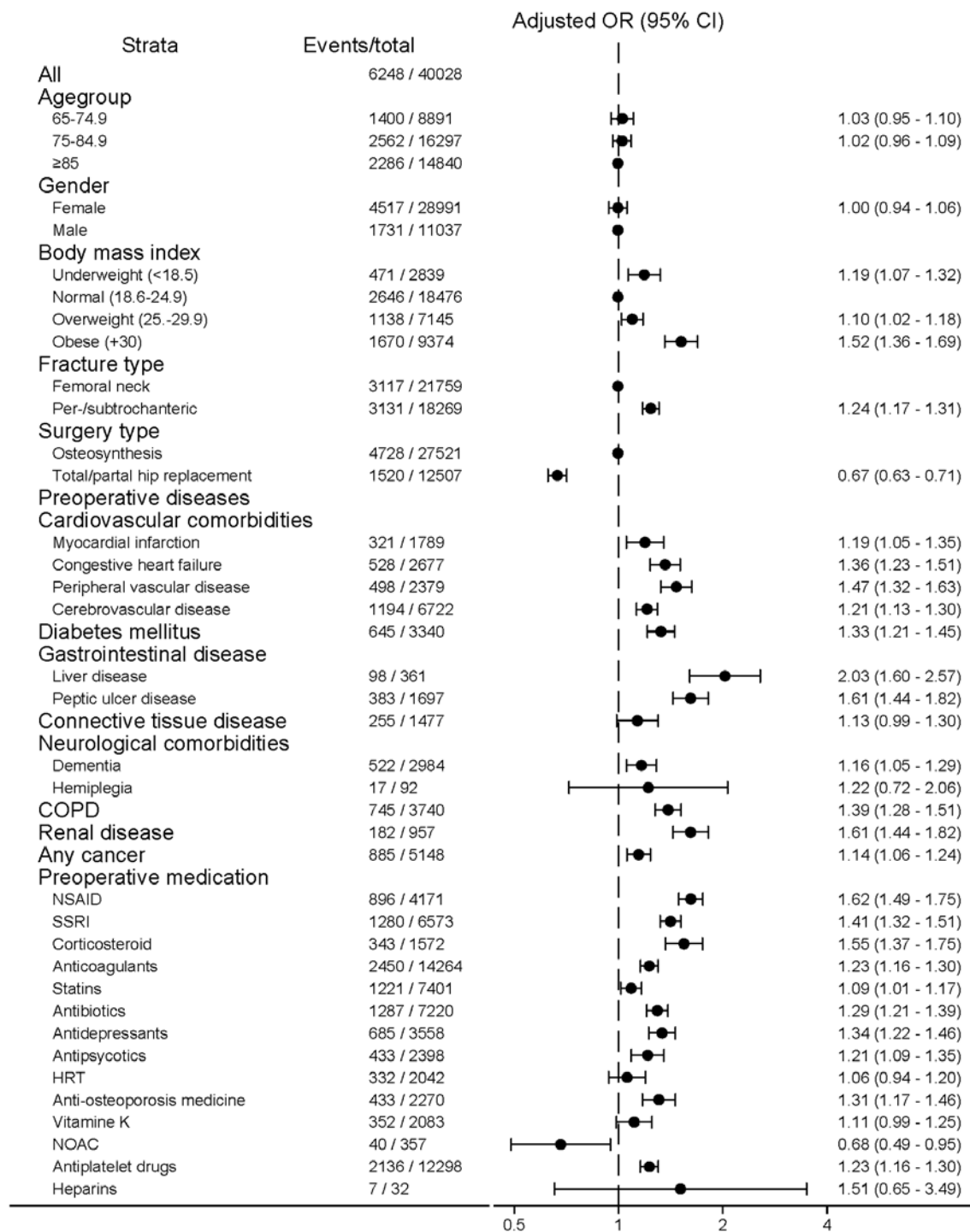
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3		Tramadol N02AX02	
4		Tapentadol N02AX06	
5		Buprenorphin N02AE01	
6		Codein R05DA04	
7		Codein and paracetamol N02AJ06	
8	<i>Hormone replacement therapy</i>	Estrogen G03C	
9		Estrogen L02AA	
10		Progesteron and estrogen in combination G03F	
11		Antiandrogen G03H	
12		Progesteron G03D	
13			
14	<i>Anti-osteoporosis medication</i>		
15		<i>Bisfosfonats</i>	
16			Etidronat M05BA01
17			Clodronate M05BA02
18			Pamidronate M05BA03
19			Alendronat M05BA04
20			Alendronat and colecalciferol M05BB03
21			Alendronat, calcium and colecalciferol M05BB05
22			Tiludronate M05BA05
23			Ibandronat M05BA06
24			Risedronat M05BA07
25			Risedronat and calcium M05BB02
26			Risedronat, calcium and colecalciferol M05BB04
27	Zoledronat		
28	<i>Other drugs affecting bone structure and mineralization</i>	Denosumab M05BX04	
29		Strontiumranelat M05BX03	
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ATC codes: Anatomical Therapeutic Chemical Classification System





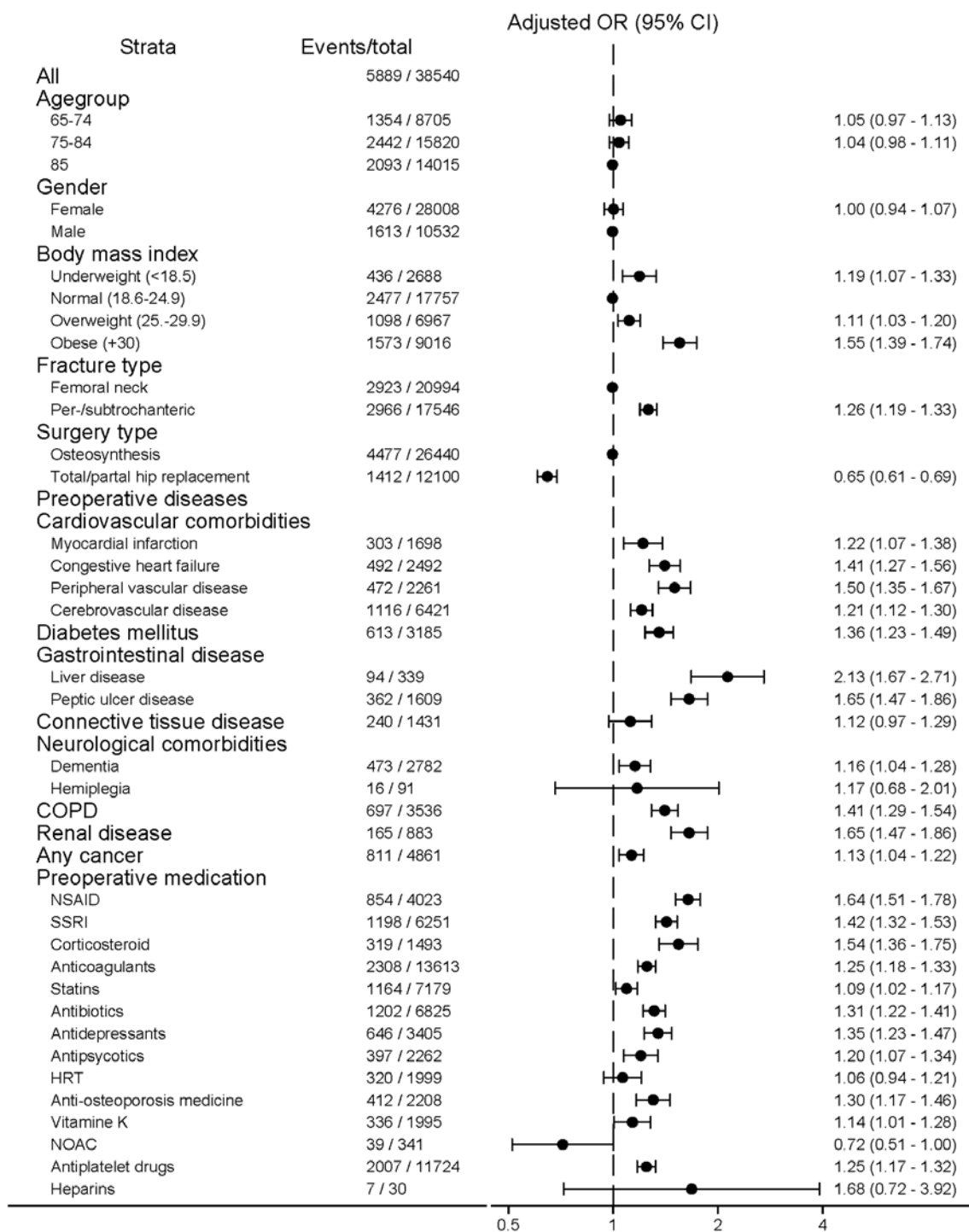
Appendix figure 1: Risk factors for developing new chronic opioid use after hip fracture surgery among patient with no opioid use before surgery and those who were alive 12 months after surgery, crude odds ratios. COPD: Chronic pulmonary disease, NSAID: nonsteroidal anti-inflammatory drug, SSRI: selective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

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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.

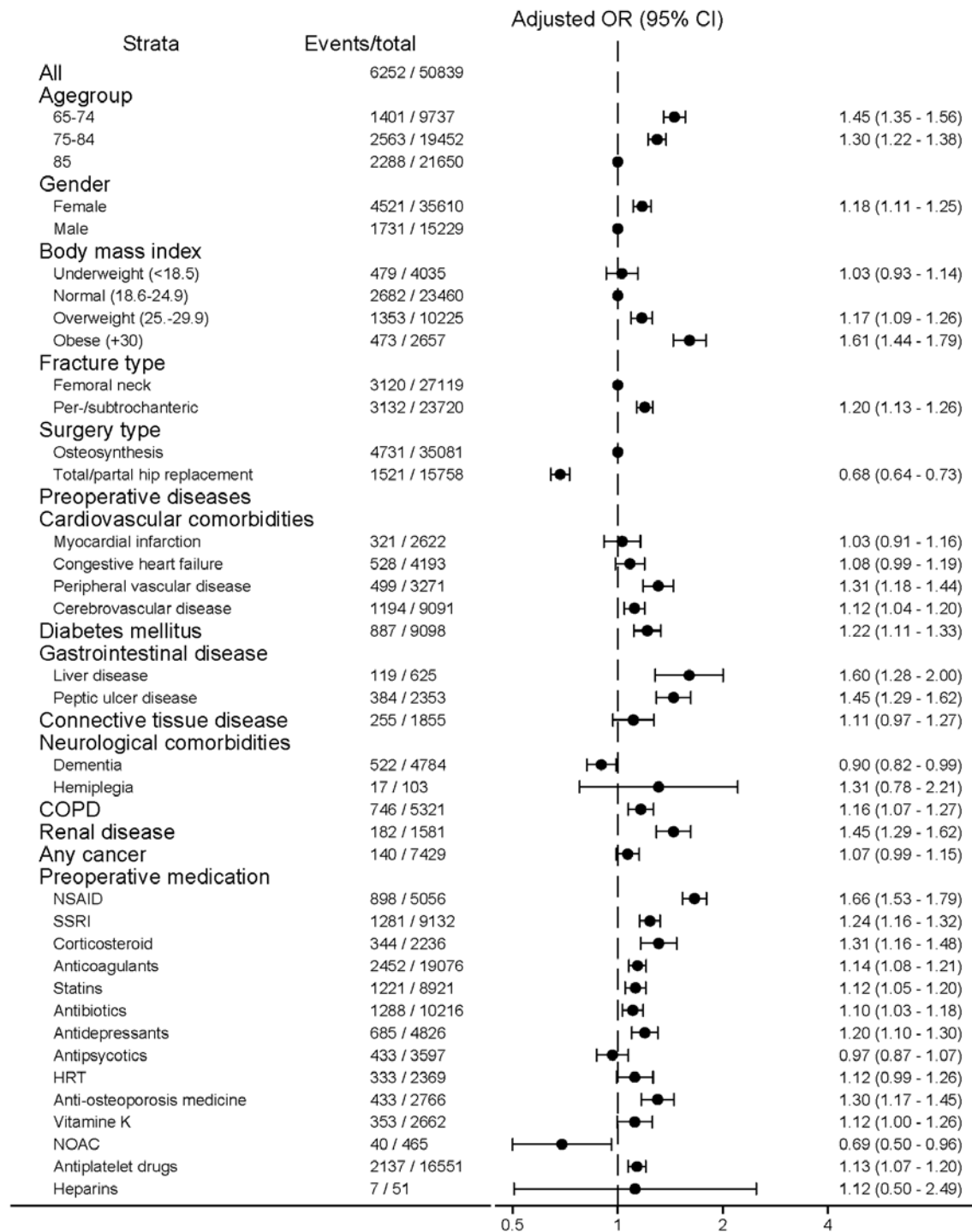
COPD: Chronic pulmonary disease, NSAID: nonsteroidal anti-inflammatory drug, SSRI: selective serotonin reuptake inhibitors, HRT: Hormone Replacement Therapy, NOAC: novel oral anticoagulant. Odds ratios (ORs) with 95% confidence intervals (CI)

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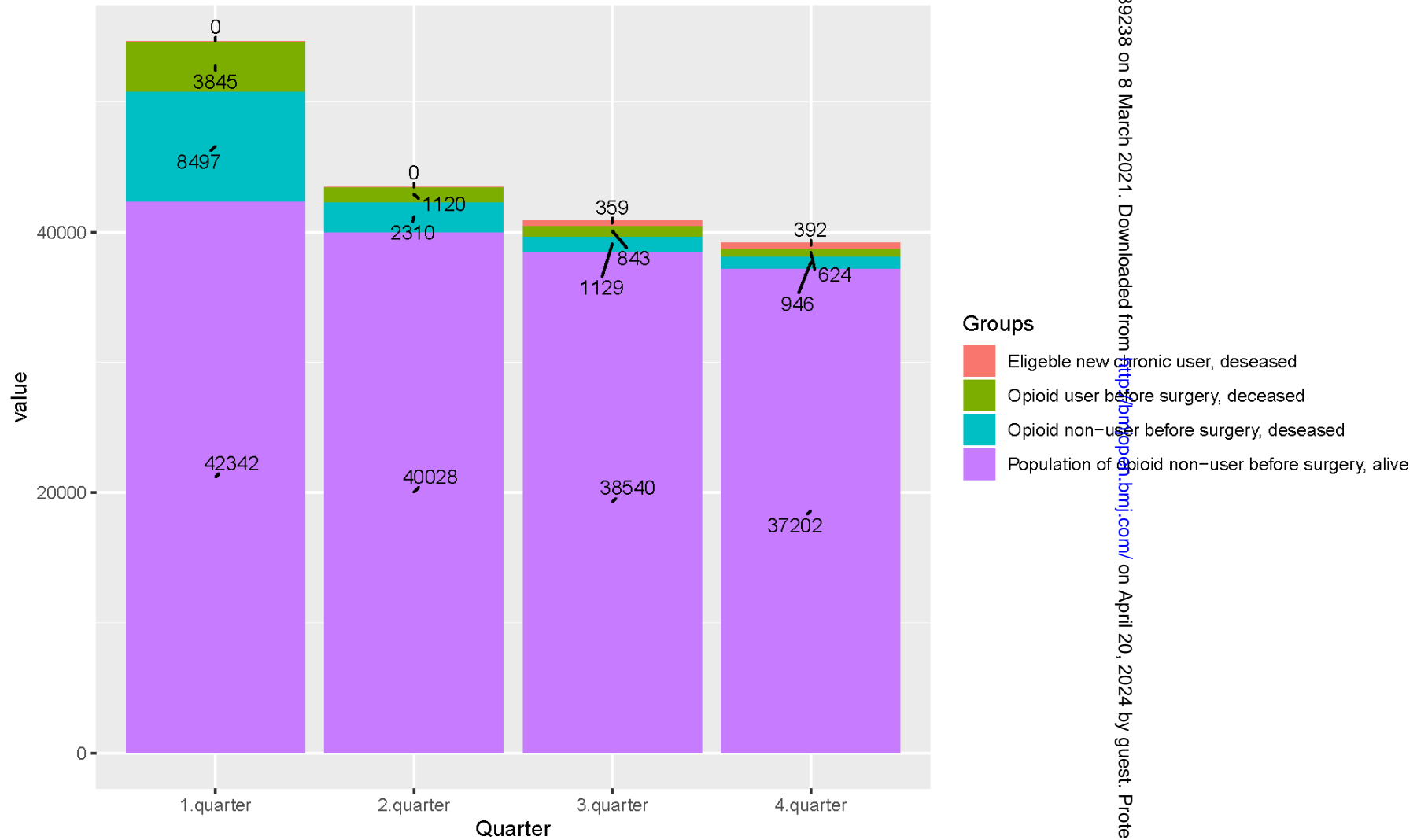
Appendix figure 3: Landmark analyses at 9 months: Risk factors for developing new chronic opioid use after hip fracture surgery among patients with no opioid use before surgery, when excluding the patients who died in the first, second, and third quarter of surgery, odds ratios adjusted for age and sex.

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)



Appendix 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.

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 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 cohort reporting guidelines, and cite them as:

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

		Page
	Reporting Item	Number
<b>Title and abstract</b>		
Title	<a href="#">#1a</a> Indicate the study's design with a commonly used term in the title or the abstract	1

1	Abstract	<a href="#">#1b</a>	Provide in the abstract an informative and balanced summary	3
2			of what was done and what was found	
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6	<b>Introduction</b>			
7				
8				
9	Background /	<a href="#">#2</a>	Explain the scientific background and rationale for the	5
10	rationale		investigation being reported	
11				
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14	Objectives	<a href="#">#3</a>	State specific objectives, including any prespecified	5
15			hypotheses	
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20	<b>Methods</b>			
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22				
23	Study design	<a href="#">#4</a>	Present key elements of study design early in the paper	6
24				
25				
26	Setting	<a href="#">#5</a>	Describe the setting, locations, and relevant dates, including	6
27			periods of recruitment, exposure, follow-up, and data	
28			collection	
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34	Eligibility criteria	<a href="#">#6a</a>	Give the eligibility criteria, and the sources and methods of	6
35			selection of participants. Describe methods of follow-up.	
36				
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38				
39	Eligibility criteria	<a href="#">#6b</a>	For matched studies, give matching criteria and number of	6
40			exposed and unexposed	
41				
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45	Variables	<a href="#">#7</a>	Clearly define all outcomes, exposures, predictors, potential	7
46			confounders, and effect modifiers. Give diagnostic criteria, if	
47			applicable	
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53	Data sources /	<a href="#">#8</a>	For each variable of interest give sources of data and details	6
54	measurement		of methods of assessment (measurement). Describe	
55			comparability of assessment methods if there is more than	
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one group. Give information separately for for exposed and unexposed groups if applicable.

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6	Bias	<a href="#">#9</a>	Describe any efforts to address potential sources of bias	8
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9	Study size	<a href="#">#10</a>	Explain how the study size was arrived at	6
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12	Quantitative	<a href="#">#11</a>	Explain how quantitative variables were handled in the	7
13				
14	variables		analyses. If applicable, describe which groupings were	
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16			chosen, and why	
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19	Statistical	<a href="#">#12a</a>	Describe all statistical methods, including those used to	8
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21	methods		control for confounding	
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25	Statistical	<a href="#">#12b</a>	Describe any methods used to examine subgroups and	8
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27	methods		interactions	
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30	Statistical	<a href="#">#12c</a>	Explain how missing data were addressed	8
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36	Statistical	<a href="#">#12d</a>	If applicable, explain how loss to follow-up was addressed	8
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41	Statistical	<a href="#">#12e</a>	Describe any sensitivity analyses	8
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43	methods			
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46	<b>Results</b>			
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49	Participants	<a href="#">#13a</a>	Report numbers of individuals at each stage of study—eg	9
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exposed and unexposed groups if applicable.

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6	Participants	<a href="#">#13b</a>	Give reasons for non-participation at each stage	9
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9	Participants	<a href="#">#13c</a>	Consider use of a flow diagram	9
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12	Descriptive data	<a href="#">#14a</a>	Give characteristics of study participants (eg demographic,	9
13			clinical, social) and information on exposures and potential	
14			confounders. Give information separately for exposed and	
15			unexposed groups if applicable.	
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22	Descriptive data	<a href="#">#14b</a>	Indicate number of participants with missing data for each	9
23			variable of interest	
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27	Descriptive data	<a href="#">#14c</a>	Summarise follow-up time (eg, average and total amount)	9
28				
29				
30	Outcome data	<a href="#">#15</a>	Report numbers of outcome events or summary measures	9
31			over time. Give information separately for exposed and	
32			unexposed groups if applicable.	
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38	Main results	<a href="#">#16a</a>	Give unadjusted estimates and, if applicable, confounder-	9
39			adjusted estimates and their precision (eg, 95% confidence	
40			interval). Make clear which confounders were adjusted for	
41			and why they were included	
42				
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48	Main results	<a href="#">#16b</a>	Report category boundaries when continuous variables were	9
49			categorized	
50				
51				
52				
53	Main results	<a href="#">#16c</a>	If relevant, consider translating estimates of relative risk into	9
54			absolute risk for a meaningful time period	
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1	Other analyses	<a href="#">#17</a>	Report other analyses done—e.g., analyses of subgroups	9
2			and interactions, and sensitivity analyses	
3				
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6	<b>Discussion</b>			
7				
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9				
10	Key results	<a href="#">#18</a>	Summarise key results with reference to study objectives	10
11				
12				
13	Limitations	<a href="#">#19</a>	Discuss limitations of the study, taking into account sources	10
14			of potential bias or imprecision. Discuss both direction and	
15			magnitude of any potential bias.	
16				
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20	Interpretation	<a href="#">#20</a>	Give a cautious overall interpretation considering objectives,	11
21			limitations, multiplicity of analyses, results from similar	
22			studies, and other relevant evidence.	
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27				
28	Generalisability	<a href="#">#21</a>	Discuss the generalisability (external validity) of the study	12
29			results	
30				
31				
32				
33	<b>Other Information</b>			
34				
35				
36	Funding	<a href="#">#22</a>	Give the source of funding and the role of the funders for the	14
37			present study and, if applicable, for the original study on	
38			which the present article is based	
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# 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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5 2 Danish nationwide cohort study from 2005 to 2016 using the Danish  
6 3 multidisciplinary hip fracture registry  
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3 10 **Risk factors for new chronic opioid use after hip fracture surgery: a Danish nationwide**  
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5 12 **Registry**

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3 **46 Abstract**

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5  
6 *47 Objective*

7  
8 To examine the risk factors for new chronic opioid use in elderly hip fracture surgery  
9 patients.

10  
11  
12 *50 Design*

13  
14  
15 Prospective population-based cohort study.

16  
17 *52 Setting and participants*

18  
19 Using Danish nationwide health registries, we identified all opioid non-user patients aged  
20  $\geq 65$  years who had undergone hip fracture surgery from 2005-2016 and were alive within the  
21 first year following surgery.  
22  
23

24  
25 *56 Main outcome measures*

26  
27 New chronic opioid use defined by the dispensing of at least 2 prescription opioids within 2  
28 of the last 3 quarters during the first year following surgery.  
29

30  
31 *59 Results*

32  
33 We identified 37,202 opioid non-user patients who underwent hip fracture surgery. Of these,  
34 5,497 (15%) developed new chronic opioid user within 1 year of surgery.  
35  
36

37  
38 Risk factors for new chronic opioid use were BMI  $< 18.5$  (adjusted Odds Ratio (aOR) 1.22  
39 (95% confidence interval (95% CI) 1.09-1.36)), BMI 25-29.9 (aOR 1.12 (95% CI 1.04-  
40 1.21)), and BMI  $\geq 30$  (aOR 1.57 (95% CI 1.40-1.76)) with BMI 18.6-24.9 as reference, a per-  
41 /subtrochanteric fracture (aOR 1.27 (95% CI 1.20-1.34)) with femoral neck fracture as  
42 reference, preoperative use (versus no-use) of NSAID (aOR 1.68 (95% CI 1.55-1.83)), SSRI  
43 (aOR 1.42 (95% CI 1.32-1.53)), antidepressants (aOR 1.36 (95% CI 1.24-1.49)),  
44  
45 antipsychotics (aOR 1.21 (95% CI 1.07-1.35)), corticosteroids (aOR 1.54 (95% CI 1.35-  
46 1.76)), statins (aOR 1.09 (95% CI 1.02-1.18)), antibiotics (aOR 1.32 (95% CI 1.22-1.42)),  
47  
48 anti-osteoporosis drugs (aOR 1.33 (95% CI 1.19-1.49)), and anticoagulatives (aOR 1.24  
49 (95% CI 1.17-1.32)). Presence of cardiovascular comorbidities, diabetes, gastrointestinal  
50 diseases, dementia, COPD, or renal diseases were further identified as risk factors.  
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57  
58 *73 Conclusion*  
59  
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74 In this large nationwide cohort study, we identified several risk factors associated with new  
75 chronic opioid use after hip fracture surgery among patients who were alive within the first  
76 year following surgery.

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

79

## 80 **Article Summary**

### 81 *Strengths and limitations of this study*

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

98



## 99 **Introduction**

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

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

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

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

126

## 127 **Patients and Methods**

128 *Study design and setting*

1  
2  
3 129 We conducted this population-based cohort study in Denmark using prospectively collected  
4  
5 130 administrative health data from health registries, which cover all contacts to the health sector  
6  
7 131 <sup>10</sup>. The Danish National Health Services provide tax-supported primary and secondary health  
8  
9 132 care for the entire population<sup>10</sup>, ensuring that all eligible hip fracture patients undergo surgery  
10  
11 133 at a public hospital. All Danish citizens can be identified using a 10-digit personal  
12  
13 134 identification number, which goes through all Danish health registries allowing for  
14  
15 135 unambiguous individually record linkage of data <sup>11</sup>.

#### 16 136 *Data sources*

17  
18 137 The Danish Civil Registration System (DCRS) was initiated in 1968. Daily updated  
19  
20 138 information on migration and vital status allows for virtually complete long-term follow-up  
21  
22 139 on emigration and death <sup>11</sup>.

23  
24 140 The Danish Multidisciplinary Hip Fracture Registry (DMHFR) was initiated in 2003 and  
25  
26 141 contains nationwide population-based data about all patients undergoing primary hip fracture  
27  
28 142 surgery <sup>12</sup>. The positive predictive value of the hip fracture diagnosis is between 90% and  
29  
30 143 98% depending on fracture type <sup>13</sup>.

31  
32 144 The Danish National Health Service Prescription Database (DNHSPD) has kept information  
33  
34 145 on all prescriptions for reimbursed drugs dispensed by community pharmacies in Denmark  
35  
36 146 since 2004 according to Anatomical Therapeutic Chemical classification system (ATC  
37  
38 147 codes). Data from the DNHSPH can account for patient's medication <sup>14</sup>.

39  
40 148 The Danish National Patient Registry (DNPR) is an administrative registry established in  
41  
42 149 1977 covering all somatic contacts in all Danish hospitals <sup>15</sup>. Information reported to the  
43  
44 150 DNPR includes administrative data, diagnoses, treatments and examinations. Primary and  
45  
46 151 secondary diagnoses are reported to the DNPR according to the International Disease  
47  
48 152 Classification tenth revision (ICD-10) since 1995 <sup>15</sup>. The positive predictive value of the  
49  
50 153 diagnoses included in the medical comorbidities are more than 90% <sup>16</sup>.

#### 51 154 *Study population*

52  
53 155 We used the DMHFR to identify all patients aged 65 or older who were treated for a fracture  
54  
55 156 of the femoral neck, per-, or sub-trochanteric fracture with osteosynthesis or total/partial hip  
56  
57 157 replacement surgery between January 1, 2005 and December 31, 2015 (appendix 1). Patients  
58  
59 158 were indexed on their surgery date and followed up for 12 months (to December 31, 2016).  
60  
159 Patients who had dispensed an opioid in the 6 months prior to index were excluded to ensure

1  
2  
3 160 they were opioid non-users at the index date. Patients who died from any cause within 12  
4  
5 161 months following their index date were also excluded (figure 1).  
6

### 7 162 *Outcome*

8  
9  
10 163 We characterized patients with new chronic opioid use as having dispensed an opioid  
11 164 prescription in at least 2 of the 3 last quarters (3-months periods per quarter) within the first  
12 165 year following surgery among previously opioid non-user patients (figure 2)<sup>8 17</sup>. Prescription  
13 166 opioids dispensed by community pharmacies seven days prior to index and within the first  
14 167 quarter after index were not included in the outcome definition because they are likely to  
15 168 have been associated with the initial opioid treatment to manage acute postoperative pain<sup>4</sup>.  
16 169 Thus, we were only interested in subsequent opioid prescriptions beyond the early  
17 170 perioperative period (quarters 2-4). Our definition of chronic opioid use after surgery was  
18 171 aligned with the definition from the International Association for the Study of Pain, which  
19 172 defines chronic postsurgical pain as pain that develops after a surgical procedure and persists  
20 173 for at least 3 months after surgery<sup>18</sup>.  
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28

29 174 The following prescription opioids were included in the analysis: morphine, hydromorphone,  
30 175 nicomorphine, oxycodone, oxycodone combined with naloxone, pethidine, fentanyl,  
31 176 ketobemidone, methadone, codeine, tramadol, tapentadol, and buprenorphine.  
32  
33  
34

### 35 177 *Risk factors*

36  
37 178 Based on previous literature and clinical experience, the below-mentioned patient- and  
38 179 surgery-related factors were considered and examined as potential risk factors for new  
39 180 chronic opioid use<sup>8 9</sup>. From the DMHFR, we obtained information on age (in categories 65-  
40 181 74, 75-84 and  $\geq 85$  years), sex, fracture type (femoral neck and per-/subtrochanteric fracture),  
41 182 and surgery type (osteosynthesis and total/partial hip replacement). Body mass index (BMI)  
42 183 was calculated using information on height and weight (weight in kilograms divided by  
43 184 height in metres squared) and divided into groups (underweight defined as BMI <18.5,  
44 185 normal as BMI 18.6-24.9, overweight as BMI 25-29.9 and obese as BMI  $\geq 30$ ). We examined  
45 186 several specific medical comorbidities including myocardial infarction, congestive heart  
46 187 failure, peripheral vascular disease, cerebrovascular disease, diabetes, liver disease, peptic  
47 188 ulcer disease, connective tissue disease, dementia, hemiplegia, chronic obstructive pulmonary  
48 189 disease, renal disease and cancer (Table 1). BMI and various comorbidities were in previous  
49 190 studies found to be associated with increased risk of mortality and could be associated with  
50 191 increased risk of chronic opioid use<sup>8 19-21</sup>.  
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3 192 We also included data on preoperative dispensing of the following co-medications:  
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5 193 nonsteroidal anti-inflammatory drug (NSAID), selective serotonin reuptake inhibitors (SSRI),  
6  
7 194 any antidepressants, antipsychotics, oral corticosteroids, statins, antibiotics, hormone  
8  
9 195 replacement therapy, anti-osteoporosis medication, vitamin K, any anticoagulants, novel oral  
10  
11 196 anticoagulant (NOAC), antiplatelet drugs and heparins (appendix 2). These drugs are  
12  
13 197 included as potential risk factors because they can influence general healthcare utilization and  
14  
15 198 behaviour, or are associated with increased mortality<sup>22</sup>. The preoperative medication for each  
16  
17 199 drug was defined as at least 1 dispensing in the 1 year before surgery.

### 200 *Statistical analyses*

201 For the presentation of demographic data, descriptive statistics were used and presented for  
22  
23 202 the entire study population at the time of surgery and separately for patients with new chronic  
24  
25 203 use. Odds ratios (ORs) with 95% confidence intervals (CI) were calculated using multiple  
26  
27 204 logistic regression and adjusted for age and sex (aOR). Several sensitivity analyses were  
28  
29 205 performed: 1. An analysis when using logistic regression and adjusting for multiple relevant  
30  
31 206 factors. 2. An analysis where all patients who died within the first year were included. 3.  
32  
33 207 Landmark analysis at 6 months (only excluding the patients who died in the first and second  
34  
35 208 quarter), and at 9 months (only excluding the patients who died in the first, second, and third  
36  
37 209 quarter)<sup>23 24</sup>. 4. An analysis when only including patients, who sustained a fracture of the  
38  
39 210 femoral neck to analyze the treatment with total/partial hip replacement and osteosynthesis.  
40  
41 211 All statistical analyses were performed in STATA version 15 (STATA Corp, TX, USA).

42  
43 212 The study was approved by the Danish Data Protection Agency's journal number (2015-57-  
44  
45 213 0002) and Aarhus University's journal number (2016-051-000001), record number 880.

46  
47 214 This paper was reported following the Strengthening the Reporting of Observational Studies  
48  
49 215 in Epidemiology (STROBE) statement<sup>25</sup>, and the Reporting of studies Conducted using  
50  
51 216 Observational Routinely-collected Data (RECORD) statement<sup>26</sup>.

### 52 *Patient and Public Involvement*

53  
54 217 No patient involved

55  
56 218

## 57 **Results**

### 58 59 219 *Description of the study population*

1  
2  
3 222 In total, 69,456 patients with hip fracture surgery were identified (figure 1). We excluded  
4  
5 223 18,617 hip fracture patients due to opioid use before surgery, leaving us with 50,839 eligible  
6  
7 224 hip fracture patients. Of these, 13,637 patients died within the first year. The final study  
8  
9 225 population included 37,202 hip fracture patients.

10  
11 226 Overall, 27,133 patients (73%) were female and the mean age at the time of surgery was 81  
12  
13 227 years (range 65-107). In our study population, 5,497 (15%) developed new chronic opioid use  
14  
15 228 within 1 year of surgery.

16  
17 229 The proportion of patients who developed new chronic opioid use in relation to all hip  
18  
19 230 fracture patients was 15% for both females and males, 13% for patients with femoral neck  
20  
21 231 fractures, and 16% for patients with a per- or subtrochanteric fracture (Table 1).

22  
23 232 The characteristics of patients with new chronic opioid use were similar to the characteristics  
24  
25 233 of the total population of hip fracture patients with small differences seen in the distribution  
26  
27 234 of BMI, fracture type, surgery type, and preoperative medication use (Table 1).

#### 28 235 *Risk factors for new chronic opioid use*

29  
30  
31 236 The risk factors for new chronic opioid use were being underweight (aOR 1.22 (CI 1.09-  
32  
33 237 1.36)), overweight (aOR 1.12 (CI 1.04-1.21)), or obese (aOR 1.57 (CI 1.40-1.76)) with  
34  
35 238 normal weight as reference and sustaining a per-/subtrochanteric fracture (aOR 1.27 (CI 1.20-  
36  
37 239 1.34)) with fracture of the femoral neck as reference. Treatment with total/partial hip  
38  
39 240 replacement was associated with lower risk of new chronic opioid use, with osteosynthesis as  
40  
41 241 reference (aOR 0.65 (CI 0.60-0.69)) (figure 3 and appendix figure 1).

42  
43 242 Preoperative use of NSAIDs (aOR 1.68 (CI 1.55-1.83)), SSRIs (aOR 1.42 (CI 1.32-1.53)),  
44  
45 243 antidepressants (aOR 1.36 (CI 1.24-1.49)), antipsychotics (aOR 1.21 (CI 1.07-1.35)),  
46  
47 244 corticosteroids (aOR 1.54 (CI 1.35-1.76)), statins (aOR 1.09 (CI 1.02-1.18)), antibiotics (aOR  
48  
49 245 1.32 (CI 1.22-1.42)), anti-osteoporosis drugs (aOR 1.33 (CI 1.19-1.49)), anticoagulants (aOR  
50  
51 246 1.24 (CI 1.17-1.32)), and antiplatelet drugs (aOR 1.24 (CI 1.16-1.32)) were identified as risk  
52  
53 247 factors for new chronic opioid use (figure 3 and appendix figure 1).

54  
55 248 The presence of the following preoperative comorbidities were further associated with risk of  
56  
57 249 new chronic opioid use: cardiovascular comorbidity, diabetes, gastrointestinal diseases,  
58  
59 250 dementia, COPD, and renal diseases (figure 3 and appendix figure 1).  
60

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

261

## 262 Discussion

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

### 270 *Strength and limitations*

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

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

1  
2  
3 282 intended indications of opioid prescriptions. We know that patients have collected the opioid  
4 prescription at the pharmacy, but we have no knowledge regarding the patient's compliance.  
5 283 Even so, using prescription opioid dispensing data is considered a better measure of  
6 284 medication use than most alternative measures<sup>28</sup>. Second, we excluded all deceased patients  
7 285 within the first year following surgery, which might have compromised the external validity  
8 286 of our study. Thus, we can only conclude that identified risk factors for new chronic opioid  
9 287 use apply for hip fracture patients that survived one year after surgery. The number of  
10 288 deceased patients was substantial. A total of 13,637 of the 50,839 hip fracture patients died  
11 289 within the first year (please see appendix figure 4). Including these in the study population  
12 290 would have an impact on our results (please see figure 4). A total of 751 of the 13,637  
13 291 deceased hip fracture patients were potentially eligible to be included in our study as new  
14 292 chronic opioid users. These patients had redeemed two opioid prescriptions in either the  
15 293 second, third or fourth quarter cf. our definition (please see appendix figure 4). In general,  
16 294 immortal time can bias the effect estimates in pharmaco-epidemiological studies<sup>23</sup>. The  
17 295 landmark approach is one of the methods often used when addressing immortal time bias;  
18 296 however, its simplicity comes at the cost of difficulty in interpreting the results<sup>23 24</sup>. The  
19 297 performed landmark analyses illustrated, that including the deceased patients from the third  
20 298 and fourth quarter in our primary analysis would not affect our results substantially (please  
21 299 see appendix figure 2 and 3). The effect of the different analytical assumptions on the results  
22 300 are summarized in figure 5, showing the changes from analysis to analysis plotted side by  
23 301 side. Third, we were not able to include reoperation in our analysis. This may have  
24 302 overestimated the risk of new chronic opioid use in younger female patients, since hip  
25 303 fracture patients are at risk of reoperation, which may lead to prolonged or restarted opioid  
26 304 use. We know that 6% of hip fracture patients are reoperated<sup>29</sup> and that individuals aged 80  
27 305 years or younger and male gender are associated with risk of reoperation<sup>30</sup>.  
28 306

### 307 *Comparison with previous studies*

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

1  
2  
3 315 were opioid users at 6 months. The study reported further that osteoporosis and opioid use  
4  
5 316 prior to admission were predictors for postoperative opioid use at 6 months. In contrast to our  
6  
7 317 study, they did not define opioid use, and the follow-up period ended at 6 months after hip  
8  
9 318 fracture<sup>5</sup>. We studied the risk factors in a large nationwide setup, whereby we uncover trends  
10  
11 319 across the entire country and not only from a single institution.

12  
13 320 In general, there is evidence that younger biological age is a predictor of persistent opioid use  
14  
15 321 in the general surgical population<sup>6 8</sup>. This is explained by a wide variety of factors in the  
16  
17 322 aging population such as a decline in the production of several proteins and neuropeptides, a  
18  
19 323 decline of the immune response and an increase in the inflammatory response<sup>31</sup>. Our study  
20  
21 324 shows the same tendency.

22  
23 325 Several studies have shown the prevalence of chronic pain and consumption of opioids tend  
24  
25 326 to be higher in females than males<sup>17 32</sup>. Psychological, biological, cultural, and social factors  
26  
27 327 all play a role in the differences between the sex in pain responses and management<sup>17 33</sup>. Our  
28  
29 328 study demonstrates a weak association between the female sex and new chronic opioid use  
30  
31 329 after hip fracture surgery.

32  
33 330 Overweight and obesity have been shown to be associated with a proinflammatory state after  
34  
35 331 surgery inducing hyperalgesia, suggesting an increase in opioid use, which correlates with  
36  
37 332 findings by Westermann et al. of an association between obesity and prolonged postoperative  
38  
39 333 opioid use<sup>19 20 34</sup>. This is in line with our findings of an association between overweight and  
40  
41 334 obesity and developing a new chronic opioid use after surgery.

42  
43 335 Our data suggest that fracture type and surgery type is associated with new chronic opioid  
44  
45 336 use. Hip fracture patients with a trochanteric fracture experience more and severe pain than  
46  
47 337 patients with femoral neck fractures<sup>35</sup>. Similarly, patients with osteosynthesis experience  
48  
49 338 more pain than the patients with a stable arthroplasty<sup>36</sup>. The reported mechanisms being  
50  
51 339 shortening of the limb length and range of motion limitations<sup>36</sup>. Another explanation to why  
52  
53 340 surgery type is associated with new chronic opioid use could be that these patients might  
54  
55 341 have a higher rate of reoperation converting to a total hip arthroplasty performed by a more  
56  
57 342 experienced surgeon. However, we do not have data to support this statement.

58  
59 343 Several preoperative comorbidities were associated with risk of new chronic opioid use after  
60  
344 surgery. Although we excluded all hip fracture patients with prior use of opioids, it is  
345 possible that some patients had an unmanaged pain condition prior to surgery. These patients  
346 may have continued to use prescription opioids intended for treating postsurgical pain in



1  
2  
3 347 order to treat their pre-existing chronic pain.<sup>6</sup> Inacio et al. support this behaviour as they  
4  
5 348 found back pain prior to surgery was associated with chronic opioid use<sup>8</sup>. Comorbidities  
6  
7 349 associated with unrelieved chronic pain conditions are heart failure and COPD. These  
8  
9 350 comorbidities have been associated with chronic opioid use, which concords with our study<sup>6</sup>  
10  
11 351<sup>8</sup>. Diabetes has also been associated with a constant chronic inflammatory state inducing  
12  
13 352 neuropathy, which has also been associated with unrelieved chronic pain. This mechanism is  
14  
15 353 a potential risk factor for chronic pain, which is in accordance with our study<sup>6,8</sup>. Other  
16  
17 354 comorbidities have also been associated with chronic pain and chronic opioid use such as  
18  
19 355 liver disease and depression<sup>8</sup>. By knowing the impact of these comorbidities on the risk of  
20  
21 356 new chronic opioid use, attainment of a greater focus on comorbidity pre- and postoperative  
22  
23 357 may reduce new chronic opioid use after surgery.

24  
25 358 Medication use is frequent in hip fracture patients and nearly all of the included medications  
26  
27 359 in our study were identified as a risk factor for chronic opioid use<sup>37</sup>. Medication use is  
28  
29 360 closely related to comorbidities. Treatment of chronic medical conditions is a complex task  
30  
31 361 that require multidisciplinary approach. It is possible that surgeons and patients are  
32  
33 362 preoccupied with attempting to manage chronic pain conditions leaving long-term opioid use  
34  
35 363 as a secondary priority. Some drugs when taken on their own or in combination, might  
36  
37 364 change the level of sensitivity to opioids which could result in patients who continue to take  
38  
39 365 opioids even though their level of pain decreases over time and does not necessarily coincide  
40  
41 366 with the prescribed opioid dose.

### 42 367 *Chronic opioid use*

43  
44 368 There are no standard guidelines in Denmark for post-discharge clinical follow-up of hip  
45  
46 369 fracture patients. However, many orthopaedic and geriatric departments focus on the  
47  
48 370 reduction of prescription opioid exposure after surgery by instituting a plan for opioid  
49  
50 371 tapering. Patients do not receive follow-up appointments in outpatient clinics or at the general  
51  
52 372 practitioner unless they take the initiative themselves. Since hip fracture patients often are  
53  
54 373 characterized as being frail, receiving several medications, and having multimorbidity, they  
55  
56 374 may lack the resources to follow such a tapering plan. Thus, it is important to ensure that  
57  
58 375 patients are well informed and included in the development of a tapering plan, and  
59  
60 376 understand the risks and benefits of prescription opioids for the treatment of postsurgical  
377 pain. However, it is important to note that not all hip fracture surgeries are successful and

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

### 380 *Conclusion*

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

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

391

### 392 **Authors' Contributions**

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

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401 Multidisciplinary Hip Fracture Registry.

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404 or not-for-profit sectors.

### 405 **Competing interests**

406 None declared.

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3 407 **Patient consent for publication**  
4

5 408 Not required  
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7  
8 409 **Data sharing statement**  
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10 410 No additional data are available  
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3 536 **Legends**  
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5 537 Figure 1: Flowchart of the patients from the Danish Multidisciplinary Hip Fracture Registry  
6 to the study population.  
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11 540 Figure 2: New chronic opioid use was defined as patients with at least 2 prescriptions  
12 dispensed in 2 of the 3 latter quarters in the first year following surgery.  
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18 543 Figure 3: Risk factors for developing new chronic opioid use after hip fracture surgery among  
19 patient with no opioid use before surgery in those who were alive 12 months after surgery,  
20 odds ratios adjusted for age and sex.  
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23 546 COPD: Chronic pulmonary disease, NSAID: nonsteroidal anti-inflammatory drug, SSRI:  
24 selective serotonin reuptake inhibitors, HRT: Hormone Replacement Therapy, NOAC: novel  
25 oral anticoagulant. Odds ratios (ORs) with 95% confidence intervals (CI)  
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31 550 Figure 4: Risk factors for developing new chronic opioid use after hip fracture surgery among  
32 patients with no opioid use before surgery, including patient who were alive and those who  
33 died within 12 months of surgery, odds ratios adjusted for age and sex.  
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36 553 COPD: Chronic pulmonary disease, NSAID: nonsteroidal anti-inflammatory drug, SSRI:  
37 selective serotonin reuptake inhibitors, HRT: Hormone Replacement Therapy, NOAC: novel  
38 oral anticoagulant. Odds ratios (ORs) with 95% confidence intervals (CI)  
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43 557 Figure 5: United forest plot. A. Analysis, when including patient who were alive and those  
44 who died within 12 months of surgery. B. Landmark analysis at 6 months: Analysis, when  
45 including patients with no opioid use before surgery, and excluding the patients who died in  
46 the first and second quarter of surgery. C. Landmark analysis at 9 months: Analysis, when  
47 including patients with no opioid use before surgery, and excluding the patients who died in  
48 the first, second, and third quarter of surgery. Odds ratios adjusted for age and sex.  
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53 563 COPD: Chronic pulmonary disease, NSAID: nonsteroidal anti-inflammatory drug, SSRI:  
54 selective serotonin reuptake inhibitors, HRT: Hormone Replacement Therapy, NOAC: novel  
55 oral anticoagulant.  
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3 567 Appendix figure 1: Risk factors for developing new chronic opioid use after hip fracture  
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5 568 surgery among patient with no opioid use before surgery and those who were alive 12 months  
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7 569 after surgery, crude odds ratios.

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9 570 COPD: Chronic pulmonary disease, NSAID: nonsteroidal anti-inflammatory drug, SSRI:  
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11 571 selective serotonin reuptake inhibitors, HRT: Hormone Replacement Therapy, NOAC: novel  
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13 572 oral anticoagulant. Odds ratios (ORs) with 95% confidence intervals (CI)

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16 574 Appendix figure 2: Landmark analysis at 6 months: Risk factors for developing new chronic  
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18 575 opioid use after hip fracture surgery among patients with no opioid use before surgery, when  
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20 576 excluding the patients who died in the first and second quarter of surgery, odds ratios  
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22 577 adjusted for age and sex.

23 578 COPD: Chronic pulmonary disease, NSAID: nonsteroidal anti-inflammatory drug, SSRI:  
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25 579 selective serotonin reuptake inhibitors, HRT: Hormone Replacement Therapy, NOAC: novel  
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27 580 oral anticoagulant. Odds ratios (ORs) with 95% confidence intervals (CI)

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30 582 Appendix figure 3: Landmark analysis at 9 months: Risk factors for developing new chronic  
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32 583 opioid use after hip fracture surgery among patients with no opioid use before surgery, when  
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34 584 excluding the patients who died in the first, second, and third quarter of surgery, odds ratios  
35  
36 585 adjusted for age and sex.

37 586 COPD: Chronic pulmonary disease, NSAID: nonsteroidal anti-inflammatory drug, SSRI:  
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39 587 selective serotonin reuptake inhibitors, HRT: Hormone Replacement Therapy, NOAC: novel  
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41 588 oral anticoagulant. Odds ratios (ORs) with 95% confidence intervals (CI)

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47 591 Appendix figure 4: Number of hip fracture patients identified at the time of hip fracture and  
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49 592 during the first year following surgery. Patients who were opioid users before surgery were  
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51 593 not included in our analyses (number of deceased in this group in each of the 4 quarters of  
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53 594 surgery is presented with green color). Our analyses were based on patients with no opioid  
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55 595 use before surgery. We presented the number of opioid non-users alive in each of the 4  
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57 596 quarters of surgery with purple color. We presented the number of opioid non-users who dead  
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59 597 in each of the 4 quartets of surgery with blue color. Number of eligible new chronic users are  
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3 598 patients, who have redeemed two opioid prescriptions, but have died in the first year  
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5 599 following surgery, and are therefore not included in our primary analyses (red color).  
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10 601 Table 1: Patient characteristics for the all hip fracture patients and new chronic users  
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12 602 Appendix 1: Following diagnoses- and procedure codes were used to identify patients  
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14 603 undergoing hip fracture surgery.  
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16 604 Appendix 2: ATC codes for all medication in the study  
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Table 1: Patient characteristics for the all hip fracture patients and new chronic users

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

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

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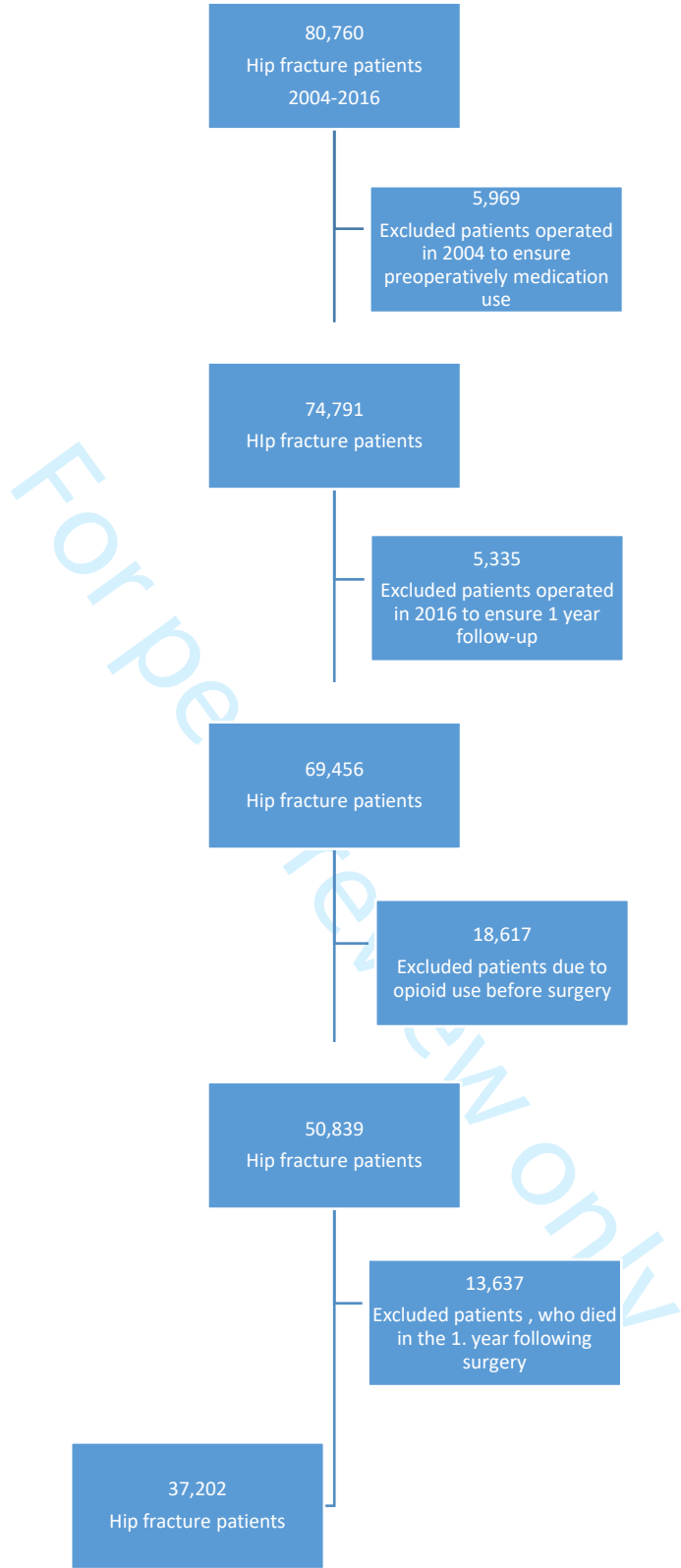


Figure 1: Flowchart of the patients from the Danish Multidisciplinary Hip Fracture Registry to the study population.

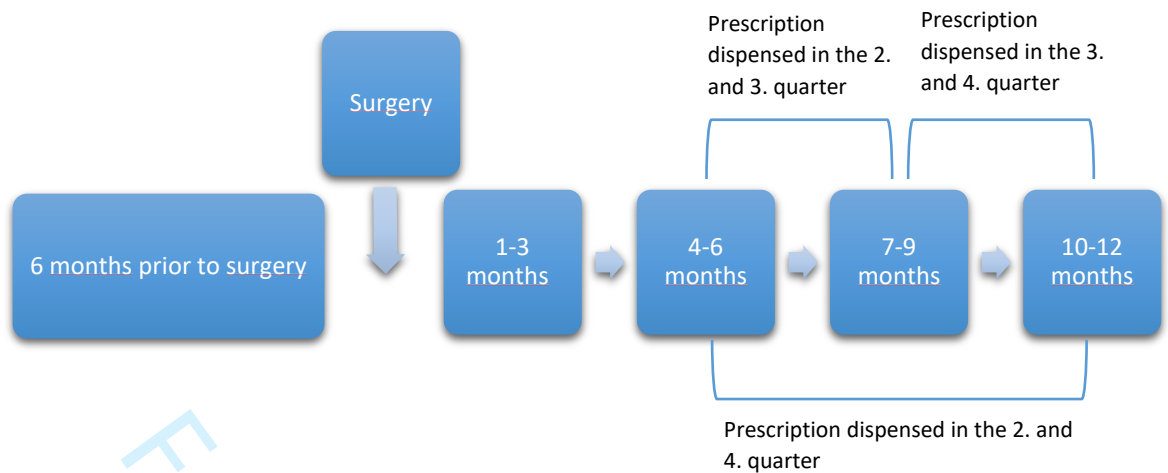


Figure 2: Chronic opioid use was defined as patients with at least 2 prescriptions dispensed in 2 of the 3 latter quarters in the first year following surgery

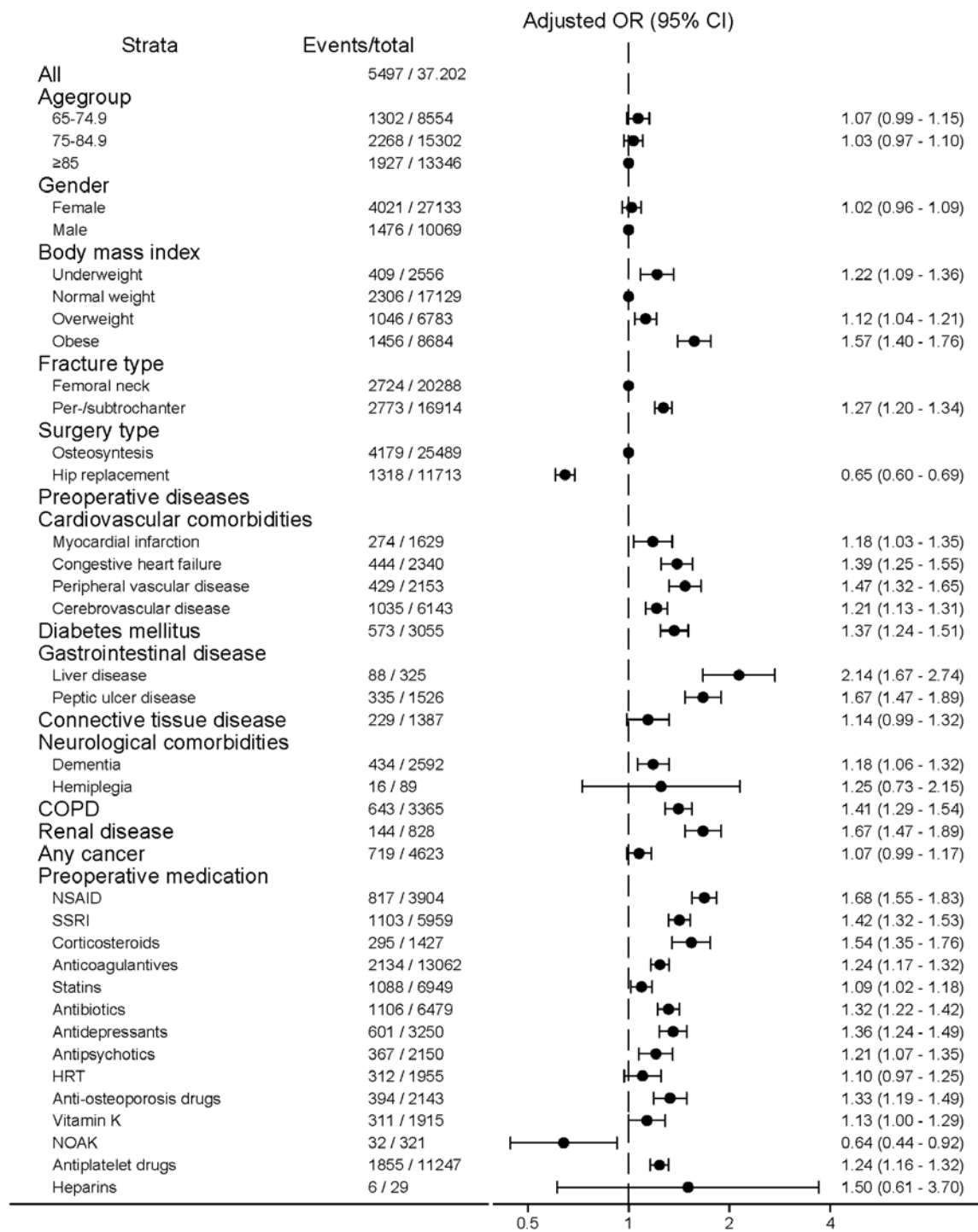


Figure 3: Risk factors for developing new chronic opioid use after hip fracture surgery among patient with no opioid use before surgery and those who were alive 12 months after surgery, odds ratios adjusted for age and sex.

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)

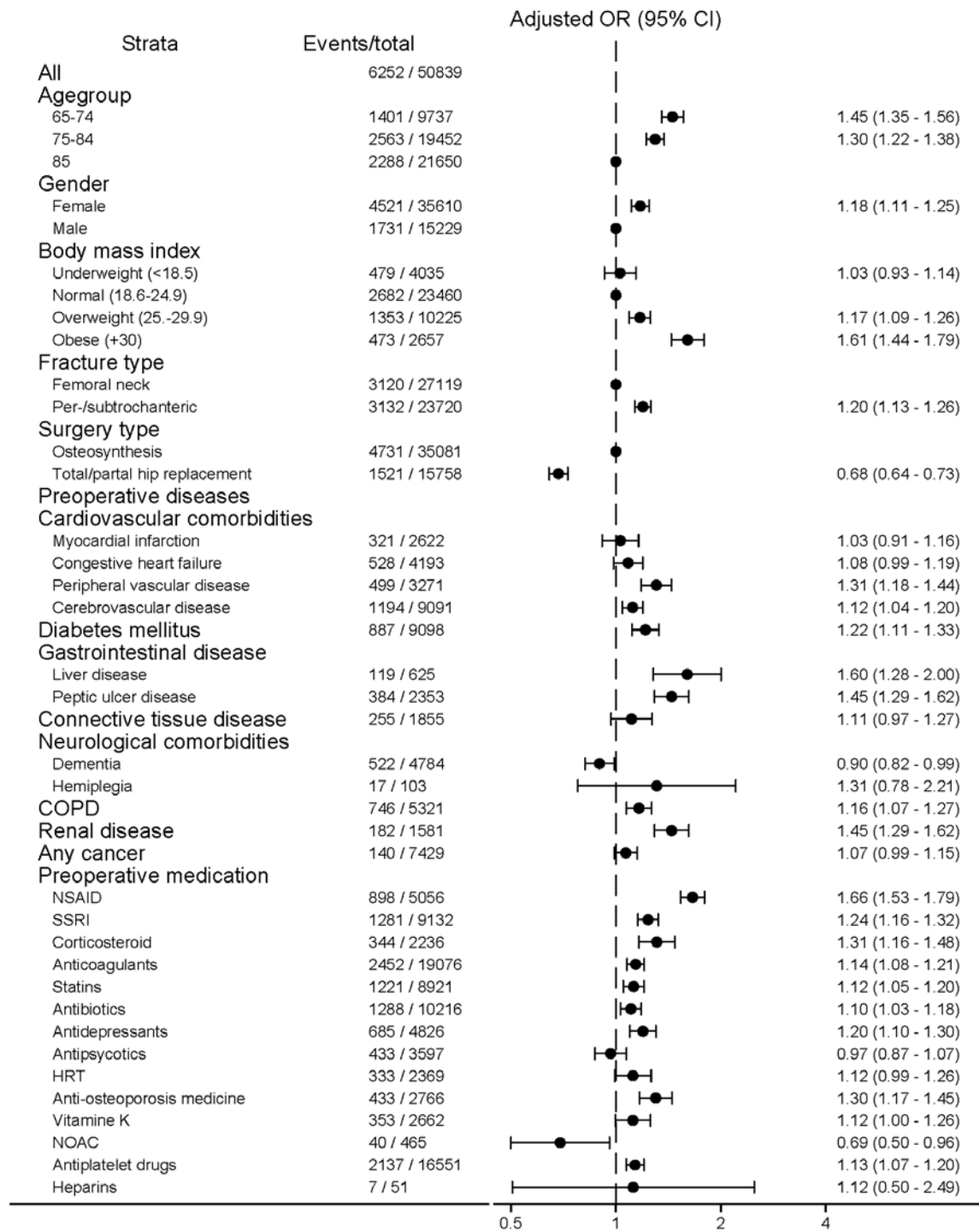


Figure 4: Risk factors for developing new chronic opioid use after hip fracture surgery among patients with no opioid use before surgery, including patient who were alive and those who died within 12 months of surgery, odds ratios adjusted for age and sex.

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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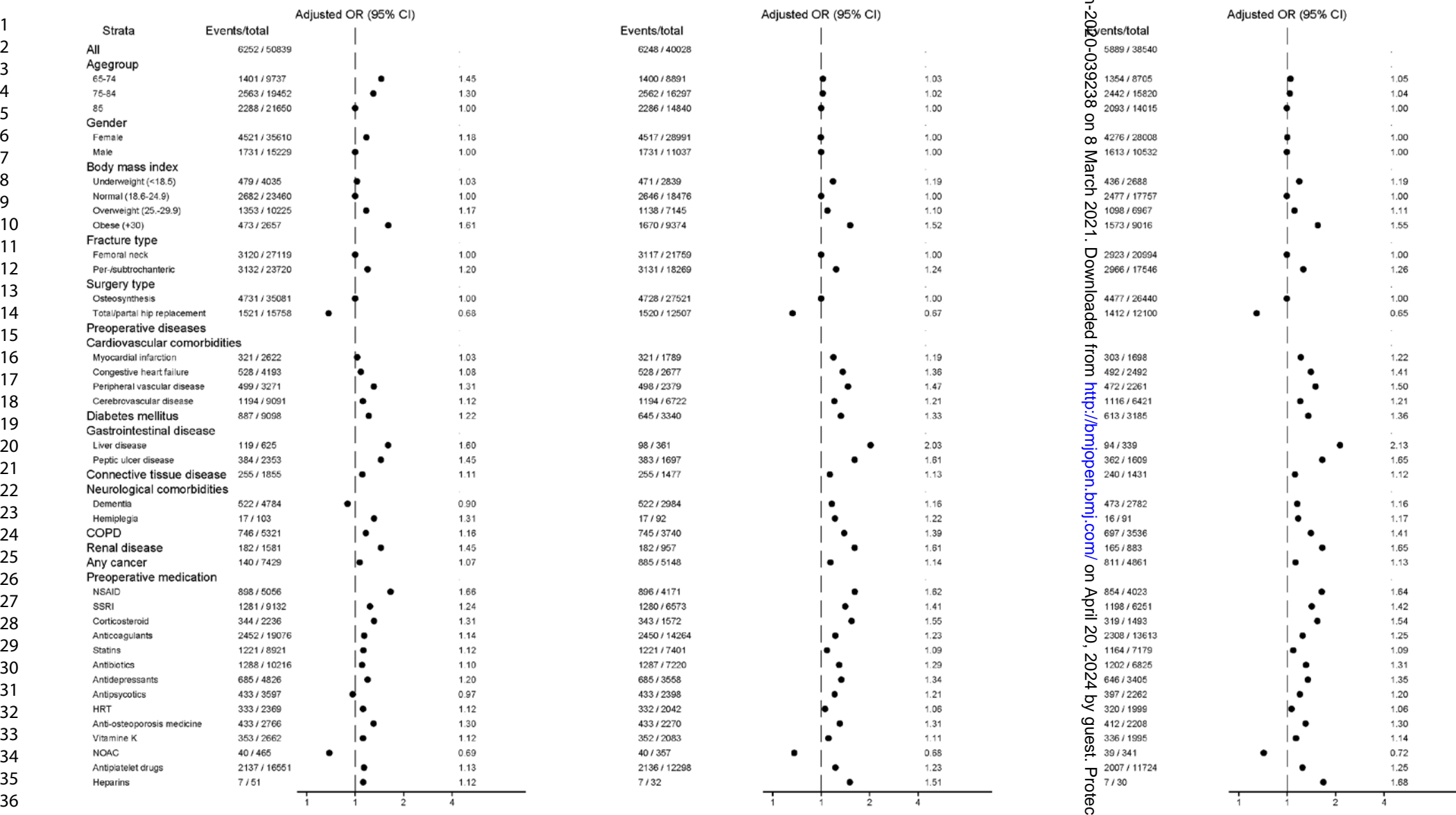


Figure 5: United forest plot. A. Analysis, when including patient who were alive and those who died within 12 months of surgery. B. Landmark analysis at 6 months: Analysis, when including patients with no opioid use before surgery, and excluding the patients who died in the first and second quarter of 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. COPD: Chronic pulmonary disease, NSAID: nonsteroidal anti-inflammatory drug, SSRI: selective serotonin reuptake inhibitors, HRT: Hormone Replacement Therapy, NOAC: novel oral anticoagulant.

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

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

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

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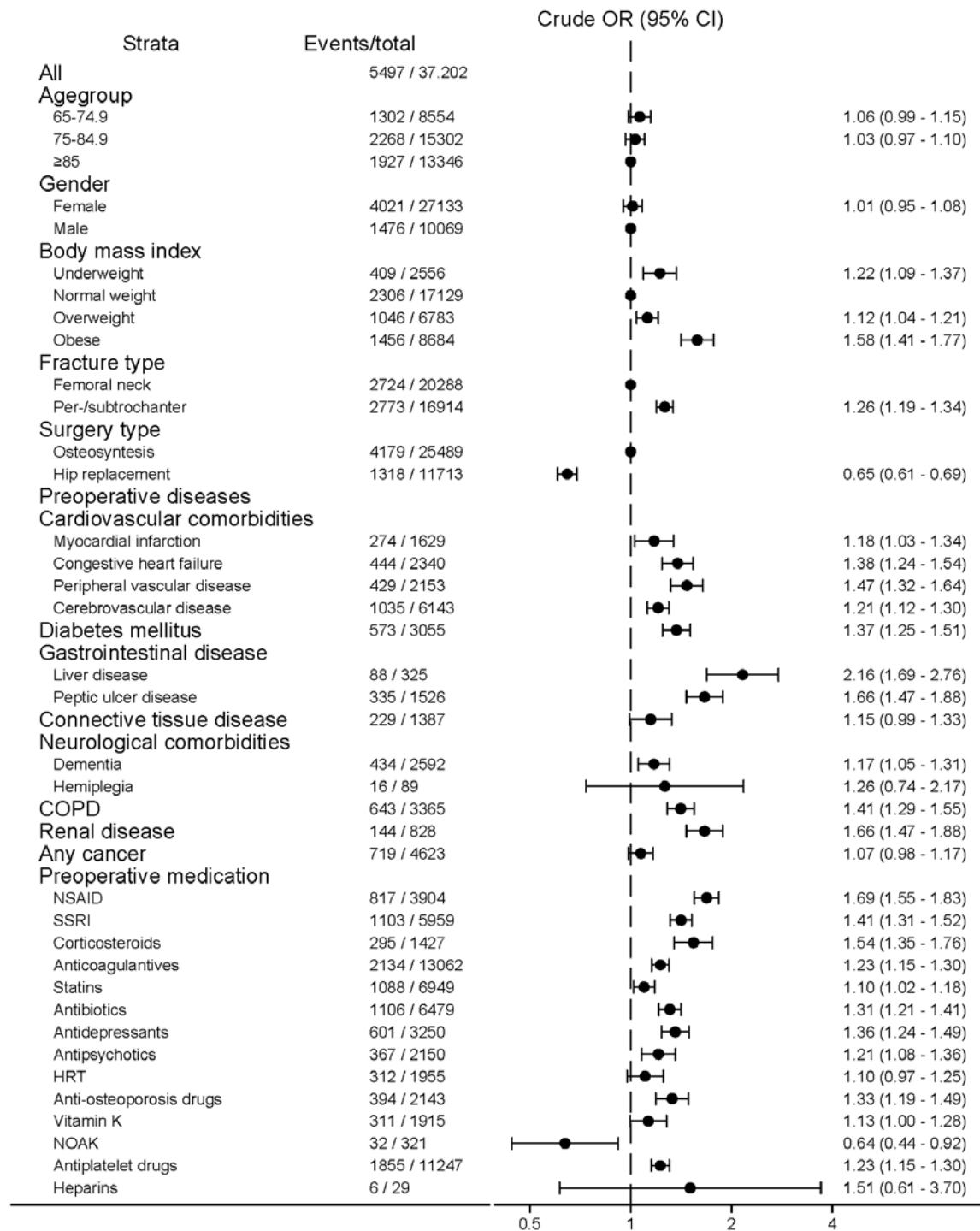
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*Appendix 2: ATC codes for all medication in the study*

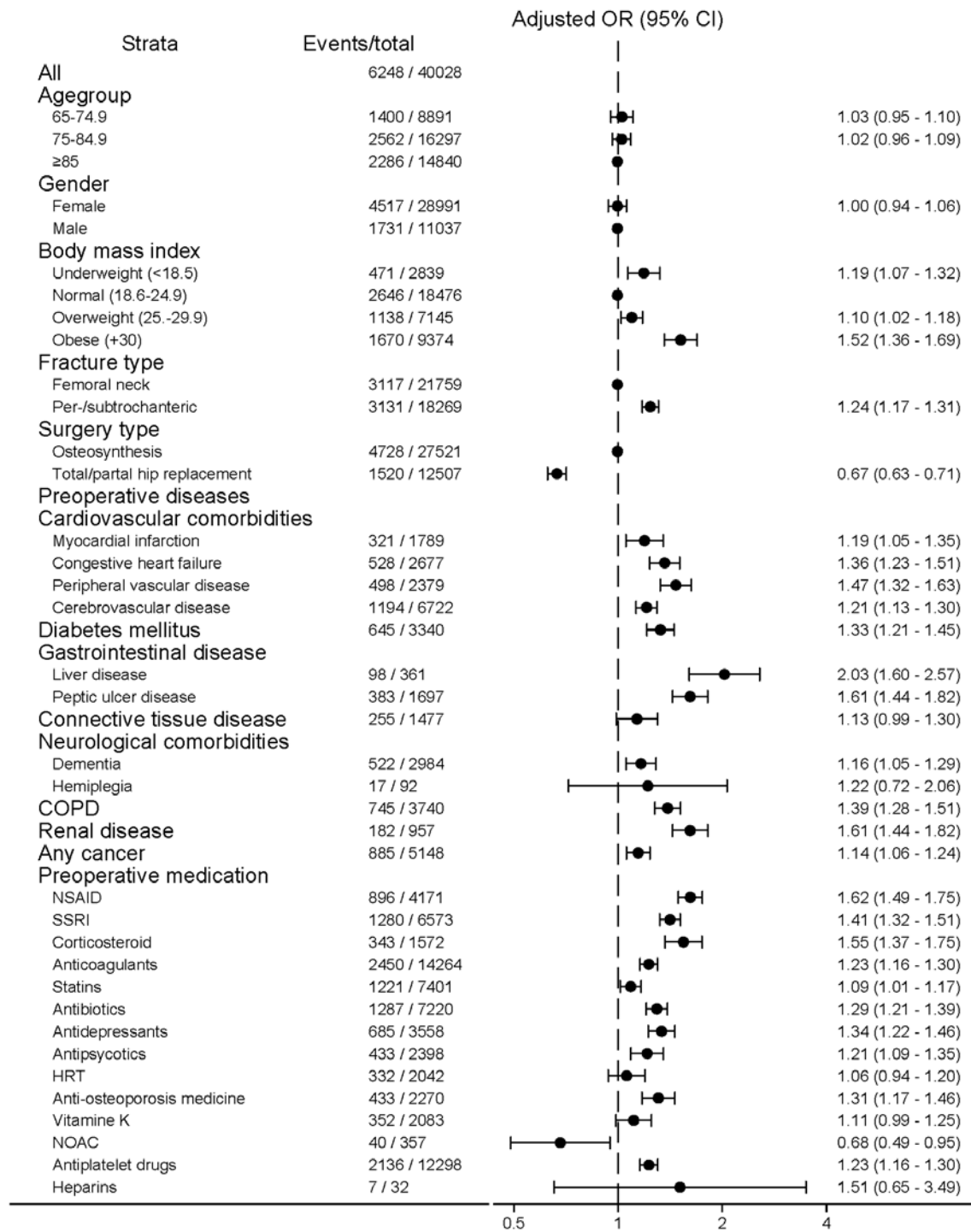
<i>Categories</i>	<b>Name</b>	<b>ATC code</b>	
<i>Non-steroidal anti-inflammatory drugs (NSAIDs):</i>	Celecoxib	M01AH01	
	Rofecoxib	M01AH	
	Valdecoxib	M01AH03	
	Etoricoxib	M01AH05	
	Lornoxicam	M01AC05	
	Diclofenac	M01AB05	
<i>Selective serotonin reuptake inhibitors (SSRIs)</i>	Meloxicam	M01AC06	
	Fluoxetine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

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3		Tramadol N02AX02
4		Tapentadol N02AX06
5		Buprenorphin N02AE01
6		Codein R05DA04
7		Codein and paracetamol N02AJ06
8	<i>Hormone replacement therapy</i>	Estrogen G03C
9		Estrogen L02AA
10		Progesteron and estrogen in combination G03F
11		Antiandrogen G03H
12		Progesteron G03D
13	<i>Anti-osteoporosis medication</i>	
14	<i>Bisfosfonats</i>	
15		Etidronat M05BA01
16		Clodronate M05BA02
17		Pamidronate M05BA03
18		Alendronat M05BA04
19		Alendronat and colecalciferol M05BB03
20		Alendronat, calcium and colecalciferol M05BB05
21		Tiludronate M05BA05
22		Ibandronat M05BA06
23		Risedronat M05BA07
24		Risedronat and calcium M05BB02
25		Risedronat, calcium and colecalciferol M05BB04
26		Zoledronat
27	<i>Other drugs affecting bone structure and mineralization</i>	Denosumab M05BX04
28		Strontiumranelat M05BX03
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ATC codes: Anatomical Therapeutic Chemical Classification System

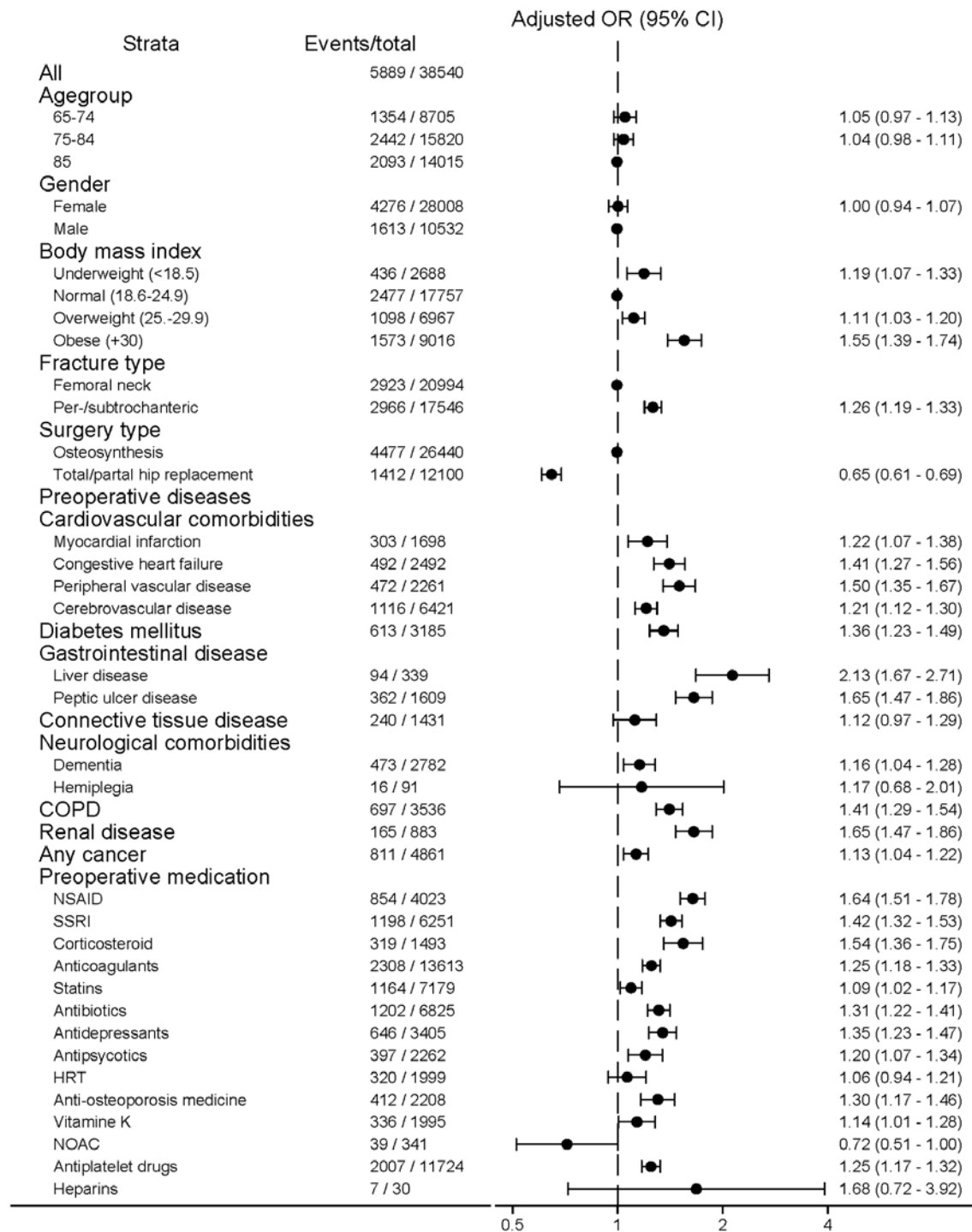


Appendix figure 1: Risk factors for developing new chronic opioid use after hip fracture surgery among patient with no opioid use before surgery and those who were alive 12 months after surgery, crude odds ratios. COPD: Chronic pulmonary disease, NSAID: nonsteroidal anti-inflammatory drug, SSRI: selective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



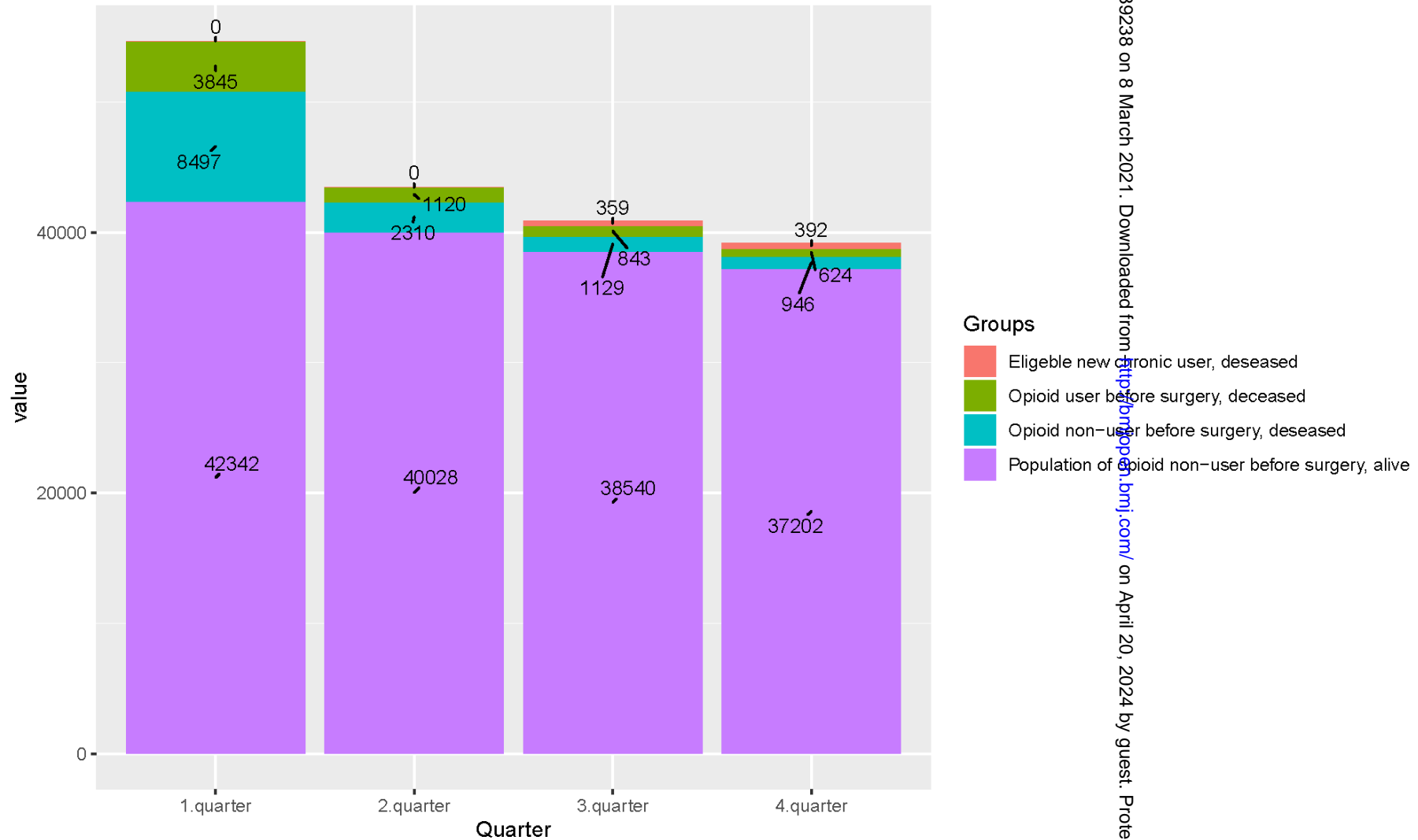
Appendix figure 2: Landmark analyses at 6 months: Risk factors for developing new chronic opioid use after hip fracture surgery among patients with no opioid use before surgery, when excluding the patients who died in the first and second quarter of surgery, odds ratios adjusted for age and sex.

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.

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 4: 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 died in each of the 4 quarters 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 cohort reporting guidelines, and cite them as:

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

		Page
	Reporting Item	Number
<b>Title and abstract</b>		
Title	<a href="#">#1a</a> Indicate the study's design with a commonly used term in the title or the abstract	1



1	Abstract	<a href="#">#1b</a>	Provide in the abstract an informative and balanced summary	3
2			of what was done and what was found	
3				
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6	<b>Introduction</b>			
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10	Background /	<a href="#">#2</a>	Explain the scientific background and rationale for the	5
11	rationale		investigation being reported	
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15	Objectives	<a href="#">#3</a>	State specific objectives, including any prespecified	5
16			hypotheses	
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20	<b>Methods</b>			
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23	Study design	<a href="#">#4</a>	Present key elements of study design early in the paper	6
24				
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26	Setting	<a href="#">#5</a>	Describe the setting, locations, and relevant dates, including	6
27			periods of recruitment, exposure, follow-up, and data	
28			collection	
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34	Eligibility criteria	<a href="#">#6a</a>	Give the eligibility criteria, and the sources and methods of	6
35			selection of participants. Describe methods of follow-up.	
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39	Eligibility criteria	<a href="#">#6b</a>	For matched studies, give matching criteria and number of	6
40			exposed and unexposed	
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45	Variables	<a href="#">#7</a>	Clearly define all outcomes, exposures, predictors, potential	7
46			confounders, and effect modifiers. Give diagnostic criteria, if	
47			applicable	
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53	Data sources /	<a href="#">#8</a>	For each variable of interest give sources of data and details	6
54	measurement		of methods of assessment (measurement). Describe	
55			comparability of assessment methods if there is more than	
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one group. Give information separately for for exposed and unexposed groups if applicable.

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6	Bias	<a href="#">#9</a>	Describe any efforts to address potential sources of bias	8
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9	Study size	<a href="#">#10</a>	Explain how the study size was arrived at	6
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12	Quantitative	<a href="#">#11</a>	Explain how quantitative variables were handled in the	7
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14	variables		analyses. If applicable, describe which groupings were	
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16			chosen, and why	
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19	Statistical	<a href="#">#12a</a>	Describe all statistical methods, including those used to	8
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21	methods		control for confounding	
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25	Statistical	<a href="#">#12b</a>	Describe any methods used to examine subgroups and	8
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27	methods		interactions	
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30	Statistical	<a href="#">#12c</a>	Explain how missing data were addressed	8
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32	methods			
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36	Statistical	<a href="#">#12d</a>	If applicable, explain how loss to follow-up was addressed	8
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38	methods			
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41	Statistical	<a href="#">#12e</a>	Describe any sensitivity analyses	8
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43	methods			
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46	<b>Results</b>			
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49	Participants	<a href="#">#13a</a>	Report numbers of individuals at each stage of study—eg	9
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51			numbers potentially eligible, examined for eligibility,	
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53			confirmed eligible, included in the study, completing follow-	
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up, and analysed. Give information separately for for  
exposed and unexposed groups if applicable.

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6	Participants	<a href="#">#13b</a>	Give reasons for non-participation at each stage	9
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9	Participants	<a href="#">#13c</a>	Consider use of a flow diagram	9
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12	Descriptive data	<a href="#">#14a</a>	Give characteristics of study participants (eg demographic,	9
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14			clinical, social) and information on exposures and potential	
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16			confounders. Give information separately for exposed and	
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18			unexposed groups if applicable.	
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22	Descriptive data	<a href="#">#14b</a>	Indicate number of participants with missing data for each	9
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24			variable of interest	
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27	Descriptive data	<a href="#">#14c</a>	Summarise follow-up time (eg, average and total amount)	9
28				
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30	Outcome data	<a href="#">#15</a>	Report numbers of outcome events or summary measures	9
31				
32			over time. Give information separately for exposed and	
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34			unexposed groups if applicable.	
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38	Main results	<a href="#">#16a</a>	Give unadjusted estimates and, if applicable, confounder-	9
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40			adjusted estimates and their precision (eg, 95% confidence	
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42			interval). Make clear which confounders were adjusted for	
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44			and why they were included	
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48	Main results	<a href="#">#16b</a>	Report category boundaries when continuous variables were	9
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50			categorized	
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53	Main results	<a href="#">#16c</a>	If relevant, consider translating estimates of relative risk into	9
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55			absolute risk for a meaningful time period	
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1	Other analyses	<a href="#">#17</a>	Report other analyses done—e.g., analyses of subgroups	9
2			and interactions, and sensitivity analyses	
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6	<b>Discussion</b>			
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10	Key results	<a href="#">#18</a>	Summarise key results with reference to study objectives	10
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13	Limitations	<a href="#">#19</a>	Discuss limitations of the study, taking into account sources	10
14			of potential bias or imprecision. Discuss both direction and	
15			magnitude of any potential bias.	
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20	Interpretation	<a href="#">#20</a>	Give a cautious overall interpretation considering objectives,	11
21			limitations, multiplicity of analyses, results from similar	
22			studies, and other relevant evidence.	
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28	Generalisability	<a href="#">#21</a>	Discuss the generalisability (external validity) of the study	12
29			results	
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33	<b>Other Information</b>			
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35				
36	Funding	<a href="#">#22</a>	Give the source of funding and the role of the funders for the	14
37			present study and, if applicable, for the original study on	
38			which the present article is based	
39				
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