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Published in:
European Journal of Pain

DOI (link to publication from Publisher):
[10.1002/ejp.1392](https://doi.org/10.1002/ejp.1392)

Publication date:
2019

Document Version
Accepted author manuscript, peer reviewed version

[Link to publication from Aalborg University](#)

Citation for published version (APA):

Simoni, A. H., Nikolajsen, L., Olesen, A. E., Christiansen, C. F., & Pedersen, A. B. (2019). Opioid use after hip fracture surgery: A Danish nationwide cohort study from 2005 to 2015. *European Journal of Pain*, 23(7), 1309-1317. <https://doi.org/10.1002/ejp.1392>

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Opioid use after hip fracture surgery: A Danish nationwide cohort study from 2005-2015

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Short running head: Opioid use after hip fracture surgery

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Category: Original article

Funding sources: None declared

Conflicts of interest: None declared

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/ejp.1392

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Significance:

Opioid use one year after hip fracture surgery is common, both in patients who were opioid users and non-users before the surgery. These significant findings point out the need for indication of benefits and risks of opioid use in the acute and long-term management of patients undergoing hip fracture surgery.

What's already known about this topic?

- Few small studies reported on the risk of opioid use six months after hip fracture surgery, but none of the studies considered late initiation of opioids months after surgery.

What does this study add?

- One year after hip fracture surgery, 28.2% of all patients used opioids
- Among patients without opioid use before surgery, 16.8% used opioids one year after surgery

Abstract:

Background: There is currently a knowledge gap regarding persistent opioid use after hip fracture surgery. Thus, opioid use within a year after hip fracture surgery in patients with/without opioid use before surgery was examined.

Methods: This population-based cohort study included all patients (aged ≥ 65) undergoing primary hip fracture surgery in Denmark (2005-2015) identified from the Danish Multidisciplinary Hip Fracture Database. Opioid use was assessed from The Danish National Health Service Prescription Database as redeemed prescriptions. The proportion of patients with ≥ 1 opioid prescription was computed within six-month before surgery and each of four three-month periods (quarters) after surgery, among patients alive first day in each period. Proportion differences (95%CI) were calculated for each quarter compared to before surgery. Proportions were calculated for users and non-users before surgery, including initiators after first quarter.

Results: This study included 69,456 patients. Proportion differences of opioid users were 35.0 (95%CI 34.5-35.5), 7.0 (95%CI 6.5-7.5), 2.9 (95%CI 2.4-3.4), and 1.4 percentage-points (95%CI 0.9-1.9) the four quarters after surgery compared to before. Among opioid non-users before surgery, 54.7% (95%CI 54.3-55.1) 21.8% (95%CI 21.4-22.2), 17.8% (95%CI 17.4-18.2), and 16.8% (95%CI 16.4-17.2) were opioid users in 1st-4th quarter after surgery. However, 8.5% (95%CI 8.2-8.7) of the non-users before surgery in 4th quarter initiated opioid use more than a quarter after surgery.

Conclusions: The proportion of opioid users increased after hip fracture surgery and was 1.4 percentage-points increased in fourth quarter compared to before. Of opioid non-users before surgery, 16.8% were opioid users fourth quarter after surgery.

1. Introduction

Opioid use has increased substantially worldwide during the past 20 years, in particular in United States and Canada, but also in many European countries including Denmark (Birke et al., 2016; Gomes et al., 2018; Wetzel et al., 2018). The highest consumption of opioids is found in individuals aged 65 years or older (Birke et al., 2016). This is unfortunate, as elderly are more prone to opioid-related adverse events which occur in 80% of patients on opioid therapy, and include dizziness, cognitive impairment, addiction, mortality, and increased fall and fracture risk, including hip fractures (Birke et al., 2017; Lindestrand et al., 2015; Teng et al., 2015).

Hip fracture is a leading cause of hospitalization and a major worldwide public health problem. Scandinavian countries, in particular Denmark, have the highest annual hip fracture incidence rate in the world (Kanis et al., 2012). Many patients present with comorbid disease and polypharmacy (Agustí et al., 2012; Driessen et al., 2016) which is a strong prognostic factors for 1-year mortality after hip fractures (Pedersen et al., 2017).

Few studies have investigated opioid use before and after hip fracture surgery and reported a slight increase in the proportion of patients who used opioids six months after hip fracture surgery compared to before surgery (Kragh et al., 2011; Lindestrand et al., 2015; Sjöberg et al., 2010). Additionally, one of the studies found, that 2.9% of patients who did not use opioids before surgery, used opioids six month after surgery (N=413) (Lindestrand et al., 2015). However, the study only considered opioid use at the time of admission and after exactly three and six months (Lindestrand et al., 2015). In addition, neither of the studies considered late initiation of opioids months after surgery and studies are limited by small numbers of patients. Thus, there remain doubts surrounding the actual proportion of patients who use persistent opioids related to hip fracture surgery. Thus, a complete clarification of opioid use within the year after hip fracture surgery, based on available nationwide population-based data is lacking.

The aim of this Danish nationwide cohort study was to examine opioid use within a year after hip fracture surgery in elderly patients with/without opioid use before surgery.

2. Methods

2.1 Settings

This population-based cohort study was conducted in Denmark, using prospectively collected data from medical and administrative registries, which cover all contacts to the health sector (Sørensen, 1997). Primary and secondary medical care of all Danish citizens are provided nationally by tax-supported healthcare. Data were linked on an individual-level by the ten-digit personal identification number (CPR number), which is used in all Danish public registries. (Frank, 2000) The present study was approved by the Danish Data Protection Agency (Central Denmark Region record number: 1-16-02-467-15).

2.2 Data sources

The Danish Civil Registration System was initiated in 1968 and contains information on date of birth, age, sex and continuously updated information on vital status (Schmidt et al., 2014).

The Danish Multidisciplinary Hip Fracture Database contains nationwide population-based data about all patients undergoing primary hip fracture surgery since 2003 (Kristensen et al., 2016). All orthopedic departments in Denmark provide data to the database and reporting is mandatory. Preoperative and perioperative data are collected prospectively upon hospital admission.

The Danish National Health Service Prescription Database maintains information on all prescriptions for dispensing by community pharmacies in Denmark since 2004 according to Anatomical Therapeutic Chemical classification system (ATC codes). The database includes name and brand of the drug, quantity, formulation, date of refill, codes identifying the prescribing physicians, and the dispensing pharmacy (Johannesdottir et al., 2012). Information on hospital dispensaries are not included in the database.

Furthermore, the Danish National Patient Registry provides comprehensive information on all somatic patients from Danish hospitals since 1977 and on all outpatient clinic and emergency room visits since 1995. Primary and secondary diagnoses are coded according to the International disease classification of diseases 10th edition (ICD-10). Data was retrieved on all somatic diagnosis before the hip fracture in order to measure comorbidity (Schmidt et al., 2015). Codes for diagnoses, procedures, and drugs are available in the supplemental.

2.3 Study Population

The study included all hospitalizations for patients aged 65 years or older sustaining fracture of femoral neck, per-, or sub-trochanter fracture and undergoing a surgical procedure for osteosynthesis or total/partial hip replacement at the same hospital admission in Denmark from 1st of January 2005 to 31th of December 2015 and registered in the Danish Multidisciplinary Hip Fracture Database (TableS1). For patients with more than one hip fracture during the study period, only the first admission was included in the study cohort.

2.4 Opioid prescriptions

Prescriptions for opioids were identified for the following periods; six month before surgery and one year after surgery divided into four three-month periods (quarters). Opioid prescriptions dispensed by community pharmacies within a seven-day period before and after hip fracture surgery were not included because the topic of interest was not perioperative opioid use and because data on in-hospital opioid use are not available in the Danish National Health Service Prescription Database.

The patients were identified as opioid users in each period if they redeemed one or more of any opioid prescriptions and as opioid non-users if they did not redeem any opioid prescriptions in the given period. The variables for redeemed prescriptions of opioids, including possible patterns of changing between being opioid user and opioid non-user in the different periods are illustrated in Fig. 1.

Patients were identified as late initiators of opioids, if they did not redeem opioids in one (or more) quarter after surgery, but redeemed opioids in a subsequent quarter. The following opioids were included in the analysis; morphine, hydromorphone, nicomorphine, oxycodone, oxycodone combined with naloxone, pethidine, fentanyl, ketobemidone, methadone, codeine, tramadol, tapentadol, and buprenorphine (TableS2).

2.5 Covariates

Information on age (in categories 65-74, 75-84 and ≥ 85 years), sex, fracture type (femoral neck and per-/subtrochanter fracture), and surgery type (osteosynthesis and total/partial hip replacement) were identified from the Danish Multidisciplinary Hip Fracture Database. For each patient, the Charlson Comorbidity Index (CCI) score (Charlson et al., 1987; Thygesen et al., 2011) was computed as a measure of comorbidity using primary and secondary diagnoses from any in- or outpatient contact ten years preceding the date of hip fracture surgery. CCI was calculated from the ICD-10 diagnoses based on the 19 diseases categories (TableS3). All patients were categorized according to one of the three levels of comorbidity defined as: a score of 0 (low), given to patients with no previous record of diseases included in the CCI; a score of 1-2 (medium); and a score of 3 or more (high).

2.6 Statistics

Median age and interquartile ranges were calculated for the study population. Characteristics of the study population (numbers and proportions) at the time of surgery were calculated overall and separately for opioid users and opioid non-users before surgery. The number and proportions of patients who redeemed prescriptions for the different types of opioids were calculated and presented.

Patients had to be alive on the first day of each of the four quarters after surgery in order to be included in the calculation of proportion of opioid users in the particular period. The differences between overall proportions of opioid users in each quarter compared to before surgery were

calculated with corresponding 95% confidence intervals (CI). Furthermore, the proportion of opioid users and late initiators of opioids after hip fracture surgery were illustrated graphically separately for opioid users and opioid non-users before surgery. A chi-square for test of trends of proportions of opioid users after surgery were performed both among opioid users and opioid non-users before surgery. The trends were considered significant if $P < 0.05$.

Statistical analyses were performed in STATA version 15 (StataCorp, TX, USA) and Microsoft Excel (2013, Microsoft, Seattle, Washington, USA).

3. Results

3.1 Patient characteristics

A total of 69,456 patients, aged 65 or more underwent primary hip fracture surgery in Denmark from the 1st of January 2005 to the 31st of December 2015. Median age for patients at the time of surgery was 83 years (interquartile range: 77-88). Characteristics of the patients are presented in Table 1. Women comprised 49,714 (71.6%) of the patients. Opioid users before surgery had a higher comorbidity level compared with opioid non-users. Among all patients, 18,109 (26.1%) died before the fourth quarter after surgery, this concerned 5,808 (31.2%) of the opioid users and 12,301 (24.2%) of the opioid non-users before surgery.

3.2 All patients undergoing hip fracture surgery

Before hip fracture surgery, 18,617 (26.8%) of all patients redeemed at least one opioid prescription and were classified as opioid users. After hip fracture surgery, 41,291 (61.8%), 19,288 (33.8%), 15,950 (29.7%) and 14,464 (28.2%) patients were opioid users in the first to fourth quarter, respectively. The proportions of patients who were opioid users in each period are illustrated in Fig. 2. The proportion of opioid users increased by 35.0 percentage-points (95% CI: 34.5-35.5) in the first quarter, 7.0 percentage-points (95% CI: 6.5-7.5) in the second quarter, 2.9 percentage-points (95% CI: 2.4-3.4) in the third quarter, and 1.4 percentage-points (95% CI: 0.9-1.9) in the fourth quarter after hip fracture surgery compared to the proportion of opioid users before surgery. The number and proportions of patients who redeemed prescriptions for the different types of opioids are presented in table 2. The prescription rates of the opioid types change to some extent during the year after surgery. The most frequently prescribed opioids before hip fracture surgery were tramadol, morphine, oxycodone and codeine whereas the most frequently prescribed opioid after surgery during each quarter were tramadol, oxycodone, morphine and fentanyl. Additionally, codeine and tramadol seemed less frequently prescribed in third and fourth quarter after hip fracture surgery than before surgery. Still, this did not point out whether the weak or strong opioids are mostly prescribed in the different periods.

3.3 Opioid non-users before surgery

The proportion of patients who were opioid non-users before hip fracture surgery but became opioid users in each quarter after the hip fracture surgery are presented in Fig. 3 a. Additionally, the proportion of patients who were opioid non-users before surgery, but initiated opioids after the first quarter is illustrated. Among patients who were opioid non-users before surgery, 26,791 (54.7%, 95% CI: 54.3-55.1), 9,243 (21.8%, 95% CI: 21.4-22.2), 7,110 (17.8%, 95% CI: 17.4-18.2) and 6,470 (16.8%, 95% CI: 16.4-17.2) became opioid users in the first to fourth quarter after hip fracture surgery, respectively. Further, 1,370 (3.2%, 95% CI: 3.1-3.4), 2,646 (6.6%, 95% CI: 6.4-6.9), and 3,897 (8.5%, 95% CI: 8.2-8.7) of patients who were opioid non-users before surgery were late initiators of opioids in the second to fourth quarter after surgery. In addition, 2,573 (8.3%, 95% CI: 7.9-8.8) of the opioid non-users before surgery redeemed opioid prescriptions in all four quarters the year after hip fracture surgery. The test of trends for proportions among opioid non-users before surgery indicated a decreasing proportion of opioid users the year after surgery ($P < 0.001$).

3.4 Opioid users before surgery

The proportions of patients who were opioid users before surgery as well as in each quarter after surgery are presented in Fig. 3 b. Additionally, the proportions of late initiators of opioids in second to fourth quarter after surgery among opioid users before surgery are illustrated. Of the opioid users before surgery, 14,500 (81.2%, 95% CI: 80.6-81.8), 10,045 (68.0%, 95% CI: 67.2-68.8), 8,840 (64.8%, 95% CI: 63.9-65.6) and 7,994 (62.4%, 95% CI: 61.6-63.2) were also considered opioid users in the four quarters after surgery, respectively. Further, 443 (3.0%, 95% CI: 2.7-3.3), 1,052 (7.7%, 95% CI: 7.3-8.1), and 1,297 (10.1%, 95% CI: 9.6-10.7) of the opioid users before surgery, re-initiated opioid use after being opioid non-users in at least one quarter, in second to fourth quarter after surgery, respectively. In addition, 6,697 (52.3%, 95% CI: 51.3-53.3) of the opioid users before surgery redeemed opioid prescriptions in all four quarters the year after hip fracture surgery. The test of trends for proportions among opioid users before surgery indicated a decreasing proportion of opioid users the year after surgery ($P < 0.001$).

4. Discussion

In this nationwide cohort study, 26.8% of patients undergoing hip fracture surgery were opioid users before surgery. In the first quarter after surgery, 61.8% were opioid users decreasing to 28.2% in the fourth quarter. Thus, the proportion of opioid users was 1.4 percentage-points (95%CI 0.9-1.9) higher one year after surgery compared to before surgery. Additionally, 16.8% (95%CI: 16.4-17.2) of patients who were opioid non-users before surgery became opioid users in the fourth quarter after surgery, and 8.3% (95%CI 7.9-8.8) were opioid users in all four quarters after surgery.

The short term increase in proportion of opioid users in first quarter after surgery compared to before surgery in the present study (35.0 percentage-points, 95%CI: 34.5-35.5 in first quarter) is similar to findings from previous studies. In a study by Lindestrand et al., (2015), 81% of 413 patients undergoing hip fracture surgery used opioids at hospital discharge compared to 24% prior to the surgery (Lindestrand et al., 2015). After other types of surgery, similar results within the first three months have been reported (Helmerhorst et al., 2014; Wunsch et al., 2016). These findings are important since opioid use immediate after hip fracture surgery has been established as a risk factor for long-term opioid use (Brummett et al., 2017). On the other hand, opioid therapy may be necessary in regard of pain control after surgery, and evidence support that relevant and adequate postoperative treatment, including treatment with opioids, limit the risk of persistent opioid use (Cassim et al., 2013; Colón-Emeric, 2012).

Only few previous studies examined opioid use six months after hip fracture surgery (Kragh et al., 2011; Lindestrand et al., 2015; Sjöberg et al., 2010). Identified proportions of opioid use before surgery ranged from 21-24% at admission and were slightly increased at six month after surgery ranging from 22-30% (Lindestrand et al., 2015; Sjöberg et al., 2010). The present study extended these finding by focusing on opioid use up to one year after surgery. The proportion of opioid users in the present study was still increased in fourth quarter after hip fracture surgery (1.4 percentage-points, 95% CI 0.9-1.9). The proportion of opioid users after the surgery were not expected to decrease below the level before surgery and thus, the increase in opioid users may seem minor. Nevertheless, any rise in long-term opioid users after hip fracture is concerning, since it is a risk factor for secondary fractures and there seems to be an interplay between long-term opioid use after surgery, high opioid doses, comorbidity level, and the high mortality in the hip fracture population (Lindestrand et al., 2015; Pedersen et al., 2017).

Results from the present study showed that the proportion of patients who were opioid non-users before surgery but became opioid users up to a year after hip fracture surgery (16.8%, 95% CI: 16.4-17.2 in fourth quarter after surgery) were considerably higher than the 2.9% identified six months after hip fracture surgery in a study by Lindestrand et al. (2015) on 413 patients (Lindestrand et al., 2015). In general, surgery has been found to induce chronic opioid use in about 3% of patients who

did not use opioids prior to the surgery (Clarke et al., 2014; Uhrbrand et al., 2018). However, even after taking late initiators of opioids into account, data from the present study suggest that exposure to opioids for postoperative pain treatment may lead to prolonged use. The higher identified proportion may be explained by the somewhat higher age in the present study and the dissimilar measure points for opioid use. Other studies define opioid use as recipients at exact time points (at admission and three and six month after the surgery), whereas the present study defined opioid users as patients redeeming any opioid prescriptions during four quarters after the surgery. Additionally, Lindestrand et al. (2015) stated that more than half of the patients were discharged with an opioid withdrawal plan (Lindestrand et al., 2015). Information about withdrawal plan was not available in the present cohort.

The proportion of opioid users before surgery who were opioid users in fourth quarter after the surgery (62.4%, 95% CI: 61.6-63.2), were considerably higher than indicated in previous studies concerning other types of surgery (Armaghani et al., 2014; Goesling et al., 2016; Inacio et al., 2016; Raebel et al., 2013). For instance, a study by Goesling et al. (2016), found that only 34.7% of 103 arthrosis patients who used opioids before total hip arthroplasty received opioids six month after the surgery. However, the arthrosis patients presents with a considerably lower median age and, opposite hip fractures, arthrosis may be associated with chronic pain, which may resolve after surgery (Goesling et al., 2016). Persistent opioid use after hip fracture surgery may not be unexpected as opioid use prior to a hip fracture is most likely related to other, clinical conditions, since hip fractures are acute events (Goesling et al., 2016; Lindestrand et al., 2015).

Treatment of postsurgical chronic pain could explain the long-term opioid use found in the present study. A study by Fletcher et al. (2015) found that nearly 12% of patients undergoing elective surgery (especially orthopedic surgery e.g. total hip arthroplasty) suffered from moderate to severe pain 12 month after surgery. (Fletcher et al., 2015) Additionally, this indicates that opioid use long-term after surgery could be appropriate due to a high request for pain relief. However, it is important to consider that elective hip arthroplasty is indicated by arthrosis, which may itself, opposite hip fractures, cause chronic joint pain both before and after surgery (Lindestrand et al., 2015). Furthermore, lack of sufficient opioid treatment is common, and cause poor pain management in many elderly patients. Opioids may be superior to non-opioid alternatives in the elderly as regards safety and effectiveness. Thus, continuous monitoring of pain level is appropriate to secure adequacy of the opioids. (Abdulla et al., 2013; Aret and Schug, 2005; Scholten et al., 2018)

4.1 Study strength and limitations

Study strengths include the large nationwide population-based design with access to universal healthcare system and individual patient-data-linkage. Prospective data collection and complete follow-up reduce selection bias. The positive predictive value of the hip fracture diagnosis is between 68% and 98%, depending on fracture and surgery-type (Baron et al., 1994; Hudson et al., 2013;

Kristensen et al., 2016; Schmidt et al., 2015) Since hip fracture is an acute conditions requiring hospitalization and surgery, the risk of bias due to lack of registration of patients in the Danish National Patient Registry is low. Additionally, dispensing according to the Danish National Health Service Prescription Database is considered a good measure of medication intake even in the presence of some misclassification (Schneeweiss and Avorn, 2005).

Potential limitations in the present study include lack of data on the intended clinical indication for each prescribed opioid treatment, which limited the ability to assess the appropriateness of the observed opioid use (Goesling et al., 2015, 2016). Patients' pain status and benefit from opioid use were not available in the present study. Furthermore, information on whether prescribed opioids were intended for regular use or as needed, and daily dose were not available (Ruan et al., 2017). Thus, it is unknown whether patients consuming lower doses were more likely to quit the opioids. Finally, information about other drugs were not available in our dataset, drugs which could potentially affect opioid use, such as antidepressants, non-steroid anti-inflammatory drugs or fall prophylactic drugs.

4.2 Clinical implications

A large population worldwide may start up a long-term opioid use annually after hip fracture surgery. Due to the high incidence of hip fracture, fragility, comorbidity, polypharmacy, and adverse events, preventive measures should be investigated and implemented to limit inappropriate and ineffective opioid use after hip fracture surgery.

5. Conclusion

Use of opioids the year after hip fracture surgery in elderly patients is common. One year after hip fracture surgery 28.2% of patients were opioid users, which is 1.4 percentage-points increased compared to before surgery. Among patients who were opioid non-users before surgery, 16.8% became opioid users one year after surgery, and 8.5% of the opioid non-users before surgery initiated opioid use more than a quarter after surgery and were opioids users in the fourth quarter after surgery.

Acknowledgements:

The authors wish to thank the biostatistician Bianka Darvalics for the help regarding data management.

Author contributions:

All authors discussed the results and commented on the manuscript.

References:

- Abdulla, A., Adams, N., Bone, M., Elliott, A.M., Gaffin, J., Jones, D., Knaggs, R., Martin, D., Sampson, L., Schofield, P., British Geriatric Society, P., Society, B.G. (2013). Guidance on the management of pain in older people. *Age Ageing* 42 Suppl 1, i1-57.
- Agustí, A., Pagès, E., Cuxart, A., Ballarín, E., Vidal, X., Teixidor, J., Tomás, J., Villar, M.M., Laporte, J.R. (2012). Exposure to medicines among patients admitted for hip fracture and the case-fatality rate at 1 year: A longitudinal study. *Eur J Clin Pharmacol* 68, 1525–1531.
- Armaghani, S.J., Lee, D.S., Bible, J.E., Archer, K.R., Shau, D.N., Kay, H., Zhang, C., McGirt, M.J., Devin, C.J. (2014). Preoperative opioid use and its association with perioperative opioid demand and postoperative opioid independence in patients undergoing spine surgery. *Spine (Phila Pa 1976)* 39, E1524–E1530.
- Auret, K., Schug, S.A. (2005). Underutilisation of opioids in elderly patients with chronic pain approaches to correcting the problem. *Drugs and Aging* 22, 641–654.
- Baron, J.A., Lu-yao, G., Barrett, J., McLerran, D., Fisher, E.S., Epidemiology, S., Sep, N., Fisher, S. (1994). Internal Validation of Medicare Claims Data. 5, 541–544.
- Birke, H., Ekholm, O., Sjøgren, P., Kurita, G.P., Højsted, J. (2017). Long-term opioid therapy in Denmark: A disappointing journey. *Eur J Pain (United Kingdom)* 21, 1516–1527.
- Birke, H., Kurita, G.P., Sjøgren, P., Højsted, J., Simonsen, M.K., Juel, K., Ekholm, O., Ekholm, O. (2016). Chronic non-cancer pain and the epidemic prescription of opioids in the Danish population: trends from 2000 to 2013. *Acta Anaesthesiol Scand* 60, 623–633.
- Brummett, C.M., Waljee, J.F., Goesling, J., Moser, S., Lin, P., Englesbe, M.J., Bohnert, A.S.B., Kheterpal, S., Nallamothu, B.K. (2017). New Persistent Opioid Use After Minor and Major Surgical Procedures in US Adults. *JAMA Surg* 152, e170504.
- Cassim, B., Lipschitz, S., Paruk, F., Tipping, B. (2013). Recommendations for the acute and long-term medical management of low-trauma hip fractures. *J Endocrinol Metab Diabetes South Africa* 18, 21–32.
- Charlson, M.E., Pompei, P., Ales, K.L., MacKenzie, C.R. (1987). A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *J Chronic Dis* 40, 373–383.
- Clarke, H., Soneji, N., Ko, D.T., Yun, L., Wijeyesundera, D.N. (2014). Rates and risk factors for prolonged opioid use after major surgery: population based cohort study. *Bmj* 348, g1251–g1251.
- Colón-Emeric, C.S. (2012). Postoperative management of hip fractures: interventions associated with

improved outcomes. *Bonekey Rep* 1.

Driessen, J.H.M., Hansen, L., Eriksen, S.A., van Onzenoort, H.A.W., Henry, R.M.A., van den Bergh, J., Abrahamsen, B., Vestergaard, P., de Vries, F. (2016). The epidemiology of fractures in Denmark in 2011. *Osteoporos Int* 27, 2017–2025.

Fletcher, D., Stamer, U.M., Pogatzki-Zahn, E., Zaslansky, R., Tanase, N.V., Perruchoud, C., Kranke, P., Komann, M., Lehman, T., Lavand homme, P., Vercauteren, M., Meissner, W., Iohom, G., Cinnella, G., Aurilio, C., Belii, A., Filipescu, D., Rehberg-Klug, B., Decostered, I., Suter, M.R., Blumenthal, S., Puig, M., Garcia-Filoso, A., Brandner, B., Varvinskiy, A.M., Lisnyy, I., Kuchyn, I. (2015). Chronic postsurgical pain in Europe: An observational study. *Eur J Anaesthesiol* 32, 725–734.

Frank, L. (2000). Epidemiology: When an Entire Country Is a Cohort. *Science* (80-) 287, 2398–2399.

Goesling, J., Henry, M.J., Moser, S.E., Rastogi, M., Hassett, A.L., Clauw, D.J., Brummett, C.M. (2015). Symptoms of Depression Are Associated with Opioid Use Regardless of Pain Severity and Physical Functioning among Treatment-Seeking Patients with Chronic Pain. *J Pain* 16, 844–851.

Goesling, J., Moser, S.E., Zaidi, B., Hassett, A.L., Hilliard, P., Hallstrom, B., Clauw, D., Brummett, C.M. (2016). Trends and predictors of opioid use after total knee and total hip arthroplasty. *Pain* 157, 1259–1265.

Gomes, T., Tadrous, M., Mamdani, M.M., Paterson, J.M., Juurlink, D.N. (2018). The Burden of Opioid-Related Mortality in the United States. *JAMA Netw Open* 1, e180217.

Helmerhorst, G.T.T., Vranceanu, A.-M., Vrahas, M., Smith, M., Ring, D. (2014). Risk Factors for Continued Opioid Use One to Two Months After Surgery for Musculoskeletal Trauma. *J Bone Jt Surg* 96, 495–499.

Hudson, M., Avina-Zubieta, A., Lacaille, D., Bernatsky, S., Lix, L., Jean, S. (2013). The validity of administrative data to identify hip fractures is high - A systematic review. *J Clin Epidemiol* 66, 278–285.

Inacio, M.C.S., Hansen, C., Pratt, N.L., Graves, S.E., Roughead, E.E. (2016). Risk factors for persistent and new chronic opioid use in patients undergoing total hip arthroplasty: a retrospective cohort study. *BMJ Open* 6, e010664.

Johannesdottir, S.A., Horváth-Puhó, E., Ehrenstein, V., Schmidt, M., Pedersen, L., Sørensen, H.T. (2012). Existing data sources for clinical epidemiology: The Danish National database of reimbursed prescriptions. *Clin Epidemiol* 4, 303–313.

Kanis, J.A., Odén, A., McCloskey, E. V, Johansson, H., Wahl, D.A., Cooper, C., IOF Working Group on Epidemiology and Quality of Life, C. (2012). A systematic review of hip fracture incidence and

probability of fracture worldwide. *Osteoporos Int* 23, 2239–2256.

Kragh, A., Elmståhl, S., Atroshi, I., Atroshi, I. (2011). Older adults' medication use 6 months before and after hip fracture: a population-based cohort study. *J Am Geriatr Soc* 59, 863–868.

Kristensen, P.K., Thillemann, T.M., Søballe, K., Johnsen, S.P. (2016). Can improved quality of care explain the success of orthogeriatric units? A population-based cohort study. *Age Ageing* 45, 66–71.

Lindestrand, A.G., Christiansen, M.L.S., Jantzen, C., Van Der Mark, S., Andersen, S.E. (2015). Opioids in hip fracture patients: An analysis of mortality and post hospital opioid use. *Injury* 46, 1341–1345.

Pedersen, A.B., Ehrenstein, V., Szépligeti, S., Lunde, A., Lagerros, Y.T., Westerlund, A., Tell, G.S., Sørensen, H.T. (2017). 35-Year Trends in First-Time Hospitalization for Hip Fracture, One Year Mortality, and the Prognostic Impact of Comorbidity. *Epidemiology* 1.

Raebel, M.A., Newcomer, S.R., Reifler, L.M., Boudreau, D., Elliott, T.E., DeBar, L., Ahmed, A., Pawloski, P.A., Fisher, D., Donahoo, W.T., Bayliss, E.A. (2013). Chronic use of opioid medications before and after bariatric surgery. *JAMA - J Am Med Assoc* 310, 1369–1376.

Ruan, X., Wu, H., Kaye, A.D. (2017). Persistent Opioid Use After Major Surgery. *JAMA Surg* 152, 411.

Schmidt, M., Pedersen, L., Sørensen, H.T. (2014). The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol* 29, 541–549.

Schmidt, M., Schmidt, S.A.J., Sandegaard, J.L., Ehrenstein, V., Pedersen, L., Sørensen, H.T. (2015). The Danish National patient registry: A review of content, data quality, and research potential. *Clin Epidemiol* 7, 449–490.

Schneeweiss, S., Avorn, J. (2005). A review of uses of health care utilization databases for epidemiologic research on therapeutics. *J Clin Epidemiol* 58, 323–337.

Scholten, W., Christensen, A.-E., Olesen, A.E., Drewes, A.M. (2018). Quantifying the Adequacy of Opioid Analgesic Consumption Globally: An Updated Method and Early Findings. *Am J Public Health*.

Sjöberg, C., Bladh, L., Klintberg, L., Mellström, D., Ohlsson, C., Wallerstedt, S.M. (2010). Treatment with fall-risk-increasing and fracture-preventing drugs before and after a hip fracture: An observational study. *Drugs and Aging* 27, 653–661.

Sørensen, H.T. (1997). Regional administrative health registries as a resource in clinical epidemiology. *Int J Risk Saf Med* 10, 1–22.

Teng, Z., Zhu, Y., Wu, F., Zhu, Y., Zhang, X., Zhang, C., Wang, S., Zhang, L., Zhang, L. (2015). Opioids contribute to fracture risk: a meta-analysis of 8 cohort studies. *PLoS One* 10, e0128232.

Thygesen, S.K., Christiansen, C.F., Christensen, S., Lash, T.L., Sørensen, H.T. (2011). The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. *BMC Med Res Methodol* 11, 83.

Uhrbrand, P., Simoni, A.H., Olesen, A.E., Pedersen, A.B., Christiansen, C.F., Nikolajsen, L. (2018). Morfinafhængighed som komplikation i forbindelse med kirurgi. *Ugeskr Læger* V01180083, 2–5.

Wetzel, M., Hockenberry, J., Raval, M. (2018). Interventions for Postsurgical Opioid Prescribing: A Systematic Review. *JAMA Surg*.

Wunsch, H., Wijeyesundera, D.N., Passarella, M.A., Neuman, M.D. (2016). Opioid Prescribing After Low-Risk Surgical Procedures in the United States, 2004-2012. *Jama* 315, 1654–1657.

Figure legends:

Fig. 1: Flowchart for opioid users before and after hip fracture surgery. The flowchart illustrates data on redeemed opioid prescriptions. For each period, patients were categorized as opioid users (+) if they redeemed at least one opioid prescription and as opioid non-users (÷) user if they did not redeem an opioid prescription. The arrows illustrate the possible patterns of switching between status of opioid user and non-user in the periods. The red arrows illustrate the definition of late initiation of opioids after hip fracture surgery. Redeemed prescriptions seven days before and after surgery (the grey area) are not included.

Fig. 2: Opioid users before and after hip fracture surgery. Illustration of the proportion of patients (alive at day one of the period), who were opioid users before surgery and each quarter the first year after surgery. Each dot illustrates the percentage of living patients (y-axis) who were opioid users in the certain period (x-axis). The vertical solid line illustrates the date of hip fracture surgery, and the dashed lines illustrate 7 days before and after surgery, which were not included in the prescription analysis. (Q1; n= 66,836, Q2; n=57,113, Q3; n=53,678, Q4; n=51,347). Q: Quarter.

Fig. 3: Opioid users after hip fracture surgery among previous opioid non-users and users. Opioid users each quarter one year after hip fracture surgery among patients who were opioid non-users (a; n=50,839) and opioid users (b; n=18,617) before surgery. The total bars illustrate all the patients in the group who were opioid users in each quarter after surgery. The red bars illustrate the percentage of patients who initiated opioids later than first quarter after hip fracture surgery. Q: Quarter.

Table legends:

Table 1: Characteristics of the hip fracture cohort according to opioid-status before surgery, Denmark, 2005-2015. N: Number of patients in the group, CCI: Charlson Comorbidity Index.

Table 2: The distribution of different types of opioids at the different periods. The number and proportion of patients redeeming opioids of the different types 6 month before surgery and the four quarters after surgery. Some patients redeem prescriptions for more than one type of opioid at each stage, thus, the high proportions. Q: Quarter

Table 1: Characteristics of the hip fracture cohort according to opioid-status before surgery, Denmark, 2005 – 2015. N: Number of patients in the group, CCI: Charlson Comorbidity Index.

| | All patients (n=69,456) | Opioid-non-users before surgery (n=50,839) | Opioid-users before surgery (n=18,617) |
|---|----------------------------|--|--|
| Age: | | | |
| 65-74 | 13,246 (19.1%) | 9,737 (19.2%) | 3,509 (18.9%) |
| 75-84 | 26,817 (38.6%) | 19,452 (38.3%) | 7,365 (39.6%) |
| ≥85 | 29,393 (42.3%) | 21,650 (42.6%) | 7,743 (41.6%) |
| Sex: | | | |
| Male | 19,742 (28.4%) | 15,229 (30.0%) | 4,513 (24.2%) |
| Female | 49,714 (71.6%) | 35,610 (70.0%) | 14,104 (75.8%) |
| Fracture type: | | | |
| Femoral neck | 36,603 (52.7%) | 27,119 (53.3%) | 9,484 (50.9%) |
| Per-/sub-trochanter | 32,853 (47.3%) | 23,720 (46.7%) | 9,133 (49.6%) |
| Surgery type: | | | |
| Osteosynthesis | 48,138 (69.3%) | 35,081 (69.0%) | 13,057 (70.1%) |
| Total/partial hip replacement | 21,318 (30.7%) | 15,758 (31.0%) | 5,560 (29.9%) |
| CCI: | | | |
| Low (0) | 28,112 (40.5%) | 22,716 (44.7%) | 5,396 (29.0%) |
| Medium (1-2) | 28,067 (40.4%) | 20,008 (39.4%) | 8,059 (43.3%) |
| High (≥3) | 13,277 (19.1%) | 8,115 (16.0%) | 5,162 (27.7%) |
| Status in 4th quarter | | | |
| Alive | 51,347 (73.9%) | 38,538 (75.8%) | 12,809 (68.8%) |
| Dead | 18,109 (26.1%) | 12,301 (24.2%) | 5,808 (31.2%) |

Table 2: The distribution of different types of opioids in the different periods. The number and proportion of patients redeeming opioids of the different types 6 month before surgery and the four quarters after surgery. Some patients redeem prescriptions for more than one type of opioid at each stage, thus, the high proportions. *Q*: Quarter

| Opioids | Before surgery | 1 <i>Q</i> | 2 <i>Q</i> | 3 <i>Q</i> | 4 <i>Q</i> |
|-------------------------------------|----------------|----------------|---------------|---------------|---------------|
| Opioid agonists: | | | | | |
| Morphine | 3,397 (4.2%) | 11,021 (14.2%) | 3,884 (5.8%) | 3,005 (4.8%) | 2,638 (4.5%) |
| Hydromorphone | 12 (0.01%) | 6 (0.01%) | 9 (0.01%) | 5 (0.01%) | 5 (0.01%) |
| Nicomorphine | 100 (0.1%) | 382 (0.5%) | 161 (0.2%) | 99 (0.2%) | 80 (0.1%) |
| Oxycodone | 3,091 (3.8%) | 16,278 (20.9%) | 5,473 (8.2%) | 4,127 (6.6%) | 3,516 (6.0%) |
| Oxycodone & naloxone | 14 (0.02%) | 11 (0.01%) | 4 (0.01%) | 6 (0.01%) | 8 (0.01%) |
| Pethidine | 104 (0.1%) | 272 (0.4%) | 150 (0.2%) | 123 (0.2%) | 88 (0.2%) |
| Fentanyl | 2,316 (2.9%) | 4,110 (5.3%) | 2,825 (4.2%) | 2,306 (3.7%) | 2,113 (3.6%) |
| Ketobemidone | 993 (1.2%) | 1,444 (1.9%) | 761 (1.1%) | 582 (0.9%) | 505 (0.9%) |
| Codeine | 2,885 (3.6%) | 2,360 (3.0%) | 1,509 (2.3%) | 1,341 (2.1%) | 1,229 (2.1%) |
| Methadone | 246 (0.3%) | 243 (0.3%) | 178 (0.3%) | 147 (0.2%) | 137 (0.2%) |
| Dual action opioid agonists: | | | | | |
| Tramadol | 12,187 (15.1%) | 21,838 (28.1%) | 9,819 (14.7%) | 7,949 (12.7%) | 7,172 (12.2%) |
| Tapentadol | 20 (0.02%) | 27 (0.03%) | 19 (0.03%) | 27 (0.04%) | 24 (0.04%) |
| Partial opioid agonists: | | | | | |
| Buprenorphine | 2,352 (2.9%) | 3,637 (4.7%) | 2,522 (3.8%) | 2,165 (3.5%) | 1,928 (3.3%) |





