Title: Opioid use prior to total knee replacement: comparative analysis of trends in England and Sweden

Running Headline: *Opioid use trend before TKR in Sweden and England*

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ABSTRACT

Objectives

To describe and compare trends in the frequency of opioid prescribing/dispensing in English and Swedish patients with osteoarthritis prior to total knee replacement (TKR).

Methods

49,043 patients from an English national database (Clinical Practice Research Datalink) and 5,955 patients from the Swedish *Skåne Healthcare register* undergoing TKR between 2015-2019 were included, alongside 1:1 age-, sex-, and practice (residential area) matched controls. Annual prevalence and prevalence rates ratio (PRR) of opioid prescribing/dispensing (any, by strength) in the 10 years prior to TKR (or matched index date for controls) were estimated using Poisson regression.

Results

In England and Sweden, the prevalence of patients with osteoarthritis receiving any opioid prior to TKR increased towards the date of surgery from 24% to 44% in England and from 16% to 33% in Sweden. Prescribing in controls was stable, resulting in an increasing PRR (1.6 to 2.7) between 10-1 years prior to index date in both countries. No relevant cohort or period effect was observed in either country. Prevalence of opioid prescribing was higher in English cases and controls; weaker opioids were more commonly prescribed in England, stronger opioids in Sweden.

Conclusions

Temporal prevalence patterns of opioid prescribing between cases and controls are similar in England and Sweden. Opioids are still commonly used in TKR cases in both countries highlighting the lack of valid alternatives for OA pain management.

Key words: total knee replacement, opioid, electronic health care record

INTRODUCTION

Knee replacement is the definitive intervention for end-stage knee osteoarthritis (OA) [1] but more needs to be done to optimise conservative care earlier in the course of the disease. The 8-year interval between median age at first recorded diagnosis of OA (62 years [2]) and median age of primary knee replacement (70 years [3]) implies many years of non-surgical symptom management, predominantly in community and primary care settings. International clinical practice guidelines recommend a range of pharmacological and non-pharmacological options [4 5 6] but there is consistent evidence of both the underuse of 'high value care' and overuse of 'low value care' [7]. The overuse of opioid analgesia for OA pain control has been of increasing concern in recent years [8], given evidence from 22 placebo-controlled trials showing a lack of relative effectiveness [9], an unfavourable efficacy/safety profile amid wider concerns of an 'opioid crisis' [10]. While several recent guidelines now recommend against the routine use of oral opioids [11 4 12 13], limited use in certain circumstances (e.g. in patients with contraindications to NSAIDs, where other therapies have been ineffective, or with a lack of available surgical options) is still recognised [12].

Previous studies have reported high use of opioids prior to TKR, but despite the long duration of symptoms prior to joint replacement, these studies were limited to study periods of a maximum of 24 months [14 15 16 17]. One longer-term study reported high numbers of opioid use between the time of OA diagnosis until TKR, but temporal trends in opioid use were not presented [18]. Investigating opioid utilisation patterns several years preceding TKR, in addition to only a few months prior to surgery, would provide unique information on possible differences in opioid utilization patterns between OA patients preceding TKR and possible differences in opioid utilization patterns between OA patients preceding TKR and the population, as well as information on possible fluctuations/increases in opioid use preceding surgery that further would reflect on the need of additional or other treatment alternatives for this patient group.

International comparative studies offer the opportunity to identify similarities and differences in opioid use between different healthcare systems and populations. Whilst condition-specific comparisons between England and Sweden are scarce, previous literature suggests higher rates of opioid prescribing in England than in Sweden [19, 20], although it remains unclear whether this trend is also seen in patients that undergo knee replacement.

In this multi-national study, we aimed to investigate the patterns of prevalence for opioid prescriptions/dispensations prior to primary TKR, and compare the prevalence patterns between England and Sweden. Furthermore, this study aimed to investigate whether the prevalence patterns differ among OA patients with subsequent TKR and the general population.

METHODS

Data setting

The study was set within England and the Skåne region in Sweden - two countries with different healthcare and coding systems, but similarities in the prevalence, and approach to management, of OA. For instance, as of 2010, annual prevalence figures for OA within primary care were comparable [21], and the Organisation for Economic Co-operation and Development (OECD) suggests similar rates of knee replacement in 2017 (Sweden 132, UK 145 per 100,000 population) (**Supplemental Table 1**).

In England, anonymized data were extracted from the Clinical Practice Research Datalink

In England, anonymized data were extracted from the Clinical Practice Research Datalink (CPRD) Aurum database. At the time of this study (December 2019 release), CPRD Aurum provided data for 23.1 million patients (of which 2.5 million were active), collected from 883 general practices in England using the EMIS practice software system [22]. Scientific and ethical approval was received from the CPRD Independent Scientific Advisory Committee (ISAC Protocol 20_000099).

In Sweden, Skåne is the southernmost region with 1.3 million inhabitants and all healthcare contacts are registered in regional databases. The Skåne Healthcare Register (SHR) holds details for primary, secondary and inpatient care provided in the region. For each visit to a physician, the date, personal identification number, details of the clinic or primary care unit, ICD-10 diagnostic codes, and KVÅ care measure codes are registered. For the present study we retrieved data from 2000 to 2019. The use of Swedish register data was approved by the Lund University Ethics Committee (Dnr 2011-432 with amendment Dnr 2014_276, and Dnr 2018_233.

Case definition

An eligible case met the following criteria: 1) aged 45 years and over; 2) having a recorded primary knee replacement between 1 January 2015 (1 July 2015 in Sweden) and 31 December 2019; 3) registration in the respective electronic health record (EHR) database for a minimum of 10 years prior to the index TKR (a look back period permitting the capture of exposure and covariate information, and the exclusion of patients with previous/prevalent TKR); 4) not having any knee replacement within the 10-year look back period, and thus the index TKR more likely represents a primary TKR.

Primary TKR was identified within CPRD using the Medcodes coded using a combination of SNOMED CT (UK edition) and Read codes as presented in www.keele.ac.uk/mrr. In the

SNOMED CT (UK edition) and Read codes as presented in www.keele.ac.uk/mrr. In the English data, TKR cases were not restricted to those with an OA diagnostic code. 97.4% of primary TKRs are performed for knee OA: a proportion that has changed little since National

Joint Registry data collection began in 2003 [23]. However, due to under-recording in the primary care record, as few as 43.7% of TKR patients may have a diagnosis of OA recorded in the prior 10 years [24]. Primary TKR for knee OA in Sweden was identified using diagnostic ICD codes (M17) and knee reconstructive KVÅ codes (NGB*) registered at the same occasion within SHR.

Population controls

For each case, one population control was randomly selected, matched on 5-year age-stratification (45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, 80-84, ≥85 years), sex, and general practice (or county in the Swedish data). We selected controls using risk set sampling to ensure controls had the equivalent length of risk-free time to outcome compared to their matched cases [25]. Controls were assigned an index date (identical to the corresponding cases in the Swedish, and the English data; the last day of the index year, as the sampling process is restricted by the large size of the denominator population). In England, the eligible controls should have been registered at the same general practice as their matched controls for a minimum of 10 years before the index date. In Sweden, the eligible controls should have the same residential area as their matched controls by the index date.

Exposure definition

The Swedish Prescribed Drug Register contains information on all drugs prescribed and dispensed at a pharmacy, and includes all healthcare institutions in the country. Data are available from July 2005 to December 2019. In England, CPRD Aurum contains data on all medications prescribed, but not necessarily dispensed, within primary care.

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BNF codes in England and ATC codes in Sweden were used to identify all relevant opioid prescriptions/dispensations. Opioids prescribed/dispensed as single preparations or as combinations were stratified by opioid strength (weak and strong) as per prior literature [26 27 28 29].

The ten years prior to a patient's index date were stratified in to yearly bands (0-12 months, 13-24 months, ..., 109-120 months). Patients with at least one recorded opioid prescription in these pre-specified time windows were defined as exposed individuals.

Patient characteristics / covariates

Beyond the matched variables (age, gender, and practice/county), a patient's index year, presence of common comorbidities (cardiovascular diseases, cancer, and diabetes), as well as lower back pain, and other musculoskeletal disorders (all musculoskeletal disorders except OA in the English data and knee OA in the Swedish data) were presented to allow comparisons between cases and controls. Comorbidities were defined by developed code lists (**Supplemental Table 2**) and recorded at any time within the 10 years prior to the index dates.

Statistical analysis

Contingency tables were generated for English and Swedish populations to describe the frequency of cases and controls by sex, age-strata, and index year. Prevalence with 95% confidence intervals (CI) of having at least one recorded opioid prescription in each specific time-window among cases and controls was estimated by overall, sex, age-strata, and index year using Poisson regression models. Period effects on prevalence in cases and controls were visualised by presenting the prevalence in each time window for each index year cohort. The prevalence rate ratio (PRR) between cases and controls (reference group: prevalence in control group) was estimated by overall, sex, age-strata, and index year using prevalence in control group) was estimated by overall, sex, age strata, and index year using Poisson regression models.

Secondary analysis

There were several secondary analyses both for prevalence and PRR. First, prevalence and PRR for opioids prescribed within 0-3, 4-6, 7-9, and 10-12 months prior to TKR were estimated to investigate the short-term opioid prescription prior to TKR. Second, prevalence and PRR for opioid prescription stratified by opioid strength [30] were estimated.

RESULTS

In this study, 47,045 and 5,955 patients with TKR performed between 2015-2019, in England and Sweden respectively, were included alongside their 1:1 matched controls. (**Table-1)**. The age and gender distribution was similar in Sweden and England. In both countries, the annual number of new TKR cases remained stable throughout the study period, and the cases were more likely to have non-OA musculoskeletal conditions, and back pain, compared to controls. In Sweden, the prevalence of cardiovascular diseases and diabetes were higher among the cases, whilst the prevalence of cancer was similar between cases and controls. In England, the prevalence of cancer and cardiovascular diseases were slightly higher in the control group, and the prevalence of diabetes was similar between cases and controls.

General patterns of opioid prescribing/dispensing (overall and stratified by strength) were similar between cases and controls in England and Sweden (**Figure-1**). Among the cases, the prevalence of opioid prescribing increased gradually from between 10 to 3 years prior to TKR, and sharply rose in the 2 years preceding surgery, as the prevalence was 23.28 (95% confidence interval: 22.84-23.71)%, 31.01 (30.51-31.51)%, and 43.24 (42.65-43.83)% in England, 16.42 (15.43-17.49)%, 22.23 (21.07-23.46)% and 32.86 (31.44-34.35)% in Sweden, at 10-, 3-, and 1-year prior to TKR, respectively. In contrast, the prevalence of opioid prescriptions/dispensations in controls remained stable across all time-windows opioid prescriptions/dispensations in controls remained stable across all time windows.

Similar patterns were observed following stratification by sex although in England and Sweden, female cases and controls had a consistently higher prevalence of opioid prescribing compared to their male counterparts.

Similar prevalence patterns for case and control groups in England and Sweden were also observed by age-strata for having any (**Supplemental Figure 1**), strong (**Supplemental Figure 2**) and weak opioid (**Supplemental Figure 3**); and by index year for having any (**Supplemental Figure 4**), strong (**Supplemental Figure 5**) and weak opioid (**Supplemental Figure 6**).

There was no strong evidence of a period effect between 2015-2019 (**Figure-2)**.

The prevalence of having any, strong and weak opioid, was also observed within 12 months prior to index date by 3-months intervals (**Supplemental Figure 7**). In both countries the prevalence of receiving any opioid among cases increased in the 12 to 4 months, and remained stable in the 3 to 1 months prior to index date, whilst in controls, the prevalence remained stable throughout the 12 months. In England, the proportion of patients receiving a strong opioid remained stable among both cases and controls in the 12 months preceding index date; the increased prevalence of opioid prescribing in cases compared to controls was largely driven by the prescription of weak opioids. In contrast, cases in Sweden were more likely to receive a strong opioid compared to controls, whilst the trends of receiving weak opioids were similar between the groups.

PRR for having any, strong or weak opioid within 10 to 1 year prior to index date between the case and control group is presented in **Figure 3**. Overall, the PRR for having received any opioid increased from 1.60 (1.56-1.65) to 2.72 (2.65-2.79), and from 1.60 (1.40-1.70) to 2.60 (2.40-2.80), between 10 and 1 year before index date, in England and in Sweden, [illegible] ([illegible]), between 10 and 1 year before index date, in England and in Sweden, respectively. The PRR for having received a strong opioid increased from 1.62 (1.32-1.97) to 2.26 (2.06-2.47) in England, whereas it increased from 1.60 (1.40-1.80) to 2.60 (2.40-

2.80) in Sweden. The PRR of having received a weak opioid increased from 1.55 (1.50-1.60) to 2.71 (2.64-2.78) in England and from 1.60 (1.40-1.80) to 2.90 (2.60-3.30) in Sweden.

Similar PRR patterns for having any, strong or weak opioid in England and Sweden were also observed by sex (**Supplemental Figure 8**), age-strata (**Supplemental Figure 9**) and index year (**Supplemental Figure 10**).

DISCUSSION

Our international comparative study set in two high income countries suggests that the likelihood of being prescribed an opioid rises substantially in the 12-24 months prior to receiving a total knee replacement. This trajectory is seen in men and women of all ages over 45 years undergoing TKR in England and in Sweden each year from 2015-2019. The absolute prevalence of any opioid prescription was higher in England than in Sweden (43% vs 33% respectively for any opioid prescription in the 12 months prior to TKR), but the use of strong opioids was greater in Sweden than in England (23% vs 3%). Despite these absolute differences, the risk of opioid prescription among TKR cases relative to matched population controls was remarkably consistent between the two countries (2.4 -to 2.8-fold higher). Differences between countries in the type and rate of opioid prescribing for patients with osteoarthritis are therefore driven, in part, by differences in underlying national 'norms' of opioid access and prescribing. For example, in Sweden, codeine is the only available weak opioid, is listed among "drugs of risk for the elderly", and recommended not to be given priority over more potent opioids like oxycodone and morphine.

Study findings stratified by age-group, sex and index years were similar to the overall findings, which might reflect that opioids are commonly prescribed in the case population findings, which might reflect that opioids are commonly prescribed in the case population (i.e. those with chronic pain) irrespective age, sex and period effect.

The pattern of findings and the absence of a similar trajectory of opioid prescription among population controls in each country argues against period effects in the underlying population rates. The time interval is too long to be explained by short-term, peri-operative use and secondary analyses confirmed this. Due to the structure of data within EHR, opioid prescriptions cannot be definitively attributed to use for OA knee pain control. However, there were no major differences in cancer prevalence between cases and controls in each country, suggesting that use for comorbid cancer pain is unlikely to explain our findings. The presence of other non-musculoskeletal conditions was higher in cases than in controls but it is hard to imagine why the use of opioids for these would increase prior to TKR. In the English dataset we were unable to restrict TKR cases to those being performed for knee OA, but such misclassification would affect less than 3% cases. Instead, based on the pattern of findings and prior evidence of similar worsening trajectories in knee pain intensity and cartilage loss prior to TKR [31] [32] [33] we interpret this general phenomenon of increasing use of opioid 12-24 months prior to TKR as the resort to opioids for OA pain control in a substantial minority of patients who may be experiencing disease and symptom progression. Beyond the 12-24 months prior to TKR, the higher rates of opioid use in cases may reflect that TKR was deemed appropriate earlier in the process for some patients, but due to waiting times, and willingness of patients (i.e. psychological disorders), TKR was delayed and alternative symptom management without opioid was very limited or underutilised. Given the lack of efficacy and safety concerns over opioid use for OA pain, our findings question whether this constitutes evidence of ingrained low-value care. The scale of use we found is greater than might be expected from limited, ‘last resort’ use of short-to-medium-term, low-dose opioid therapy in carefully selected patients in monitored settings [34]. However, we did observe a modest reduction between 2015 and 2019 in the proportion of TKR patients receiving an opioid prescription. Furthermore, information on dose, duration, (contra)indications, and monitoring arrangements would add useful detail. These were beyond the scope of the current study; some cannot be ascertained through routinely beyond the scope of the current study. Some cannot be ascertained through routinely collected EHR data. In addition, the availability of effective and acceptable physical, behavioural, and psychological treatment alternatives is likely to be a critical contextual driver of low-value opioid prescription, but data on these are still seldom routinely collected and integrated into health systems. Finally, the acceptable proportion of OA patients prescribed opioids will be greater than zero but we cannot specify an optimal level given the absence of studies estimating the proportion of patients that clearly meet circumstances that warrant opioid prescription.

Our findings reinforce the need for better pre-operative opioid stewardship, and an urgent need to improve the provision and uptake of effective alternatives to opioids, particularly targeted at patients, professionals and points in the OA care pathway where opioids are most often resorted to (e.g. when referral for consideration of TKR is made). The duration of opioid use may be closely related to waiting times for elective orthopaedic surgery. Initiatives to reduce surgical waiting times may reduce cumulative exposure to opioids. Conversely, longer waiting times may increase exposure, a current concern in many countries given disruption to elective surgery due to COVID-19. Since pre-operative opioid use is strongly associated with post-operative use [35 36], our findings also imply the need for proactive de-prescribing of opioids after TKR.

There are some limitations in the current study. First, in the English dataset we were unable to restrict TKR cases to those being performed for knee OA, but such misclassification would affect less than 3% cases. Second, our findings on opioid prescription patterns cannot be interpreted purely as a proxy for average trajectories in pain severity, as opioid prescription is expected to be associated with pain severity but with considerable discordance. Notwithstanding these limitations and caveats, based on the pattern of findings and prior evidence of similar worsening trajectories in knee pain intensity and cartilage loss prior to TKR [31 32 33], we interpret this general phenomenon of increasing use of opioid 12-24 months prior to TKR as the resort to opioids for OA pain control in a minority of patients who months prior to TKA as the resort to opioids for OA pain control in a minority of patients who may be experiencing disease and symptom progression. Third, limited by the study design, other individual-level confounders (such as surgery, injury or psychological disorders) were not further investigated in the study as the study was aimed to describe the population-level prevalence of opioid prescription in the representative case and control population over the time period, compounded by the reasons for opioid prescription not being routinely recorded in EHR data. Fourth, due to differences in recording of opioid prescriptions between the countries, the estimated opioid use in Sweden includes opioids that have been both prescribed and dispensed, whilst in England only those prescribed, and not necessarily dispensed, are included. However, we believe that the vast majority of prescribed opioids are also dispensed, rendering these differences of little clinical impact, and rendering the groups comparable. Finally, although a slightly higher prevalence of depression at the index date (as a proxy for psychological disorder) was found in the case population, compared to the control population, the temporal order of psychological disorders and opioid use is unknown. Further, adjusting for comorbidities such as depression is beyond the scope of this descriptive study.

CONCLUSION

Despite differences in the healthcare system in England and Sweden, the increase in opioid prescribing among patients undergoing TKR compared to matched controls had the same magnitude. Opioid prescribing was 60% more common in patients subsequently undergoing TKR 10 years prior to surgery, and this increased to 270% in the year prior to the date of surgery. This may suggest that the pre-arthroplasty pain trajectory is a key contributory factor to timing of surgery. Decreased opioid prescription in recent years in both countries may reflect the same health strategies on analgesics to reduce potential adverse effects. Whilst similarities were observed in general prescribing patterns through the study period and between groups, differences in prescribing by opioid strength were observed across England and Sweden. This reflects possible differences in pharmaceutical strategy. Future studies are therefore warranted to understand pre-surgical clinical pathways among TKR cases.

cases.

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Contributor and guarantor information

DY,AT,ME, and GP conceived and designed the study. DY and AT acquired the data. DY and AT performed the analysis. All authors interpreted the results. DY, CH, TA, AT anf GP drafted the manuscript. All authors contributed to the critical revision of the manuscript for important intellectual content. ME and GP supervised the study. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Competing interests

This study had no financial competing interests.

The authors declare that they have no conflict of interest.

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Role of the funding sources

The sponsors did not participate in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript and the decision to submit the manuscript for publication.

Studies involving humans or animals

No direct participant recruitment was done for the study. This study was approved by the independent scientific advisory com- mittee for CPRD research (ISAC reference: 20_000099).

Data sharing statement

We used anonymised data on individual patients on which the analysis, results, and conclusions reported in the paper are based. The CPRD data is not distributable under licence. However, the relevant data can be obtained directly from the agency (https:// www.cprd.com/).

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TABLES AND FIGURES

Table-1. Characteristics of study population

	1:1 matched TKR case and control 2015-2019 from Sweden		1:1 matched TKR case and control 2015-2019 from England	
	N=5,955 cases vs 5,955 controls		N=47,045 cases vs 47,045 controls	
	n	%	n	%
Female gender	3,373	56.6	26,173	55.6
Age groups				
45-54 years	395	6.6	5,269	11.2
55-64 years	1,505	25.3	14,685	31.2
65-74 years	2,347	39.4	15,118	32.1
75-84 years	1,528	25.7	10,242	21.8
85 + years	180	3.0	1,731	3.7
TKR performed year				
2015*	558	9.4	9,162	19.5
2016	1,300	21.8	9,454	20.1
2017	1,357	22.8	9,756	20.7
2018	1,324	22.2	9,197	19.6
2019	1,416	23.8	9,476	20.1
	Cases, %	Controls, %	Cases, %	Controls, %
Cancer, n (%)	1,138(19.1)	1,129(19.0)	4,514 (9.6)	5,148 (10.9)
Cardiovascular disease, n (%)	1,229(20.6)	1,322 (22.2)	5,022 (10.2)	5,738 (11.7)
Diabetes, n (%)	830(13.9)	828(13.9)	6,710 (14.3)	6,828 (14.5)
Depression, n(%)	957 (16.1)	861 (14.5)	5,365 (11.4)	4,505 (9.6)
Osteoarthritis †, n (%)	2,622 (44.0)	1,074(18.0)	20,543 (43.7)	5,849 (12.4)
Other (non-osteoarthritis) musculoskeletal diseases, n (%)	5164 (86.7)	3,959 (66.5)	37,922 (80.6)	29,264 (62.2)
Back pain, n(%)	2,054 (34.5)	1,492 (25.1)	18,321 (38.9)	14,498 (30.8)

*In Sweden from July 1st 2015

† Indicates osteoarthritis in other joints in Sweden and any diagnosed osteoarthritis in England.

Figure 1. **Prevalence of having any, strong or weak, opioid prescription within 10-1 years prior to incidence knee replacement in case and control group, overall and by gender**

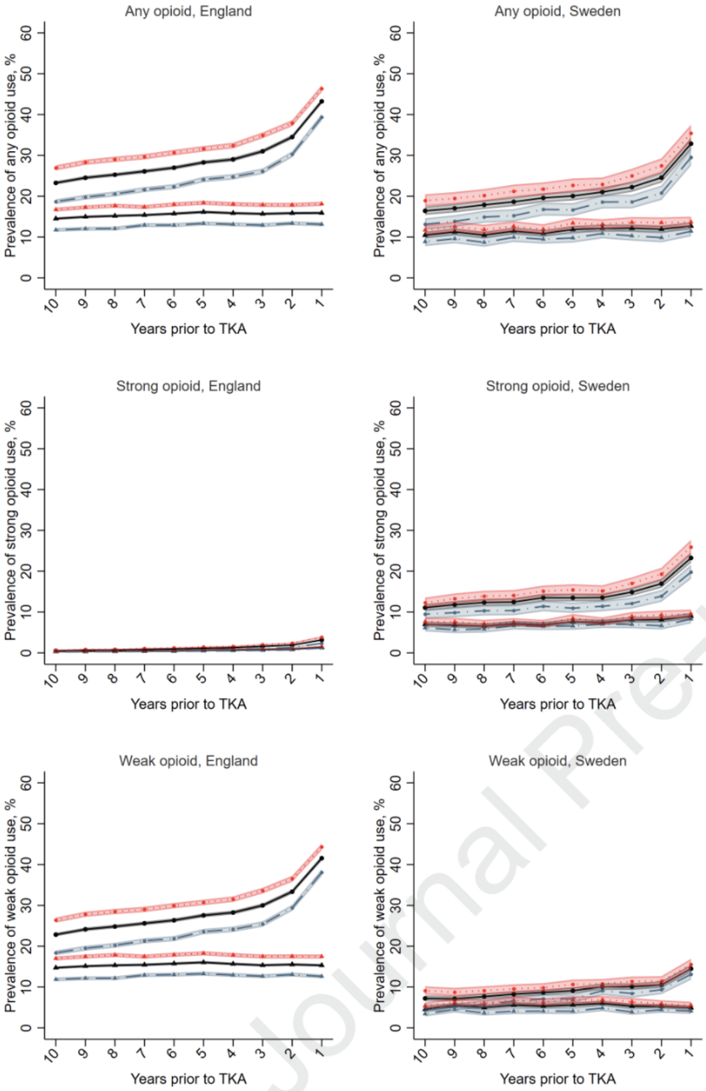
Grey, blue and red line indicates prevalence for overall, men and women, respectively.
Triangle line and dot line represents prevalence of control and case group, respectively.

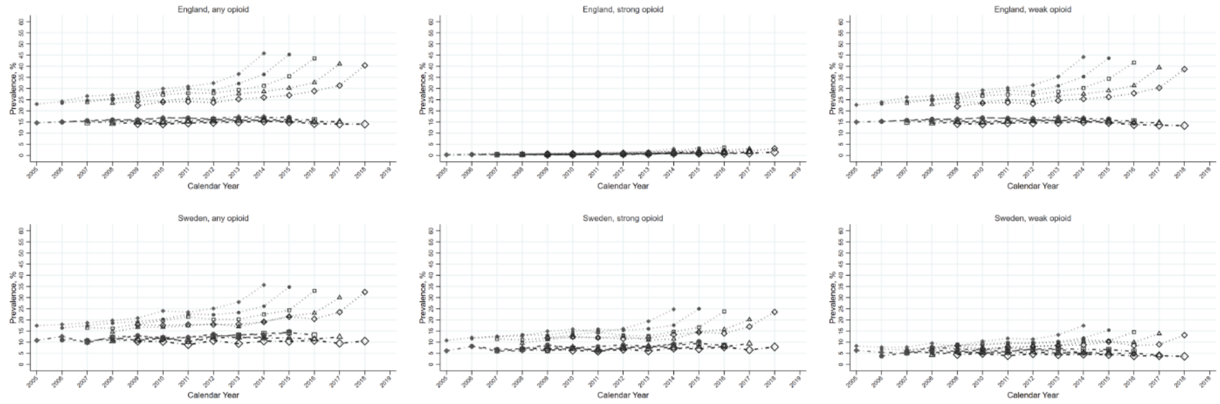
Figure 2. Period and cohort effect in having any, strong, and weak opioid prescriptions within 10-1 years prior to incidence knee replacement in case and control group

The solid diamond line, solid circle line, hollow square line, hollow triangle line, and hollow diamond line indicates prevalence of index year of 2015, 2016, 2017, 2018, and 2019, respectively. The small patterns are for case group and big patterns are for control group.

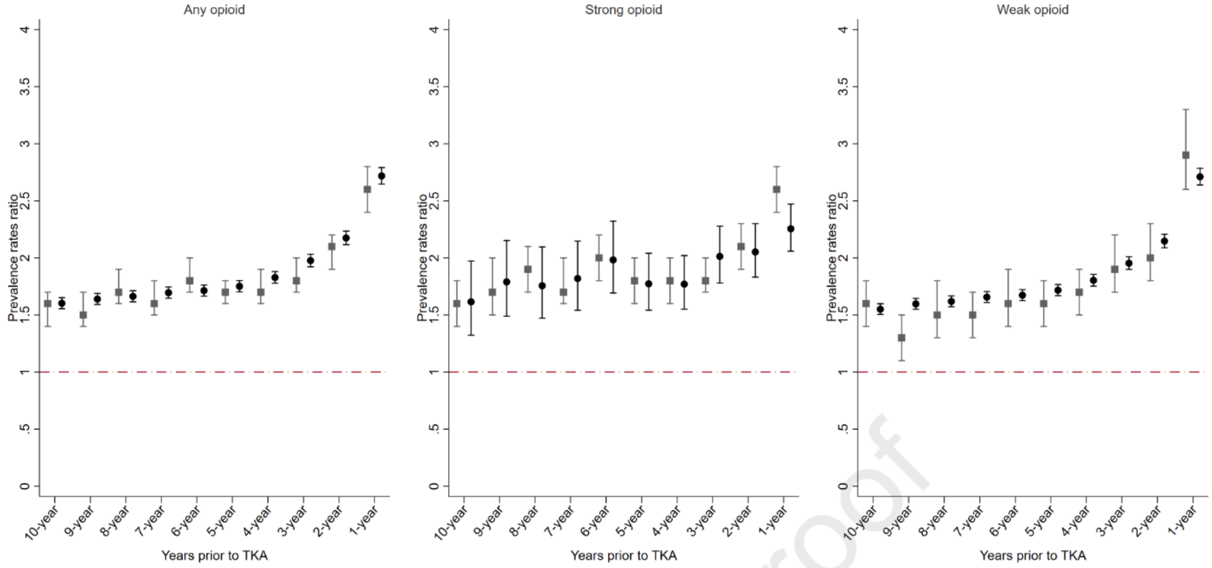
Figure-3. Overall prevalence rates ratio for having any, strong or weak opioid within 10-1 years prior to incidence knee replacement in England and Sweden

Grey and black colour indicates estimations for Sweden and England, respectively.


Any opioid, England
Any opioid, Sweden
Strong opioid, England
Strong opioid, Sweden
Weak opioid, England
Weak opioid, Sweden
Prevalence of any opioid use, %
Prevalence of strong opioid use, %
Prevalence of weak opioid use, %
Years prior to TKA
0
10
20
30
40
50
60
10
9
8
7
6
5
4
3
2
1



England, any opioid
England, strong opioid
England, weak opioid
Sweden, any opioid
Sweden, strong opioid
Sweden, weak opioid
Prevalence, %
Calendar Year


Any opioid
Strong opioid
Weak opioid
Prevalence rates ratio
0
.5
1
1.5
2
2.5
3
3.5
4
10-year
9-year
8-year
7-year
6-year
5-year
4-year
3-year
2-year
1-year
Years prior to TKA