Persistent postoperative opioid use after total hip or knee arthroplasty: A systematic review and meta-analysis

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Purpose. To identify the proportion of patients with continued opioid use after total hip or knee arthroplasty.

Methods. This systematic review and meta-analysis searched Embase, MEDLINE, the Cochrane Central Register of Controlled Trials, and International Pharmaceutical Abstracts for articles published from January 1, 2009, to May 26, 2021. The search terms (*opioid, postoperative, hospital discharge, total hip or knee arthroplasty,* and *treatment duration*) were based on 5 key concepts. We included studies of adults who underwent total hip or knee arthroplasty, with at least 3 months postoperative follow-up.

Results. There were 30 studies included. Of these, 17 reported on outcomes of total hip arthroplasty and 19 reported on outcomes of total knee arthroplasty, with some reporting on outcomes of both procedures. In patients having total hip arthroplasty, rates of postoperative opioid use at various time points were as follows: at 3 months, 20% (95% CI, 13%-26%); at 6 months, 17% (95% CI, 12%-21%); at 9 months, 19% (95% CI, 13%-24%); and at 12 months, 16% (95% CI, 15%-16%). In patients who underwent total knee arthroplasty, rates of postoperative opioid use were as follows: at 3 months, 26% (95% CI, 19%-33%); at 6 months, 20% (95% CI, 17%-24%); at 9 months, 23% (95% CI, 17%-28%); and at 12 months, 21% (95% CI, 12%-29%). Opioid naïve patients were less likely to have continued postoperative opioid use than those who were opioid tolerant preoperatively.

Conclusion. Over 1 in 5 patients continued opioid use for longer than 3 months after total hip or knee arthroplasty. Clinicians should be aware of this trajectory of opioid consumption after surgery.

Keywords: hip replacement arthroplasty, knee replacement arthroplasty, opioid analgesics, postoperative pain, pain management

Total hip arthroplasty (THA) and total knee arthroplasty (TKA) are among the most common elective procedures.[1-3] The demand for these surgeries is projected to increase substantially in the next decade.[4] Postoperative pain after these surgeries is often severe, and opioid use in the immediate postoperative period is indicated.[5-7] However, there is lack of information regarding how long patients continue to require opioids after hospitalization. Increasing duration of opioid use after surgery has been associated with opioid dependence, abuse, and overdose.[8] Thus, international guidelines for acute postoperative pain recommend that opioids should be used only when necessary, at the lowest effective dose, and for the shortest duration.[9,10]

A better understanding of the trajectory of opioid use following THA or TKA is needed to help guide clinicians and patients for care planning and harm prevention. Identifying patients who are susceptible to prolonged opioid use allows processes to be implemented to mitigate this risk. In patients undergoing THA or TKA, the surgery itself is meant to alleviate pain by correcting the underlying cause. Thus, prolonged use of opioids postoperatively is not routinely expected.[11] Guidance endorsed by the US Centers for Disease Control and Prevention suggest opioid prescribing for less than 14 days for severe pain after THA or TKA.[11] Also, chronic severe postsurgical pain has been shown to occur in 6% to 15% of patients after THA or TKA.[12] Previous reviews have assessed the prevalence of postoperative opioid use after general surgery and trauma.[13-15] However, there are no systematic reviews or meta-analyses regarding this topic in patients undergoing THA or TKA. Therefore, the primary aim of this systematic review and meta-analysis was to identify the proportion of adult patients taking opioids at 3 to 12 months after THA or TKA. Our secondary objective was to compare duration of postoperative opioid use between patients who were opioid naïve and those who were opioid tolerant preoperatively.

Methods

Protocol and registration. The review was developed and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement.[16] The review protocol was registered in the PROSPERO international prospective register of systematic reviews (registration number CRD42020145241).[17] There was no funding source for this systematic review and meta-analysis.

Information source and search strategy. Database searches were conducted in Embase, MEDLINE, the Cochrane Central Register of Controlled Trials (CENTRAL), and International Pharmaceutical Abstracts. The search terms (*opioid, postoperative, hospital discharge, total hip or knee arthroplasty,* and *treatment duration*) were based on 5 key concepts and adapted for each database search. The full electronic search strategy for Embase is provided in the supplementary appendix. The search was limited to articles on research in humans, published in the English language, and with a publication year from 2009 to the present; the latest search was conducted on May 26, 2021. Any studies published prior to this time frame were not considered to be reflective of contemporary practice. The bibliographies of included studies were screened to identify any additional literature that met our eligibility criteria.

Eligibility criteria. The following question was used to identify relevant articles: In adult patients having THA or TKA, what is the duration of postoperative opioid use in randomized controlled trials and observational studies? Studies were included if the proportion of patients taking an opioid at a postoperative time point (3-12 months) were reported or could be calculated based on the data presented. Studies were excluded if the

postoperative follow-up period was less than 3 months or involved cancer or palliative care or if the data for THA or TKA could not be extracted separately.

Study selection. After removal of duplicate publications, titles and abstracts were screened for potentially relevant studies. Full-text articles were retrieved and reviewed to identify studies that met the eligibility criteria. Two reviewers independently performed database searches and assessed the eligibility of studies. Any inconsistencies were resolved through discussion with a third reviewer.

Data extraction. Data extracted included author, year of publication, country of origin, study design, data source, sample size, patient age, surgical procedures, duration of follow-up, definition of opioid use, and the proportion of patients taking an opioid at postoperative time points defined for each study. The opioid data was collected for the total sample and also for predefined subgroups. The subgroups of interest were those who had preoperative opioid consumption (ie, opioid-tolerant patients) and those who did not have preoperative opioid consumption (ie, opioid-naïve patients). One reviewer extracted the data, which was verified by a second reviewer. Inconsistencies between reviewers were resolved through discussion with a third reviewer.

Risk of bias assessment. The quality of included studies was assessed independently by 2 reviewers (H.P.T. and X.W.) using the Newcastle-Ottawa Quality Assessment Scale for cohort studies, with a maximum score of 9 stars.[18] The scale has 3 domains: (1) selection of the study groups, (2) comparability of the groups, and (3) ascertainment of outcome. A maximum of 9 stars can be awarded to studies of the highest quality. Discrepancies regarding quality assessment were resolved through discussion or in consultation with a third reviewer.

Outcomes

The primary outcome measure was the duration of postoperative opioid use, reported here as the proportion of patients taking opioids at 3 months, 6 months, 9 months, or 12 months following THA or TKA. The secondary outcome was the proportion of patients with prolonged postoperative opioid use among opioid-naïve and opioid-tolerant patients. The definition of prolonged or persistent opioid use has not been established and varies substantially between studies.[19] Based on the definition of chronic postsurgical pain, we used a time period cutoff of 3 months.[12] However, we acknowledge that shorter periods may be more desirable for assessing what is considered optimal use.

Quantitative analysis and meta-analysis. All studies that satisfied our selection criteria and research question were included in the systematic review. The results were first categorized by type of surgery (THA or TKA). The overall proportion of patients with opioid use was reported for each time period within these strata. For each type of surgery, the groups were stratified by preoperative opioid use status (opioid naïve or tolerant). The Metaprop package in STATA, version 16.0 (StataCorp LLC, College Station, TX) was used for the meta-analysis.[20] The results were reported as proportions with 95% confidence intervals (CIs). A random effects model with inverse variance was used. Heterogeneity was determined according to definitions in the Cochrane handbook, with an I^2 value of <40% indicating "might not be important heterogeneity"; a value of 30% to 60%, "may represent moderate heterogeneity"; a value of 50% to 90%, "may represent substantial heterogeneity"; and a value of >75%, "considerable heterogeneity."[21]

Sensitivity analysis. There was considerable heterogeneity present, and we considered that this could be because of the difference between opioid-naïve and opioid-tolerant patients. Thus, the results were stratified by preoperative opioid consumption to

address this possibility. Furthermore, some studies were conducted in military personnel; as this population could be different with regard to postoperative opioid use, the analysis was repeated using only studies involving civilian populations.

Definitions of pre- and postoperative opioid use. The definitions of preoperative and postoperative opioid users for each study are provided in Table 1. Most studies reported opioid use based on opioid prescriptions filled at a certain time (eg, 3 months postoperatively) or within a timeframe (eg, 3-9 months postoperatively). Studies that reported opioid use within a timeframe were categorized according to the starting point of the timeframe. For example, patients who had documented opioid use between 3 and 6 months after surgery were considered as taking opioids for at least 3 months postoperatively.

Some studies specified a minimum threshold of opioid consumption based on dose and duration (eg, a minimum of 20 mg per day of morphine equivalents for 30 continuous days within 6 months after surgery) for a patient to be considered a postoperative opioid user. Participants who did not reach this threshold were considered to be nonusers or a separate group; however, the duration of postoperative opioid use could not be ascertained separately for the latter group. We defined postoperative opioid users as patients who met the specific criteria used in the respective studies and considered the remaining patients as non–opioid users. The same applied to the definitions of preoperative opioid use.

Results

Study selection. The initial search yielded 1,363 articles. After removal of duplicates and screening of titles and abstracts, 82 articles were retrieved for full-text review. Thirty

articles[22-51] met the eligibility criteria and were included. Figure 1 shows a PRISMA flow diagram that summarizes the selection process.

Study characteristics. Table 1 summarizes the characteristics of the 30 studies (total *n* = 1,148,318) included in this review. Twenty-six studies[22-25,27-33,37-51] were conducted in the United States, 2 studies in Australia,[34,35] 1 study in Denmark,[36] and 1 study [26] included participants from both the United States and United Kingdom [26] Most (*n* = 29) were observational retrospective studies,[22-31,33-51] and 1 was a secondary analysis of a prospective study.[32] Data on opioid use were sourced from administrative claims databases (*n* = 15),[22-27,29,31,33-35,41,45,47,50] a nationwide reimbursed prescription database (*n* = 1),[36] a state-controlled substance prescription monitoring registry (*n* = 7)[30,37,39,40,48,49,51] electronic medical records (*n* = 7)[26,30,38,42-44,46] surgeon surveys (*n* = 1),[31] or patient surveys (*n* = 1).[32] Four studies were conducted in veterans or military settings.[33-35,41] Patient sex was reported in 23 studies.[22-28,30,31,33-39,41-47,49-51] The proportion of females in these studies ranged from 6.5% to 67%.

Risk of bias assessment. Supplementary Table 1 presents the results from the risk of bias assessment based on the Newcastle-Ottawa scale. One study was assigned 5 stars,[41] and the remainder were assigned 7 to 9 stars. Fourteen studies were deemed to involve risk of bias in the selection of study groups.[30-32,34-36,38-42,49-51]

Postoperative opioid use duration. In total, 19 studies[22-27,29,30,32-35,38,42-44,46,49,50] reported postoperative opioid use at 3 months, 16 studies[22,23,29,32,33,37,39,40,42-48,51] at 6 months, 8 studies [22,23,29,36,42-44,46] at 9 months, and 6 studies [22,23,28,29,31,41] at 12 months (Table 2).

Total hip arthroplasty. Seventeen studies reported opioid use after THA.[22,24,25,28,30,32,35,36,38,39,42,46-51] The proportion of patients taking prescription opioids after

THA were as follows (Figure 2): at 3 months, 20% (95% CI, 13%-26%]); at 6 months, 17% (95% CI, 12%-21%); at 9 months, 19% (95% CI, 13%-24%); and at 12 months, 16% (95% CI, 15%-16%). There was considerable heterogeneity at each time point (I^2 values of 99%-100%). The proportions of patients in the opioid-naïve and opioid-tolerant subsets are reported in Table 3 and also depicted in the forest plots in the supplementary material. We also conducted a sensitivity analysis by excluding studies involving military or veteran populations; the results were similar (Table 3).

Total knee arthroplasty. Nineteen studies reported opioid use after TKA.[23,26-34,36,37,40,41,43-45,49,50] The proportions of patients taking prescription opioids after TKA were as follows (Figure 3): at 3 months, 26% (95% CI, 19%-33%); at 6 months, 20% (95% CI, 17%-24%); at 9 months, 23% (95% CI, 17%-28%); and at 12 months, 21% (95% CI, 12%-29%). There was considerable heterogeneity at each time point (I^2 values of 99%-100%). The proportions of patients in the opioid-naïve and opioid-tolerant subsets are shown in Table 4 and also depicted in the forest plots in the supplementary material. In the sensitivity analysis that excluded studies involving military or veteran populations, the opioid consumption appeared to be lower at 12 months (Table 4), suggesting greater chronic opioid use in military versus civilian populations.

Trend of postoperative opioid use across time points. Ten studies[22,23,27,29,32,33,42-44,46] reported outcomes at multiple time points. All studies showed a trend of decreasing opioid use as postoperative duration increased. The decline in the proportion of individuals using opioids between 3 and 6 months postoperatively was larger than the decline among those using opioids between 6 and 9 months or between 9 and 12 months postoperatively. For example, in the study by Namba et al,[43] the proportion of opioid users dropped sharply from

42.1% to 32.2% between 3 months and 6 months and then decreased slightly to 29.6% at 9 months after surgery. Data from all 10 studies are reported in Table 2.

Preoperative opioid use status. A total of 17 studies[22-24,28-36,39,40,45,48,51] stratified the reporting of postoperative opioid use based on whether or not patients had preoperative opioid consumption. Preoperative opioid users showed a higher risk of continuing postoperative opioid than nonusers at all evaluated time points. For instance, at 3 months after THA, the proportion with continued opioid use was 10% (95% CI, 6%-15%) for opioid-naïve patients and 47% (95% CI, 34%-60%) for opioid-tolerant patients. Similarly, 3 months after TKA, the proportions with continued opioid use were 11% (95% CI, 5%-18%) and 60% (95% CI, 53%-68%) for opioid-naïve and opioid-tolerant patients, respectively. These data are reported for each time point for both THA and TKA in Table 3 and Table 4, respectively. In the subgroup of preoperative opioid users, studies that were conducted in veterans or in military settings[33-35] reported higher proportions of postoperative opioid users than studies that were conducted in the general population (Table 2).

Discussion

To our knowledge, this is the first systematic review to focus on the duration of opioid use after THA or TKA. Overall, more than 1 in 5 patients had continued opioid use that was sustained for 12 months postoperatively. However, there were substantial differences between those who were opioid naïve versus opioid tolerant preoperatively. For example, while about 10% of patients in the opioid-naïve group continued opioid use postoperatively, up to half of the patients who were opioid tolerant had continued use. Thus, this is an important factor that should be considered when determining risk of prolonged postoperative opioid consumption. Existing guidelines generally recommend

opioid prescriptions of no more than 3 to 7 days for the treatment of acute pain.[10,52,53] Although recovery after TKA or THA may take longer, opioids should not be prescribed for longer than 14 days for most patients.[11] Given the high volumes of THA and TKA procedures, the findings showed that a large proportion of patients might be taking opioids for longer than the recommended duration, which has the potential for harm.

Regarding trends of opioid use across the various study periods, it was expected that the proportion of patients taking opioids would decrease with time. However, the decline appeared to be greater in the early postoperative period (from 3 to 6 months after surgery). This suggests that the likelihood of opioid cessation decreases with the duration of postoperative opioid exposure. A possible explanation for the observed slower decline in the rate of opioid use in the late postoperative period is the increased risk of developing opioid dependence and addiction over time.[54] Also, the longer patients continue to take opioids, the more difficult it may be to achieve cessation of therapy. Clinicians may be less likely to successfully cease therapy in these circumstances. Although approximately half of patients with preexisting opioid use had persistent use of opioids post surgery, we would expect this proportion to be lower because chronic severe postsurgical pain has been shown to occur in 6% to 15% of patients after THA or TKA.[12]

There was considerable heterogeneity in duration of opioid use between studies. This could be attributed to a lack of consistency in the definitions of postoperative opioid use. A recent study by Jivraj et al[19] reported a more than 100-fold difference in the rates of persistent opioid use when different definitions were applied to the same patient cohort. The influence of opioid use definitions on the reported incidence of opioid use could have masked the effect of other factors such as patient characteristics and prescribing pattern. This makes it difficult to compare results across studies. The issue of inconsistency in

definitions has also been discussed by authors of previous studies.[13,14] In relation to this issue, an expert consensus statement[55] has recommended standard definitions of persistent postoperative opioid use based on preoperative opioid use status. For opioid-naïve patients (ie, those with no history of opioid use in the 90 days before surgery), persistent postoperative opioid use was defined as filling a prescription for at least a 60 days' supply of opioids during days 90 to 365 after surgery. For preoperative opioid users, persistent use was defined as any increase in opioid use relative to baseline during days 90 to 365 after surgery.[55] These definitions could be a good starting point to improve the comparability of future studies. We were unable to apply this definition to the reviewed studies because it was not possible to identify patients fulfilling these criteria due to variable study reporting. Nonetheless, we found great differences in outcomes between opioid-naïve and opioid-tolerant patients, which suggests that the definitions used were able to discriminate between patients adequately.

The higher proportion of persistent postoperative opioid use in the subgroup of preoperative opioid users further supports the findings from previous studies that the history of opioid use before surgery is a major risk factor for long-term or chronic postoperative opioid use.[56,57] Preoperative opioid use appeared to have a different magnitude of effect across studies. This finding could be explained in part by the inconsistency in definitions of preoperative opioid users specified in each study. History of opioid use is a well-established risk factor for postoperative prolonged and chronic opioid use. Preoperative opioid prescribing may be modified to reduce the risk of prolonged postoperative opioid use.[58]

Codeine and tramadol were not considered as opioids in some studies included in our review.[22,23,27,38] They are 2 very commonly used opioid analgesics. The exclusion of these

2 opioids probably led to the underestimation of opioid use in those studies. Codeine can be used for the treatment of indications other than pain, such as for its antitussive properties. Thus, it would be hard to differentiate between indications for this opioid. In addition, codeine and tramadol are frequently not included in studies because they are less potent than other opioids such as oxycodone and are thought to pose a lower risk of abuse or addiction.[59] However, studies on the safety of tramadol versus other opioids have reported contradictory findings.[60-62] For example, a recent study found that tramadol posed a similar or somewhat higher risk of prolonged use after surgery relative to other short-acting opioids.[61] The abuse and misuse potential of codeine and tramadol and their contribution to the opioid epidemic should not be overlooked. Future research should include codeine and tramadol as opioids or analyze their use in subgroup analyses.

One of the strengths of this review is that the included studies reflect contemporary practice, because the search was limited to the past 12 years and most of the included studies were published within the past 2 years. The outcomes were presented at several time points, allowing us to observe trends of opioid use in the postoperative period. This review should be considered in the light of some limitations. First, the majority of the studies measured opioid use status based solely on prescriptions filled. This may not have reflected the actual opioid consumption by the patients, because some filled prescriptions may have gone unused.[63] Data on the dose or the number of tablets prescribed were also unavailable. Second, there was substantial variability between studies in term of population baseline characteristics, data source and collection, definitions of opioid use status, and reporting of results. This contributed to variability between studies. Thirdly, studies did not report whether persistent opioid use was for indications or comorbidities other than postoperative pain. It is possible that some patients were taking opioids for other pain

conditions. Finally, studies did not stratify the results by other factors that could influence persistent opioid use, such as history of substance abuse or mental health.

Future research should consider using prospective study designs to measure patient-reported postoperative opioid consumption. The reporting of other data, such as pain assessments and patients' perceptions and experiences of pain and opioid analgesics, could be helpful to give an overall picture of how patient factors affect postoperative opioid use. More research is needed to investigate non–patient-related risk factors, such as prescribing and dispensing habits, healthcare system characteristics, and types of opioid medications, that may be associated with persistent postoperative opioid use. Identification of contributing factors will facilitate the development of possible interventions. This review highlights and quantifies the problem of prolonged opioid use after THA or TKA. Patients with persistent opioid use should be evaluated for opioid deprescribing. There is an important role for opioid stewardship and, potentially, for pharmacists to address this issue. The reason for continued opioid use needs to be elucidated. For example, THA and TKA are meant to alleviate joint pain. If surgery is successful, it is anticipated that chronic opioid use would not be indicated.

Conclusion

Among patients who have THA or TKA, over 20% have persistent opioid use for longer than 3 months postoperatively, and this use may be sustained for over 12 months. Opioid-naïve patients are less likely to have continued postoperative opioid use than those who are opioid tolerant preoperatively. Clinicians involved in the care of these patients should be aware of this trajectory of opioid consumption after surgery.

Disclosures

The authors have declared no potential conflicts of interest.

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Figure 1. PRISMA flow chart of article selection.

Figure 2. Forest plot of proportion of patients taking prescription opioids after total hip arthroplasty. ES indicates effective size.

Figure 3. Forest plot of proportion of patients taking prescription opioids after total knee arthroplasty. ES indicates effective size.

Key Points

- A better understanding of the trajectory of opioid use following total hip or knee arthroplasty is needed to help guide clinicians and patients in care planning and harm prevention.
- Thirty studies were identified for full review and ultimate inclusion in this study, and the results showed that 1 in 5 patients may continue opioid use for longer than 3 months after total hip or knee arthroplasty.
- Clinicians should be aware of this trajectory of opioid consumption after surgery and focus on deprescribing.

Table 1. Characteristics and Definitions of Opioid Use in the Included Studies

Study (Year Published)	Country	Procedure	Patient Age[a]	Female, %	Funding Source(s)	Mental Disorder Comorbidity,%	Population	Definitions of Opioid Use	
								Preoperative[b]	Postoperative
Bedard, Pugely, Dowdle, et al (2017)[22]	US	THA	<50: 2.7% ≥50: 97.3%	41	NA	Anxiety or depression: 6.5	Civilian	At least 1 opioid prescription filled within 3 months before surgery Non–opioid users: No history of opioid prescription filled before surgery	Monthly opioid prescription filling rate for the first 12 months after surgery
Bedard, Pugely, Westermann, et al (2017)[23]	US	TKA	<50: 1.4% ≥50: 98.6%	63.8	NA	Anxiety or depression: 37.5	Civilian	At least 1 opioid prescription filled within 3 months before surgery Non–opioid users: No history of opioid prescription filled before surgery	Monthly opioid prescription filling rate for the first 12 months after surgery
Bell et al (2020)[24]	US	THA	Range: 20-85 <65: 19% 65-69: 25% 70-74: 28%	67	NA	Depression: 30	Civilian	At least 1 opioid prescription filled within 4 months before surgery	At least 1 opioid prescription filled 3-6 months after surgery

			75-79: 18% 80-84: 10%						
Bolarinwa et al (2019)[25]	US	THA	<40: 0.6% 40-49: 2.8% 50-59: 10.9% 60-69: 31.2% 70-79: 39.3% ≥80: 15.2%	58.4	NA	Depression: 31.1	Civilian	NA	At least 1 opioid prescription filled between 3 and 6 months after surgery
Burn et al[c] (2019)[26]	US, UK	TKA	Range: ≥40 40-44: 0.8%-2.6% 45-49: 4.3%-8.0% 50-54: 0.1%-19.1% 55-59: 0.4%-28.3% 60-64: 1.2%-38.8% 65-69: 3.1%-27.1% 70-74: 7.1%-29.0% 75-79: 5.9%-21.9% 80-84: 0.8%-14.1% 85-89: 2.0%-5.2% 90-94:	47.9-53.3	EU/European Federation of Pharmaceutical Industries and Associations Innovative Medicines Initiative (2) Joint Undertaking (EHDEN)	Depression: 4.6-14.2	Civilian	NA	Written or dispensed opioid prescription during days 91-365 after surgery

			0.3%-0.7%						
Cancienne et al (2018)[27]	US	TKA	<40: 0.1% 40-49: 1.5% 50-59: 9.6% 60-69: 34.9% 70-79: 41.8% ≥80: 12.1%	63.5	NA	Depression: 34.2	Civilian	NA	At least 1 opioid prescription filled between 3 and 6 months after surgery
Cook et al (2019)[28]	US	THA, TKA	0-19: 0% 20-29: 0% 30-39: 0% 40-49: 2% 50-59: 9% 60-69: 31% 70-79: 45% 80-89: 12% ≥90: 2%	61.8* THA: 63.4* TKA: 58.4*	NA	NR	Civilian	Opioid users: Filled at least 2 opioid prescription within the 6 months before surgery Non–opioid users: Did not fill an opioid prescription within the 6 months before surgery	At least 1 opioid prescription filled at 12 months after surgery
DeMik et al (2020)[29]	US	TKA	NR	NR	NA	NR	Civilian	At least 1 opioid or tramadol prescription filled within 3 months before surgery	Monthly opioid or tramadol prescription filling rate for the first 12 months after surgery
Dwyer et al (2018)[30]	US	THA, TKA	Mean (SD) age: 65.2	Overall: 52.5 THA:	NA	Anxiety or depression: 27.2	Civilian	At least 1 opioid prescription filled	At least 1 opioid prescription filled at 3

			(10.7); THA: 62.9 (11.5) TKA: 67.0 (9.3)	51.4 TKA: 53.7		THA: 24.3 TKA: 30.2		within 12 months before surgery, history of long-term opioid use, history of narcotic dependence	months after surgery
Franklin et al (2010)[31]	US	TKA	Mean: 68 >65: 66%	66.6	NA	NR	Civilian	At least 1 opioid prescription before surgery	At least 1 opioid prescription at 12 months after surgery
Goesling et al (2016)[32]	US	THA, TKA	Range: ≥18	NR	National Institute of Arthritis and Musculoskeletal and Skin Diseases	NR	Civilian	Patient-reported opioid use on the day of surgery	Patient-reported opioid use at 3 and 6 months after surgery
Hadlandsmyth et al (2018)[33]	US	TKA	Median: 66 <60: 24% 60-70: 53% >70: 23%	7	NA	Psychiatric diagnoses (anxiety, bipolar, depression, psychotic disorders, PTSD): 34	Veteran	At least 90 days of continuous opioid use within 12 months before surgery	At least 1 opioid prescription filled at 3, 6, and 12 months after surgery
Hansen et al (2017)[34]	AU	TKA	Range: ≥18 Median (5th-95th percentile): 79 (61-87)	49.5	NA	NR	Veteran	At least 90 days of continuous opioid use or 120 days of noncontinuous use within 275 days before surgery	At least 90 days of continuous opioid use or at least 120 days of non-continuous opioid use during days 91-365 after surgery

Inacio et al (2016)[35]	AU	THA	Range: ≥18 Median (5th-95th percentile): 80 (76-84)	51.3	Australian Government National Health and Medical Research Council	Anxiety: 12.3 Bipolar: 0.3 Depression: 17.8 Psychosis: 2	Veteran	At least 90 days of continuous opioid use or 120 days of noncontinuous use within 275 days before surgery	At least 90 days of continuous opioid use or at least 120 days of non-continuous opioid use during days 91-365 after surgery
Jorgensen et al (2018)[36]	DK	THA, TKA	Range: ≥18 Mean: 67.7 (11.0) THA: 68.0 (11.5) TKA: 67.4 (10.4)	57.9 THA: 54.1 TKA: 62.3	Danish National Database of Reimbursed Prescriptions	Psychiatric disease: 15 THA: 14.4 TKA: 15.8	Civilian	At least 1 opioid prescription filled within 1 month before surgery	At least 1 opioid prescription filled during 1-4, 5-8, and 9-12 months after surgery
Kalbian et al (2019)[37]	US	TKA	Mean: 65.4 (8.43)	57.7	NA	NR	Civilian	NA	Continued opioid use for beyond 6 months
Karhade et al (2019)[38]	US	THA	Range: ≥18 Median (IQR): 66.0 (57.0-74.0)	49.5	NA	Depression: 9.3 Psychosis: 0.5	Veteran: 15%	NA	Continuous opioid prescriptions to at least 3 months after surgery
Kim et al (2018)[40]	US	TKA	NR	NR	NA	NR	Civilian	At least 30 days of continuous opioid use (minimum 20 mg/d of morphine equivalents) within 3 months before surgery	At least 30 days of continuous opioid use (minimum 20 mg/d in morphine equivalents) within 6 months after surgery

Kim et al (2020)[39]	US	THA	Mean: 63.1*	54.3*	NA	NR	Civilian	At least 30 days of continuous opioid use (minimum 20 mg/d of morphine equivalents) within 3 months before surgery	At least 30 days of continuous opioid use (minimum 20 mg/d in morphine equivalents) within 6 months after surgery
Kuo et al (2019)[41]	US	TKA	≤50: 6% 51-60: 25% 61-70: 49% 71-80: 16% >80: 4%	6.5	VA National Center for Patient Safety	Depression: 30.9 PTSD: 18	Veteran	NA	At least 1 opioid prescription filled after postoperative month 12
Namba et al (2016)[42]	US	THA	Range: ≥18 Median (IQR): 67 (59-75)	58	NA	Anxiety: 9.9 Bipolar: 0.8 Depression: 8.7 PTSD: 0.3	Civilian	NA	At least 1 opioid prescription filled during days 91-180, days 181-270, and days 271-360 after surgery
Namba, Inacio et al (2018)[43]	US	TKA	Range: ≥18 Median (IQR): 68 (61-75)	62.7	NA	Anxiety: 10.6 Bipolar: 0.8 Depression: 9.4 PTSD: 0.3	Civilian	NA	At least 1 opioid prescription filled during days 91-180, days 181-270, and days 271-360 after surgery
Namba, Singh et al (2018)[44]	US	TKA	Range: ≥18 Median (IQR): 68 (61-75)	62.9	NA	Anxiety: 10.9 Bipolar: 0.9 Depression: 9.6 PTSD: 0.4	Civilian	NA	At least 1 opioid prescription filled during days 91-180, days 181-270, and days 271-

									360 after surgery
Politzer et al (2018)[45]	US	TKA	≤44: 0.3% 45-59: 6.1% ≥60: 93.6%	63.4	NA	NR	Civilian	At least 1 opioid prescription filled within 12 months before surgery	At least 1 opioid prescription filled at 3 months after surgery
Prentice et al (2019)[46]	US	THA	Range: ≥18 Median (IQR): 67 (59-75)	58.5	NA	Anxiety: 9.9 Bipolar: 0.7 Depression: 8.8 PTSD: 0.4	Civilian	NA	Opioid prescriptions for longer than 6 consecutive months after surgery
Ruddell et al (2020)[49]	US	THA, TKA	Mean (SD): 66.6 (10.4) THA: 64.7 (11.9) TKA: 67.8 (9.1)	63.1 THA: 58.6 TKA: 66	NA	NA	Civilian	Any opioid prescription filled within 30 days before surgery	Opioid use between 91 to 150 days after surgery given prior use in the period of 31-90 days
Schwartz et al (2020)[47]	US	THA	Range: >18 <55: 23.7% 55-64: 43.3% 65-74: 18.2% 75-84: 12.3% ≥85: 2.9%	47.7	NA	Depression: 7.5[d]	Civilian	NA	At least 1 opioid prescription filled between 6 and 12 months after surgery
Soffin et al (2021)[50]	US	THA, TKA	Median (IQR): THA: females, 57 (52-61); males,	THA: 47.8[d] TKA: 57.6[d]	NA	Discharge antidepressant: 0.8[d] Discharge anxiolytic: 2.6[d]	Civilian	Opioid prescription in the year before surgery	At least 10 opioid prescriptions or prescriptions for at least 120 pills between 90 days to 1 year

			56 (51-60) TKA: females, 58 (54-61); males, 58 (54-61)						after discharge
Tan et al (2020)[48]	US	THA	NR	NR	NA	NR	Civilian	Opioid prescription during 6 months before surgery	Continued opioid use past 6 months after surgery
Wilt et al (2020)[51]	US	TKA	NR	NR	NA	NR	Civilian	At least 1 opioid prescription filled within the 6 months before surgery.	At least 1 opioid prescription filled more than 6 months after surgery

Abbreviations: AU, Australia; DK, Denmark; IQR, interquartile range; NA, not applicable; NR, not reported; PTSD, posttraumatic stress disorder; SD, standard deviation; THA, total hip arthroplasty; TKA, total knee arthroplasty; UK, United Kingdom; US, United States.

[a]Age reported differently across studies.

[b]Non–opioid users were participants who did not meet the definitions of opioid user unless otherwise specified. Definitions of preoperative opioid use were not recorded in this table for studies that did not report percentage of postoperative opioid user stratified by preoperative opioid use.

[c]Burn et al (2020) reported patient characteristics separately for each of the 5 databases; therefore, the range of the reported data is shown in this table.

[d]Value calculated from data reported in the studies.

Table 2. Outcomes of Included Studies

		Postoperative Opioid Use, No. (%)[a]		
Study (Year Published)	**Sample Size**	**Total Population**	**Preoperative Use**	**No Preoperative Use**
		Total Hip Arthroplasty		
Bedard, Pugely, Dowdle et al (2017)[22]	37,393	3 mo: 6,979 (18.7) 6 mo: 5,643 (15.1) 9 mo: 5,256 (14.1) 12 mo: 5,139 (13.7)	3 mo: 5,516 (38.5) 6 mo: 4,619 (32.3) 9 mo: 4,326 (30.2) 12 mo: 4,012 (28.0)	3 mo: 730 (4.8) 6 mo: 460 (3.0) 9 mo: 430 (2.8) 12 mo: 440 (2.9)
Bell et al (2020)[24]	5,304	3 mo: 2,595 (48.9)	3 mo: 2,056 (58.1)	3 mo: 539 (30)
Bolarinwa et al (2019)[25]	55,354	3 mo: 14,996 (27)		
Cook et al (2019)[28]	22,701	12 mo: (20.7)[b]	12 mo: (47.0)	12 mo: (10.0)
Dwyer et al (2018)[30]	197	3 mo: 0 (0.0)		3 mo: 0(0.0)
Goesling et al (2016)[32]	331	3 mo: 43 (14.5)[b] 6 mo: 34 (12.9)[b]	3 mo: 34 (37.8) 6 mo: 26 (34.7)	3 mo: 9 (4.3) 6 mo: 8 (4.2)
Inacio et al (2016)[35]	9,525	3 mo: 492 (5.2)	3 mo: 302 (50.9)	3 mo: 190 (2.1)[b]
Jorgensen et	4,849	9 mo: 662 (13.7)[b]	9 mo: 436 (33.8)[b]	9 mo: 226 (6.3)

al (2018)[36]				
Karhade et al (2019)[38]	5,507	3 mo: 345 (6.3)		
Kim et al (2020)[39]	256	6 mo: 15 (5.9)	6 mo: 13 (24.1)	6 mo: 2 (1.0)
Namba et al (2016)[42]	12,859	3 mo: 3,461 (27) 6 mo: 3,019 (24) 9 mo: 2,896 (23)		
Prentice et al (2019)[46]	12,560	3 mo: 3,506 (27.9) 6 mo: 3,093 (24.6) 9 mo: 3,009 (24.0)		
Ruddell (2020)[49]	198	3 mo: 24 (12.1)		
Schwartz et al (2020)[47]	171,258 (patients with 1 year of postoperative data: 127,510)	6 mo: 33,504 (26.3)[b]		
Soffin et al (2021)[50]	29,038	3 mo: 2,333 (8.0)[b]		
Tan et al (2020)[48]	619	6 mo: 65 (10.5)[b]	6 mo: 54 (25.0)	6 mo: 11 (2.7)
Wilt et al	676	6 mo: 80 (11.8)	6 mo: 58 (28.3)	6 mo: 22 (4.7)

(2020)[51]				
Total Knee Arthroplasty				
Bedard, Pugely, Westermann et al (2017)[23]	73,959	3 mo: 18,451 (24.9) 6 mo: 12,070 (16.3) 9 mo: 10,995 (14.9) 12 mo: 10,825 (14.6)	3 mo: 11,850 (50.4) 6 mo: 9,024 (38.3) 9 mo: 8,366 (35.6) 12 mo: 7811 (33.2)	3 mo: 3,046 (10.2) 6 mo: 1,191 (4.0) 9 mo: 951 (3.2) 12 mo: 969 (3.3)
Burn et al (2019)[26]	250,377	3 mo: 87,460 (34.9)		
Cancienne et al (2018)[27]	113,337	3 mo: 35,770 (31.6)		
Cook et al (2019)[28]	46,667	12 mo: (24.1)[b]	12 mo: (62.0)	12 mo: (13.0)
DeMik et al (2020)[29]	107,973	3 mo: 32,638 (30.2)[b] 6 mo: 22,625 (21.0)[b] 9 mo: 20,775 (19.2)[b] 12 mo: 20,752 (19.2)[b]	3 mo: 22,260 (50.1) 6 mo: 17,273 (38.9) 9 mo:15,959 (35.9) 12 mo: 15,857 (35.7)	3 mo: 10,378 (16.3) 6 mo: 5,352 (8.4) 9 mo: 4,816 (7.6) 12 mo: 4,895 (7.7)
Dwyer et al (2018)[30]	186	3 mo: 0 (0.0)		3 mo: 0 (0.0)
Franklin et al (2010)[31]	6,346	12 mo: 351 (6.1)[b]	12 mo: 221 (16.3)[b]	12 mo: 130 (3.0)[b]

Goesling et al (2016)[32]	243	3 mo: 54 (24.2)[b] 6 mo: 36 (18.8)[b]	3 mo: 26 (48.1) 6 mo: 24 (53.3)	3 mo: 28 (16.6) 6 mo: 12 (8.2)
Hadlandsmyth et al (2018)[33]	6,653	3 mo: (26)[b] 6 mo: (17)[b] 12 mo: (13)[b]	3 mo: (82.0) 6 mo: (69.0) 12 mo: (57.0)	3 mo: (12.0) 6 mo: (4.0) 12 mo: (2.0)
Hansen et al (2017)[34]	15,020	3 mo: 787 (5.2)	3 mo: 479 (66.5)	3 mo: 308 (2.1)[b]
Jorgensen et al (2018)[36]	4,126	9 mo: 765 (18.5)[b]	9 mo: 440 (51.9)[b]	9 mo: 325 (9.9)
Kalbian et al (2019)[37]	676	6 mo: 80 (11.8)		
Kim et al (2018)[40]	338	6 mo: 37 (10.9)[b]	6 mo: 23 (42.6)	6 mo: 14 (4.9)
Kuo et al (2019)[41]	33,927	12 mo: (46.0)		
Namba, Inacio et al (2018)[43]	24,105	3 mo: 9,914 (41.5) 6 mo: 7,431 (31.4) 9 mo: 6,946 (29.6)		
Namba, Singh et al (2018)[44]	23,726	3 mo: 9,993 (42.1) 6 mo: 7,638 (32.2) 9 mo: 7,218 (30.4)		
Politzer et al (2018)[45]	66,950	6 mo: 14,286 (21.3)	6 mo: 12,762 (34.8)*	6 mo: 1,524 (5.0)
Ruddell (2020)[49]	309	3 mo: 49 (15.9)		

Soffin et al (2021)[50]	48,523	3 mo: 5,365 (11.1)[b]

[a]Number (percentage) of postoperative opioid users at various postoperative time points.

[b]Value calculated from data reported in the studies.

	Opioid-Naïve Patients		Opioid-Tolerant Patients		Total Sample	
Postdischarge Time Point	**Proportion**	**95% Confidence Interval**	**Proportion**	**95% Confidence Interval**	**Proportion**	**95% Confidence Interval**
3 months	10%	6%-15%	47%	34%-60%	20%	13% –26%
	13%[a]	–3% to 30%[a]	45%[a]	29%-61%[a]	21%[a]	14%-28%[a]
6 months	3%	2%-4%	29%	25%-33%	17%	12%-21%
9 months	3%	3%-3%	31%	30%-31%	19%	13%-24%
12 months	4%	4%-5%	33%	32%-33%	16%	15%-16%

Table 3. Sensitivity Meta-analysis Results: Total Hip Arthroplasty

[a]Subset excluding studies that involved military population.

Table 4. Sensitivity Meta-analysis Results: Total Knee Arthroplasty

	Opioid-Naïve Patients		Opioid-Tolerant Patients		Total Sample	
Postdischarge Time Point	**Proportion**	**95% Confidence Interval**	**Proportion**	**95% Confidence Interval**	**Proportion**	**95% Confidence Interval**
3 months	11%	5%-18%	60%	53%-68%	26%	19%-33%
	14%[a]	9%-19%[a]	50%[a]	50%-51%[a]	29%[a]	22%-36%[a]
6 months	6%	4%-8%	45%	41%-50%	20%	17%-24%
			38%[a]	35%-41%[a]	21%[a]	17%-25%[a]
9 months	7%	3%-10%	40%	37%-43%	23%	17%-28%
12 months	6%	2%-9%	41%	30%-52%	21%	12%-29%
	7%[a]	3%-11%[a]	37%[a]	25%-49%[a]	16%[a]	11%-21%[a]

[a]Subset excluding studies that involved military population.

FIGURE 1

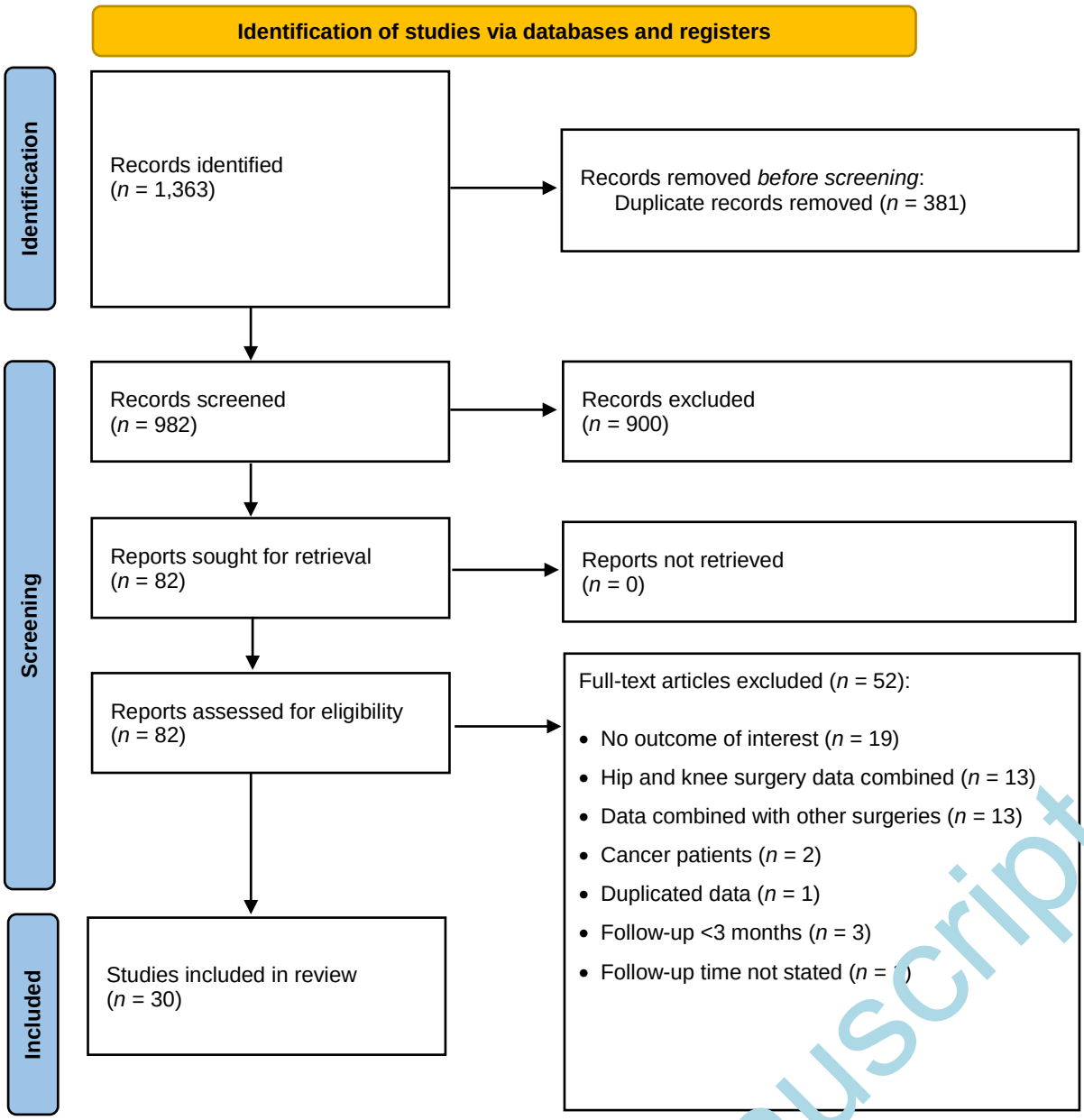


Figure 2

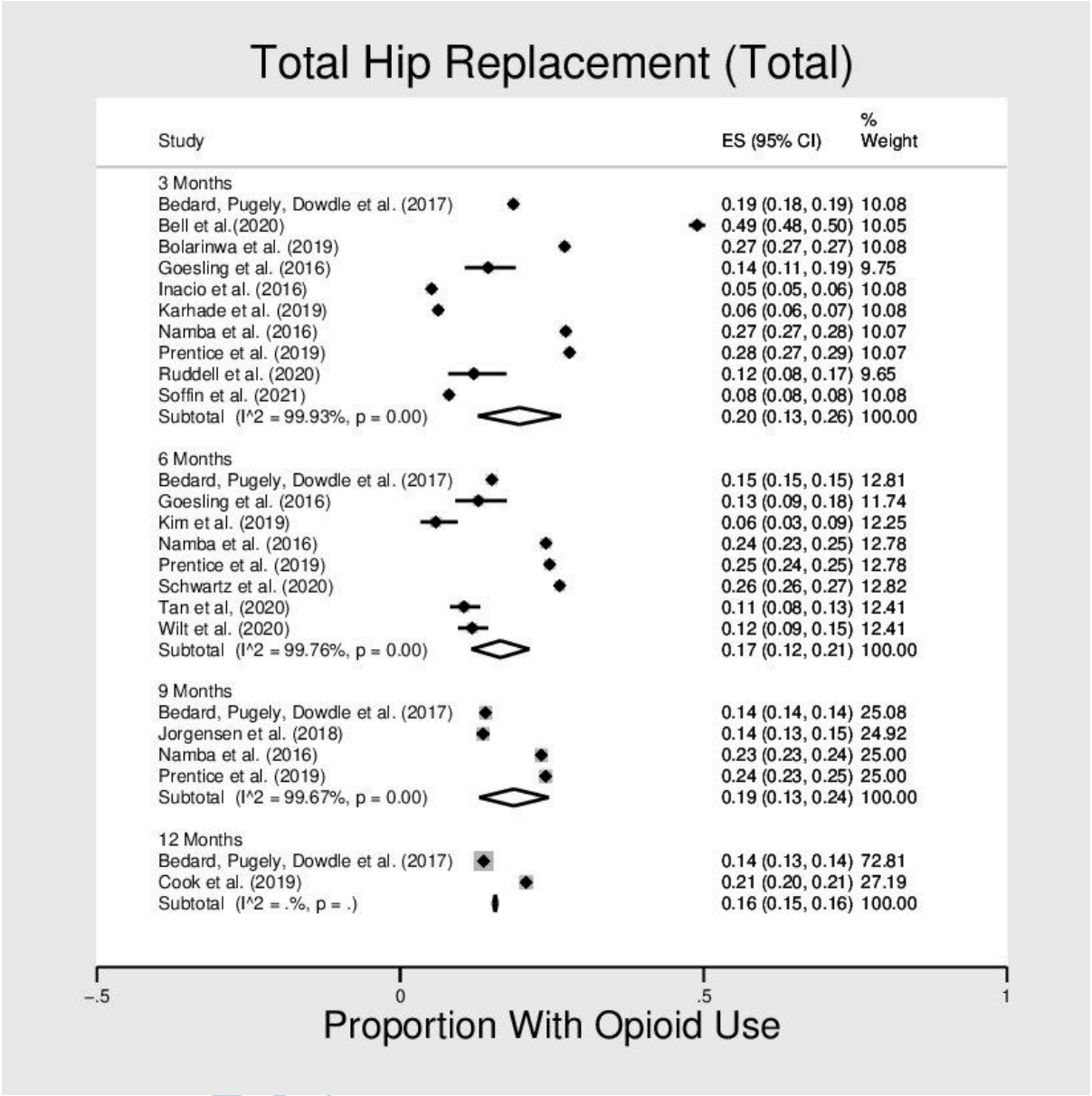
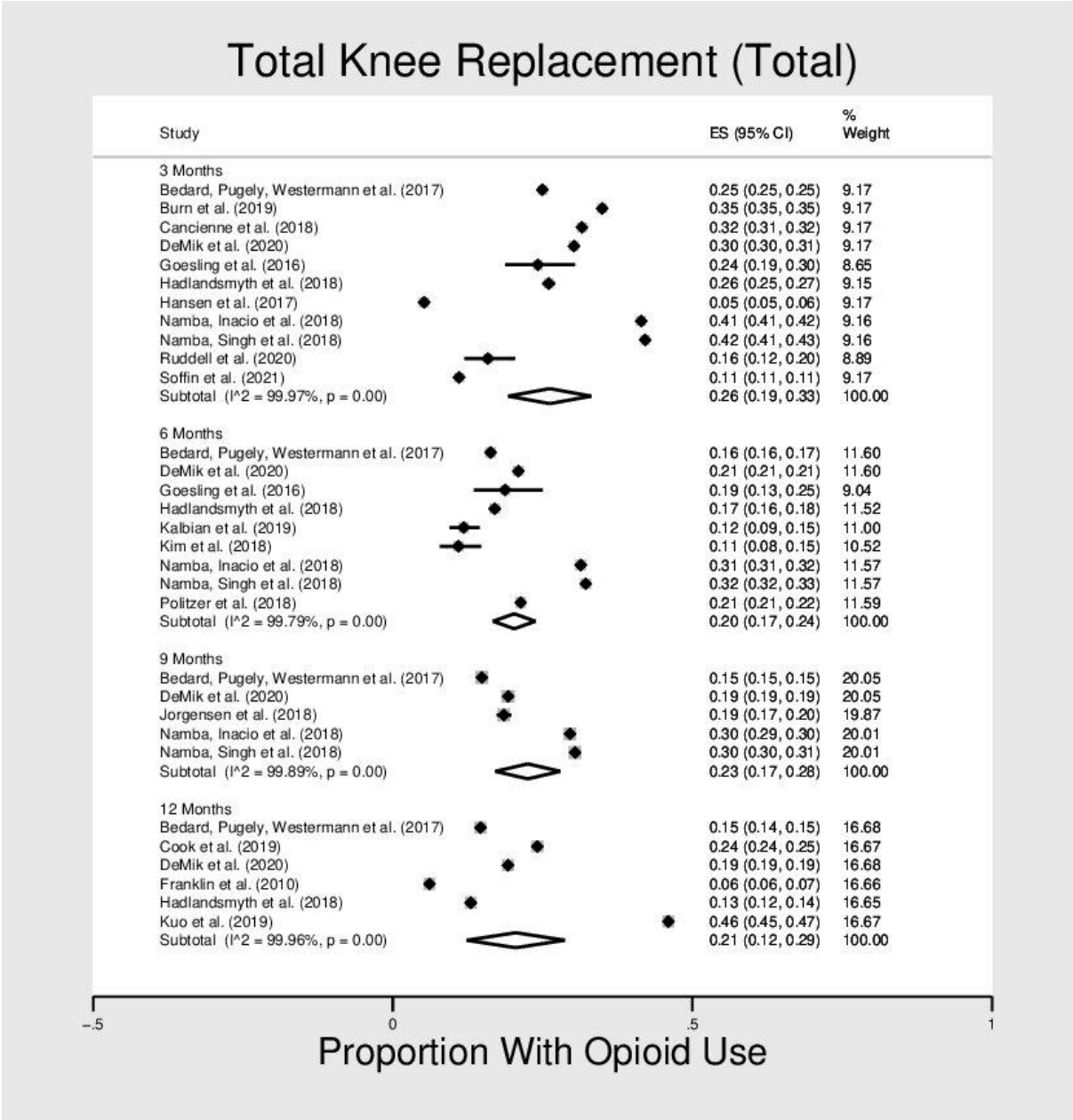

Total Hip Replacement (Total)
Study
ES (95% CI)
% Weight
3 Months
Bedard, Pugely, Dowdle et al. (2017) 0.19 (0.18, 0.19) 10.08
Bell et al.(2020) 0.49 (0.48, 0.50) 10.05
Bolarinwa et al. (2019) 0.27 (0.27, 0.27) 10.08
Goesling et al. (2016) 0.14 (0.11, 0.19) 9.75
Inacio et al. (2016) 0.05 (0.05, 0.06) 10.08
Karhade et al. (2019) 0.06 (0.06, 0.07) 10.08
Namba et al. (2016) 0.27 (0.27, 0.28) 10.07
Prentice et al. (2019) 0.28 (0.27, 0.29) 10.07
Ruddell et al. (2020) 0.12 (0.08, 0.17) 9.65
Soffin et al. (2021) 0.08 (0.08, 0.08) 10.08
Subtotal (I^2 = 99.93%, p = 0.00) 0.20 (0.13, 0.26) 100.00
6 Months
Bedard, Pugely, Dowdle et al. (2017) 0.15 (0.15, 0.15) 12.81
Goesling et al. (2016) 0.13 (0.09, 0.18) 11.74
Kim et al. (2019) 0.06 (0.03, 0.09) 12.25
Namba et al. (2016) 0.24 (0.23, 0.25) 12.78
Prentice et al. (2019) 0.25 (0.24, 0.25) 12.78
Schwartz et al. (2020) 0.26 (0.26, 0.27) 12.82
Tan et al, (2020) 0.11 (0.08, 0.13) 12.41
Wilt et al. (2020) 0.12 (0.09, 0.15) 12.41
Subtotal (I^2 = 99.76%, p = 0.00) 0.17 (0.12, 0.21) 100.00
9 Months
Bedard, Pugely, Dowdle et al. (2017) 0.14 (0.14, 0.14) 25.08
Jorgensen et al. (2018) 0.14 (0.13, 0.15) 24.92
Namba et al. (2016) 0.23 (0.23, 0.24) 25.00
Prentice et al. (2019) 0.24 (0.23, 0.25) 25.00
Subtotal (I^2 = 99.67%, p = 0.00) 0.19 (0.13, 0.24) 100.00
12 Months
Bedard, Pugely, Dowdle et al. (2017) 0.14 (0.13, 0.14) 72.81
Cook et al. (2019) 0.21 (0.20, 0.21) 27.19
Subtotal (I^2 = .%, p = .) 0.16 (0.15, 0.16) 100.00
-.5
0
.5
1
Proportion With Opioid Use

Figure 3


Total Knee Replacement (Total)
Study
ES (95% CI)
% Weight
3 Months
Bedard, Pugely, Westermann et al. (2017) 0.25 (0.25, 0.25) 9.17
Burn et al. (2019) 0.35 (0.35, 0.35) 9.17
Cancienne et al. (2018) 0.32 (0.31, 0.32) 9.17
DeMik et al. (2020) 0.30 (0.30, 0.31) 9.17
Goesling et al. (2016) 0.24 (0.19, 0.30) 8.65
Hadlandsmyth et al. (2018) 0.26 (0.25, 0.27) 9.15
Hansen et al. (2017) 0.05 (0.05, 0.06) 9.17
Namba, Inacio et al. (2018) 0.41 (0.41, 0.42) 9.16
Namba, Singh et al. (2018) 0.42 (0.41, 0.43) 9.16
Ruddell et al. (2020) 0.16 (0.12, 0.20) 8.89
Soffin et al. (2021) 0.11 (0.11, 0.11) 9.17
Subtotal (I^2 = 99.97%, p = 0.00) 0.26 (0.19, 0.33) 100.00
6 Months
Bedard, Pugely, Westermann et al. (2017) 0.16 (0.16, 0.17) 11.60
DeMik et al. (2020) 0.21 (0.21, 0.21) 11.60
Goesling et al. (2016) 0.19 (0.13, 0.25) 9.04
Hadlandsmyth et al. (2018) 0.17 (0.16, 0.18) 11.52
Kalbian et al. (2019) 0.12 (0.09, 0.15) 11.00
Kim et al. (2018) 0.11 (0.08, 0.15) 10.52
Namba, Inacio et al. (2018) 0.31 (0.31, 0.32) 11.57
Namba, Singh et al. (2018) 0.32 (0.32, 0.33) 11.57
Politzer et al. (2018) 0.21 (0.21, 0.22) 11.59
Subtotal (I^2 = 99.79%, p = 0.00) 0.20 (0.17, 0.24) 100.00
9 Months
Bedard, Pugely, Westermann et al. (2017) 0.15 (0.15, 0.15) 20.05
DeMik et al. (2020) 0.19 (0.19, 0.19) 20.05
Jorgensen et al. (2018) 0.19 (0.17, 0.20) 19.87
Namba, Inacio et al. (2018) 0.30 (0.29, 0.30) 20.01
Namba, Singh et al. (2018) 0.30 (0.30, 0.31) 20.01
Subtotal (I^2 = 99.89%, p = 0.00) 0.23 (0.17, 0.28) 100.00
12 Months
Bedard, Pugely, Westermann et al. (2017) 0.15 (0.14, 0.15) 16.68
Cook et al. (2019) 0.24 (0.24, 0.25) 16.67
DeMik et al. (2020) 0.19 (0.19, 0.19) 16.68
Franklin et al. (2010) 0.06 (0.06, 0.07) 16.66
Hadlandsmyth et al. (2018) 0.13 (0.12, 0.14) 16.65
Kuo et al. (2019) 0.46 (0.45, 0.47) 16.67
Subtotal (I^2 = 99.96%, p = 0.00) 0.21 (0.12, 0.29) 100.00
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0
.5
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Proportion With Opioid Use