Opioid use, post-operative complications, and implant survival after unicompartmental versus total knee replacement: a population-based network study

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Abstract

Background

The aim of this study was to compare unicompartmental and total knee replacement (UKR and TKR), emulating the design of the Total or Partial Knee Arthroplasty Trial (TOPKAT) using routinely-collected data. The primary outcome in TOPKAT was patient-reported outcomes, with secondary outcomes including post-operative complications and implant survival.

Methods

Five US and UK healthcare databases, part of the Observational Health Data Sciences and Informatics (OHDSI) network, were analysed. Opioid use from 91 to 365 days after surgery, as a proxy for persistent pain, was assessed. Post-operative complications (venous thromboembolism, infection, readmission, and mortality) were considered over 60 days following surgery and implant survival over five years following surgery. Propensity score matched Cox proportional hazards models were fitted for each outcome. Calibrated hazard ratios (cHRs) were generated for each database to account for observed differences in control outcomes and these were combined using meta-analysis.

Findings

In total, 32,379 and 250,377 individuals who received UKR and TKR were matched and included in the analysis. UKR was associated with a reduced risk of post-operative opioid use (cHR from meta-analysis: 0.81 (95% CI: 0.73 to 0.90)). UKR was also associated with a reduced risk of venous thromboembolism (cHR: 0.62 (0.36 to 0.95)), but little difference was seen for infection (cHR: 0.85 (0.51 to 1.37)) and readmission (cHR: 0.79 (0.47 to 1.25)). There was insufficient evidence to conclude there was a reduction in risk of mortality. UKR was also associated with an increased risk of revision (cHR: 1.64 (1.40 to 1.94)).

Interpretation

UKR was associated with a reduced risk of opioid use compared to TKR, which may indicate a reduced risk of persistent pain after surgery. UKR was associated with a lower risk of venous thromboembolism. UKR was also, however, associated with an increased risk of revision compared to TKR.

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Research in context

Evidence before this study

Prior research has found unicompartmental and total knee replacement (UKR and TKR) to result in broadly similar patient-reported outcomes, UKR to have a lower risk of some post-operative complications, notably venous thromboembolism, infection, and mortality, but TKR to have a lower risk of revision procedures. A recent randomised controlled trial, the Total or Partial Knee Arthroplasty Trial (TOPKAT), compared UKR and TKR, with 264 patients randomised into each arm of the trial. The primary outcome for TOPKAT was post-operative patient-reported outcomes, with secondary outcomes including post-operative complications and implant survival. Consistent with previous observational studies, post-operative patient-reported outcomes were similar at 5 years and fewer complications seen for those who had UKR. However, rates of revision were seen to be similar for UKR and TKR at 5 years. Direct comparisons between the randomised evidence from TOPKAT and observational studies are, however, made difficult though due to differences in study designs.

Added value of this study

This study emulates the TOPKAT design using routinely-collected data. Where possible, similar eligibility criteria were specified and outcomes assessed in a similar manner. Patient-reported outcomes (the primary outcome in TOPKAT) were not available, and so opioid prescriptions were used as a proxy for persistent pain following surgery. Post-operative complications and implant survival were also assessed. The findings from this study will provide further evidence to inform considerations of the relative merits of UKR and TKR.

Implications of all the available evidence

In this study, UKR was associated with a reduced risk of post-operative opioid use between 91 to 365 days after surgery relative to TKR, and this may indicate a reduced risk of persistent pain after UKR. As seen in this study and in previous research, UKR also appears to have a lower risk of venous thromboembolism compared to TKR. However, while revision rates were similar for UKR and TKR in TOPKAT, the findings from this study support that of previous observational research showing UKR to have an increased risk of revision.

Introduction

Knee replacement is one of the most common surgical procedures and typically leads to substantial improvements in pain, function and quality of life.[1] However, there is variation in how knee replacements are performed. One area of particular uncertainty is around whether to use unicompartmental or total knee replacement (UKR or TKR) for those individuals with osteoarthritis confined to a single compartment of the knee. While all the compartments of the joint are replaced in TKR, only the affected part of the joint is replaced in UKR.

With patient-reported pain and function key indications for knee and hip replacement, it follows that they should also be considered as a key measure of the effectiveness of surgery. Previous research has generally found UKR and TKR to result in broadly similar gains in patient-reported outcomes after surgery.[2] Both UKR and TKR are major orthopaedic procedures and so are accompanied by a risk of post-operative complications. Findings from previous research suggests that UKR, which is a quicker and less-invasive procedure relative to TKR, may have a lower risk of some post-operative complications, notably venous thromboembolism, infection, and mortality.[2] As well as the short-term risk of post-operative complications, patients who have had a knee and hip replacement have a long-term risk of revision surgery, in which implant components are removed, added or exchanged. Revision procedures are associated with significant morbidity for individuals, with those undergoing revision surgery generally reporting worse patient-reported outcomes before and after revision procedures compared with those undergoing primary procedures.[3] Observational research has consistently found UKR to have a higher risk of revision procedures compared to TKR, with the increased risk maintained over 25 years after the primary procedure.[2,4]

In a recently published randomised controlled trial comparing UKR and TKR, the Total or Partial Knee Arthroplasty Trial (TOPKAT), 264 patients were randomly assigned UKR with another 264 assigned TKR, with 245 and 269 going on to receive UKR and TKR, respectively. Surgeons performing the procedures were either 'equipoise' surgeons who performed both surgeries, or 'expertise' surgeons who performed only one of the procedures while another 'expertise' surgeon in the same centre performed the other. To perform a given procedure surgeons needed to have been practising it for at a year and to have performed it at least ten times in the previous year.[5] The trial was powered to assess the primary outcome which was self-reported pain and function, as measured by the Oxford Knee Score (OKS).[5] Both groups achieved substantial improvements in OKS relative to baseline scores, with the gains broadly similar across the two comparator groups. Post-operative complications and implant survival were also assessed in TOPKAT as secondary outcomes. Fewer individuals had a post-operative complication after UKR compared to TKR. In contrast to the previous observational research, UKR and TKR were also seen to have similar rates of revision after 5 years in the trial.[6]

The aim of this study was to emulate the TOPKAT trial design using routinely-collected data, so as to answer the same causal question. A study which uses routinely-collected data to emulate the 'target trial' should be harmonised, with similar study designs applied to allow for meaningful comparisons.[7,8] The primary outcome was patient-reported pain and function. As this was not possible, the effect of type of procedure (UKR or TKR) on persistent pain after surgery was considered. Secondary outcomes in the target trial included post-operative complications and implant survival, and these were also assessed in this study.

Methods

A network cohort study was conducted across 5 observational health care databases from the US and the UK. The study period was from 1 January 2005 to 30 April 2018. The study was designed and

performed before the results of TOPKAT became available. To promote transparency and reproducibility, the full study protocol, all code lists used, and source code for the study execution are publicly available at https://github.com/OHDSI/StudyProtocols/tree/master/UkaTkaSafetyEffectiveness.

Data sources

We used data from the following 5 healthcare databases: 1) IBM MarketScan® Commercial Database (CCAE), which includes claims data from individuals in the United States (US) enrolled in employer-sponsored insurance health plans; 2) IBM MarketScan® Medicare Supplemental and Coordination of Benefits Database (MDCR), which includes claims data from older adults in the US with primary or Medicare supplemental coverage through privately insured fee-for-service, point-of-service, or capitated health plans; 3) Optum® de-identified Clinformatics® Datamart, Extended - Date of Death (Optum), which includes US patients fully insured in commercial plans or covered with administrative services only and commercial Medicare; 4) PharMetrics™ Plus (PharMetrics), an adjudicated claims database of privately insured US individuals; and, 5) The Health Improvement Network (THIN), which includes pseudonymised electronic primary care medical records from a representative sample of UK inhabitants. These 5 databases were converted to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM), which enables consistent application of analyses across disparate data sources.[9]

Exposure cohorts

Individuals who underwent either a UKR or TKR were identified. Study participants were required to have data captured over at least the year prior to surgery. We excluded patients using published exclusion criteria of TOPKAT,[5] with individuals required to be aged 40 or over at surgery, and have no prior evidence of knee arthroplasty, knee fracture, knee surgery except for diagnostic procedures, rheumatoid arthritis, inflammatory arthropathies, or septic arthritis. In addition, patients with spine, hip, or foot pathology in the year prior to surgery were also excluded. These criteria were intended to identify patients who were eligible for either type of knee replacement, and exclude patients who were not indicated for either UKR or TKR.

Outcome definitions

Relating to patient-reported outcomes which were the primary outcome in the target trial, persistent pain after surgery was assessed using opioid use (identified by a written or dispensed opioid prescription) as a proxy, with a time-at-risk 91 days after surgery to 1 year after surgery. The 90-day washout period intended to exclude those prescriptions which could be considered as a routine consequence of undergoing surgery. Opioid use was assessed in all databases.

Post-operative complications assessed were symptomatic venous thromboembolism (identified by a diagnosis code of either deep vein thrombosis or pulmonary embolism), infection (identified by a diagnosis of an infection that could be associated with knee replacement), readmission (identified by an inpatient or emergency room visit for any cause), and all-cause mortality. Venous thromboembolism and infection were assessed in all databases, readmission in CCAE, Optum, and MDCR, and mortality in Optum and THIN. Time-at-risk for post-operative complications was from the date of surgery to 60 days after surgery. Meanwhile, implant survival was assessed in terms of revision (identified by a relevant procedure code) with the time-at-risk from date of surgery to 5 years after surgery. Implant survival was assessed in all databases.

Statistical methods

Propensity score matching was used to minimise confounding by observed characteristics.[10] A large set of patient-level baseline covariates (representing demographics, health services utilization, and prior diagnoses, medications, lab tests, and procedures) were constructed for propensity score model input. These covariates were assessed over varying time windows relative to an individual's index date, with them identified from 30 days, 365 days, 1095 days and all available days prior to the index date. Propensity scores were generated using a large-scale regularized logistic regression fitted with a Laplace prior (LASSO) and the optimal hyperparameter determined through 10-fold cross validation in order to balance baseline covariates while avoiding overfitting.[11,12] In the primary analyses, patients were matched on the propensity score using variable-ratio matching with a maximum ratio of UKR to TKR of 1:10. The balance of propensity score-matched cohorts was evaluated using standardized mean difference, with values of <0.1 taken to indicate negligible group differences.[13] Propensity score distribution plots, normalized to the preference scale, were used to evaluate empirical equipoise.[14]

Cox proportional hazards models, with procedure type (UKR or TKR) as the sole explanatory variable and conditioned on the matched sets, were fitted to estimate the average treatment effect among UKR patients on the outcomes listed above. Proportionality of hazards was checked visually using Kaplan-Meier plots. Cox models were also estimated for 39 pre-specified negative control conditions (detailed in Appendix Table A1) believed to have no causal relationship with type of knee replacement. To control for residual confounding, hazard ratios (HRs) for the outcomes of interest were calibrated based on the estimated residual error from negative control outcomes and synthetic positive control outcomes.[15,16] Empirical calibration is a process whereby the residual error of an estimator is quantified and incorporated into a calibrated version of the estimator. The calibrated HR (cHR), in this case, reflects the distribution of estimates on the negative control outcomes. For example, if the negative control estimates are on average greater than the null, an increased risk for the outcome of interested will be attenuated following calibration. The cHRs were only estimated if a sufficient number of control outcomes were observed during a given time-at-risk window. Each analysis was conducted separately in each database.

Findings across databases were combined using meta-analysis, with the inverse variance random-effects approach used.[17] At the request of peer review, results were meta-analysed for each of the outcomes. An I^2 above 40% can, however, be taken to indicate substantial heterogeneity across databases. [18] Estimates for negative and positive controls were pooled before performing empirical calibration on the pooled estimates.

Sensitivity analyses

Pre-specified sensitivity analyses were run for each of the outcomes of interest, with variations of cohort definitions, time-at-risk, and approaches to matching (Appendix Table 2).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report

Results

32,379 individuals who had UKR and 250,377 who had TKR were matched using propensity scores (see Appendix Figure A1 for study flowcharts). Prior to matching, individuals undergoing UKR were younger and healthier than those undergoing TKR (Appendix Table A3). Diagnostics for propensity score matching and control outcome findings are summarised in Appendix Figure A2. After

matching, both cohorts appeared largely comparable in terms of observed characteristics (Table 1 and Appendix Figure 2). Individuals in the matched CCAE, Optum, and PharMetrics cohorts were generally younger and had fewer comorbidities compared to THIN and, in particular, MDCR. THIN covered the broadest age range of individuals. Pre-operative opioid use was well balanced for the comparator groups, with between 30% to 45% of individuals classified as an opioid user before surgery.

UKR was consistently associated with a reduced risk of opioid use after surgery relative to TKR, with cHRs for the use of opioids in the 3 to 12 months post-surgery ranging from 0.70 (0.57 to 0.90) for THIN to 0.86 (0.78 to 0.96) for Optum. The estimate from meta-analysis was 0.81 (0.73 to 0.90). The cumulative incidence of opioid use in the 3 to 12 months post-surgery was around 35% to 40% for UKR and about 5 percentage points higher for TKR in the 4 databases from the US. Opioid use was around 20% for UKR and 25% for TKR in the database from the UK (Appendix Figure A2). These findings were generally similar across sensitivity analyses. When considered up to 5 years, UKR was still associated with a reduced risk of opioid use, but the estimated effects were slightly attenuated with cHRs ranging from 0.86 (0.78 to 0.96) for CCAE to 0.90 (0.82 to 1.02) for MDCR, with no meta-analysis performed for these outcomes.

UKR was consistently associated with a lower risk of venous thromboembolism compared to TKR. The cHRs ranged between 0.47 (0.32 to 0.71) for MDCR and 0.76 (0.59 to 0.99) for CCAE, with the estimate from meta-analysis 0.62 (0.36 to 0.95), see Figure 1. Point estimates for risk of infection and readmission varied from a protective effect for UKR to no difference between the procedures, with cHRs for infection ranged from 0.73 (0.44 to 1.24) for PharMetrics to 1.04 (0.77 to 1.43) for CCAE, while cHRs for readmission ranged from 0.66 (0.46 to 0.97) for MDCR to 0.99 (0.71 to 1.48) for Optum (Figure 1). Estimates from meta-analysis were 0.85 (0.51 to 1.37) and 0.79 (0.47 to 1.25) for infection and readmission, respectively, although in both cases I^2 was above 0.5. Finally, there was little evidence of an association between procedure and mortality, with a cHR of 1.26 (0.55 to 3.09) in Optum and a HR of 0.51 (0.03 to 2.51) in THIN. Findings were broadly similar across sensitivity analyses. There was stronger evidence, however, that UKR was associated with a reduced risk of readmission when considered over the year following surgery rather than 60 days in CCAE and MDCR, cHRs 0.75 (0.66 to 0.86) and 0.76 (0.64 to 0.93), respectively.

UKR was consistently associated with an increased risk of revision compared to TKR over the five years following surgery (Figure 1), with cHRs ranging from 1.48 (1.25 to 1.83) for PharMetrics to 2.16 (1.63 to 3.15) for MDCR. The estimate from meta-analysis was 1.64 (1.40 to 1.94), although I^2 was 0.5. After 5 years, implant survival was generally around 97.5% to 95% for TKR and 95% to 92.5% following UKR (Appendix Figure A3). These findings were similar across the various sensitivity analyses considered.

Results for the primary analysis and each sensitivity analysis are detailed in Appendix Table A4. These can also be viewed, along with study flow charts, characteristics of study participants before and after matching, and propensity score distributions, using the interactive web-based application at http://data.ohdsi.org/UkaTkaSafetyEffectiveness.

Discussion

In summary, compared to TKR, UKR was associated with a reduced risk of post-operative opioid use. This may indicate that UKR has a lower risk of post-operative persistent pain. UKR was also associated with a decreased risk of post-operative venous thromboembolism. There was insufficient

evidence to conclude there UKR led to a reduction in risk of infection, readmission, or mortality. TKR was associated with a lower risk of revision.

The primary outcome in TOPKAT was patient-reported pain and function, as measured by OKS. Outcome scores were broadly similar for the two comparator groups. The mean difference at five years was 1.04 in favour of UKR but this was not statistically significant, with a 95% confidence interval spanning -0.42 to 2.50,[6] and unlikely to be clinically meaningful with the minimal important difference in OKS being 5 points.[19] This finding is in accordance with previous research that has also generally found UKR and TKR to result in broadly similar gains in patient-reported outcomes after surgery.[2] In this study, however, we found UKR to have a lower risk of opioid use, with the absolute effect particularly pronounced for study participants in the US. This suggests that UKR may be associated with a lower risk of persistent pain after surgery. Although few studies have previously assessed procedure choice and opioid use, our findings are consistent with two studies that have.[20,21]

There were fewer post-operative complications for those who received UKR in TOPKAT, with UKR associated with a relative risk reduction of 28% (95% CI: 47% to 2%).[6] This finding is line with those from previous observational studies, where UKR has been associated with a reduced risk for a range of complications relative to TKR.[2,22–24] In particular, a meta-analysis of previous studies of national or large multicentre databases or of joint registry data found UKR to be associated with a risk ratios of 0.39 (0.27 to 0.57) for venous thromboembolism and 0.27 (0.16 to 0.45) for mortality relative to TKR.[2] The results from this study confirm the risk reduction for venous thromboembolism. This risk reduction appears most pronounced for older patients, with the largest effect of procedure seen in MDCR. However, with mortality only available in two databases, there was insufficient evidence to conclude there was a reduction in risk of mortality for UKR in this study. Prior observational studies have typically accounted for differences in the observed characteristics of those undergoing the two procedures, either through propensity score matching or multivariable regression. It is notable that the additional calibration on control outcomes used in this study generally led to associations in favour of UKR being somewhat attenuated.

UKR and TKR were seen to have similar rates of revision in TOPKAT, with rates of revision around 4% at 5 years for both procedures.[6] This finding is in contrast to much of the body of previous observational research, which have consistently found UKR to have a higher risk of revision.[2,4,22,25,26] Indeed, while risk of revision over 5 years after UKR is currently around 6% in the UK, risk for TKR is approximately 2.5%.[26] The incidence of revision for study participants from the UK included in this study are in line with these previous findings, with revision risks seen to be slightly higher for study participants from the US. As with previous observational studies, UKR was also consistently associated with an increased risk of revision in this study. UKR can therefore be expected to have a higher risk of revision than TKR.

This analysis has been informed by data from 280,000 patients across 5 databases in 2 countries. This retrospective analysis relied though on data captured in electronic health records and administrative claims, and therefore our ability to emulate the inclusion criteria used the TOPKAT trial was limited. In particular, these data did not have radiographic information and so it was not possible to assess whether an individual's osteoarthritis was confined to one compartment of the knee. Patient-reported outcomes, the primary outcome in TOPKAT, was also not captured in the databases used and so opioid use was used as a proxy for persistent pain. This has limitations, however, as opioids may not necessarily have been taken even if dispensed. We used large-scale propensity score matching to balance the two cohorts using more than 10,000 candidate baseline characteristics. However, as with all observational studies, there remains the potential risk of

confounding due to unmeasured factors. We employed a large panel of negative control outcomes to mitigate the threat of systematic error. While the definitions for exposures and outcomes were clinically reviewed and relied on codes used in prior published studies,[20,27–30] individual cases were not validated and may be subject to misclassification. There may be measurement errors, for example with baseline characteristics, such as comorbidities, and outcomes, such as revision, potentially not recorded within the databases, in which case they would also be missed in the analysis. As patients in this study were selected on the basis of their inclusion criteria for the TOPKAT trial, the results from this study may also not necessarily generalise to those patients excluded from the trial but are eligible for both procedures. In addition, while meta-analysis was used to combine findings across databases, in a number of cases substantial heterogeneity was present and so the resulting estimates should be interpreted with caution.

In conclusion, with a lower risk of post-operative opioid use, UKR may be associated with a reduced risk of persistent pain compared to TKR. UKR is also associated with a lower risk of venous thromboembolism. UKR is also, however, associated with an increased risk of revision. The merit of using real-world data for assessing the effectiveness of treatments is still debated,[31,32] and randomised controlled trials remain the 'gold standard' for establishing efficacy. This study has demonstrated the value of real-world evidence for complementing the evidence produced from randomised trials.

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Author contributions

All authors made substantial contributions to the conception or design of the work; DPA and PBR led the acquisition of the data; all authors were involved in the analysis and interpretation of data for the work; All authors have contributed to the drafting and revising critically the manuscript for important intellectual content; all authors have given final approval and agree to be accountable for all aspects of the work.

Declaration of interest

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: AS, JW, MvS, NH and PR are full-time employees of Janssen Research & Development, a pharmaceutical company of Johnson & Johnson, and shareholders in Johnson & Johnson. The Johnson & Johnson family of companies also includes DePuy Synthes, which is the maker of medical devices for joint reconstruction. DPA reports research grants from AMGEN, UCB Biopharma and Les Laboratoires Servier. APU reports grants from MRC - DTP Funding. COL is a part-time employee of IQVIA. EB, BB, DM, DR, DY, LHJ, HMS, RC, RPV, SK, TD, WS, YH, AD, RW, TB, VYS and DJC have nothing to disclose.

Ethical approval

This study was approved by THIN's Scientific Review Committee (reference number: 18THIN100).

References

1 Carr AJ, Robertsson O, Graves S, *et al.* Knee replacement. *Lancet* 2012; **379**: 1331–40.

2 Wilson HA, Middleton R, Abram SGF, *et al.* Patient relevant outcomes of unicompartmental versus total knee replacement: systematic review and meta-analysis. *BMJ* 2019; **364**: l352.

3 Greidanus N V., Peterson RC, Masri BA, Garbuz DS. Quality of Life Outcomes in Revision Versus Primary Total Knee Arthroplasty. *J Arthroplasty* 2011; **26**: 615–20.

4 Evans JT, Walker RW, Evans JP, Blom AW, Sayers A, Whitehouse MR. How long does a knee replacement last? A systematic review and meta-analysis of case series and national registry reports with more than 15 years of follow-up. *Lancet* 2019; **393**: 655–63.

5 Beard D, Price A, Cook J, *et al.* Total or Partial Knee Arthroplasty Trial - TOPKAT: Study protocol for a randomised controlled trial. *Trials* 2013; **14**. DOI:10.1186/1745-6215-14-292.

6 Beard DJ, Davies LJ, Cook JA, *et al.* The clinical and cost-effectiveness of total versus partial knee replacement in patients with medial compartment osteoarthritis (TOPKAT): 5-year outcomes of a randomised controlled trial. *Lancet* 2019; **6736**: 5–9.

7 Hernán MA, Robins JM. Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available. *Am J Epidemiol* 2016; **183**: 758–64.

8 Lodi S, Phillips A, Lundgren J, *et al.* Effect estimates in randomized trials and observational studies: comparing apples with apples. *Am J Epidemiol* 2019. DOI:10.1093/aje/kwz100.

9 Voss EA, Makadia R, Matcho A, *et al.* Feasibility and utility of applications of the common data model to multiple, disparate observational health databases. *J Am Med Inf Assoc* 2015; **22**: 553–64.

10 Rubin DJ. Estimating Causal Effects from Large Data Sets Using Propensity Scores. *Ann Intern Med* 1997; **127**. DOI:10.7326/0003-4819-127-8_Part_2-199710151-00064.

11 Suchard MA, Simpson SE, Zorych I, Ryan P, Madigan D. Massive parallelization of serial inference algorithms for a complex generalized linear model. *ACM Trans Model Comput Simul* 2014; **23**: 1–23.

12 Tian Y, Schuemie MJ, Suchard MA. Evaluating large-scale propensity score performance through real-world and synthetic data experiments. *Int J ofEpidemiology* 2018; : 2005–14.

13 Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res* 2011; **46**: 399–424.

14 Walker A, Patrick, Lauer, *et al.* A tool for assessing the feasibility of comparative effectiveness research. *Comp Eff Res* 2013; : 11.

15 Schuemie MJ, Ryan PB, Dumouchel W, Suchard MA, Madigan D. Interpreting observational studies: Why empirical calibration is needed to correct p-values. *Stat Med* 2014; **33**: 209–18.

16 Schuemie MJ, Hripcsak G, Ryan PB, Madigan D, Suchard MA. Empirical confidence interval calibration for population-level effect estimation studies in observational healthcare data. *PNAS* 2018; **115**: 2571–2577.

17 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; **7**: 177–88.

18 Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; **327**: 557–60.

19 Beard DJ, Harris K, Dawson J, *et al.* Meaningful changes for the Oxford hip and knee scores after joint replacement surgery. *J Clin Epidemiol* 2015; **68**: 73–9.

20 Bedard NA, DeMik DE, Dowdle SB, Callaghan JJ. Trends and risk factors for prolonged opioid use after unicompartmental knee arthroplasty. *Bone Joint J* 2018; **100**-**B**: 62–7.

21 Fuzier R, Serres I, Bourrel R, Palmaro A, Montastruc J, Lapeyre-Mestre M. Analgesic drug consumption increases after knee arthroplasty : A pharmacoepidemiological study investigating postoperative pain. *Pain* 2014; **155**: 1339–45.

22 Liddle AD, Judge A, Pandit H, Murray DW. Adverse outcomes after total and unicompartmental knee replacement in 101 330 matched patients: a study of data from the National Joint Registry for England and Wales. *Lancet* 2014; **384**: 1437–45.

23 Hunt LP, Ben-Shlomo Y, Clark EM, *et al.* 45-day mortality after 467779 knee replacements for osteoarthritis from the National Joint Registry for England and Wales: An observational study. *Lancet* 2014; **384**: 1429–36.

24 Brown NM, Sheth NP, Davis K, *et al.* Total Knee Arthroplasty Has Higher Postoperative Morbidity Than Unicompartmental Knee Arthroplasty : A Multicenter Analysis. *J Arthroplasty* 2012; **27**: 86–90.

25 Price AJ, Alvand A, Troelsen A, *et al.* Knee replacement. *Lancet* 2018; **392**: 1672–82.

26 Green M, Wishart N, Young E, Mccormack V, Swanson M. NJR 14th Annual Report. 2017.

27 Bawa H, Weick JW, Dirschl DR, Luu HH. Trends in Deep Vein Thrombosis Prophylaxis and Deep Vein Thrombosis Rates After Total Hip and Knee Arthroplasty. *JAAOS - J Am Acad Orthop Surg* 2018; **26**. https://journals.lww.com/jaaos/Fulltext/2018/10010/Trends_in_Deep_Vein_Thrombosis_Prophylaxis_and.6.aspx.

28 Tamariz L, Harkins T, Nair V. A systematic review of validated methods for identifying venous thromboembolism using administrative and claims data. *Pharmacoepidemiol Drug Saf* 2012; **21**: 154–62.

29 Calderwood MS, Ma A, Khan YM, *et al.* Use of Medicare Diagnosis and Procedure Codes to Improve Detection of Surgical Site Infections following Hip Arthroplasty, Knee Arthroplasty, and Vascular Surgery. *Infect Control & Hosp Epidemiol* 2012; **33**: 40–9.

30 Bedard NA, DeMik DE, Dowdle SB, Owens JM, Liu SS, Callaghan JJ. Preoperative Opioid Use and Its Association With Early Revision of Total Knee Arthroplasty. *J Arthroplasty* 2018; **33**: 3520–3.

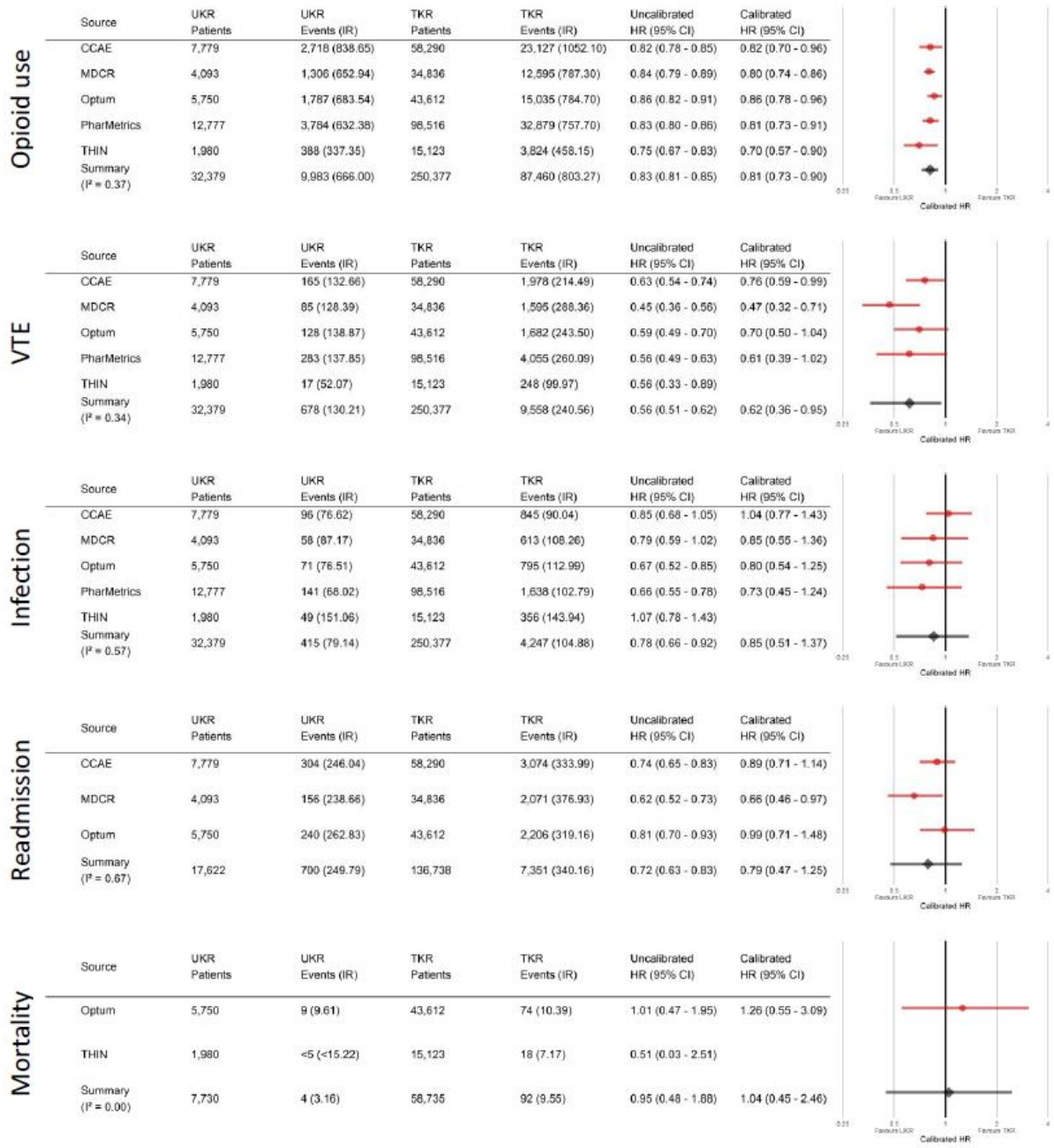
31 Gerstein HC, Mcmurray J, Holman RR. Real-world studies no substitute for RCTs in establishing efficacy. *Lancet* 2019; **393**: 210–1.

32 Sharma M, Nazareth I, Petersen I. Observational studies of treatment effectiveness: worthwhile or worthless? *Clin Epidemiol* 2019; **11**: 35–42.

Figures

Figure 1. Effect of procedure choice (UKR or TKR) on post-operative complications, opioid use, and revision

Numbers of propensity score matched individuals, observed events, HRs and cHRs for UKR relative TKR. Readmission data were not available in PharMetrics and THIN. Mortality data were only available in Optum and THIN. Calibration of hazard ratios was infeasible for post-operative complications in THIN because there were too few negative control events observed during the 60-day time-at-risk. Adjusted HRs account for residual confounding identified by negative control outcomes analyses. Calibrated HRs were not estimated for 60-day outcomes in THIN due to too few control outcomes being observed. UKR: unicompartmental knee replacement; TKR: total knee replacement; HR: Hazard ratio; CI: confidence interval; IR: incidence rate; VTE: venous thromboembolism; MDCR: Medicare Supplemental Database; CCAE: Commercial Database; Optum: Optum De-Identified Clinformatics Data Mart Database; PharMetrics: PharMetrics™ Plus; THIN: The Health Improvement Network.


Opioid use
Source | UKR Patients | UKR Events (IR) | TKR Patients | TKR Events (IR) | Uncalibrated HR (95% CI) | Calibrated HR (95% CI)
CCAE | 7,779 | 2,718 (838.65) | 58,290 | 23,127 (1052.10) | 0.82 (0.78 - 0.85) | 0.82 (0.70 - 0.96)
MDCR | 4,093 | 1,306 (652.94) | 34,836 | 12,595 (787.30) | 0.84 (0.79 - 0.89) | 0.80 (0.74 - 0.86)
Optum | 5,750 | 1,787 (683.54) | 43,612 | 15,035 (784.70) | 0.86 (0.82 - 0.91) | 0.86 (0.78 - 0.96)
PharMetrics | 12,777 | 3,784 (632.38) | 98,516 | 32,879 (757.70) | 0.83 (0.80 - 0.86) | 0.81 (0.73 - 0.91)
THIN | 1,980 | 388 (337.35) | 15,123 | 3,824 (458.15) | 0.75 (0.67 - 0.83) | 0.70 (0.57 - 0.90)
Summary (I² = 0.37) | 32,379 | 9,983 (666.00) | 250,377 | 87,460 (803.27) | 0.83 (0.81 - 0.85) | 0.81 (0.73 - 0.90)
Favours UKR
Favours TKR
Calibrated HR
VTE
Source | UKR Patients | UKR Events (IR) | TKR Patients | TKR Events (IR) | Uncalibrated HR (95% CI) | Calibrated HR (95% CI)
CCAE | 7,779 | 165 (132.66) | 58,290 | 1,978 (214.49) | 0.63 (0.54 - 0.74) | 0.76 (0.59 - 0.99)
MDCR | 4,093 | 85 (128.39) | 34,836 | 1,595 (288.36) | 0.45 (0.36 - 0.56) | 0.47 (0.32 - 0.71)
Optum | 5,750 | 128 (138.87) | 43,612 | 1,682 (243.50) | 0.59 (0.49 - 0.70) | 0.70 (0.50 - 1.04)
PharMetrics | 12,777 | 283 (137.85) | 98,516 | 4,055 (260.09) | 0.56 (0.49 - 0.63) | 0.61 (0.39 - 1.02)
THIN | 1,980 | 17 (52.07) | 15,123 | 248 (99.97) | 0.56 (0.33 - 0.89) |
Summary (I² = 0.34) | 32,379 | 678 (130.21) | 250,377 | 9,558 (240.56) | 0.56 (0.51 - 0.62) | 0.62 (0.36 - 0.95)
Favours UKR
Favours TKR
Calibrated HR
Infection
Source | UKR Patients | UKR Events (IR) | TKR Patients | TKR Events (IR) | Uncalibrated HR (95% CI) | Calibrated HR (95% CI)
CCAE | 7,779 | 96 (76.62) | 58,290 | 845 (90.04) | 0.85 (0.68 - 1.05) | 1.04 (0.77 - 1.43)
MDCR | 4,093 | 58 (87.17) | 34,836 | 613 (108.26) | 0.79 (0.59 - 1.02) | 0.85 (0.55 - 1.36)
Optum | 5,750 | 71 (76.51) | 43,612 | 795 (112.99) | 0.67 (0.52 - 0.85) | 0.80 (0.54 - 1.25)
PharMetrics | 12,777 | 141 (68.02) | 98,516 | 1,638 (102.79) | 0.66 (0.55 - 0.78) | 0.73 (0.45 - 1.24)
THIN | 1,980 | 49 (151.06) | 15,123 | 356 (143.94) | 1.07 (0.78 - 1.43) |
Summary (I² = 0.57) | 32,379 | 415 (79.14) | 250,377 | 4,247 (104.88) | 0.78 (0.66 - 0.92) | 0.85 (0.51 - 1.37)
Favours UKR
Favours TKR
Calibrated HR
Readmission
Source | UKR Patients | UKR Events (IR) | TKR Patients | TKR Events (IR) | Uncalibrated HR (95% CI) | Calibrated HR (95% CI)
CCAE | 7,779 | 304 (246.04) | 58,290 | 3,074 (333.99) | 0.74 (0.65 - 0.83) | 0.89 (0.71 - 1.14)
MDCR | 4,093 | 156 (238.66) | 34,836 | 2,071 (376.93) | 0.62 (0.52 - 0.73) | 0.66 (0.46 - 0.97)
Optum | 5,750 | 240 (262.83) | 43,612 | 2,206 (319.16) | 0.81 (0.70 - 0.93) | 0.99 (0.71 - 1.48)
Summary (I² = 0.67) | 17,622 | 700 (249.79) | 136,738 | 7,351 (340.16) | 0.72 (0.63 - 0.83) | 0.79 (0.47 - 1.25)
Favours UKR
Favours TKR
Calibrated HR
Mortality
Source | UKR Patients | UKR Events (IR) | TKR Patients | TKR Events (IR) | Uncalibrated HR (95% CI) | Calibrated HR (95% CI)
Optum | 5,750 | 9 (9.61) | 43,612 | 74 (10.39) | 1.01 (0.47 - 1.95) | 1.26 (0.55 - 3.09)
THIN | 1,980 | <5 (<15.22) | 15,123 | 18 (7.17) | 0.51 (0.03 - 2.51) |
Summary (I² = 0.00) | 7,730 | 4 (3.16) | 58,735 | 92 (9.55) | 0.95 (0.48 - 1.88) | 1.04 (0.45 - 2.46)
Favours UKR
Favours TKR
Calibrated HR

Tables

Table 1. Selected patient characteristics after propensity score matching

	CCAE			MDCR			Optum			THIN			PharMetrics		
	UKR (%)	TKR (%)	SMD	UKR (%)	TKR (%)	SMD	UKR (%)	TKR (%)	SMD	UKR (%)	TKR (%)	SMD	UKR (%)	TKR (%)	SMD
N	7,779	58,290		4,093	34,836		5,750	43,612		1,980	15,123		12,777	98,516	
Age group															
40-44	2.9	2.6	0.02				1.5	1.2	0.03	1.3	0.8	0.05	2.3	2.2	0.01
45-49	8.2	8.0	0.00				4.3	4.3	0.00	5.4	5.5	0.00	6.8	7.2	-0.02
50-54	19.0	19.1	0.00	<0.1	0.1	-0.01	8.8	9.4	-0.02	10.3	11.0	-0.02	14.6	15.0	-0.01
55-59	29.3	28.3	0.02	0.2	0.4	-0.05	12.8	14.0	-0.03	13.9	16.1	-0.06	22.5	22.9	-0.01
60-64	37.5	38.8	-0.03	0.7	1.2	-0.06	16.0	17.0	-0.03	18.7	20.1	-0.04	27.1	26.9	0.00
65-69	3.1	3.1	0.00	26.9	27.3	-0.01	17.3	17.5	-0.01	18.5	18.1	0.01	12.2	12.0	0.01
70-74				29.2	29.0	0.00	16.6	15.9	0.02	14.2	12.9	0.04	7.5	7.1	0.02
75-79				22.2	21.9	0.01	12.1	11.1	0.03	10.5	9.0	0.05	5.9	5.9	0.00
80-84				14.1	14.1	0.00	7.8	7.3	0.02	4.9	4.2	0.03	1.1	0.8	0.02
85-89				5.8	5.2	0.03	2.8	2.3	0.03	1.8	2.0	-0.02			
90-94				0.9	0.7	0.02				0.5	0.3	0.03			
Gender: female	52.8	53.3	-0.01	47.1	47.9	-0.02	48.3	48.2	0.00	51.4	51.3	0.00	49.4	49.0	0.01
Medical history: General															
Atrial fibrillation	2.3	2.5	-0.01	10.9	10.5	0.02	7.4	7.0	0.02	1.8	2.1	-0.02	4.6	4.3	0.02
Chronic obstructive lung disease	3.7	3.3	0.02	10.2	10.4	-0.01	7.8	7.5	0.01	1.7	1.6	0.01	5.1	5.0	0.00
Depressive disorder	12.2	12.2	0.00	7.9	7.3	0.02	14.4	14.2	0.00	3.8	4.6	-0.04	13.1	13.5	-0.01

Diabetes mellitus	17.7	17.1	0.02	24.3	23.1	0.03	22.3	20.7	0.04	4.0	4.1	0.00	18.7	18.0	0.02
Hyperlipidemia	55.3	54.9	0.01	59.0	57.9	0.02	70.6	68.8	0.04	4.9	4.0	0.05	61.0	60.4	0.01
Hypertensive disorder	56.7	55.4	0.03	72.0	70.2	0.04	68.5	65.6	0.06	10.5	9.9	0.02	60.9	60.1	0.02
Obesity	13.5	13.6	0.00	6.1	6.0	0.00	17.8	17.1	0.02	2.1	1.9	0.01			
Osteoarthritis	90.2	90.2	0.00	89.4	89.0	0.01	92.6	92.6	0.00	48.1	44.9	0.06	91.1	91.4	-0.01
Renal impairment	2.7	2.7	0.00	8.1	7.2	0.03	9.5	9.0	0.02	4.8	4.5	0.02	3.8	3.7	0.00
Peripheral vascular disease	10.1	9.9	0.01	27.7	26.5	0.02	20.4	19.6	0.02	3.6	3.0	0.03	14.0	13.3	0.02
Pulmonary embolism	0.5	0.5	0.00	0.7	0.9	-0.02	0.8	0.9	0.00	0.3	0.4	-0.02	0.7	0.6	0.01
Venous thrombosis	2.4	2.6	-0.01	4.4	4.4	0.00	2.8	3.1	-0.02	2.8	2.2	0.04	3.0	2.9	0.00
Medication use															
Antibacterials for systemic use	75.8	75.5	0.01	76.9	76.6	0.01	68.8	68.2	0.01	10.1	9.6	0.02	61.3	61.8	-0.01
Antidepressants	29.6	29.4	0.00	22.9	22.2	0.02	23.4	23.7	-0.01	0.5	0.9	-0.04	23.0	23.2	-0.01
Antiinflammatory and antirheumatic products	62.1	61.9	0.00	53.2	53.2	0.00	50.6	49.9	0.01	1.6	1.8	-0.01	47.6	47.8	0.00
Antithrombotic agents	17.7	17.7	0.00	26.6	25.9	0.02	19.3	19.3	0.00	1.8	1.2	0.06	14.1	14.0	0.00
Opioids	44.2	44.2	0.00	38.9	38.9	0.00	39.2	39.2	0.00	<0.3	0.5	-0.05	30.9	31.3	-0.01

Select characteristics after propensity score matching, showing the weighted percentage of subjects with the characteristics in the UKR and TKR cohorts.
UKR: unicompartmental knee replacement; TKR: total knee replacement; SMD: standardised mean difference; MDCR: Medicare Supplemental Database;
CCAE: Commercial Database; Optum: Optum De-Identified Clinformatics Data Mart Database; THIN: The Health Improvement Network; PharMetrics:
PharMetrics™ Plus

Appendix

Table A1. Negative control outcomes

1	Acquired hallux malleus	21	Hyperlipidemia
2	Acquired hallux valgus	22	Hypermetropia
3	Acquired trigger finger	23	Hypothyroidism
4	Allergic rhinitis	24	Impacted cerumen
5	Astigmatism	25	Kidney stone
6	Benign neoplasm of colon	26	Menopausal syndrome
7	Breast lump	27	Nicotine dependence
8	Carpal tunnel syndrome	28	Otitis media
9	Cataract	29	Presbyopia
10	Chronic obstructive lung disease	30	Rosacea
11	Diaphragmatic hernia	31	Sleep apnea
12	Disorder of brain	32	Tear film insufficiency
13	Disorder of breast	33	Tinnitus
14	Disorder of lung	34	Type 2 diabetes mellitus
15	Diverticular disease of colon	35	Uncomplicated asthma
16	Essential hypertension	36	Urinary incontinence
17	Gastroesophageal reflux disease with esophagitis	37	Vitamin B deficiency
18	Gastroesophageal reflux disease	38	Vitamin D deficiency
19	Glaucoma	39	Wrist joint pain
20	Hand pain		

Table A2. Tabulation of sensitivity analyses

Target cohort	Comparator cohort	Outcome(s)	Analysis	Time-at-risk	PS matching	Trimming
UKR	TKR	Post-operative complications	Primary	60 days	1:10 variable	None
			Sensitivity	1 year	1:10 variable	None
				5 years	1:10 variable	None
				60 days	1:10 variable	5%
				60 days	1:1	None
		Revision	Primary	5 years	1:10 variable	None
			Sensitivity	1 year	1:10 variable	None
				5 years	1:10 variable	5%
				5 years	1:1	None
		Opioid use	Primary	91 days-1 year	1:10 variable	None
			Sensitivity	91 days-5 years	1:10 variable	None
				91 days-1 year	1:10 variable	5%
				91 days-1 year	1:1	None
UKR without prior spine-hip-foot pathology restriction	TKR without prior spine-hip-foot pathology restriction	Post-operative complications	Sensitivity	60 days	1:10 variable	None
				1 year	1:10 variable	None
				5 years	1:10 variable	None
				60 days	1:10 variable	5%
				60 days	1:1	None
		Revision	Sensitivity	5 years	1:10 variable	None
				1 year	1:10 variable	None
				5 years	1:10 variable	5%
				5 years	1:1	None
		Opioid use	Sensitivity	91 days-1 year	1:10 variable	None
				91 days-5 years	1:10 variable	None
				91 days-1 year	1:10 variable	5%
				91 days-1 year	1:1	None

Figure A1. Study flow charts

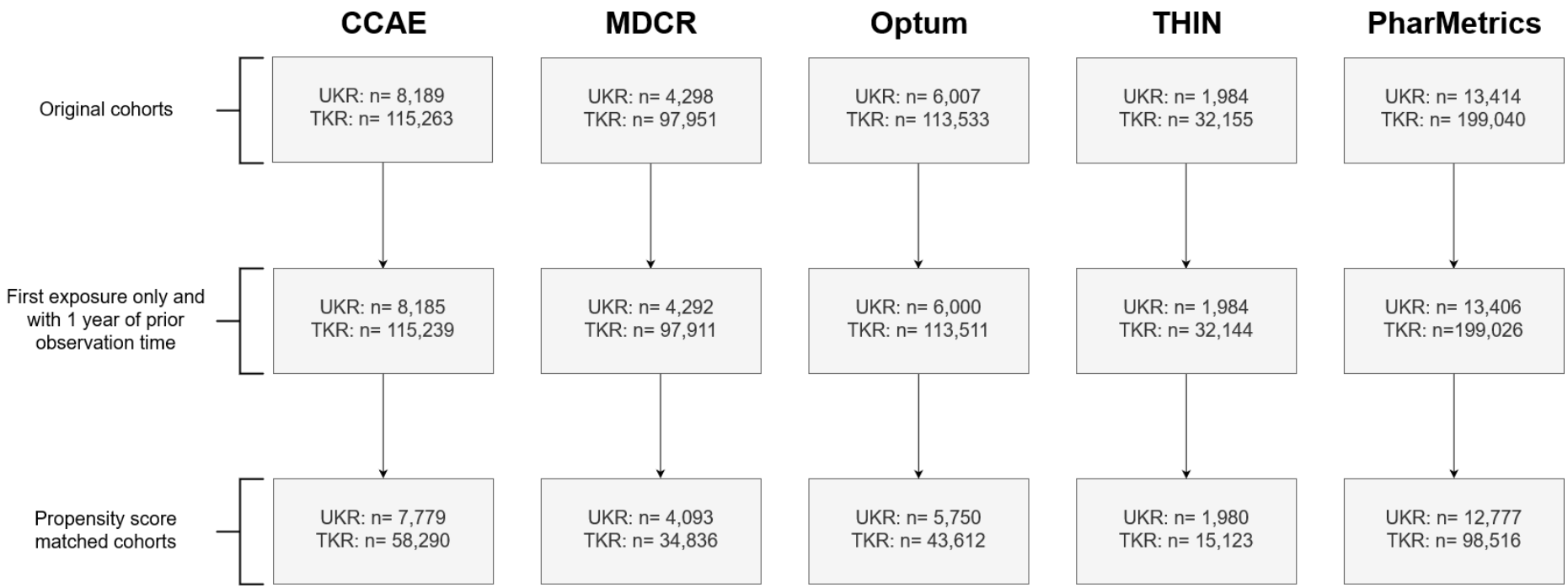


Table A3. Patient characteristics before propensity score matching

	CCAE			MDCR			Optum			THIN			PharMetrics		
	UKR (%)	TKR (%)	SMD	UKR (%)	TKR (%)	SMD	UKR (%)	TKR (%)	SMD	UKR (%)	TKR (%)	SMD	UKR (%)	TKR (%)	SMD
Age group															
40-44	3.0	1.1	0.13				1.5	0.5	0.10	1.3	0.4	0.11	2.4	0.8	0.12
45-49	8.2	4.6	0.15				4.4	1.8	0.16	5.4	1.3	0.23	6.9	3.2	0.17
50-54	19.1	14.0	0.14	<0.1	0.1	0.00	8.9	5.0	0.15	10.3	3.9	0.25	14.7	10.1	0.14
55-59	29.4	30.2	-0.02	0.2	0.3	-0.01	12.9	10.2	0.09	13.9	7.9	0.19	22.7	20.8	0.05
60-64	37.4	45.7	-0.17	0.7	0.7	0.00	16.1	14.5	0.05	18.7	14.2	0.12	27.0	30.3	-0.08
65-69	3.1	4.3	-0.07	27.1	24.2	0.07	17.2	19.1	-0.05	18.4	18.9	-0.01	12.1	15.1	-0.09
70-74				29.2	28.6	0.01	16.5	20.2	-0.10	14.2	19.6	-0.15	7.3	10.6	-0.12
75-79				22.0	24.4	-0.06	11.8	16.5	-0.13	10.4	17.9	-0.22	5.9	7.9	-0.08
80-84				14.0	15.5	-0.04	7.7	10.0	-0.08	4.9	11.0	-0.23	1.1	1.1	0.00
85-89				5.7	5.5	0.01	2.9	2.3	0.03	1.8	4.3	-0.15			
90-94				0.9	0.7	0.02				0.5	0.5	0.00			
Gender: female	52.8	57.1	-0.09	46.4	58.3	-0.24	48.3	58.0	-0.20	51.3	56.6	-0.11	49.0	55.7	-0.13
Medical history: General															
Atrial fibrillation	2.3	3.7	-0.08	10.8	11.7	-0.03	7.3	9.2	-0.07	1.8	3.2	-0.09	4.6	6.2	-0.07
Chronic obstructive lung disease	3.7	4.2	-0.03	10.2	11.2	-0.03	7.7	9.5	-0.06	1.7	2.3	-0.05	5.0	6.4	-0.06
Depressive disorder	12.2	12.6	-0.01	7.9	7.8	0.00	14.4	14.6	0.00	3.8	3.9	-0.01	13.1	13.8	-0.02
Diabetes mellitus	17.4	23.5	-0.15	24.1	27.1	-0.07	22.2	27.8	-0.13	4.0	6.4	-0.11	18.6	24.7	-0.15
Hyperlipidemia	55.2	57.5	-0.05	59.2	55.9	0.07	70.4	72.6	-0.05	5.0	4.2	0.04	61.0	63.9	-0.06
Hypertensive disorder	56.3	65.4	-0.19	71.9	76.1	-0.10	68.2	76.9	-0.20	10.5	12.0	-0.05	60.6	69.7	-0.19
Obesity	13.4	20.0	-0.18	6.1	9.2	-0.12	17.8	23.2	-0.13	2.1	2.0	0.01			

Osteoarthritis	90.3	91.1	-0.02	89.4	89.7	-0.01	92.7	93.9	-0.05	48.1	53.1	-0.10	91.2	91.9	-0.02
Renal impairment	2.7	3.7	-0.06	8.0	8.7	-0.02	9.4	11.7	-0.08	4.8	7.9	-0.13	3.7	5.5	-0.08
Peripheral vascular disease	10.2	12.7	-0.08	27.6	28.5	-0.02	20.4	24.4	-0.10	3.6	3.8	-0.01	13.7	17.6	-0.10
Pulmonary embolism	0.5	0.8	-0.04	0.6	1.2	-0.06	0.8	1.2	-0.04	0.3	0.4	-0.02	0.7	0.9	-0.02
Venous thrombosis	2.4	3.3	-0.05	4.5	5.3	-0.04	2.8	4.3	-0.08	2.8	2.7	0.01	3.0	3.8	-0.04
Medication use															
Antibacterials for systemic use	75.7	75.6	0.00	76.9	78.0	-0.03	69.1	67.9	0.03	10.1	10.8	-0.02	61.3	62.8	-0.03
Antidepressants	29.6	29.9	-0.01	22.9	24.4	-0.04	23.4	23.5	0.00	0.5	0.9	-0.05	22.9	23.1	0.00
Antiinflammatory and antirheumatic products	62.2	63.7	-0.03	53.3	56.3	-0.06	50.9	50.0	0.02	1.6	1.7	-0.01	47.5	48.0	-0.01
Antithrombotic agents	17.6	21.2	-0.09	26.4	29.7	-0.08	19.3	22.2	-0.07	1.8	1.8	0.00	13.8	17.7	-0.11
Opioids	44.2	45.9	-0.04	39.0	42.8	-0.08	39.4	40.2	-0.02	<0.3	0.6	-0.06	30.9	32.1	-0.03

Select characteristics after propensity score matching, showing the weighted percentage of subjects with the characteristics in the UKR and TKR cohorts.
UKR: unicompartmental knee replacement; TKR: total knee replacement; SMD: standardised mean difference; MDCR: Medicare Supplemental Database; CCAE: Commercial Database; Optum: Optum De-Identified Clinformatics Data Mart Database; THIN: The Health Improvement Network; PharMetrics: PharMetrics™ Plus

Figure A2. Diagnostics for primary analysis by database

The first column is the preference score distribution of the UKR and TKR cohorts. The preference score is a transformation of the propensity score that adjusts for differences in the sizes of the two treatment groups. A higher overlap indicates subjects in the two groups were more similar in terms of their predicted probability of receiving one treatment over the other. The second column represents covariate balance before and after matching. Each dot represents the standardizes difference of means for a single covariate before and after matching on the propensity score. The third, fourth, and fifth columns are the effect estimates of negative control outcomes during 60 day, 91 day to 1 year, and 5 year time-at-risk, respectively. Each blue dot represents the estimated hazard ratio and standard error (related to the width of the confidence interval) of each of the negative control outcomes. Estimates below the dashed line have uncalibrated $p < .05$.

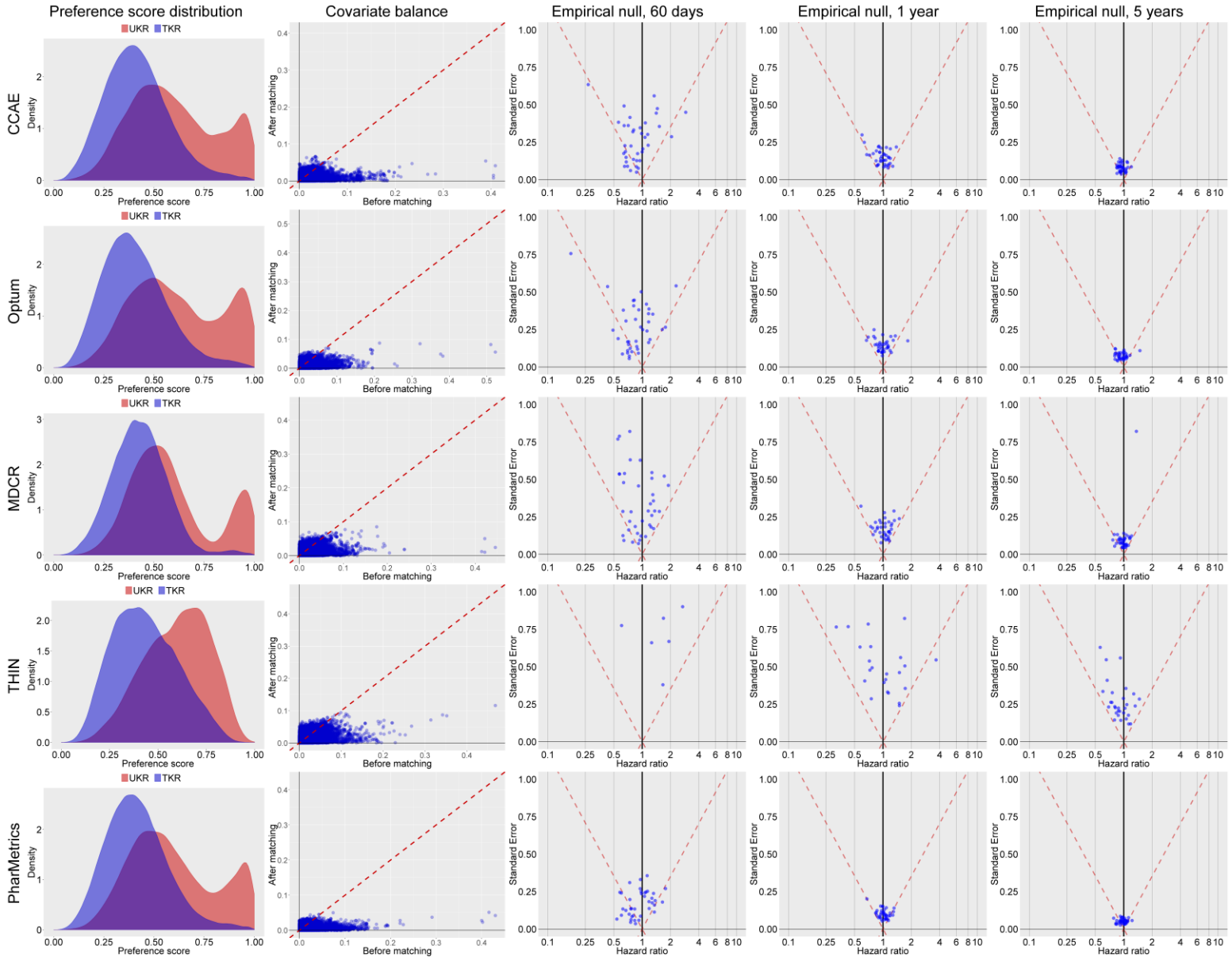

Preference score distribution
Covariate balance
Empirical null, 60 days
Empirical null, 1 year
Empirical null, 5 years
UKR TKR
CCAE
Optum
MDCR
THIN
PharMetrics
Density
Preference score
After matching
Before matching
Standard Error
Hazard ratio

Figure A3. Kaplan-Meier estimates for opioid use (from 91 days after surgery to 1 year) and revision (from day of surgery to 5 years) following unicompartmental knee replacement (UKR) and total knee replacement (TKR)

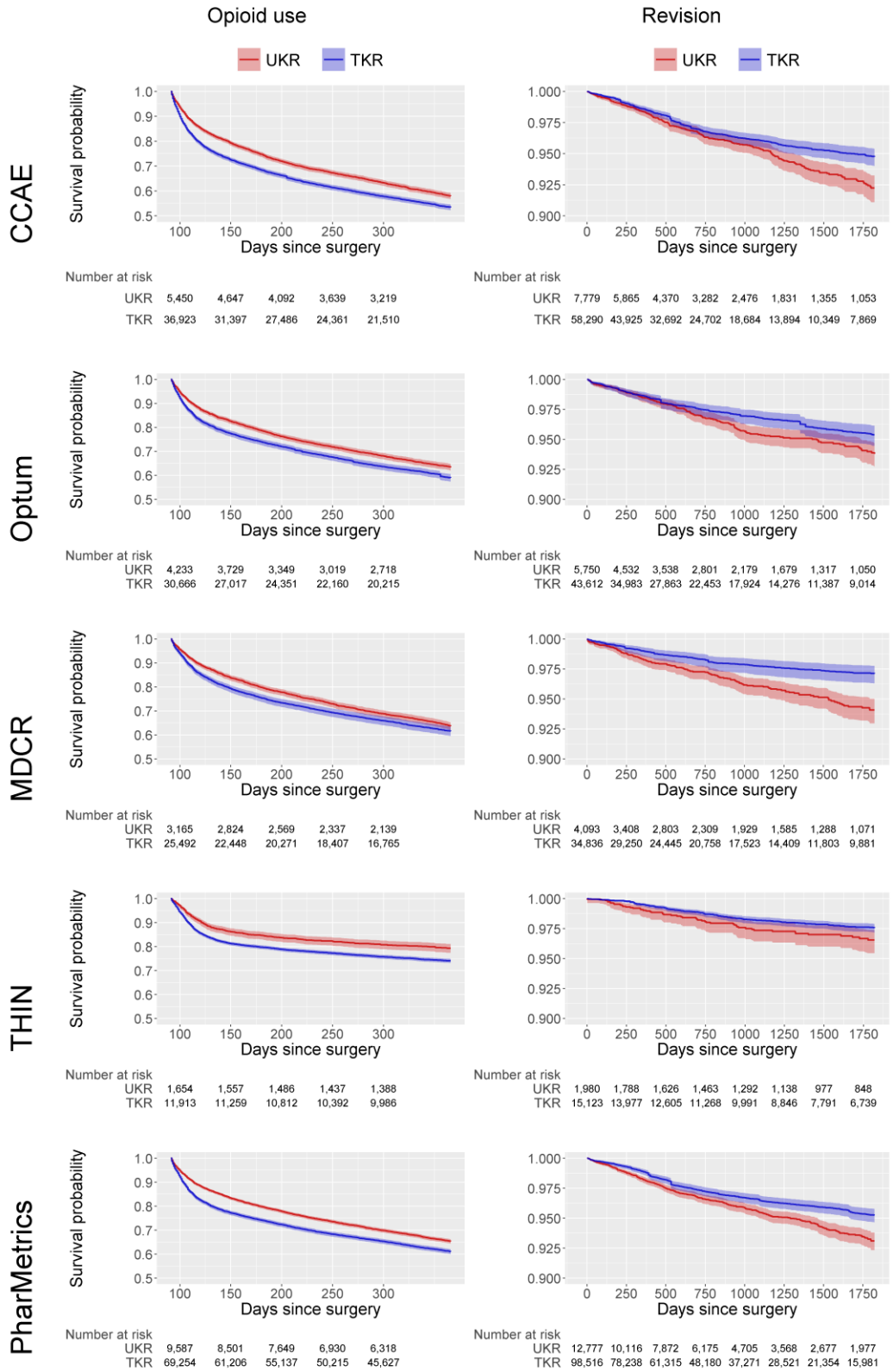


Table A4. Results from all analyses

Outcome	Source	Analysis Name	Analysis	UKR IR	TKR IR	HR (95% CI)	Cal. HR (95% CI)
Venous thromboembolism	CCAE	Primary	10:1 variable ratio matching, 60 day time-at-risk	165 (132.66)	1,978 (214.49)	0.63 (0.54 - 0.74)	0.76 (0.59 - 0.99)
Venous thromboembolism	CCAE	Sensitivity	10:1 variable ratio matching, 1 year time-at-risk	233 (37.04)	2,554 (55.11)	0.67 (0.59 - 0.77)	0.72 (0.60 - 0.87)
Venous thromboembolism	CCAE	Sensitivity	10:1 variable ratio matching, 5 year time-at-risk	319 (19.81)	3,246 (27.47)	0.71 (0.63 - 0.80)	0.74 (0.64 - 0.86)
Venous thromboembolism	CCAE	Sensitivity	10:1 variable ratio matching 5% trim, 60 day time-at-risk	125 (146.03)	1,627 (212.49)	0.69 (0.57 - 0.83)	0.82 (0.63 - 1.07)
Venous thromboembolism	CCAE	Sensitivity	1:1 ratio matching, 60 day time-at-risk	165 (132.66)	279 (227.58)	0.58 (0.48 - 0.71)	0.69 (0.53 - 0.93)
Venous thromboembolism	CCAE	Sensitivity	10:1 variable ratio matching, 60 day time-at-risk; without prior spine-hip-foot pathology restriction	204 (130.40)	2,428 (209.94)	0.63 (0.55 - 0.73)	0.74 (0.56 - 1.01)
Venous thromboembolism	CCAE	Sensitivity	10:1 variable ratio matching, 1 year time-at-risk; without prior spine-hip-foot pathology restriction	293 (37.33)	3,138 (54.40)	0.70 (0.62 - 0.79)	0.73 (0.60 - 0.90)
Venous thromboembolism	CCAE	Sensitivity	10:1 variable ratio matching, 5 year time-at-risk; without prior spine-hip-foot pathology restriction	410 (20.90)	4,005 (27.86)	0.76 (0.69 - 0.85)	0.79 (0.69 - 0.93)
Venous thromboembolism	CCAE	Sensitivity	10:1 variable ratio matching 5% trim, 60 day time-at-risk; without prior spine-hip-foot pathology restriction	147 (136.99)	1,996 (207.78)	0.66 (0.56 - 0.78)	0.78 (0.53 - 1.16)
Venous thromboembolism	CCAE	Sensitivity	1:1 ratio matching, 60 day time-at-risk; without prior spine-hip-foot pathology restriction	204 (130.40)	326 (210.56)	0.62 (0.52 - 0.75)	0.75 (0.57 - 1.00)

Venous thromboembolism	MDCR	Primary	10:1 variable ratio matching, 60 day time-at-risk	85 (128.39)	1,595 (288.36)	0.45 (0.36 - 0.56)	0.47 (0.32 - 0.71)
Venous thromboembolism	MDCR	Sensitivity	10:1 variable ratio matching, 1 year time-at-risk	138 (39.11)	2,183 (74.37)	0.53 (0.45 - 0.63)	0.53 (0.42 - 0.67)
Venous thromboembolism	MDCR	Sensitivity	10:1 variable ratio matching, 5 year time-at-risk	281 (26.11)	3,334 (36.41)	0.71 (0.62 - 0.80)	0.71 (0.60 - 0.84)
Venous thromboembolism	MDCR	Sensitivity	10:1 variable ratio matching 5% trim, 60 day time-at-risk	60 (127.42)	1,317 (291.42)	0.44 (0.34 - 0.57)	0.46 (0.29 - 0.75)
Venous thromboembolism	MDCR	Sensitivity	1:1 ratio matching, 60 day time-at-risk	85 (128.39)	185 (284.53)	0.45 (0.35 - 0.59)	0.51 (0.33 - 0.83)
Venous thromboembolism	MDCR	Sensitivity	10:1 variable ratio matching, 60 day time-at-risk; without prior spine-hip-foot pathology restriction	120 (144.09)	2,096 (302.30)	0.48 (0.40 - 0.58)	0.50 (0.35 - 0.72)
Venous thromboembolism	MDCR	Sensitivity	10:1 variable ratio matching, 1 year time-at-risk; without prior spine-hip-foot pathology restriction	203 (46.32)	2,929 (80.25)	0.57 (0.49 - 0.66)	0.57 (0.46 - 0.72)
Venous thromboembolism	MDCR	Sensitivity	10:1 variable ratio matching, 5 year time-at-risk; without prior spine-hip-foot pathology restriction	372 (28.55)	4,402 (39.80)	0.70 (0.63 - 0.78)	0.69 (0.59 - 0.83)
Venous thromboembolism	MDCR	Sensitivity	10:1 variable ratio matching 5% trim, 60 day time-at-risk; without prior spine-hip-foot pathology restriction	83 (141.20)	1,683 (300.16)	0.47 (0.37 - 0.58)	0.48 (0.33 - 0.70)
Venous thromboembolism	MDCR	Sensitivity	1:1 ratio matching, 60 day time-at-risk; without prior spine-hip-foot pathology restriction	120 (144.09)	256 (312.72)	0.47 (0.37 - 0.58)	0.47 (0.31 - 0.73)
Venous thromboembolism	Optum	Primary	10:1 variable ratio matching, 60 day time-at-risk	128 (138.87)	1,682 (243.50)	0.59 (0.49 - 0.70)	0.70 (0.50 - 1.04)

Venous thromboembolism	Optum	Sensitivity	10:1 variable ratio matching, 1 year time-at-risk	192 (40.36)	2,250 (62.66)	0.66 (0.56 - 0.76)	0.72 (0.58 - 0.91)
Venous thromboembolism	Optum	Sensitivity	10:1 variable ratio matching, 5 year time-at-risk	309 (23.50)	3,239 (31.78)	0.74 (0.65 - 0.84)	0.77 (0.64 - 0.94)
Venous thromboembolism	Optum	Sensitivity	10:1 variable ratio matching 5% trim, 60 day time-at-risk	97 (163.31)	1,333 (240.40)	0.69 (0.56 - 0.84)	0.85 (0.59 - 1.31)
Venous thromboembolism	Optum	Sensitivity	1:1 ratio matching, 60 day time-at-risk	128 (138.87)	225 (247.57)	0.55 (0.44 - 0.69)	0.69 (0.53 - 0.92)
Venous thromboembolism	Optum	Sensitivity	10:1 variable ratio matching, 60 day time-at-risk; without prior spine-hip-foot pathology restriction	173 (141.27)	2,269 (244.75)	0.59 (0.50 - 0.69)	0.71 (0.53 - 0.99)
Venous thromboembolism	Optum	Sensitivity	10:1 variable ratio matching, 1 year time-at-risk; without prior spine-hip-foot pathology restriction	267 (42.63)	3,060 (64.07)	0.67 (0.59 - 0.77)	0.71 (0.57 - 0.90)
Venous thromboembolism	Optum	Sensitivity	10:1 variable ratio matching, 5 year time-at-risk; without prior spine-hip-foot pathology restriction	430 (25.54)	4,388 (33.11)	0.77 (0.69 - 0.86)	0.78 (0.66 - 0.93)
Venous thromboembolism	Optum	Sensitivity	10:1 variable ratio matching 5% trim, 60 day time-at-risk; without prior spine-hip-foot pathology restriction	126 (158.71)	1,792 (240.72)	0.66 (0.55 - 0.79)	0.81 (0.61 - 1.15)
Venous thromboembolism	Optum	Sensitivity	1:1 ratio matching, 60 day time-at-risk; without prior spine-hip-foot pathology restriction	173 (141.27)	325 (269.34)	0.52 (0.43 - 0.63)	0.67 (0.53 - 0.87)
Venous thromboembolism	thin	Primary	10:1 variable ratio matching, 60 day time-at-risk	17 (52.07)	248 (99.97)	0.56 (0.33 - 0.89)	0.33 (0.20 - 0.53)
Venous thromboembolism	thin	Sensitivity	10:1 variable ratio matching, 1 year time-at-risk	31 (16.83)	369 (26.25)	0.70 (0.47 - 0.99)	NA (NA - NA)

Venous thromboembolism	thin	Sensitivity	10:1 variable ratio matching, 5 year time-at-risk	75 (11.08)	666 (12.89)	0.91 (0.70 - 1.16)	0.95 (0.75 - 1.23)
Venous thromboembolism	thin	Sensitivity	10:1 variable ratio matching 5% trim, 60 day time-at-risk	13 (52.56)	204 (99.45)	0.54 (0.29 - 0.91)	0.36 (0.20 - 0.66)
Venous thromboembolism	thin	Sensitivity	1:1 ratio matching, 60 day time-at-risk	17 (52.07)	29 (89.07)	0.61 (0.33 - 1.10)	0.44 (0.25 - 0.77)
Venous thromboembolism	thin	Sensitivity	10:1 variable ratio matching, 60 day time-at-risk; without prior spine-hip-foot pathology restriction	18 (49.39)	291 (104.24)	0.51 (0.30 - 0.80)	0.30 (0.18 - 0.49)
Venous thromboembolism	thin	Sensitivity	10:1 variable ratio matching, 1 year time-at-risk; without prior spine-hip-foot pathology restriction	33 (16.03)	443 (28.02)	0.60 (0.41 - 0.84)	0.55 (0.39 - 0.79)
Venous thromboembolism	thin	Sensitivity	10:1 variable ratio matching, 5 year time-at-risk; without prior spine-hip-foot pathology restriction	83 (10.97)	765 (13.15)	0.87 (0.68 - 1.09)	0.88 (0.70 - 1.11)
Venous thromboembolism	thin	Sensitivity	10:1 variable ratio matching 5% trim, 60 day time-at-risk; without prior spine-hip-foot pathology restriction	13 (46.78)	253 (109.31)	0.43 (0.23 - 0.72)	0.22 (0.12 - 0.44)
Venous thromboembolism	thin	Sensitivity	1:1 ratio matching, 60 day time-at-risk; without prior spine-hip-foot pathology restriction	18 (49.39)	34 (93.52)	0.50 (0.27 - 0.88)	0.39 (0.22 - 0.69)
Venous thromboembolism	pmtx	Primary	10:1 variable ratio matching, 60 day time-at-risk	283 (137.85)	4,055 (260.09)	0.56 (0.49 - 0.63)	0.61 (0.39 - 1.02)
Venous thromboembolism	pmtx	Sensitivity	10:1 variable ratio matching, 1 year time-at-risk	419 (39.40)	5,235 (65.06)	0.64 (0.58 - 0.71)	0.68 (0.55 - 0.86)
Venous thromboembolism	pmtx	Sensitivity	10:1 variable ratio matching, 5 year time-at-risk	627 (21.77)	6,962 (31.90)	0.70 (0.65 - 0.77)	0.76 (0.67 - 0.87)

Venous thromboembolism	pmtx	Sensitivity	10:1 variable ratio matching 5% trim, 60 day time-at-risk	207 (145.49)	3,368 (259.88)	0.57 (0.49 - 0.65)	0.61 (0.36 - 1.08)
Venous thromboembolism	pmtx	Sensitivity	1:1 ratio matching, 60 day time-at-risk	283 (137.85)	494 (243.91)	0.56 (0.48 - 0.65)	0.64 (0.42 - 1.01)
Venous thromboembolism	pmtx	Sensitivity	10:1 variable ratio matching, 60 day time-at-risk; without prior spine-hip-foot pathology restriction	362 (137.65)	5,182 (259.72)	0.56 (0.51 - 0.63)	0.62 (0.40 - 1.00)
Venous thromboembolism	pmtx	Sensitivity	10:1 variable ratio matching, 1 year time-at-risk; without prior spine-hip-foot pathology restriction	537 (39.69)	6,738 (65.77)	0.64 (0.58 - 0.70)	0.67 (0.55 - 0.85)
Venous thromboembolism	pmtx	Sensitivity	10:1 variable ratio matching, 5 year time-at-risk; without prior spine-hip-foot pathology restriction	808 (22.45)	8,926 (32.58)	0.72 (0.66 - 0.77)	0.77 (0.68 - 0.88)
Venous thromboembolism	pmtx	Sensitivity	10:1 variable ratio matching 5% trim, 60 day time-at-risk; without prior spine-hip-foot pathology restriction	264 (145.13)	4,281 (258.68)	0.57 (0.50 - 0.64)	0.60 (0.35 - 1.05)
Venous thromboembolism	pmtx	Sensitivity	1:1 ratio matching, 60 day time-at-risk; without prior spine-hip-foot pathology restriction	362 (137.65)	627 (242.23)	0.57 (0.50 - 0.65)	0.65 (0.45 - 0.98)
Venous thromboembolism	Meta-analysis	Primary	10:1 variable ratio matching, 60 day time-at-risk	678 (130.21)	9,558 (240.56)	0.56 (0.51 - 0.62)	0.62 (0.36 - 0.95)
Venous thromboembolism	Meta-analysis	Sensitivity	10:1 variable ratio matching, 1 year time-at-risk	1,013 (37.45)	12,591 (61.08)	0.64 (0.59 - 0.69)	0.66 (0.53 - 0.81)
Venous thromboembolism	Meta-analysis	Sensitivity	10:1 variable ratio matching, 5 year time-at-risk	1,611 (21.31)	17,447 (30.00)	0.72 (0.68 - 0.76)	0.75 (0.66 - 0.84)
Venous thromboembolism	Meta-analysis	Sensitivity	10:1 variable ratio matching 5% trim, 60 day time-at-risk	502 (139.79)	7,849 (239.80)	0.59 (0.51 - 0.69)	0.63 (0.36 - 1.02)

Venous thromboembolism	Meta-analysis	Sensitivity	1:1 ratio matching, 60 day time-at-risk	678 (130.21)	1,212 (235.99)	0.55 (0.50 - 0.60)	0.63 (0.39 - 0.94)
Venous thromboembolism	Meta-analysis	Sensitivity	10:1 variable ratio matching, 60 day time-at-risk; without prior spine-hip-foot pathology restriction	877 (132.56)	12,266 (242.83)	0.57 (0.52 - 0.62)	0.62 (0.38 - 0.94)
Venous thromboembolism	Meta-analysis	Sensitivity	10:1 variable ratio matching, 1 year time-at-risk; without prior spine-hip-foot pathology restriction	1,333 (39.11)	16,308 (62.67)	0.65 (0.60 - 0.69)	0.66 (0.52 - 0.82)
Venous thromboembolism	Meta-analysis	Sensitivity	10:1 variable ratio matching, 5 year time-at-risk; without prior spine-hip-foot pathology restriction	2,103 (22.60)	22,486 (31.27)	0.74 (0.70 - 0.78)	0.76 (0.65 - 0.87)
Venous thromboembolism	Meta-analysis	Sensitivity	10:1 variable ratio matching 5% trim, 60 day time-at-risk; without prior spine-hip-foot pathology restriction	633 (139.07)	10,005 (240.96)	0.58 (0.51 - 0.66)	0.62 (0.37 - 0.97)
Venous thromboembolism	Meta-analysis	Sensitivity	1:1 ratio matching, 60 day time-at-risk; without prior spine-hip-foot pathology restriction	877 (132.56)	1,568 (240.29)	0.55 (0.50 - 0.61)	0.63 (0.41 - 0.90)
Post-operative infection	CCAE	Primary	10:1 variable ratio matching, 60 day time-at-risk	96 (76.62)	845 (90.04)	0.85 (0.68 - 1.05)	1.04 (0.77 - 1.43)
Post-operative infection	CCAE	Sensitivity	10:1 variable ratio matching, 1 year time-at-risk	164 (25.84)	1,396 (29.53)	0.88 (0.74 - 1.03)	0.94 (0.76 - 1.18)
Post-operative infection	CCAE	Sensitivity	10:1 variable ratio matching, 5 year time-at-risk	231 (14.18)	1,996 (16.55)	0.86 (0.74 - 0.99)	0.90 (0.76 - 1.07)
Post-operative infection	CCAE	Sensitivity	10:1 variable ratio matching 5% trim, 60 day time-at-risk	68 (78.76)	673 (86.36)	0.93 (0.71 - 1.18)	1.12 (0.81 - 1.57)
Post-operative infection	CCAE	Sensitivity	1:1 ratio matching, 60 day time-at-risk	96 (76.62)	122 (97.73)	0.81 (0.61 - 1.05)	0.99 (0.70 - 1.43)
Post-operative infection	CCAE	Sensitivity	10:1 variable ratio matching, 60 day time-at-risk; without prior spine-hip-foot pathology restriction	123 (78.09)	1,100 (93.57)	0.84 (0.69 - 1.01)	1.00 (0.72 - 1.42)
Post-operative infection	CCAE	Sensitivity	10:1 variable ratio matching, 1 year time-at-risk; without prior spine-hip-foot pathology restriction	199 (25.12)	1,815 (30.89)	0.82 (0.70 - 0.95)	0.85 (0.68 - 1.09)

Post-operative infection	CCAE	Sensitivity	10:1 variable ratio matching, 5 year time-at-risk; without prior spine-hip-foot pathology restriction	281 (14.14)	2,581 (17.61)	0.81 (0.71 - 0.92)	0.84 (0.71 - 1.01)
Post-operative infection	CCAE	Sensitivity	10:1 variable ratio matching 5% trim, 60 day time-at-risk; without prior spine-hip-foot pathology restriction	88 (81.39)	899 (92.09)	0.90 (0.72 - 1.11)	1.07 (0.71 - 1.64)
Post-operative infection	CCAE	Sensitivity	1:1 ratio matching, 60 day time-at-risk; without prior spine-hip-foot pathology restriction	123 (78.09)	135 (85.66)	0.90 (0.70 - 1.15)	1.10 (0.79 - 1.56)
Post-operative infection	MDCR	Primary	10:1 variable ratio matching, 60 day time-at-risk	58 (87.17)	613 (108.26)	0.79 (0.59 - 1.02)	0.85 (0.55 - 1.36)
Post-operative infection	MDCR	Sensitivity	10:1 variable ratio matching, 1 year time-at-risk	85 (23.87)	943 (31.12)	0.73 (0.57 - 0.91)	0.72 (0.55 - 0.98)
Post-operative infection	MDCR	Sensitivity	10:1 variable ratio matching, 5 year time-at-risk	147 (13.30)	1,524 (15.91)	0.79 (0.65 - 0.94)	0.79 (0.64 - 0.99)
Post-operative infection	MDCR	Sensitivity	10:1 variable ratio matching 5% trim, 60 day time-at-risk	44 (93.10)	493 (106.50)	0.87 (0.63 - 1.18)	0.94 (0.56 - 1.66)
Post-operative infection	MDCR	Sensitivity	1:1 ratio matching, 60 day time-at-risk	58 (87.17)	82 (123.58)	0.71 (0.51 - 1.00)	0.84 (0.50 - 1.47)
Post-operative infection	MDCR	Sensitivity	10:1 variable ratio matching, 60 day time-at-risk; without prior spine-hip-foot pathology restriction	70 (83.42)	779 (109.66)	0.75 (0.58 - 0.96)	0.81 (0.54 - 1.23)
Post-operative infection	MDCR	Sensitivity	10:1 variable ratio matching, 1 year time-at-risk; without prior spine-hip-foot pathology restriction	108 (24.32)	1,185 (31.34)	0.74 (0.60 - 0.91)	0.75 (0.58 - 1.00)
Post-operative infection	MDCR	Sensitivity	10:1 variable ratio matching, 5 year time-at-risk; without prior spine-hip-foot pathology restriction	191 (14.19)	1,910 (16.41)	0.81 (0.69 - 0.94)	0.80 (0.65 - 1.01)
Post-operative infection	MDCR	Sensitivity	10:1 variable ratio matching 5% trim, 60 day time-at-risk; without prior spine-hip-foot pathology restriction	51 (86.18)	619 (107.76)	0.80 (0.59 - 1.05)	0.85 (0.56 - 1.31)
Post-operative infection	MDCR	Sensitivity	1:1 ratio matching, 60 day time-at-risk; without prior spine-hip-foot pathology restriction	70 (83.42)	87 (103.52)	0.80 (0.58 - 1.10)	0.87 (0.52 - 1.48)
Post-operative infection	Optum	Primary	10:1 variable ratio matching, 60 day time-at-risk	71 (76.51)	795 (112.99)	0.67 (0.52 - 0.85)	0.80 (0.54 - 1.25)
Post-operative infection	Optum	Sensitivity	10:1 variable ratio matching, 1 year time-at-risk	124 (25.82)	1,248 (34.00)	0.73 (0.60 - 0.88)	0.79 (0.62 - 1.05)
Post-operative infection	Optum	Sensitivity	10:1 variable ratio matching, 5 year time-at-risk	177 (13.18)	1,791 (17.00)	0.76 (0.64 - 0.89)	0.79 (0.63 - 1.00)

Post-operative infection	Optum	Sensitivity	10:1 variable ratio matching 5% trim, 60 day time-at-risk	46 (76.80)	633 (112.09)	0.70 (0.51 - 0.93)	0.86 (0.56 - 1.41)
Post-operative infection	Optum	Sensitivity	1:1 ratio matching, 60 day time-at-risk	71 (76.51)	99 (106.81)	0.72 (0.53 - 0.98)	0.93 (0.65 - 1.35)
Post-operative infection	Optum	Sensitivity	10:1 variable ratio matching, 60 day time-at-risk; without prior spine-hip-foot pathology restriction	90 (72.90)	1,083 (114.68)	0.62 (0.49 - 0.76)	0.74 (0.54 - 1.09)
Post-operative infection	Optum	Sensitivity	10:1 variable ratio matching, 1 year time-at-risk; without prior spine-hip-foot pathology restriction	160 (25.24)	1,687 (34.54)	0.71 (0.59 - 0.83)	0.74 (0.59 - 0.97)
Post-operative infection	Optum	Sensitivity	10:1 variable ratio matching, 5 year time-at-risk; without prior spine-hip-foot pathology restriction	239 (13.86)	2,429 (17.75)	0.75 (0.65 - 0.86)	0.75 (0.63 - 0.93)
Post-operative infection	Optum	Sensitivity	10:1 variable ratio matching 5% trim, 60 day time-at-risk; without prior spine-hip-foot pathology restriction	54 (67.40)	835 (110.12)	0.60 (0.45 - 0.78)	0.73 (0.51 - 1.10)
Post-operative infection	Optum	Sensitivity	1:1 ratio matching, 60 day time-at-risk; without prior spine-hip-foot pathology restriction	90 (72.90)	160 (130.22)	0.56 (0.43 - 0.73)	0.73 (0.54 - 1.01)
Post-operative infection	thin	Primary	10:1 variable ratio matching, 60 day time-at-risk	49 (151.06)	356 (143.94)	1.07 (0.78 - 1.43)	0.61 (0.45 - 0.83)
Post-operative infection	thin	Sensitivity	10:1 variable ratio matching, 1 year time-at-risk	55 (30.27)	424 (30.30)	1.02 (0.76 - 1.34)	NA (NA - NA)
Post-operative infection	thin	Sensitivity	10:1 variable ratio matching, 5 year time-at-risk	78 (11.64)	592 (11.45)	1.02 (0.79 - 1.29)	1.05 (0.83 - 1.36)
Post-operative infection	thin	Sensitivity	10:1 variable ratio matching 5% trim, 60 day time-at-risk	39 (158.84)	292 (142.77)	1.18 (0.83 - 1.62)	0.82 (0.58 - 1.16)
Post-operative infection	thin	Sensitivity	1:1 ratio matching, 60 day time-at-risk	49 (151.06)	47 (145.31)	1.04 (0.70 - 1.57)	0.73 (0.50 - 1.06)
Post-operative infection	thin	Sensitivity	10:1 variable ratio matching, 60 day time-at-risk; without prior spine-hip-foot pathology restriction	55 (151.98)	392 (140.70)	1.11 (0.82 - 1.46)	0.67 (0.49 - 0.92)
Post-operative infection	thin	Sensitivity	10:1 variable ratio matching, 1 year time-at-risk; without prior spine-hip-foot pathology restriction	66 (32.54)	475 (30.14)	1.10 (0.84 - 1.41)	1.02 (0.78 - 1.32)
Post-operative infection	thin	Sensitivity	10:1 variable ratio matching, 5 year time-at-risk; without prior spine-hip-foot pathology restriction	95 (12.71)	678 (11.64)	1.10 (0.87 - 1.36)	1.08 (0.87 - 1.37)
Post-operative infection	thin	Sensitivity	10:1 variable ratio matching 5% trim, 60 day time-at-risk; without prior spine-hip-foot pathology restriction	46 (167.00)	323 (139.77)	1.23 (0.89 - 1.66)	0.73 (0.47 - 1.24)

Post-operative infection	thin	Sensitivity	1:1 ratio matching, 60 day time-at-risk; without prior spine-hip-foot pathology restriction	55 (151.98)	63 (174.26)	0.89 (0.61 - 1.28)	0.68 (0.47 - 0.98)
Post-operative infection	pmtx	Primary	10:1 variable ratio matching, 60 day time-at-risk	141 (68.02)	1,638 (102.79)	0.66 (0.55 - 0.78)	0.73 (0.45 - 1.24)
Post-operative infection	pmtx	Sensitivity	10:1 variable ratio matching, 1 year time-at-risk	227 (21.02)	2,569 (31.07)	0.69 (0.60 - 0.79)	0.74 (0.58 - 0.95)
Post-operative infection	pmtx	Sensitivity	10:1 variable ratio matching, 5 year time-at-risk	347 (11.78)	3,768 (16.69)	0.72 (0.64 - 0.80)	0.77 (0.67 - 0.90)
Post-operative infection	pmtx	Sensitivity	10:1 variable ratio matching 5% trim, 60 day time-at-risk	90 (62.53)	1,336 (100.85)	0.61 (0.49 - 0.75)	0.66 (0.37 - 1.20)
Post-operative infection	pmtx	Sensitivity	1:1 ratio matching, 60 day time-at-risk	141 (68.02)	219 (106.06)	0.63 (0.51 - 0.78)	0.72 (0.46 - 1.18)
Post-operative infection	pmtx	Sensitivity	10:1 variable ratio matching, 60 day time-at-risk; without prior spine-hip-foot pathology restriction	195 (73.46)	2,193 (107.62)	0.69 (0.59 - 0.80)	0.76 (0.48 - 1.25)
Post-operative infection	pmtx	Sensitivity	10:1 variable ratio matching, 1 year time-at-risk; without prior spine-hip-foot pathology restriction	312 (22.74)	3,521 (33.48)	0.69 (0.61 - 0.78)	0.73 (0.58 - 0.93)
Post-operative infection	pmtx	Sensitivity	10:1 variable ratio matching, 5 year time-at-risk; without prior spine-hip-foot pathology restriction	475 (12.91)	5,118 (18.08)	0.72 (0.65 - 0.79)	0.77 (0.68 - 0.89)
Post-operative infection	pmtx	Sensitivity	10:1 variable ratio matching 5% trim, 60 day time-at-risk; without prior spine-hip-foot pathology restriction	128 (69.62)	1,774 (104.93)	0.66 (0.55 - 0.79)	0.70 (0.40 - 1.25)
Post-operative infection	pmtx	Sensitivity	1:1 ratio matching, 60 day time-at-risk; without prior spine-hip-foot pathology restriction	195 (73.46)	291 (110.28)	0.67 (0.56 - 0.80)	0.77 (0.52 - 1.19)
Post-operative infection	Meta-analysis	Primary	10:1 variable ratio matching, 60 day time-at-risk	415 (79.14)	4,247 (104.88)	0.78 (0.66 - 0.92)	0.85 (0.51 - 1.37)
Post-operative infection	Meta-analysis	Sensitivity	10:1 variable ratio matching, 1 year time-at-risk	655 (23.97)	6,580 (31.19)	0.78 (0.69 - 0.89)	0.82 (0.64 - 1.02)
Post-operative infection	Meta-analysis	Sensitivity	10:1 variable ratio matching, 5 year time-at-risk	980 (12.74)	9,671 (16.14)	0.80 (0.72 - 0.89)	0.83 (0.71 - 0.96)
Post-operative infection	Meta-analysis	Sensitivity	10:1 variable ratio matching 5% trim, 60 day time-at-risk	287 (79.28)	3,427 (102.72)	0.82 (0.65 - 1.03)	0.88 (0.50 - 1.52)
Post-operative infection	Meta-analysis	Sensitivity	1:1 ratio matching, 60 day time-at-risk	415 (79.14)	569 (108.86)	0.74 (0.64 - 0.86)	0.85 (0.53 - 1.31)

Post-operative infection	Meta-analysis	Sensitivity	10:1 variable ratio matching, 60 day time-at-risk; without prior spine-hip-foot pathology restriction	533 (79.97)	5,547 (107.78)	0.77 (0.65 - 0.91)	0.84 (0.51 - 1.33)
Post-operative infection	Meta-analysis	Sensitivity	10:1 variable ratio matching, 1 year time-at-risk; without prior spine-hip-foot pathology restriction	845 (24.53)	8,683 (32.60)	0.78 (0.68 - 0.89)	0.80 (0.62 - 1.01)
Post-operative infection	Meta-analysis	Sensitivity	10:1 variable ratio matching, 5 year time-at-risk; without prior spine-hip-foot pathology restriction	1,281 (13.51)	12,716 (17.16)	0.81 (0.72 - 0.90)	0.82 (0.69 - 0.97)
Post-operative infection	Meta-analysis	Sensitivity	10:1 variable ratio matching 5% trim, 60 day time-at-risk; without prior spine-hip-foot pathology restriction	367 (79.99)	4,450 (105.18)	0.80 (0.64 - 1.00)	0.86 (0.50 - 1.43)
Post-operative infection	Meta-analysis	Sensitivity	1:1 ratio matching, 60 day time-at-risk; without prior spine-hip-foot pathology restriction	533 (79.97)	736 (110.75)	0.74 (0.62 - 0.88)	0.84 (0.55 - 1.26)
Readmission	CCAE	Primary	10:1 variable ratio matching, 60 day time-at-risk	304 (246.04)	3,074 (333.99)	0.74 (0.65 - 0.83)	0.89 (0.71 - 1.14)
Readmission	CCAE	Sensitivity	10:1 variable ratio matching, 1 year time-at-risk	1,018 (171.85)	10,746 (252.35)	0.70 (0.65 - 0.75)	0.75 (0.66 - 0.86)
Readmission	CCAE	Sensitivity	10:1 variable ratio matching, 5 year time-at-risk	1,811 (135.35)	17,195 (184.78)	0.75 (0.71 - 0.79)	0.78 (0.71 - 0.86)
Readmission	CCAE	Sensitivity	10:1 variable ratio matching 5% trim, 60 day time-at-risk	222 (261.15)	2,523 (330.17)	0.79 (0.68 - 0.90)	0.94 (0.74 - 1.20)
Readmission	CCAE	Sensitivity	1:1 ratio matching, 60 day time-at-risk	304 (246.04)	400 (326.32)	0.75 (0.64 - 0.87)	0.91 (0.71 - 1.19)
Readmission	CCAE	Sensitivity	10:1 variable ratio matching, 60 day time-at-risk; without prior spine-hip-foot pathology restriction	407 (262.31)	3,904 (338.66)	0.78 (0.71 - 0.87)	0.93 (0.71 - 1.25)
Readmission	CCAE	Sensitivity	10:1 variable ratio matching, 1 year time-at-risk; without prior spine-hip-foot pathology restriction	1,313 (178.24)	13,675 (258.67)	0.71 (0.67 - 0.75)	0.74 (0.62 - 0.89)
Readmission	CCAE	Sensitivity	10:1 variable ratio matching, 5 year time-at-risk; without prior spine-hip-foot pathology restriction	2,296 (141.64)	21,663 (192.07)	0.74 (0.70 - 0.77)	0.77 (0.69 - 0.86)
Readmission	CCAE	Sensitivity	10:1 variable ratio matching 5% trim, 60 day time-at-risk; without prior spine-hip-foot pathology restriction	286 (268.78)	3,213 (335.52)	0.81 (0.71 - 0.91)	0.96 (0.67 - 1.40)
Readmission	CCAE	Sensitivity	1:1 ratio matching, 60 day time-at-risk; without prior spine-hip-foot pathology restriction	407 (262.31)	506 (327.45)	0.80 (0.70 - 0.91)	0.97 (0.76 - 1.27)
Readmission	MDCR	Primary	10:1 variable ratio matching, 60 day time-at-risk	156 (238.66)	2,071 (376.93)	0.62 (0.52 - 0.73)	0.66 (0.46 - 0.97)

Readmission	MDCR	Sensitivity	10:1 variable ratio matching, 1 year time-at-risk	729 (224.28)	7,915 (295.50)	0.76 (0.70 - 0.82)	0.76 (0.64 - 0.93)
Readmission	MDCR	Sensitivity	10:1 variable ratio matching, 5 year time-at-risk	1,576 (196.18)	15,191 (232.35)	0.84 (0.79 - 0.89)	0.85 (0.76 - 0.97)
Readmission	MDCR	Sensitivity	10:1 variable ratio matching 5% trim, 60 day time-at-risk	98 (210.39)	1,570 (348.57)	0.61 (0.49 - 0.74)	0.64 (0.41 - 1.03)
Readmission	MDCR	Sensitivity	1:1 ratio matching, 60 day time-at-risk	156 (238.66)	249 (385.64)	0.61 (0.49 - 0.75)	0.70 (0.46 - 1.12)
Readmission	MDCR	Sensitivity	10:1 variable ratio matching, 60 day time-at-risk; without prior spine-hip-foot pathology restriction	217 (264.15)	2,747 (399.46)	0.66 (0.57 - 0.76)	0.70 (0.50 - 1.00)
Readmission	MDCR	Sensitivity	10:1 variable ratio matching, 1 year time-at-risk; without prior spine-hip-foot pathology restriction	949 (235.30)	10,139 (305.24)	0.77 (0.72 - 0.83)	0.78 (0.65 - 0.96)
Readmission	MDCR	Sensitivity	10:1 variable ratio matching, 5 year time-at-risk; without prior spine-hip-foot pathology restriction	1,985 (204.51)	19,014 (241.06)	0.84 (0.79 - 0.88)	0.83 (0.73 - 0.98)
Readmission	MDCR	Sensitivity	10:1 variable ratio matching 5% trim, 60 day time-at-risk; without prior spine-hip-foot pathology restriction	140 (240.97)	2,070 (371.14)	0.67 (0.56 - 0.79)	0.70 (0.50 - 0.99)
Readmission	MDCR	Sensitivity	1:1 ratio matching, 60 day time-at-risk; without prior spine-hip-foot pathology restriction	217 (264.15)	324 (397.99)	0.69 (0.58 - 0.82)	0.73 (0.48 - 1.12)
Readmission	Optum	Primary	10:1 variable ratio matching, 60 day time-at-risk	240 (262.83)	2,206 (319.16)	0.81 (0.70 - 0.93)	0.99 (0.71 - 1.48)
Readmission	Optum	Sensitivity	10:1 variable ratio matching, 1 year time-at-risk	842 (189.27)	8,036 (241.02)	0.79 (0.73 - 0.85)	0.86 (0.72 - 1.07)
Readmission	Optum	Sensitivity	10:1 variable ratio matching, 5 year time-at-risk	1,567 (145.63)	14,078 (173.64)	0.84 (0.80 - 0.89)	0.88 (0.75 - 1.06)
Readmission	Optum	Sensitivity	10:1 variable ratio matching 5% trim, 60 day time-at-risk	156 (264.52)	1,730 (311.79)	0.86 (0.72 - 1.01)	1.08 (0.75 - 1.65)
Readmission	Optum	Sensitivity	1:1 ratio matching, 60 day time-at-risk	240 (262.83)	311 (342.69)	0.77 (0.65 - 0.92)	1.00 (0.79 - 1.29)
Readmission	Optum	Sensitivity	10:1 variable ratio matching, 60 day time-at-risk; without prior spine-hip-foot pathology restriction	343 (283.07)	3,017 (325.24)	0.86 (0.77 - 0.97)	1.05 (0.78 - 1.54)
Readmission	Optum	Sensitivity	10:1 variable ratio matching, 1 year time-at-risk; without prior spine-hip-foot pathology restriction	1,155 (197.55)	11,131 (251.94)	0.80 (0.75 - 0.85)	0.84 (0.70 - 1.05)

Readmission	Optum	Sensitivity	10:1 variable ratio matching, 5 year time-at-risk; without prior spine-hip-foot pathology restriction	2,116 (154.31)	19,117 (183.12)	0.86 (0.81 - 0.90)	0.87 (0.76 - 1.02)
Readmission	Optum	Sensitivity	10:1 variable ratio matching 5% trim, 60 day time-at-risk; without prior spine-hip-foot pathology restriction	231 (294.03)	2,353 (315.78)	0.93 (0.81 - 1.06)	1.16 (0.86 - 1.68)
Readmission	Optum	Sensitivity	1:1 ratio matching, 60 day time-at-risk; without prior spine-hip-foot pathology restriction	343 (283.07)	440 (365.00)	0.78 (0.68 - 0.90)	1.03 (0.83 - 1.32)
Readmission	Meta-analysis	Primary	10:1 variable ratio matching, 60 day time-at-risk	700 (249.79)	7,351 (340.16)	0.72 (0.63 - 0.83)	0.79 (0.47 - 1.25)
Readmission	Meta-analysis	Sensitivity	10:1 variable ratio matching, 1 year time-at-risk	2,589 (190.05)	26,697 (259.92)	0.75 (0.69 - 0.81)	0.78 (0.63 - 0.95)
Readmission	Meta-analysis	Sensitivity	10:1 variable ratio matching, 5 year time-at-risk	4,954 (153.98)	46,464 (194.00)	0.81 (0.75 - 0.87)	0.84 (0.73 - 0.95)
Readmission	Meta-analysis	Sensitivity	10:1 variable ratio matching 5% trim, 60 day time-at-risk	476 (249.79)	5,823 (329.09)	0.75 (0.63 - 0.90)	0.80 (0.46 - 1.34)
Readmission	Meta-analysis	Sensitivity	1:1 ratio matching, 60 day time-at-risk	700 (249.79)	960 (345.45)	0.71 (0.63 - 0.81)	0.82 (0.51 - 1.25)
Readmission	Meta-analysis	Sensitivity	10:1 variable ratio matching, 60 day time-at-risk; without prior spine-hip-foot pathology restriction	967 (269.75)	9,668 (349.27)	0.77 (0.67 - 0.88)	0.83 (0.51 - 1.31)
Readmission	Meta-analysis	Sensitivity	10:1 variable ratio matching, 1 year time-at-risk; without prior spine-hip-foot pathology restriction	3,417 (198.13)	34,945 (268.26)	0.76 (0.70 - 0.81)	0.78 (0.62 - 0.96)
Readmission	Meta-analysis	Sensitivity	10:1 variable ratio matching, 5 year time-at-risk; without prior spine-hip-foot pathology restriction	6,397 (161.42)	59,794 (201.97)	0.81 (0.74 - 0.89)	0.83 (0.70 - 0.96)
Readmission	Meta-analysis	Sensitivity	10:1 variable ratio matching 5% trim, 60 day time-at-risk; without prior spine-hip-foot pathology restriction	657 (270.29)	7,636 (337.80)	0.80 (0.67 - 0.95)	0.85 (0.51 - 1.39)
Readmission	Meta-analysis	Sensitivity	1:1 ratio matching, 60 day time-at-risk; without prior spine-hip-foot pathology restriction	967 (269.75)	1,270 (356.26)	0.76 (0.70 - 0.83)	0.87 (0.59 - 1.27)
Mortality	Optum	Primary	10:1 variable ratio matching, 60 day time-at-risk	9 (9.61)	74 (10.39)	1.01 (0.47 - 1.95)	1.26 (0.55 - 3.09)
Mortality	Optum	Sensitivity	10:1 variable ratio matching, 1 year time-at-risk	22 (4.50)	207 (5.51)	0.94 (0.58 - 1.45)	1.04 (0.63 - 1.76)
Mortality	Optum	Sensitivity	10:1 variable ratio matching, 5 year time-at-risk	103 (7.47)	764 (6.99)	1.05 (0.83 - 1.32)	1.11 (0.83 - 1.55)

Mortality	Optum	Sensitivity	10:1 variable ratio matching 5% trim, 60 day time-at-risk	6 (9.93)	59 (10.32)	0.97 (0.37 - 2.07)	1.23 (0.47 - 3.45)
Mortality	Optum	Sensitivity	1:1 ratio matching, 60 day time-at-risk	9 (9.61)	10 (10.67)	0.90 (0.36 - 2.23)	1.18 (0.44 - 3.29)
Mortality	Optum	Sensitivity	10:1 variable ratio matching, 60 day time-at-risk; without prior spine-hip-foot pathology restriction	10 (8.04)	83 (8.68)	1.08 (0.52 - 2.01)	1.34 (0.63 - 3.19)
Mortality	Optum	Sensitivity	10:1 variable ratio matching, 1 year time-at-risk; without prior spine-hip-foot pathology restriction	29 (4.50)	288 (5.76)	0.86 (0.57 - 1.24)	0.90 (0.58 - 1.45)
Mortality	Optum	Sensitivity	10:1 variable ratio matching, 5 year time-at-risk; without prior spine-hip-foot pathology restriction	124 (6.99)	1,051 (7.39)	0.98 (0.79 - 1.19)	1.00 (0.77 - 1.32)
Mortality	Optum	Sensitivity	10:1 variable ratio matching 5% trim, 60 day time-at-risk; without prior spine-hip-foot pathology restriction	8 (9.91)	68 (8.86)	1.18 (0.52 - 2.32)	1.50 (0.66 - 3.78)
Mortality	Optum	Sensitivity	1:1 ratio matching, 60 day time-at-risk; without prior spine-hip-foot pathology restriction	10 (8.04)	13 (10.43)	0.83 (0.35 - 1.93)	1.10 (0.44 - 2.84)
Mortality	thin	Primary	10:1 variable ratio matching, 60 day time-at-risk	<5 (<15.22)	18 (7.17)	0.51 (0.03 - 2.51)	0.30 (0.03 - NA)
Mortality	thin	Sensitivity	10:1 variable ratio matching, 1 year time-at-risk	9 (4.83)	84 (5.86)	0.96 (0.45 - 1.81)	NA (NA - NA)
Mortality	thin	Sensitivity	10:1 variable ratio matching, 5 year time-at-risk	53 (7.63)	564 (10.53)	0.82 (0.61 - 1.09)	0.87 (0.66 - 1.16)
Mortality	thin	Sensitivity	10:1 variable ratio matching 5% trim, 60 day time-at-risk	<5 (<20.09)	14 (6.74)	0.71 (0.04 - 3.53)	0.48 (0.05 - 4.99)
Mortality	thin	Sensitivity	1:1 ratio matching, 60 day time-at-risk	<5 (<15.22)	<5 (<15.23)	0.50 (0.02 - 5.22)	0.37 (0.03 - 4.61)
Mortality	thin	Sensitivity	10:1 variable ratio matching, 60 day time-at-risk; without prior spine-hip-foot pathology restriction	<5 (<13.64)	13 (4.60)	0.68 (0.04 - 3.44)	0.40 (0.04 - NA)
Mortality	thin	Sensitivity	10:1 variable ratio matching, 1 year time-at-risk; without prior spine-hip-foot pathology restriction	11 (5.29)	90 (5.57)	1.06 (0.53 - 1.90)	0.98 (0.52 - 1.86)
Mortality	thin	Sensitivity	10:1 variable ratio matching, 5 year time-at-risk; without prior spine-hip-foot pathology restriction	60 (7.72)	652 (10.80)	0.83 (0.63 - 1.09)	0.85 (0.66 - 1.11)
Mortality	thin	Sensitivity	10:1 variable ratio matching 5% trim, 60 day time-at-risk; without prior spine-hip-foot pathology restriction	<5 (<17.89)	11 (4.69)	0.88 (0.05 - 4.50)	0.50 (0.04 - 7.12)

Mortality	thin	Sensitivity	1:1 ratio matching, 60 day time-at-risk; without prior spine-hip-foot pathology restriction	<5 (<13.64)	<5 (<13.59)	1.00 (0.04 - 25.27)	0.77 (0.03 - 19.01)
Mortality	Meta-analysis	Primary	10:1 variable ratio matching, 60 day time-at-risk	4 (3.16)	92 (9.55)	0.95 (0.48 - 1.88)	1.04 (0.45 - 2.46)
Mortality	Meta-analysis	Sensitivity	10:1 variable ratio matching, 1 year time-at-risk	31 (4.59)	291 (5.61)	0.95 (0.65 - 1.39)	0.99 (0.64 - 1.54)
Mortality	Meta-analysis	Sensitivity	10:1 variable ratio matching, 5 year time-at-risk	156 (7.52)	1,328 (8.15)	0.95 (0.74 - 1.20)	0.98 (0.75 - 1.27)
Mortality	Meta-analysis	Sensitivity	10:1 variable ratio matching 5% trim, 60 day time-at-risk	1 (1.17)	73 (9.37)	0.93 (0.42 - 2.07)	1.00 (0.38 - 2.68)
Mortality	Meta-analysis	Sensitivity	1:1 ratio matching, 60 day time-at-risk	4 (3.16)	5 (3.95)	0.85 (0.36 - 2.02)	0.97 (0.36 - 2.63)
Mortality	Meta-analysis	Sensitivity	10:1 variable ratio matching, 60 day time-at-risk; without prior spine-hip-foot pathology restriction	5 (3.10)	96 (7.75)	1.04 (0.55 - 1.99)	1.14 (0.51 - 2.55)
Mortality	Meta-analysis	Sensitivity	10:1 variable ratio matching, 1 year time-at-risk; without prior spine-hip-foot pathology restriction	40 (4.69)	378 (5.72)	0.91 (0.65 - 1.27)	0.94 (0.62 - 1.40)
Mortality	Meta-analysis	Sensitivity	10:1 variable ratio matching, 5 year time-at-risk; without prior spine-hip-foot pathology restriction	184 (7.21)	1,703 (8.41)	0.92 (0.78 - 1.09)	0.94 (0.76 - 1.16)
Mortality	Meta-analysis	Sensitivity	10:1 variable ratio matching 5% trim, 60 day time-at-risk; without prior spine-hip-foot pathology restriction	3 (2.76)	79 (7.88)	1.15 (0.57 - 2.33)	1.24 (0.52 - 2.98)
Mortality	Meta-analysis	Sensitivity	1:1 ratio matching, 60 day time-at-risk; without prior spine-hip-foot pathology restriction	5 (3.10)	8 (4.96)	0.84 (0.37 - 1.92)	0.96 (0.38 - 2.45)
Opioid use	CCAE	Primary	10:1 variable ratio matching, 91 days to 1 year time-at-risk	2,718 (838.65)	23,127 (1052.10)	0.82 (0.78 - 0.85)	0.82 (0.70 - 0.96)
Opioid use	CCAE	Sensitivity	10:1 variable ratio matching, 91 days to 5 years time-at-risk	3,988 (565.81)	31,451 (664.58)	0.86 (0.83 - 0.89)	0.86 (0.78 - 0.96)
Opioid use	CCAE	Sensitivity	10:1 variable ratio matching 5% trim, 91 days to 1 year time-at-risk	1,883 (835.33)	18,962 (1022.91)	0.84 (0.79 - 0.88)	0.83 (0.74 - 0.95)
Opioid use	CCAE	Sensitivity	1:1 ratio matching, 91 days to 1 year time-at-risk	2,718 (838.65)	3,082 (1076.29)	0.77 (0.73 - 0.82)	0.79 (0.61 - 1.05)
Opioid use	CCAE	Sensitivity	10:1 variable ratio matching, 91 days to 1 year time-at-risk; without prior spine-hip-foot pathology restriction	3,604 (923.96)	30,440 (1157.30)	0.80 (0.77 - 0.83)	0.79 (0.69 - 0.90)

Opioid use	CCAE	Sensitivity	10:1 variable ratio matching, 91 days to 5 years time-at-risk; without prior spine-hip-foot pathology restriction	5,091 (617.38)	40,238 (727.15)	0.84 (0.81 - 0.86)	0.84 (0.77 - 0.92)
Opioid use	CCAE	Sensitivity	10:1 variable ratio matching 5% trim, 91 days to 1 year time-at-risk; without prior spine-hip-foot pathology restriction	2,460 (903.23)	25,011 (1127.98)	0.81 (0.78 - 0.85)	0.78 (0.71 - 0.87)
Opioid use	CCAE	Sensitivity	1:1 ratio matching, 91 days to 1 year time-at-risk; without prior spine-hip-foot pathology restriction	3,604 (923.96)	4,069 (1162.04)	0.80 (0.76 - 0.84)	0.76 (0.72 - 0.82)
Opioid use	MDCR	Primary	10:1 variable ratio matching, 91 days to 1 year time-at-risk	1,306 (652.94)	12,595 (787.30)	0.84 (0.79 - 0.89)	0.80 (0.74 - 0.86)
Opioid use	MDCR	Sensitivity	10:1 variable ratio matching, 91 days to 5 years time-at-risk	2,257 (446.41)	20,079 (481.31)	0.91 (0.86 - 0.95)	0.90 (0.82 - 1.02)
Opioid use	MDCR	Sensitivity	10:1 variable ratio matching 5% trim, 91 days to 1 year time-at-risk	925 (645.66)	10,128 (765.37)	0.85 (0.79 - 0.91)	0.81 (0.75 - 0.87)
Opioid use	MDCR	Sensitivity	1:1 ratio matching, 91 days to 1 year time-at-risk	1,306 (652.94)	1,445 (769.62)	0.82 (0.75 - 0.89)	0.77 (0.70 - 0.84)
Opioid use	MDCR	Sensitivity	10:1 variable ratio matching, 91 days to 1 year time-at-risk; without prior spine-hip-foot pathology restriction	1,745 (721.04)	16,735 (865.73)	0.84 (0.80 - 0.89)	0.82 (0.70 - 0.98)
Opioid use	MDCR	Sensitivity	10:1 variable ratio matching, 91 days to 5 years time-at-risk; without prior spine-hip-foot pathology restriction	2,878 (480.66)	25,650 (532.04)	0.89 (0.85 - 0.93)	0.88 (0.77 - 1.02)
Opioid use	MDCR	Sensitivity	10:1 variable ratio matching 5% trim, 91 days to 1 year time-at-risk; without prior spine-hip-foot pathology restriction	1,234 (715.03)	13,327 (839.91)	0.87 (0.82 - 0.92)	0.84 (0.74 - 0.97)
Opioid use	MDCR	Sensitivity	1:1 ratio matching, 91 days to 1 year time-at-risk; without prior spine-hip-foot pathology restriction	1,745 (721.04)	1,972 (865.87)	0.79 (0.74 - 0.86)	0.75 (0.70 - 0.82)
Opioid use	Optum	Primary	10:1 variable ratio matching, 91 days to 1 year time-at-risk	1,787 (683.54)	15,035 (784.70)	0.86 (0.82 - 0.91)	0.86 (0.78 - 0.96)
Opioid use	Optum	Sensitivity	10:1 variable ratio matching, 91 days to 5 years time-at-risk	2,771 (426.36)	22,669 (464.18)	0.89 (0.85 - 0.93)	0.88 (0.79 - 1.00)
Opioid use	Optum	Sensitivity	10:1 variable ratio matching 5% trim, 91 days to 1 year time-at-risk	1,136 (662.15)	12,016 (769.16)	0.86 (0.80 - 0.91)	0.87 (0.82 - 0.93)
Opioid use	Optum	Sensitivity	1:1 ratio matching, 91 days to 1 year time-at-risk	1,787 (683.54)	1,972 (792.44)	0.85 (0.78 - 0.91)	0.85 (0.79 - 0.92)
Opioid use	Optum	Sensitivity	10:1 variable ratio matching, 91 days to 1 year time-at-risk; without prior spine-hip-foot pathology restriction	2,530 (760.35)	21,527 (880.52)	0.86 (0.82 - 0.90)	0.83 (0.74 - 0.94)

Opioid use	Optum	Sensitivity	10:1 variable ratio matching, 91 days to 5 years time-at-risk; without prior spine-hip-foot pathology restriction	3,784 (470.86)	31,173 (516.18)	0.89 (0.86 - 0.93)	0.86 (0.80 - 0.93)
Opioid use	Optum	Sensitivity	10:1 variable ratio matching 5% trim, 91 days to 1 year time-at-risk; without prior spine-hip-foot pathology restriction	1,627 (744.04)	17,128 (856.08)	0.87 (0.82 - 0.91)	0.87 (0.82 - 0.92)
Opioid use	Optum	Sensitivity	1:1 ratio matching, 91 days to 1 year time-at-risk; without prior spine-hip-foot pathology restriction	2,530 (760.35)	2,738 (865.85)	0.86 (0.81 - 0.92)	0.81 (0.76 - 0.86)
Opioid use	thin	Primary	10:1 variable ratio matching, 91 days to 1 year time-at-risk	388 (337.35)	3,824 (458.15)	0.75 (0.67 - 0.83)	0.70 (0.57 - 0.90)
Opioid use	thin	Sensitivity	10:1 variable ratio matching, 91 days to 5 years time-at-risk	637 (138.13)	5,770 (174.43)	0.81 (0.74 - 0.88)	0.86 (0.77 - 0.98)
Opioid use	thin	Sensitivity	10:1 variable ratio matching 5% trim, 91 days to 1 year time-at-risk	290 (328.94)	3,170 (459.19)	0.73 (0.65 - 0.83)	0.73 (0.65 - 0.82)
Opioid use	thin	Sensitivity	1:1 ratio matching, 91 days to 1 year time-at-risk	388 (337.35)	488 (446.56)	0.76 (0.66 - 0.88)	0.74 (0.66 - 0.84)
Opioid use	thin	Sensitivity	10:1 variable ratio matching, 91 days to 1 year time-at-risk; without prior spine-hip-foot pathology restriction	446 (349.07)	4,444 (475.50)	0.74 (0.67 - 0.82)	0.68 (0.58 - 0.83)
Opioid use	thin	Sensitivity	10:1 variable ratio matching, 91 days to 5 years time-at-risk; without prior spine-hip-foot pathology restriction	730 (142.88)	6,672 (181.43)	0.80 (0.74 - 0.86)	0.82 (0.73 - 0.92)
Opioid use	thin	Sensitivity	10:1 variable ratio matching 5% trim, 91 days to 1 year time-at-risk; without prior spine-hip-foot pathology restriction	334 (338.87)	3,670 (472.16)	0.73 (0.65 - 0.82)	0.70 (0.63 - 0.79)
Opioid use	thin	Sensitivity	1:1 ratio matching, 91 days to 1 year time-at-risk; without prior spine-hip-foot pathology restriction	446 (349.07)	566 (462.66)	0.77 (0.67 - 0.88)	0.76 (0.68 - 0.85)
Opioid use	pmtx	Primary	10:1 variable ratio matching, 91 days to 1 year time-at-risk	3,784 (632.38)	32,879 (757.70)	0.83 (0.80 - 0.86)	0.81 (0.73 - 0.91)
Opioid use	pmtx	Sensitivity	10:1 variable ratio matching, 91 days to 5 years time-at-risk	6,008 (405.65)	48,936 (454.32)	0.88 (0.85 - 0.90)	0.89 (0.83 - 0.96)
Opioid use	pmtx	Sensitivity	10:1 variable ratio matching 5% trim, 91 days to 1 year time-at-risk	2,625 (621.74)	27,048 (742.27)	0.84 (0.81 - 0.87)	0.83 (0.75 - 0.92)
Opioid use	pmtx	Sensitivity	1:1 ratio matching, 91 days to 1 year time-at-risk	3,784 (632.38)	4,236 (767.67)	0.80 (0.76 - 0.84)	0.79 (0.74 - 0.84)
Opioid use	pmtx	Sensitivity	10:1 variable ratio matching, 91 days to 1 year time-at-risk; without prior spine-hip-foot pathology restriction	5,198 (704.89)	44,827 (838.86)	0.83 (0.81 - 0.86)	0.81 (0.73 - 0.90)

Opioid use	pmtx	Sensitivity	10:1 variable ratio matching, 91 days to 5 years time-at-risk; without prior spine-hip-foot pathology restriction	7,930 (446.92)	64,475 (496.52)	0.87 (0.85 - 0.89)	0.88 (0.82 - 0.95)
Opioid use	pmtx	Sensitivity	10:1 variable ratio matching 5% trim, 91 days to 1 year time-at-risk; without prior spine-hip-foot pathology restriction	3,551 (680.64)	36,823 (819.89)	0.83 (0.81 - 0.86)	0.82 (0.74 - 0.90)
Opioid use	pmtx	Sensitivity	1:1 ratio matching, 91 days to 1 year time-at-risk; without prior spine-hip-foot pathology restriction	5,198 (704.89)	5,882 (869.28)	0.79 (0.76 - 0.83)	0.74 (0.67 - 0.83)
Opioid use	Meta-analysis	Primary	10:1 variable ratio matching, 91 days to 1 year time-at-risk	9,983 (666.00)	87,460 (803.27)	0.83 (0.81 - 0.85)	0.81 (0.73 - 0.90)
Opioid use	Meta-analysis	Sensitivity	10:1 variable ratio matching, 91 days to 5 years time-at-risk	15,661 (411.85)	128,905 (462.57)	0.88 (0.85 - 0.90)	0.88 (0.81 - 0.94)
Opioid use	Meta-analysis	Sensitivity	10:1 variable ratio matching 5% trim, 91 days to 1 year time-at-risk	6,859 (652.86)	71,324 (786.06)	0.84 (0.81 - 0.86)	0.82 (0.74 - 0.92)
Opioid use	Meta-analysis	Sensitivity	1:1 ratio matching, 91 days to 1 year time-at-risk	9,983 (666.00)	11,223 (810.89)	0.80 (0.78 - 0.83)	0.79 (0.71 - 0.88)
Opioid use	Meta-analysis	Sensitivity	10:1 variable ratio matching, 91 days to 1 year time-at-risk; without prior spine-hip-foot pathology restriction	13,523 (738.96)	117,973 (887.91)	0.82 (0.80 - 0.85)	0.80 (0.70 - 0.90)
Opioid use	Meta-analysis	Sensitivity	10:1 variable ratio matching, 91 days to 5 years time-at-risk; without prior spine-hip-foot pathology restriction	20,413 (452.38)	168,208 (508.84)	0.86 (0.84 - 0.89)	0.85 (0.79 - 0.93)
Opioid use	Meta-analysis	Sensitivity	10:1 variable ratio matching 5% trim, 91 days to 1 year time-at-risk; without prior spine-hip-foot pathology restriction	9,206 (717.04)	95,959 (866.58)	0.83 (0.80 - 0.86)	0.81 (0.73 - 0.90)
Opioid use	Meta-analysis	Sensitivity	1:1 ratio matching, 91 days to 1 year time-at-risk; without prior spine-hip-foot pathology restriction	13,523 (738.96)	15,227 (899.35)	0.81 (0.78 - 0.83)	0.76 (0.70 - 0.83)
Revision	CCAE	Primary	10:1 variable ratio matching, 5 year time-at-risk	271 (16.66)	1,347 (11.03)	1.42 (1.23 - 1.65)	1.51 (1.24 - 1.88)
Revision	CCAE	Sensitivity	10:1 variable ratio matching, 1 year time-at-risk	107 (16.72)	598 (12.48)	1.26 (1.01 - 1.56)	1.36 (1.05 - 1.83)
Revision	CCAE	Sensitivity	10:1 variable ratio matching 5% trim, 5 year time-at-risk	189 (16.40)	1,081 (10.54)	1.51 (1.27 - 1.79)	1.59 (1.29 - 2.02)
Revision	CCAE	Sensitivity	1:1 ratio matching, 5 year time-at-risk	271 (16.66)	185 (11.64)	1.43 (1.13 - 1.83)	1.57 (1.16 - 2.27)
Revision	CCAE	Sensitivity	10:1 variable ratio matching, 1 year time-at-risk; without prior spine-hip-foot pathology restriction	147 (18.41)	761 (12.77)	1.32 (1.09 - 1.59)	1.41 (1.07 - 1.91)

Revision	CCAE	Sensitivity	10:1 variable ratio matching, 5 year time-at-risk; without prior spine-hip-foot pathology restriction	342 (17.23)	1,714 (11.53)	1.39 (1.21 - 1.58)	1.46 (1.21 - 1.83)
Revision	CCAE	Sensitivity	10:1 variable ratio matching 5% trim, 5 year time-at-risk; without prior spine-hip-foot pathology restriction	239 (17.06)	1,383 (11.06)	1.49 (1.28 - 1.73)	1.58 (1.28 - 2.02)
Revision	CCAE	Sensitivity	1:1 ratio matching, 5 year time-at-risk; without prior spine-hip-foot pathology restriction	342 (17.23)	257 (13.25)	1.28 (1.04 - 1.57)	1.35 (1.03 - 1.88)
Revision	MDCR	Primary	10:1 variable ratio matching, 5 year time-at-risk	145 (13.11)	631 (6.44)	2.02 (1.65 - 2.45)	2.16 (1.63 - 3.15)
Revision	MDCR	Sensitivity	10:1 variable ratio matching, 1 year time-at-risk	63 (17.54)	289 (9.38)	1.76 (1.31 - 2.33)	1.81 (1.26 - 2.73)
Revision	MDCR	Sensitivity	10:1 variable ratio matching 5% trim, 5 year time-at-risk	101 (12.43)	484 (5.96)	2.19 (1.74 - 2.74)	2.33 (1.69 - 3.58)
Revision	MDCR	Sensitivity	1:1 ratio matching, 5 year time-at-risk	145 (13.11)	84 (7.42)	1.89 (1.38 - 2.63)	2.07 (1.39 - 3.45)
Revision	MDCR	Sensitivity	10:1 variable ratio matching, 1 year time-at-risk; without prior spine-hip-foot pathology restriction	83 (18.54)	375 (9.76)	1.77 (1.37 - 2.27)	1.84 (1.30 - 2.73)
Revision	MDCR	Sensitivity	10:1 variable ratio matching, 5 year time-at-risk; without prior spine-hip-foot pathology restriction	179 (13.29)	828 (6.96)	1.77 (1.47 - 2.10)	1.86 (1.42 - 2.65)
Revision	MDCR	Sensitivity	10:1 variable ratio matching 5% trim, 5 year time-at-risk; without prior spine-hip-foot pathology restriction	126 (12.67)	640 (6.52)	1.99 (1.63 - 2.43)	2.08 (1.56 - 3.06)
Revision	MDCR	Sensitivity	1:1 ratio matching, 5 year time-at-risk; without prior spine-hip-foot pathology restriction	179 (13.29)	92 (6.67)	1.68 (1.26 - 2.24)	1.76 (1.21 - 2.82)
Revision	Optum	Primary	10:1 variable ratio matching, 5 year time-at-risk	189 (14.04)	900 (8.36)	1.50 (1.26 - 1.79)	1.62 (1.24 - 2.26)
Revision	Optum	Sensitivity	10:1 variable ratio matching, 1 year time-at-risk	76 (15.67)	442 (11.83)	1.26 (0.96 - 1.61)	1.38 (1.00 - 2.01)
Revision	Optum	Sensitivity	10:1 variable ratio matching 5% trim, 5 year time-at-risk	128 (14.23)	694 (7.88)	1.75 (1.42 - 2.14)	1.90 (1.41 - 2.79)
Revision	Optum	Sensitivity	1:1 ratio matching, 5 year time-at-risk	189 (14.04)	136 (10.02)	1.26 (0.96 - 1.67)	1.38 (0.97 - 2.11)
Revision	Optum	Sensitivity	10:1 variable ratio matching, 1 year time-at-risk; without prior spine-hip-foot pathology restriction	104 (16.26)	638 (12.84)	1.16 (0.92 - 1.43)	1.23 (0.91 - 1.74)

Revision	Optum	Sensitivity	10:1 variable ratio matching, 5 year time-at-risk; without prior spine-hip-foot pathology restriction	250 (14.45)	1,288 (9.21)	1.44 (1.23 - 1.67)	1.50 (1.19 - 2.01)
Revision	Optum	Sensitivity	10:1 variable ratio matching 5% trim, 5 year time-at-risk; without prior spine-hip-foot pathology restriction	172 (14.81)	981 (8.53)	1.72 (1.44 - 2.03)	1.81 (1.41 - 2.50)
Revision	Optum	Sensitivity	1:1 ratio matching, 5 year time-at-risk; without prior spine-hip-foot pathology restriction	250 (14.45)	190 (10.92)	1.24 (0.99 - 1.56)	1.31 (0.98 - 1.88)
Revision	thin	Primary	10:1 variable ratio matching, 5 year time-at-risk	51 (7.49)	239 (4.51)	1.60 (1.15 - 2.18)	1.58 (1.16 - 2.19)
Revision	thin	Sensitivity	10:1 variable ratio matching, 1 year time-at-risk	18 (9.71)	48 (3.35)	2.42 (1.34 - 4.20)	NA (NA - NA)
Revision	thin	Sensitivity	10:1 variable ratio matching 5% trim, 5 year time-at-risk	33 (6.32)	195 (4.43)	1.40 (0.94 - 2.03)	1.45 (1.02 - 2.09)
Revision	thin	Sensitivity	1:1 ratio matching, 5 year time-at-risk	51 (7.49)	28 (4.02)	2.00 (1.21 - 3.40)	1.63 (1.06 - 2.51)
Revision	thin	Sensitivity	10:1 variable ratio matching, 1 year time-at-risk; without prior spine-hip-foot pathology restriction	21 (10.14)	63 (3.91)	2.24 (1.31 - 3.70)	2.08 (1.24 - 3.50)
Revision	thin	Sensitivity	10:1 variable ratio matching, 5 year time-at-risk; without prior spine-hip-foot pathology restriction	61 (8.03)	275 (4.60)	1.50 (1.11 - 2.00)	1.44 (1.08 - 1.95)
Revision	thin	Sensitivity	10:1 variable ratio matching 5% trim, 5 year time-at-risk; without prior spine-hip-foot pathology restriction	43 (7.36)	224 (4.50)	1.53 (1.07 - 2.12)	1.49 (1.10 - 2.08)
Revision	thin	Sensitivity	1:1 ratio matching, 5 year time-at-risk; without prior spine-hip-foot pathology restriction	61 (8.03)	36 (4.60)	1.69 (1.07 - 2.70)	1.48 (0.99 - 2.23)
Revision	pmtx	Primary	10:1 variable ratio matching, 5 year time-at-risk	450 (15.33)	2,178 (9.48)	1.60 (1.42 - 1.79)	1.53 (1.27 - 1.90)
Revision	pmtx	Sensitivity	10:1 variable ratio matching, 1 year time-at-risk	196 (18.06)	916 (10.91)	1.66 (1.40 - 1.95)	1.72 (1.29 - 2.37)
Revision	pmtx	Sensitivity	10:1 variable ratio matching 5% trim, 5 year time-at-risk	335 (16.09)	1,768 (9.17)	1.72 (1.51 - 1.95)	1.64 (1.37 - 2.07)
Revision	pmtx	Sensitivity	1:1 ratio matching, 5 year time-at-risk	450 (15.33)	270 (9.28)	1.67 (1.38 - 2.02)	1.48 (1.19 - 1.91)
Revision	pmtx	Sensitivity	10:1 variable ratio matching, 1 year time-at-risk; without prior spine-hip-foot pathology restriction	258 (18.69)	1,338 (12.52)	1.49 (1.29 - 1.71)	1.53 (1.17 - 2.07)

Revision	pmtx	Sensitivity	10:1 variable ratio matching, 5 year time-at-risk; without prior spine-hip-foot pathology restriction	587 (16.01)	3,011 (10.44)	1.50 (1.36 - 1.66)	1.44 (1.22 - 1.77)
Revision	pmtx	Sensitivity	10:1 variable ratio matching 5% trim, 5 year time-at-risk; without prior spine-hip-foot pathology restriction	432 (16.61)	2,424 (10.00)	1.62 (1.45 - 1.81)	1.56 (1.31 - 1.92)
Revision	pmtx	Sensitivity	1:1 ratio matching, 5 year time-at-risk; without prior spine-hip-foot pathology restriction	587 (16.01)	423 (11.54)	1.43 (1.22 - 1.67)	1.29 (1.06 - 1.63)
Revision	Meta-analysis	Primary	10:1 variable ratio matching, 5 year time-at-risk	1,106 (14.37)	5,295 (8.67)	1.60 (1.43 - 1.79)	1.64 (1.40 - 1.94)
Revision	Meta-analysis	Sensitivity	10:1 variable ratio matching, 1 year time-at-risk	460 (16.70)	2,293 (10.69)	1.53 (1.27 - 1.83)	1.61 (1.24 - 2.14)
Revision	Meta-analysis	Sensitivity	10:1 variable ratio matching 5% trim, 5 year time-at-risk	786 (14.37)	4,222 (8.30)	1.72 (1.52 - 1.94)	1.75 (1.48 - 2.11)
Revision	Meta-analysis	Sensitivity	1:1 ratio matching, 5 year time-at-risk	1,106 (14.37)	703 (9.15)	1.57 (1.36 - 1.81)	1.58 (1.31 - 1.93)
Revision	Meta-analysis	Sensitivity	10:1 variable ratio matching, 1 year time-at-risk; without prior spine-hip-foot pathology restriction	613 (17.65)	3,175 (11.73)	1.46 (1.24 - 1.72)	1.52 (1.17 - 2.02)
Revision	Meta-analysis	Sensitivity	10:1 variable ratio matching, 5 year time-at-risk; without prior spine-hip-foot pathology restriction	1,419 (14.96)	7,116 (9.42)	1.50 (1.39 - 1.61)	1.51 (1.30 - 1.80)
Revision	Meta-analysis	Sensitivity	10:1 variable ratio matching 5% trim, 5 year time-at-risk; without prior spine-hip-foot pathology restriction	1,012 (15.01)	5,652 (8.97)	1.65 (1.51 - 1.81)	1.67 (1.43 - 2.00)
Revision	Meta-analysis	Sensitivity	1:1 ratio matching, 5 year time-at-risk; without prior spine-hip-foot pathology restriction	1,419 (14.96)	998 (10.50)	1.39 (1.26 - 1.54)	1.37 (1.15 - 1.68)