Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Dual GIP/GLP-1 Receptor Agonist Versus Selective GLP-1 Receptor Agonist in Patients Undergoing Primary Total Knee or Hip Arthroplasty

Spencer C Davis
Case Western Reserve University
Shlok V Patel
Cleveland Clinic
Shane Fletcher
Case Western Reserve University
John P McLaughlin
Cleveland Clinic
Matthew E Deren
Cleveland Clinic
Nicolas S Piuzzi
piuzzin@ccf.org

Cleveland Clinic

Research Article

Keywords: tirzepatide, semaglutide, GLP-1 receptor agonist, total knee arthroplasty, total hip arthroplasty, periprosthetic joint infection

Posted Date: September 4th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10744245/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: Competing interest reported. Spencer C. Davis, Shlok V. Patel and Shane Fletcher declare they have no competing interests. John P. McLaughlin has the following disclosures, none related to the present study: consultant for Zimmer Biomet, Smith and Nephew, and OrthAlign. Matthew E. Deren has the following disclosures, none related to the present study: paid speaker for Brasseler; stock options in ROM Technologies; governing board of The Journal of Knee Surgery. Nicolas

S. Piuzzi has the following disclosures, none related to the present study: grants or contracts from Osteal Therapeutics, Peptilogics, RegenLab, Signature Orthopedics, Zimmer and Stryker; consulting fees from Zimmer, Pacira Pharmaceutical and Stryker; editorial board member or leadership role with JBJS, the American Association of Hip and Knee Surgeons and the Orthopaedic Research Society.

Version of Record: A version of this preprint was published at European Journal of Orthopaedic Surgery & Traumatology on October 21st, 2026. See the published version at https://doi.org/10.1007/s00590-026-05000-9.

Abstract

Purpose

Tirzepatide is a dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist, whereas semaglutide is selective for the GLP-1 receptor. We compared post-operative outcomes after primary total knee or hip arthroplasty (TKA/THA) between patients prescribed tirzepatide and those prescribed semaglutide.

Methods

A retrospective cohort study was performed using the TriNetX US Collaborative Network. Adults undergoing primary TKA or THA with at least two coded prescription fills for tirzepatide or semaglutide within six months of surgery were identified, and patients taking both agents were excluded. Cohorts were propensity score matched 1:1 (2,858 per group, all standardized differences below 0.05). Odds ratios (OR) with 95% confidence intervals (CI) were calculated at 90 days, 1 year, and 2 years.

Results

Of 669,698 patients who underwent primary TKA or THA, 8,797 (1.3%) had ≥ 2 tirzepatide or semaglutide prescriptions. At 90 days and 1 year, no surgical, medical, or implant-related outcome differed significantly. At 2 years, tirzepatide exposure was associated with lower odds of mechanical complications (OR 0.64, 95% CI 0.42 to 0.96) and periprosthetic joint infection (PJI) (OR 0.64, 95% CI 0.41 to 0.999; P = .048). Reoperation did not differ significantly (OR 0.68, 95% CI 0.43 to 1.08).

Conclusion

Tirzepatide and semaglutide prescriptions were associated with similar 90 day and 1 year outcomes, while tirzepatide was associated with lower 2-year mechanical complications and PJI. The distinction between dual GIP/GLP-1 agonism and selective GLP-1 agonism may therefore carry clinical relevance, and these agents should not be presumed equivalent.

Introduction

Total knee and total hip arthroplasty (TKA/THA) are among the most frequently performed operations worldwide, and utilization has continued to rise across international health systems [1, 2]. In the United States they are among the most common and reliable orthopaedic procedures [3], and their effectiveness has prompted calls for arthroplasty to be recognized as an essential surgical service worldwide [4]. More than 7 million Americans currently live with a knee or hip replacement, and the annual volume of both procedures is projected to rise through 2030 [3, 5]. As incidence of these

procedures increases, being able to identify modifiable patient factors that influence post-operative outcomes, such as periprosthetic joint infection and revision, becomes more important both clinically and economically [6, 7].

Glucagon-like peptide-1 receptor agonists (GLP-1RA) have become popular recently for treating type 2 diabetes and obesity [8, 9], and national prescribing has risen steeply over the past decade [10], which makes their perioperative management an increasingly common consideration in patients presenting for TKA or THA [11]. Pre-operative optimization in arthroplasty has traditionally used body mass index thresholds [12]. Because obesity and diabetes are established and modifiable risk factors for complications such as PJI and revision after surgery, these medications have received more attention as tools for pre-operative risk optimization as there is growing evidence that GLP-1RA exposure is associated with improved osteoarthritis symptoms and greater time to arthroplasty [13, 14]. Previous systematic reviews and institutional studies have generally reported comparable or lower complication rates among GLP-1RA users undergoing total joint arthroplasty, with lower or comparable rates of readmission, wound complications, and periprosthetic joint infection [15, 16].

Despite this, most previous literature has treated GLP-1RA as a single pharmacologic class, and direct comparisons between individual agents have not been well characterized. Tirzepatide is both a glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonist, while semaglutide is a selective GLP-1 receptor agonist [17, 18]. In recent clinical trial comparisons of these two drugs, tirzepatide has been shown to produce greater weight loss and glycemic improvement than semaglutide [17, 19]. Tirzepatide, which acts through dual GIP and GLP-1 receptor agonism, has been associated with reductions in liver fat content and visceral adipose tissue volume [20] and with lower circulating inflammatory markers [21], while GIP receptor activation has been associated with increased osteoblast-mediated bone formation and limited bone resorption [22]. Current research supports holding GLP-1RA prior to surgery to reduce aspiration risk but has not examined whether or not these drugs are associated with different post-operative complications [23, 24]. In this study, we compared associations with post-operative outcomes in patients taking tirzepatide vs semaglutide prior to primary TKA or THA.

Materials and Methods

Study Design and Data Source

We performed a retrospective cohort study using the TriNetX Research Network (TriNetX, LLC, Cambridge, MA), a federated database of de-identified electronic health record data from over 60 participating health care organizations. The complete TriNetX query criteria and outcome definitions used to construct each study cohort are provided in the Supplementary Material. Because all data in this platform are de-identified and contain no accessible protected health information (PHI), institutional review board approval and individual patient consent were not required for this study. Post-operative pain was managed according to the protocols of each contributing health care organization. Analgesic regimens are not recorded in a standardized form in the TriNetX database and therefore could not be

characterized or compared between cohorts. Our analysis used the United States Collaborative Network, which contained a total of more than 116 million patients across 66 contributing healthcare organizations at the time of our analysis. Our query was run on May 31, 2026. This study was designed and reported in accordance with the STROBE guidelines [25], and an overview of this study's cohorts and methods is summarized in Fig. 1.

Cohort Definitions

Over the study period, 389,434 patients underwent primary TKA (CPT 27447) and 280,264 underwent primary THA (CPT 27130) in the network, for a total of 669,698 primary arthroplasties. Eligible patients for this study were adults who underwent primary TKA or THA and had at least two documented prescription fills for either tirzepatide (RxNorm 2601723) or semaglutide (RxNorm 1991302) within six months on or before the date of surgery. The two-fill requirement was used to strengthen our confidence that patients were taking the medication and reduce single-fill misclassification. Patients with any documented use of both medications were excluded.

Covariates and Matching

Cohorts were matched 1:1 using propensity score matching. Matching covariates included: age at index, sex, race, ethnicity, overweight and obesity (ICD-10 E66), hyperlipidemia (E78.5), type 2 diabetes mellitus (E11), long-term current use of insulin (Z79.4), chronic kidney disease (N18), nicotine dependence (F17), alcohol-related disorders (F10), and opioid-related disorders (F11). Covariate balance was assessed using standardized mean differences, with a value below 0.10 considered adequate balance.

Outcomes

Outcomes were assessed at three time-points after surgery: 90 days, 1 year, and 2 years. Ninety-day outcomes included surgical site infection or infection following a procedure (ICD-10 T81.40 to T81.44 and T81.49), sepsis (A40, A41, R65.2), cellulitis of the lower extremity (L03.115, L03.116, L03.119), wound dehiscence or disruption (T81.3), mechanical complications, emergency department visits, and readmission. One- and two-year outcomes included: any mechanical complications, periprosthetic fracture (M97.0, M97.1), instability or dislocation (T84.02 group), reoperation (CPT 27134, 27137, 27138, 27090, 27091, 27486, 27487, 27488), and PJI (T84.50 to T84.59). Any mechanical complications represented any of the following: broken or dislocated prosthesis, instability, mechanical loosening, periprosthetic osteolysis, or articular bearing surface wear.

Statistical Analysis

Odds ratios (OR) with 95% confidence intervals (CI) were calculated within the TriNetX platform using 1:1 logistic regression, with statistical significance defined as $P < .05$. Our propensity-matched cohorts were

analyzed across 90-day, 1-year, and 2-year timepoints. Outcomes with insufficient patient counts for analysis were not reported.

Results

Cohort Characteristics

Of the 669,698 patients who underwent primary TKA or THA over the study period, 8,797 (1.3%) had at least two documented fills of tirzepatide or semaglutide within 6 months of surgery. Before propensity-score matching, 2,864 patients (0.4% of all primary TKA or THA) taking only tirzepatide and 5,933 (0.9%) taking only semaglutide met the inclusion criteria. These groups differed across several demographic and comorbidity variables, including age, race, ethnicity, overweight and obesity, type 2 diabetes mellitus, and hyperlipidemia (Table 1). After 1:1 propensity matching, 2,858 patients remained in each group, and all standardized differences were below 0.05, which confirmed adequate matching balance between cohorts (Table 1).

Table 1
Baseline characteristics before and after 1:1 propensity matching

Variable	Tirzepatide	Semaglutide	Std. Diff.	P-value
Before matching (Tirzepatide N = 2,864; Semaglutide N = 5,933)				
Age at index, mean ± SD	63.1 ± 8.49	63.8 ± 8.65	0.081	**< .001**
Female	1,899 (66.3)	3,873 (65.3)	0.022	.342
White	2,311 (80.7)	4,553 (76.7)	0.097	**< .001**
Black or African American	364 (12.7)	973 (16.4)	0.105	**< .001**
Asian	22 (0.8)	66 (1.1)	0.036	.128
Other / unknown race	175 (6.1)	341 (5.7)	NA	NA
Not Hispanic or Latino	2,389 (83.4)	4,705 (79.3)	0.106	**< .001**
Hispanic or Latino	103 (3.6)	267 (4.5)	0.046	**.048**
Unknown ethnicity	372 (13.0)	961 (16.2)	0.091	**< .001**
Overweight and obesity	2,530 (88.3)	4,962 (83.6)	0.136	**< .001**
Type 2 diabetes mellitus	1,763 (61.6)	4,087 (68.9)	0.154	**< .001**
Hyperlipidemia	1,938 (67.7)	4,181 (70.5)	0.061	**.007**
Long-term (current) insulin use	562 (19.6)	1,307 (22.0)	0.059	**.010**
Chronic kidney disease	518 (18.1)	1,216 (20.5)	0.061	**.008**
Nicotine dependence	460 (16.1)	966 (16.3)	0.006	.793
Alcohol-related disorders	159 (5.6)	312 (5.3)	0.013	.567
Opioid-related disorders	118 (4.1)	253 (4.3)	0.007	.753
After 1:1 propensity matching (N = 2,858 per group)				
Age at index, mean ± SD	63.1 ± 8.48	63.3 ± 8.56	0.016	.553
Female	1,894 (66.3)	1,906 (66.7)	0.009	.737
White	2,311 (80.9)	2,323 (81.3)	0.011	.685
Black or African American	364 (12.7)	371 (13.0)	0.007	.782
Asian	22 (0.8)	14 (0.5)	0.035	.181
Other / unknown race	169 (5.9)	159 (5.6)	NA	NA
Not Hispanic or Latino	2,383 (83.4)	2,374 (83.1)	0.008	.750
Hispanic or Latino	103 (3.6)	111 (3.9)	0.015	.577

Variable	Tirzepatide	Semaglutide	Std. Diff.	P-value
Before matching (Tirzepatide N = 2,864; Semaglutide N = 5,933)				
Unknown ethnicity	372 (13.0)	373 (13.1)	0.001	.969
Overweight and obesity	2,524 (88.3)	2,528 (88.5)	0.004	.869
Type 2 diabetes mellitus	1,763 (61.7)	1,754 (61.4)	0.006	.807
Hyperlipidemia	1,937 (67.8)	1,941 (67.9)	0.003	.910
Long-term (current) insulin use	562 (19.7)	557 (19.5)	0.004	.868
Chronic kidney disease	518 (18.1)	513 (17.9)	0.005	.863
Nicotine dependence	460 (16.1)	442 (15.5)	0.017	.514
Alcohol-related disorders	159 (5.6)	167 (5.8)	0.012	.648
Opioid-related disorders	118 (4.1)	107 (3.7)	0.020	.454

Values are n (%) unless otherwise specified. Std. Diff., standardized difference; a value below 0.10 indicates adequate balance after matching. Bold P-values denote statistical significance (P < .05). SD, standard deviation. Race categories may not sum to the cohort total because more than one race may be recorded per patient.

Outcomes at 90 Days

At 90 days, infection and wound-related outcomes were comparable between tirzepatide and semaglutide patients, including surgical site infection (OR 0.71, 95% CI 0.41 to 1.22), sepsis (OR 0.95, 95% CI 0.51 to 1.78), cellulitis (OR 0.87, 95% CI 0.54 to 1.39), and wound dehiscence or disruption (OR 0.69, 95% CI 0.43 to 1.11). Emergency department visits (OR 0.91, 95% CI 0.77 to 1.08), readmission (OR 1.14, 95% CI 0.99 to 1.32), and early mechanical complications (OR 1.92, 95% CI 0.92 to 3.98) did not differ significantly between cohorts (Table 2, Fig. 2).

Outcomes at 1 Year

At 1 year, all implant-related outcomes remained comparable between groups, with every confidence interval crossing one. These included any mechanical complication (OR 0.94, 95% CI 0.57 to 1.54), periprosthetic fracture (OR 0.93, 95% CI 0.45 to 1.94), instability or dislocation (OR 1.07, 95% CI 0.52 to 2.22), reoperation (OR 0.87, 95% CI 0.51 to 1.47), and PJI (OR 0.73, 95% CI 0.45 to 1.17) (Table 2, Fig. 2).

Outcomes at 2 Years

At 2 years, tirzepatide use was associated with significantly lower odds of mechanical complications (OR 0.64, 95% CI 0.42 to 0.96) and PJI (OR 0.64, 95% CI 0.41 to 0.999; P = .048). Reoperation did not

differ significantly (OR 0.68, 95% CI 0.43 to 1.08). Periprosthetic fracture (OR 0.75, 95% CI 0.38 to 1.47) and instability or dislocation (OR 0.73, 95% CI 0.40 to 1.32) also did not differ significantly (Table 2, Fig. 2).

Table 2
Post-operative outcomes after primary TKA/THA following 1:1 propensity matching

Outcome	Tirzepatide *n*	Semaglutide *n*	OR (95% CI)	P-value
90 days (N = 2,858 per group)				
Surgical site infection / infection following procedure	22	31	0.71 (0.41–1.22)	.214
Sepsis	19	20	0.95 (0.51–1.78)	.872
Cellulitis of lower extremity	33	38	0.87 (0.54–1.39)	.550
Mechanical complications	21	11	1.92 (0.92–3.98)	.076
Wound dehiscence / disruption	30	43	0.69 (0.43–1.11)	.126
Emergency department visit	286	312	0.91 (0.77–1.08)	.261
Readmission	454	406	1.14 (0.99–1.32)	.076
1 year				
Mechanical complications	31	33	0.94 (0.57–1.54)	.801
Periprosthetic fracture	14	15	0.93 (0.45–1.94)	.852
Instability / dislocation	15	14	1.07 (0.52–2.22)	.852
Reoperation	26	30	0.87 (0.51–1.47)	.591
Periprosthetic joint infection	30	41	0.73 (0.45–1.17)	.189
2 years				
Mechanical complications	38	59	**0.64 (0.42–0.96)**	**.032**
Periprosthetic fracture	15	20	0.75 (0.38–1.47)	.397
Instability / dislocation	19	26	0.73 (0.40–1.32)	.295

Outcome	Tirzepatide *n*	Semaglutide *n*	OR (95% CI)	P-value
90 days (N = 2,858 per group)				
Reoperation	30	44	0.68 (0.43–1.08)	.101
Periprosthetic joint infection	33	51	**0.64 (0.41–0.999)**	**.048**

n, number of patients with the outcome in each cohort; OR, odds ratio; CI, confidence interval. OR < 1.0 favors tirzepatide. The matched cohort comprised 2,858 patients per group. Bold rows denote statistical significance (P < .05). TKA, total knee arthroplasty; THA, total hip arthroplasty; PJI, periprosthetic joint infection.

Discussion

Tirzepatide or semaglutide was documented in 8,797 (1.3%) of the 669,698 patients who underwent primary TKA or THA in this network. In this propensity-matched cohort analysis, tirzepatide and semaglutide use within 6 months prior to surgery were associated with comparable post-operative outcomes through 1 year across medical, surgical, and implant-related outcomes. At 2 years follow-up, tirzepatide use was associated with significantly lower odds of mechanical complications and PJI, while reoperation did not differ significantly. We are currently aware of no prior study that has directly compared individual GLP-1RA agents in patients undergoing total knee or hip arthroplasty.

These findings build on literature that has primarily examined outcomes of GLP-1RA grouped as a single pharmacologic class [11]. Prior systematic reviews and large database analyses have generally reported comparable or decreased complications among GLP-1RA users undergoing arthroplasty, including lower rates of readmission, wound complications, and PJI, and single-agent and mixed-class analyses have also found no increase in early complications [15, 16]. Our results are consistent with these previous studies through one year post-operatively and add additional evidence that tirzepatide and semaglutide were not associated with completely similar outcomes at 2 years post-operatively.

The reason for the divergence in our reported associations at 2 years is likely multifactorial. Tirzepatide has been shown to produce greater and longer lasting weight loss than semaglutide in comparative clinical trials [17, 19], and because obesity is among the most important modifiable risk factors for PJI and several mechanical complications [7], the greater weight reduction association with tirzepatide could plausibly contribute to the lower odds observed in this study. The additional GIP receptor activity of tirzepatide compared to semaglutide may also be relevant, as GIP receptors are expressed on osteoblasts and osteoclasts, where incretin signaling has been associated with increased bone formation and reduced bone resorption and could possibly strengthen implant fixation and preserve

periprosthetic bone quality [22]. GLP-1 signaling has also been associated with anti-inflammatory effects that are consistent with the associations with lower odds of PJI found in our study [18].

These findings carry several clinical implications. The comparable early outcome associations observed in this study could suggest that neither semaglutide nor tirzepatide is associated with adverse medical outcomes at 90 days, which is reassuring given that current perioperative guidance focuses on the aspiration risk of GLP-1RA and the timing of medication cessation rather than on choice of medication [23, 24]. The divergence in associations observed at 2 years could suggest that the distinction between dual GIP/GLP-1 agonism and selective GLP-1 agonism may carry clinical relevance and supports continued perioperative use of tirzepatide where otherwise appropriate rather than presuming equivalence across all GLP-1RA.

Strengths and Limitations

Strengths of this study include the direct comparison of two individual agents rather than the pharmacologic class as a whole, propensity score matching with all standardized differences below 0.05, and follow-up extending to 2 years. This analysis also has several limitations. Most importantly, medication exposure was defined from electronic health record coding, which does not confirm that medications were taken, and adherence to medications may correlate with metabolic control and other factors that could independently influence perioperative risk. We could not stratify by dosage, treatment duration, or indication, and we could not distinguish patients treated for diabetes from those treated for obesity. Overweight and obesity diagnosis (ICD-10 E66) was included as a matching covariate, but residual confounding by the degree and trajectory of previous weight change cannot be excluded. All outcomes were identified from coded diagnoses and procedures, which are subject to misclassification, and we could not distinguish ipsilateral from contralateral events. Patient event counts were limited for several implant-related outcomes, which reduced precision and prevented analysis of rarer outcomes. Multiple outcomes were assessed across three time points without adjustment for multiple comparisons, which increases the likelihood that at least one significant association could reflect chance. Finally, this was a retrospective database study and cannot establish causation.

Conclusion

Among propensity-matched patients who underwent primary TKA or THA, tirzepatide and semaglutide exposure, documented in 1.3% of all primary TKA or THA performed in this network, were associated with comparable post-operative outcomes through 1 year. By 2 years, tirzepatide exposure was associated with significantly lower odds of mechanical complications and periprosthetic joint infection, while reoperation did not differ significantly. These findings suggest that the pharmacologic distinction between dual GIP/GLP-1 receptor agonism and selective GLP-1 receptor agonism may carry clinical significance for arthroplasty patients and that the two agents should not be presumed equivalent. Prospective comparative studies that incorporate dispensing data, dosing, and weight trajectory are

needed to confirm these observations and to determine whether agent selection can be used to reduce later implant-related complications.

Declarations

Competing Interests

Spencer C. Davis, Shlok V. Patel and Shane Fletcher declare they have no competing interests. John P. McLaughlin has the following disclosures, none related to the present study: consultant for Zimmer Biomet, Smith and Nephew, and OrthAlign. Matthew E. Deren has the following disclosures, none related to the present study: paid speaker for Brasseler; stock options in ROM Technologies; governing board of The Journal of Knee Surgery. Nicolas S. Piuzzi has the following disclosures, none related to the present study: grants or contracts from Osteal Therapeutics, Peptilogics, RegenLab, Signature Orthopedics, Zimmer and Stryker; consulting fees from Zimmer, Pacira Pharmaceutical and Stryker; editorial board member or leadership role with JBJS, the American Association of Hip and Knee Surgeons and the Orthopaedic Research Society.

Author Contribution

S.C.D, S.V.P, and S.F were involved in idea conception, data collection and analysis, creating all tables and figures, and writing and revising manuscript text. J.P.M, M.E.D, and N.S.P were involved in idea conception, project supervision, and writing and revising of manuscript text.

Data Availability

The aggregated data supporting the findings of this study were generated within the TriNetX Research Network and are available to investigators at institutions holding a TriNetX subscription. Patient-level data are not available to the authors, as the platform returns only aggregated counts and summary statistics derived from de-identified records.

References

1. Ferguson RJ, Palmer AJR, Taylor A, Porter ML, Malchau H, Glyn-Jones S (2018) Hip replacement. Lancet 392:1662–1671. https://doi.org/10.1016/S0140-6736(18)31777-X
2. Price AJ, Alvand A, Troelsen A, Katz JN, Hooper G, Gray A et al (2018) Knee replacement. Lancet 392:1672–1682. https://doi.org/10.1016/S0140-6736(18)32344-4
3. Sloan M, Premkumar A, Sheth NP (2018) Projected volume of primary total joint arthroplasty in the U.S., 2014 to 2030. J Bone Joint Surg Am 100:1455–1460. https://doi.org/10.2106/JBJS.17.01617
4. Delaney PG, Piuzzi NS (2026) A call for inclusion of arthroplasty as essential surgery. Bull World Health Organ 104:274–281. https://doi.org/10.2471/BLT.25.294300

5. Maradit Kremers H, Larson DR, Crowson CS, Kremers WK, Washington RE, Steiner CA et al (2015) Prevalence of total hip and knee replacement in the United States. J Bone Joint Surg Am 97:1386–1397. https://doi.org/10.2106/JBJS.N.01141
6. Kurtz SM, Lau E, Watson H, Schmier JK, Parvizi J (2012) Economic burden of periprosthetic joint infection in the United States. J Arthroplasty 27:61–65e1. https://doi.org/10.1016/j.arth.2012.02.022
7. Carender CN, Fruth KM, Lewallen DG, Berry DJ, Abdel MP, Bedard NA (2024) Obesity and primary total hip arthroplasty: the absolute versus relative risk of periprosthetic joint infection at 15 years. J Arthroplasty 39. https://doi.org/10.1016/j.arth.2024.03.033. S436-S443.e1
8. Wilding JPH, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I et al (2021) Once-weekly semaglutide in adults with overweight or obesity. N Engl J Med 384:989–1002. https://doi.org/10.1056/NEJMoa2032183
9. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA et al (2016) Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 375:1834–1844. https://doi.org/10.1056/NEJMoa1607141
10. Hammond MM, Krishnan V, Petito LC, Kazi DS, Khan SS, Huang X (2026) Trends in usage and payments for glucagon-like peptide-1 receptor agonists in the United States, 2017 to 2022: a nationally representative repeated cross-sectional study. J Am Heart Assoc. https://doi.org/10.1161/JAHA.125.046302
11. Abdelaziz O, Zayed ZG, Khalafallah MA, Hanafy MA, Hadhoud AM, Elmenawi KA (2026) Glucagon-like peptide-1 receptor agonists in total joint arthroplasty: a comprehensive systematic review of what orthopaedic surgeons should know. Arthroplasty 8:23. https://doi.org/10.1186/s42836-026-00375-w
12. Arnold N, Anis H, Barsoum WK, Bloomfield MR, Brooks PJ, Higuera CA et al (2020) Preoperative cut-off values for body mass index deny patients clinically significant improvements in patient-reported outcomes after total hip arthroplasty. Bone Joint J 102–B:683–692. https://doi.org/10.1302/0301-620X.102B6.BJJ-2019-1644.R1
13. Bliddal H, Bays H, Czernichow S, Uddén Hemmingsson J, Hjelmesæth J, Hoffmann Morville T et al (2024) Once-weekly semaglutide in persons with obesity and knee osteoarthritis. N Engl J Med 391:1573–1583. https://doi.org/10.1056/NEJMoa2403664
14. Porto JR, Lavu MS, Hecht CJ, Kaelber DC, Sculco PK, Heckmann ND et al (2025) The impact of contemporary glucagon-like peptide-1 receptor agonists on the onset, severity, and conversion to arthroplasty in hip and knee osteoarthritis. Orthop J Sports Med 13:23259671241297157. https://doi.org/10.1177/23259671241297157
15. Mashayekhi Y, Asgari AM, Pahlevan-Fallahy MT, Karimi MA, Jalali R, Shaker F (2025) Impact of glucagon-like peptide-1 receptor agonists on postoperative complications after total joint arthroplasty: a systematic review and meta-analysis. J Orthop Surg (Hong Kong) 33:10225536251391959. https://doi.org/10.1177/10225536251391959

16. Heo KY, Goel RK, Woltemath A, Fuqua A, Hrudka BT, Syed O et al (2025) Glucagon-like peptide-1 receptor agonist use is not associated with increased complications after total hip arthroplasty in patients who have type 2 diabetes. J Arthroplasty 40:1413–1418e1. https://doi.org/10.1016/j.arth.2024.10.099
17. Frías JP, Davies MJ, Rosenstock J, Pérez Manghi FC, Fernández Landó L, Bergman BK et al (2021) Tirzepatide versus semaglutide once weekly in patients with type 2 diabetes. N Engl J Med 385:503–515. https://doi.org/10.1056/NEJMoa2107519
18. Drucker DJ (2018) Mechanisms of action and therapeutic application of glucagon-like peptide-1. Cell Metab 27:740–756. https://doi.org/10.1016/j.cmet.2018.03.001
19. Aronne LJ, Horn DB, le Roux CW, Ho W, Falcon BL, Gomez Valderas E et al (2025) Tirzepatide as compared with semaglutide for the treatment of obesity. N Engl J Med 393:26–36. https://doi.org/10.1056/NEJMoa2416394
20. Gastaldelli A, Cusi K, Fernández Landó L, Bray R, Brouwers B, Rodríguez Á (2022) Effect of tirzepatide versus insulin degludec on liver fat content and abdominal adipose tissue in people with type 2 diabetes (SURPASS-3 MRI): a substudy of the randomised, open-label, parallel-group, phase 3 SURPASS-3 trial. Lancet Diabetes Endocrinol 10:393–406. https://doi.org/10.1016/S2213-8587(22)00070-5
21. Kanbay M, Shah E, AlShiab R, Ozbek L, Ay S, Rustamov A et al (2026) Effects of GLP-1 receptor agonists and dual GIP/GLP-1 receptor agonists on inflammatory and metabolic biomarkers in type 2 diabetes: a systematic review and meta-analysis. Diabetes Obes Metab. https://doi.org/10.1111/dom.71106
22. Nauck MA, Meier JJ (2018) Incretin hormones: their role in health and disease. Diabetes Obes Metab 20(Suppl 1):5–21. https://doi.org/10.1111/dom.13129
23. Ushakumari DS, Sladen RN (2024) ASA consensus-based guidance on preoperative management of patients on glucagon-like peptide-1 receptor agonists. Anesthesiology 140:346–348. https://doi.org/10.1097/ALN.0000000000004776
24. Kindel TL, Wang AY, Wadhwa A, Schulman AR, Sharaiha RZ, Kroh M et al (2025) Multisociety clinical practice guidance for the safe use of glucagon-like peptide-1 receptor agonists in the perioperative period. Clin Gastroenterol Hepatol 23:2083–2085. https://doi.org/10.1016/j.cgh.2024.10.003
25. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP (2007) The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 370:1453–1457. https://doi.org/10.1016/S0140-6736(07)61602-X

Figures

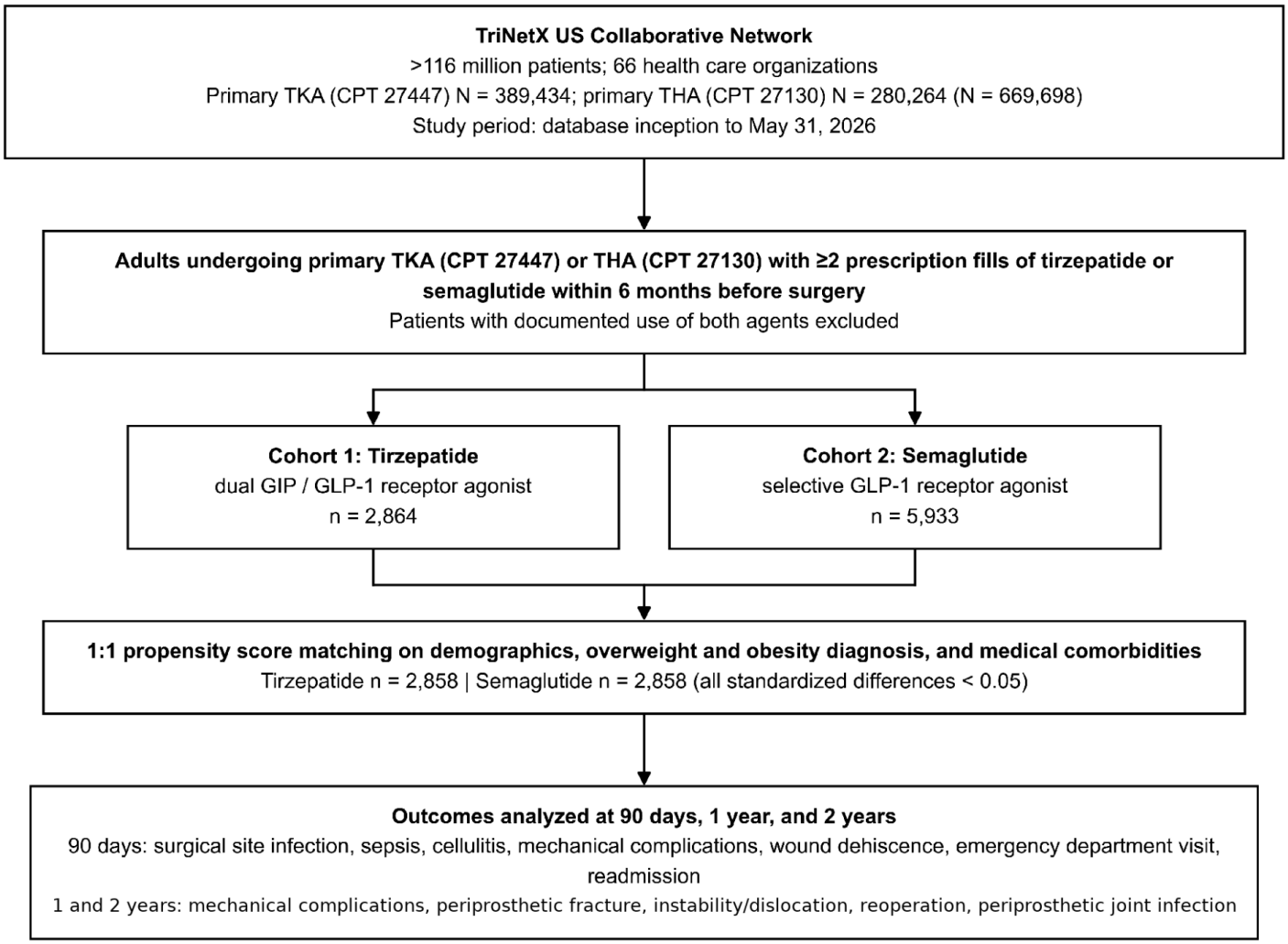

Figure 1

Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) diagram of TriNetX cohort selection. TKA, total knee arthroplasty; THA, total hip arthroplasty; CPT, Current Procedural Terminology; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1

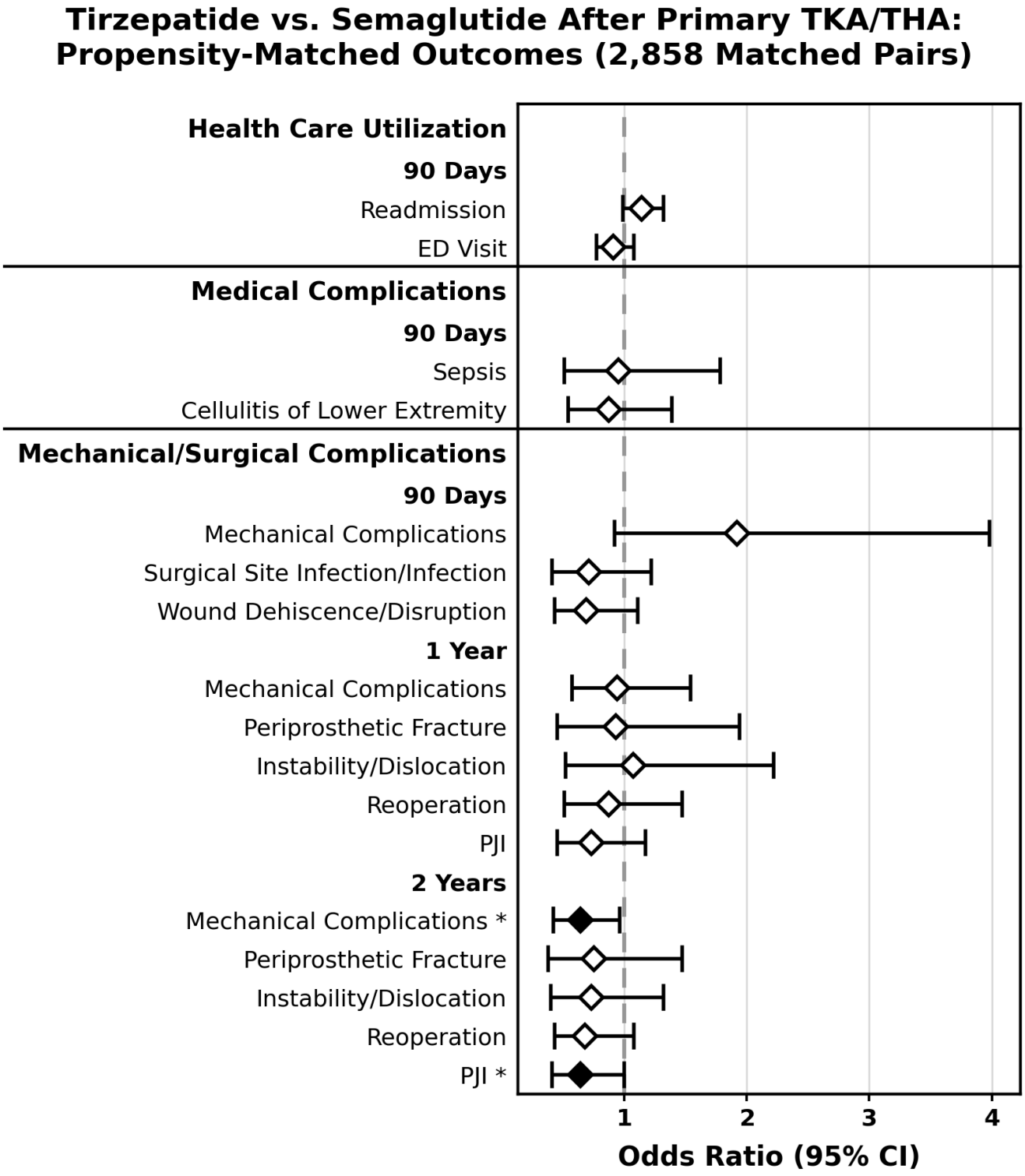

Figure 2

Propensity-matched odds ratios for tirzepatide versus semaglutide across all outcomes at 90 days, 1 year, and 2 years following primary TKA/THA. Odds ratios below 1.0 favor tirzepatide. Filled diamonds and asterisks denote P < .05. OR, odds ratio; CI, confidence interval; ED, emergency department; PJI, periprosthetic joint infection; TKA, total knee arthroplasty; THA, total hip arthroplasty

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryMaterial.docx