Obesity

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ORIGINAL ARTICLE

Clinical Trials and Investigations

Real-World Effectiveness of Semaglutide and Tirzepatide Compared With Bariatric Surgery

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ABSTRACT

Objective: Directly compare the real-world effectiveness of semaglutide and tirzepatide to bariatric operations: sleeve gastrectomy and gastric bypass.

Methods: This study included adults with BMI ≥ 35 who received injectable semaglutide or tirzepatide (GLP-1RAs) or sleeve gastrectomy or gastric bypass (bariatric surgery) at two urban health systems from 2018 to 2024. Total weight loss (TWL) was compared up to 3 years post treatment with inverse probability weighting and mixed linear models. Intention-to-treat (any GLP-1RA) and per-protocol (1 year of continuous GLP-1RA orders) analyses were performed.

Results: Of 44,025 patients studied, bariatric surgery was associated with greater weight loss at 1, 2, and 3 years post treatment: semaglutide ($n = 25{,}804$) TWL (95% CI): 5.4% (5.3%–5.6%), 6.5% (6.4%–6.7%), and 7.4% (7.3%–7.6%); tirzepatide ($n = 7308$): 9.1% (8.9%–9.4%) and 10.8% (10.2%–11.3%); sleeve gastrectomy ($n = 8728$): 24.4% (24.3%–24.6%), 22.4% (22.3%–22.5%), and 22.0% (21.8%–22.1%); gastric bypass ($n = 2185$): 29.8% (29.7%–29.9%), 28.1% (28.0%–28.2%), and 28.4% (28.3%–28.5%). With 1 year of continuous GLP-1RA, findings were: semaglutide TWL: 7.2% (7.0%–7.4%), 8.0% (7.8%–8.2%), and 8.8% (8.6%–9.0%); tirzepatide TWL: 11.7% (11.4%–11.9%) and 11.9% (11.5%–12.3%).

Conclusions: In this retrospective two-center study, bariatric surgery was associated with greater weight loss than GLP-1RAs among patients eligible for both options.

1 | Introduction

Obesity is one of the most prevalent diseases in the world, affecting over 1 billion people worldwide [1]. Bariatric surgery has long been the gold standard treatment for obesity and metabolic disorders, yielding sustained total weight loss (TWL) between 20% and 30% [2–4]. Recently, the newer glucagon-like peptide-1 receptor agonists (GLP-1RAs) semaglutide and tirzepatide have demonstrated weight loss rivaling bariatric surgery and have been approved for the treatment of obesity, leading to a rapid increase in utilization, with one in eight US adults reporting a history of GLP-1RA use [5].

Though patients seeking effective obesity treatment can now choose between GLP-1RAs and bariatric surgery, most previous research on these interventions has been performed separately, with few real-world, direct comparative studies among the four leading options for the indication of obesity: semaglutide, tirzepatide, and the most prevalent bariatric/metabolic procedures, sleeve gastrectomy and Roux-en-Y gastric bypass [6]. The landmark trials of semaglutide and tirzepatide demonstrated substantial weight loss, from 15% (semaglutide) to 21% (tirzepatide) [7, 8]. However, these trials only compared GLP-1RAs to placebo and lifestyle interventions (TWL 5%–10%). Additionally, there are significant baseline differences in these trial populations

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relative to those undergoing bariatric surgery, with 40% of GLP-1RA clinical trial patients having a baseline BMI below 35 [7, 8]. For direct comparisons, studies with comparable populations of patients receiving GLP-1RAs or bariatric surgery are needed. Finally, while GLP-1RAs represent a revolutionary change in the treatment of obesity and metabolic disorders, early real-world studies suggest they may not be as effective as seen in clinical trials [9, 10].

To that end, the purpose of this study was to compare the effectiveness of GLP-1RAs to bariatric surgery among patients with obesity eligible for both treatments. Specifically, we conducted a large, retrospective analysis of real-world weight loss and safety outcomes at 3 years for patients with BMI ≥ 35 treated with semaglutide or tirzepatide versus sleeve gastrectomy or Roux-en-Y gastric bypass. Our findings will inform patients and clinicians deciding on treatment strategies for obesity and metabolic syndrome.

2 | Methods

2.1 | Data Source and Study Population

We conducted a retrospective analysis comparing weight reduction between GLP-1RA (weekly injectable semaglutide or tirzepatide) initiators and bariatric surgery patients (minimally invasive sleeve gastrectomy or Roux-en-Y gastric bypass) from 2018 to 2024 among adult patients (≥ 18 years) with a baseline BMI ≥ 35 in two large, diverse health systems in the New York City metropolitan area—one public health system (NYC Health+Hospitals), one private (NYU Langone Health). GLP-1RA use was examined among patients with at least one medication order and among those with 1 year of continuous orders of semaglutide or tirzepatide. One-year continuous use was defined as ten 1-month medication orders in 11 months (to allow for brief lapses in prescription supply). Patients who had both bariatric surgery and GLP-1RA use, missing baseline BMI, history of bariatric surgery before the study period, unknown intervention date or baseline weight, or no recorded post-intervention weights were dropped from the cohort. Baseline weight was defined as the measurement closest to or on the day of intervention initiation up to 1 year before the intervention. GLP-1RA patients whose initial dose was greater than 0.25 mg for semaglutide or 2.5 mg for tirzepatide were removed from the study population, as they were assumed to have initiated the GLP-1RA medication before study inclusion. Due to substantially lower effectiveness, older GLP-1RA medications (e.g., liraglutide, dulaglutide) and oral agents were not considered. Patients with a baseline weight < 80 lb were excluded and post-intervention weights < 80 lb were removed due to suspected charting errors. A total of 13.8% of bariatric surgery patients with an unknown age were assumed to be ≥ 18 years. This study was approved by the NYU Langone Health Institutional Review Board.

Based on ICD-10 codes, patient characteristics and comorbidities were examined among bariatric surgery, GLP-1RA any use, and 1-year continuous GLP-1RA use patients overall and by those diagnosed with diabetes at baseline. Differences were examined using standardized mean differences, and p values were calculated using Fisher's exact test, χ^2 test, and Wilcoxon rank sum test as appropriate.

2.2 | Outcomes and Statistical Analysis

Our primary outcome was %TWL following bariatric surgery or GLP-1RA initiation. Each patient's %TWL from baseline was calculated. A linear mixed effects model was fit to %TWL over time with patient-level random intercepts. Due to the pronounced early drop in weight followed by slight weight regain leveling off over time, a linear spline at 0.05 years was combined with a cubic spline. Additionally, knots were included at 1, 2, and 3 years to allow for fluctuations in the rate of weight loss (tirzepatide outcomes were only reported to 2 years given its US approval in 2022 and the end of data collection in 2024). In this context, a "spline" is a flexible curve used to model nonlinear change over time, and "knots" (here placed at 1, 2, and 3 years) are the time points at which the slope of the curve is allowed to change to better fit the observed pattern of weight loss. The analysis was stratified by specific intervention (semaglutide, tirzepatide, sleeve gastrectomy, gastric bypass), length of GLP-1RA treatment (any or 1-year continuous use), and diabetes status. All analyses were weighted by age, sex, race (White/Black), hypertension, diabetes, COPD, hyperlipidemia, sleep apnea, GERD, liver disease, renal insufficiency, and baseline BMI category (35–40/40+) at baseline. Weights were constructed using average treatment effect (ATE) such that, for example, bariatric surgery patients were given a weight of 1/(propensity score) and GLP-1RA users were given a weight of 1/(1-propensity score). The baseline intercept was removed from weighted analyses to constrain weight loss to 0% at baseline. For the four-way comparison of intervention type (gastric bypass, sleeve gastrectomy, semaglutide, tirzepatide) ATE weights were constructed using multinomial logistic regression with age, sex, race, hypertension, diabetes, COPD, and baseline BMI category (35–40/40+).

The change in HbA1c from baseline was calculated up to 3 years following the intervention. Trends were examined using a linear regression with shaded areas to indicate the 95% confidence error with a Gaussian error assumption. ATE weights were computed using the same covariates. A two-sided α of 0.05 was considered statistically significant. Data were pulled and analyzed using SQL and RStudio (v.4.0.3/4.1.2).

3 | Results

Between 2018 and 2024, 10,913 patients underwent primary bariatric surgery (8728 sleeve gastrectomy and 2185 gastric bypass, Table 1). During the same period, 33,112 patients initiated a GLP-1RA medication (25,804 semaglutide and 7308 tirzepatide). Mean BMI was 43 in the surgery group and 40 in GLP-1RA group (patients with BMI < 35 were excluded). Surgery patients were younger than GLP-1RA patients ($p < 0.001$). Both groups were majority female. GLP-1RA patients were predominantly White (55.8% vs. 8.3%, $p < 0.001$), and surgery patients were predominantly Hispanic/multiracial/other (57.9% vs. 9.4%, $p < 0.001$). Type 2 diabetes was significantly more prevalent in

TABLE 1 | Baseline demographic and clinical characteristics by weight loss intervention.

Characteristic	Bariatric surgery, $N = 10.913$[a]	GLP-1, $N = 33.112$[a]	SMD (95% CI)	p[b]
Surgery type				
Gastric bypass	2185 (20.0%)	—	—	—
Sleeve gastrectomy	8728 (80.0%)	—	—	—
GLP type				
Semaglutide	—	25,804 (77.9%)	—	—
Tirzepatide	—	7308 (22.1%)	—	—
Hospital	—	—	1.9 (1.8, 1.9)	**< 0.001**
NYC Health+Hospitals	7155 (65.6%)	469 (1.4%)	—	—
New York University Langone Health	3758 (34.4%)	32,643 (98.6%)	—	—
Age (years)	—	—	1.5 (1.5, 1.5)	**< 0.001**
18–29	2759 (25.3%)	2306 (7.0%)	—	—
30–39	2697 (24.7%)	4656 (14.1%)	—	—
40–49	1769 (16.2%)	6481 (19.6%)	—	—
50–59	1012 (9.3%)	8666 (26.2%)	—	—
60–69	232 (2.1%)	7302 (22.1%)	—	—
≥ 70	34 (0.3%)	3701 (11.2%)	—	—
Unknown	2410 (22.1%)	0 (0.0%)	—	—
Gender	—	—	0.54 (0.52, 0.57)	**< 0.001**
Female	7648 (70.1%)	21,781 (65.8%)	—	—
Male	2178 (20.0%)	11,323 (34.2%)	—	—
Other/unknown	1087 (10.0%)	8 (0.0%)		
Race	—	—	1.5 (1.5, 1.6)	**< 0.001**
White	904 (8.3%)	18,492 (55.8%)	—	—
Black or African American	1109 (10.2%)	6298 (19.0%)	—	—
Hispanic/multiracial/other	6315 (57.9%)	3096 (9.4%)	—	—
Unknown	2585 (23.7%)	5226 (15.8%)	—	—
Insurance	—	—	1.1 (1.1, 1.2)	**< 0.001**
Commercial	3130 (28.7%)	13,794 (41.7%)	—	—
Medicaid	5016 (46.0%)	4604 (13.9%)	—	—
Medicare	294 (2.7%)	5747 (17.4%)	—	—
Other public	3 (0.0%)	4781 (14.4%)	—	—
Self-pay	525 (4.8%)	166 (0.5%)	—	—
Other/unknown	1945 (17.8%)	4020 (12.1%)	—	—
Baseline A1c[c]	5.7 (5.4, 6.0)	6.0 (5.5, 7.0)	−0.46 (−0.49, −0.44)	**< 0.001**
Baseline weight (lb)	245 (218, 280)	248 (222, 280)	−0.04 (−0.06, −0.02)	**< 0.001**
Baseline BMI	43 (39, 53)	40 (37, 44)	0.57 (0.55, 0.59)	**< 0.001**
Type 2 diabetes	666 (6.1%)	5416 (16.4%)	0.33 (0.31, 0.35)	**< 0.001**

(Continues)

TABLE 1 | (Continued)

Characteristic	Bariatric surgery, $N = 10.913$[a]	GLP-1, $N = 33.112$[a]	SMD (95% CI)	p[b]
COPD	29 (0.3%)	351 (1.1%)	0.10 (0.08, 0.12)	**< 0.001**
GERD	716 (6.6%)	2371 (7.2%)	0.02 (0.00, 0.05)	**0.03**
Liver disease	531 (4.9%)	771 (2.3%)	0.14 (0.11, 0.16)	**< 0.001**
Hypertension	1343 (12.3%)	8692 (26.3%)	0.36 (0.34, 0.38)	**< 0.001**
Hyperlipidemia	1121 (10.3%)	6796 (20.5%)	0.29 (0.27, 0.31)	**< 0.001**
Renal insufficiency	48 (0.4%)	398 (1.2%)	0.08 (0.06, 0.11)	**< 0.001**
Sleep apnea	1189 (10.9%)	2642 (8.0%)	0.10 (0.08, 0.12)	**< 0.001**

Abbreviation: SMD = standardized mean difference.
[a]*Dn* (%); Median (Q1, Q3).
[b]Fisher's exact test, χ^2 test, Wilcoxon rank sum test; bold values indicate statistical significance ($p < 0.05$).
[c]Baseline A1c was missing for 3326 bariatric surgery patients and 11,040 GLP-1 patients.

the GLP-1RA group (16.4% vs. 6.1%, $p < 0.001$). GLP-1RA patients had a higher prevalence of hypertension (26.3% vs. 12.3%, $p < 0.001$), hyperlipidemia (20.5% vs. 10.3%, $p < 0.001$), COPD (1.1% vs. 0.3%, $p < 0.001$), renal insufficiency (1.2% vs. 0.4%, $p < 0.001$), and GERD (7.2% vs. 6.6%, $p = 0.03$), but surgery patients had a greater prevalence of sleep apnea (10.9% vs. 8.0%, $p < 0.001$) and liver disease (4.9% vs. 2.3%, $p < 0.001$). More patients initiated GLP-1RA medication at the private health system (98.6% vs. 1.4%, $p < 0.001$), whereas more of the bariatric surgeries were performed at the public health system (65.6% vs. 34.4%, $p < 0.001$). The most common type of insurance used among surgery patients was Medicaid (46.0%) and among GLP-1RA patients was commercial (41.7%). After weighting, the standardized mean difference reduced, particularly between age (1.48 to 0.34), sex (0.54 to 0.22), and binary race (1.18 to 0.03) (Table S4).

3.1 | Medication Dose Escalation and Discontinuation

Table 2 shows the progression of medication dosing and discontinuation over time. A total of 33.9% of GLP-1RA users discontinued the medication after two 1-month orders; 54.3% were prescribed fewer than six 1-month orders. Discontinuation rates were higher in semaglutide than in tirzepatide. By their sixth order, 5.3% of semaglutide and 2.8% of tirzepatide users reached the highest dose of each agent.

3.2 | Unweighted Analysis

In the unweighted analysis, mean TWL among all bariatric surgery patients was 25.6% (25.5%–25.8%), 23.6% (23.5%–23.7%), and 22.2% (22.1%–22.4%) at 1, 2, and 3 years (Figure S1). Among all GLP-1RA patients, TWL was 6.0% (5.9%–6.1%) and 7.0% (6.9%–7.0%) at 1 and 2 years. By procedure, TWL for sleeve gastrectomy was 24.9% (24.7%–25.0%), 22.4% (22.2%–22.5%), and 21.0% (20.9%–21.2%), and for gastric bypass was 28.4% (28.1%–28.7%), 27.9% (27.6%–28.2%), and 26.7% (26.4%–27.1%) at 1, 2, and 3 years (Figure S2A). By medication, TWL for semaglutide was 5.4% (5.3%–5.5%), 6.5% (6.5%–6.6%), and 7.6% (7.5%–7.7%) at 1, 2, and 3 years, and for tirzepatide was 9.1% (8.8%–9.3%) and 10.9% (10.3%–11.5%) at 1 and 2 years. Among GLP-1RA patients with at least 1 year of continuous treatment, TWL was 7.6% (7.5%–7.8%) and 8.4% (8.3%–8.6%) at 1 and 2 years (Figure S1). By medication, TWL for 1-year continuous semaglutide was 7.2% (7.0%–7.3%), 8.1% (7.9%–8.2%), and 9% (8.8%–9.1%) at 1, 2, and 3 years, and for 1-year continuous tirzepatide was 10.9% (10.4%–11.3%) and 12.5% (11.6%–13.4%) at 1 and 2 years (Figure S2B).

3.3 | Weighted Analysis

In the weighted analysis, TWL among bariatric surgery patients was 25.6% (25.5%–25.7%), 23.6% (23.6%–23.7%), and 23.5% (23.4%–23.6%) at 1, 2, and 3 years (Figure 1A); TWL among GLP-1RA patients was 6.0% (5.9%–6.1%) and 6.9% (6.8%–7.0%) at 1 and 2 years. By procedure, TWL for sleeve gastrectomy was 24.4% (24.3%–24.6%), 22.4% (22.3%–22.5%), and 22.0% (21.8%–22.1%), and for gastric bypass was 29.8% (29.7%–29.9%), 28.1% (28.0%–28.2%), and 28.4% (28.3%–28.5%) at 1, 2, and 3 years (Figure 2A). By medication, TWL for semaglutide was 7.2% (7.0%–7.4%), 8.0% (7.8%–8.2%), and 8.8% (8.6%–9.0%) at 1, 2, and 3 years, and for tirzepatide was 9.1% (8.9%–9.4%) and 10.8% (10.2%–11.3%) at 1 and 2 years. Among patients with at least 1 year of continuous GLP-1RA use, TWL for 1-year continuous semaglutide was 7.2% (7.0%–7.4%), 8.0% (7.8%–8.2), and 8.8% (8.6%–9.0%) at 1, 2, and 3 years (Figure 2B); TWL for 1-year continuous tirzepatide was 11.7% (11.4%–11.9%) and 11.9% (11.5%–12.3%) at 1 and 2 years.

Among patients without diabetes, TWL from bariatric surgery was 25.8% (25.7%–25.9%), 24.2% (24.1%–24.3%), and 24.1% (24.0%–24.2%) at 1, 2, and 3 years (Figure 3A); GLP-1RA TWL was 6.3% (6.2%–6.4%) and 7.1% (7.0%–7.3%) at 1 and 2 years. With 1-year continuous use, GLP-1RA TWL was 8.2% (8.0%–8.3%) and 8.8% (8.7%–9.0%) at 1 and 2 years (Figure 3B).

Among patients with diabetes, TWL from bariatric surgery was 23.5% (23.2%–23.7%), 20.4% (20.2%–20.6%), and 21.0% (20.8%–21.2%) at 1, 2, and 3 years (Figure 3C); GLP-1RA TWL was 4.6% (4.4%–4.9%) and 6.0% (5.7–6.2) at 1 and 2 years. With 1-year continuous use, GLP-1RA TWL was 5.5% (5.1%–5.8%) and 6.5% (6.2%–6.8%) at 1 and 2 years (Figure 3D).

TWL from bariatric surgery and GLP-1RA use stratified by sex is presented in Figure S6.

TABLE 2 | GLP-1 medication orders and dosing over time.

GLP-1 dose	Box 1 $N = 33.112$[a]	Box 2, $N = 33.12$[a]	Box 3, $N = 33.112$[a]	Box 4, $N = 33.112$[a]	Box 5 $N = 33.112$[a]	Box 6, $N = 33.112$[a]
Semaglutide 0.25–0.5 mg	25,807 (77.9%)	16,047 (48.5%)	11,253 (34.0%)	8052 (24.3%)	5845 (17.7%)	4206 (12.7%)
Semaglutide 1–1.7 mg	0 (0.0%)	3038 (9.2%)	4070 (12.3%)	4799 (14.5%)	4958 (15.0%)	4819 (14.6%)
Semaglutide 2–2.4 mg	0 (0.0%)	297 (0.9%)	527 (1.6%)	754 (2.3%)	1103 (3.3%)	1370 (4.1%)
Tirzepatide 2.5–5 mg	7305 (22.1%)	6320 (19.1%)	5146 (15.5%)	4273 (12.9%)	3481 (10.5%)	2902 (8.8%)
Tirzepatide 7.5–10 mg	0 (0.0%)	352 (1.1%)	810 (2.4%)	1165 (3.5%)	1465 (4.4%)	1624 (4.9%)
Tirzepatide 12.5–15 mg	0 (0.0%)	73 (0.2%)	75 (0.2%)	81 (0.2%)	129 (0.4%)	204 (0.6%)
Discontinued	0 (0.0%)	6985 (21.1%)	11,231 (33.9%)	13,988 (42.2%)	16,131 (48.7%)	17,987 (54.3%)

Note: Each "box" (column) represents a 1-month order of medication.
[a]*n* (%).

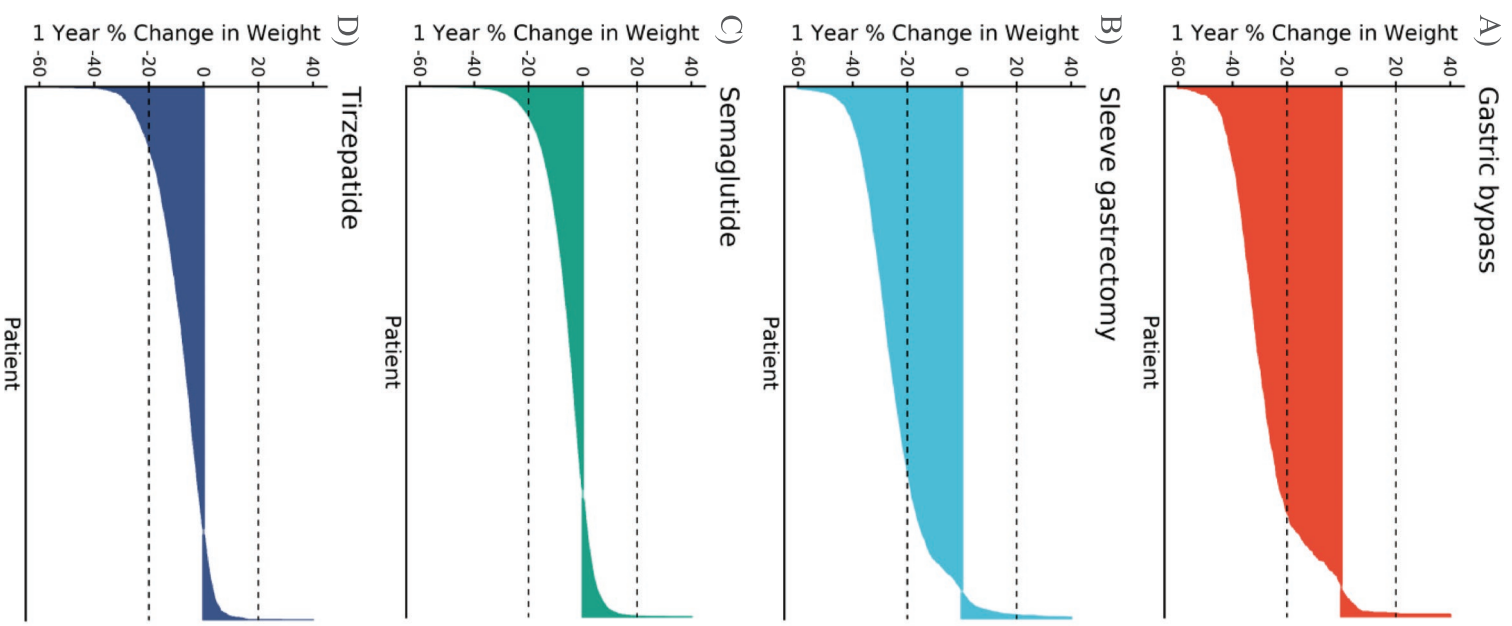


FIGURE 1 | Waterfall plot of weight loss by treatment at 1 year for (A) gastric bypass, (B) sleeve gastrectomy, (C) semaglutide, and (D) tirzepatide. Truncated at −60% and 40%. [Color figure can be viewed at wileyonlinelibrary.com]

3.4 | HbA1c

In the unweighted analysis, restricted to the 6082 patients with diabetes, bariatric surgery and GLP-1RA groups had comparable reductions in HbA1c. Semaglutide patients had 0.65%

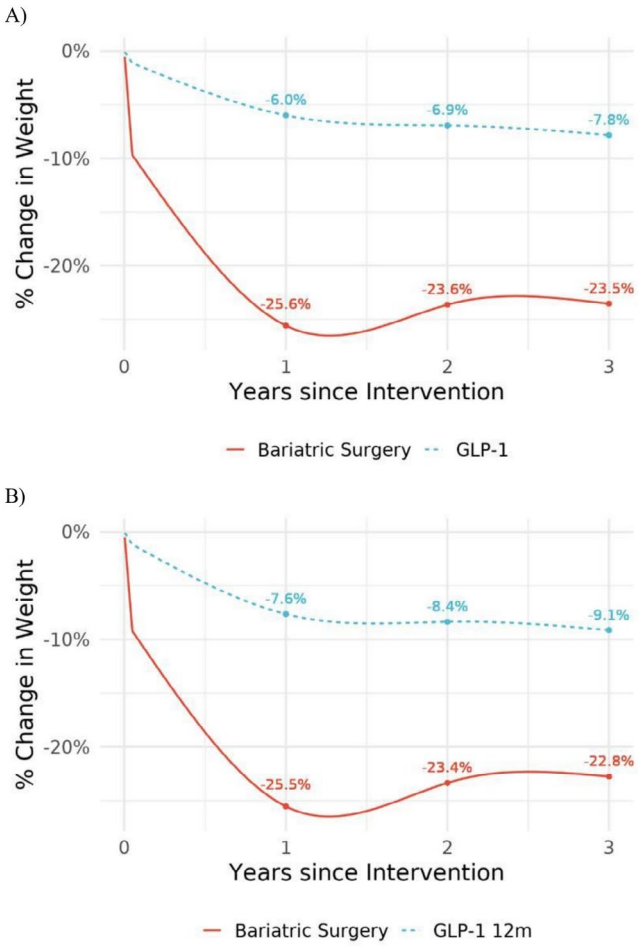


FIGURE 2 | Weighted percent weight loss over time following bariatric surgery and (A) GLP-1 use ever without diabetes, (B) 1-year continuous GLP-1 use without diabetes, (C) GLP-1 use ever with diabetes, and (D) 1-year continuous GLP-1 use with diabetes. Abbreviation: 12 m = 1-year continuous GLP-1 use. [Color figure can be viewed at wileyonlinelibrary.com]

(0.58%–0.72%), 0.77% (0.67%–0.86%), and 1.00% (0.76%–1.24%) point decreases in HbA1c at 1, 2, and 3 years post initiation, and tirzepatide patients had 0.86% (0.78%–0.94%) and 0.67% (0.48%–0.85%) point reductions at 1 and 2 years post initiation. Sleeve gastrectomy was associated with 0.47% (0.45%–0.50%), 0.46% (0.42%–0.49%), and 0.44% (0.37%–0.50%) point decreases at 1, 2, and 3 years post surgery, whereas gastric bypass was associated with 0.62% (0.56%–0.68%), 0.62% (0.55%–0.68%), and 0.62% (0.55%–0.68%) point decreases in HbA1c at 1, 2, and 3 years post surgery.

In the weighted analysis, semaglutide was associated with 0.64% (0.57%–0.70%), 0.76% (0.67%–0.85%), and 0.99% (0.75%–1.22%) point decreases in HbA1c at 1, 2, and 3 years post initiation, and tirzepatide patients had 0.88% (0.80%–0.96%) and 0.67% (0.48%–0.86%) point reductions at 1 and 2 years post initiation. Sleeve gastrectomy was associated with 0.56% (0.50%–0.62%), 0.69% (0.61%–0.76%), and 0.59% (0.40%–0.79%) point decreases at 1, 2, and 3 years post surgery, whereas gastric bypass was associated with 0.52% (0.39%–0.66%), 0.52% (0.35%–0.69%), and 0.54% (0.13%–0.95%) point decreases in HbA1c at 1, 2, and 3 years post surgery (Figure 4).

4 | Discussion

In this study, we found that both sleeve gastrectomy and gastric bypass were associated with greater real-world weight loss than semaglutide or tirzepatide 2 and 3 years after intervention. This finding persisted when analysis was restricted to patients with 1 year of continuous semaglutide or tirzepatide orders and when stratified by patients with and without diabetes. Together, these findings demonstrate that bariatric surgery is more effective than GLP-1RAs for patients with obesity eligible for both treatment options, and that the real-world effectiveness of semaglutide and tirzepatide is lower than reported in their initial clinical trials.

Most prior studies comparing bariatric surgery to GLP-1RAs have been restricted to specific clinical subpopulations (e.g., chronic kidney disease [11] and/or type 2 diabetes [12, 13]) and included older, less effective GLP-1RAs such as liraglutide and dulaglutide that are no longer widely used [6]. Our results confirm prior studies in a larger cohort, while adding 3-year follow-up data and focusing exclusively on semaglutide and tirzepatide as the most relevant GLP-1RA options today.

Bariatric surgery has been shown to have long-term, sustained weight loss in both retrospective and prospective studies [14, 15]. We observed similar outcomes in our weighted analysis of patients eligible for surgery or GLP-1RA treatment, with surgery patients experiencing a weighted mean TWL of 23.6% (23.6%–23.7%) 2 years post surgery compared with 6.9% (6.8%–7.0%) with GLP-1RAs in the intention-to-treat group. As seen in prior studies, weight loss was higher following gastric bypass than sleeve gastrectomy, with less rebound weight increase after year two.

Our findings on semaglutide and tirzepatide contrast with those of the industry-sponsored clinical trials of these agents for obesity. In the landmark STEP trial, patients were treated with semaglutide for 68 weeks, with 14.9% TWL at 1 year [8]. Of note, patients were uptitrated to 2.4 mg dosing by 4 months of treatment. In the SURMOUNT-1 trial, patients were treated with tirzepatide for 72 weeks, including up to 5 months of dose escalation, and reported weight loss of 15%–20.9% at 1 year [7]. Our real-world analysis found lower weight loss, perhaps due to lower treatment dosing and duration. Importantly, discontinuation in routine practice likely reflects not only treatment persistence and tolerability but also access barriers, including out-of-pocket cost, insurance coverage restrictions, and intermittent medication shortages. These factors may preferentially affect who is able to initiate and continue GLP-1RAs.

However, even among the minority of real-world patients continuing GLP-1RA treatment for 1 year, we observed lower TWL compared with clinical trial outcomes. Several factors may explain this gap in effectiveness. First, GLP-1RA discontinuation rates were 15%–17% at 1 year in clinical trials versus 56% by 6 months in our cohort [7, 8]. Multiple recent analyses have confirmed real-world discontinuation rates between 50% and 70% within 1 year [16–21]. However, our analysis of patients with continuous prescriptions suggests that drug discontinuation does not fully account for inferior real-world weight loss

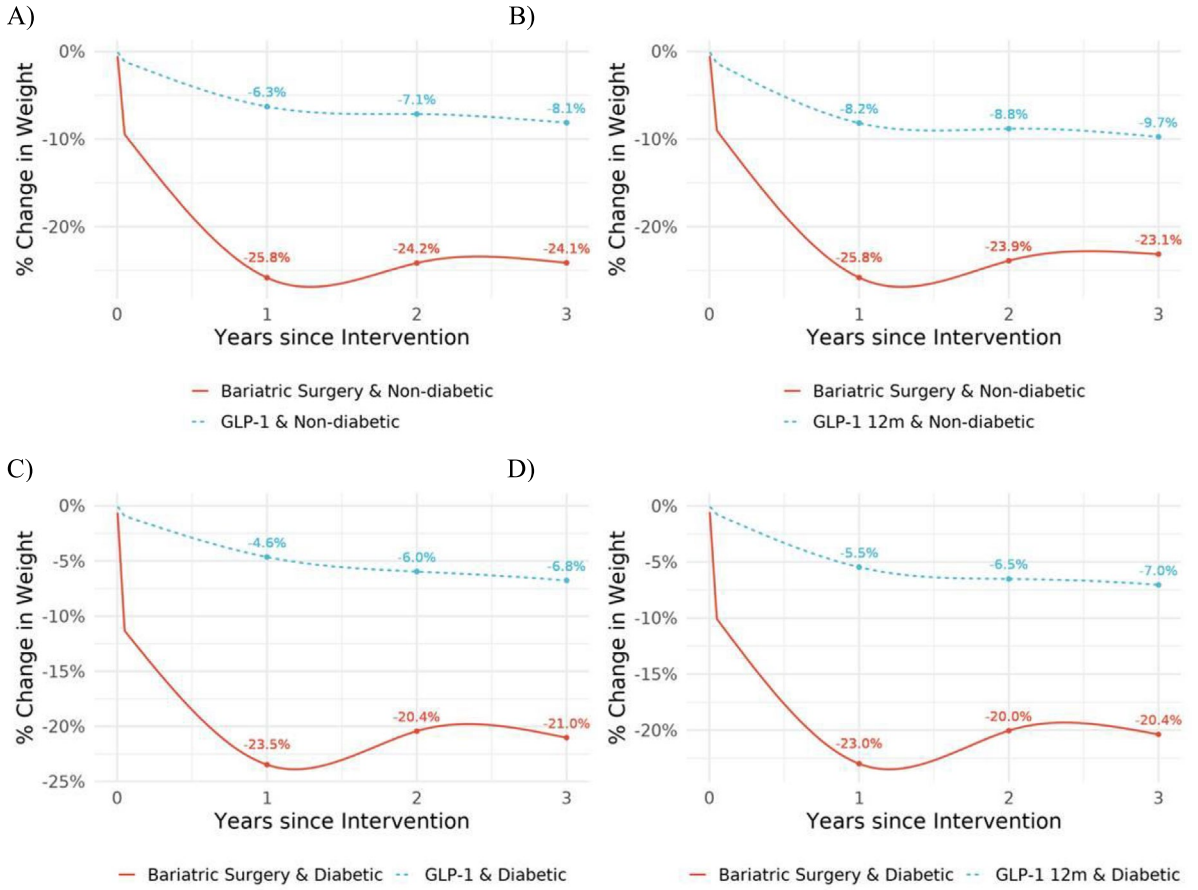


FIGURE 3 | Weighted percent weight loss over time following bariatric surgery and (A) GLP-1 use ever and (B) 1-year continuous GLP-1 use. Abbreviation: 12 m = 1-year continuous GLP-1 use. [Color figure can be viewed at wileyonlinelibrary.com]

outcomes—even patients with 1-year continuous orders had weight loss averaging 8.85% at 3 years. Second, only 13.4% of patients achieved maximal medication doses by 1 year, in line with a recent study by Samuels et al. showing that 12%–28% of patients starting a GLP-1RA medication achieved maximum doses of semaglutide or tirzepatide within 1 year. This study also confirmed that dosing intensity is associated with the extent of weight loss [21]. Third, clinical trial centers may have provided more comprehensive or frequent counseling (regarding side effects, lifestyle modifications, etc.) than is provided in real-world settings, contributing to greater weight loss. Strategies such as standardized follow-up schedules, proactive GLP-1RA dose titration, integration of multidisciplinary weight management support, and improved documentation of weight and medication use in the EHR may help reduce this gap and provide clinicians with more reliable, practice-based benchmarks when counseling patients.

Prior studies of bariatric surgery and GLP-1RAs have shown that type 2 diabetes is associated with decreased weight loss relative to patients without diabetes [22–24]. Our findings were robust to stratifying on the presence of diabetes before intervention, with 18.1% (sleeve) to 26.1% (bypass) TWL from bariatric surgery at 2 years versus 5.8% (semaglutide) to 9.5% (tirzepatide) weight loss from GLP-1RAs in this subgroup. In clinical trials, weight loss from GLP-1RAs was lower in patients with diabetes than those with obesity alone—9.6% (semaglutide) to 15% (tirzepatide) among patients with diabetes [25, 26] versus 15% (semaglutide) to 21% (tirzepatide) among patients without diabetes [7, 8]. However, our stratified analysis confirmed that confounding from diabetes does not explain the weight loss gap between real-world findings and clinical trials.

In our weighted analysis, HbA1c reductions were nonsignificantly greater in the GLP-1RA groups. The HbA1c reductions in bariatric surgery at 0.5% (bypass) and 0.6% (sleeve) at 3 years in our real-world patients were lower than those in a longer-term randomized clinical trial which demonstrated a 1.6% point HbA1c reduction at 7 years from bariatric surgery [27]. Semaglutide was associated with a 1.0% point HbA1c reduction at 3 years, in line with other shorter-term real-world studies [28, 29]; however, the durability of this HbA1c reduction in light of high rates of medication discontinuation may not be sustained in the long term.

This study has several limitations. First, as a retrospective cohort study, this study could not account for all possible causes of confounding. We used weighting methods based on detailed clinical data to account for measured confounders, but this design still has the potential for unmeasured confounding. Second, we used prescription orders as a proxy for medication utilization, but patients may not have filled all prescriptions. This is a limitation common to other real-world EHR-based

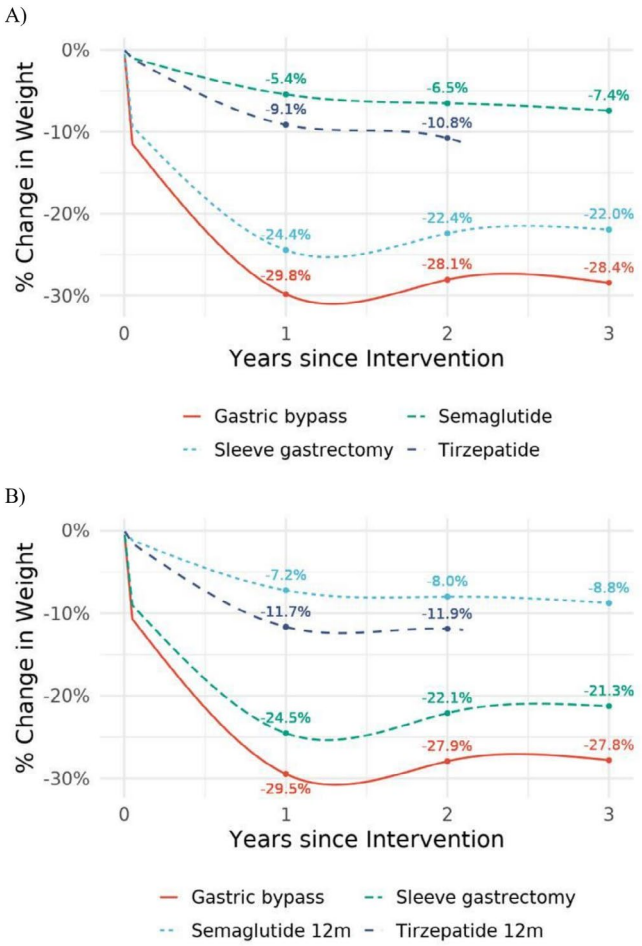


FIGURE 4 | Weighted percent weight loss over time following gastric bypass, sleeve gastrectomy and (A) semaglutide and tirzepatide and (B) semaglutide 1-year continuous use and and tirzepatide 1-year continuous use. Abbreviation: 12 m = 1-year continuous GLP-1 use. [Color figure can be viewed at wileyonlinelibrary.com]

studies of this topic [11, 13]. Third, we did not have data on patients' specific indication for GLP-1RA treatment, and it is possible that some patients may have been kept at lower doses if they were being treated for type 2 diabetes or obesity with adequate improvement. However, we did analyze patients without diabetes in an effort to approximate the obesity indication. Fourth, the patient cohort is not necessarily representative of the broader US or international population, though it is drawn from the socioeconomically and ethnically diverse New York metropolitan area. In fact, the inclusion of racial minorities and publicly insured patients may represent a strength unique to our database. Fifth, by restricting our cohort to patients with BMI $\geq 35\,kg/m^2$, we improved comparability between GLP-1RA treatment and bariatric surgery patients but limited generalizability of our findings to lower-BMI individuals treated with semaglutide or tirzepatide, who may have different comorbidity profiles, treatment goals, insurance coverage, and likelihood of being considered for surgery. Finally, many patients had limited follow-up outcome data (e.g., weight, HbA1c), likely because they received care from multiple health systems. However, this is a limitation common to real-world studies of this topic.

In conclusion, in real-world patients with obesity, sleeve gastrectomy and gastric bypass were associated with greater weight loss than semaglutide and tirzepatide. Semaglutide and tirzepatide were also associated with substantially less weight loss in the real-world setting than in clinical trials.

Author Contributions

A.B., E.S., T.M., and M.P. contributed to data collection. A.B., S.S.P., A.K., and A.M. performed the data analysis. A.B., S.S.P., and A.K. directly accessed and verified the data. A.B., S.S.P, A.K., A.M., B.J.O., and K.R.C. contributed to data interpretation and writing of the manuscript and vouch for data accuracy and fidelity to the protocol. A.H.V., S.D., D.S.Z., D.S., A.U.W., and C.R.-F. provided data and provided critical revisions. All authors approved the final version of the manuscript.

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Conflicts of Interest

K.R.C. has received consulting fees from Olympus and GI Windows Surgical, unrelated to the current work. D.S. has received payment or honoraria from AstraZeneca, CareDx, Moderna Therapeutics, Novavas, Regeneron, Springer Publishing, Hansa, Optum, OrgonOx, Medscape, Roche, Houston Methodist, Northwell Health, Optum Health Education, WedMd, and ASN. The other authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** Unweighted percent weight loss over time following bariatric surgery and (A) GLP-1 use ever and (B) 1-year continuous GLP-1 use. Abbreviation: 12 m = 1-year continuous GLP-1 use. **Figure S2:** Unweighted percent weight loss over time following gastric bypass, sleeve gastrectomy, (A) semaglutide, and tirzepatide and (B) semaglutide 1-year continuous use, and tirzepatide 1-year continuous use. Abbreviation: 12 m = 1-year continuous GLP-1 use. **Figure S3:** Percent weight loss over time following gastric bypass, sleeve gastrectomy, semaglutide, and tirzepatide with diabetes (A) unweighted (B) and weighted. **Figure S4:** Percent weight loss over time following gastric bypass, sleeve gastrectomy, semaglutide, and tirzepatide without diabetes (A) unweighted (B) and weighted. **Figure S5:** Percent weight loss over time following bariatric surgery and GLP-1 use among NYU patients (A) unweighted and (B) weighted. NYU bariatric surgery $n = 3758$. NYU GLP-1RA $n = 32{,}643$. **Figure S6:** Weighted percent weight loss over time following bariatric surgery and (A) GLP-1 use ever and (B) 1-year continuous GLP-1 use by sex. Abbreviation: 12 m = 1-year continuous GLP-1 use. **Table S1:** Baseline demographic and clinical characteristics by weight loss intervention. **Table S2:** Baseline demographic and clinical characteristics by weight loss intervention among patients with diabetes. **Table S3:** Baseline demographic and clinical characteristics by weight loss intervention among patients without diabetes. **Table S4:** Standardized mean differences before and following applying average treatment effect weighting among bariatric surgery and GLP-1 patients.