

Article

Semaglutide and Tirzepatide in Type 1 Diabetes: Real-World Insulin-Dose Reduction, Metabolic Outcomes and Safety Assessment

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Abstract

Background: Semaglutide and tirzepatide are not approved for type 1 diabetes (T1D), and their real-world effects on insulin requirements, metabolic outcomes, and safety are uncertain. **Methods:** Using de-identified electronic health record data from a federated U.S. network (2018–2025), adults with T1D who initiated semaglutide ($n = 1447$) or tirzepatide ($n = 568$) were matched 1:1 to unexposed adults with T1D on demographics, comorbidities, glycated hemoglobin (HbA1c), body mass index (BMI), estimated glomerular filtration rate (eGFR), T1D duration, healthcare utilization, and calendar year (Cohort A). Insulin total daily dose (TDD) was analyzed in a second cohort additionally matched on baseline TDD and insulin delivery modality (Cohort B; 337 semaglutide and 117 tirzepatide pairs). **Results:** At 12 months, TDD changed by -12.9% with semaglutide versus -2.6% in matched controls (difference -10.4 percentage points [pp]; $p < 0.001$) and by -10.4% with tirzepatide versus $+13.3\%$ (difference -23.7 pp; $p = 0.02$); a $\geq 10\%$ TDD reduction was reached by 41% versus 21% of patients with semaglutide and 47% versus 11% with tirzepatide (both $p < 0.001$). Among semaglutide-treated patients, 6-month-TDD reduction was -24.1% , -12.6% , and -5.6% with $\geq 10\%$ weight loss, 0 to $<10\%$ loss, and weight gain ($p < 0.001$), but did not vary with HbA1c change ($p = 0.95$) or semaglutide dose ($p = 0.50$). At 12 months, HbA1c fell 0.31 pp more with semaglutide than in controls ($p < 0.001$) and 0.19 pp more with tirzepatide ($p = 0.07$); body weight fell 3.3 pp and 5.1 pp more with semaglutide and tirzepatide, respectively (both $p < 0.001$). Relative to matched controls, the 365-day risk of nausea or vomiting rose 8.6 pp after semaglutide or tirzepatide initiation ($p < 0.001$) and constipation rose 3.4 pp ($p = 0.003$), whereas diabetic ketoacidosis ($+0.3$ pp; $p = 0.63$) and severe hypoglycemia (-0.8 pp; $p = 0.39$) did not change significantly. **Conclusions:** In routine care, adjunctive semaglutide and tirzepatide were associated with lower insulin requirements, modest HbA1c improvement, and weight loss in adults with T1D, with a gastrointestinal-predominant adverse-event profile. Randomized trials are needed to establish efficacy and safety.



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1. Introduction

Type 1 diabetes (T1D) is defined by dependence on exogenous insulin, but insulin replacement alone is often not adequate to eliminate the progressive metabolic and cardiovascular burden of the disease. Contemporary care has been transformed by continuous

glucose monitoring, insulin pump therapy and automated insulin delivery systems, but many adults continue to face high insulin requirements, weight gain, glycemic variability, hypoglycemia risk and persistent cardiovascular and kidney complications [1,2]. These challenges are increasingly salient as overweight and obesity are now common in people living with T1D, partly reflecting the intersection of population-level obesity trends, insulin-associated weight gain, insulin resistance and longer survival [3,4]. Because escalating insulin doses can improve glycemia while also reinforcing weight gain and cardiometabolic risk, adjunctive therapies that safely reduce insulin requirements, improve weight and preserve glycemic control remain an important unmet need in T1D.

Glucagon-like peptide-1 receptor agonists and dual glucose-dependent insulintropic polypeptide and glucagon-like peptide-1 receptor agonists have reshaped the treatment of type 2 diabetes and obesity through effects on body weight, appetite, gastric emptying, glycemia and cardiometabolic risk [5,6]. However, semaglutide and tirzepatide are not approved for type 1 diabetes, so their use in this population remains off-label. This distinction is clinically important because adults with T1D differ from those with type 2 diabetes in endogenous insulin reserve, susceptibility to ketosis, dependence on precise insulin titration and risk of hypoglycemia. Any adjunctive therapy that lowers body weight, appetite or insulin requirement in T1D must therefore be evaluated not only for glycemic and metabolic benefit, but also for diabetic ketoacidosis, severe hypoglycemia, gastrointestinal intolerance, pancreatobiliary events, retinopathy progression, kidney safety and real-world feasibility of dosing and titration.

Previous adjunctive-therapy studies of incretin-based agents in T1D have suggested that this therapeutic axis can reduce body weight and insulin requirements, with more modest and variable effects on HbA1c. The ADJUNCT ONE and ADJUNCT TWO randomized trials showed that liraglutide reduced HbA1c, body weight and insulin dose in adults with T1D, but they also raised safety and tolerability concerns, including increased symptomatic hypoglycemia and hyperglycemia with ketosis at higher doses [7,8]. More recent semaglutide trials have renewed interest in this approach. In adults with T1D using automated insulin delivery, semaglutide improved glucose time in range without increasing the risk of hypoglycemia, although recurrent euglycemic ketosis without acidosis was observed [9]. In a randomized trial studying adults with T1D and obesity, semaglutide improved a composite of glycemic and weight outcomes [10]. Evidence for tirzepatide in T1D is more limited, but early observational and phase 2 trial data suggest clinically meaningful weight loss and metabolic improvement in selected adults with T1D and obesity [11,12]. Collectively, these studies support biological plausibility but leave substantial uncertainty regarding real-world dosing, insulin adjustment and longer-term safety.

Real-world evidence can complement clinical trials by describing how therapies are prescribed, titrated, tolerated and associated with clinical outcomes in routine care. This is particularly relevant for semaglutide and tirzepatide in T1D, where off-label use is occurring despite limited evidence to guide patient selection, insulin adjustment and safety monitoring. Electronic health records (EHRs) provide an opportunity to study larger and more heterogeneous populations than those enrolled in early trials, including adults treated with multiple daily injections or insulin pump therapy and patients with varying degrees of obesity, glycemic burden and cardiometabolic comorbidity. At the same time, observational analyses are vulnerable to confounding by indication, treatment-selection bias, misaligned time origins, missingness and incomplete capture of medication adherence and adverse events; their findings must be interpreted as associations that can inform, rather than replace, prospective randomized evaluation [13–15].

In this study, we used de-identified longitudinal EHR data from a federated U.S. clinical network to evaluate adults with T1D who initiated semaglutide or tirzepatide and

propensity-score matched adults with T1D who had no semaglutide or tirzepatide exposure. We examined real-world dosing and titration, insulin total daily dose trajectories against controls matched on baseline insulin dose, HbA1c, body weight and kidney function, and prespecified adverse events before and after initiation in treated patients and their matched controls.

2. Materials and Methods

2.1. Study Design

This retrospective cohort study evaluated adults with T1D who initiated semaglutide or tirzepatide and matched adults with T1D without semaglutide or tirzepatide exposure, using de-identified longitudinal EHR data from a federated U.S. network. The study period was 1 January 2018 to 31 December 2025. Two matched cohorts were constructed from the same eligible population: Cohort A, used for laboratory and anthropometric outcomes and adverse events; and Cohort B, restricted to patients with a documented baseline insulin total daily dose (TDD) and additionally matched on baseline TDD and insulin delivery modality, used for all insulin-dose analyses.

2.2. Cohort Definition and Matching

T1D was ascertained at the cohort level by ≥ 2 ICD codes for T1D, a T1D-to-(T1D + T2D) ICD code ratio greater than 0.5 [16], confirmation of the T1D diagnosis in clinical notes via AI augmented curation, and at least one outpatient order for insulin (rapid-, regular-, short-, intermediate-, or long-acting) during the study period.

The exposure cohort comprised adults with T1D with an order or administration of semaglutide or tirzepatide during the study period after the T1D diagnosis. The index date was the first semaglutide or tirzepatide order or administration. The control cohort comprised adults with T1D with no order or administration of semaglutide or tirzepatide during the study period; the index date was a randomly selected outpatient insulin order date during the study period and after the T1D diagnosis. Both cohorts were required to be aged 18 years or older at index, to have at least 1 year of baseline EHR data, and to have at least 30 days of post-index follow-up. Patients with any order or administration of another blood glucose-lowering medication (metformin, SGLT2 inhibitors, DPP-4 inhibitors, sulfonylureas, thiazolidinediones, meglitinides, another GLP-1 receptor agonist, or a dual GIP/GLP-1 receptor agonist) in the 12 months before index were excluded.

One-to-one propensity score matching without replacement was performed on the logit of the propensity score using a caliper of 0.2 standard deviations. For Cohort A, the propensity score was estimated by logistic regression with age, sex, race, ethnicity, hypertension, hyperlipidemia, atherosclerotic cardiovascular disease, heart failure, diabetic microvascular complications, tobacco use, HbA1c category, body mass index category, estimated glomerular filtration rate (eGFR) category, T1D duration (years between first T1D diagnosis and index), healthcare utilization (number of encounters in the 12 months before index), and index calendar year. Cohort B was restricted to patients with a documented TDD within 180 days before index and matched on the Cohort A covariates plus baseline TDD (continuous) and insulin delivery modality (pump, multiple daily injections, or other). Matching was performed for the combined semaglutide-or-tirzepatide cohort; drug-specific comparisons used each treated patient's own matched control. Standardized mean differences (SMDs) were used to assess balance before and after matching, with values below 0.10 considered acceptable; multi-level categorical variables were summarized with the multivariate SMD.

2.3. Insulin TDD Extraction and Validation

Insulin TDD and insulin delivery modality were extracted from clinical notes using AI augmented curation with a large language model (LLM). We used gpt-oss-20b with a maximum generated-token limit of 16,384 and temperature 0.7. The prompt asked the model to extract only explicit, patient-attributed current insulin doses, together with dose units, the basis of the TDD (explicit or summed from basal and bolus components), delivery modality, and the finding date or note-date relationship, and to return valid JSON (Supplementary Methods). Outputs were parsed and standardized to units per day, implausible values were removed, duplicate mentions were deduplicated, and dose dates were aligned to the index date. Semaglutide and tirzepatide doses were taken from structured medication orders and were not extracted from notes.

Extraction of insulin TDD was validated against manual chart review of 150 clinical notes, one note from each of 150 randomly selected patients: 50 treated with semaglutide, 50 treated with tirzepatide, and 50 controls. Adjudication was done by two reviewers blinded to the model output. An extraction was labelled correct when the TDD value, units, and temporality agreed with the note. Accuracy was 94.7% (142/150) overall, 96.0% (48/50) for semaglutide, 90.0% (45/50) for tirzepatide, and 98.0% (49/50) for control notes. The eight incorrect extractions were attributed to wrong numeric values of summed insulin components and unit or formulation error. Accuracy reflects the precision of extracted values; recall of doses that were documented but not extracted was not assessed.

2.4. Insulin TDD Trajectory Analyses

Insulin TDD was anchored at Month -12 , -9 , -6 , and -3 before index (each ± 30 days), at index (± 7 days), and at Month 3, 6, 9, and 12 (each ± 30 days), Month 18 (± 45 days), and Month 24 (± 60 days) after index. Baseline TDD was the documented value closest to the index date within the 180-day pre-index window. TDD at each anchor was the documented value closest to the anchor day within the tolerance window, while patients with no value at an anchor were excluded from that anchor. Absolute TDD at each anchor, percent change from baseline at each post-index anchor, and the proportion of patients with a $\geq 10\%$ reduction from baseline were compared between each treated group and its matched controls using two-sample Welch *t*-tests (absolute TDD and percent change) and two-proportion *z*-tests ($\geq 10\%$ reduction), with 95% confidence intervals for the between-group difference. Anchors with fewer than 11 patients in either arm were not reported.

2.5. Semaglutide and Tirzepatide Dose Trajectories

Semaglutide and tirzepatide doses from structured orders were summarized at index and at Month 3, 6, 9, 12, 18, and 24 using the same tolerance windows described in 2.4, taking the dose closest to the anchor day within the window. The proportion of patients in each dose category (semaglutide: 0.25, 0.5, 1, 1.7, 2.0, 2.4 mg; tirzepatide: 2.5, 5, 7.5, 10, 12.5, 15 mg) and the median dose were reported among all eligible exposed patients with a documented dose at the anchor.

2.6. TDD Change by Weight Change, HbA1c Change, and Dose

Among all eligible exposed patients with a baseline TDD and a TDD at the 6-month anchor (Day 180; window 90 to 270 days, value closest to Day 180), percent change in TDD was stratified by three variables measured in the same window: (1) percent body weight change from baseline ($\geq 10\%$ loss, 0 to $<10\%$ loss, or gain); (2) absolute HbA1c change from baseline (reduction ≥ 0.5 percentage points, reduction 0 to <0.5 percentage points, or increase); and (3) semaglutide dose (0.25 mg; 0.5 to 1 mg; ≥ 1.7 mg) or tirzepatide dose (2.5 mg; 5 to 7.5 mg; ≥ 10 mg). Baseline body weight and HbA1c were the documented

values closest to index within the 180-day pre-index window. Heterogeneity across strata within each drug was tested with one-way ANOVA.

2.7. Laboratory and Anthropometric Analyses

In Cohort A, change from baseline in HbA1c (percentage points), body weight (percent and kilograms), and eGFR (mL/min/1.73 m²) was computed at Month 6 (Day 180 ± 30 days) and Month 12 (Day 365 ± 30 days), taking the value closest to the anchor day within the window. Baseline values were the documented value closest to index within the 180-day pre-index window. Patients with no value at an anchor were excluded from that anchor. Mean change was compared between each treated group and its matched controls with two-sample Welch *t*-tests and 95% confidence intervals for the difference.

2.8. Adverse Event Analysis

Thirteen prespecified adverse events in four categories were examined: glycemic (diabetic ketoacidosis, severe hypoglycemia, any hypoglycemia), gastrointestinal (nausea or vomiting, diarrhea, abdominal pain, constipation, decreased appetite, gastroparesis), pancreatobiliary (pancreatitis, gallbladder disease), and other (retinopathy progression, acute kidney injury). Events were ascertained by AI augmented curation of clinical notes, requiring at least two positive mentions within 14 days. For each patient, a symmetric pre-versus post-index window was defined with length equal to the smaller of 365 days and the days to the last encounter. The risk difference (post minus pre, in percentage points) was computed in the treated cohort and, separately, in the matched control cohort, and the net difference (treated minus control) was computed to account for changes in event documentation unrelated to treatment. Confidence intervals and *p* values for the within-arm risk differences were computed from the paired 2 × 2 cell counts with Tango score confidence intervals for the paired-proportion difference and McNemar exact tests. The net difference was tested with a *z*-test using the sum of the two variances. Benjamini–Hochberg (BH) adjusted *p* values were computed across the 13 events within each comparison (combined cohort, semaglutide, tirzepatide) separately for the treated, control, and net estimates.

2.9. Missing Data and Persistence

All anchor-based analyses used complete cases at each anchor without imputation. The number of patients contributing at each anchor is reported for every outcome and arm. To characterize attrition in the insulin-dose analyses, baseline characteristics of Cohort B patients with and without a documented TDD 12 months or later after index were compared within each arm, and balance between treated and control patients with a 12-month TDD was assessed. All analyses classified patients by initial exposure regardless of subsequent discontinuation or dose changes.

2.10. Statistical Analysis

Continuous variables are reported as mean and standard deviation, categorical variables as counts and percentages and dose distributions as counts, percentages, and medians. Between-group differences in mean change were assessed with two-sample Welch *t*-tests, ≥10% TDD reduction with two-proportion *z*-tests, within-drug differences across strata with one-way ANOVA, and adverse-event risk differences as described in Section 2.8. All tests were two-sided with $\alpha = 0.05$. The BH procedure was applied across the 13 prespecified adverse events within each comparison; both unadjusted and BH-adjusted values are reported, and findings significant only before adjustment are described as nominal. Patient counts below 11 are reported as <11.

2.11. Data Source

This study analyzed de-identified EHR data from academic medical centers in the United States via the nference federated analytics platform. Prior to analysis, all data underwent expert determination de-identification satisfying HIPAA Privacy Rule requirements (45 CFR §164.514(b)(1)), employing a multi-layered transformation approach for both structured data (cryptographic hashing of identifiers, date-shifting, geographic truncation) and unstructured clinical text (ensemble deep learning and rule-based methods with >99% recall for personally identifiable information detection) [17]. nference established secure data environments within each participating center, housing these de-identified patient data governed by expert determination. These de-identified data environments were specifically designed to enable data access and analysis without requiring Institutional Review Board oversight, approval, or exemption confirmation. Accordingly, informed consent and IRB review were not required for this study.

2.12. Data Availability

This study involves the analysis of de-identified EHR data via the nference nSights Federated Clinical Analytics Platform (nSights). Data shown and reported in this manuscript were extracted from this environment using an established protocol for data extraction, aimed at preserving patient privacy. The data have been de-identified pursuant to an expert determination in accordance with the HIPAA Privacy Rule. Any data beyond those reported in the manuscript, including but not limited to the raw EHR data, cannot be shared, or released due to the parameters of the expert determination to maintain the data de-identification. The corresponding author should be contacted for additional details regarding nSights.

2.13. De-Identification and HIPAA Compliance Certification

Prior to analysis, all EHR data were de-identified under an expert determination consistent with the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule (45 CFR §164.514(b)(1)). The de-identification methodology employed a multi-layered transformation approach to both structured and unstructured data fields [17]. In structured data, direct identifiers including patient names and precise geographic locations were excluded entirely, while indirect identifiers underwent specific transformations: patient identifiers, medical record numbers, and accession numbers were replaced with one-way cryptographic hashes using confidential salts to preserve linkage across patient encounters; all dates were shifted backward by patient-specific random offsets (1–31 days) to preserve temporal relationships while obscuring exact event timing; the ZIP codes were truncated to two-digit state-level resolution; and continuous variables including age, height, weight, and body mass index were thresholded to prevent identification of extreme values (for example, ages ≥ 89 years transformed to '89+' and BMI > 40 transformed to '40+'). In unstructured clinical text, an ensemble de-identification system that combines attention-based deep learning models with rule-based methods achieved an estimated >99% recall for personally identifiable information (PII) detection, with detected identifiers replaced by plausible fictional surrogates [17].

2.14. Data Harmonization

To address heterogeneity in EHR data, we harmonized clinical variables including medications, anthropometric measurements, and diagnoses to standardized concepts. For medications, we first constructed a standardized drug concept database combining the nSights knowledge graph with RXNorm (<https://www.nlm.nih.gov/research/umls/rxnorm/index.html>; date accessed: 1 July 2026) hierarchies to capture ingredient,

brand, and dose-specific information [18]. EHR medication records were matched using a hierarchical approach prioritizing RXNorm codes when available, followed by ingredient-level matching, and finally augmented curation and pattern matching on free-text medication orders when structured codes were absent. For anthropometric measurements (height, weight, BMI), we created a unified vocabulary from SNOMED (<https://www.snomed.org/>, <https://athena.ohdsi.org>; date accessed: 1 July 2026) and LOINC (<https://loinc.org/>; date accessed: 1 July 2026) terminologies and matched EHR measurement descriptions using standardized text matching algorithms with abbreviation expansion and synonym resolution; ambiguous mappings were resolved using OpenAI GPT-4o (<https://platform.openai.com/docs/models/gpt-4o>; date accessed: 1 July 2026) with summary statistics as context, followed by manual verification. For diagnoses, we developed a hierarchical disease concept database from the nSights knowledge graph and matched EHR diagnosis descriptions and codes by identifying the most specific common child concept in the hierarchy. This approach enabled consistent identification of clinical entities while preserving granularity where available.

2.15. Code Availability

The analysis code is not publicly available. The corresponding author should be contacted for additional details.

3. Results

3.1. Cohort Derivation and Baseline Characteristics

The network contained 51,344 adults with T1D and an outpatient insulin order during the study period (Figure 1). Of 4862 with an order or administration of semaglutide or tirzepatide after the T1D diagnosis, 2206 met all eligibility criteria (1571 semaglutide, 635 tirzepatide); of 46,482 without semaglutide or tirzepatide exposure, 13,290 met the criteria and formed the control pool. Matching produced 2015 pairs in Cohort A (1447 semaglutide, 568 tirzepatide). Among eligible patients, 598 treated and 2651 control patients had a documented baseline TDD; matching produced 454 pairs in Cohort B (337 semaglutide, 117 tirzepatide). Before matching, treated patients were more often female, had higher body mass index, more hypertension and hyperlipidemia, and later index dates than the control pool (Table 1). After matching, all SMDs in Cohort A were below 0.10. Matched patients had a mean age of 46 years, 67% were female, 43% had hypertension, and 51% had hyperlipidemia; index year and healthcare utilization were balanced. In Cohort B, baseline TDD was 71.6 units/day in treated patients and 53.3 units/day in the control pool before matching (SMD 0.51) and 68.1 versus 67.0 units/day after matching (SMD 0.03); insulin pump use was 74% versus 72% (Table 2). The remaining SMDs were below 0.10 except race (0.10) and index year (0.11), which reflect categories with fewer than 11 patients.

3.2. Real-World Semaglutide and Tirzepatide Dose Escalation

Dose titration among all eligible exposed patients before matching (1571 semaglutide, 635 tirzepatide) was slow and incomplete, with most patients remaining at starting or low maintenance doses through follow-up (Figure S1; Table S1). Median semaglutide dose was 0.25 mg at index, 0.5 mg from Month 3 through Month 12, and 1 mg at Month 18 and 24. At Month 12, 34% of patients with a documented dose remained on 0.25 mg, 17% were on 0.5 mg, 28% on 1 mg, and 21% on 1.7 mg or higher. Median tirzepatide dose was 2.5 mg at index and 5 mg from Month 6 onward. At Month 12, 41% remained on 2.5 mg, 28% were on 5 mg, and 21% were on 10 mg or higher. The number of patients with a documented

dose declined from 981 at Month 6 to 638 at Month 24 for semaglutide and from 551 to 160 for tirzepatide.

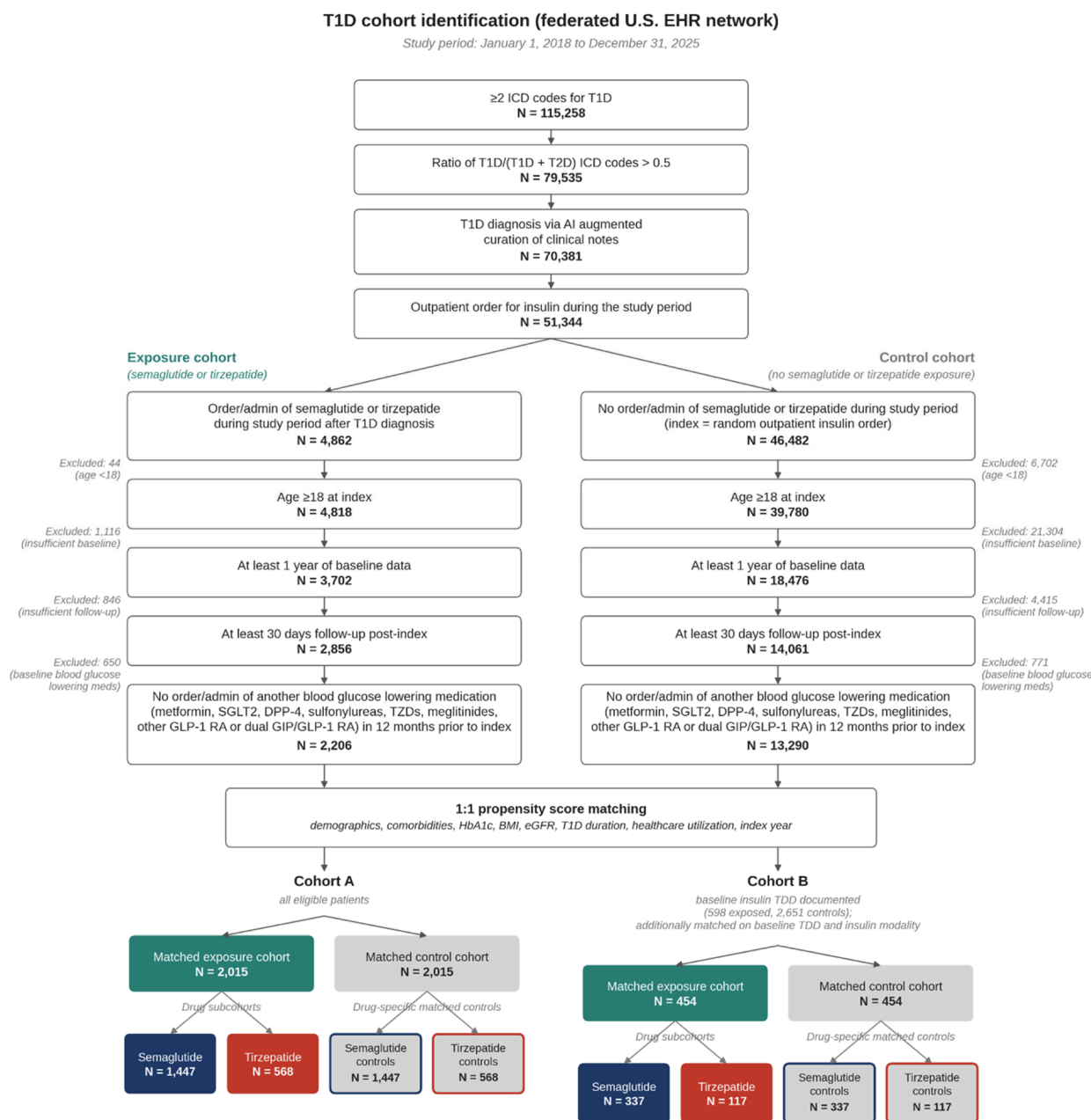


Figure 1. Cohort identification and matching. Adults with T1D were identified in a federated U.S. EHR network (study period 1 January 2018 to 31 December 2025) by ≥ 2 ICD codes for T1D, a T1D-to-(T1D + T2D) ICD code ratio greater than 0.5, confirmation of the diagnosis in clinical notes via AI augmented curation, and at least one outpatient insulin order during the study period. The exposure cohort had an order or administration of semaglutide or tirzepatide after the T1D diagnosis; the control cohort had no semaglutide or tirzepatide exposure during the study period and was indexed at a randomly selected outpatient insulin order. Both cohorts were restricted to age ≥ 18 years at index, ≥ 1 year of baseline data, ≥ 30 days of follow-up, and no other blood glucose-lowering medication in the 12 months before index. One-to-one propensity score matching on demographics, comorbidities, HbA1c, BMI, eGFR, T1D duration, healthcare utilization, and index year produced Cohort A (2015 matched pairs; 1447 semaglutide, 568 tirzepatide). Cohort B comprised patients with a documented baseline insulin total daily dose, additionally matched on baseline dose and insulin delivery modality (454 matched pairs; 337 semaglutide, 117 tirzepatide). Drug-specific matched controls are shown beneath each matched control cohort.

Table 1. Baseline characteristics of the exposure and control cohorts before and after propensity-score matching (Cohort A).

Characteristic	Control (n = 13,290)	Before Matching Semaglutide or Tirzepatide (n = 2206)	SMD	Control (n = 2015)	After Matching Semaglutide or Tirzepatide (n = 2015)	SMD
Age, years, mean (SD)	44.2 (18.0)	46.3 (14.0)	0.13	45.9 (14.8)	46.3 (14.4)	0.03
Female sex, n (%)	6381 (48.0)	1517 (68.8)	0.43	1360 (67.5)	1346 (66.8)	0.01
Race, n (%)			0.03			0.03
White	11,670 (87.8)	1940 (87.9)		1784 (88.5)	1784 (88.5)	
Black or African American	974 (7.3)	168 (7.6)		150 (7.4)	143 (7.1)	
Asian	107 (0.8)	16 (0.7)		16 (0.8)	15 (0.7)	
Other	201 (1.5)	34 (1.5)		29 (1.4)	30 (1.5)	
Unknown	338 (2.5)	48 (2.2)		36 (1.8)	43 (2.1)	
Ethnicity, n (%)			0.09			0.03
Hispanic or Latino	408 (3.1)	66 (3.0)		69 (3.4)	60 (3.0)	
Not Hispanic or Latino	10,101 (76.0)	1758 (79.7)		1591 (79.0)	1597 (79.3)	
Unknown	2781 (20.9)	382 (17.3)		355 (17.6)	358 (17.8)	
Duration of type 1 diabetes, years, mean (SD)	7.4 (6.5)	8.5 (6.9)	0.17	8.3 (6.9)	8.5 (6.8)	0.03
Body mass index, kg/m ² , n (%)			1.23			0.07
<25	4766 (35.9)	80 (3.6)		63 (3.1)	80 (4.0)	
25 to <30	4105 (30.9)	350 (15.9)		363 (18.0)	350 (17.4)	
30 to <35	2080 (15.7)	711 (32.2)		718 (35.6)	673 (33.4)	
≥35	984 (7.4)	753 (34.1)		577 (28.6)	617 (30.6)	
Missing	1355 (10.2)	312 (14.1)		294 (14.6)	295 (14.6)	
HbA1c, %, n (%)			0.24			0.05
<7.0	2495 (18.8)	411 (18.6)		391 (19.4)	377 (18.7)	
7.0 to <8.0	2351 (17.7)	522 (23.7)		468 (23.2)	464 (23.0)	
8.0 to <9.0	1531 (11.5)	313 (14.2)		274 (13.6)	276 (13.7)	
≥9.0	2374 (17.9)	244 (11.1)		198 (9.8)	228 (11.3)	
Missing	4539 (34.2)	716 (32.5)		684 (33.9)	670 (33.3)	
eGFR, mL/min/1.73 m ² , n (%)			0.20			0.06
≥90	5668 (42.6)	830 (37.6)		758 (37.6)	785 (39.0)	
60 to <90	2845 (21.4)	623 (28.2)		550 (27.3)	547 (27.1)	
45 to <60	673 (5.1)	120 (5.4)		99 (4.9)	108 (5.4)	
30 to <45	455 (3.4)	75 (3.4)		61 (3.0)	66 (3.3)	
15 to <30	328 (2.5)	41 (1.9)		38 (1.9)	38 (1.9)	
<15	360 (2.7)	25 (1.1)		31 (1.5)	23 (1.1)	
Missing	2961 (22.3)	492 (22.3)		478 (23.7)	448 (22.2)	
Comorbidities, n (%)						
Hypertension	4757 (35.8)	986 (44.7)	0.18	868 (43.1)	878 (43.6)	0.01
Hyperlipidemia	5443 (41.0)	1159 (52.5)	0.23	1018 (50.5)	1044 (51.8)	0.03
Atherosclerotic cardiovascular disease	1986 (14.9)	312 (14.1)	0.02	267 (13.3)	289 (14.3)	0.03
Heart failure	697 (5.2)	94 (4.3)	0.05	84 (4.2)	87 (4.3)	0.01
Diabetic microvascular complications	2719 (20.5)	475 (21.5)	0.03	417 (20.7)	433 (21.5)	0.02
Tobacco use, n (%)	812 (6.1)	58 (2.6)	0.17	54 (2.7)	55 (2.7)	0.00
Healthcare utilization, encounters in prior 12 months, mean (SD)	24.6 (26.1)	26.5 (23.6)	0.08	25.5 (22.8)	25.9 (23.4)	0.02
Index year, n (%)			0.61			0.06
2019	1317 (9.9)	57 (2.6)		74 (3.7)	56 (2.8)	
2020	1679 (12.6)	79 (3.6)		74 (3.7)	78 (3.9)	
2021	1947 (14.7)	161 (7.3)		137 (6.8)	158 (7.8)	
2022	2172 (16.3)	333 (15.1)		310 (15.4)	313 (15.5)	
2023	2320 (17.5)	588 (26.7)		525 (26.1)	525 (26.1)	
2024	2568 (19.3)	661 (30.0)		608 (30.2)	599 (29.7)	
2025	1287 (9.7)	327 (14.8)		287 (14.2)	286 (14.2)	

Values are n (%) unless stated. SMD, absolute standardized mean difference; multi-level variables use the multivariate SMD. Counts below 11 are shown as <11. eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; SD, standard deviation.

Table 2. Baseline characteristics of patients with a documented baseline insulin total daily dose before and after propensity-score matching (Cohort B).

Characteristic	Control (n = 2651)	Before Matching Semaglutide or Tirzepatide (n = 598)	SMD	Control (n = 454)	After Matching Semaglutide or Tirzepatide (n = 454)	SMD
Age, years, mean (SD)	43.2 (19.0)	46.7 (14.1)	0.21	46.1 (15.8)	46.8 (14.5)	0.05
Female sex, n (%)	1364 (51.5)	426 (71.2)	0.41	312 (68.7)	309 (68.1)	0.01
Race, n (%)			0.09			0.10
White	2324 (87.7)	512 (85.6)		399 (87.9)	393 (86.6)	
Black or African American	212 (8.0)	62 (10.4)		39 (8.6)	42 (9.3)	
Asian	24 (0.9)	<11		<11	<11	
Other	22 (0.8)	<11		<11	<11	
Unknown	69 (2.6)	14 (2.3)		12 (2.6)	12 (2.6)	
Ethnicity, n (%)			0.06			0.01
Hispanic or Latino	70 (2.6)	21 (3.5)		13 (2.9)	14 (3.1)	
Not Hispanic or Latino	1795 (67.7)	408 (68.2)		320 (70.5)	319 (70.3)	
Unknown	786 (29.6)	169 (28.3)		121 (26.7)	121 (26.7)	
Duration of type 1 diabetes, years, mean (SD)	7.2 (6.4)	7.7 (6.3)	0.09	7.6 (6.0)	7.7 (5.8)	0.01
Body mass index, kg/m ² , n (%)			1.36			0.11
<25	975 (36.8)	<11		<11	<11	
25 to <30	874 (33.0)	102 (17.1)		102 (22.5)	100 (22.0)	
30 to <35	417 (15.7)	222 (37.1)		171 (37.7)	161 (35.5)	
≥35	209 (7.9)	179 (29.9)		120 (26.4)	119 (26.2)	
Missing	176 (6.6)	88 (14.7)		58 (12.8)	67 (14.8)	
HbA1c, %, n (%)			0.24			0.05
<7.0	654 (24.7)	134 (22.4)		122 (26.9)	113 (24.9)	
7.0 to <8.0	577 (21.8)	169 (28.3)		116 (25.6)	123 (27.1)	
8.0 to <9.0	289 (10.9)	93 (15.6)		68 (15.0)	66 (14.5)	
≥9.0	386 (14.6)	68 (11.4)		49 (10.8)	50 (11.0)	
Missing	745 (28.1)	134 (22.4)		99 (21.8)	102 (22.5)	
eGFR, mL/min/1.73 m ² , n (%)			0.35			0.09
≥90	1113 (42.0)	217 (36.3)		167 (36.8)	172 (37.9)	
60 to <90	620 (23.4)	217 (36.3)		160 (35.2)	154 (33.9)	
45 to <60	136 (5.1)	31 (5.2)		23 (5.1)	21 (4.6)	
30 to <45	103 (3.9)	24 (4.0)		14 (3.1)	16 (3.5)	
15 to <30	60 (2.3)	17 (2.8)		<11	12 (2.6)	
<15	74 (2.8)	<11		<11	<11	
Missing	545 (20.6)	90 (15.1)		75 (16.5)	77 (17.0)	
Comorbidities, n (%)						
Hypertension	943 (35.6)	265 (44.3)	0.18	193 (42.5)	190 (41.9)	0.01
Hyperlipidemia	1106 (41.7)	332 (55.5)	0.28	250 (55.1)	242 (53.3)	0.04
Atherosclerotic cardiovascular disease	423 (16.0)	93 (15.6)	0.01	67 (14.8)	69 (15.2)	0.01
Heart failure	148 (5.6)	23 (3.8)	0.08	14 (3.1)	16 (3.5)	0.02
Diabetic microvascular complications	575 (21.7)	157 (26.3)	0.11	116 (25.6)	114 (25.1)	0.01
Tobacco use, n (%)	143 (5.4)	<11	0.20	11 (2.4)	<11	0.03
Healthcare utilization, encounters in prior 12 months, mean (SD)	29.2 (31.3)	28.4 (23.0)	0.03	27.9 (23.9)	27.0 (21.6)	0.04
Baseline insulin total daily dose, units/day, mean (SD)	53.3 (30.9)	71.6 (40.4)	0.51	67.0 (38.0)	68.1 (37.1)	0.03
Insulin delivery modality, n (%)			0.26			0.03
Insulin pump	1648 (62.2)	446 (74.6)		328 (72.2)	335 (73.8)	
Multiple daily injections	948 (35.8)	144 (24.1)		120 (26.4)	114 (25.1)	
Other or unknown	35 (1.3)	<11		<11	<11	
Index year, n (%)			0.49			0.11
2019	220 (8.3)	25 (4.2)		26 (5.7)	19 (4.2)	
2020	315 (11.9)	26 (4.3)		26 (5.7)	24 (5.3)	
2021	355 (13.4)	37 (6.2)		25 (5.5)	30 (6.6)	
2022	405 (15.3)	80 (13.4)		57 (12.6)	66 (14.5)	
2023	503 (19.0)	160 (26.8)		115 (25.3)	110 (24.2)	
2024	565 (21.3)	184 (30.8)		138 (30.4)	142 (31.3)	
2025	288 (10.9)	86 (14.4)		67 (14.8)	63 (13.9)	

Values are n (%) unless stated. SMD, absolute standardized mean difference; multi-level variables use the multivariate SMD. Counts below 11 are shown as <11. eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; SD, standard deviation. Cohort B additionally matched on baseline insulin total daily dose and insulin delivery modality.

3.3. Insulin Total Daily Dose

Absolute TDD was similar in treated patients and matched controls at every pre-index anchor and at index (Figure 2A,B). After index, TDD declined in treated patients and was stable in controls. For semaglutide, TDD was 59.0 versus 64.6 units/day at Month 12 ($p = 0.10$), 57.0 versus 64.4 at Month 18 ($p = 0.05$), and 55.0 versus 64.6 at Month 24 ($p = 0.02$); for tirzepatide, 58.0 versus 67.4 at Month 12 ($p = 0.15$) and 52.3 versus 69.6 at Month 24 ($p = 0.04$) (Table 3). Percent change from baseline separated from Month 3 onward (Figure 2C,D). For semaglutide, mean percent change was -10.0% versus $+3.9\%$ in matched controls at Month 6 (difference -13.9 percentage points, 95% CI -21.6 to -6.3), -12.9% versus -2.6% at Month 12 (-10.4 , 95% CI -15.9 to -4.9), and -16.1% versus $+11.4\%$ at Month 24 (-27.5 , 95% CI -42.0 to -13.0 ; all $p < 0.001$). For tirzepatide, mean change was -11.0% versus $+10.4\%$ at Month 6 (-21.4 , 95% CI -36.8 to -6.0 ; $p = 0.007$), -10.4% versus $+13.3\%$ at Month 12 (-23.7 , 95% CI -44.2 to -3.2 ; $p = 0.02$), and -15.2% versus $+26.9\%$ at Month 24 (-42.2 , 95% CI -81.8 to -2.5 ; $p = 0.04$). The proportion of patients with a $\geq 10\%$ reduction in TDD from baseline rose over follow-up in treated patients and was lower in controls at every post-index anchor (Figure 2E,F). With semaglutide, 34% versus 16% of control patients reached this threshold at Month 6, 41% versus 21% at Month 12, and 49% versus 23% at Month 24; with tirzepatide, 40% versus 15% of control patients at Month 6, 47% versus 11% at Month 12, and 58% versus 24% at Month 24 (all $p \leq 0.01$), with 167 semaglutide-treated and 19 tirzepatide-treated patients contributing at Month 24.

The number of patients contributing at each anchor is shown in Figure 2 and Table S2. Of the 454 Cohort B pairs, 243 treated and 208 control patients had a documented TDD 12 months or later after index. Patients without a 12-month value were indexed in 2024 or 2025 in 67% (treated) and 62% (control) of cases, compared with 26% and 25% of patients with a 12-month value; baseline TDD, insulin modality, HbA1c, and body mass index did not differ by availability of a 12-month value (Table S3). Among patients with a 12-month TDD, treated and control patients remained balanced on baseline TDD (68.9 versus 67.2 units/day, SMD 0.04), healthcare utilization, and T1D duration; SMDs for age, hypertension, atherosclerotic cardiovascular disease, and insulin modality were between 0.20 and 0.30.

3.4. TDD Change at 6 Months by Weight Change, HbA1c Change, and Dose

Among semaglutide-treated patients with a baseline and 6-month TDD ($n = 354$), mean TDD change at 6 months was -24.1% with $\geq 10\%$ weight loss, -12.6% with 0 to $<10\%$ weight loss, and -5.6% with weight gain (ANOVA $p < 0.001$) (Figure 3A; Table S4). TDD change did not differ by HbA1c change (-12.0% , -12.2% , and -13.1% for reduction ≥ 0.5 percentage points, reduction 0 to <0.5 percentage points, and increase; $p = 0.95$) (Figure 3B) or by dose reached (-14.5% at 0.25 mg, -11.2% at 0.5 to 1 mg, -15.3% at ≥ 1.7 mg; $p = 0.50$) (Figure 3C). Among tirzepatide-treated patients ($n = 126$), mean TDD change was -19.8% with $\geq 10\%$ weight loss, -15.4% with 0 to $<10\%$ loss, and -5.6% with weight gain ($p = 0.09$) (Figure 3D; Table S4), with no difference by HbA1c change ($p = 0.50$) (Figure 3E) or dose (-11.1% at 2.5 mg, -15.8% at 5 to 7.5 mg, -18.3% at ≥ 10 mg; $p = 0.52$) (Figure 3F).

3.5. HbA1c, Body Weight, and eGFR

In Cohort A, HbA1c changed by -0.32 percentage points with semaglutide versus -0.09 in matched controls at Month 6 (difference -0.23 , 95% CI -0.32 to -0.13 ; $p < 0.001$) and by -0.40 versus -0.08 at Month 12 (-0.31 , 95% CI -0.42 to -0.20 ; $p < 0.001$) (Figure 4A; Table 4). With tirzepatide, HbA1c changed by -0.35 versus -0.13 percentage points at Month 6 (-0.22 , 95% CI -0.38 to -0.07 ; $p = 0.005$) and -0.36 versus -0.18 at Month 12 (-0.19 , 95% CI -0.39 to 0.02 ; $p = 0.07$) (Figure 4D). Body weight changed by -2.7% versus

−0.8% at Month 6 and −3.9% versus −0.6% at Month 12 with semaglutide (differences −1.8 and −3.3 percentage points; both $p < 0.001$), and by −4.6% versus −1.3% and −6.7% versus −1.6% with tirzepatide (−3.4 and −5.1 percentage points; both $p < 0.001$) (Figure 4B,E). Mean eGFR change did not differ significantly between treated patients and controls for either drug at either anchor (Figure 4C,F).

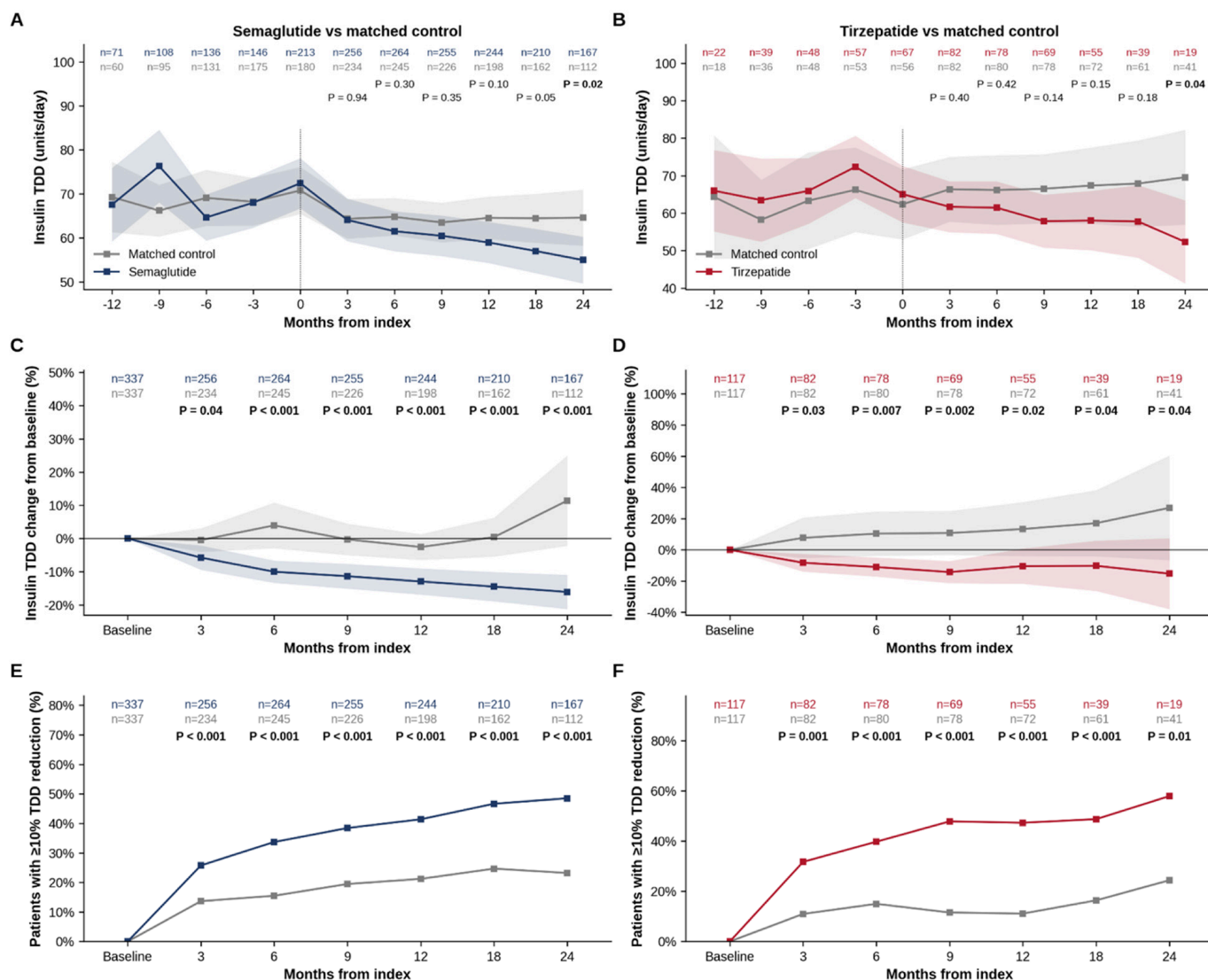


Figure 2. Insulin total daily dose in patients treated with semaglutide (left) or tirzepatide (right) and their matched controls (Cohort B). (A,B) Mean absolute insulin total daily dose (TDD) with 95% confidence intervals from 12 months before index through 24 months after index; the value at 0 is the dose recorded within 7 days of index. (C,D) Mean percent change from baseline TDD with 95% confidence intervals at post-index anchors; baseline is the dose recorded within 180 days before index and is fixed at 0. (E,F) Proportion of patients with a $\geq 10\%$ reduction in TDD from baseline. Treated patients are shown in navy (semaglutide) or red (tirzepatide) and matched controls in gray. The number of patients contributing at each anchor is shown above each panel, colored by arm; at baseline this is the number of matched pairs. p values are from two-sample Welch t -tests (A–D) or two-proportion z -tests (E,F) comparing treated patients with matched controls at each anchor and are shown in bold when $p < 0.05$. Anchors with fewer than 11 patients in either arm are not shown.

Table 3. Insulin total daily dose in patients treated with semaglutide or tirzepatide and matched controls (Cohort B).

Months from Index	n, Exposed	n, Control	Exposed, Mean (SD)	Control, Mean (SD)	Difference (95% CI)	p Value
A. Insulin total daily dose (units/day)						
Semaglutide (n = 337 matched pairs)						
3	256	234	64.1 (39.4)	64.3 (35.0)	−0.3 (−6.9, 6.3)	0.94
6	264	245	61.5 (37.5)	64.8 (33.7)	−3.3 (−9.5, 2.9)	0.30
9	255	226	60.5 (37.4)	63.5 (34.2)	−3.0 (−9.4, 3.4)	0.35
12	244	198	59.0 (37.0)	64.6 (34.5)	−5.6 (−12.3, 1.1)	0.10
18	210	162	57.0 (37.0)	64.4 (35.9)	−7.4 (−14.9, 0.0)	0.05
24	167	112	55.0 (34.8)	64.6 (33.9)	−9.6 (−17.9, −1.4)	0.02
Tirzepatide (n = 117 matched pairs)						
3	82	82	61.7 (30.8)	66.4 (39.3)	−4.7 (−15.6, 6.2)	0.40
6	78	80	61.5 (31.0)	66.2 (41.8)	−4.7 (−16.3, 6.8)	0.42
9	69	78	57.9 (29.4)	66.5 (40.9)	−8.6 (−20.2, 2.9)	0.14
12	55	72	58.0 (29.3)	67.4 (43.2)	−9.3 (−22.1, 3.4)	0.15
18	39	61	57.8 (29.8)	67.9 (45.0)	−10.1 (−24.9, 4.8)	0.18
24	19	41	52.3 (23.0)	69.6 (40.1)	−17.3 (−33.7, −0.9)	0.04
B. Change from baseline (%)						
Semaglutide (n = 337 matched pairs)						
3	256	234	−5.8 (29.7)	−0.5 (27.5)	−5.3 (−10.4, −0.2)	0.04
6	264	245	−10.0 (27.7)	3.9 (54.5)	−13.9 (−21.6, −6.3)	<0.001
9	255	226	−11.4 (30.2)	−0.3 (36.1)	−11.1 (−17.1, −5.1)	<0.001
12	244	198	−12.9 (31.2)	−2.6 (27.7)	−10.4 (−15.9, −4.9)	<0.001
18	210	162	−14.5 (32.5)	0.4 (37.7)	−14.9 (−22.2, −7.6)	<0.001
24	167	112	−16.1 (33.8)	11.4 (72.6)	−27.5 (−42.0, −13.0)	<0.001
Tirzepatide (n = 117 matched pairs)						
3	82	82	−8.2 (25.8)	7.7 (59.0)	−15.9 (−30.0, −1.9)	0.03
6	78	80	−11.0 (27.1)	10.4 (63.9)	−21.4 (−36.8, −6.0)	0.007
9	69	78	−14.2 (29.4)	10.8 (62.5)	−25.0 (−40.7, −9.3)	0.002
12	55	72	−10.4 (41.8)	13.3 (73.5)	−23.7 (−44.2, −3.2)	0.02
18	39	61	−10.2 (49.6)	17.1 (82.7)	−27.3 (−53.6, −1.0)	0.04
24	19	41	−15.2 (47.1)	26.9 (106.2)	−42.2 (−81.8, −2.5)	0.04
C. Patients with ≥10% reduction from baseline						
Semaglutide (n = 337 matched pairs)						
3	256	234	66 (25.8)	32 (13.7)	12.1 (5.2, 19.0)	<0.001
6	264	245	89 (33.7)	38 (15.5)	18.2 (10.9, 25.5)	<0.001
9	255	226	98 (38.4)	44 (19.5)	19.0 (11.1, 26.9)	<0.001
12	244	198	101 (41.4)	42 (21.2)	20.2 (11.8, 28.6)	<0.001
18	210	162	98 (46.7)	40 (24.7)	22.0 (12.5, 31.4)	<0.001
24	167	112	81 (48.5)	26 (23.2)	25.3 (14.4, 36.2)	<0.001
Tirzepatide (n = 117 matched pairs)						
3	82	82	26 (31.7)	<11	20.7 (8.6, 32.9)	0.001
6	78	80	31 (39.7)	12 (15.0)	24.7 (11.4, 38.1)	<0.001
9	69	78	33 (47.8)	<11	36.3 (22.5, 50.0)	<0.001
12	55	72	26 (47.3)	<11	36.2 (21.1, 51.2)	<0.001
18	39	61	19 (48.7)	<11	32.3 (14.1, 50.6)	<0.001
24	19	41	11 (57.9)	<11	33.5 (7.7, 59.3)	0.01

Panel A reports the insulin total daily dose recorded within ± 7 days of each anchor; panels B and C use the baseline dose recorded within 180 days before index. In panel C, values are n (%) and the difference is in percentage points. *p* values from Welch's *t*-test (A, B) or the two-proportion *z*-test (C). Anchors with fewer than 11 patients in either arm are not shown. CI, confidence interval; SD, standard deviation.

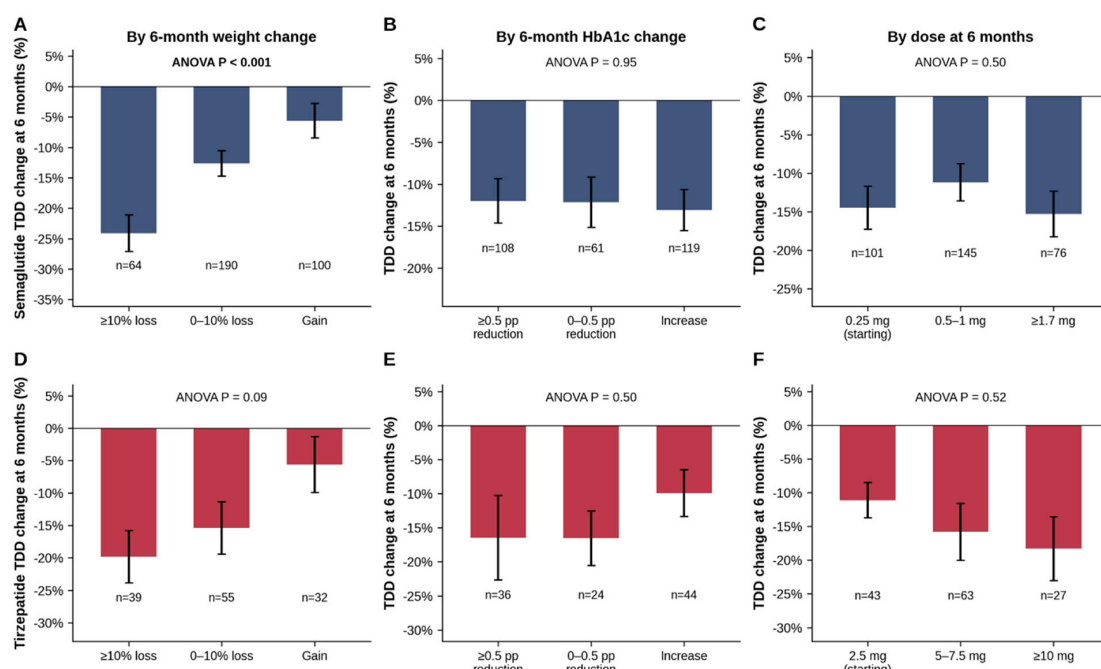


Figure 3. Change in insulin TDD at 6 months by weight change, HbA1c change, and dose reached. Mean percent change in TDD from baseline to the 6-month anchor, with standard error, among all eligible semaglutide-treated (A–C, navy) and tirzepatide-treated (D–F, red) patients with a baseline and 6-month TDD. Patients are stratified by percent body weight change at 6 months (A,D), absolute HbA1c change at 6 months (B,E), and dose at 6 months (C,F). The number of patients in each stratum is shown beneath each bar and the one-way ANOVA p value across strata at the top of each panel.

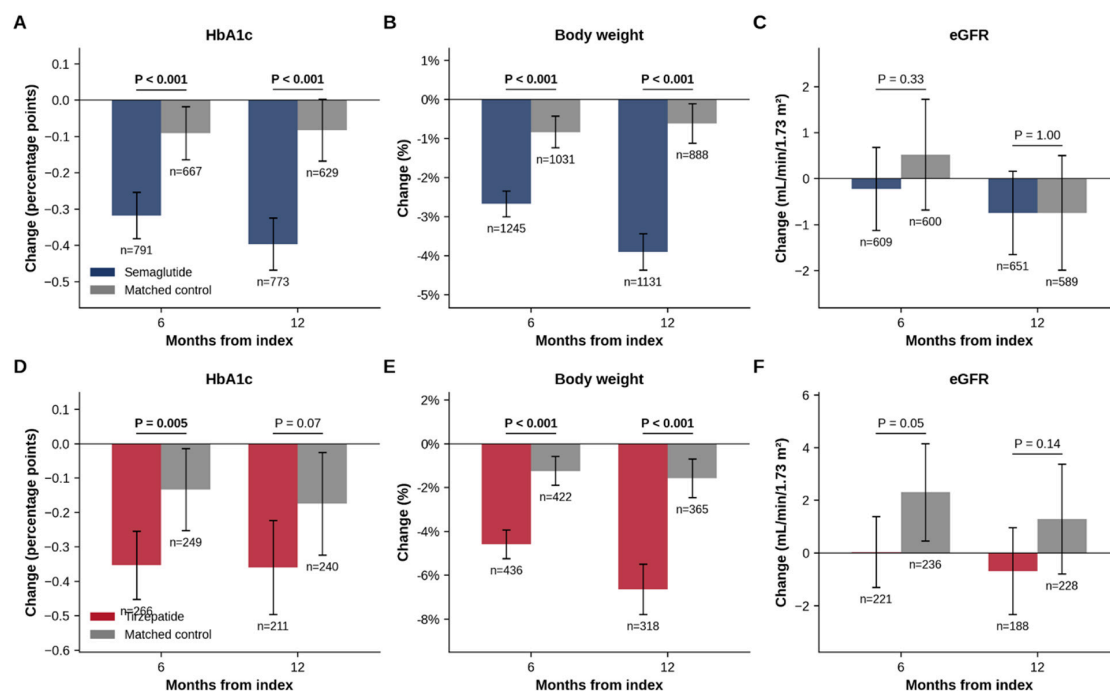


Figure 4. Change in HbA1c, body weight, and eGFR from baseline in treated patients and matched controls (Cohort A). Bars show the mean change from baseline at Month 6 and Month 12 with 95% confidence intervals for semaglutide (A–C, navy) and tirzepatide (D–F, red) versus matched controls (gray): Absolute HbA1c change in percentage points (A,D), body weight change in percent of baseline (B,E), and eGFR change in mL/min/1.73 m² (C,F). The number of patients contributing is shown beneath each bar. Horizontal brackets give the p value from a two-sample Welch t -test comparing treated patients with controls at each anchor, in bold when $p < 0.05$.

Table 4. Change in HbA1c, body weight, and eGFR from baseline in patients treated with semaglutide or tirzepatide and matched controls (Cohort A).

Endpoint and Months from Index	n, Exposed	n, Control	Exposed, Mean Change (SD)	Control, Mean Change (SD)	Difference (95% CI)	p Value
Semaglutide						
HbA1c, percentage points						
6 months	791	667	−0.32 (0.91)	−0.09 (0.96)	−0.23 (−0.32, −0.13)	<0.001
12 months	773	629	−0.40 (1.02)	−0.08 (1.08)	−0.31 (−0.42, −0.20)	<0.001
Body weight, %						
6 months	1245	1031	−2.7 (5.9)	−0.8 (6.6)	−1.8 (−2.4, −1.3)	<0.001
12 months	1131	888	−3.9 (8.0)	−0.6 (7.6)	−3.3 (−4.0, −2.6)	<0.001
Body weight, kg						
6 months	1245	1031	−2.7 (5.7)	−0.8 (5.9)	−1.8 (−2.3, −1.3)	<0.001
12 months	1131	888	−3.9 (7.9)	−0.7 (6.9)	−3.3 (−3.9, −2.6)	<0.001
eGFR, mL/min/1.73 m ²						
6 months	609	600	−0.2 (11.3)	0.5 (15.0)	−0.7 (−2.2, 0.8)	0.33
12 months	651	589	−0.7 (11.8)	−0.7 (15.4)	0.0 (−1.5, 1.5)	1.00
Tirzepatide						
HbA1c, percentage points						
6 months	266	249	−0.35 (0.82)	−0.13 (0.96)	−0.22 (−0.38, −0.07)	0.005
12 months	211	240	−0.36 (1.01)	−0.18 (1.17)	−0.19 (−0.39, 0.02)	0.07
Body weight, %						
6 months	436	422	−4.6 (6.9)	−1.2 (6.9)	−3.4 (−4.3, −2.4)	<0.001
12 months	318	365	−6.6 (10.4)	−1.6 (8.6)	−5.1 (−6.5, −3.6)	<0.001
Body weight, kg						
6 months	436	422	−4.5 (7.0)	−1.4 (7.1)	−3.1 (−4.0, −2.1)	<0.001
12 months	318	365	−6.8 (10.6)	−1.7 (8.8)	−5.1 (−6.6, −3.6)	<0.001
eGFR, mL/min/1.73 m ²						
6 months	221	236	0.0 (10.1)	2.3 (14.4)	−2.3 (−4.6, 0.0)	0.05
12 months	188	228	−0.7 (11.4)	1.3 (16.0)	−2.0 (−4.6, 0.7)	0.14

Change from the baseline value closest to index. *p* values from Welch's *t*-test. CI, confidence interval; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; SD, standard deviation.

3.6. Adverse Events Before and After Initiation in Treated Patients and Matched Controls

In the combined treated cohort (*n* = 2015), the 365-day risk of nausea or vomiting rose from 32.3% before index to 41.0% after (risk difference +8.7 percentage points, 95% CI 6.3 to 11.2), and risk rose for constipation (+3.6, 95% CI 2.0 to 5.3), any hypoglycemia (+3.3, 95% CI 1.0 to 5.6), diarrhea (+2.4, 95% CI 0.7 to 4.2), acute kidney injury (+1.3, 95% CI 0.4 to 2.3), and decreased appetite (+1.0, 95% CI 0.4 to 1.9); all six remained significant after BH adjustment (Figure 5; Table S5). In matched controls over the same windows, risk changed by less than 1 percentage point for nausea or vomiting, constipation, diarrhea, decreased appetite and gastroparesis, fell by 2.1 percentage points for abdominal pain (95% CI −3.8 to −0.4), and rose by 2.1 percentage points for severe hypoglycemia (95% CI 0.8 to 3.5).

Net of controls, nausea or vomiting increased by 8.6 percentage points (95% CI 5.6 to 11.7; *p* < 0.001, BH *p* < 0.001) and constipation by 3.4 (95% CI 1.2 to 5.7; *p* = 0.003, BH *p* = 0.02); net increases in any hypoglycemia (+4.1, 95% CI 0.8 to 7.4) and abdominal pain (+3.0, 95% CI 0.6 to 5.4) were nominal (both *p* = 0.02, BH *p* = 0.05), as was diarrhea (+2.6, 95% CI 0.2 to 5.0; *p* = 0.03, BH *p* = 0.09). The net difference for diabetic ketoacidosis was +0.3 percentage points (95% CI −1.1 to 1.8; *p* = 0.63; treated 3.3% to 4.2%, controls 7.4% to 7.9%) and for severe hypoglycemia −0.8 (95% CI −2.6 to 1.0; *p* = 0.39). Pancreatitis, gallbladder disease, gastroparesis, and retinopathy progression did not differ before and after index in either arm. By drug, the net increase in nausea or vomiting was 9.6 percentage points

with semaglutide (95% CI 5.9 to 13.3; BH $p < 0.001$) and 6.2 with tirzepatide (95% CI 0.5 to 11.8; $p = 0.03$, BH $p = 0.22$) (Figure S2; Table S5). With semaglutide, net increases in any hypoglycemia (+6.1, 95% CI 2.2 to 10.0; BH $p = 0.010$), constipation (+4.1, 95% CI 1.5 to 6.8; BH $p = 0.010$), abdominal pain (+3.6, 95% CI 0.8 to 6.4; BH $p = 0.03$), and acute kidney injury (+2.1, 95% CI 0.6 to 3.7; BH $p = 0.03$) also remained significant after adjustment; with tirzepatide, no net difference.

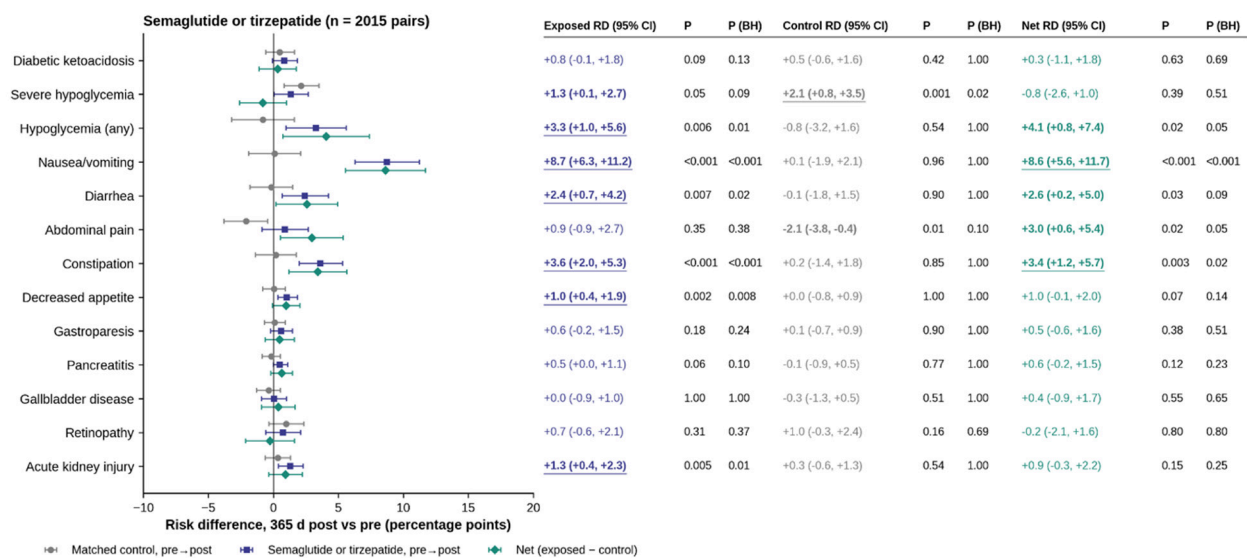


Figure 5. Adverse events in the 365 days before and after index in treated patients and matched controls (Cohort A, combined cohort). Forest plot of risk differences, in percentage points, comparing the 365 days after index with the 365 days before, for 13 prespecified events in the combined semaglutide-or-tirzepatide cohort (squares; n = 2015), in the matched control cohort over the same windows (circles), and net of controls (treated minus control; diamonds). Markers show the point estimate and horizontal bars the 95% confidence interval (Tango score interval for the within-arm risk differences; normal approximation with summed paired variances for the net difference). The table lists each risk difference with its 95% confidence interval and, for the net difference, the p value and the Benjamini–Hochberg adjusted p value across the 13 events. Estimates with $p < 0.05$ are bold; estimates that remain significant after adjustment are bold and underlined. The vertical line at zero indicates no change in risk; positive values indicate higher risk after index.

4. Discussion

In this matched cohort study of adults with T1D from a federated U.S. EHR network, initiation of semaglutide or tirzepatide was associated with progressive reductions in insulin total daily dose (TDD), a modest reduction in HbA1c, and progressive weight loss compared with matched adults with T1D who had no semaglutide or tirzepatide exposure. Insulin-dose comparisons were made against controls matched on baseline insulin dose and delivery modality, whose dose trajectories were flat before and after index. The difference was established by 6 months and maintained at 12 months; the 18- and 24-month estimates are exploratory, because the number of patients with a documented dose fell steadily over follow-up, to about half of the semaglutide-treated patients and fewer than one in five of the tirzepatide-treated patients by 24 months. Real-world dose escalation was slow and incomplete: one third of semaglutide-treated patients remained on the 0.25 mg starting dose at 12 months, and two fifths of tirzepatide-treated patients remained on 2.5 mg. Adjunctive semaglutide or tirzepatide in adults with T1D was therefore associated with insulin-dose reduction and metabolic change at doses well below those used in trials.

The insulin findings are clinically salient because adults with T1D frequently experience rising insulin requirements, weight gain and insulin resistance over time [3,4]. An

intervention associated with lower insulin dose, lower HbA1c and weight loss may represent a useful adjunctive strategy for carefully selected patients, particularly those with obesity or high insulin requirements [7–11]. The size of the insulin-dose reduction tracked weight loss: patients losing 10% or more of body weight by 6 months reduced insulin dose by roughly one quarter, whereas those who gained weight reduced it by 5%. Insulin-dose reduction was not shown to vary with HbA1c change or with the dose reached, suggesting insulin reduction is not explained by titration alone. Because weight change, HbA1c change, and dose are post-index variables, these stratified results are descriptive. The direction of the association between insulin-dose reduction and weight loss cannot be resolved in this design; lower insulin exposure can itself promote weight loss, so the relationship may be bidirectional.

Our findings extend prior incretin-based studies in T1D. The ADJUNCT trials established that liraglutide can reduce insulin dose and body weight in T1D but highlighted the need for careful safety assessment [7,8]. More recent trials have shown a metabolic benefit from semaglutide and tirzepatide in selected adults with T1D, particularly those with obesity or automated insulin delivery [9–11]. In a 12-week phase 2 placebo-controlled trial, tirzepatide reduced body weight and lowered HbA1c by about 0.4 percentage points versus placebo alongside a substantial placebo-adjusted reduction in insulin dose [12]. The HbA1c and weight changes observed here at real-world doses are of a similar order, and the insulin-dose reduction is smaller than in trials, which is consistent with incomplete titration in routine care. The present study complements those trials by characterizing prescribing, titration, insulin trajectories and adverse events in a larger and more heterogeneous adult T1D population [13–15].

The adverse-event profile was predominantly gastrointestinal as expected given patterns seen with incretin therapies writ large. Nausea or vomiting and constipation increased after initiation net of the change in matched controls and after adjustment for multiple comparisons, and any hypoglycemia and abdominal pain increased nominally. Comparing each treated patient's pre- and post-index windows with those of a matched control matters here: the increase in any hypoglycemia was driven by semaglutide and was not seen with tirzepatide, and further, diabetic ketoacidosis and severe hypoglycemia rose by similar amounts in both arms. The absence of a net diabetic ketoacidosis signal is reassuring but not definitive. In T1D, any therapy that reduces appetite, food intake, body weight or insulin requirement could increase vulnerability to insulin underdosing, ketosis, dehydration or hypoglycemia if not accompanied by structured insulin-adjustment and sick-day protocols [7–9], and the event counts here do not exclude a modest increase in risk.

Several design choices address biases that are common in observational comparisons of this kind [13,19]. Controls were indexed at an outpatient insulin order, so both arms were anchored to a prescribing decision at a comparable level of care contact, and matching on index year and healthcare utilization aligned calendar time and engagement with care between arms. Insulin-dose outcomes were analyzed only in patients matched on baseline insulin dose and delivery modality, and the pre-index dose trajectories of the two arms overlapped for a year before index, which argues against regression to the mean or confounding by high baseline insulin requirements as the explanation for the post-index divergence. Residual confounding by indication, obesity severity, prescribing preference and access to medication nevertheless remains possible, and the results should be interpreted as associations to test in prospective trials.

The study has other limitations. Insulin TDD was documented in notes for a minority of eligible patients, so Cohort B is smaller than Cohort A and represents patients under closer insulin management. Documented doses may be carried forward between visits, which would bias percent change toward zero. Analyses were complete-case; patients

without a 12-month insulin value were predominantly those indexed in 2024 or 2025 with insufficient follow-up. Patients were classified by initial exposure without censoring at discontinuation, and the declining number of patients with a documented dose over follow-up indicates that some discontinued or transferred care; later anchors should be read as intention-to-treat comparisons among patients who remained in the network. The 18- and 24-month insulin-dose estimates in particular rest on substantially reduced samples, especially for tirzepatide, and should be read as exploratory. EHR data may incompletely capture adverse events, events outside the network, continuous glucose monitoring metrics, insulin pump settings, C-peptide levels, autoantibody status, nutritional intake, physical activity, and patient-reported tolerability [14,15]. Taken together, these estimates reflect what was documented for patients who remained in care, and the limitations described above may attenuate the observed differences.

In summary, semaglutide or tirzepatide initiation in adults with T1D was associated with lower insulin requirements, modest HbA1c improvement and weight loss compared with matched controls, and with a gastrointestinal-predominant adverse-event profile, with no statistically detectable net increase in diabetic ketoacidosis or severe hypoglycemia. These findings support prospective randomized trials of GLP-1 receptor agonist and dual GIP/GLP-1 receptor agonist adjunctive therapy in selected adults with T1D, with endpoints capturing insulin requirements, glycemic control, weight, and tolerability.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/diabetology7100189/s1>, Table S1. Distribution of documented semaglutide and tirzepatide doses over follow-up (all eligible exposed patients); Table S2. Number of patients contributing data at each anchor, by outcome and arm.; Table S3. Baseline characteristics of Cohort B by availability of an insulin total daily dose at 12 months or later after index.; Table S4. Change in insulin total daily dose at 6 months by weight change, HbA1c change, and dose reached.; Table S5. Adverse events in the 365 days before and after index in treated patients and matched controls, combined and by drug; Figure S1. Documented semaglutide and tirzepatide doses over follow-up. Stacked bars show the proportion of patients with a documented dose in each dose category at index and at Month 3, 6, 9, 12, 18, and 24 among all eligible exposed patients, with the number of patients with a documented dose above each bar. (A) Semaglutide, 0.25 to 2.4 mg. (B) Tirzepatide, 2.5 to 15 mg. Segment labels give the percentage of patients in each category; segments below 6% are unlabelled.; Figure S2. Adverse events before and after index by drug. As Figure 5, for (A) semaglutide (1447 treated patients and their matched controls) and (B) tirzepatide (568 treated patients and their matched controls), with the treated and control risk differences, the net difference, and the corresponding *p* values and Benjamini-Hochberg adjusted *p* values.; Supplementary Methods—LLM Prompt used for extracting insulin total daily dosage.

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Institutional Review Board Statement: This retrospective study was conducted solely using de-identified data made available to the researchers within secure, academic-medical-center-hosted data environments. The researchers had no access to identifiable private information and did not interact or intervene with any individuals. Accordingly, the study did not constitute human-subject research under 45 C.F.R. § 46.102(e)(1), and IRB review was not required.

Informed Consent Statement: This retrospective study was conducted solely using de-identified data made available to the researchers within secure, academic-medical-center-hosted data environments. The researchers had no access to identifiable private information and did not interact or intervene

with any individuals. Accordingly, the study did not constitute human-subject research under 45 C.F.R. § 46.102(e)(1), and informed consent was not required.

Data Availability Statement: This study involves the analysis of de-identified Electronic Health Record (EHR) data via the nference Federated System. Data shown and reported in this manuscript were extracted from this environment using an established protocol for data extraction, aimed at preserving patient privacy. The data has been de-identified pursuant to an expert determination in accordance with the HIPAA Privacy Rule. Any data beyond what is reported in the manuscript, including but not limited to the raw EHR data, cannot be shared or released due to the parameters of the expert determination to maintain the data de-identification.

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Conflicts of Interest: The authors are employees of nference, Inc., which conducts research collaborations with various biopharmaceutical companies whose therapeutic products are included in this study. None of these companies, nor any other nference collaborator, funded, supported, or had any role in the independent study design, data acquisition, analysis, interpretation, manuscript preparation, or the decision to submit this work for publication. All analyses were conducted by the authors using de-identified electronic health record data. The authors declare no additional competing interests.

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