Diabetes, Obesity and Metabolism

WILEY

ORIGINAL ARTICLE OPEN ACCESS

Tirzepatide Is Associated With Improved Metabolic Outcomes in People With Type 1 Diabetes and Overweight or Obesity: A Retrospective Cohort Study

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Received: 7 April 2026 | **Revised:** 22 June 2026 | **Accepted:** 23 June 2026

Handling Editor: Richard Donnelly

Keywords: antiobesity drug | continuous glucose monitoring (CGM) | database research | GLP-1 analogue | incretin therapy | real-world evidence

ABSTRACT

Aims: To evaluate the effect of tirzepatide on body weight, glycaemic control, insulin requirements, continuous glucose monitoring (CGM) metrics and cardiorenal parameters in adults with Type 1 diabetes (T1D) and overweight or obesity.

Materials and Methods: In this retrospective matched cohort study, adults with T1D, BMI ≥ 27 kg/m^2, CGM use and available baseline and follow-up electronic medical record data from Royal North Shore Hospital and the Northern Sydney Endocrine Centre between 2020 and 2025 were included. Twenty-three adults treated with tirzepatide were identified and propensity score-matched to 23 control participants. Primary outcomes included changes in percentage change in body weight, HbA1c, total daily insulin dose and CGM-derived metrics from baseline to follow-up. Exploratory outcomes included changes in blood pressure and biochemical markers.

Results: Mean follow-up duration in the tirzepatide and control groups were 28 and 31 weeks, respectively. The most common dose of tirzepatide was 5 mg/week (52.2% participants). Compared with controls, tirzepatide was associated with greater reductions in body weight (−10.01% ± 4.74% vs. +0.69% ± 3.77%, adj-$p < 0.0001$) and total daily insulin dose (−21.82 ± 16.30 vs. +5.62 ± 11.63 U/day; adj-$p = 0.002$). From baseline to end-of-study, tirzepatide was associated with a reduction in glucose management indicator, glucose SD and daily carbohydrate intake. Other CGM, blood pressure, lipid, hepatic and renal outcomes did not differ.

Conclusions: In adults with T1D and overweight or obesity, adjunctive tirzepatide treatment was associated with clinically meaningful reductions in percentage body weight and insulin requirements. Larger prospective studies are needed to confirm efficacy, ensure safety and assess broader cardiometabolic effects.

1 | Introduction

Overweight and obesity are increasingly common in adults living with Type 1 diabetes (T1D). Data from the US-based T1D Exchange Clinic Registry, a large cohort of people living with T1D receiving specialist diabetes care, indicates that approximately half of adults with T1D are living with overweight or obesity [1]. Similarly, longitudinal data from the German/Austrian DPV Registry show a sustained upward shift of body mass index (BMI) over recent decades that exceeds trends observed in the general population [2]. Importantly, excess adiposity in T1D amplifies insulin resistance, increases daily insulin requirements and contributes to an adverse cardiometabolic risk profile thereby compounding the burden of microvascular and

macrovascular disease risk in a population already vulnerable to cardiovascular complications [3]. Despite major advances in continuous glucose monitoring (CGM) and automated insulin delivery, these technologies do not directly address obesity-driven insulin resistance and its downstream metabolic and cardiovascular consequences.

Adjunctive agents such as metformin, sodium-glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists have been investigated to address insulin resistance and weight gain in T1D, but clinical benefits have varied by agent. Metformin yields modest short-term improvements in body weight and insulin dose, with limited long-term durability [4]. SGLT2 inhibitors improve weight and glycaemic outcomes but are constrained by an increased risk of diabetic ketoacidosis [5, 6]. GLP-1 receptor agonists have been associated with reductions in body weight, improvements in glycaemic outcomes and lower insulin requirements in T1D [7], but evidence for newer dual incretin agonists in T1D remains limited.

Tirzepatide, a dual GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptor agonist, has demonstrated marked reductions in glycated haemoglobin (HbA1c), body weight and several cardiometabolic risk factors in type 2 diabetes and obesity [8–11]. Emerging case reports and small observational studies in adults with T1D suggest that tirzepatide induces clinically meaningful weight loss, reduced insulin requirements and improved glycaemic variability [12, 13]. A recent small clinical trial has now demonstrated that, in 22 adults with T1D and obesity, tirzepatide produced markedly greater weight loss than placebo over a short 12-week duration, alongside reductions in HbA1c and total daily insulin dose [14]. Nonetheless, robust real-world data remains limited, particularly regarding CGM-derived glycaemic variability and the impact on other cardiometabolic measurements used in routine clinical care.

This retrospective, observational cohort study evaluated the effect of tirzepatide on body weight, HbA1c, CGM metrics and cardiometabolic parameters in adults with T1D and overweight or obesity. It was hypothesised that tirzepatide would improve metabolic outcomes in this population, including body weight, glycaemic control and insulin requirements, compared with standard care alone.

2 | Materials and Methods

2.1 | Study Design and Participants

This study was a retrospective, observational cohort study of patients with T1D, seen at Royal North Shore Hospital (RNSH), a public hospital clinic, or the Northern Sydney Endocrine Centre (NSEC), a private endocrinology clinic, between 2020 and 2025. Adults (aged ≥ 18 years) with a clinical diagnosis of T1D and overweight or obesity (BMI ≥ 27 kg/m^2) at the time of tirzepatide initiation, were eligible for inclusion in this study. Additional inclusion criteria were the use of a CGM and at least one clinic visit within 3 months before starting tirzepatide and at least one follow-up visit within the study window. Both insulin pump and multiple daily injection users were included in this study. Individuals using glucose-lowering agents known to have weight loss benefits (e.g., SGLT2 inhibitors, metformin, GLP-1 receptor agonists) or with insufficient baseline or follow-up data were excluded from the treatment and control groups.

2.2 | Comparator Cohort and Matching

A comparator cohort of adults with T1D who had not received tirzepatide was identified from the same clinic population. Controls were selected using 1:1 nearest-neighbour propensity score matching without replacement. Propensity scores were estimated using logistic regression, with baseline BMI and HbA1c included as covariates. These variables were selected as clinically relevant baseline characteristics likely to influence tirzepatide prescribing. For controls, the interval between baseline and follow-up was selected to approximate the observation period of the corresponding tirzepatide-treated participant.

2.3 | Data Collection and Outcomes

Data was obtained from electronic medical records using a standardised extraction template. Outcomes were assessed at baseline and at the final available visit within the observation window. These measures included age, sex, duration of diabetes, BMI, body weight, HbA1c, total daily insulin dose, daily carbohydrate intake, insulin-to-carbohydrate ratio, CGM metrics (percentage time in range [3.9–10.0 mmol/L], percentage time above range [> 10.0 mmol/L], percentage time below range [< 3.9 mmol/L], glucose management indicator, mean glucose, glucose standard deviation (SD) and coefficient of variation), blood pressure and a range of blood and urine measures including alanine aminotransferase, aspartate aminotransferase, total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides, estimated glomerular filtration rate and urinary albumin-to-creatinine ratio. Daily carbohydrate intake was derived from self-reported carbohydrate entries recorded in insulin pumps for insulin dosing.

The primary outcomes were change from baseline to end-of-study in percentage change in body weight, BMI, HbA1c, total daily insulin dose, percentage time-in-range, percentage time-below-range and coefficient of variation. Secondary outcomes included change in a range of CGM- and insulin pump-derived metrics, blood pressure and biochemical markers.

2.4 | Statistical Analysis

Baseline and end-of study data are presented as mean and SD. Baseline characteristics were compared using standardised mean differences (SMD). End-of-study outcomes were analysed as change from baseline and between-group differences were compared within matched pairs using paired *t*-tests. To account for multiple testing across primary outcomes, Bonferroni-adjusted *p*-values (adj-*p*) were calculated. Sensitivity analysis using G*Power (version 3.1.9.6) indicated that, for seven primary outcomes, with 23 matched pairs, 80% power and a Bonferroni-adjusted alpha of 0.007, the study was powered to detect a large effect size (dz ≥ 0.80). Secondary outcomes were considered exploratory and were not adjusted for multiplicity. Within-group

changes from baseline to end-of-study were analysed using paired *t*-tests among participants with data available at baseline and end-of-study.

Due to incomplete data availability for some variables, the number of participants included in individual analyses varied. All analyses were performed using available data without imputation. The numbers of participants contributing to the relevant analyses are listed in Tables S1 and S2. Statistical significance was defined as $p < 0.05$, and all statistical analyses were performed using R Studio (version 2026.04.0).

2.5 | Ethics

The study protocol received approval from the Northern Sydney Local Health District Human Research Ethics Committee (#2024/ETH00590).

3 | Results

3.1 | Study Population

Searches of the RNSH and NSEC databases identified 23 individuals that met the eligibility criteria and comprised the tirzepatide cohort. An equal number of propensity score-matched participants were selected as the control group.

3.2 | Baseline Characteristics

Baseline characteristics are shown in Table 1. The tirzepatide and control groups were closely comparable for age (44.87 ± 9.35 vs. 44.83 ± 11.89 years; SMD: 0.00), T1D duration (23.35 ± 10.99 vs. 24.22 ± 12.28 years; SMD: −0.07) and baseline HbA1c (7.14% ± 0.95% vs. 7.08% ± 0.97%; SMD: 0.06). The proportion of participants using multiple daily injections was similar between groups (26.09% vs. 21.74%; SMD: 0.10), although automated insulin delivery use in those with insulin pumps was higher in the tirzepatide group than in controls (82.35% vs. 61.11%; SMD: 0.48). Mild residual imbalance remained for BMI (34.97 ± 6.34 vs. 33.90 ± 5.87 kg/m^2; SMD: 0.17) and sex, with a higher proportion of males in the tirzepatide group than in controls.

Residual imbalance was also evident for several non-matched cardiometabolic and laboratory variables, as shown in Table 1. Thus, while matching improved comparability for key baseline variables, it did not fully eliminate baseline differences across all clinical characteristics.

3.3 | Tirzepatide Treatment Is Associated With Improved Anthropometric and Glycaemic Outcomes

The most common maximum tirzepatide dose was 5 mg/week, reached by 12 participants (52.2%), followed by 2.5 mg/week in 4 participants (17.4%) and 7.5 mg/week in 3 participants (13.0%). Only 2 participants (8.7%) reached 12.5 mg/week, while 10 mg/week and 15 mg/week were each reached by 1 participant (4.3% each). Tirzepatide was generally initiated at 2.5 mg/week and up-titrated according to standard clinical practice. The average observation duration was 28.0 ± 12.8 weeks in the tirzepatide group and 31.3 ± 14.2 weeks in the control group.

In the paired primary analysis, tirzepatide treatment was associated with a 10.01% ± 4.74% decrease in body weight compared with a 0.69% ± 3.77% increase in controls (adj-$p < 0.0001$, Table 2). This equates to a BMI reduction of 3.30 ± 1.61 kg/m^2 in the tirzepatide group compared to a 0.18 ± 1.35 kg/m^2 increase in the control group (adj-$p < 0.0001$, Table 2).

There was no significant difference in HbA1c, percentage time in range, percentage time below range or coefficient of variation after adjustment for multiple comparisons. However, tirzepatide treatment was associated with a significant difference in total daily insulin dose, which decreased by 21.82 ± 16.30 U/day compared to a 5.62 ± 11.63 U/day increase in controls (adj-$p = 0.002$, Table 2). In an exploratory analysis adjusted for body weight, total daily insulin dose expressed as U/kg/day decreased with tirzepatide but increased in controls (−0.18 ± 0.21 vs. +0.05 ± 0.11 U/kg/day; $p = 0.004$, Table 3). In both groups, insulin dosing was typically reviewed at least every 3 months, with advice given and changes made as clinically indicated.

Sensitivity analyses adjusting for matched pair, sex, age and baseline outcome values produced results consistent with the primary analysis, with estimated treatment effects continuing to favour tirzepatide for change in body weight, BMI, HbA1c and total daily insulin dose (Table S3).

3.4 | Exploratory Glycaemic, Cardiometabolic and Renal Outcomes

Exploratory outcomes are shown in Table 3. Compared with controls, tirzepatide treatment was associated with a decrease in systolic blood pressure (−6.30 ± 16.35 vs. +6.00 ± 12.82 mmHg; $p = 0.015$), carbohydrate intake (−49.46 ± 47.03 vs. +11.77 ± 25.37 g/day; $p = 0.001$) and glucose SD (−0.24 ± 0.43 vs. +0.16 ± 0.35 mmol/L; $p = 0.022$). Tirzepatide treatment was associated with a higher insulin-to-carbohydrate ratio compared with controls, indicating fewer insulin units per gram of carbohydrate intake (+0.61 ± 0.99 vs. −0.07 ± 0.33 g/insulin unit; $p = 0.049$).

Within-group exploratory analyses showed a reduction in glucose management indicator ($p = 0.045$), improvement in glucose SD ($p = 0.006$) and reduced carbohydrate intake ($p = 0.007$) in the tirzepatide group. In the control group, aspartate aminotransferase decreased over follow-up ($p = 0.025$). Other exploratory cardiometabolic, renal, liver enzyme, lipid and CGM outcomes did not differ between groups (Table 3).

3.5 | Safety and Treatment Discontinuation

The reporting of safety outcomes was limited. Adverse events reported were predominantly gastrointestinal, including four reports of nausea, one report of constipation and one report of gastro-oesophageal reflux. There was one reported episode of

TABLE 1 | Baseline characteristics.

	Tirzepatide	Control	SMD
Number	23	23	
Age (years)	44.87 (9.35)	44.83 (11.89)	0.00
Duration of diabetes (years)	23.35 (10.99)	24.22 (12.28)	−0.07
Sex, male	14/23 (60.87%)	9/23 (39.13%)	0.45
Body weight (kg)	102.90 (21.47)	95.57 (13.60)	0.41
BMI (kg/m^2)	34.97 (6.34)	33.90 (5.87)	0.17
HbA1c (%)	7.14 (0.95)	7.08 (0.97)	0.06
Mode of insulin delivery and insulin pump metrics			
Multiple daily injection users	6/23 (26.09%)	5/23 (21.74%)	0.10
Insulin pump users	17/23 (73.91%)	18/23 (78.26%)	−0.10
Automated insulin delivery users	14/17 (82.35%)	11/18 (61.11%)	0.48
Total daily insulin dose (U/day)	70.42 (32.27)	66.07 (25.86)	0.15
Weight-corrected total daily insulin dose (U/kg/day)	0.70 (0.29)	0.67 (0.21)	0.12
Carbohydrate intake (g/day)	144.83 (68.12)	156.38 (63.68)	−0.18
Insulin-to-carbohydrate ratio (g/insulin unit)	2.43 (0.90)	2.27 (1.01)	0.16
Continuous glucose monitoring metrics			
Time in range (%)	64.78 (19.44)	67.95 (11.32)	−0.20
Time below range (%)	1.09 (1.00)	1.82 (2.36)	−0.40
Time above range (%)	34.13 (19.99)	30.23 (11.81)	0.24
Glucose management indicator (%)	7.24 (0.68)	7.13 (0.45)	0.18
Mean glucose (mmol/L)	9.08 (1.62)	8.82 (1.02)	0.19
Glucose SD (mmol/L)	2.79 (0.56)	2.92 (0.58)	−0.24
Coefficient of variation (%)	31.41 (4.06)	33.18 (5.13)	−0.38
Cardiorenal and hepatic measures			
Systolic blood pressure (mmHg)	128.52 (13.50)	119.95 (15.02)	0.60
Diastolic blood pressure (mmHg)	75.78 (10.00)	73.42 (12.65)	0.21
Mean arterial pressure (mmHg)	93.36 (10.49)	87.92 (10.05)	0.53
Total cholesterol (mmol/L)	4.20 (1.02)	4.73 (1.10)	−0.51
High-density lipoprotein (mmol/L)	1.32 (0.33)	1.44 (0.40)	−0.34
Low-density lipoprotein (mmol/L)	2.38 (0.97)	2.72 (0.85)	−0.38
Triglycerides (mmol/L)	1.13 (0.51)	1.35 (1.28)	−0.22
Alanine aminotransferase (U/L)	34.00 (28.11)	33.52 (21.09)	0.02
Aspartate aminotransferase (U/L)	35.79 (40.39)	29.96 (13.78)	0.19
ALT/AST ratio	1.02 (0.45)	1.10 (0.32)	−0.21
Urine albumin-creatinine ratio (mg/mmol)	14.66 (38.17)	30.86 (92.28)	−0.23
Estimated glomerular filtration rate (mL/min/1.73 m^2)	82.58 (13.74)	83.61 (17.12)	−0.07

Note: Continuous data represented as mean (SD). Categorical data represented as number/total number (%). SMD refers to standardised mean difference and ALT/AST ratio refers to alanine aminotransferase to aspartate aminotransferase ratio. For metrics in which there is missing data, the exact number of participants included in each baseline comparison is detailed in Table S1.

TABLE 2 | Primary outcome measures.

	Tirzepatide	Control	Adj-*p*	*N*
Change in body weight (%)	−10.01 (4.74)	0.69 (3.77)	**< 0.0001**	22
Change in BMI (kg/m^2)	−3.30 (1.61)	0.18 (1.35)	**< 0.0001**	22
Change in HbA1c (%)	−0.37 (0.71)	−0.02 (0.49)	0.317	21
Change in total daily insulin dose (U/day)	−21.82 (16.30)	5.62 (11.63)	**0.002**	11
Change in time in range (%)	6.45 (15.47)	−1.25 (6.76)	0.543	20
Change in time below range (%)	−0.20 (0.77)	0.35 (1.35)	1.000	20
Change in coefficient of variation (%)	−2.08 (4.02)	1.96 (4.27)	0.088	20

Note: Data represented as mean change from baseline (SD). Adjusted *p*-values (Adj-*p*) represent between-group comparisons of change from baseline to end-of-study. *N* refers to the number of matched pairs included in each paired *t*-test. Bonferroni correction was applied for multiple comparisons across the primary outcomes.

symptomatic hypoglycaemia and no reported diabetic ketoacidosis. At the time of this review, 14 participants (60.9%) were continuing tirzepatide treatment. For participants who ceased tirzepatide use, documented reasons included cost, pregnancy planning, reaching a target weight or cessation without a recorded reason.

4 | Discussion

In this retrospective, propensity score-matched cohort study of adults with T1D and overweight or obesity, adjunctive tirzepatide use was associated with clinically meaningful reductions in percentage body weight, BMI and total daily insulin dose over a mean treatment duration of approximately 28 weeks. These findings add to the limited real-world evidence for tirzepatide use in T1D.

The magnitude of weight loss observed in this cohort aligns with the limited emerging evidence for tirzepatide in T1D. This is particularly promising given the high proportion of included individuals who remained on relatively low doses (≤ 5 mg). In an observational study of 26 adults with T1D, tirzepatide was associated with approximately 10% weight loss at 8 months together with a HbA1c reduction of 0.59%. Similarly, a phase 2 placebo-controlled trial in adults with T1D and obesity demonstrated greater weight loss and improved HbA1c with tirzepatide than placebo over 12 weeks [14]. In the present study, HbA1c was not significantly different between groups. This may reflect limited statistical power as the study was powered to detect large effects only and may not have reliably detected modest differences in glycaemic outcomes. This is particularly relevant given that the observed effect size for HbA1c was smaller than that seen for body weight and insulin dose.

The reduction in total daily insulin dose observed in the subsample with available data is clinically important, particularly in adults with T1D and overweight or obesity, where high insulin requirements may reflect underlying insulin resistance and contribute to further weight gain. However, this finding should not be interpreted as evidence of a direct pharmacological effect of tirzepatide alone. Rather, the observed reduction in insulin dose likely reflects several related factors, including tirzepatide use, reduced appetite and carbohydrate intake and routine clinical insulin titration. In pump-treated individuals, changes in insulin-to-carbohydrate ratios may have further reduced prandial insulin delivery, particularly in the setting of reduced carbohydrate intake or improved postprandial glycaemia. Because insulin pump settings were adjusted as part of routine care and were not standardised for this retrospective study, the relative contribution of each factor cannot be determined. This should be considered when interpreting the insulin dose findings, particularly because insulin dose data was only available in a smaller matched subsample.

The observed associations in this study are biologically plausible and consistent with the established effects of tirzepatide in Type 2 diabetes and obesity [16, 17]. Appetite suppression, delayed gastric emptying and reduced glucagon secretion are known pharmacological mechanisms that improve postprandial glycaemia and facilitate lower exogenous insulin requirements [18]. Reduced insulin requirements may offer practical benefits in T1D, including lower insulin costs, reduced use of pump consumables and potentially less insulin-associated weight gain. This is particularly relevant given the well-established association between intensive insulin therapy and weight gain in T1D, and resultant adiposity is linked to a higher risk of cardiometabolic comorbidity in this population [19, 20].

The CGM-derived outcomes observed in this study should be interpreted cautiously. Time in range, time below range and coefficient of variation were not significantly different between groups in the primary analysis. These outcomes are clinically important, but the study may not have reliably detected smaller differences across multiple glycaemic endpoints. CGM data was incomplete for several participants, and residual baseline imbalance in some non-matched glycaemic and clinical characteristics may complicate interpretation of subsequent comparisons. Larger prospective studies with standardised CGM data capture and prespecified glycaemic endpoints are needed to determine whether tirzepatide is associated with reproducible improvements in glycaemic variability in adults with T1D.

The safety findings are descriptive and should be interpreted conservatively. One episode of symptomatic hypoglycaemia was identified on review of the clinical records, while no episodes of diabetic ketoacidosis were observed. However, given the small sample size and retrospective data collection, the low number of serious events does not permit conclusions regarding safety. Nevertheless, a recent observational study and a Phase 2 trial

TABLE 3 | Secondary outcome measures.

	Tirzepatide	Control	*p*	*N*
Weight-corrected total daily insulin dose (U/kg/day)	−0.18 (0.21)*	0.05 (0.11)	**0.004**	11
Change in time above range (%)	−3.04 (24.78)	0.90 (7.50)	0.527	20
Change in glucose management indicator (%)	−0.26 (0.59)*	0.02 (0.31)	0.126	16
Change in mean glucose (mmol/L)	−0.49 (1.34)	−0.21 (1.22)	0.541	20
Change in glucose SD (mmol/L)	−0.24 (0.43)**	0.16 (0.35)	**0.022**	16
Change in carbohydrate intake (g/day)	−49.46 (47.03)**	11.77 (25.37)	**0.001**	11
Change in insulin-to-carbohydrate ratio (g/insulin unit)	0.61 (0.99)	−0.07 (0.33)	**0.049**	10
Change in systolic blood pressure (mmHg)	−6.30 (16.35)	6.00 (12.82)	**0.015**	20
Change in diastolic blood pressure (mmHg)	−3.60 (11.20)	1.43 (14.74)	0.301	20
Change in mean arterial pressure (mmHg)	−4.50 (12.25)	4.07 (10.46)	0.054	20
Change in alanine aminotransferase (U/L)	−5.59 (19.68)	−3.12 (10.19)	0.704	17
Change in aspartate aminotransferase (U/L)	−8.35 (40.86)	−4.76 (8.74)*	0.741	17
Change in ALT/AST ratio	0.00 (0.34)	0.03 (0.28)	0.782	17
Change in total cholesterol (mmol/L)	−0.13 (0.77)	−0.16 (0.82)	0.937	18
Change in high-density lipoprotein (mmol/L)	0.02 (0.18)	0.00 (0.15)	0.823	17
Change in low-density lipoprotein (mmol/L)	−0.01 (0.75)	−0.00 (0.61)	0.960	17
Change in triglycerides (mmol/L)	−0.19 (0.49)	−0.19 (0.39)	1.000	17
Change in urine albumin-creatinine ratio (mg/mmol)	−7.75 (15.36)	−27.38 (89.97)	0.572	8
Change in estimated glomerular filtration rate (mL/min/1.73 m^2)	−0.28 (7.14)	−0.39 (4.67)	0.959	18

Note: Data represented as mean change from baseline (SD). *p*-values represent between-group comparisons of change from baseline to end-of-study. *N* refers to the number of matched pairs included in each paired between-group comparison. Bold values indicate any significant values and is intended to improve visibility for readers. *Indicates a significant within-group change from baseline to end-of-study, where *$p < 0.05$ and **$p < 0.01$. Where data was missing for within-group analyses, the number of participants included in each baseline-to-end-of-study comparison is provided in Table S2.

reported no serious adverse events during short-term follow-up [14, 21]. Further controlled clinical trials are required to appropriately assess the risks of ketoacidosis and severe hypoglycaemia in this population.

This study did not find evidence of broader cardiovascular, renal, or hepatic benefit over the study period. Similarly, in a 12-week trial of tirzepatide in adults with T1D, no significant between-group differences were seen in fasting lipids or blood pressure [14]. However, longer-term observational data of tirzepatide in adults with T1D over 21 months suggest improvement in several cardiometabolic and renal markers, including total and low-density lipoprotein, triglycerides, systolic blood pressure and estimated glomerular filtration rate [13]. Furthermore, a large target trial emulation found that GLP-1 receptor agonist therapy in T1D, including with albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide, semaglutide and tirzepatide, was associated with lower risks of major adverse cardiovascular events and end-stage kidney disease [22]. Overall, this suggests that the absence of clear cardiometabolic effects in our cohort may reflect the small sample size and short duration.

The limitations of this study must be acknowledged. First, this was a retrospective observational study and causality cannot be inferred. Although propensity score matching improved comparability for baseline BMI and HbA1c, residual baseline imbalance remained for sex and several non-matched cardiometabolic characteristics. The higher prevalence of automated insulin delivery use in the tirzepatide group represents a residual confound that may have influenced CGM-derived outcomes, including time in range and glycaemic variability and limits the interpretation of between-group differences in these endpoints. Further matching utilising additional variables relevant to tirzepatide prescription, such as total daily insulin dose, was not possible without significantly reducing the number of included participants. Second, the sample size was modest, and missing data reduced the effective sample size for several analyses. This is particularly relevant for the analysis of total daily insulin dose, which was limited to 11 matched pairs due to incomplete retrospective documentation of this outcome measure. It therefore cannot be confirmed that this subsample was representative of the full matched cohort, and this finding should be interpreted cautiously. The study was powered to detect large effects only, therefore smaller differences may have been missed. Third, although correction for multiplicity was applied across the primary outcomes, exploratory outcomes were not adjusted and should therefore be interpreted cautiously. Fourth, at the time of this study, tirzepatide was not subsidised for obesity or T1D in Australia, and access was dependent on private prescription and out-of-pocket cost. This may have introduced selection

bias and unmeasured differences in treatment access and patient characteristics such as socioeconomic status. The health institutions captured by this retrospective study include endocrine centres in a high socioeconomic health district within metropolitan Sydney, Australia. This suggests that access across both the tirzepatide and untreated populations may be higher than that of more generalised cohorts. Fifth, tirzepatide exposure was heterogeneous, with variation in maximum tolerated dose and titration schedule. These factors may have had a meaningful impact on primary outcomes, such as body weight, HbA1c and insulin dose as higher doses of tirzepatide have been associated with increased efficacy in alternative cohorts [23]. However, given the small proportion of participants receiving higher doses (> 10 mg), formal dose-response analyses for weight and glycaemic outcomes were not viable. Finally, waist circumference and waist-hip ratio were not consistently recorded, and the variables required to calculate estimated glucose disposal rate were not reliably available. The absence of formal insulin resistance measures limits mechanistic interpretation, particularly given the relevance of insulin resistance to tirzepatide use in T1D with overweight or obesity.

Future studies should include larger cohorts and randomised trials with standardised insulin-adjustment protocols, systematic adverse-event collection, and longer follow-up to assess durability and broader cardiometabolic outcomes. Mechanistic studies are also needed to clarify the extent to which glycaemic improvement is mediated by weight loss and reduced insulin resistance, as compared to direct effects of tirzepatide on gastric emptying, glucagon physiology, appetite and glycaemic variability in T1D. Importantly, tirzepatide is not approved for use in T1D, and the findings of this retrospective study should not be used to guide prescribing outside formal clinical trial settings or closely monitored specialist care. Adequately powered prospective trials with systematic safety ascertainment are required before clinical adoption of tirzepatide in T1D can be recommended.

Overall, adjunctive tirzepatide use was associated with reduced percentage body weight and reduced insulin requirements in adults with T1D and overweight or obesity. These findings are encouraging but should be interpreted in the context of a small retrospective study with limited power for smaller effects and no formal safety assessment. Larger prospective studies and randomised trials are now warranted to confirm these findings, better define safety and determine which individuals are most likely to benefit from adjunctive tirzepatide therapy.

Author Contributions

A.R.P., M.S.G.L. and S.J.G. conceptualised the research question for this study. All authors contributed to the preparation of the human ethics application associated with this study. A.R.P. performed data collection, conducted the statistical analysis and prepared the manuscript. M.S.G.L., N.R. and S.J.G. reviewed and edited the manuscript. S.J.G. is the guarantor of this work.

Acknowledgements

A.R.P. was supported by the University of Sydney Postgraduate Award, Australian Centre for Accelerating Diabetes Innovations PhD Grant and the Breakthrough T1D PhD Top-Up Scholarship. The authors would like to acknowledge Dr. Purnima (Darshi) Cheruvu for her contributions to the preparation of the ethics application for this study. Open access publishing facilitated by The University of Sydney, as part of the Wiley - The University of Sydney agreement via the Council of Australasian University Librarians

Funding

The authors have nothing to report.

Conflicts of Interest

S.J.G. has received honoraria and travel support from pharmaceutical companies including Lilly, Novo Nordisk, and Sanofi. 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.

Peer Review

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.71063.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Number of participants included in analyses in Table 1. **Table S2:** Number of participants included in paired *t*-tests for within-group analyses for change from baseline to end-of-study in Table 3. **Table S3:** Sensitivity analyses for primary outcomes.