Received: 30 June 2023 | Revised: 17 August 2023 | Accepted: 20 August 2023

DOI: 10.1111/dom.15269

ORIGINAL ARTICLE

WILEY

Tirzepatide reduces the predicted risk of developing type 2 diabetes in people with obesity or overweight: Post hoc analysis of the SURMOUNT-1 trial

Emily R. Hankosky PhD[1] | Hui Wang PhD[2] | Lisa M. Neff MD[1] | Hong Kan PhD[1] | Fangyu Wang MS[1] | Nadia N. Ahmad MD[1] | Adam Stefanski MD[1] | W. Timothy Garvey MD[3]

[1]Eli Lilly and Company, Indianapolis, Indiana, USA

[2]Tech Data Service, King of Prussia, Pennsylvania, USA

[3]University of Alabama at Birmingham, Birmingham, Alabama, USA

Correspondence
W. Timothy Garvey, Department of Nutrition Sciences, The University of Alabama at Birmingham, 1675 University Boulevard, Birmingham, AL 35294-3360, USA.
Email: garveyt@uab.edu

Funding information
Eli Lilly and Company

Abstract

Aim: We assessed the impact of tirzepatide on 10-year predicted risk of developing type 2 diabetes (T2D) among participants in the SURMOUNT-1 trial.

Materials and Methods: In this post hoc analysis of SURMOUNT-1, the Cardiometabolic Disease Staging risk engine was used to calculate the 10-year predicted risk of T2D at baseline, week 24 and week 72 among participants randomized to receive 5, 10, or 15 mg tirzepatide or placebo. Mean changes in risk scores from baseline to weeks 24 and 72 were compared between tirzepatide and placebo groups. Subgroup analyses were conducted based on participants' glycaemic status and body mass index at baseline.

Results: Mean baseline T2D predicted risk scores did not differ between tirzepatide and placebo groups (range: 22.9%-24.3%). At week 72, mean absolute T2D predicted risk score reductions were significantly greater in tirzepatide groups (5 mg, 12.4%; 10 mg, 14.4%; 15 mg, 14.7%) versus placebo (0.7%). At week 72, median relative predicted risk reductions following tirzepatide treatment ranged from 60.3% to 69.0%. For participants with and without prediabetes, risk reductions were significantly greater in tirzepatide groups versus placebo. At week 72, participants with prediabetes (range: 16.0%-20.3%) had greater mean risk score reductions from baseline versus those without prediabetes (range: 10.1%-11.3%). Across body mass index subgroups, mean reductions from baseline were significantly greater in tirzepatide groups versus placebo.

Conclusion: Tirzepatide treatment significantly reduced the 10-year predicted risk of developing T2D compared with placebo in participants with obesity or overweight, regardless of baseline glycaemic status.

KEYWORDS
anti-medications, obesity, prediabetes, risk prediction, tirzepatide, type 2 diabetes

1 | INTRODUCTION

Obesity is a chronic and progressive disease, and its prevalence in the United States and globally is increasing rapidly.[1–4] Obesity is strongly linked to increased risk of type 2 diabetes (T2D) and other serious diseases such as cardiovascular disease, hypertension and dyslipidaemia.[5] People with obesity are nearly three times more likely to develop T2D than those without obesity.[6] Moreover, the risk of developing T2D is higher in the presence of prediabetes.[7] There is a positive correlation among higher body mass index (BMI), larger waist circumference and the risk of developing T2D.[8] Weight reduction in obesity improves existing obesity-related complications and reduces their risk in the future.[9–11] Lifestyle modification (including nutrition and physical activity) is the foundation of obesity treatment, and additional therapies (e.g. pharmacotherapy or bariatric surgery) can be considered based on individual characteristics and health goals or when lifestyle-based interventions have been unsuccessful.[9,12–14]

The goal of obesity management is to improve the health of patients with this disease.[9] Even a 5%-10% body weight reduction from baseline is considered clinically meaningful, resulting in improved metabolic markers, blood pressure, insulin sensitivity and pancreatic beta-cell function.[11,15,16] Furthermore, among adults without T2D, studies showed that lifestyle intervention leading to more than 7% weight reduction corresponded to nearly 60% reduced incidence of T2D and with every kilogram of weight lost, there was a 16% reduction in risk of developing diabetes.[17,18]

Treatment with glucagon-like peptide-1 (GLP-1) receptor agonists such as liraglutide (3 mg) or semaglutide (2.4 mg) induced significant weight reduction and improvement in glycaemic control in adults with or without diabetes.[19–23] GLP-1 receptor agonist treatment also resulted in reduced waist circumference along with improvements in systolic blood pressure (SBP), triglycerides and high-density lipoprotein cholesterol.[19,20] Tirzepatide, a novel glucose-dependent insulinotropic polypeptide and GLP-1 receptor agonist approved for T2D and in development for obesity, promoted weight reduction among people with or without T2D.[24–27] Specifically, in the Phase 3 randomized clinical trial SURMOUNT-1, 72 weeks of tirzepatide treatment resulted in a mean weight reduction of up to 22.5% among people with obesity or overweight without T2D (efficacy estimand).[27] In a network meta-analysis, tirzepatide resulted in significantly greater weight reduction compared with semaglutide and liraglutide among people with obesity without T2D.[28]

The effect of tirzepatide on the long-term risk of developing T2D in people with obesity or overweight is currently unknown. Cardiometabolic Disease Staging (CMDS) provides a robust validated 10-year risk estimate of future diabetes,[29] and provides an opportunity to assess the impact of tirzepatide. The goal of this study was to assess the impact of tirzepatide treatment on the 10-year predicted risk of developing T2D using CMDS among participants in the SURMOUNT-1 trial with obesity or overweight.

2 | MATERIALS AND METHODS

2.1 | Study design and population

This was a post hoc analysis of individual patient level data from the SURMOUNT-1 trial (NCT04184622), a Phase 3, randomized, double-blind, placebo-controlled study in participants ≥18 years with obesity (BMI ≥30 kg/m^2) or overweight (BMI ≥27 kg/m^2 and at least one weight-related complication) and without T2D.[27] Trial participants were randomized 1:1:1:1 to receive 5, 10 or 15 mg of tirzepatide, or placebo once-weekly for 72 weeks as an adjunct to lifestyle intervention. This study used data from the SURMOUNT-1 efficacy analysis set, which included data from all randomized participants who had received at least one dose of the study intervention during the treatment period, excluding data after study drug discontinuation.

The original SURMOUNT-1 participant consent covered the analyses in this study. The SURMOUNT-1 protocol was approved by institutional review boards or independent ethics committees. This study was conducted in accordance with the ethical principles of Good Clinical Practice and the Declaration of Helsinki and its guidelines.

2.2 | Variables and outcomes

Participants' demographic and baseline clinical characteristics were summarized descriptively by treatment group,[27] and included age, sex, race, ethnicity, BMI, waist circumference, SBP and diastolic blood pressure (DBP), among others. The outcomes were (a) assessment of 10-year T2D predicted risk scores at baseline, week 24 and week 72, and (b) mean change of risk score from baseline to weeks 24 and 72.

The CMDS risk engine was used to calculate predicted risk for T2D at baseline and weeks 24 and 72. CMDS was designed as a tool for assessment of T2D risk as a guide to clinicians regarding interventions for T2D prevention and uses quantitative data readily available to clinicians that would probably be available in the electronic medical record. One iteration of CMDS employs metabolic syndrome trait thresholds to assign patients to five risk strata for point-of-care use by clinicians.[30] The current analysis uses a Bayesian logistic regression equation based on the continuous severity of metabolic syndrome traits and provides a quantitative measure of 10-year T2D risk.[29] The quantitative CMDS equation was developed using a large nationally sampled cohort of White or Black/African American individuals, the REasons for Geographic And Racial Differences in Stroke (REGARDS) study,[31] and was validated in the Atherosclerosis Risk in Communities (ARIC) cohort data.[32] CMDS was shown to be more robust compared with other risk tools (e.g. the Framingham diabetes risk estimate) when applied to these same study populations.[29]

The following were used as model inputs in the current analysis: age, sex, race, waist circumference, fasting glucose, SBP, DBP,

TABLE 1 Demographic and baseline clinical characteristics of SURMOUNT-1 participants

Characteristics	Placebo (n = 643)	TZP 5 mg (n = 630)	TZP 10 mg (n = 636)	TZP 15 mg (n = 630)	Total (N = 2539)
Age, years	44.4 (12.5)	45.6 (12.7)	44.7 (12.4)	44.9 (12.3)	44.9 (12.5)
Female[a]	436 (67.8)	426 (67.6)	427 (67.1)	425 (67.5)	1714 (67.5)
BMI, kg/m^2	38.2 (6.9)	37.4 (6.6)	38.2 (7.0)	38.1 (6.7)	38.0 (6.8)
SBP, mmHg	122.9 (12.8)	123.6 (12.5)	123.8 (12.8)	123.0 (12.9)	123.3 (12.7)
DBP, mmHg	79.6 (8.0)	79.3 (8.1)	79.9 (8.3)	79.3 (8.2)	79.5 (8.2)
Current smoker[a]	69 (10.7)	94 (14.9)	75 (11.8)	87 (13.8)	325 (12.8)
Waist circumference, cm	114.0 (14.9)	113.2 (14.3)	114.8 (15.8)	114.4 (15.6)	114.1 (15.2)
Country/region[a]					
United States	288 (44.8)	282 (44.8)	287 (45.1)	284 (45.1)	1141 (44.9)
Brazil	59 (9.2)	59 (9.4)	61 (9.6)	60 (9.5)	239 (9.4)
China	7 (1.1)	9 (1.4)	7 (1.1)	7 (1.1)	30 (1.2)
India	8 (1.2)	9 (1.4)	9 (1.4)	6 (1.0)	32 (1.3)
Japan	33 (5.1)	30 (4.8)	30 (4.7)	31 (4.9)	124 (4.9)
Mexico	108 (16.8)	110 (17.5)	107 (16.8)	108 (7.1)	433 (17.1)
Russian Federation	32 (5.0)	29 (4.6)	30 (4.7)	27 (4.3)	118 (4.6)
Taiwan	15 (2.3)	12 (1.9)	15 (2.4)	16 (2.5)	58 (2.3)
Argentina	93 (14.5)	90 (14.3)	90 (14.2)	91 (14.4)	364 (14.3)
Race[a]					
White	450 (70.0)	447 (71.0)	452 (71.1)	443 (70.3)	1792 (70.6)
Asian	71 (11.0)	68 (10.8)	71 (11.2)	66 (10.5)	276 (10.9)
Black or African American	55 (8.6)	48 (7.6)	47 (7.4)	51 (8.1)	201 (7.9)
Native Hawaiian or other Pacific islander	2 (0.3)	2 (0.3)	2 (0.3)	3 (0.5)	9 (0.4)
American Indian or Alaska native	58 (9.0)	56 (8.9)	58 (9.1)	59 (9.4)	231 (9.1)
Multiple	7 (1.1)	9 (1.4)	6 (0.9)	8 (1.3)	30 (1.2)
Ethnicity[a]					
Hispanic or Latino	310 (48.2)	308 (48.9)	297 (46.7)	299 (47.5)	1214 (47.8)
Not reported	52 (8.1)	46 (7.3)	53 (8.3)	51 (8.1)	202 (8.0)
HbA1c, %	5.6 (0.4)	5.6 (0.4)	5.6 (0.4)	5.6 (0.4)	5.6 (0.4)
eGFR, ml/min/1.73 m^2	98.1 (18.3)	97.6 (17.9)	98.3 (18.3)	98.2 (17.7)	98.1 (18.0)

Note: All variables are presented as mean (SD), unless otherwise mentioned.
Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; N, number of participants in total population; n, number of participants in treatment group; SBP, systolic blood pressure; SD, standard deviation; TZP, tirzepatide.
[a]Data are presented as n (%).

triglycerides and high-density lipoprotein cholesterol.[29] The T2D predicted risk scores were calculated at baseline, week 24 and week 72 as all the necessary model inputs were collected at these time points. Missing predictors were not imputed and risk scores for participants with missing predictors were missing from analyses.

2.3 | Statistical analysis

For the primary analysis, a mixed model for repeated measures (MMRM) was performed on the change from baseline T2D predicted risk scores, with model terms of treatment group, time point, treatment by time point interaction, country and baseline T2D predicted risk score. The least squares (LS) mean, mean change from baseline and differences in the mean change of risk scores between treatment groups were assessed. Subgroup analyses were conducted by baseline glycaemic status (participants with and without prediabetes) as defined by the American Diabetes Association Standards of Medical Care in Diabetes (fasting glucose, 100-125 mg/dl; 2 h glucose during oral glucose tolerance test, 140-199 mg/dl; glycated haemoglobin, 5.7%-6.4%; at least two abnormal tests were required to diagnose prediabetes)[27,33] and baseline BMI subgroups (<35; ≥35 to <40 and ≥40 kg/m^2). Interactions between treatment group and subgroups were assessed in an MMRM model similar to the primary analysis but with additional model terms of subgroup,

TABLE 2 Demographic and baseline clinical characteristics of SURMOUNT-1 participants with or without prediabetes

Variable	Prediabetes (n = 987)	Without prediabetes (n = 1552)	Total (N = 2539)
Age, years	48.1 (11.8)	42.8 (12.5)	44.9 (12.5)
Female[a]	632 (64.0)	1082 (69.7)	1714 (67.5)
BMI, kg/m^2	38.7 (7.1)	37.5 (6.6)	38.0 (6.8)
Waist circumference, cm	116.5 (15.6)	112.6 (14.7)	114.1 (15.2)
Race[a]			
White	726 (73.6)	1066 (68.7)	1792 (70.6)
Asian	99 (10.0)	177 (11.4)	276 (10.9)
Black or African American	75 (7.6)	126 (8.1)	201 (7.9)
Native Hawaiian or another Pacific islander	4 (0.4)	5 (0.3)	9 (0.4)
American Indian or Alaska native	71 (7.2)	160 (10.3)	231 (9.1)
Multiple	12 (1.2)	18 (1.2)	30 (1.2)
Ethnicity[a]			
Hispanic or Latino	466 (47.2)	748 (48.2)	1214 (47.8)
Not reported	71 (7.2)	131 (8.4)	202 (8.0)
Current smoker[a]	106 (10.7)	219 (14.1)	325 (12.8)
SBP, mmHg	125.5 (12.7)	121.9 (12.6)	123.3 (12.7)
DBP, mmHg	80.5 (8.2)	78.9 (8.1)	79.5 (8.2)
eGFR, ml/min/1.73 m^2	94.8 (18.0)	100.1 (17.7)	98.1 (18.0)
HbA1c, %	5.8 (0.4)	5.4 (0.3)	5.6 (0.4)
Fasting serum glucose, mg/dl	101.4 (9.5)	91.8 (8.4)	95.5 (10.1)
Serum triglycerides, mg/dl	153.2 (83.6)	140.5 (114.3)	145.4 (103.6)
Serum cholesterol, mg/dl	191.4 (38.4)	192.4 (39.2)	192.0 (38.9)
Serum HDL cholesterol, mg/dl	47.9 (12.2)	49.7 (13.6)	49.0 (13.1)
Serum LDL cholesterol, mg/dl	113.4 (33.0)	115.4 (32.7)	114.6 (32.8)

Note: All variables are presented as mean (SD), unless otherwise mentioned.
Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; N, number of participants in total population; n, number of participants in each subgroup; SBP, systolic blood pressure; SD, standard deviation.
[a]Data are presented as n (%).

treatment by subgroup, subgroup by time point, and treatment group by subgroup by time interactions. In addition, the following sensitivity analyses were performed to assess the robustness of the study methodology: (a) the T2D predicted risk scores were determined using BMI instead of waist circumference as a model input, and (b) the analyses were performed among White or Black/African American participants ≥45 years to reflect the population in which the CMDS risk engine was developed and validated. The subgroup and sensitivity analyses used similar MMRM models as the primary analysis.

Categorical variables (e.g. sex, race and ethnicity) were presented using frequencies and percentages; continuous variables (e.g. age, BMI and waist circumference) were described using means and SD. The *p*-values for differences in baseline characteristics between participants with and without prediabetes were computed using chi-squared test for categorical variables and analysis of variance for continuous variables. The two-sided significance level was set at .05. All analyses were conducted using SAS software version 9.4 (2016; SAS Institute Inc.).

3 | RESULTS

3.1 | Participant characteristics

The SURMOUNT-1 efficacy analysis set had 2539 participants (placebo, n = 643; 5 mg, n = 630; 10 mg, n = 636; 15 mg, n = 630). Table 1 summarizes the participants' demographic and baseline clinical characteristics: mean (SD) age: 44.9 (12.5) years; female: 67.5%; White: 70.6%. The majority of the population (95.5%) had BMI[27] ≥30 kg/m^2 and the mean (SD) BMI was 38.0 (6.8) kg/m^2. Overall, the mean (SD) SBP was 123.3 (12.7) mmHg, mean (SD) DBP was 79.5 (8.2) mmHg, mean (SD) fasting serum glucose was 95.5 (10.1) mg/dl and mean (SD) glycated haemoglobin was 5.6% (0.4). Mean age, sex and factors such as BMI, waist circumference, SBP, DBP, fasting serum glucose and triglycerides were significantly different between participants with (n = 987) and without prediabetes (n = 1552; Table 2).

TABLE 3 Descriptive statistics of cardiometabolic disease staging risk engine model inputs

Variables	Visit/time	Placebo (n = 643)	TZP 5 mg (n = 630)	TZP 10 mg (n = 636)	TZP 15 mg (n = 630)
Serum cholesterol, mg/dl	Baseline	191.4 (39.2)	191.2 (39.7)	194.3 (38.7)	191.1 (38.0)
	Week 24	188.6 (38.3)	175.6 (36.6)	177.7 (34.4)	170.9 (34.7)
	Week 72	188.2 (39.7)	181.5 (37.1)	182.1 (36.1)	177.1 (35.8)
Serum HDL cholesterol, mg/dl	Baseline	48.3 (13.0)	49.3 (13.3)	49.2 (13.0)	49.1 (12.8)
	Week 24	48.3 (12.4)	48.1 (11.8)	47.3 (10.8)	46.1 (10.6)
	Week 72	48.2 (13.4)	52.4 (13.7)	53.3 (13.4)	52.9 (13.6)
Serum LDL cholesterol combined,[a] mg/dl	Baseline	114.3 (33.8)	113.3 (31.9)	117.0 (32.9)	113.9 (32.6)
	Week 24	112.6 (32.8)	104.3 (31.0)	108.1 (30.4)	103.4 (29.7)
	Week 72	113.3 (34.7)	107.3 (31.5)	108.3 (31.9)	105.1 (30.1)
Serum triglycerides, mg/dl	Baseline	146.8 (82.0)	149.5 (149.4)	142.5 (86.2)	142.9 (81.3)
	Week 24	140.2 (75.9)	116.1 (63.4)	112.5 (48.8)	108.0 (54.8)
	Week 72	134.0 (66.1)	110.8 (89.1)	102.7 (51.5)	98.1 (63.8)
Fasting serum glucose, mg/dl	Baseline	95.7 (9.5)	95.4 (9.7)	95.5 (10.7)	95.3 (10.3)
	Week 24	95.1 (11.8)	87.5 (8.6)	86.2 (12.0)	85.1 (8.7)
	Week 72	96.3 (14.0)	87.8 (12.1)	85.8 (10.6)	84.7 (11.1)
SBP, mmHg	Baseline	122.9 (12.8)	123.6 (12.5)	123.8 (12.8)	123.0 (12.9)
	Week 24	121.6 (12.6)	115.5 (12.1)	115.1 (13.4)	114.5 (12.5)
	Week 72	121.9 (12.0)	116.0 (12.7)	114.9 (13.3)	115.3 (13.3)
DBP, mmHg	Baseline	79.6 (8.0)	79.3 (8.1)	79.9 (8.3)	79.3 (8.2)
	Week 24	78.7 (8.3)	74.9 (8.3)	75.6 (9.2)	75.4 (9.0)
	Week 72	78.4 (8.2)	74.0 (8.8)	74.0 (9.3)	74.7 (9.3)
BMI, kg/m^2	Baseline	38.2 (6.9)	37.4 (6.6)	38.2 (7.0)	38.1 (6.7)
	Week 24	37.1 (6.9)	33.1 (6.5)	32.9 (7.1)	32.5 (6.6)
	Week 72	36.9 (7.3)	31.2 (6.5)	30.0 (7.2)	29.5 (6.5)
Waist circumference, cm	Baseline	114.0 (14.9)	113.2 (14.3)	114.8 (15.8)	114.4 (15.6)
	Week 24	109.9 (14.9)	102.7 (14.5)	102.2 (16.1)	101.5 (15.4)
	Week 72	110.0 (16.1)	98.1 (15.8)	95.2 (17.3)	94.4 (15.9)

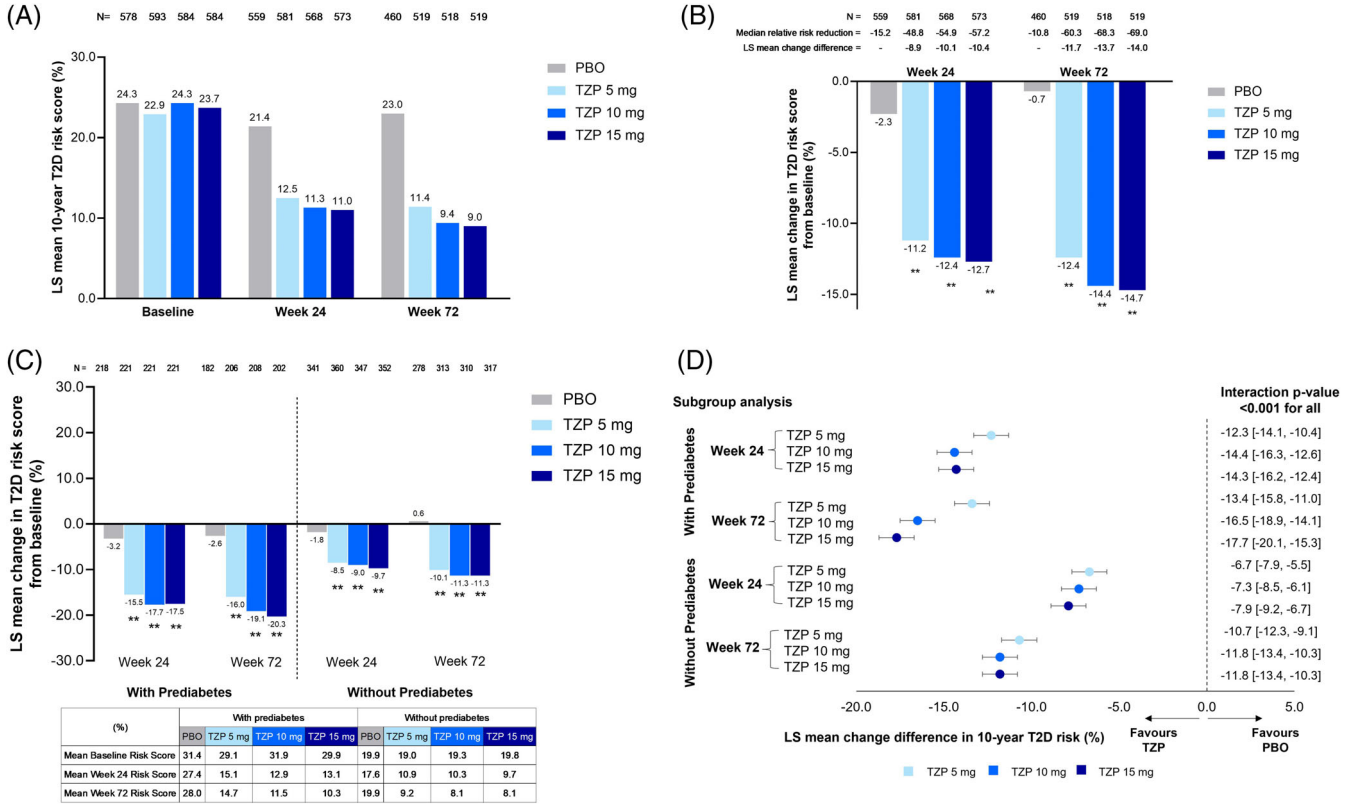
Note: All variables are presented as mean (SD).
Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; n, number of participants in the analysis population; SBP, systolic blood pressure; SD, standard deviation; TZP, tirzepatide.
[a]Represents both calculated and measured values.

Overall, the model inputs for the predictive risk factors used in the CMDS risk engine were comparable at baseline across treatment groups (Table 3).

3.2 | Mean 10-year predicted risk of type 2 diabetes

In total, 2339 participants with at least one post-baseline measurable T2D risk score at week 24 or week 72 were included in the primary analysis (5 mg, n = 593; 10 mg, n = 584; 15 mg; n = 584; placebo, n = 578). The mean 10-year T2D predicted risk scores at baseline did not differ between the placebo and tirzepatide treatment groups and ranged from 22.9% to 24.3% (Figure 1A). At week 24, the LS mean risk scores were: 5 mg, 12.5%; 10 mg, 11.3%; 15 mg; 11.0%; placebo, 21.4% (Figure 1A). The changes in the LS mean T2D predicted risk scores from baseline to week 24 were significantly greater in the tirzepatide treatment groups (5 mg, −11.2%; 10 mg, −12.4%; 15 mg, −12.7%) compared with placebo (−2.3%; Figure 1B). The median relative risk reductions ranged from 48.8% to 57.2% for the tirzepatide treatment groups versus 15.2% for the placebo group (Figure 1B). The difference in risk reduction between tirzepatide groups (5, 10 and 15 mg) and placebo was −8.9%, −10.1% and −10.4%, respectively ($p < .001$ for all).

At week 72, the LS mean risk scores were: 5 mg, 11.4%; 10 mg, 9.4%; 15 mg; 9.0%; placebo, 23.0% (Figure 1A). The changes in LS mean T2D predicted risk scores from baseline to week 72 were significantly greater in the tirzepatide treatment groups (5 mg, −12.4%; 10 mg, −14.4%; 15 mg, −14.7%) compared with the placebo group (−0.7%; Figure 1B). The median relative risk reductions at week 72 ranged from 60.3% to 69.0% for the tirzepatide treatment groups versus 10.8% for



(%)	With prediabetes				Without prediabetes			
	PBO	TZP 5 mg	TZP 10 mg	TZP 15 mg	PBO	TZP 5 mg	TZP 10 mg	TZP 15 mg
Mean Baseline Risk Score	31.4	29.1	31.9	29.9	19.9	19.0	19.3	19.8
Mean Week 24 Risk Score	27.4	15.1	12.9	13.1	17.6	10.9	10.3	9.7
Mean Week 72 Risk Score	28.0	14.7	11.5	10.3	19.9	9.2	8.1	8.1

FIGURE 1 Effect of TZP on 10-year predicted risk of T2D in participants with obesity or overweight. (A) LS mean T2D predicted risk scores at baseline, week 24 and week 72. (B) LS mean change in T2D predicted risk scores from baseline at weeks 24 and 72. (C) Change in LS mean T2D predicted risk scores from baseline at weeks 24 and 72 by glycaemic status. (D) T2D predicted risk reduction differences in TZP versus PBO group (with 95% CI) by glycaemic status. All comparisons of risk reductions from baseline between TZP dose groups and PBO were significant at $^{**}p < .001$. LS means are presented, unless otherwise noted. Change in 10-year predicted T2D risk from baseline to weeks 24 and 72 was derived from MMRM analysis using the SURMOUNT-1 efficacy analysis set, which included data from all randomized participants who had received at least one dose of the study intervention during the treatment period. Analyses excluded data after study drug discontinuation. Numbers of participants in each group are presented at the top of (A)-(C). Median relative risk reduction from baseline risk scores is presented at the top of (B). Only participants with at least one non-missing post-baseline value of the response variable were included in analysis. CI, confidence intervals; LS, least squares; MMRM, mixed model for repeated measures; N, number of participants in total population; PBO, placebo; T2D, type 2 diabetes; TZP, tirzepatide.

the placebo group (Figure 1B). The difference in risk reduction between tirzepatide dose groups (5, 10 and 15 mg) and placebo was −11.7%, −13.7% and −14.0%, respectively ($p < .001$ for all).

Results of sensitivity analyses 1 (using BMI instead of waist circumference as a model input) and 2 (among White or Black/African American participants ≥45 years) were consistent with the primary analyses (Figure S1). The mean T2D predicted risk scores and reductions in mean risk scores at weeks 24 and 72 were significantly different between tirzepatide treatment groups and placebo ($p < .001$ for all; Figure S1).

3.3 | Mean 10-year predicted risk of type 2 diabetes by glycaemic status and body mass index subgroup

The mean baseline 10-year T2D predicted risk scores of participants with or without prediabetes did not differ between the tirzepatide and placebo treatment groups, and the T2D predicted risk was higher for participants with prediabetes (range: 29.1%-31.9%) than for participants without prediabetes (range: 19.0%-19.9%; Figure 1C). Reductions in the LS mean T2D predicted risk scores from baseline were significantly greater in tirzepatide-treated participants with prediabetes (week 24, ranging from 15.5% to 17.7%; week 72, ranging from 16.0% to 20.3%) compared with those without prediabetes (week 24, ranging from 8.5% to 9.7%; week 72, ranging from 10.1% to 11.3%; Figure 1C). The risk reductions at weeks 24 and 72 for participants with and without prediabetes were significantly greater for the tirzepatide treatment groups than for the placebo group ($p < .001$ for all). The LS mean difference in risk reduction between tirzepatide-treated participants and placebo participants was greater for those with prediabetes (week 24: ranging from −12.3% to −14.4%; week 72: ranging from −13.4% to −17.7%) compared with those without prediabetes (week 24: ranging from −6.7% to −7.9%; week 72: ranging from −10.7% to −11.8%; Figure 1D). There was an interaction

between treatment and baseline glycaemic status at both weeks 24 and 72 (interaction $p < .001$).

The subgroup analysis of the 10-year T2D predicted risk scores by baseline BMI was consistent with the primary analysis. Participants with higher BMI (≥40 kg/m^2) had higher mean T2D predicted risk scores at baseline relative to the lower BMI subgroups (Figure S2A). The mean reductions from baseline in the T2D predicted risk scores at week 72 were significantly greater in the tirzepatide treatment groups compared with placebo across all BMI subgroups ($p < .001$ for all; Figure S2A,B). There was an interaction between treatment and higher baseline BMI subgroup at week 72 ($p < .001$) but not at week 24 ($p = .152$).

4 | DISCUSSION

This post hoc analysis of the SURMOUNT-1 trial showed that treatment with tirzepatide significantly reduced the 10-year predicted risk of developing T2D compared with placebo regardless of the participants' glycaemic status at baseline. Tirzepatide reduced the predicted relative risk of T2D by about half at week 24 and by about two-thirds at week 72. Notably, most of the reduction in predicted risk of T2D following tirzepatide treatment was achieved by week 24. The interaction between the treatment and higher baseline BMI at week 72 suggests that tirzepatide may lead to greater T2D risk reduction compared with placebo in patients with higher BMI.

Various factors such as waist circumference, SBP, DBP, lipid levels and glycaemic status are associated with the elevated risk of T2D in people with obesity or overweight.[7,8] In the SURMOUNT-1 population, tirzepatide treatment led to improvements in SBP, DBP and lipid levels, and significantly more participants with prediabetes in the tirzepatide treatment groups had achieved normal glycaemic levels compared with placebo.[27] In this study, 72 weeks of tirzepatide treatment resulted in a relative risk reduction of up to 69%, whereas a recent study, which used the same CMDS risk engine, reported that 68 weeks of semaglutide (2.4 mg) treatment reduced the 10-year predicted risk of T2D by 61%.[34] A potential explanation for this difference may be the greater weight reduction following tirzepatide treatment compared with semaglutide treatment.[35–37] It has been shown that the greater weight reduction is associated with a greater reduction in T2D risk.[17]

Regarding other risk factors for T2D, CMDS does not employ polygenic risk scores as these data are not readily available to clinicians and does not incorporate qualitative information requiring self-report such as family history of T2D and cigarette smoking. Suffice it to say that CMDS was designed to use quantitative data readily available to clinicians and is highly predictive of future T2D irrespective of the inclusion of other risk factors.

In this study, T2D risk reductions were greater in participants with prediabetes compared with those without prediabetes. Our findings align with previous reports of lower diabetes risk following weight reduction with lifestyle-based or pharmacological interventions among people with prediabetes.[18,35–38] A meta-analysis by Haw and colleagues showed that weight reduction interventions reduced the risk of diabetes in individuals at high risk by up to 39%.[39] Furthermore, Penn et al. found that interventions promoting weight reduction lowered the cumulative T2D incidence among people with impaired glucose tolerance by 57%, with 65% lower T2D incidence in those who achieved at least 5% weight reduction.[40] In addition, the time to diabetes onset was significantly longer following treatment with liraglutide (3 mg) among adults with obesity or overweight with prediabetes compared with placebo.[41] Sustained weight management through pharmacological interventions, therefore, may reduce the long-term risk of T2D and the resulting burden of disease on people with obesity or overweight.

To our knowledge, this is the first study to provide indirect evidence of reduction in the long-term predicted risk of T2D among people with obesity or overweight following tirzepatide treatment, with benefits seen as early as 6 months and persisting at 18 months. Results from the ongoing SURMOUNT-1 trial extension and the SURMOUNT-MMO trial, a Phase 3, randomized controlled trial assessing the effect of tirzepatide on the reduction of morbidity and mortality in adults with obesity (NCT05556512), will provide direct evidence of the impact of tirzepatide treatment on progression from prediabetes to T2D. If these data confirm our findings, the benefits of treatment with tirzepatide might extend beyond glycaemic control and weight management, leading to reduction in diabetes-related complications and mortality.

This study has several strengths. A validated model that incorporates multiple risk factors to quantitatively assess risk was used, thereby providing credible predictions of T2D risk. The CMDS risk engine was preferred to the Framingham model as it was developed and validated in a more generalizable population. The large size of the global SURMOUNT-1 sample further strengthens the generalizability of the study results. The results of the subgroup and sensitivity analyses were consistent with the primary analyses, thereby verifying the robustness of the findings.

The study also has certain limitations. First, as the CMDS risk engine calculates only the T2D predicted risk scores, the results of this modelling study should not be considered as confirmatory against hard outcomes. Second, the CMDS risk engine was developed and validated in populations that were different from the SURMOUNT-1 trial population. However, we accounted for this limitation by conducting a sensitivity analysis in White or Black/African American patients ≥45 years, which confirmed the findings of the primary analysis. Finally, the majority of the SURMOUNT-1 population was female, White and had a BMI ≥30 kg/m^2, and the results may not be reflective of the general population with obesity or overweight. Further research using randomized controlled trials in broader populations may help substantiate the results of this study.

5 | CONCLUSION

In summary, 24 weeks of tirzepatide treatment reduced the 10-year predicted risk of developing T2D in participants with obesity or

overweight, an effect that was sustained up to 72 weeks, regardless of glycaemic status. The significantly greater risk reduction in participants with prediabetes compared with those without was noteworthy. However, further research in a broader population is needed to substantiate the clinical significance of the study findings.

AUTHOR CONTRIBUTIONS

All named authors meet the International Committee of Medical Journal Editors criteria for authorship for this article, take responsibility for the integrity of the entire work and have given their approval for this version to be published. ERH, LMN, HK, AS, NNA and WTG contributed to study design and interpretation; FW contributed to data collection, statistical analysis and interpretation; and HW contributed to interpretation and statistical analysis. All authors were involved in the drafting, critical revision and approval of the final version of the manuscript.

ACKNOWLEDGMENTS

The authors thank the participants of the SURMOUNT-1 trial. Richa Kapoor and Era Seth, employees of Eli Lilly Services India Pvt. Ltd, provided medical writing and project management support for this manuscript. This study was sponsored by Eli Lilly and Company, Indianapolis, IN, USA.

CONFLICT OF INTEREST STATEMENT

ERH, LMN, HK, FW, NNA and AS are employees and shareholders of Eli Lilly and Company. HW is an employee of TechData Service Company, which is contracted by Eli Lilly and Company. WTG has served as a consultant on advisory boards for Boehringer Ingelheim, Eli Lilly and Company, Novo Nordisk, Pfizer, Fractyl Health, Alnylam Pharmaceuticals, Inogen and Merck, and as a site principal investigator for multicentred clinical trials sponsored by his university and funded by Novo Nordisk, Eli Lilly and Company, Epitomee, Neurovalens and Pfizer.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.15269.

DATA AVAILABILITY STATEMENT

Eli Lilly and Company provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request six months after the indication studied has been approved in the US and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, blank or annotated case report forms for the SURMOUNT-1 study (NCT04184622) will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at http://www.vivli.org.

ORCID

Emily R. Hankosky https://orcid.org/0000-0001-9934-584X
W. Timothy Garvey https://orcid.org/0000-0003-0822-0860

REFERENCES

1. Bray GA, Kim KK, Wilding JPH. Obesity: a chronic relapsing progressive disease process. A position statement of the world obesity federation. *Obes Rev*. 2017;18(7):715-723.
2. Stierman B, Afful J, Carroll M, et al. National health and nutrition examination survey 2017–March 2020 prepandemic data files—development of files and prevalence estimates for selected health outcomes. National Health Statistics Reports; NHSR No. 158. 2021.
3. Ward ZJ, Bleich SN, Cradock AL, et al. Projected U.S. state-level prevalence of adult obesity and severe obesity. *N Engl J Med*. 2019;381(25):2440-2450.
4. World Health Organization. Obesity and overweight. 2021 https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight Accessed 26 April 2023.
5. CDC. Consequences of obesity. 2022 https://www.cdc.gov/obesity/basics/consequences.html Accessed 20 April 2023.
6. Cameron NA, Petito LC, McCabe M, et al. Quantifying the sex-race/ethnicity-specific burden of obesity on incident diabetes mellitus in the United States, 2001 to 2016: MESA and NHANES. *J Am Heart Assoc*. 2021;10(4):e018799.
7. Tabák AG, Herder C, Rathmann W, Brunner EJ, Kivimäki M. Prediabetes: a high-risk state for diabetes development. *Lancet*. 2012;379(9833):2279-2290.
8. Jayedi A, Soltani S, Motlagh SZ, et al. Anthropometric and adiposity indicators and risk of type 2 diabetes: systematic review and dose-response meta-analysis of cohort studies. *BMJ*. 2022;376:e067516.
9. Garvey WT, Mechanick JI, Brett EM, et al. American Association of Clinical Endocrinologists and American College of Endocrinology Comprehensive Clinical Practice guidelines for medical care of patients with obesity. *Endocr Pract*. 2016;22(Suppl 3):1-203.
10. Lingvay I, Sumithran P, Cohen RV, le Roux CW. Obesity management as a primary treatment goal for type 2 diabetes: time to reframe the conversation. *Lancet*. 2022;399(10322):394-405.
11. Ryan DH, Yockey SR. Weight loss and improvement in comorbidity: differences at 5%, 10%, 15%, and over. *Curr Obes Rep*. 2017;6(2):187-194.
12. Jensen MD, Ryan DH, Apovian CM, et al. AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association task force on practice guidelines and the Obesity Society. *J Am Coll Cardiol*. 2014;63(25 Pt B):2985-3023.
13. Wharton S, Lau DCW, Vallis M, et al. Obesity in adults: a clinical practice guideline. *CMAJ*. 2020;192(31):E875-E891.
14. Yumuk V, Tsigos C, Fried M, et al. European guidelines for obesity management in adults. *Obes Facts*. 2015;8(6):402-424.
15. Magkos F, Fraterrigo G, Yoshino J, et al. Effects of moderate and subsequent progressive weight loss on metabolic function and adipose tissue biology in humans with obesity. *Cell Metab*. 2016;23(4):591-601.
16. Williamson DA, Bray GA, Ryan DH. Is 5% weight loss a satisfactory criterion to define clinically significant weight loss? *Obesity (Silver Spring)*. 2015;23(12):2319-2320.
17. Hamman RF, Wing RR, Edelstein SL, et al. Effect of weight loss with lifestyle intervention on risk of diabetes. *Diabetes Care*. 2006;29(9):2102-2107.

18. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;346(6):393-403.
19. Zhang F, Tong Y, Su N, et al. Weight loss effect of glucagon-like peptide-1 mimetics on obese/overweight adults without diabetes: a systematic review and meta-analysis of randomized controlled trials. *J Diabetes*. 2015;7(3):329-339.
20. Iqbal J, Wu HX, Hu N, et al. Effect of glucagon-like peptide-1 receptor agonists on body weight in adults with obesity without diabetes mellitus-a systematic review and meta-analysis of randomized control trials. *Obes Rev*. 2022;23(6):e13435.
21. Huthmacher JA, Meier JJ, Nauck MA. Efficacy and safety of short- and long-acting glucagon-like peptide 1 receptor agonists on a background of basal insulin in type 2 diabetes: a meta-analysis. *Diabetes Care*. 2020;43(9):2303-2312.
22. Yeh TL, Tsai MC, Tsai WH, Tu YK, Chien KL. Effect of glucagon-like peptide-1 receptor agonists on glycemic control, and weight reduction in adults: a multivariate meta-analysis. *PloS One*. 2023;18(1):e0278685.
23. Tan HC, Dampil OA, Marquez MM. Efficacy and safety of semaglutide for weight loss in obesity without diabetes: a systematic review and meta-analysis. *J ASEAN Fed Endocr Soc*. 2022;37(2):65-72.
24. Lazzaroni E, Ben Nasr M, Loretelli C, et al. Anti-diabetic drugs and weight loss in patients with type 2 diabetes. *Pharmacol Res*. 2021;171:105782.
25. MOUNJARO (tirzepatide) injection, US prescribing information. 2022; https://pi.lilly.com/us/mounjaro-uspi.pdf?s=pi. Accessed 9 May 2023.
26. Garvey WT, Frias JP, Jastreboff AM, et al. Tirzepatide once weekly for the treatment of obesity in people with type 2 diabetes (SURMOUNT-2): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet*. 2023;402(10402):613-626.
27. Jastreboff AM, Aronne LJ, Ahmad NN, et al. Tirzepatide once weekly for the treatment of obesity. *N Engl J Med*. 2022;387(3):205-216.
28. Alkhezi OS, Alahmed AA, Alfayez OM, Alzuman OA, Almutairi AR, Almohammed OA. Comparative effectiveness of glucagon-like peptide-1 receptor agonists for the management of obesity in adults without diabetes: a network meta-analysis of randomized clinical trials. *Obes Rev*. 2023;24(3):e13543.
29. Wilkinson L, Yi N, Mehta T, Judd S, Garvey WT. Development and validation of a model for predicting incident type 2 diabetes using quantitative clinical data and a Bayesian logistic model: a nationwide cohort and modeling study. *PLoS Med*. 2020;17(8):e1003232.
30. Guo F, Moellering DR, Garvey WT. The progression of cardiometabolic disease: validation of a new cardiometabolic disease staging system applicable to obesity. *Obesity (Silver Spring)*. 2014;22(1):110-118.
31. Howard VJ, Cushman M, Pulley L, et al. The reasons for geographic and racial differences in stroke study: objectives and design. *Neuroepidemiology*. 2005;25(3):135-143.
32. Schmidt MI, Duncan BB, Bang H, et al. Identifying individuals at high risk for diabetes: the atherosclerosis risk in communities study. *Diabetes Care*. 2005;28(8):2013-2018.
33. ADA. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes-2019. *Diabetes Care*. 2019;42(Suppl 1):S13-S28.
34. Garvey WT, Holst-Hansen T, Laursen PN, Rinnov AR, Wilkinson LJ. 2-LB: Semaglutide 2.4 mg reduces the 10-year T2D risk in people with overweight/obesity. *Diabetes*. 2022;71(Suppl_1):2-LB.
35. Lindström J, Louheranta A, Mannelin M, et al. The Finnish diabetes prevention study (DPS): lifestyle intervention and 3-year results on diet and physical activity. *Diabetes Care*. 2003;26(12):3230-3236.
36. LeBlanc ES, Patnode CD, Webber EM, Redmond N, Rushkin M, O'Connor EA. Behavioral and pharmacotherapy weight loss interventions to prevent obesity-related morbidity and mortality in adults: updated evidence report and systematic review for the US preventive services task force. *Jama*. 2018;320(11):1172-1191.
37. Torgerson JS, Hauptman J, Boldrin MN, Sjöström L. XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. *Diabetes Care*. 2004;27(1):155-161.
38. Garvey WT, Ryan DH, Henry R, et al. Prevention of type 2 diabetes in subjects with prediabetes and metabolic syndrome treated with phentermine and topiramate extended release. *Diabetes Care*. 2014;37(4):912-921.
39. Haw JS, Galaviz KI, Straus AN, et al. Long-term sustainability of diabetes prevention approaches: a systematic review and meta-analysis of randomized clinical trials. *JAMA Intern Med*. 2017;177(12):1808-1817.
40. Penn L, White M, Lindström J, et al. Importance of weight loss maintenance and risk prediction in the prevention of type 2 diabetes: analysis of European diabetes prevention study RCT. *PloS One*. 2013;8(2):e57143.
41. le Roux CW, Astrup A, Fujioka K, et al. 3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial. *Lancet*. 2017;389(10077):1399-1409.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Hankosky ER, Wang H, Neff LM, et al. Tirzepatide reduces the predicted risk of developing type 2 diabetes in people with obesity or overweight: Post hoc analysis of the SURMOUNT-1 trial. *Diabetes Obes Metab*. 2023;25(12):3748-3756. doi:10.1111/dom.15269