Received: 14 January 2025 | Revised: 30 April 2025 | Accepted: 2 May 2025

DOI: 10.1111/dom.16463

ORIGINAL ARTICLE

WILEY

Tirzepatide and health-related quality of life in adults with obesity or overweight: Results from the SURMOUNT-3 phase 3 randomized trial

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Funding information
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Abstract

Aims: Tirzepatide reduced weight significantly more than placebo in adults with obesity/overweight who had already achieved ≥5% weight reduction with a 12-week intensive lifestyle intervention (randomized population) in SURMOUNT-3, a phase 3, 72-week, randomized, double-blind clinical trial. This analysis evaluated health-related quality of life (HRQoL) with tirzepatide versus placebo treatment in the SURMOUNT-3 randomized population and selected subgroups.

Materials and Methods: The randomized population received placebo ($N = 292$) or tirzepatide maximum tolerated dose ($N = 287$) for 72 weeks. HRQoL was assessed from randomization to week 72 using the Short Form-36 Version 2 Health Survey acute form, Impact of Weight on Quality of Life-Lite Clinical Trials Version, 5-level EQ-5D version Health State Index, EQ visual analogue scale and the Patient Global Impression of Status (PGIS) for Physical Activity. In tirzepatide recipients, changes in HRQoL scores from randomization to week 72 were descriptively summarized by achievement of weight reduction thresholds, and for those with versus without physical function limitations at randomization (identified with PGIS for Physical Activity).

Results: Tirzepatide was associated with significantly larger improvements than placebo in most HRQoL measures from randomization to 72 weeks. Improvements in tirzepatide recipients were generally numerically larger in those who met greater weight reduction thresholds. HRQoL score changes showed greater improvements for adults with versus without physical function limitations for all measures.

Conclusions: Tirzepatide improved HRQoL in adults with obesity/overweight and was generally associated with larger improvements in adults meeting greater weight reduction thresholds and in adults with versus without reported physical function limitations at randomization.

Plain Language Summary

What is the context and purpose of this research study?

In a clinical trial called SURMOUNT-3, tirzepatide was significantly better than placebo for reducing weight in adults with obesity/overweight who had already lost ≥5% weight following a 12-week intensive lifestyle programme. This analysis looked at the effects of tirzepatide compared with placebo for 72 weeks on quality of life (QoL) in SURMOUNT-3. In addition, among tirzepatide recipients, the relationship between meeting different weight reduction thresholds and changes in QoL was described as was the association of tirzepatide with QoL in study participants who had physical limitations at randomization.

What was done?

Eligible adults with obesity/overweight were enrolled in a 12-week intensive lifestyle programme. Those who lost ≥5% of initial weight at the end of the 12 weeks were invited to continue participating in the study and were randomly assigned to receive injections of either their maximum tolerated dose of tirzepatide (10 or 15 mg) or placebo for 72 weeks via single-dose pens. QoL was measured using a number of well-established surveys that assessed general health, the impact of weight on QoL and the impact of health on the level of physical ability in day-to-day life. These surveys were completed by the study participants when they were first assigned treatment with tirzepatide or placebo (randomization) and again after 72 weeks of treatment. The difference in scores from randomization to week 72 was then calculated to determine whether or not the QoL of participants had improved with treatment. In addition, in participants who took tirzepatide, changes in QoL scores from randomization to week 72 were summarized by weight reduction thresholds (≥5%, ≥10%, ≥15%, ≥20%, ≥25%), and for those with versus without physical limitations at randomization.

What were the main results?

Adults with obesity/overweight who had already lost ≥5% weight with a 12-week intensive lifestyle programme who then took tirzepatide for 72 weeks not only had significantly more weight loss compared with those taking placebo, but they also had significantly improved QoL. These improvements in QoL were generally larger with greater weight loss and in adults who reported physical limitations at randomization compared to those who reported no such limitations. The improvements in QoL were observed in physical function as well as in general mental health and weight-related psychological and social functions.

What is the originality and relevance of this study?

Findings of this study show that in addition to reducing weight in people who have already lost ≥5% weight after lifestyle interventions, tirzepatide improved QoL. This is important because other studies have shown that people with obesity have reduced QoL. Tirzepatide was generally associated with improved QoL the most in adults who had greater weight loss and in adults who reported physical limitations at randomization.

KEYWORDS

obesity, overweight, phase 3, quality of life, tirzepatide, weight reduction

1 | INTRODUCTION

The adverse effects of obesity on health are well known to healthcare professionals and people who live with this chronic disease.[1–6] This includes negative effects of obesity on general physical and mental health-related quality of life (HRQoL) as well as HRQoL specifically related to weight.[7–9]

Lifestyle interventions, such as behavioural counselling, dietary modifications and increased physical activity, are recommended in the management of obesity.[4,10–13] Such interventions can induce mean

reductions of 5%–8% of baseline weight with accompanying improvements in health. This includes reduced risk of developing type 2 diabetes,[6] improved cardiometabolic risk factors and other obesity-related complications[10,11,14–16] and decreased cardiovascular mortality.[17–19] Some, but not all, studies of lifestyle interventions have demonstrated improvements in general and weight-related HRQoL.[20,21] However, improvements are often seen for only some components of HRQoL, with benefits being most consistent for physical HRQoL and more variable for mental HRQoL. Heterogeneity in study findings may be due in part to the commonly seen relationship between weight loss and improvements in quality of life, such that greater weight loss is associated with greater quality of life improvement.[22] In addition, one aspect of lifestyle-based weight reduction is regular physical activity (≥150 min per week).[10] Individuals with physical limitations may find it difficult to engage in high levels of physical activity and thus may experience fewer benefits.

Interventions that can improve physical and mental HRQoL among individuals with obesity are urgently needed. Tirzepatide is a first-in-class, once-weekly single molecule that activates the glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptors.[23] It is approved in many countries, including the United States, as an adjunct to diet and physical activity for the treatment of adults with type 2 diabetes, for chronic weight management in adults with obesity (initial body mass index [BMI] ≥30 kg/m^2), or overweight (BMI ≥ 27 kg/m^2) in the presence of at least one weight-related comorbid condition, and for moderate to severe obstructive sleep apnoea in adults with obesity.[24–26] In the double-blind, randomized, placebo-controlled SURMOUNT-3 trial, adults with obesity or overweight with at least one obesity-related complication (excluding diabetes) achieved substantial weight loss of approximately 18%, with 87.5% achieving ≥5% weight reduction after 72 weeks of treatment with tirzepatide.[27] These participants had already achieved ≥5% weight reduction after a 12-week intensive lifestyle intervention before losing the additional weight while on tirzepatide.

We evaluated the effects of tirzepatide on a number of patient-reported HRQoL outcomes after 72 weeks of tirzepatide treatment in adults enrolled in SURMOUNT-3. In addition, we assessed, in post-hoc analyses, the association between achievement of weight reduction thresholds with tirzepatide and change in patient-reported outcomes (PROs) and changes in HRQoL among SURMOUNT-3 tirzepatide-treated participants who reported physical function limitations at randomization.

2 | MATERIALS AND METHODS

The design and methodology of SURMOUNT-3 have already been published in full,[27] and are reproduced in the Supplementary material. In brief, SURMOUNT-3 was an 84-week, multicentre, randomized, parallel-arm, double-blind, placebo-controlled trial conducted at 62 medical research centres in the United States, Argentina and Brazil. The study consisted of four periods: a 2-week screening period; a 12-week lead-in period during which participants received intensive lifestyle intervention to achieve ≥5% body weight reduction; a 72-week double-blind, placebo-controlled treatment period (including a 20-week dose escalation period); and a 4-week safety follow-up period.

Eligible participants were enrolled in a 12-week intensive lifestyle intervention lead-in period, including eight lifestyle counselling sessions, behaviour modification strategies, dietary recommendations (which could include up to two meal replacements per day) and encouragement to engage in at least 150 min of moderate-intensity physical activity per week. They were asked to complete 3-day diet and exercise logs before each counselling visit. Participants who achieved ≥5% weight reduction at the end of the 12-week lead-in period were randomly assigned in a 1:1 ratio to receive either their maximum tolerated dose (MTD) of tirzepatide (10 or 15 mg) or placebo for 72 weeks via single-dose pens. Assignment to treatment group was determined by a computer-generated random sequence using a validated interactive web-response system. All participants, investigators, and the sponsor were masked to treatment assignment, and the single-dose pens were identical between active product and placebo. Randomization was stratified according to country, sex (female, male) and percentage weight reduction at the end of the lead-in period (<10% vs. ≥10%).

Tirzepatide and matched placebo were administered once weekly as a subcutaneous injection. The starting dose of tirzepatide was 2.5 mg, increasing by 2.5 mg every 4 weeks until an MTD dose of 10 or 15 mg was reached. To optimize tolerability and adherence, gastrointestinal symptoms could be managed by dietary counselling, symptomatic medications according to the investigator's discretion or skipping a single dose of treatment. Participants continued to consult with a dietitian or other qualified healthcare professional throughout the post-randomization period. Lifestyle counselling sessions occurred every 12 weeks and focused on consumption of a healthy balanced diet, with a 500 kcal per day deficit and continuation of physical activity. Use of the diet and exercise log was encouraged. In between counselling sessions, diet and exercise goals were reinforced by site staff at every monthly visit.

This study is registered with ClinicalTrials.gov (NCT04657016). The protocol was approved by local institutional review boards and the trial complied with the International Conference on Harmonization Good Clinical Practice guidelines and the Declaration of Helsinki. All participants provided written informed consent.

2.1 | Participants

Participants eligible to enter the screening period were ≥18 years of age and had obesity (BMI ≥ 30 kg/m^2), or overweight (BMI ≥ 27 kg/m^2) with at least one obesity-related complication, and a history of at least one self-reported unsuccessful dietary effort to lose body weight. Female enrolment was capped at 70% to ensure adequate representation of the male population.

People with type 1 or 2 diabetes mellitus or at least one laboratory value suggestive of diabetes mellitus during screening, or other medical conditions that could affect weight loss outcomes, were excluded from study entry, as were those with a self-reported change in body weight >5 kg within 3 months before screening. People with a history of substantial active or unstable major depressive disorder or

other severe psychiatric disorder within the past 2 years were also excluded.

2.2 | Study outcomes

Results of the primary, secondary and safety findings from the SURMOUNT-3 trial have been reported.[28] The coprimary endpoints of the SURMOUNT-3 trial were percentage change in body weight and the proportion of study participants who achieved ≥5% weight reduction from randomization to week 72. Key secondary endpoints, controlled for type 1 error rate, included the proportion of study participants who achieved ≥10%, ≥15% or ≥20% weight reduction from randomization to week 72. The proportion of study participants who achieved ≥25% reduction in body weight was a prespecified exploratory endpoint. Key secondary endpoints also included the proportion of participants who, at week 72, maintained ≥80% of the body weight loss achieved during the 12-week lead-in period, as well as change in waist circumference (cm) from randomization to week 72.

The present work reported on additional endpoints which included the PROs, Short Form-36 Version 2 Health Survey acute form (SF-36v2), Impact of Weight on Quality of Life-Lite-Clinical Trials Version (IWQOL-Lite-CT), 5-level EQ-5D version (EQ-5D-5L) Health State Index (UK) and associated EQ visual analogue scale (VAS), and the Patient Global Impression of Status (PGIS) for Physical Activity. These PROs were completed at randomization and 72 weeks or early discontinuation.

The SF-36v2 is a 36-item tool with eight individually scored domains (Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional and Mental Health) that contribute to two component summary scores, the Physical Component Summary (PCS) and Mental Component Summary (MCS).[28] Items are answered using a Likert scale of varying lengths (3-, 5- or 6-point scales) and the domain and component summary scores are norm-based to the United States general population with a mean of 50 and standard deviation (SD) of 10, with higher scores indicating better function and HRQoL. The SF-36v2 Physical Functioning domain score was a secondary endpoint, and other SF-36v2 scores were exploratory endpoints of the study.

The IWQOL-Lite-CT is a 20-item PRO instrument for use in populations typically targeted for weight loss clinical trials.[29] It assesses two primary domains of obesity-related HRQoL: the Physical composite (7 items) and the Psychosocial composite (13 items), with an additional 5-item subset of the Physical composite, the Physical Function composite. Items are rated on a 5-point frequency ('never' to 'always') or a 5-point truth ('not at all true' to 'completely true') scale. The overall score range is from 0 to 100 with higher scores associated with better HRQoL. The IWQOL-Lite-CT Physical Function composite score was a secondary endpoint, and other IWQOL-Lite-CT scores were exploratory endpoints of the study.

The EQ-5D-5L is a standardized generic 5-dimension HRQoL instrument that includes mobility, self-care, usual activities, pain/discomfort and anxiety/depression.[30] Each dimension is scored on a 5-point scale ('no problems' to 'unable to perform/extreme problems') for a total of 3125 possible health states, with reductions in scores indicating improvement. A single Health State Index can be derived that is based on weighted scores for each dimension. This Health State Index ranges between <0 (where 0 is a health state equivalent to death; negative values are considered worse than dead) to 1 (perfect health). In addition, a VAS records the respondent's self-rated health status on a vertical graduated (0 to 100) scale. Higher Health State Index and VAS scores reflected better levels of functioning and health. EQ-5D-5L scores were exploratory endpoints.

The PGIS for Physical Activity was specifically developed for this study and is a participant-rated assessment of current limitation on physical activity due to health. It is rated using a 5-point scale (1—'not at all limited' to 5—'extremely limited'). Lower scores indicate better physical activity. The PGIS for Physical Activity was an exploratory endpoint.

2.3 | Statistical analysis

For SF-36v2, IWQOL-Lite-CT and EQ-5D-5L scores, least squares mean (LSM) difference in change from randomization to week 72 for tirzepatide versus placebo was calculated using analysis of covariance with the last observation before discontinuation carried forward. Variables included in the model were randomization score, country, sex, lead-in period weight loss (<10%, ≥10%) and treatment (Type III sum of squares). The proportions of participants in each PGIS for Physical Activity response group at randomization and week 72 were reported descriptively. The proportion of participants achieving meaningful within-patient change (MWPC) in the SF-36v2 physical functioning domain score (norm-based; change from randomization ≥5.76) from randomization to week 72 was also assessed. The shift in PGIS for Physical Activity response group from randomization to week 72 (excluding off-treatment data) was also tabulated for participants receiving tirzepatide and placebo. Statistical analyses were carried out using SAS v.9.4, unless otherwise specified.

2.3.1 | Post-hoc analyses

Two sets of post-hoc analyses were performed:

1. Mean changes in SF-36v2 norm-based, IWQOL-Lite-CT and EQ-5D-5L scores from randomization to week 72 by weight reduction thresholds (≥5%, ≥10%, ≥15%, ≥20%, ≥25%) were descriptively summarized for adults who received tirzepatide.
2. Participants with physical function limitations at randomization were identified using the PGIS for Physical Activity. Participants were considered to have limitations if the PGIS for Physical Activity was rated 'moderately', 'very much', or 'extremely' impaired; participants were considered to have no limitations if their rating was 'not at all' or 'a little' impaired. Mean SF-36v2 norm-based,

IWQOL-Lite-CT and EQ-5D-5L scores at randomization and mean (SD) score changes from randomization to week 72 were summarized descriptively for participants receiving tirzepatide with versus without physical function limitations at randomization.

3 | RESULTS

Of 806 adults with obesity/overweight enrolled in SURMOUNT-3 between 12 April 2021 and 3 September 2021 (the study was completed 12 May 2023), 579 achieved ≥5% weight reduction with 12 weeks of intensive lifestyle intervention and were randomized to placebo ($N = 292$) or tirzepatide (10 or 15 mg, $N = 287$) for 72 weeks (Supplementary Figure 1). Mean weight loss during the lead period was 6.9%.

Overall, 86.0% of the 579 randomized participants were white, 53.9% were Hispanic or Latino and 62.9% were female, with an overall mean (SD) age of 45.6 (12.2) years. Participants were enrolled in three countries: Argentina (15.0%), Brazil (20.6%) or the United States (64.4%). The mean (SD) duration of obesity was 15.1 (11.2) years, and 66.1% had a medical history of one or more obesity-related complications, most commonly hypertension (34.4%), dyslipidaemia (26.3%) and anxiety/depression (20.0%). At randomization, 12.1% of participants had a BMI of ≥27 to <30 kg/m^2, 35.8% had a BMI of ≥30 to <35 kg/m^2, 30.1% had a BMI of ≥35 to <40 kg/m^2 and 19.2% had a BMI of ≥40 kg/m^2; the remaining 2.9% had a BMI of <27 kg/m^2. Patient demographics and clinical characteristics at randomization (week 0) were similar across the tirzepatide and placebo groups, as were weight reductions and cardiometabolic changes during the lead-in period.[27]

The primary and key secondary efficacy and safety endpoints of SURMOUNT-3 have already been published.[27] Briefly, the coprimary endpoints of mean percent weight change from randomization to week 72 and the percent of participants achieving weight reduction ≥5% additional to that achieved during the lifestyle modification phase were met. The mean percent weight change from randomization to week 72 was −18.4% with tirzepatide and 2.5% with placebo (estimated treatment difference − 20.8 percentage points [95% confidence interval [CI] −23.2%, −18.5%; $p < 0.001$]) and 87.5% of participants treated with tirzepatide and 16.5% of those who received placebo achieved weight loss ≥5% (odds ratio 34.6%; 95% CI 19.2%, 62.6%; $p < 0.001$). The most common adverse events with tirzepatide were gastrointestinal, with most being mild to moderate in severity.

3.1 | HRQoL outcomes for tirzepatide versus placebo

At week 72, significantly greater improvements from randomization in the SF-36v2 Physical Component Score as well as scores for the domains Physical Functioning, Role-Physical, Bodily Pain, Vitality, Social Functioning, Role-emotional, Mental Health and General Health were observed with tirzepatide compared to placebo ($p < 0.05$) (Table 1). The proportion of participants achieving a MWPC (≥5.76) in SF-36v2 Physical Functioning from randomization to week 72 was higher with tirzepatide than with placebo (29.4% vs. 14.8%). The change from randomization to week 72 in SF-36v2 Mental Component Summary scores was comparable between tirzepatide and placebo.

TABLE 1 Least squares mean change in SF-36v2 domain and component scores from randomization to week 72 (LOCF) in adults with obesity/overweight treated with tirzepatide MTD or placebo after an intensive–lifestyle intervention.

	Tirzepatide MTD ($n = 231$)		Placebo ($n = 209$)		
SF-36v2 score	LSM (SE) score at randomization	LSM (SE) score at week 72	LSM (SE) score at randomization	LSM (SE) score at week 72	LSM change difference (95% CI)
Mental component score	53.9 (0.4)	53.8 (0.5)	54.0 (0.5)	52.8 (0.5)	0.9 (−0.4, 2.3); $p = 0.182$
Physical component score	52.7 (0.4)	55.8 (0.4)	52.7 (0.5)	51.8 (0.4)	4.0 (2.8, 5.1); $p < 0.001$
Domain scores					
Physical functioning (norm-based)	51.8 (0.4)	55.0 (0.4)	51.6 (0.5)	51.1 (0.4)	3.8 (2.8, 4.9); $p < 0.001$
Role-physical (norm-based)	53.1 (0.4)	54.8 (0.4)	52.8 (0.5)	52.3 (0.4)	2.5 (1.4, 3.6); $p < 0.001$
Bodily pain (norm-based)	52.7 (0.5)	54.9 (0.5)	52.6 (0.6)	51.5 (0.5)	3.3 (1.9, 4.8); $p < 0.001$
General health (norm-based)	54.3 (0.5)	56.9 (0.4)	54.8 (0.5)	52.8 (0.5)	4.1 (2.8, 5.3); $p < 0.001$
Vitality (norm-based)	56.2 (0.5)	57.5 (0.5)	56.2 (0.5)	55.1 (0.5)	2.4 (1.0, 3.8); $p < 0.001$
Social functioning (norm-based)	53.3 (0.4)	54.1 (0.4)	53.4 (0.4)	52.5 (0.4)	1.6 (0.5, 2.7); $p = 0.005$
Role-emotional (norm-based)	51.7 (0.5)	52.5 (0.5)	51.4 (0.5)	50.6 (0.5)	1.9 (0.5, 3.3); $p = 0.008$
Mental health (norm-based)	54.1 (0.5)	54.4 (0.5)	54.2 (0.5)	53.0 (0.5)	1.5 (0.1, 2.8); $p = 0.036$

Abbreviations: CI, confidence interval; LOCF, last observation carried forward; LSM, least squares mean; MTD, maximum tolerated dose (10 or 15 mg); SE, standard error; SF-36 v2, Short Form-36 Version 2 Health Survey acute form.

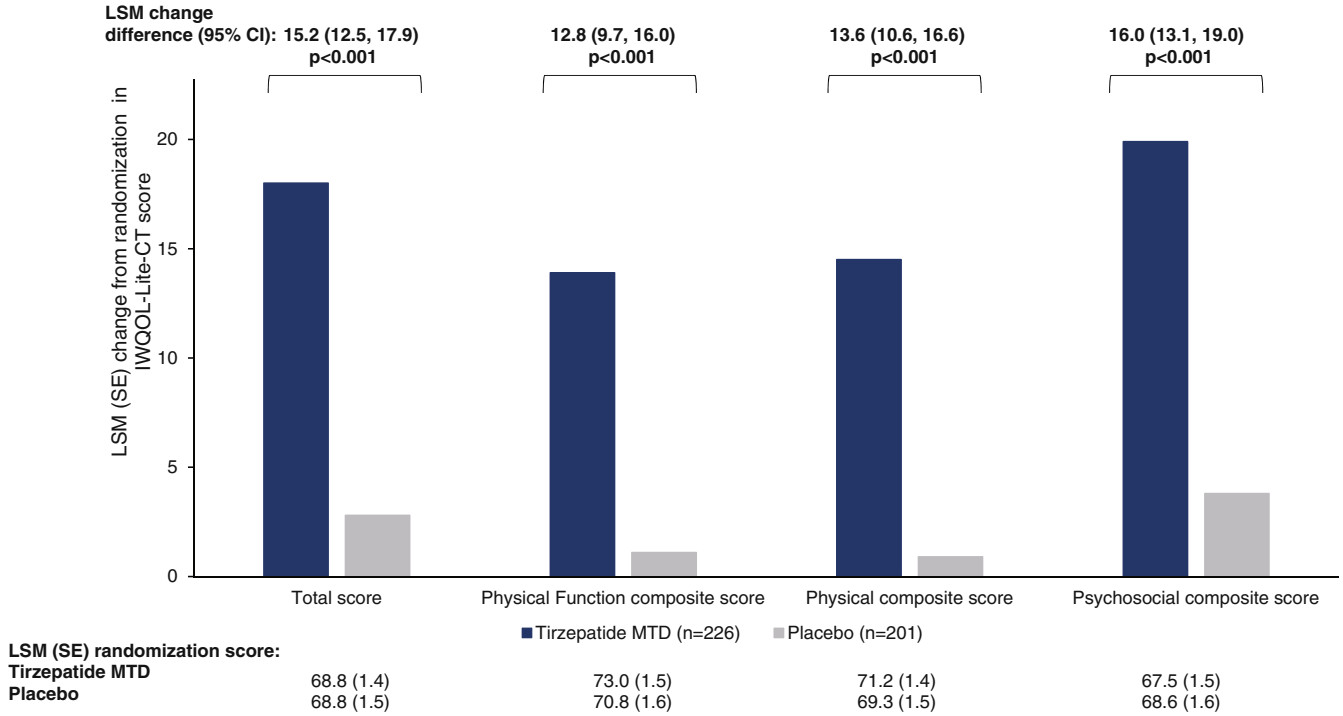


FIGURE 1 Least squares mean change in IWQOL-Lite-CT scores from randomization to week 72 (LOCF) in adults with obesity/overweight treated with tirzepatide MTD or placebo. Only subjects with non-missing randomization values and at least one non-missing post-randomization value of the response variable were included in the analysis. CI, confidence interval; IWQOL-Lite-CT, Impact of Weight on Quality of Life-Lite-Clinical Trials version; LOCF, last observation carried forward; LSM, least squares mean; MTD, maximum tolerated dose (10 or 15 mg); SE, standard error.

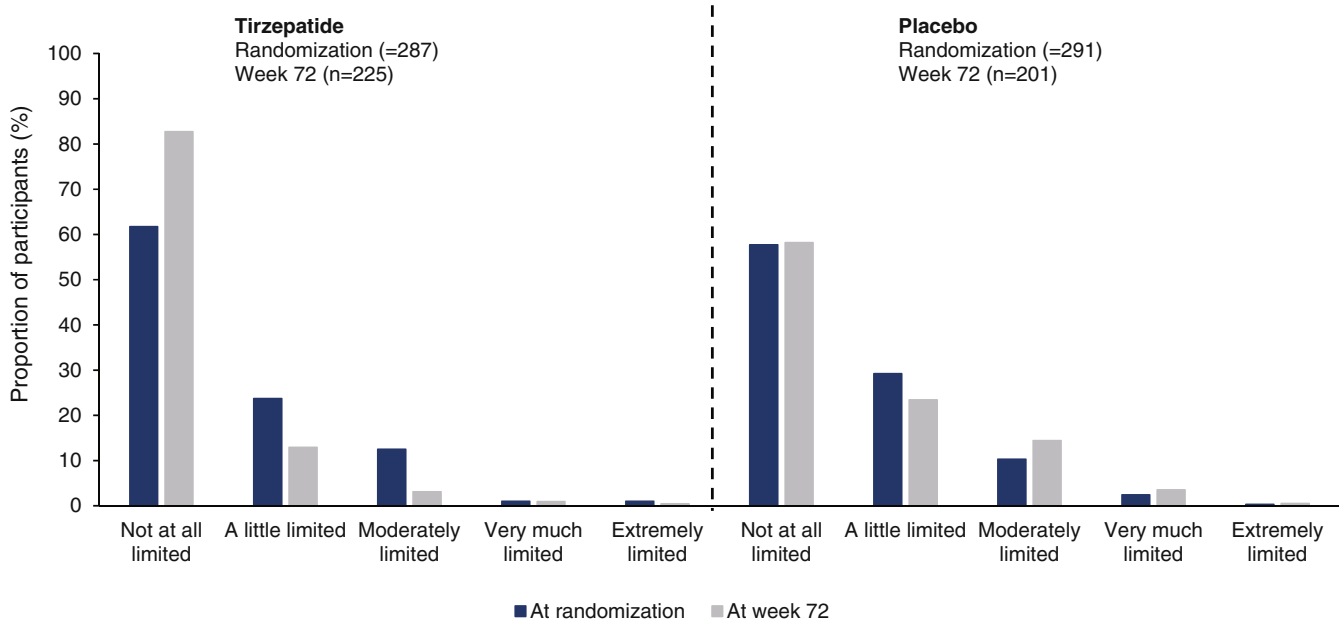


FIGURE 2 Proportions of adults with obesity/overweight treated with tirzepatide MTD or placebo in each PGIS for Physical Activity response group at randomization and week 72 (LOCF). LOCF, last observation carried forward; MTD, maximum tolerated dose (10 or 15 mg); PGIS, Patient Global Impression of Status.

LSM change differences from randomization to week 72 in IWQOL-Lite-CT total, Physical Function composite, Physical composite and Psychosocial composite scores for participants treated with tirzepatide were significantly better than those for participants who received placebo (Figure 1; all $p < 0.001$).

EQ-5D-5L Health State Index (UK) and EQ-VAS scores improved significantly more with tirzepatide than with placebo from randomization to week 72 ($p < 0.001$ for both tirzepatide vs. placebo comparisons). The LSM EQ-5D-5L Health State Index (UK) significantly increased from 0.86 to 0.89 in the tirzepatide group (LSM change

0.03, $p < 0.001$) and significantly decreased from 0.86 to 0.84 in the placebo group (−0.02, $p = 0.031$). Respective changes from randomization to week 72 in LSM EQ VAS scores were 81.1–87.4 (LSM change 5.9, $p < 0.001$) and 81.9–79.4 (−2.1, $p = 0.010$).

The proportions of participants in each PGIS for Physical Activity response group are shown in Figure 2. Numerically more participants reported 'not at all limited' after treatment with tirzepatide compared to at randomization and after treatment with placebo.

3.2 | Relationship between extent of weight reduction with tirzepatide and HRQoL

At week 72, few tirzepatide-treated participants had <5% loss of body weight ($n = 3$), so data for this extent of weight loss were not analysed.

Irrespective of the weight reduction threshold achieved, numerical improvements from randomization to week 72 were seen for most HRQoL scores across all participants in the tirzepatide group (Table 2).

For SF-36v2, numerical improvements were seen across all weight reduction threshold groups for Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, Mental Health and Physical Component Score mean scores; improvements were less consistent for the mean Mental Component Score (Table 2). For IWQOL-Lite-CT, numerical improvements by weight reduction threshold were seen for Total, Physical Function composite, Physical composite and Psychosocial composite mean scores (Table 2). Similarly, EQ-5D-5L health state index (UK) and EQ VAS mean scores improved across all weight reduction threshold groups (Table 2). Generally, greater improvements from randomization in PRO scores were observed in adults meeting greater weight reduction thresholds.

TABLE 2 Mean change in SF-36v2 domain and component scores, IWQOL-Lite-CT scores, and EQ-5D-5L scores from randomization to week 72 (LOCF) in adults with obesity/overweight treated with tirzepatide MTD after an intensive lifestyle intervention by categorical weight reduction threshold achieved.

	Weight reduction threshold achieved					
HRQoL score, mean (SD)	**≥5%**	**≥10%**	**≥15%**	**≥20%**	**≥25%**	**≥30%**
SF-36v2	$n = 228$	$n = 208$	$n = 182$	$n = 134$	$n = 88$	$n = 43$
Mental component score	−0.1 (8.0)	−0.2 (7.8)	−0.1 (7.6)	0.3 (8.0)	−0.2 (8.6)	0.9 (8.4)
Physical component score	3.2 (6.1)	3.3 (6.1)	3.8 (6.0)	4.5 (6.4)	4.7 (6.7)	5.2 (6.9)
Domain scores						
Physical functioning (norm-based)	3.4 (6.1)	3.4 (6.2)	3.8 (6.0)	4.4 (6.6)	4.3 (6.9)	4.2 (6.3)
Role-physical (norm-based)	1.9 (6.4)	1.8 (6.5)	2.2 (6.6)	2.9 (6.8)	2.8 (7.1)	3.4 (8.5)
Bodily pain (norm-based)	2.3 (8.1)	2.5 (8.0)	3.1 (7.8)	3.7 (7.8)	3.9 (8.2)	5.6 (7.3)
General health (norm-based)	2.6 (7.7)	2.7 (7.7)	3.0 (7.4)	3.3 (7.8)	3.4 (7.9)	4.0 (8.3)
Vitality (norm-based)	1.3 (8.3)	1.3 (8.2)	1.5 (8.1)	1.8 (8.4)	1.4 (8.2)	2.0 (8.6)
Social functioning (norm-based)	0.8 (7.1)	0.9 (7.2)	1.1 (7.3)	2.2 (7.0)	2.4 (7.4)	3.8 (8.1)
Role-emotional (norm-based)	0.9 (7.9)	0.8 (7.4)	1.0 (7.6)	1.5 (7.8)	0.9 (8.3)	1.2 (8.3)
Mental health (norm-based)	0.5 (8.4)	0.4 (8.5)	0.7 (8.4)	0.8 (8.9)	0.4 (9.8)	1.9 (10.6)
IWQOL-Lite-CT	$n = 224$	$n = 206$	$n = 180$	$n = 133$	$n = 87$	$n = 43$
Total score	18.2 (18.1)	18.6 (18.3)	19.7 (18.3)	22.9 (19.1)	24.1 (19.5)	28.8 (21.9)
Physical function composite score	13.6 (19.4)	14.1 (19.3)	14.9 (19.2)	17.1 (20.1)	17.3 (21.1)	20.6 (22.8)
Physical composite score	14.3 (18.4)	14.9 (18.5)	15.7 (18.4)	18.3 (19.2)	19.3 (20.0)	22.7 (21.0)
Psychosocial composite score	20.3 (20.3)	20.6 (20.5)	21.8 (20.7)	25.3 (21.5)	26.7 (21.9)	32.0 (25.2)
EQ-5D-5L	$n = 222$	$n = 205$	$n = 179$	$n = 133$	$n = 87$	$n = 43$
EQ-5D-5L health state index (UK)	0.04 (0.16)	0.04 (0.16)	0.04 (0.17)	0.06 (0.17)	0.06 (0.19)	0.05 (0.19)
	$n = 228$	$n = 207$	$n = 181$	$n = 134$	$n = 88$	$n = 43$
EQ-5D-5L usual activities	−0.15 (0.62)	−0.16 (0.65)	−0.18 (0.67)	−0.26 (0.65)	−0.25 (0.70)	−0.16 (0.69)
EQ-5D-5L mobility	−0.11 (0.49)	−0.11 (0.50)	−0.13 (0.46)	−0.16 (0.48)	−0.16 (0.52)	−0.09 (0.43)
EQ-5D-5L anxiety/depression	−0.03 (0.87)	−0.01 (0.75)	−0.04 (0.76)	−0.04 (0.84)	−0.01 (0.90)	0.047 (1.1)
EQ-5D-5L pain/discomfort	−0.16 (0.81)	−0.17 (0.81)	−0.20 (0.81)	−0.28 (0.77)	−0.26 (0.82)	−0.26 (0.69)
EQ-5D-5L self-care	−0.07 (0.33)	−0.07 (0.34)	−0.08 (0.36)	−0.10 (0.40)	−0.11 (0.47)	−0.12 (0.54)
EQ VAS score	6.3 (13.3)	6.4 (13.6)	6.7 (14.0)	8.5 (13.9)	8.8 (15.5)	13.4 (16.9)

Abbreviations: EQ-5D-5L, 5-level EQ-5D version; HRQoL, health-related quality of life; IWQOL-Lite-CT, Impact of Weight on Quality of Life-Lite-Clinical Trials version; LOCF, last observation carried forward; MTD, maximum tolerated dose (10 or 15 mg); SD, standard deviation; SF-36 v2, Short Form-36 Version 2 Health Survey acute form; VAS, visual analogue scale.

3.3 | Changes in physical functioning among participants treated with tirzepatide who had limitations with physical activity at randomization

At randomization, 42 (14.6%) tirzepatide participants reported physical function limitations, and 245 (85.4%) tirzepatide participants reported none; 35 and 191 of these provided HRQoL data, respectively. All mean HRQoL scores at randomization were numerically lower in participants with versus without physical function limitations (Supplementary Table 1).

At week 72, mean changes from randomization in scores were numerically larger (better) for adults with versus without physical function limitations for all SF-36v2 and IWQOL-Lite-CT scores, EQ-5D-5L Health State Index (UK) and EQ VAS scores (Figure 3).

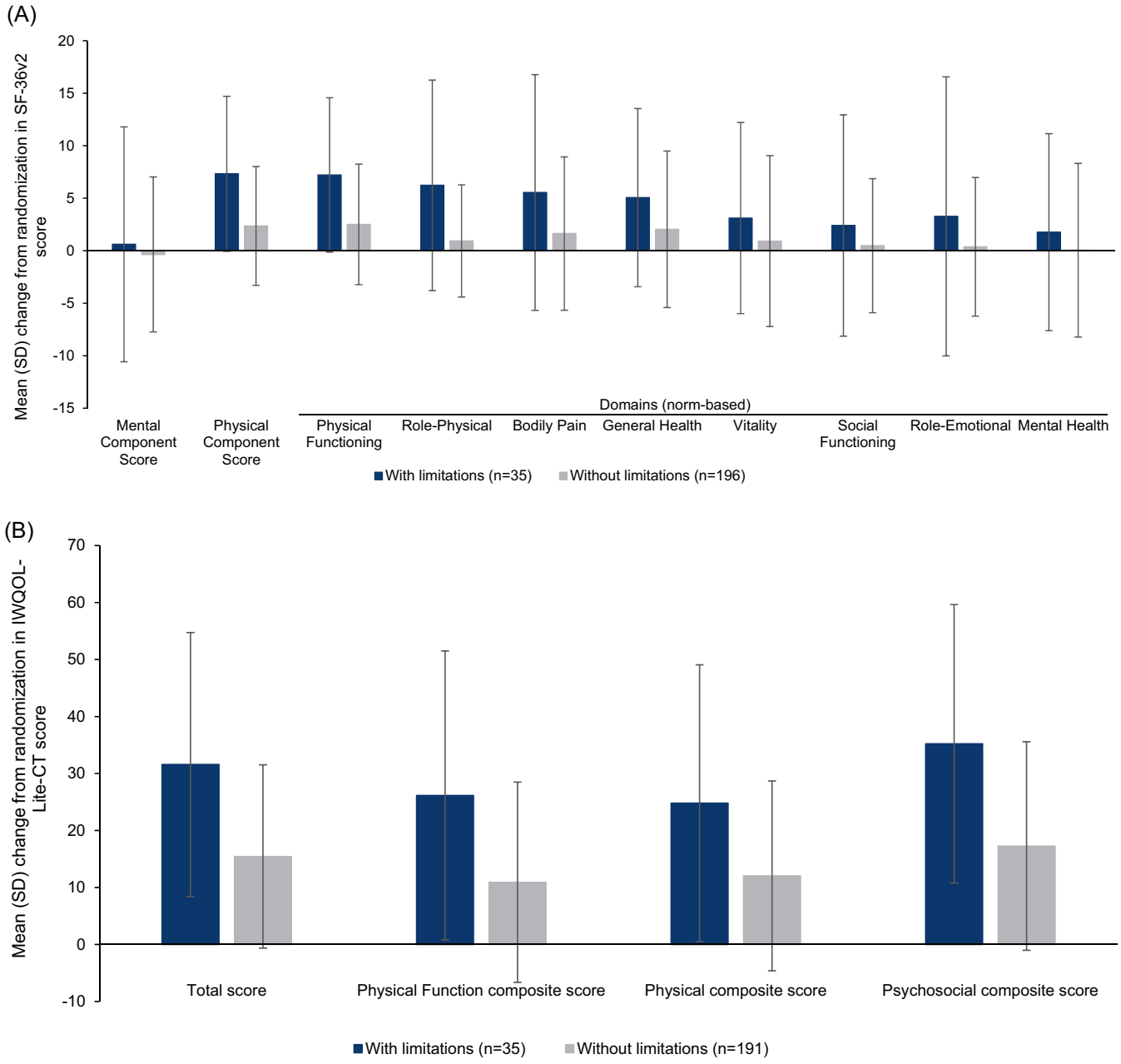
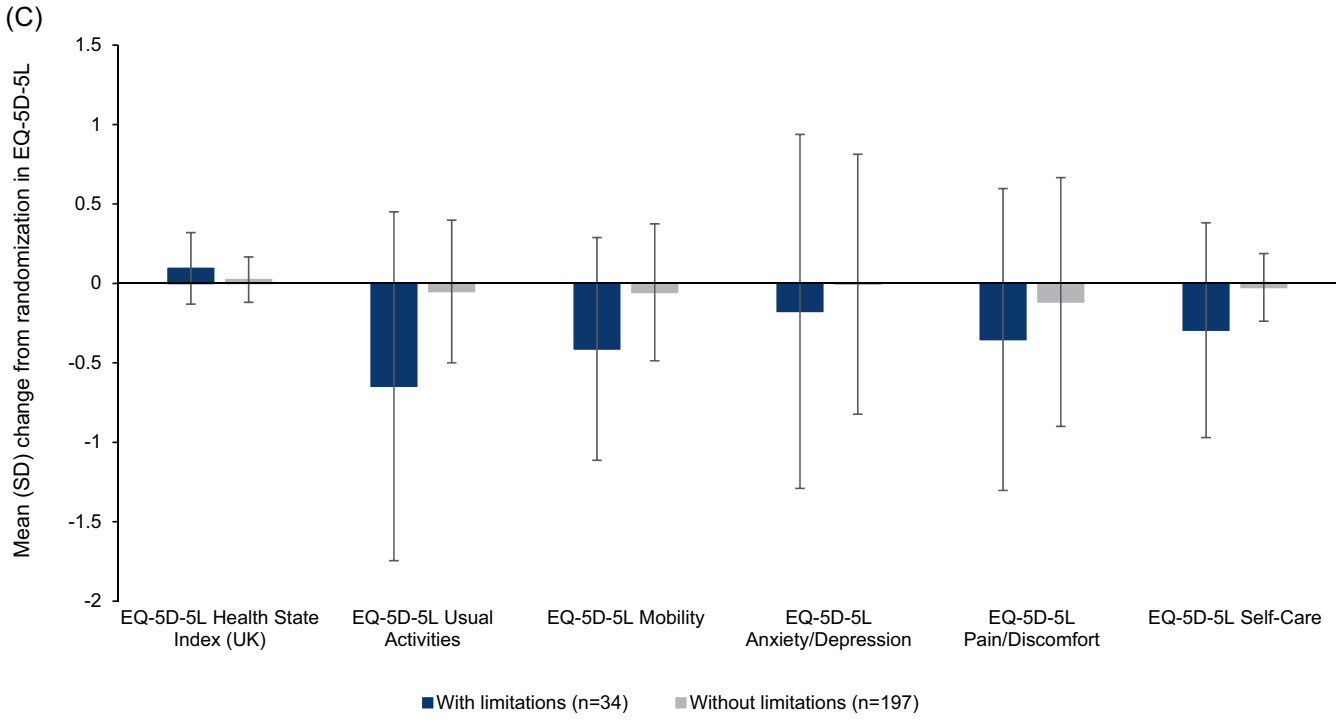


FIGURE 3 Mean change in (A) SF-36v2 scores, (B) IWQOL-Lite-CT scores, (C) EQ-5D-5L Health state Index and dimension scores, and (D) EQ VAS scores from randomization to week 72 (LOCF) in adults with obesity/overweight treated with tirzepatide MTD according to the presence/absence of physical limitations at randomization. Only subjects with non-missing randomization values and at least one non-missing post-randomization value of the response variable were included in the analysis. EQ-5D-5L, 5-level EQ-5D version; IWQOL-Lite-CT, Impact of Weight on Quality of Life-Lite-Clinical Trials version; LOCF, last observation carried forward; MTD, maximum tolerated dose (10 or 15 mg); SD, standard deviation; SF-36 v2, Short Form-36 Version 2 Health Survey acute form; VAS, visual analogue scale.

Participants receiving tirzepatide appeared less likely to report worsening limitations from randomization to week 72 than participants receiving placebo (Supplementary Table 2).

4 | DISCUSSION

In the SURMOUNT-3 trial, tirzepatide MTD not only significantly improved clinical outcomes,[27] it also significantly improved HRQoL compared with placebo in adults with obesity/overweight who had already lost ≥5% body weight with intensive lifestyle intervention. Additionally, we have shown that these improvements in HRQoL were generally numerically larger in adults achieving greater weight reduction thresholds and in adults who reported physical function limitations at randomization than in those who reported no such limitations. The improvements in HRQoL were observed for physical functioning as well as multiple domains of general health and weight-related psychosocial function as assessed by all SF-36v2 and IWQOL-



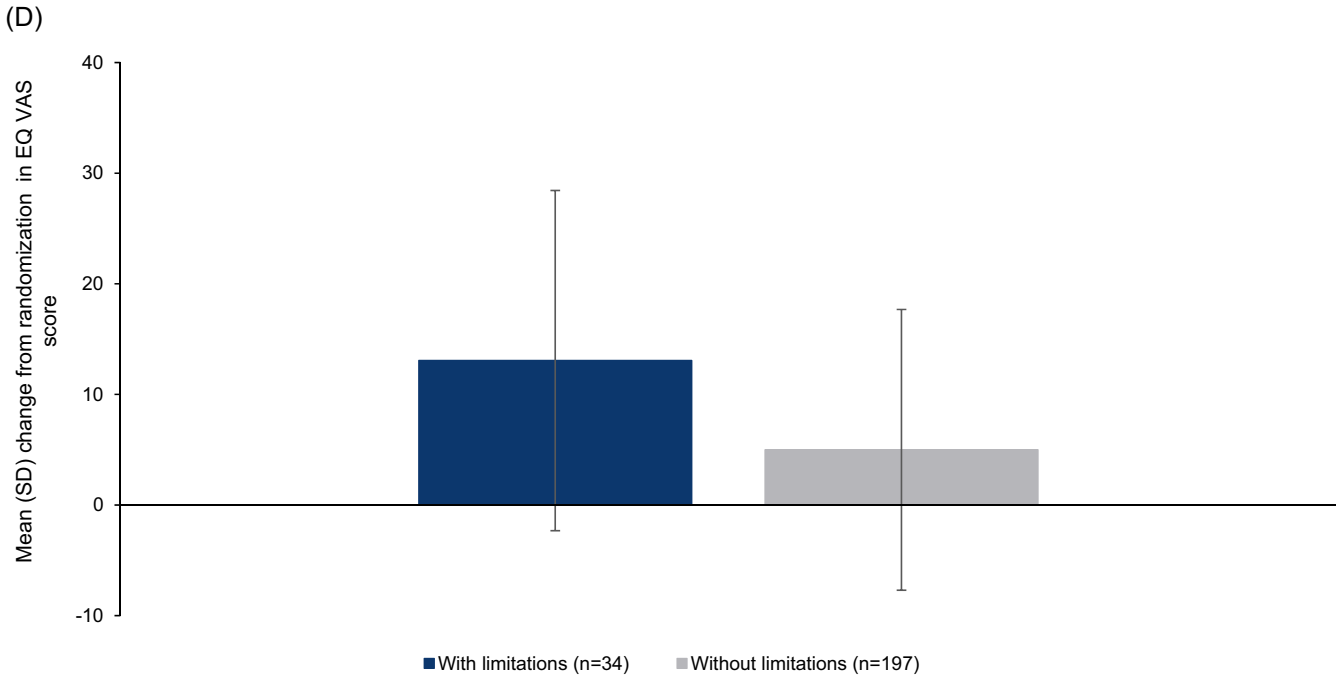


FIGURE 3 (Continued)

Lite-CT scores. Although Mental Component Summary scores were comparable between tirzepatide and placebo, improvements were seen with tirzepatide for aspects of mental health (Vitality, Social Functioning, Role-emotional and Mental Health).

The findings reported here build on those reported in trials of different obesity management medications[31,32] as well as other studies of tirzepatide in adults with obesity/overweight. For example, the phase 3 double-blind, randomized, placebo-controlled SURMOUNT-1 trial showed improvements in SF-36v2 physical function scores after 72 weeks of treatment with tirzepatide 10 or 15 mg that were larger than those observed with placebo.[33] Similarly, in SURMOUNT-2, a phase 3 double-blind, randomized, placebo-controlled trial in participants with overweight/obesity and type 2 diabetes, physical function improved more with tirzepatide 10 or 15 mg than with placebo, as demonstrated by greater improvements in SF-36v2 physical function scores and IWQOL-Lite-CT Physical Function composite score at week 72 ($p < 0.01$ for all). In addition, greater improvements in IWQOL-Lite-CT Psychosocial composite score were seen with both doses of tirzepatide compared to placebo at week 72 ($p < 0.0001$).[34] SURMOUNT-4 was a phase 3, randomized withdrawal trial with a 36-week, open-label tirzepatide lead-in period followed by a 52-week, double-blind, placebo-controlled period.[35] In this trial, improvements in SF-36v2 Physical Functioning, Role-Physical, Role-Emotional and Mental Health domain scores, as well as the IWQOL-Lite-CT Physical Function composite score, were observed after 36 weeks, with further improvements to 88 weeks, with tirzepatide MTD (10 or 15 mg). The improvements from week 36 to week 88 with tirzepatide were significantly greater ($p < 0.05$) than those observed with placebo.[35]

Decreasing baseline body weight by 5%–10% reduces the likelihood of developing type 2 diabetes while also improving cardiometabolic risk factors and other obesity-related complications,[6,10,11,15,16] with larger weight reductions necessary for achieving optimal control of obesity-related complications,[11,14–16] and decreasing cardiovascular mortality.[17–19] We show that reductions in body weight are also associated with improved HRQoL, underscoring the additional benefits that patients may receive from treatment with tirzepatide after first losing weight with intensive lifestyle intervention. Although lifestyle intervention is recommended for all people with obesity,[4,10–13] as shown in our study, weight loss can be limited with the use of this strategy alone, and it is possible that selected people may not gain the optimal benefits from lifestyle intervention since one aspect is physical activity. In SURMOUNT-3, 14.6% of the tirzepatide group had physical limitations at randomization. These participants had improvements in HRQoL following treatment with tirzepatide, including in domains relating to physical functioning. Such improvements in physical function could also increase the ability to engage in physical activity, thus potentially improving cardiometabolic health and translating into further weight loss in these adults.

Limitations of SURMOUNT-3 include that it was geographically restricted to North and South America and that the study population was predominantly white. In addition, participants who did not lose at least 5% of baseline weight in the intensive lifestyle intervention were not randomized to medication, thus potentially limiting the generalizability of the findings. Finally, the study was not powered for these non-primary and post-hoc analyses.

5 | CONCLUSION

In conclusion, in the SURMOUNT-3 trial, tirzepatide demonstrated clinically meaningful additional body weight reductions in adults with overweight or obesity following initial weight loss with intensive lifestyle intervention that were accompanied by improvements in physical functioning as well as in multiple domains of general mental health and weight-related psychosocial function. These improvements in HRQoL were generally numerically larger in adults meeting greater weight reduction thresholds and in adults who reported physical function limitations at randomization than in those who reported no such limitations. These findings support the role of tirzepatide treatment in helping adults with overweight or obesity achieve clinically meaningful improvement in HRQoL along with substantial weight reduction.

ACKNOWLEDGEMENTS

The authors would like to acknowledge Caroline Spencer and Sheridan Henness, PhD (Rx Communications, Mould, UK) for medical writing assistance with the preparation of this manuscript, funded by Eli Lilly and Company.

FUNDING INFORMATION

Funding for this study and the analyses presented was provided by Eli Lilly and Company. Theresa Hunter Gibble has made substantial contributions to the conception and design of the work and interpretation of data; has been involved in revising the manuscript critically for important intellectual content; has given final approval of the version to be published; and has agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Dachuang Cao has made substantial contributions to the design of the work, and analysis and interpretation of data; been involved in revising the manuscript critically for important intellectual content; given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Tammy Forrester has made substantial contributions to the interpretation of data; has been involved in revising the manuscript critically for important intellectual content; has given final approval of the version to be published; and has agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Julia Fraseur Brumm has made substantial contributions to the interpretation of data; has been involved in revising the manuscript critically for important intellectual content; has given final approval of the version to be published; and has agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of

any part of the work are appropriately investigated and resolved. Ariana M. Chao has made substantial contributions to the acquisition and interpretation of data; has been involved in revising the manuscript critically for important intellectual content; has given final approval of the version to be published; and has agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST STATEMENT

Theresa Hunter Gibble: Employee and stockholder, Eli Lilly and Company. Dachuang Cao: Employee and stockholder, Eli Lilly and Company. Tammy D. Forrester: Employee and stockholder, Eli Lilly and Company. Julia Fraseur Brumm: Employee and stockholder, Eli Lilly and Company. Ariana Chao: Support for the current manuscript, Eli Lilly and Company; consulting fees, Eli Lilly and Company, Boehringer Ingelheim; grant support, on behalf of the University of Pennsylvania WW (Weight Watchers); support for attending meetings and/or travel, Eli Lilly and Company.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.16463.

DATA AVAILABILITY STATEMENT

Eli Lilly and Company provides access to all individual participant data collected during the trial after anonymization, except for pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the USA and European Union and after primary publication acceptance, whichever is later. No expiration date for data requests is currently set once data have been 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, and blank or annotated case report forms, will be provided in a secure data-sharing environment. For details on submitting a request, see the instructions provided at https://www.vivli.org.

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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: Gibble TH, Cao D, Forrester T, Fraseur Brumm J, Chao AM. Tirzepatide and health-related quality of life in adults with obesity or overweight: Results from the SURMOUNT-3 phase 3 randomized trial. *Diabetes Obes Metab*. 2025;27(8):4268-4279. doi:10.1111/dom.16463