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Association between weight reduction achieved with tirzepatide and quality of life in adults with obesity: Results from the SURMOUNT-1 study

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Abstract

Aims: The SURMOUNT-1 trial investigated effects of tirzepatide, a glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist, on body weight in participants with obesity or overweight. This analysis evaluated changes in patient-reported outcomes (PROs) assessing physical function, psychosocial well-being, and overall health aspects of participants' health-related quality of life (HRQoL) in SURMOUNT-1.

Methods: PRO instruments included the Impact of Weight on Quality of Life-Lite Clinical Trials version (IWQOL-Lite-CT), Short Form Survey-36 version 2 (SF-36v2) and EQ-5D-5L. Scores were analysed by treatment group and by categorical degree of weight reduction group: >0 to <5%, ≥5 to <10%, ≥10 to <20% and ≥20%. Relevant PROs were evaluated for participants with or without physical or psychosocial limitations at baseline, as measured by Patient Global Impression of Status for physical activity (PGIS) and Patient Health Questionnaire-2 (PHQ-2), respectively.

Results: All tirzepatide groups demonstrated significant improvements in PRO scores versus placebo. There was a consistent trend of incremental PRO improvement with greater degrees of weight reduction, starting from ≥5% weight reduction. Participants achieving ≥20% weight reduction demonstrated the greatest changes from baseline to week 72 (SF-36v2 Physical Component Summary, 4.60; SF-36v2 Mental Component Summary, 0.80; IWQOL-Lite CT Total score, 24.7). Those with baseline physical and psychosocial limitations experienced greater improvements than those without.

Conclusions: Tirzepatide treatment was associated with improved HRQoL compared to placebo in people with overweight or obesity. Higher percentages of weight reduction were associated with greater improvements.

Clinical trial registration number for SURMOUNT-1: NCT04184622.

KEYWORDS
GIP, GLP-1, obesity therapy, patient-reported outcomes

1 | INTRODUCTION

Obesity is a chronic relapsing, progressive disease characterised by excess adiposity and ectopic fat that is associated with increased risk of numerous complications, including cardiovascular disease, and type 2 diabetes.[1–5] In addition to significant negative impacts on morbidity and mortality, the burden of obesity and its comorbidities affects individuals' health-related quality of life (HRQoL) encompassing not only physical health but also mental health, social relationships, and environmental and economic factors, all of vital relevance for people living with obesity.[6] The relationship between obesity and psychopathology is well established, with negative impacts of obesity including anxiety, low self-esteem and sleep disorders.[7] The association between weight-related stigma and impaired mental health is stronger with increasing body mass index (BMI).[2,8]

Clinical guidelines often specify weight reduction targets to improve weight-related comorbidities.[3] Weight reduction has a similarly valuable benefit to patients with regard to HRQoL, as it affects how they feel and function in their day-to-day lives.[6] Therefore, HRQoL, assessed using patient-reported outcomes (PROs), is an important outcome in anti-obesity pharmacotherapy trials.[9,10] Previous studies have found that weight reduction after metabolic and bariatric surgery is associated with significant improvements in HRQoL.[6] Historically, weight reduction achieved with non-surgical interventions has demonstrated this relationship less consistently[6]; however, a 2023 meta-analysis of randomised clinical trials of pharmacotherapy found an association between weight reduction and improved physical functioning.[11] This meta-analysis did not include any tirzepatide studies. Similarly, a recent analysis of the STEP 1–4 semaglutide trials for obesity found that greater weight reduction was associated with larger improvements in physical functioning. Effects of weight reduction on psychosocial functioning were not reported.[12] It is notable that the magnitude of weight reduction has historically been greater with surgical than with non-surgical treatments. However, the non-surgical weight reduction intervention landscape has evolved, with newer treatment options achieving weight reduction approaching that of surgical interventions.[6,13]

Tirzepatide is a once weekly glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist that has been shown to provide significant weight reduction in the SURMOUNT-1 trial.[1] HRQoL outcomes were included as prespecified secondary endpoints. Herein, we report changes in HRQoL outcomes among participants in SURMOUNT-1.

2 | METHODS

2.1 | Study design

SURMOUNT-1 (NCT04184622) was a 72-week, phase 3, multicentre, randomised, placebo-controlled, double-blinded study that evaluated the safety and efficacy of 5, 10, and 15 mg tirzepatide once weekly, compared with placebo, when used in conjunction with a reduced-calorie diet and increased physical activity for weight management. Entry criteria and study design have been previously reported.[1] The 72-week treatment period included an up to 20-week dose-escalation period up to the assigned dose, as previously described.[1] The trial was conducted at study sites in Argentina, Brazil, China, India, Japan, Mexico, Russia, Taiwan, and the United States (including Puerto Rico), in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines and was approved by an independent ethics committee or institutional review board at each trial site. All the participants provided written informed consent before participation.

2.2 | Objectives

This study assessed baseline and end of treatment (week 72 or early discontinuation) PROs in the SURMOUNT-1 trial, with a focus on physical function, psychosocial status and general/overall health. PRO scores were analysed by treatment group (tirzepatide 5 mg, $N = 630$; tirzepatide 10 mg, $N = 636$; tirzepatide 15 mg, $N = 630$; placebo, $N = 643$). The proportion of participants achieving meaningful within-patient change for physical function was calculated.

In addition to differences between treatment groups, separate post hoc analyses assessed the relationship between weight reduction and PRO improvement. Given the limited degree of weight reduction in the placebo group, only data from tirzepatide-treated participants were included in these analyses. PRO scores were evaluated by categorical percentage weight reduction groups (>0 to <5%, ≥5 to <10%, ≥10 to <20%, and ≥20%). The correlation between PRO improvement and the degree of weight reduction was calculated. The association between PRO improvement and baseline characteristics (age, sex and years of education) was assessed. Participants were also divided into groups with or without baseline physical function (based on the Patient Global Impression of Status for physical activity [PGIS]) or psychosocial limitations (based on the Patient Health Questionnaire-2 [PHQ-2]) to investigate the improvement of PRO scores by baseline status.

2.3 | Assessments

PRO instruments employed were the Short Form Survey-36 version 2 (SF-36v2) acute form, Impact of Weight on Quality of Life-Lite Clinical Trials Version (IWQOL-Lite-CT), EQ-5D-5L, PGIS and PHQ-2.

The SF-36v2 acute form is a 36-item tool with eight domains (Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional and Mental Health). Each domain is scored individually and information from these eight domains is further aggregated into two summary scores: Physical Component Summary (PCS) and Mental Component Summary (MCS). The domain and component summary scores are norm-based to the United States general population with a mean of 50 and standard deviation of 10. Higher scores indicate better function and HRQoL.[14]

The IWQOL-Lite-CT is a 20-item obesity-specific PRO instrument developed for use in obesity clinical trials. This instrument assesses two primary domains of obesity-related HRQoL: the Physical composite (7 items) and the Psychosocial composite (13 items). A five-item subset of the Physical composite, the Physical Function composite, can also be assessed. 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.[15,16]

The EQ-5D-5L is a standardised five-item instrument that includes mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The EQ-5D-5L is widely used to assess HRQoL in patients with different diseases,[17] including overweight and obesity.[18,19] A health profile and a single health state index value can be derived. This index value ranges between <0 (where 0 is a health state equivalent to death; negative values are valued as worse than dead) to 1 (perfect health). In addition, a visual analogue scale records the respondent's self-rated health status on a vertical graduated (0–100) scale.

The PGIS assessed physical function limitations. This was specifically developed for this study and is rated on a 5-point scale ranging from '1-not at all limited' to '5-extremely limited'. Physical function limitations at baseline were defined as responses of 'moderately', 'very much' or 'extremely' limited.

The Patient Health Questionnaire-9 (PHQ-9) is a validated self-reported screening tool that assesses the presence of depressive symptoms and was developed for use in primary care settings. Its subset PHQ-2 includes the first two items and was used to identify patients with psychosocial limitations at baseline. The PHQ-2 incorporates Diagnostic and Statistical Manual-IV depression criteria and assesses the following items over the preceding 2 weeks: 'Little interest or pleasure in doing things' and 'Feeling down, depressed, or hopeless'.[20,21] For each item, response options range from '0' (not at all) to '3' (nearly every day) giving a total PHQ-2 score ranging from 0 to 6. A score of 3 has been identified as the optimal cutpoint to screen for depression with scores of 3 or greater indicating major depressive disorder is likely. Limitations in psychosocial function at baseline were defined as PHQ-2 responses of ≥3.

Measures from these PRO instruments were used to assess overall HRQoL, physical function and psychosocial function as follows: (1) overall HRQoL using IWQOL-Lite-CT total score, EQ-5D-5L utility/health state index score and EQ-5D-5L visual analogue scale score; (2) physical function using the PGIS, SF-36v2 PCS score and domains of General Health, Physical Functioning, Bodily Pain, and Role-Physical, and IWQOL-Lite-CT Physical and Physical Function composite scores; (3) psychosocial function using SF-36v2 MCS score and domains of Vitality, Mental Health, Social Functioning, and Role-Emotional, IWQOL-Lite-CT Psychosocial composite score and PHQ-2 score.

2.4 | Statistical analyses

Analyses were based on the efficacy analysis set (randomised participants, excluding data after treatment discontinuation). The resulting treatment effect estimate was the average treatment effect of tirzepatide relative to placebo in the randomised participants had they remained on randomised treatment for the entire 72-week treatment period. The last post-baseline observation was carried forward (LOCF) for patients who had early discontinuation of treatment. Calculation of scores in the presence of missing items was handled according to each instrument developer's instructions.

For analyses by treatment group, an analysis of covariance model (ANCOVA) was used with treatment group and stratification factors (prediabetes status at randomisation, sex, and country/pooled country) as fixed effects and baseline PRO value as a covariate. No multiplicity adjustment was performed.

The proportion of participants reaching meaningful within-patient change was calculated overall and by baseline physical function status (with limitation, without limitation) descriptively. Meaningful within-patient change was 5.76 for the SF-36v2 Physical Functioning domain score and 25 for the IWQOL-Lite-CT Physical Function composite score (data on file). These thresholds were previously empirically determined with anchor-based and distribution-based approaches using SURMOUNT-1 data.[22]

For analyses by weight reduction category in tirzepatide-treated participants, an ANCOVA model was used with percent weight reduction subgroup as a fixed effect and baseline PRO value as a covariate. Pearson's correlation between percent weight reduction and PRO improvement was calculated with participants placed in quartiles based on baseline PRO scores, with the first quartile having the lowest baseline PRO score and the fourth quartile having the highest baseline PRO score. Association between PRO improvement and baseline characteristics (age, years of education, sex) was assessed using a linear regression with tirzepatide dose and each of the baseline characteristics of interest as independent variables. The analysis unit was set to one unit (1 year for age or years of education) for continuous variables. Mean changes in PRO scores were calculated for participants with and without physical limitations at baseline, and for participants with and without psychosocial limitations at baseline.

TABLE 1 Baseline demographics and characteristics for tirzepatide-treated participants in categorical weight reduction groups.

	Weight reduction group			
	0 to <5% (*N* = 83)	≥5 to <10% (*N* = 206)	≥10 to <20% (*N* = 620)	≥20% (*N* = 960)
Sex, *n* (%)				
Female	44 (53.0)	113 (54.9)	365 (58.9)	741 (77.2)
Age, years	42.3 (12.3)	46.5 (12.7)	46.0 (12.7)	44.3 (12.1)
Ethnicity, *n* (%)				
Hispanic or Latino	29 (34.9)	79 (38.3)	312 (50.3)	471 (49.1)
Not Hispanic or Latino	42 (50.6)	109 (52.9)	251 (40.5)	426 (44.4)
Not reported	12 (14.5)	18 (8.7)	57 (9.2)	63 (6.6)
Race, *n* (%)				
American Indian or Alaska Native	5 (6.0)	21 (10.2)	70 (11.3)	77 (8.0)
Asian	14 (16.9)	34 (16.5)	76 (12.3)	81 (8.4)
Black or African American	13 (15.7)	18 (8.7)	46 (7.4)	64 (6.7)
Native Hawaiian or other Pacific Islander	0	2 (1.0)	1 (0.2)	4 (0.4)
White	51 (61.4)	129 (62.6)	419 (67.6)	721 (75.1)
Multiple	0	2 (1.0)	8 (1.3)	13 (1.4)
Weight, kg	112.8 (27.9)	108.9 (22.6)	105.5 (22.4)	102.7 (21.5)
BMI, kg/m^2	39.9 (7.9)	38.7 (7.5)	37.7 (6.9)	37.7 (6.4)
Education duration, years	14.4 (4.1)	14.4 (4.1)	14.2 (3.6)	13.8 (3.9)
Tirzepatide dose, *n* (%)				
5 mg	31 (37.3)	100 (48.5)	271 (43.7)	219 (22.8)
10 mg	29 (34.9)	63 (30.6)	185 (29.8)	349 (36.4)
15 mg	23 (27.7)	43 (20.9)	164 (26.5)	392 (40.8)

Note: Data are presented as mean (standard deviation) unless stated otherwise. Race or ethnicity was self-reported by participants.
Abbreviations: BMI, body mass index; *N*, number of participants in the analysis population; *n*, number of participants in the specified category.

3 | RESULTS

3.1 | Patient demographics and baseline PROs

Patient demographics across treatment arms have been previously reported and key characteristics are provided in Table S1.[1] The mean age of participants was 44.9 years and 67.6% were female. Mean waist circumference was 114.1 cm, and 93.8% of the participants had a BMI ≥30. Mean education duration was 14.0 years.

In tirzepatide-treated participants, demographics were similar across weight reduction groups although the ≥10 to <20% and ≥20% weight reduction groups had more female, Hispanic or Latino, and White participants; and fewer Asian and Black or African American participants versus lower weight reduction groups. Also, the ≥20% weight reduction group had more participants treated with 15 mg tirzepatide (Table 1). Baseline demographics for participants with and without physical and psychosocial limitations at baseline are reported in Tables S2 and S3.

Baseline and change from baseline PROs for overall health, physical function and psychosocial well-being are presented in Tables 2 and 3 for all treatment arms versus placebo, and in Tables 4 and 5 for weight reduction groups in tirzepatide-treated participants.

3.2 | Overall HRQoL

Participants in the tirzepatide 5, 10 and 15 mg groups had significantly improved IWQOL-Lite-CT total score and EQ-5D-5L utility/health state index and visual analogue scale versus placebo (Table 3).

IWQOL-Lite-CT total score increased from baseline for all weight reduction categories in tirzepatide-treated participants with a trend for greater improvements with an increased percentage of weight reduction (Table 5). The EQ-5D-5L utility/health state index and visual analogue scale both increased from baseline for all weight reduction categories in tirzepatide-treated participants except 0 to <5% weight reduction with a trend for greater improvements with an increased percentage of weight reduction (Table 5).

3.3 | Physical function

Compared to placebo, participants in the tirzepatide 5, 10 and 15 mg groups had significantly improved SF-36v2 PCS score (Table 2), individual domain scores more highly weighted in the SF-36v2 PCS (Physical Functioning, Role-Physical, Bodily Pain, General Health), and IWQOL-Lite-CT Physical composite and Physical Function composite scores (Table 3).

TABLE 2 SF-36v2 scores by treatment group.

SF-36v2 parameter	Tirzepatide 5 mg (*N* = 630)	Tirzepatide 10 mg (*N* = 636)	Tirzepatide 15 mg (N = 630)	Placebo (*N* = 643)
Physical component score				
Baseline	50.97 (0.31)	50.64 (0.32)	50.69 (0.32)	50.85 (0.33)
Change from baseline to week 72	3.47 (0.23)	3.63 (0.23)	4.18 (0.23)	1.62 (0.25)
Change from baseline difference vs. placebo (95% CI)	1.84 (1.18 to 2.51)***	2.00 (1.33 to 2.67)***	2.56 (1.89 to 3.23)***	-
Physical Functioning Domain				
Baseline	49.55 (0.34)	49.56 (0.34)	49.58 (0.34)	49.68 (0.36)
Change from baseline to week 72	3.87 (0.25)	3.89 (0.25)	4.14 (0.25)	1.76 (0.26)
Change from baseline difference vs. placebo (95% CI)	2.11 (1.39 to 2.82)***	2.13 (1.42 to 2.84)***	2.38 (1.67 to 3.09)***	-
Role-physical domain				
Baseline	51.11 (0.32)	51.70 (0.32)	51.33 (0.32)	51.55 (0.34)
Change from baseline to week 72	2.52 (0.25)	2.15 (0.25)	2.76 (0.25)	1.42 (0.26)
Change from baseline difference vs. placebo (95% CI)	1.10 (0.39 to 1.82)**	0.73 (0.02 to 1.45)*	1.34 (0.62 to 2.05)***	-
Bodily pain domain				
Baseline	52.52 (0.38)	52.06 (0.38)	52.03 (0.38)	51.76 (0.40)
Change from baseline to week 72	1.68 (0.32)	2.08 (0.32)	2.85 (0.32)	0.44 (0.34)
Change from baseline difference vs. placebo (95% CI)	1.24 (0.34 to 2.15)**	1.64 (0.73 to 2.54)***	2.41 (1.50 to 3.32)***	-
General health domain				
Baseline	52.97 (0.35)	52.07 (0.35)	51.99 (0.35)	52.74 (0.37)
Change from baseline to week 72	3.30 (0.27)	3.90 (0.28)	4.20 (0.28)	1.03 (0.29)
Change from baseline difference vs. placebo (95% CI)	2.27 (1.49 to 3.06)***	2.87 (2.09 to 3.66)***	3.16 (2.38 to 3.95)***	-
Mental component score				
Baseline	53.32 (0.32)	53.81 (0.32)	53.36 (0.32)	53.47 (0.34)
Change from baseline to week 72	0.72 (0.28)	0.44 (0.29)	0.71 (0.29)	−0.47 (0.30)
Change from baseline difference vs. placebo (95% CI)	1.20 (0.38 to 2.01)**	0.91 (0.10 to 1.73)*	1.19 (0.37 to 2.00)**	-
Vitality domain				
Baseline	54.39 (0.35)	54.89 (0.35)	54.51 (0.36)	54.87 (0.38)
Change from baseline to week 72	2.76 (0.30)	2.33 (0.30)	3.19 (0.30)	0.21 (0.32)
Change from baseline difference vs. placebo (95% CI)	2.55 (1.68 to 3.42)***	2.13 (1.26 to 3.00)***	2.99 (2.12 to 3.86)***	-
Social functioning domain				
Baseline	52.57 (0.30)	52.41 (0.30)	52.61 (0.30)	52.42 (0.32)
Change from baseline to week 72	1.29 (0.26)	1.18 (0.26)	1.15 (0.26)	0.29 (0.28)
Change from baseline difference vs. placebo (95% CI)	1.00 (0.26 to 1.75)**	0.90 (0.15 to 1.64)*	0.86 (0.11 to 1.60)*	-
Mental health domain				
Baseline	53.37 (0.31)	53.98 (0.31)	53.42 (0.31)	53.42 (0.33)
Change from baseline to week 72	0.83 (0.30)	0.85 (0.30)	1.05 (0.30)	−0.23 (0.32)
Change from baseline difference vs. placebo (95% CI)	1.06 (0.20 to 1.92)*	1.08 (0.22 to 1.94)*	1.28 (0.42 to 2.15)**	-

(Continues)

TABLE 2 (Continued)

SF-36v2 parameter	Tirzepatide 5 mg (*N* = 630)	Tirzepatide 10 mg (*N* = 636)	Tirzepatide 15 mg (N = 630)	Placebo (*N* = 643)
Role-emotional domain				
Baseline	50.66 (0.36)	50.96 (0.36)	50.52 (0.36)	50.81 (0.38)
Change from baseline to week 72	1.71 (0.30)	1.35 (0.30)	1.79 (0.30)	0.32 (0.32)
Change from baseline difference vs. placebo (95% CI)	1.39 (0.54 to 2.25)**	1.03 (0.17 to 1.89)*	1.48 (0.62 to 2.33)***	-

Note: Data are presented as least squares mean (standard error). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ versus placebo.
Abbreviations: SF-36v2, Short Form Health Survey 36, version 2, acute form; *N*, number of participants in treatment group population.

TABLE 3 IWQOL-Lite-CT and EQ-5D-5L scores by treatment group.

Parameter	Tirzepatide 5 mg (*N* = 630)	Tirzepatide 10 mg (*N* = 636)	Tirzepatide 15 mg (*N* = 630)	Placebo (*N* = 643)
IWQOL-Lite-CT				
Total Score				
Baseline	64.2 (0.9)	61.9 (0.9)	63.0 (0.9)	63.2 (1.0)
Change from baseline to week 72	18.6 (0.6)	21.2 (0.6)	22.6 (0.6)	10.5 (0.7)
Change from baseline difference vs. placebo (95% CI), *p* value	8.1 (6.3 to 9.9)***	10.7 (8.9 to 12.5)***	12.1 (10.3 to 13.9)***	-
Physical Composite Score				
Baseline	64.0 (1.0)	61.5 (1.0)	62.7 (1.0)	63.3 (1.1)
Change from baseline to week 72	16.8 (0.7)	19.5 (0.7)	20.8 (0.7)	9.7 (0.7)
Change from baseline difference vs. placebo (95% CI), *p* value	7.2 (5.2 to 9.2)***	9.9 (7.9 to 11.9)***	11.1 (9.1 to 13.1)***	-
Physical Function Composite Score				
Baseline	64.4 (1.0)	61.9 (1.0)	63.3 (1.0)	64.0 (1.1)
Change from baseline to week 72	17.8 (0.7)	20.7 (0.7)	21.8 (0.7)	10.1 (0.8)
Change from baseline difference vs. placebo (95% CI), *p* value	7.7 (5.6 to 9.8)***	10.7 (8.6 to 12.8)***	11.7 (9.6 to 13.8)***	-
Psychosocial Composite Score				
Baseline	64.3 (1.0)	62.1 (1.0)	63.2 (1.0)	63.2 (1.0)
Change from baseline to week 72	19.6 (0.7)	22.1 (0.7)	23.6 (0.7)	11.0 (0.7)
Change from baseline difference vs. placebo (95% CI), *p* value	8.7 (6.7 to 10.6)***	11.2 (9.3 to 13.1)***	12.7 (10.7 to 14.6)***	-
EQ-5D-5L				
Utility/Health State Index				
Baseline	0.8 (0.01)	0.8 (0.01)	0.8 (0.01)	0.8 (0.01)
Change from baseline to week 72	0.04 (0.01)	0.05 (0.01)	0.06 (0.01)	0.02 (0.01)
Change from baseline difference vs. placebo (95% CI), *p* value	0.03 (0.01 to 0.04)**	0.03 (0.01 to 0.05)**	0.05 (0.03 to 0.06)***	-
Visual Analog Scale				
Baseline	78.9 (0.7)	78.5 (0.7)	77.7 (0.7)	79.3 (0.7)
Change from baseline to week 72	6.8 (0.5)	8.2 (0.5)	8.6 (0.5)	2.4 (0.5)
Change from baseline difference vs. placebo (95% CI), *p* value	4.4 (3.0 to 5.8)***	5.8 (4.4 to 7.3)***	6.2 (4.8 to 7.6)***	-

Note: Data are presented as least squares mean (standard error). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ versus placebo.
Abbreviations: IWQOL-Lite-CT, Impact of Weight on Quality of Life-Lite Clinical Trials Version; *N*, number of participants in treatment population.

TABLE 4 SF-36v2 scores by categorical percentage weight reduction group in tirzepatide-treated participants.

	Weight reduction group			
SF-36v2 parameter	**>0 to <5% (*N* = 83)**	**≥5 to <10% (*N* = 206)**	**≥10 to <20% (*N* = 620)**	**≥20% (*N* = 960)**
Physical component score				
Baseline	50.75 (1.30)	51.98 (0.62)	50.90 (0.32)	50.49 (0.25)
Change from baseline to week 72	−1.12 (0.94)	1.86 (0.45)	3.20 (0.23)	4.60 (0.18)
Physical functioning domain				
Baseline	49.52 (1.39)	50.50 (0.66)	49.58 (0.34)	49.41 (0.26)
Change from baseline to week 72	0.03 (1.00)	1.99 (0.48)	3.52 (0.24)	4.70 (0.19)
Role-physical domain				
Baseline	51.27 (1.31)	52.01 (0.63)	51.28 (0.32)	51.35 (0.25)
Change from baseline to week 72	−1.55 (1.00)	1.67 (0.48)	2.10 (0.24)	3.03 (0.19)
Bodily pain domain				
Baseline	54.30 (1.55)	52.87 (0.74)	52.67 (0.38)	51.73 (0.29)
Change from baseline to week 72	−2.28 (1.28)	0.95 (0.61)	1.63 (0.31)	2.82 (0.24)
General health domain				
Baseline	48.53 (1.43)	53.11 (0.68)	52.45 (0.35)	52.29 (0.27)
Change from baseline to week 72	−1.47 (1.11)	1.54 (0.53)	3.16 (0.27)	4.83 (0.21)
Mental component score				
Baseline	52.64 (1.29)	53.22 (0.62)	53.69 (0.31)	53.46 (0.24)
Change from baseline to week 72	−1.96 (1.16)	0.26 (0.56)	0.57 (0.28)	0.80 (0.22)
Vitality domain				
Baseline	55.03 (1.45)	55.83 (0.69)	55.10 (0.35)	54.08 (0.27)
Change from baseline to week 72	−2.20 (1.23)	1.55 (0.59)	2.58 (0.30)	3.30 (0.23)
Social functioning domain				
Baseline	51.95 (1.25)	53.17 (0.60)	52.67 (0.30)	52.37 (0.24)
Change from baseline to week 72	−2.30 (1.05)	0.35 (0.50)	1.18 (0.26)	1.45 (0.20)
Mental health domain				
Baseline	53.11 (1.29)	53.08 (0.61)	53.81 (0.31)	53.55 (0.24)
Change from baseline to week 72	−2.42 (1.24)	0.33 (0.59)	0.66 (0.30)	1.23 (0.23)
Role-emotional domain				
Baseline	49.68 (1.46)	50.43 (0.70)	50.64 (0.36)	50.85 (0.28)
Change from baseline to week 72	−0.32 (1.20)	0.98 (0.57)	1.37 (0.29)	1.95 (0.23)

Note: Data are presented as least squares mean (standard error).
Abbreviations: SF-36v2, Short Form Health Survey 36, version 2, acute form; *N*, number of participants in weight reduction group population.

Of 526 participants categorised as having physical function limitations at baseline based on PGIS response, 342 reported improvements to 'not at all' or 'a little' limited at 72 weeks. More participants treated with tirzepatide reported improvements versus placebo (Table S4).

SF-36v2 PCS score change from baseline to week 72 was 7.91 for participants with limitations at baseline versus 2.69 for those without limitations, and IWQOL-Lite-CT Physical Function composite score change from baseline was 30.9 for participants with limitations at baseline versus 17.4 for those without limitations (Table S5).

At week 72, 32.8%, 36.6%, 38.2% and 24.5% of participants in the 5, 10 and 15 mg tirzepatide, and placebo groups, respectively, had a within-patient change from baseline of ≥5.76 (meaningful within-patient change) in the SF-36v2 Physical Functioning domain score. Among participants with limitations in physical function at baseline, 59.5%, 62.9%, 65.0% and 41.5% in the 5, 10 and 15 mg tirzepatide, and placebo groups, respectively, had a within-patient change from baseline of ≥5.76. Significantly more participants in each tirzepatide group had a within-patient change from baseline of ≥5.76 versus participants in the placebo group (all $p < 0.05$).

At week 72, 36.3%, 43.8%, 44.7% and 26.4% of participants in the 5, 10 and 15 mg tirzepatide, and placebo groups, respectively, had a within-patient change from baseline of ≥25 (meaningful within-patient change) in the IWQOL-Lite-CT Physical Function composite score. Among participants with physical function limitations at baseline, 57.7%, 64.2%, 67.6% and 44.1% in the 5, 10 and 15 mg tirzepatide, and placebo groups, respectively, had a within-patient change from baseline of ≥25. Significantly more participants in each

TABLE 5 IWQOL-Lite-CT, EQ-5D-5L, and PHQ-2 scores by categorical percentage weight reduction group in tirzepatide-treated participants.

	Weight reduction group			
Parameter	**>0 to <5% (*N* = 83)**	**≥5 to <10% (*N* = 206)**	**≥10 to <20% (*N* = 620)**	**≥20% (*N* = 960)**
IWQOL-Lite-CT				
Total Score				
Baseline	62.3 (3.6)	67.7 (1.8)	64.9 (0.9)	61.2 (0.7)
Change from baseline to week 72	5.4 (2.3)	11.5 (1.1)	17.9 (0.6)	24.7 (0.4)
Physical Composite Score				
Baseline	63.1 (4.0)	66.6 (2.0)	63.0 (1.0)	62.0 (0.8)
Change from baseline to week 72	4.5 (2.7)	10.5 (1.3)	16.1 (0.7)	22.8 (0.5)
Physical Function Composite Score				
Baseline	65.9 (4.2)	67.8 (2.0)	63.1 (1.0)	62.44 (0.8)
Change from baseline to week 72	4.3 (2.8)	11.4 (1.3)	16.9 (0.7)	24.1 (0.5)
Psychosocial Composite Score				
Baseline	61.9 (3.9)	68.2 (1.9)	66.0 (1.0)	60.8 (0.7)
Change from baseline to week 72	5.9 (2.5)	12.1 (1.2)	18.9 (0.6)	25.6 (0.5)
EQ-5D-5L				
Utility/Health State Index				
Baseline	0.8 (0.03)	0.9 (0.01)	0.8 (0.01)	0.8 (0.01)
Change from baseline to week 72	−0.05 (0.02)	0.03 (0.01)	0.05 (0.01)	0.06 (0.01)
Visual Analog Scale				
Baseline	72.4 (2.8)	80.7 (1.4)	78.3 (0.7)	78.3 (0.5)
Change from baseline to week 72	−2.5 (1.9)	2.7 (0.9)	7.0 (0.5)	9.8 (0.4)
PHQ-2				
Baseline	0.6 (0.1)	0.5 (0.06)	0.4 (0.04)	0.5 (0.03)
Change from baseline to week 72	−0.1 (0.1)	−0.03 (0.05)	−0.2 (0.03)	−0.2 (0.02)

Note: Data are presented as least squares mean (standard error).
Abbreviations: IWQOL-Lite-CT, Impact of Weight on Quality of Life-Lite Clinical Trials Version; *N*, number of participants in weight reduction group population; PHQ-2, Patient Health Questionnaire-2.

tirzepatide group had a within-patient change from baseline of ≥25 versus participants in the placebo group (all $p < 0.05$).

SF-36v2 PCS score increased from baseline for all weight reduction categories in tirzepatide-treated participants except 0 to <5% with a trend for greater improvements with an increased percentage of weight reduction (Table 4). A similar trend was observed for the individual domain scores more highly weighted in the SF-36v2 PCS. IWQOL-Lite-CT Physical composite and Physical Function composite scores increased from baseline for all weight reduction categories in tirzepatide-treated participants with a trend for greater improvements with an increased percentage of weight reduction (Table 5).

3.4 | Psychosocial function

Compared to placebo, participants in the tirzepatide 5, 10 and 15 mg groups had significantly improved SF-36v2 MCS score (Table 2), individual domain scores more highly weighted in the MCS (Vitality, Social Functioning, Role-Emotional and Mental Health) and IWQOL-Lite-CT Psychosocial composite score (Table 3).

Participants categorised as having psychosocial function limitations at baseline (PHQ-2 score ≥3) showed greater improvements in psychosocial function than participants without baseline limitations. SF-36v2 MCS score change from baseline to week 72 was 8.90 for participants with limitations at baseline versus 0.30 for those without limitations. IWQOL-Lite-CT Psychosocial composite score change from baseline was 33.8 for participants with limitations at baseline versus 21.3 for those without limitations (Table S5).

SF-36v2 MCS score and individual domain scores more highly weighted in the MCS increased from baseline for all weight reduction categories in tirzepatide-treated participants except 0 to <5%, with a trend for greater improvements with an increased percentage of weight reduction (Table 4). IWQOL-Lite-CT Psychosocial composite score increased from baseline for all weight reduction categories in tirzepatide-treated participants with a trend for greater improvements with an increased percentage of weight reduction (Table 5). PHQ-2

scores improved from baseline for all weight reduction categories in tirzepatide-treated participants (Table 5).

3.5 | Correlation between PRO improvement and weight reduction

Correlation between weight reduction in tirzepatide-treated participants and improvement from baseline in PROs was relatively weak for the overall population. When participants were divided into quartiles based on baseline PRO scores, in general, there was a weak to moderate correlation between weight reduction and PRO improvement which decreased from quartile 1 to quartile 4 (Table S6).

3.6 | Association between PRO improvement and baseline characteristics

No correlation was observed between age and PRO improvement except for a positive relationship between age and SF-36v2 Bodily Pain domain score (Table S7). Years of education showed significant negative associations with PRO improvement for the SF-36v2 Physical Functioning and Mental Health domains and IWQOL-Lite-CT Physical Function, Physical and Psychosocial composite scores. Female sex was more positively correlated with PRO improvement in all domains, except SF-36v2 Mental Health and Vitality.

4 | DISCUSSION

Across overall health, physical and psychosocial measures, there were significant improvements in PRO scores from baseline to week 72 in participants treated with 5, 10 and 15 mg tirzepatide compared to placebo in the SURMOUNT-1 trial. Participants with physical and psychosocial limitations at baseline experienced greater improvements in PRO scores and a higher proportion of patients with baseline physical limitations achieved clinically meaningful physical functioning improvements. Categorical weight reductions in tirzepatide-treated participants were associated with improvements in HRQoL with higher percentages of weight reduction resulting in greater PRO improvements, particularly when ≥5% weight reduction was achieved. However, the correlation between weight reduction and PRO improvement was relatively weak, reflecting the complexities of the lived experience for patients with obesity, with multiple factors influencing HRQoL beyond just weight reduction.[6]

Previous studies have found that obesity has a consistent and significant impact on physical functioning. Improvement in physical function is a key outcome that patients aim to achieve with weight reduction. The SF-36v2 includes several domains assessing physical functioning, including bodily pain, while the IWQOL-Lite-CT was designed to assess physical function challenges that commonly occur among people with obesity, such as trouble bending over, inability to stand comfortably and getting tired or winded,[15] and has become a key measure in obesity trials. This study demonstrated improvement in PRO scores assessing physical function with tirzepatide treatment compared to placebo and a relationship between improved physical function and weight reduction achieved with tirzepatide, with greater weight reduction associated with greater improvements. This relationship was consistent across physical function self-reported assessment methods. Notably, we also saw clinically meaningful improvements in physical function among individuals with limitations at baseline, which may be particularly relevant to clinicians counselling patients with underlying physical limitations about expected improvements following weight reduction. Additional studies of physical function outcomes among individuals treated with highly effective anti-obesity medications such as tirzepatide may demonstrate a consistent relationship between weight reduction and physical function improvements, as has been shown with bariatric surgery.[6]

Psychosocial outcomes including social, emotional and mental health are also important to patients with obesity. Previous research has demonstrated a consistent and significant impact of obesity on mental health,[7,23] including when assessed using the SF-36. Domains assessing psychosocial outcomes in the SF-36v2 include Vitality, Social Functioning, Role-Emotional and Mental Health, while the IWQOL-Lite-CT psychosocial domain includes content such as feeling self-conscious eating in social settings, feeling judged by others and feeling frustrated shopping for clothes.[15] This study demonstrated improvement in PRO scores assessing psychosocial function with tirzepatide treatment compared to placebo and a relationship between improved psychosocial function and weight reduction achieved with tirzepatide, with greater weight reduction associated with greater improvements. Similar to physical function, this relationship was consistent across psychosocial function self-reported assessment methods. We also found decreased depressive symptoms with weight reduction, as assessed by PHQ-2. Participants with psychosocial function limitations at baseline had greater increases in psychosocial function scores versus participants without limitations. Therefore, clinicians may anticipate improvements in social, emotional and mental health among patients who lose weight with tirzepatide, particularly among patients with impaired psychosocial health. However, effects on psychosocial functioning were generally smaller than physical functioning. We speculate that this is due to the fact that the relationship between psychosocial functioning and weight is highly complex and psychosocial function is also influenced by numerous other external factors that are not influenced by weight reduction.

We note that participants treated with tirzepatide who did not achieve a weight reduction of 5% or greater had poor SF-36v2 outcomes; both the PCS and MCS scores decreased in this group (indicating worsening outcomes). In contrast, we saw improvements in both physical function and psychosocial IWQOL-Lite-CT scores for all groups including the <5% weight reduction group. This difference between SF-36v2 and IWQOL-Lite-CT outcomes may reflect differences in how the PROs assess these concepts. It is also possible that HRQoL worsened in participants who experienced little weight reduction; however, this result should be interpreted cautiously given the small size of this group ($n = 83$). Overall, these results demonstrate

the importance of using multiple PRO instruments to capture different aspects of HRQoL as individual tools may be insufficient to capture the overall patient experience.

A 2017 systematic review found a consistent relationship between weight reduction and improved HRQoL after bariatric surgery; however, this relationship was less consistently demonstrated with non-surgical interventions.[6] Newer non-surgical weight reduction treatment options have demonstrated weight reduction approaching that of surgical interventions for some patients. In SURMOUNT-1, 36.2% of participants in the 15 mg tirzepatide group achieved weight reduction of ≥25%.[1] This may explain the consistent association between weight reduction and improved HRQoL observed in this study. Our observations are consistent with the STEP 1–4 semaglutide trials and a recent meta-analysis of anti-obesity medications, both of which show improvements in physical function with weight reduction.[11,12] The current study extends these observations by demonstrating concomitant improvements in psychosocial functioning with tirzepatide as well as physical functioning.

While long-term studies on HRQoL after weight reduction interventions are limited, sustained improvements in HRQoL following bariatric surgery have been shown in several studies. The Swedish Obese Subjects (SOS) intervention study evaluated people with obesity over a 10-year period following either surgical intervention or conventional treatment for weight reduction.[24] For those who underwent surgical intervention, improvements in HRQoL peaked between 6 months and 1 year, corresponding to the period of maximum weight reduction, before gradually declining from year 1 to year 6, a period where weight regain post-surgery was observed, and then remaining stable up to 10 years. At 10 years, improvements in all assessed aspects of HRQoL were observed compared to baseline. Another study found that improvements in physical aspects of HRQoL following gastric bypass surgery peaked at 2 years and then declined up to year 12.[25] However, at 12 years post-surgery, physical aspects of HRQoL remained improved compared with baseline. Small improvements in psychosocial aspects of HRQOL at 2 years were not maintained. Other studies have also shown sustained improvements in physical aspects of HRQoL following surgical interventions for weight reduction while long-term changes in psychosocial function were minimal or even diminished compared to pre-surgery levels.[26–28] Longer term assessment of patients treated with tirzepatide for chronic weight management would provide valuable insights into the durability of HRQoL improvements associated with tirzepatide and whether similar long-term patterns in physical and psychosocial functioning changes are observed compared to bariatric surgery.

We found that baseline characteristics had some association with PRO change with a generally negative correlation between years of education and PRO improvements and a positive correlation with female sex and PRO improvement. Although there are limited prior reports examining differences in HRQoL outcomes by sex, one study that examined HRQoL in the 68-week STEP 6 trial found that a greater proportion of females than males in an East Asian population treated with semaglutide achieved clinically meaningful within-patient change in IWQOL-Lite-CT scores and in physical functioning for SF-36v2. A longitudinal study examined HRQoL using the Moorehead-Ardelt Quality of Life Questionnaire over 24 months following gastric bypass or sleeve gastrectomy surgery. The authors reported that overall HRQoL significantly improved for both male and female patients 24 months after surgery. However, for female patients, HRQoL increased between 3 and 15 months after surgery and then decreased slightly, whereas for male patients, no significant change in HRQoL was observed between 3 and 24 months after surgery. This initial improvement for female patients is consistent with the positive correlation between female sex and PRO improvement observed in the present study over 72 weeks and longer studies may be needed to determine long term impact.

Strengths of the present analysis include that SURMOUNT-1 was a large global study with 1896 tirzepatide-treated patients (tirzepatide 5 mg, $N = 630$; 10 mg, $N = 636$; 15 mg, $N = 630$). Additionally, several PRO measures were used to assess HRQoL giving a more complete picture than if only one had been used. Limitations include the relatively low percentage of participants with physical function limitations at baseline (about 20%) and the exclusion of patients with a baseline PHQ-9 of ≥15 from the trial. The impact of obesity on HRQoL is made up of a complex myriad of factors. Further studies on patients with more severe baseline physical and psychosocial limitations would provide additional insight and application to real-world clinical settings where patients with obesity and multi-morbidity may have significant physical and psychosocial limitations. Additionally, conducting a pooled meta-analysis combining data from the other SURMOUNT phase 3 trials would further explore the relationship between weight loss and HRQoL improvement. Evaluation of health utility scores to inform health economic evaluations may also be a subject of future research.

In conclusion, tirzepatide treatment was associated with improved HRQoL compared to placebo in people with overweight or obesity. In tirzepatide-treated patients, greater improvements in HRQoL were seen in participants with physical or psychosocial limitations at baseline, as well as in participants with higher percentages of weight reduction.

AUTHOR CONTRIBUTIONS

Kimberly A. Gudzune, Dachuang Cao and Jiat Ling Poon contributed to the design of the study. Adam Stefanski, Dachuang Cao, Fangyu Wang and Nadia Ahmad contributed to the collection of data. Dachuang Cao and Fangyu Wang were responsible for the data analysis. All authors contributed to the interpretation of the results. All authors participated in the drafting and critical review of the manuscript and gave approval for the final version to be published.

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CONFLICT OF INTEREST STATEMENT

Kimberly A. Gudzune was engaged in this research as a private advisor and not in her capacity as a faculty member of Johns Hopkins University. She was not financially compensated for the advising service related to this work and did not receive payment or honorarium in support of authoring activities. Kimberly A. Gudzune served as medical director for the American Board of Obesity Medicine. She has received personal fees from Johns Hopkins ACG System and PRIMED; personal fees for participation on advisory boards for Eli Lilly and Company and Novo Nordisk; and travel support from Eli Lilly and Company and Novo Nordisk. Her institution has received grant funding from Novo Nordisk. Since conduct of this work, Kimberly A. Gudzune joined the American Board of Obesity Medicine Foundation as an employee. Adam Stefanski, Dachuang Cao, Donna Mojdami, Fangyu Wang, Nadia Ahmad and Jiat Ling Poon are employees and shareholders of Eli Lilly and Company.

DATA AVAILABILITY STATEMENT

Eli Lilly and Company provides access to all individual participant data collected during the trial, after anonymisation, except for pharmacokinetic or genetic data. Data are available upon request 6 months after the indication studied has been approved in the United States and European Union and after primary publication acceptance, whichever is later. No expiration date of 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 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.

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