Improvements in health-related quality of life with liraglutide 3.0 mg compared with placebo in weight management

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What is already known about this subject?

- Obesity and overweight have a negative effect on health-related quality of life (HRQoL).
- Previous studies into the effect of weight loss on HRQoL in people with obesity or overweight have produced inconsistent results.
- Liraglutide 3.0 mg is a glucagon-like peptide-1 receptor agonist approved in the EU, US, Mexico, Brazil and Canada for chronic weight management in people with obesity or overweight with comorbidities.

What this study adds

- Liraglutide 3.0 mg, as adjunct to diet and exercise, is associated with statistically significant and meaningful improvements in HRQoL in people who have obesity or are overweight with comorbidities, compared with placebo.
- Improvements in HRQoL with liraglutide 3.0 mg were observed using both disease-specific and generic instruments, across all physical and mental HRQoL subscales; however, the greatest improvements were seen in the physical aspects of HRQoL and self-esteem.

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Summary

Obesity has a negative impact on health-related quality of life (HRQoL). The SCALE Obesity and Prediabetes study investigated the effect of liraglutide 3.0 mg, as adjunct to diet and exercise, on HRQoL in patients with obesity [body mass index (BMI) $\geq$ 30 kg m^{-2}] or overweight (BMI $\geq$ 27 kg m^{-2}) with comorbidity. Participants were advised on a 500 kcal d^{-1} deficit diet and a 150-min week^{-1} exercise programme and were randomised 2:1 to once-daily subcutaneous liraglutide 3.0 mg or placebo. HRQoL was assessed using the Impact of Weight on Quality of Life-Lite (IWQOL-Lite) and Short-Form 36 (SF-36) v2 health questionnaires. Individuals on liraglutide 3.0 mg (n = 2046) had significantly greater improvements in IWQOL-Lite total score (10.6 $\pm$ 13.3) vs. placebo (n = 1020) (7.7 $\pm$ 12.8) and SF-36 physical (PCS) and mental (MCS) component summary scores (PCS, 3.6 $\pm$ 6.8; MCS, 0.2 $\pm$ 8.1) vs. placebo (PCS, 2.2 $\pm$ 7.7; MCS, −0.9 $\pm$ 9.1). The estimated treatment differences were IWQOL-Lite total score 3.1 (95% CI: 2.2; 4.0), P < 0.0001; SF-36 PCS 1.7 (95% CI: 1.2; 2.2), P < 0.0001 and MCS 0.9 (95% CI: 0.3; 1.5), P = 0.003. All subscales of the IWQOL-Lite and SF-36 were significantly improved with liraglutide 3.0 mg vs. placebo. More patients on liraglutide 3.0 mg experienced meaningful improvement on the IWQOL-Lite total (P < 0.0001) and the SF-36 PCS (P < 0.0001) scores.

Keywords: IWQOL-Lite, liraglutide 3.0 mg, quality of life, SF-36v2.

Introduction

Obesity is a chronic disease associated with an increased risk of type 2 diabetes, cardiovascular disease, select cancers and a reduced life expectancy. A number of other comorbidities have also been linked with obesity, including urinary incontinence, joint and mobility problems and obstructive sleep apnoea (1–4). Studies have shown that the health risks of obesity, alongside social stigmatization and discrimination, have a negative impact on health-related quality of life (HRQoL), the degree of which is dependent upon the level of obesity – higher body mass index (BMI) being correlated with poorer HRQoL (5–8). HRQoL is often defined as the subjective assessment of the impact of disease and treatment across the physical, psychological and social domains of functioning and well-being (9). In addition to the acute health effects of obesity, there are also economic consequences for individuals and society through lower rates of productivity and increased absenteeism (10–13). There is a clinical imperative for improving HRQoL in people with obesity as it may represent tangible physical benefits to their daily lives, for example, walking to the shops, playing football with their children or grandchildren in the park or tying their shoelaces. Regarding the mental aspects of HRQoL, improvements related to psychosocial functioning could mean feeling more energetic, freedom from anxiety and depression or improved well-being (14).

Weight loss can improve overall health and HRQoL in people with obesity, although it should be noted that improvements in HRQoL have not been universally observed in clinical studies (8,15–18). Even when statistically significant differences in HRQoL are observed in clinical trials, they are not always of a magnitude that is meaningful to the patient (19). Recognizing the importance of HRQoL, there has been growing support for the inclusion of HRQoL scales in clinical trials to inform the decisions of drug-licensing agencies and healthcare payers (20,21).

Weight loss strategies involving diet and exercise are the first-line treatment for obesity; however, the success rates of such interventions are relatively low, particularly over the long term, with up to two-thirds of dieters regaining more weight than they lost on their diets. In many cases, pharmacological intervention, alongside diet and exercise, is ultimately required (22–27).

Liraglutide, a glucagon-like peptide-1 (GLP-1) analogue, is currently licensed for the treatment of type 2 diabetes at doses of up to 1.8 mg, and a 3.0 mg d^{-1} dose has been approved in the EU, US, Mexico, Brazil and Canada for weight management in people with obesity or overweight with comorbidity. Weight loss with liraglutide is dose-dependent up to 3.0 mg once daily and is mediated by reduced appetite and energy intake rather than by increased energy expenditure (28,29). *Satiety and Clinical Adiposity – Liraglutide Evidence (SCALE) Obesity and Prediabetes*, a phase 3a clinical trial, found that liraglutide 3.0 mg induced weight loss of 8.0% (8.4 kg) of baseline body weight over 56 weeks compared to 2.6% (2.8 kg) with placebo, both in combination with lifestyle intervention, and improved a range of weight-related comorbidities (30). The aim of this analysis was to investigate the effects of liraglutide 3.0 mg, as an adjunct to diet and exercise, on HRQoL in people with obesity or overweight with comorbidity in the *SCALE Obesity and Prediabetes* trial.

Materials and methods

The study was a 56-week, randomized, double-blind, placebo-controlled, parallel group, multi-centre, multinational trial. It enrolled adults (18 years of age or older) with obesity (BMI ≥ 30 kg m^{-2}) or overweight (BMI ≥ 27 kg m^{-2}), with treated or untreated hypertension or dyslipidaemia. People with type 2 diabetes were excluded, whilst patients with prediabetes were permitted to enrol. Additional details of the inclusion and exclusion criteria are reported elsewhere (30). Participants were advised on a 500 kcal d^{-1} deficit diet and a 150-min week^{-1} exercise programme and were randomized 2:1 to once-daily subcutaneous liraglutide 3.0 mg (*n* = 2487) or placebo (*n* = 1244), which was initiated at 0.6 mg d^{-1} and escalated in weekly increments of 0.6 mg until the target dose of 3.0 mg was reached.

Two separate questionnaires were used to evaluate HRQoL: Impact of Weight on Quality of Life-Lite (IWQOL-Lite) and the Short Form-36 version 2 (SF-36v2) health survey. Participants were assessed at baseline, mid trial (28 weeks) and end of trial (56 weeks) in those countries with linguistically validated translations (14 of 27 countries; ~82% of participants). The IWQOL-Lite is a validated, 31-item, self-reported measure of obesity-specific quality of life (31,32). The IWQOL-Lite provides a total score and scores for five subscales: physical function, self-esteem, sexual life, public distress and work. The IWQOL-Lite is sensitive to the degree of obesity and responsive to weight loss and weight gain (33–35). Scores range from 0 to 100 (with lower scores indicating greater impairment). The SF-36v2 is a generic measure of health status, comprising 36 questions distributed across eight subscales. Two summary measures – the physical component summary (PCS) and the mental component summary (MCS) – are calculated from the eight scales (36). High scores represent good health status, with a score of 50 being the mean for the US general population. The SF-36 has previously been validated in large-scale, population-based surveys and in health surveys involving people with obesity (37–39).

Statistical methods

Baseline characteristics were evaluated using descriptive statistics for both the entire trial population and the study population assessed for HRQoL. This was an exploratory analysis (without adjustment for multiple testing). Absolute change in HRQoL scores from Week 0 to Week 56 was compared between liraglutide 3.0 mg and placebo using an analysis of covariance (ANCOVA) model, with treatment, country, gender, BMI stratification factor (27.0–29.9 kg m^{-2}, 30.0–34.9 kg m^{-2}, 35.0–39.0 kg m^{-2}, >40 kg m^{-2}), prediabetes status at screening, interaction between BMI strata and prediabetes status at screening as fixed factors and baseline HRQoL scores (at Week 0) as covariates. The analysis was based on the full analysis set (FAS; all randomized participants exposed to at least one dose of the trial product and with at least one post-baseline measurement) from countries where HRQoL was assessed. From this model, the differences between the treatment groups were estimated together with the corresponding two-sided 95% confidence interval (CI) and p-value. Endpoints evaluated were absolute change from baseline (Week 0) to Week 56 in the IWQOL-Lite total score and the SF-36 PCS and MCS scores and corresponding subscales. Missing values for HRQoL questionnaires at 56 weeks were imputed using last observation carried forward (LOCF). As a sensitivity analysis, repeated measures analysis of covariance (ANCOVA) was also carried out as an alternative to LOCF.

Meaningful change was defined differently for the IWQOL-Lite and the SF-36 according to published algorithms. For the IWQOL-Lite total score, the cut-off for 'improvement' and 'deterioration' varied depending on baseline severity (40). Cut-off values are provided in Table S1, Supporting Information. For the SF-36 PCS, 'improvement' was defined as a change from baseline ≥3.8; 'no change' between –3.8 and 3.8; and 'deterioration' was a change from baseline ≤ –3.8. The corresponding values for the MCS were 'improvement' as a change from baseline ≥4.6; 'no change' –4.6 and 4.6; and 'deterioration' ≤ –4.6 (41). Proportional odds models are the most popular model for ordinal logistic regression. The resulting odds ratio (OR) for a predictor can be interpreted as a summary of the odds ratios obtained from separate binary logistic regressions using all possible cut-offs of the ordinal outcome (42). The odds of achieving a meaningful improvement in the HRQoL score were estimated using an ordinal logistic regression/proportional odds model with a cumulative logit link. The model included treatment, gender, prediabetes status at screening, BMI stratification factor and an interaction between prediabetes status at screening and BMI stratification factor as fixed factors and the baseline HRQoL score (Week 0) as a covariate.

Changes in HRQoL scores were also evaluated by categories of weight change (weight gain, weight loss 0–4.9%, weight loss 5–9.9%, weight loss 10–14.9% and weight loss ≥15%) to evaluate how the magnitude of weight loss related to HRQoL.

Results

Participant characteristics

During the study period, a total of 2487 and 1244 participants were treated with liraglutide 3.0 mg and placebo, respectively. Of these, 2046 (82%) participants in the liraglutide 3.0 mg treatment arm and 1020 (82%) participants in the placebo treatment arm were assessed for HRQoL. Patient demographic and baseline characteristics were similar for both treatment arms as well as for the entire trial population and the study population in which HRQoL was assessed (Table 1). The percentage of patients who had valid IWQOL-Lite and SF-36 assessments at Week 56 was similar to the percentage of patients who completed the trial in countries where the health questionnaires were administered (data not shown).

IWQOL-Lite results

Baseline IWQOL-Lite scores were similar for the liraglutide 3.0 mg and placebo groups, with mean total scores indicating 'moderate' impairment according to the IWQOL-Lite Manual (43) (Table 2). The proportion of participants with scores reaching the maximum value (100) varied depending on the subscale, ranging from 1.1% (total score, baseline, liraglutide 3.0 mg) up to 64.7% (work score, Week 56, liraglutide 3.0 mg) (Table 2). Analysis of treatment interaction with glycaemic status (prediabetes vs. normoglycaemia) yielded no significant differences across IWQOL-Lite total or subscales (data not shown).

At Week 56, all subscales of the IWQOL-Lite showed a significantly greater increase from baseline in the liraglutide 3.0 mg group compared with placebo. Changes in IWQOL-Lite total score were also significantly different for liraglutide 3.0 mg vs. placebo, favouring liraglutide 3.0 mg (Table 2), estimated treatment difference 3.13 (95% CI: 2.24, 4.01), *P* < 0.0001 (Fig. 1). The greatest difference between liraglutide 3.0 mg and placebo was observed in the physical function subscale [estimated treatment difference 4.80 (95% CI: 3.72, 5.89), *P* < 0.0001] (Fig. 1). In addition, the odds of achieving a meaningful improvement for the IWQOL-Lite total score were higher with liraglutide 3.0 mg than with placebo [OR 1.59 (95% CI: 1.35; 1.88), *P* < 0.0001] (Fig. 2).

Estimated treatment differences using repeated measures ANCOVA as an alternative to LOCF confirmed that scores for liraglutide 3.0 mg were significantly improved for all subscales and total score compared to placebo (data not

Table 1 Subject demographics and baseline characteristics for the entire trial population and participants in whom HRQoL was assessed

	Total trial population		HRQoL-assessed population	
	Liraglutide 3.0 mg ($n = 2487$)	Placebo ($n = 1244$)	Liraglutide 3.0 mg ($n = 2046$)	Placebo ($n = 1020$)
Age, years ± SD	45.2 ± 12.1	45.0 ± 12.0	45.5 ± 12.1	45.2 ± 12.0
Age group				
18–39 years	856 (34.4%)	415 (33.4%)	686 (33.5%)	331 (32.5%)
40–64 years	1495 (60.1%)	760 (61.1%)	1242 (60.7%)	631 (61.9%)
65–74 years	130 (5.2%)	68 (5.5%)	113 (5.5%)	57 (5.6%)
≥75 years	6 (0.2%)	1 (<0.1%)	5 (0.2%)	1 (<0.1%)
Gender				
Female	1957 (78.7%)	971 (78.1%)	1639 (80.1%)	803 (78.7%)
Male	530 (21.3%)	273 (21.9%)	407 (19.9%)	217 (21.3%)
BMI, kg m^{-2} ± SD	38.3 ± 6.4	38.3 ± 6.3	38.5 ± 6.5	38.6 ± 6.5
BMI group				
27.0–29.9 kg m^{-2}	66 (2.7%)	44 (3.5%)	55 (2.7%)	39 (3.8%)
30.0–34.9 kg m^{-2}	806 (32.4%)	388 (31.2%)	644 (31.5%)	301 (29.5%)
35.0–39.9 kg m^{-2}	787 (31.6%)	398 (32.0%)	649 (31.7%)	318 (31.2%)
>40 kg m^{-2}	828 (33.3%)	414 (33.3%)	698 (34.1%)	362 (35.5)
Waist circumference, cm ± SD	115.0 ± 14.4	114.5 ± 14.3	114.9 ± 14.7	114.8 ± 14.6
Body weight, kg ± SD	106.2 ± 21.2	106.2 ± 21.7	106.4 ± 21.5	107.0 ± 22.1
Prediabetes status				
With prediabetes	1528 (61.4%)	757 (60.9%)	1218 (59.5%)	594 (58.2%)
Without prediabetes	959 (38.6%)	487 (39.1%)	828 (40.5%)	426 (41.8)
Glycated haemoglobin, % ± SD	5.6 ± 0.4	5.6 ± 0.4	5.6 ± 0.4	5.6 ± 0.4
Fasting glucose, mg dL^{-1} ± SD	95.9 ± 10.6	95.5 ± 9.8	95.6 ± 10.6	95.1 ± 9.8
Fasting serum insulin, uIU mL^{-1} ± CV	16.3 ± 79.8	16.1 ± 89.3	16.4 ± 81.5	16.4 ± 87.6
History of cardiovascular disease*, yes (%)	216 (8.7)	105 (8.5)	192 (9.4)	93 (9.1)
Blood pressure, mmHg ± SD				
Systolic	123.0 ± 12.9	123.2 ± 12.8	122.7 ± 13.0	122.7 ± 12.7
Diastolic	78.7 ± 8.6	78.9 ± 8.5	78.6 ± 8.6	78.7 ± 8.4
Cholesterol, mg dL^{-1} ± CV				
Total	193.7 ± 19.1	194.3 ± 18.8	193.9 ± 19.2	193.9 ± 18.6
LDL	111.6 ± 27.9	112.2 ± 27.6	111.6 ± 28.3	111.6 ± 27.5
HDL	51.4 ± 26.2	51.0 ± 26.4	51.8 ± 26.1	51.3 ± 26.1
Free fatty acids, mmol L^{-1} ± CV	0.45 ± 40.5	0.46 ± 39.7	0.5 ± 40.5	0.5 ± 38.8
Triglycerides, mg dL^{-1} ± CV	126.2 ± 56.9	128.9 ± 61.0	125.7 ± 56.2	128.6 ± 50.4

*Based on standardized MedDRA queries, ischaemic heart disease, cardiac failure, central nervous system haemorrhages, cerebrovascular conditions, embolic and thrombotic events.
BMI, body mass index; CV, coefficient of variation; HDL, high-density lipoprotein; HRQoL, health-related quality of life; LDL, low-density lipoprotein; MedDRA, Medical Dictionary for Regulatory Activities; SD, standard deviation (sample).

shown). Estimated treatment difference for IWQOL-Lite total score was 3.48 [(95% CI: 2.52; 4.45), $P < 0.0001$] at end of trial.

SF-36 results

Baseline SF-36 scores were similar between the liraglutide 3.0 mg and placebo groups, with mean PCS scores below the normative mean of 50 and mean MCS scores above the normative mean (Table 2). There were no participants with the maximum score in either of the summary scores. The proportion of participants with maximum score on a subscale ranged from 1.9% (general health scale, baseline, placebo) up to 69.2% (role emotional scale, Week 56, liraglutide 3.0 mg) (Table 2). Analysis of treatment interaction

with glycaemic status (prediabetes vs. normoglycaemia) yielded no significant differences across SF-36 summary scores or subscales (data not shown).

At Week 56, all subscales of the SF-36 showed a significantly greater increase from baseline in the liraglutide 3.0 mg group compared with placebo (Table 2). Changes in PCS and MCS scores were also significantly different for liraglutide 3.0 mg vs. placebo, favouring liraglutide 3.0 mg (Table 2). Estimated treatment differences for PCS and MCS scores were 1.73 [(95% CI: 1.22, 2.24), $P < 0.0001$] and 0.90 [(95% CI: 0.30, 1.50), $P = 0.0034$], respectively (Fig. 3). The greatest difference between liraglutide 3.0 mg and placebo was observed in the bodily pain subscale [estimated treatment difference 1.88 (95% CI: 1.17, 2.59), $P < 0.0001$]. In addition, the odds of achieving a

Table 2 Change in total and subscale HRQoL scores between baseline and Week 56, by treatment arm, for IWQOL-Lite and SF-36

Summary/subscale score	Liraglutide 3.0 mg				Placebo			
	n	Baseline score (LS mean ± SD)	Change from baseline score (LS mean ± SE)	Proportion of participants having maximum score at baseline/Week 56 (%)	*n*	Baseline score (LS mean)	Change from baseline score (LS mean ± SE)	Proportion of participants having maximum score at baseline/Week 56 (%)
IWQOL-Lite total	1891	73.13 ± 18.01	10.66 ± 0.25	1.1/8.1	890	72.49 ± 17.86	7.54 ± 0.37	1.0/3.9
Physical function	1891	69.39 ± 21.65	13.36 ± 0.31	3.2/15.2	891	69.04 ± 21.98	8.55 ± 0.46	2.6/10.4
Self-esteem	1893	61.12 ± 25.90	13.88 ± 0.41	6.1/20.3	891	58.99 ± 26.00	10.64 ± 0.59	5.3/15.0
Sexual life	1853	77.48 ± 26.45	8.51 ± 0.40	38.1/54.5	877	77.63 ± 26.20	6.03 ± 0.58	38.0/51.6
Public distress	1893	83.96 ± 20.59	6.03 ± 0.28	38.3/55.2	891	83.58 ± 20.45	4.44 ± 0.41	37.3/51.3
Work	1890	86.78 ± 18.43	5.56 ± 0.27	46.7/64.7	889	86.73 ± 18.57	4.51 ± 0.40	45.8/62.6
SF-36 PCS	1690	48.25 ± 8.35	3.66 ± 0.15	0.0/0.0	799	47.67 ± 8.70	1.93 ± 0.21	0.0/0.0
SF-36 MCS	1690	53.84 ± 8.08	0.14 ± 0.17	0.0/0.0	799	53.94 ± 7.93	−0.76 ± 0.25	0.0/0.0
Physical functioning	1689	47.89 ± 8.47	3.64 ± 0.15	15.0/32.8	799	47.53 ± 8.76	2.08 ± 0.22	12.7/25.2
Role physical	1690	50.00 ± 8.25	2.76 ± 0.16	39.1/57.0	799	49.59 ± 8.64	1.29 ± 0.23	38.1/49.8
Bodily Pain	1690	50.80 ± 9.72	1.86 ± 0.21	27.6/35.7	799	50.33 ± 9.81	−0.02 ± 0.30	25.0/27.7
General health	1689	49.50 ± 8.76	3.30 ± 0.16	2.9/6.1	797	49.03 ± 8.70	1.43 ± 0.23	1.8/4.2
Vitality	1689	52.57 ± 8.88	2.43 ± 0.19	1.9/5.0	799	52.12 ± 8.69	1.10 ± 0.27	1.9/2.9
Social functioning	1689	51.89 ± 7.80	1.11 ± 0.16	61.5/68.9	799	51.91 ± 7.83	0.09 ± 0.24	61.1/64.5
Role emotional	1690	51.53 ± 7.82	0.17 ± 0.16	64.6/69.2	799	51.99 ± 7.16	−0.35 ± 0.24	66.5/66.5
Mental health	1689	53.40 ± 8.29	0.76 ± 0.18	8.1/11.4	799	53.00 ± 8.19	−0.45 ± 0.27	7.0/8.6

IWQOL-Lite, Impact of Weight on Quality of Life-Lite; MCS, mental component summary; PCS, physical component summary; SD, standard deviation; SE, standard error; SF-36, Short-Form 36; LS, least square.

meaningful improvement for the PCS score were significantly greater with liraglutide 3.0 mg than with placebo [OR 1.60 (95% CI: 1.35, 1.90), $P < 0.0001$]; however, the effect for the MCS score was not statistically significant [OR 1.14 (95% CI: 0.96, 1.35), $P = 0.1427$] (Fig. 2).

Repeated measures ANCOVA confirmed that changes in score were significantly improved with liraglutide 3.0 mg for all subscales, as well as PCS and MCS, compared to placebo (data not shown). Estimated treatment difference for SF-36 PCS and MCS scores were, respectively, 1.78 [(95% CI: 1.24; 2.33), $P < 0.0001$] and 0.97 [(95% CI: 0.33; 1.60), $P = 0.0028$].

Categorical weight loss and health-related quality of life

The proportion of patients in each weight loss category by treatment arm for IWQOL-Lite total, SF-36 PCS and SF-36 MCS scores is shown in Fig. 4. For both liraglutide 3.0 mg and placebo, there was a pattern for greater improvement in IWQOL-Lite total score and SF-36 PCS score in groups with higher weight loss (Fig. 4). However, there did not appear to be any pattern to changes in MCS by weight loss category for either liraglutide 3.0 mg or placebo.

Figure 1 IWQOL-Lite estimated treatment difference for total and subscale scores at Week 56. Data are estimated treatment difference and 95% confidence intervals. *$P < 0.0001$, †$P = 0.0004$, ††$P = 0.0013$, §$P = 0.028$. IWQOL-Lite, Impact of Weight on Quality of Life-Lite.
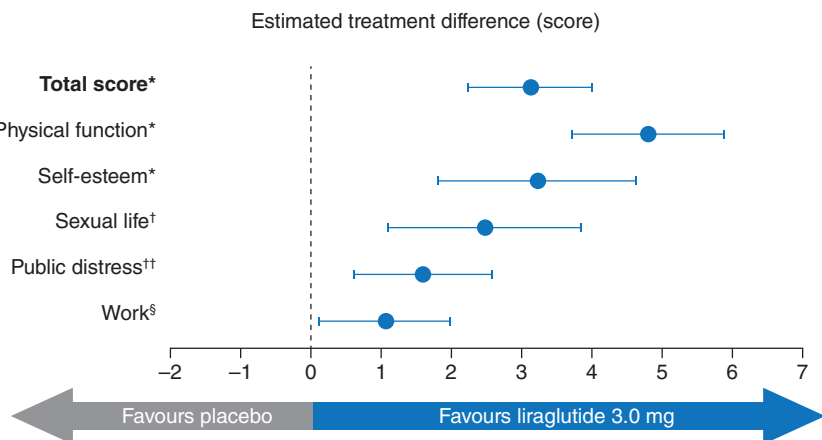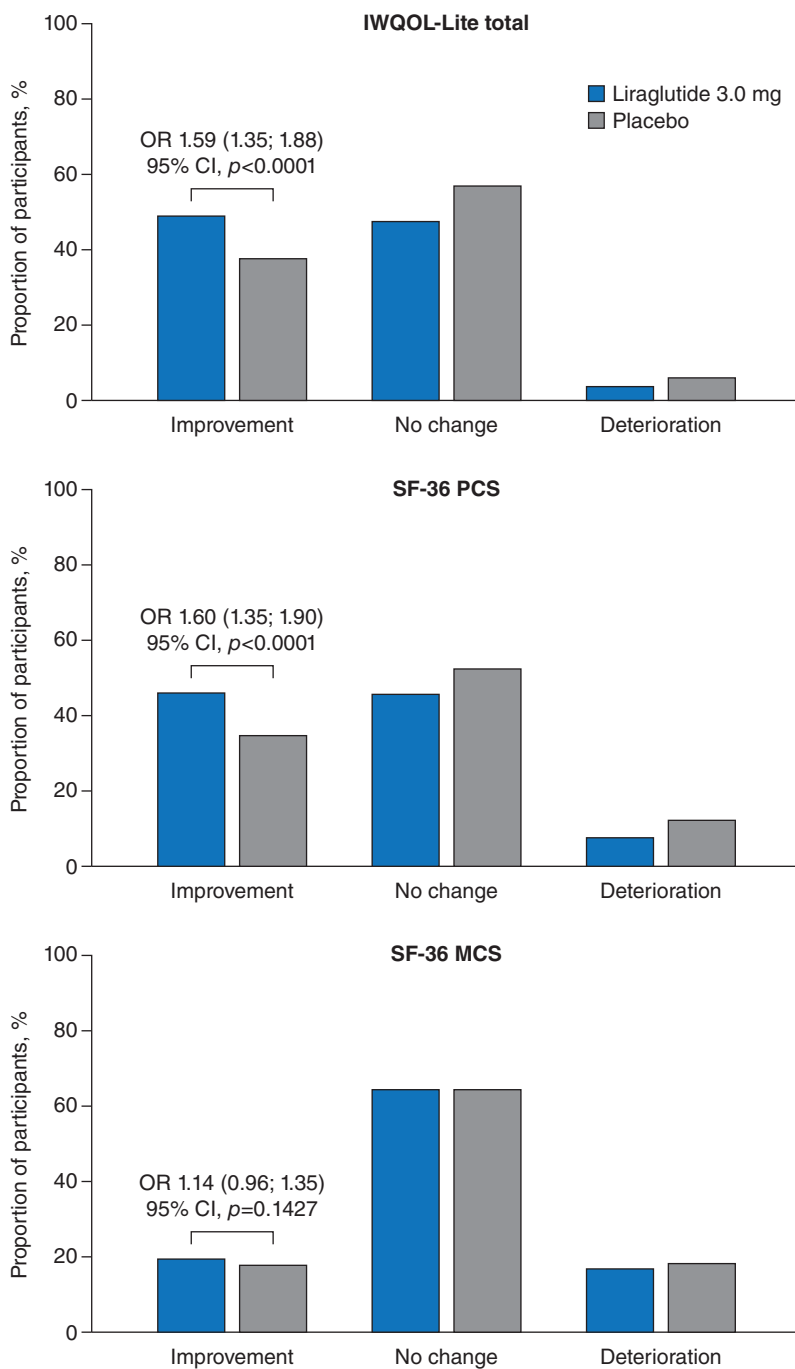
Figure 2 Meaningful change in HRQoL at Week 56 for IWQOL-Lite and SF-36. Meaningful change was defined differently for the IWQOL-Lite and the SF-36 according to published algorithms. For the IWQOL-Lite total score, the cut-off for 'improvement' and 'deterioration' varied depending on baseline severity(40). Cut-off values are provided in Table S1. For the SF-36 PCS, 'deterioration' was defined as a change from baseline ≤ −3.8; 'no change' between −3.8 and 3.8; and 'improvement' was a change from baseline ≥3.8. The corresponding values for the MCS were 'deterioration' as change from baseline ≤ −4.6; 'no change', -4.6 and 4.6 and 'improvement' ≥4.6. CI, confidence interval; HRQoL, health-related quality of life; IWQOL-Lite, Impact of Weight on Quality of Life-Lite; MCS, mental component summary; OR, odds ratio; PCS, physical component summary; SF-36, Short-Form 36.

Discussion

This analysis demonstrates that treatment with liraglutide 3.0 mg, as adjunct to diet and exercise, is associated with statistically significant improvements in HRQoL in people who have obesity or are overweight with comorbidity, compared with placebo. Improvements in HRQoL with liraglutide 3.0 mg were observed using both disease-specific and generic instruments across physical and mental HRQoL subscales; however, the greatest improvements were seen in the physical aspects of HRQoL and self-esteem. More people in the liraglutide group had meaningful improvements in their IWQOL-Lite total and SF-36 PCS scores. The categorical weight-loss results of this study suggest that increasing weight loss was associated with greater improvements in HRQoL regardless of treatment arm; however, the liraglutide 3.0 mg group experienced greater improvements in HRQoL than the placebo group, presumably because they lost more weight.
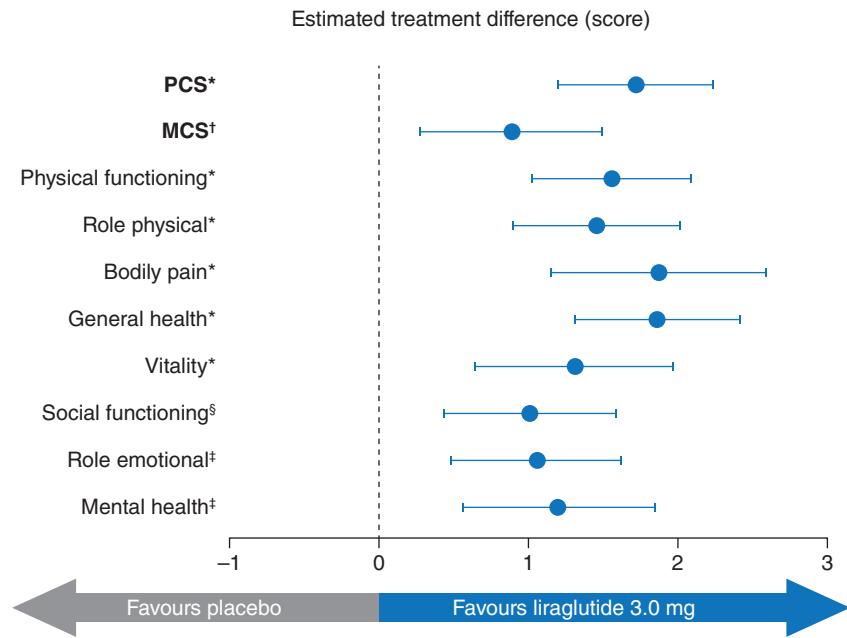
Estimated treatment difference (score)

Figure 3 SF-36 estimated treatment difference for PCS and MCS and subscale scores at Week 56. Data are estimated treatment difference and 95% confidence intervals. *$P < 0.0001$, [†]$P = 0.0034$, [‡]$P = 0.0002$, [§]$P = 0.0004$. MCS, mental component summary; PCS, physical component summary; SF-36, Short-Form 36.

Previous studies using generic and obesity-specific health questionnaires have shown mixed results concerning the effect of weight loss on HRQoL (8,15–18,44). Where improvements in HRQoL have been associated with weight loss, physical health has been the main driver, especially as measured by the SF-36 (8). The results of our study confirm the importance of physical health in HRQoL for people with obesity or overweight undergoing weight-loss interventions. However, our findings may not extend to individuals with class III obesity (BMI ≥ 40 kg m^{-2}). A meta-analysis of a broad range of study populations reports that while both physical and mental HRQoL are impaired in individuals with obesity, the patterns of impairment differ by BMI: physical HRQoL is impaired among individuals with overweight (BMI = 25–29.9 kg m^{-2}) and/or obesity (BMI = 30–39.9 kg m^{-2}), while mental HRQoL is only affected in individuals who have class III obesity (7).

The results of our analysis are strengthened by the double-blinded, randomized, placebo-controlled trial design, which reduces the risk of bias. A large and diverse population of participants was recruited to the study, giving the results a high degree of external validity. Furthermore, both the disease-specific and generic health questionnaires used in this analysis produced similar results for liraglutide 3.0 mg vs. placebo. This reinforces the results by allowing comparisons of HRQoL through different methods.

The observations in our analysis are subject to limitations. As HRQoL was not the primary endpoint of the trial, these results are exploratory rather than confirmatory. The proportions of participants with the maximum score (ceiling effect) were high in the IWQOL-Lite sexual life, public distress and work and, in SF-36, role physical,

social functioning and role emotional subscales, which may have caused us to underestimate the potential effects of liraglutide within these domains. Although not all participants in the trial had HRQoL assessed, the majority (82%) did, and the HRQoL study population was representative of the entire study population, as evidenced by similar baseline characteristics and demographics.

The results of our analysis are highly clinically relevant because they demonstrate that liraglutide 3.0 mg is associated with improvements in HRQoL, particularly in physical functioning and self-esteem, alongside weight loss, when compared with placebo; however, further investigation is needed to evaluate whether these improvements are maintained over the long term.

In summary, obesity has a serious detrimental effect on HRQoL, with negative consequences for both the individual and wider society. The results of this analysis demonstrate that treatment with liraglutide 3.0 mg, in addition to diet and exercise, is associated with better HRQoL in people with obesity or overweight with comorbidity compared with placebo. These findings will help to inform patients, clinicians and healthcare payers on the benefits of treatment with liraglutide 3.0 mg in people with obesity or overweight with comorbidity.

Conflict of interest statement

RLK has received travel support from Orexigen Therapeutics and Novo Nordisk; served as a consultant to Orexigen Therapeutics, Novo Nordisk and Eisai; served on an advisory panel for Novo Nordisk and Janssen; and receives royalties from Duke University for the IWQOL-Lite. JBB is an employee of Optum, who distributes the SF-36v2, and
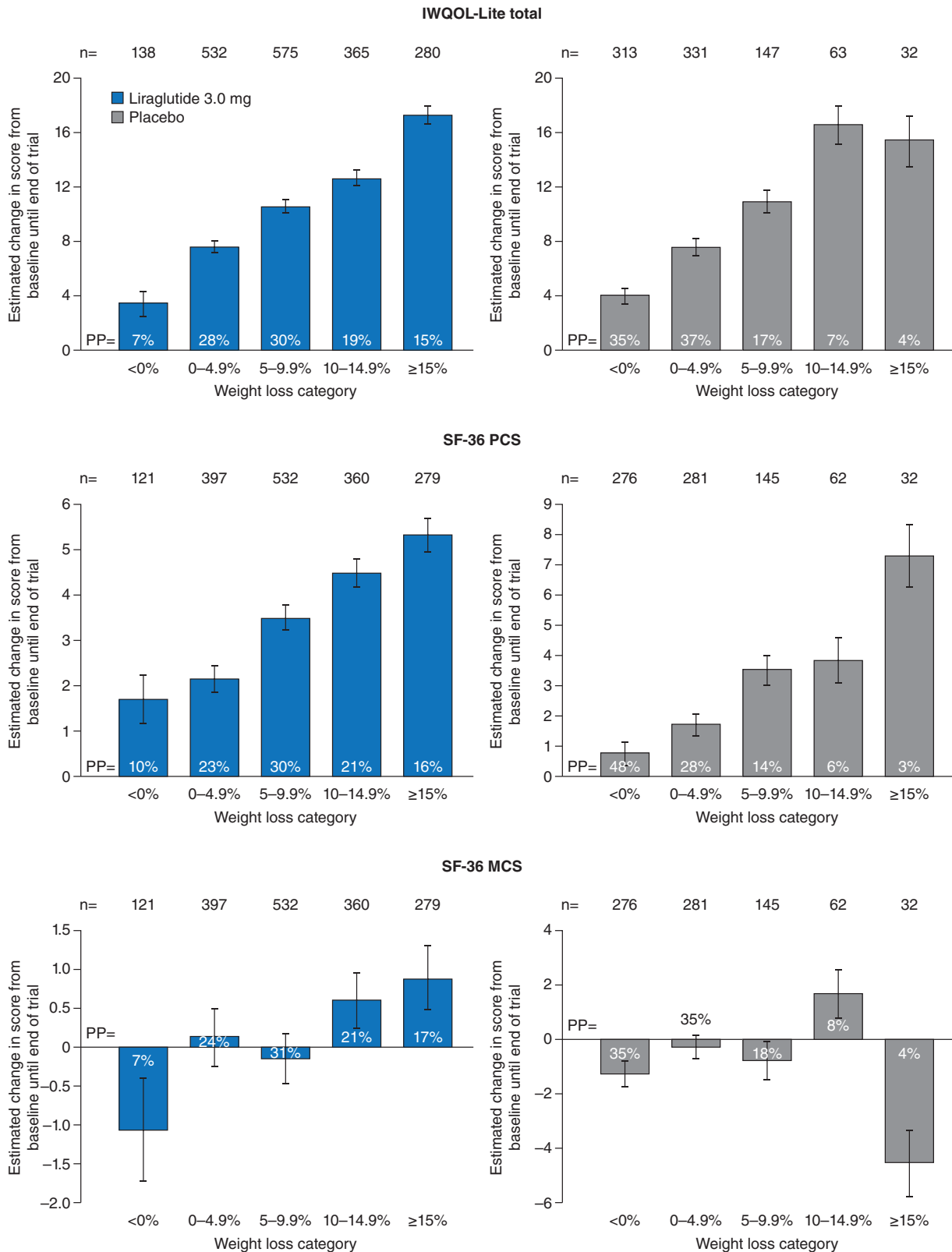
Figure 4 Estimated change in HRQoL score (IWQOL-Lite total and SF-36 PCS and MCS) by weight loss category for liraglutide 3.0 mg and placebo. Error bars are standard error. IWQOL-Lite, Impact of Weight on Quality of Life-Lite; MCS, mental component summary; PCS, physical component summary; PP, proportion of participants; SF-36, Short-Form 36.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1. Cut-off values for improvement and deterioration in IWQOL-Lite total score by baseline severity.