Healthy weight loss maintenance with exercise, GLP-1 receptor agonist, or both combined followed by one year without treatment: a post-treatment analysis of a randomised placebo-controlled trial

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eClinicalMedicine 2024;69: 102475

Published Online 19 February 2024
https://doi.org/10.1016/j.eclinm.2024.102475

Summary

Background New obesity medications result in large weight losses. However, long-term adherence in a real-world setting is challenging, and termination of obesity medication results in weight regain towards pre-treatment body weight. Therefore, we investigated whether weight loss and improved body composition are sustained better at 1 year after termination of active treatment with glucagon-like peptide-1 (GLP-1) receptor agonist, supervised exercise program, or both combined for 1 year.

Methods We conducted a post-treatment study in extension of a randomised, controlled trial in Copenhagen. Adults with obesity (aged 18–65 years and initial body mass index 32–43 kg/m^2) completed an eight-week low-calorie diet-induced weight loss of 13.1 kg (week −8 to 0) and were randomly allocated (1:1:1:1) to one-year weight loss maintenance (week 0–52) with either supervised exercise, the GLP-1 receptor agonist once-daily subcutaneous liraglutide 3.0 mg, the combination of exercise and liraglutide, or placebo. 166 Participants completed the weight loss maintenance phase. All randomised participants were invited to participate in the post-treatment study with outcome assessments one year after treatment termination, at week 104. The primary outcome of the post-treatment assessment was change in body weight from after the initial weight loss (at randomisation, week 0) to one year after treatment termination (week 104) in the intention-to-treat population. The secondary outcome was change in body-fat percentage (week 0–104). The study is registered with EudraCT, 2015-005585-32, and with ClinicalTrials.gov, NCT04122716.

Findings Between Dec 17, 2018, and Dec 17, 2020, 109 participants attended the post-treatment study. From randomisation to one year after termination of combined exercise and liraglutide treatment (week 0–104), participants had reduced body weight (−5.1 kg [95% CI −10.0; −0.2]; P = 0.040) and body-fat percentage (−2.3%-points [−4.3 to −0.3]; P = 0.026) compared with after termination of liraglutide alone. More participants who had previously received combination treatment maintained a weight loss of at least 10% of initial body weight one year after treatment termination (week −8 to 104) compared with participants who had previously received placebo (odds ratio [OR] 7.2 [2.4; 21.3]) and liraglutide (OR 4.2 [1.6; 10.8]). More participants who had previously received supervised exercise maintained a weight loss of at least 10% compared with placebo (OR 3.7 [1.2; 11.1]). During the year after termination of treatment (week 52–104), weight regain was 6.0 kg [2.1; 10.0] larger after termination of liraglutide compared with after termination of supervised exercise and 2.5 kg [−1.5 to 6.5] compared with after termination of combination treatment.

Interpretation The addition of supervised exercise to obesity pharmacotherapy seems to improve healthy weight maintenance after treatment termination compared with treatment termination of obesity pharmacotherapy alone. Body weight and body composition were maintained one year after termination of supervised exercise, in contrast to weight regain after termination of treatment with obesity pharmacotherapy alone.

Funding Helsefonden and the Novo Nordisk Foundation.

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Keywords: Obesity; Weight loss maintenance; GLP-1 receptor agonist; Exercise; Physical activity

Research in context

Evidence before this study

Newly developed incretin-based obesity pharmacotherapies result in marked weight loss. However, in real-world settings, up to half of those who initiate incretin-based therapy, have discontinued treatment within the first year. We searched PubMed for randomised controlled trials with exercise and/or pharmaceutical treatment of overweight/obesity and a post-treatment phase until September 6, 2023, with the search terms: ("exercise" OR "physical activity") OR ("glucagon-like peptide-1 receptor agonist*" OR "liraglutide" OR "semaglutide" OR "tirzepatide") AND ("follow-up" OR "extension" OR "post-treatment" OR "post treatment" OR "off-treatment" OR "off treatment" OR "termination" OR "discontinuation" OR "withdrawal" OR "after treatment") AND ("overweight" OR "obesity" OR "weight loss" OR "weight maintenance"). An off-treatment extension of a study of semaglutide, a receptor agonist of the incretin glucagon-like peptide-1 (GLP-1), showed that about two-thirds of the lost weight was regained within the first year after treatment termination. In contrast, most studies on physical activity treatment programs have reported sustained increases in physical activity levels after termination of the supervised program. In a randomised controlled trial, the combination of supervised exercise program and the GLP-1 receptor agonist liraglutide was superior to the separate treatments in terms of healthy weight loss maintenance. No studies have investigated whether improved body weight and body composition are maintained differently after the termination of a treatment regimen with exercise, pharmacotherapy, or both combined.

Added value of this study

In this study, we investigated whether weight loss and improved body composition were preserved better at 1 year after termination of active treatment with glucagon-like peptide-1 (GLP-1) receptor agonist, supervised exercise program, or both combined for 1 year. One year after treatment termination, participants who had previously received combined supervised exercise and GLP-1 receptor agonist treatment had maintained weight loss and body-fat reduction, in contrast to weight regain for participants who had previously received GLP-1 receptor agonist alone. More participants who had previously received combination treatment maintained weight losses of at least 10% one year after treatment termination compared with participants who had received placebo or GLP-1 receptor agonist alone. Weight regain during the one-year post-treatment phase was 6 kg larger after GLP-1 receptor agonist treatment compared with after supervised exercise. These results indicate that incorporating supervised exercise together with obesity pharmacotherapy helps preserve the improved body weight and body composition after termination of obesity pharmacotherapy.

Implications of all the available evidence

All available evidence shows that weight loss obtained with obesity pharmacotherapy is challenging to maintain after termination of treatment. Supervised exercise together with obesity pharmacotherapy holds more potential for preventing body weight and fat mass regain after treatment termination compared with obesity pharmacotherapy without supervised exercise.

Introduction

Obesity is a chronic and relapsing condition associated with numerous complications, including cardiovascular disease, type 2 diabetes, and impaired quality of life.[1–4]

Incretin-based treatments such as glucagon-like peptide-1 (GLP-1) receptor agonists are approved for the treatment of obesity and type 2 diabetes. GLP-1 receptor agonists induce weight loss primarily due to reduced appetite and, consequently, reduced food intake.[5,6] The S-LiTE study (Synergy effect of the appetite hormone GLP-1 (LiragluTide) and Exercise on maintenance of weight loss and health after a low-calorie diet) demonstrated superiority of the GLP-1 receptor agonist liraglutide combined with a supervised exercise program for weight maintenance and improved body composition after weight loss compared with the single treatments.[7]

New incretin-based obesity medications have shown significant therapeutic potential. The GLP-1 receptor agonist, semaglutide, resulted in 12% larger weight loss than placebo after 68 weeks.[8] The GLP-1 and glucose-dependent insulinotropic polypeptide co-agonist, tirzepatide, resulted in 18% weight loss compared with placebo after 78 weeks.[9] Despite the large weight losses with obesity medications, long-term adherence in a real-world setting is challenging since the medications are expensive and gastrointestinal adverse events are common.[8,10,11] The longest controlled trials of GLP-1 receptor agonist usage are 3–4 years,[12,13] and the long-term effects beyond this time are not well-described. In real-world settings, up to half of those who initiate treatment with a GLP-1 receptor agonist have discontinued treatment after one year.[14–17] Switching to placebo after 20 weeks of semaglutide treatment resulted in a weight regain of 6.9% body

weight in contrast to a weight reduction of 7.9% body weight with continuous semaglutide treatment at week 68, despite monthly recommendations of calorie-reduced diet and increased physical activity.[18] During a one-year off-treatment period in extension of 68 weeks of semaglutide treatment, two-thirds of the weight loss achieved with semaglutide was regained.[19] Thus, the weight-reducing effects of obesity medications seem to depend on continued usage. It is an unsolved challenge in the pharmacological treatment of obesity how medication can be terminated while minimising weight regain.

In contrast to pharmacotherapy, exercise is a low-cost intervention and represents a behavioural change that, in principle, can be continued in a real-world setting after termination of the supervised treatment. Most, but not all, studies on physical activity treatment programs have reported small, sustained increases in physical activity levels after termination of the supervised program.[20–24] These studies are heterogeneous regarding duration, physical activity intervention, degree of supervision, and study population. It is, therefore, not established whether people who have completed a long-term exercise program remain more physically active in real-world settings after termination of the supervised program. In addition, it has not been investigated whether incorporating exercise together with GLP-1 receptor agonist treatment can improve the sustainability of healthy weight loss maintenance after treatment is terminated. If exercise combined with GLP-1 receptor agonist can limit weight regain after treatment termination, as compared with GLP-1 receptor agonist alone, it would emphasize that supervised exercise programs should be available and implemented for individuals seeking obesity pharmacotherapy.

Therefore, we investigated whether weight loss and improved body composition are sustained better at 1 year after termination of active treatment with GLP-1 receptor agonist, supervised exercise program, or both combined for 1 year. Specifically, we hypothesised that weight loss and body composition were preserved better one year after termination of supervised exercise combined with a GLP-1 receptor agonist as compared with the GLP-1 receptor agonist alone.

Methods

Study design

In this article, we report the results of a post-treatment study conducted in extension of a randomised, controlled trial.[7] The study was conducted at the Department of Biomedical Sciences, University of Copenhagen, and the Department of Endocrinology, Copenhagen University Hospital—Hvidovre. The study protocol[25] and primary trial report (including reported harms)[7] have been published. The study CONSORT diagram is shown in Fig. 1.

Participants

Eligible participants were adults (aged 18–65 years) with obesity (body mass index 32–43 kg/m^2). Serious chronic illnesses, including diabetes, were exclusion criteria. All eligibility criteria are available with the protocol.[25] All participants who underwent randomisation were invited to participate in the post-treatment study regardless of completion of the active intervention.

Randomisation and masking

Adults with obesity completed an eight-week low-calorie diet with at least 5% weight loss and were randomly allocated (1:1:1:1) to exercise plus placebo, liraglutide plus usual physical activity, combined exercise plus liraglutide, or placebo plus usual physical activity for 52 weeks.[7] Randomisation was stratified by sex and age group (<40 years and ≥40 years of age). The participants, personnel, and investigators were blinded regarding study medication. Unblinding of the four intervention groups was performed after statistical analyses of body weight and body-fat percentage changes from randomisation to week 52. Participants remained blinded until they had attended the post-treatment study one year after treatment termination. The primary and secondary outcomes of the present study were analysed by a statistician blinded for group allocation.

Procedures

The study design is shown in Fig. 2. Overall, the study consisted of three phases: an eight-week weight loss phase (week –8 to 0), a 52-week randomised, controlled weight maintenance phase (week 0–52), and a one-year post-treatment phase (week 52–104). The results of the first two phases, i.e., the weight loss (week –8 to 0) and weight maintenance (week 0–52) phases, have been published previously,[7,26,27] and the results of this paper are based on the post-treatment phase alone (week 52–104) and in combination with the weight maintenance phase (week 0–104).

An initial weight loss before randomisation was chosen because the primary aim was to investigate maintenance of weight loss. To induce a similar, fast, and effective weight loss, all participants initially underwent a controlled low-calorie diet of 800 kcal/day for eight weeks, where all food was replaced with four meal replacement products per day (Cambridge Weight Plan). Participants who lost at least 5% of initial weight loss were then randomised.

Liraglutide or volume-matched placebo was administered once daily as subcutaneous injections. The starting dose was 0.6 mg per day with weekly increases of 0.6 mg until a tolerated dose of a maximum 3.0 mg per day was achieved. Liraglutide/placebo treatment was terminated after 52 weeks.

The exercise intervention started with a six-week introduction phase, where exercise volume was gradually increased. From week 7, participants were encouraged to attend supervised group exercise sessions twice per week and to exercise individually twice per week. Group exercise consisted of vigorous-intensity indoor

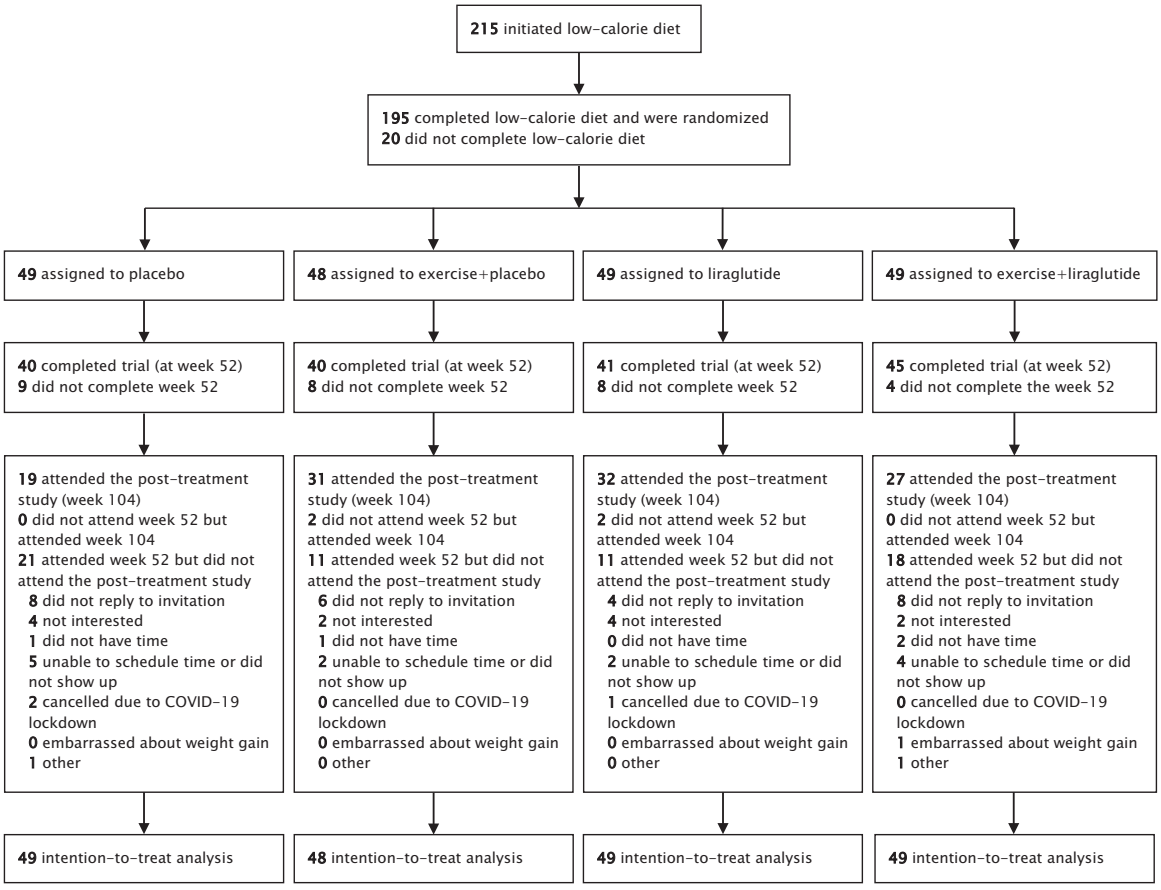

***Fig. 1:* Study CONSORT diagram**. Reasons for participants not attending the post-treatment study are shown. Reasons for participants not completing the low-calorie diet and 52-week intervention have been published previously.[7]

cycling followed by circuit training. Exercise performed individually was of moderate-to-vigorous intensity, and the type of exercise was at the participants' choice. All exercise was monitored with sports watches and heart rate monitors. Participants not allocated to exercise were encouraged to maintain habitual physical activity during

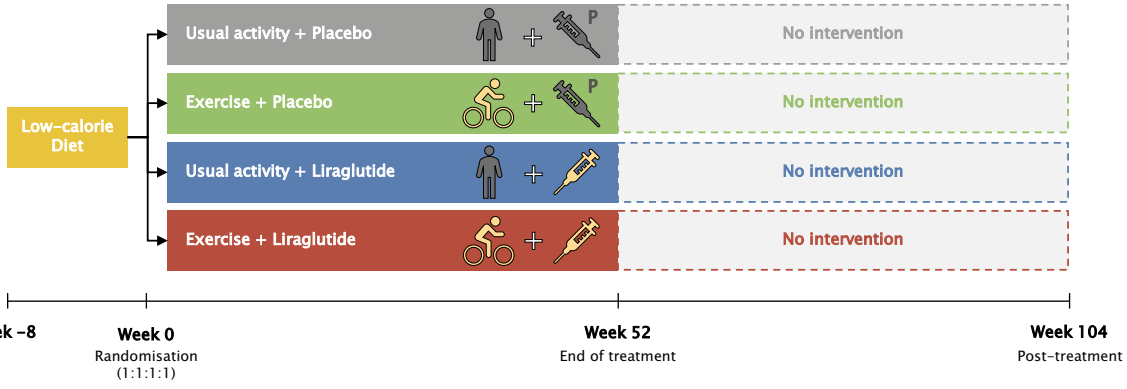

***Fig. 2:* Study profile**. Participants who obtained a weight loss of at least 5% during an 8-week low-calorie diet were randomly allocated (1:1:1:1) to exercise plus placebo, once-daily subcutaneous liraglutide 3.0 mg plus usual physical activity, combined exercise plus liraglutide, or placebo plus usual physical activity for 52 weeks. All randomised participants were invited for post-treatment outcome assessments one year after treatment was stopped. In the one-year post-treatment phase, there was no contact between study participants and study personnel.

the 52-week intervention period. At week 52, the supervised exercise program was terminated and participants returned the sports watches and heart rate monitors.

All participants who had undergone randomisation were invited to participate in the post-treatment study, which was composed of a set of outcome assessments one year after the planned completion of the 52-week weight maintenance intervention. To investigate the sustainability of the different weight maintenance treatments in a real-world setting, there was no contact between study participants and study personnel until the invitation to participate was sent by e-mail near completion of the second year. During the one-year post-treatment phase, none of the interventions were continued, and participants had neither restrictions nor encouragement in terms of weight management strategies. If the participants did not respond to the e-mail invitation, they were contacted by phone. Participants who agreed to attend, met in the morning at Hvidovre Hospital, Denmark, after having fasted for at least 10 h. The use of supplements, concomitant medication, and treatments for obesity (e.g., pharmacotherapy) were recorded.

Body weight, hip and waist circumferences, fasting glucose levels, blood pressure, and resting heart rate were measured in the fasted state before the low-calorie diet (week –8), at randomisation (week 0), at weeks 4, 13, 26, 39, 52 after randomisation, and one year after intervention completion (approximately 104 weeks after randomisation). Total body-fat and lean mass (dual-energy x-ray absorptiometry, Hologic Discovery), HbA1c, lipid levels, and self-reported quality of life were measured at weeks –8, 0, 52, and 104.

Outcomes

The primary outcome of the study was the change in body weight (kg) from randomisation to one year after termination of the weight maintenance intervention (week 0–104). The change from randomisation to week 104 is a combination of the effects of one year on active treatment and one subsequent year off treatment. This outcome was chosen since both effects on treatment and off treatment are important to evaluate the sustainable benefits in a real-world setting. The key secondary outcome was the change in body-fat percentage (calculated as fat mass (kg) divided by body weight (kg) multiplied by 100) from week 0 to 104. Other outcomes related to metabolic health were changes from week 0 to 104 in fat mass, lean mass, waist and hip circumferences, HbA1c, fasting glucose, systolic and diastolic blood pressure, resting heart rate, and plasma levels of total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides. Changes in quality-of-life outcomes were assessed with a Danish version of the RAND 36-Item Short Form Health Survey,[28] where scores in each domain range from 0 to 100, with higher scores indicating better health. Physical activity and sedentary time were objectively measured in the week leading up to the post-treatment study visit with wrist-worn accelerometers (GENEActiv, Activinsights Ltd.) analysed with the R-package GGIR v.2.9–0[29–31] and subjectively with the International Physical Activity Questionnaire.[32]

Statistical analysis

Participants were initially recruited for the weight loss and weight loss maintenance phases of the study (week –8 to 52). To investigate the sustainability of the different weight loss maintenance treatments in a real-world situation, we invited all randomised participants to the post-treatment study (week 104). A statistical analysis plan was made before data was extracted and sent to the statistician for blinded analysis of primary and secondary outcomes (see Supplementary statistical analysis plan). Changes from randomisation to one year after treatment termination (week 0–104) in body weight (primary outcome) and body-fat percentage (secondary outcome) were tested in the intention-to-treat population (defined as all randomised participants irrespective of adherence and study completion) with multiple comparisons between all four groups for a total of 12 tests (6 for each outcome). To analyse changes in continuous outcomes over time, we applied a linear mixed model with time (categorical: week-8 = 1, week 0 = 2, week 4 = 3, week 13 = 4, week 26 = 5, week 39 = 6, week 52 = 7, and week 104 = 8), treatment group, a time–group interaction, sex, and age group (<40 years, ≥40 years) as fixed effects. To account for the correlation between repeated measurements, the model assumed an unstructured covariance pattern.[33] None of the participants had missing data for any of the covariates. Missing data was implicitly handled by maximum likelihood estimation in the linear mixed model analyses. Categorical outcomes (weight loss ≥5%, ≥10%, ≥15%, and ≥20% from week –8 to 104) were analysed using logistic regression to investigate whether the probability of having sustained a weight loss one year after treatment termination was different between the four groups. The logistic regression analyses included group, sex, and age as factors. In the logistic regression analyses, for all participants who had missing body weight data at week 104, we used the predicted body weight value from the linear mixed model to calculate changes from week 0 to 104. These changes were used to categorise weight loss thresholds, and all randomised participants were therefore included in the analyses. The following supplementary analyses of primary and secondary outcomes were performed: a per-protocol analysis (excluding those who deviated from the protocol), an analysis with adjustment for the weight loss obtained during the initial low-calorie diet, a complete case analysis (excluding those who did not participate in the post-treatment study), and factor analyses testing (1) exercise groups

combined (exercise and combination groups) versus no exercise groups combined (placebo and liraglutide groups) adjusted for the effect of liraglutide and (2) liraglutide groups combined (liraglutide and combination groups) versus placebo groups combined (placebo and exercise groups) adjusted for the effect of exercise. P values are provided for the primary analyses; P values < 0.05 with a false discovery rate <0.1 were considered statistically significant. The results of all other prespecified analyses are reported with point estimates and 95% confidence intervals unadjusted for multiple testing. All statistical analyses were performed in SAS Enterprise Guide version 8.1 (SAS Institute Inc.).

Ethics

The study was approved by the Ethics Committee for the Capital Region of Denmark (H-16027082) and the Danish Medicines Agency and was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice. The study is registered with EudraCT (2015-005585-32) and ClinicalTrials.gov (NCT04122716). Written informed consents were obtained for all participants before enrolment in the main study. Separate written informed consent was obtained for all participants who attended the post-treatment study.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Participants were recruited for the randomised controlled trial between Aug 29, 2016, and Sep 14, 2018.[7] The post-treatment study was carried out from Dec 17, 2018, to Dec 17, 2020. A total of 109 participants attended the post-treatment study one year after planned intervention completion (Fig. 1), corresponding to 66% of those who completed the treatment phase. The mean time from treatment completion to post-treatment outcomes assessments was 55 ± 7 weeks. Characteristics of participants at randomisation were similar between the four intervention groups (Table S1) and similar between those who attended the post-treatment study and those who completed the active treatment but did not attend the post-treatment study (Table S2). Attendance was higher in the three groups who had received active treatment compared with placebo (Fig. 1). Four participants had initiated treatment with liraglutide in the post-treatment phase (one in the placebo group, one in the liraglutide group, and two in the exercise group).

Participants who had previously received liraglutide alone regained 9.6 kg in the one-year period after treatment was terminated (week 52–104), resulting in a net weight regain from randomisation (week 0–104) of 8.7 kg (Fig. 3A and B and Table S3). Participants who had received the combination of liraglutide and supervised exercise regained 7.1 kg in the off-treatment phase, resulting in a net weight change from randomisation (week 0–104) of 3.5 kg, which was 5.1 kg less than liraglutide alone (P = 0.040) and 4.1 kg less than placebo (P = 0.14). However, these changes did not meet the pre-specified false discovery rate (Table S4). Participants who had previously received supervised exercise alone regained 3.6 kg in the post-treatment phase. Thus, post-treatment weight regain was 6.0 kg (2.1–10.0) larger after liraglutide compared with after exercise and 2.5 kg (–1.5 to 6.5) compared with after combination treatment. The supplementary analyses of changes in body weight supported the primary analysis (Table S5). Those who attended the post-treatment study seemed to have a better response during the active treatment phase compared with those who completed the active treatment but did not attend the post-treatment study (Figure S1 and Table S6). The observed body weight measurements are shown in Fig. 3C, and the observed individual percentage weight changes from week –8 to week 104 are shown in Figure S2. More participants who had previously received combination treatment had a weight loss of at least 10% of initial body weight one year after treatment termination (week –8 to 104) compared with participants who had received placebo (odds ratio [OR] 7.2; 95% CI, 2.4; 21.3) and liraglutide (OR 4.2; 95% CI, 1.6; 10.8) (Fig. 3D and Table S7). More participants who had received exercise had a weight loss of at least 5% of initial body weight compared with liraglutide (OR 2.9; 95% CI, 1.3; 6.6) and at least 10% compared with placebo (OR 3.7, 95% CI, 1.2; 11.1). In the comparison of exercise versus non-exercise adjusted for the effect of liraglutide, exercise was associated with a weight reduction of –4.6 kg (–8.2 to –1.9) from week 0 to 104 (Fig. 3E). For liraglutide versus placebo adjusted for the effect of exercise, there was no weight reduction for liraglutide from week 0 to 104 (–0.7 kg; –4.3 to 2.9) (Fig. 3F).

From randomisation to one year after treatment termination (week 0–104), participants who had previously received the combination treatment had a 2.3%-points decrease in fat percentage compared with participants who had previously received liraglutide (P = 0.026) (Fig. 4A and B), which did not meet the prespecified false discovery rate (Table S4). The two exercise groups combined had reduced fat percentage compared with non-exercise groups (–1.5%-points; –3.0 to –0.0) (Fig. 4C) one year after treatment termination. In contrast, the two liraglutide groups combined had a similar fat percentage as placebo groups combined (0.0%-points; –1.5 to 1.5) (Fig. 4D).

The combination treatment resulted in decreased fat mass compared with liraglutide alone (Fig. 4E and Table S8) and decreased waist circumference compared

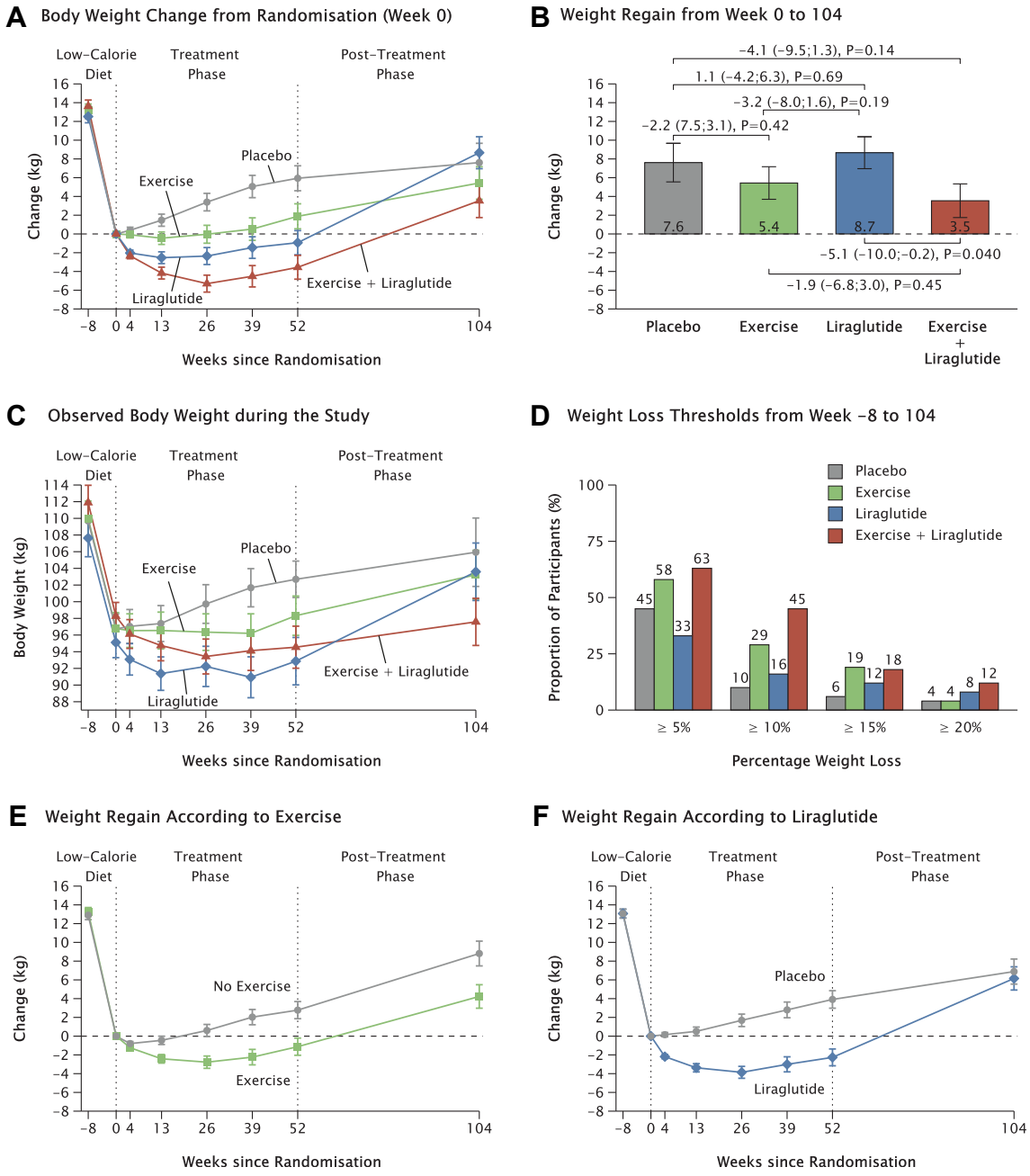

***Fig. 3*: Changes in body weight during the study**. Data are for the intention-to-treat population and reported as estimated mean ± SE changes derived from a linear mixed model with time, group, sex, age, and a time–group interaction as fixed effects unless otherwise stated. Panel A shows the estimated mean changes in body weight during a low-calorie diet (week −8 to 0), a weight maintenance intervention (week 0–52) with placebo, exercise plus placebo, liraglutide, or the combination of exercise and liraglutide, and a post-treatment phase (week 52–104). The randomisation value (week 0) is set to zero. Panel B shows the changes in body weight from randomisation (week 0) to week 104 with estimated mean differences and 95% confidence intervals between all four groups. Panel C shows the observed mean ± SE body weights in the study. Panel D shows a bar graph of the percentages of participants who had a weight loss at week 104 of at least 5%, 10%, 15%, and 20% of initial body weight (at week −8). Percentages were calculated using logistic regression. For missing data, categorisation was based on predicted values from the linear mixed model. Panel E shows the estimated mean changes in body weight from randomisation (week 0) for those who were randomised to exercise (exercise plus placebo and exercise plus liraglutide, n = 97) versus no exercise (placebo and liraglutide, n = 98) adjusted for the effect of liraglutide. Panel F shows the estimated mean changes in body weight from randomisation for those who were randomised to liraglutide (liraglutide and exercise plus liraglutide, n = 98) versus placebo (placebo and exercise plus placebo, n = 97) adjusted for the effect of exercise.

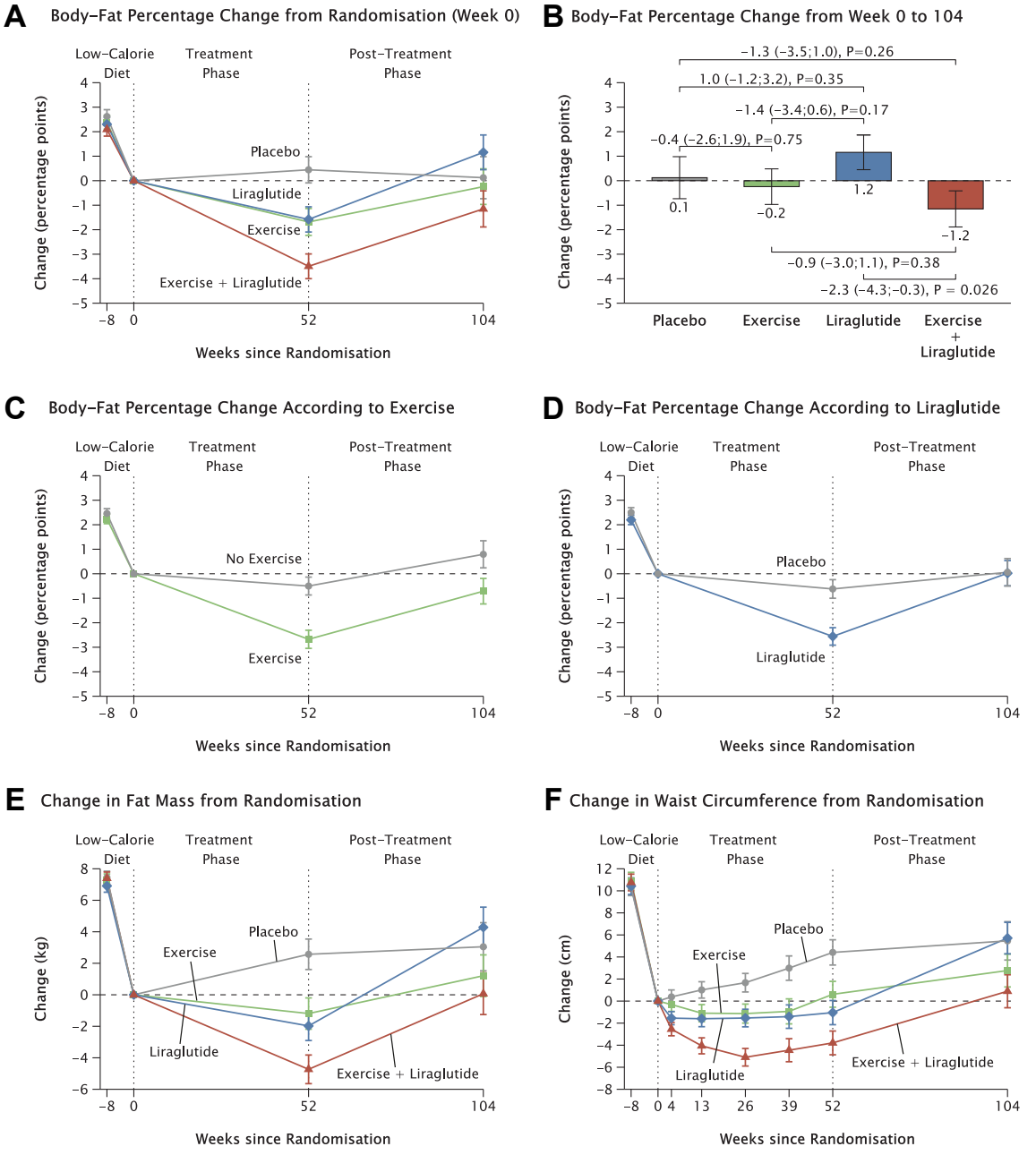

***Fig. 4:* Changes in body composition during the study**. Data are for the intention-to-treat population and reported as estimated mean ± SE changes derived from a linear mixed model with time, group, sex, age, and a time–group interaction as fixed effects unless otherwise stated. Panel A shows the estimated mean changes in body-fat percentage during a low-calorie diet (week −8 to 0), a weight maintenance intervention (week 0–52) with placebo, exercise plus placebo, liraglutide, or the combination of exercise and liraglutide, and a post-treatment phase (week 52–104). The randomisation value (week 0) is set to zero. Panel B shows the changes in body-fat percentage from randomisation (week 0) to week 104 with estimated mean differences and 95% confidence intervals between all four groups. Panel C shows the estimated mean changes in body-fat percentage from randomisation for those who were randomised to exercise (exercise plus placebo and exercise plus liraglutide, n = 97) versus no exercise (placebo and liraglutide, n = 98) adjusted for the effect of liraglutide. Panel D shows the estimated mean changes in body-fat percentage from randomisation for those who were randomised to liraglutide (liraglutide and exercise plus liraglutide, n = 98) versus placebo (placebo and exercise plus placebo, n = 97) adjusted for the effect of exercise. Panel E shows the estimated mean changes in fat mass from randomisation. Panel F shows the estimated mean changes in waist circumference from randomisation.

with placebo and liraglutide alone (Fig. 4F). All groups had similar increases in lean mass (Figure S3).

Changes in outcomes related to metabolic health are shown in Figures S3 and S4 and Table S8. The improvements in HbA1c and fasting glucose that were obtained with liraglutide alone and combined with exercise were lost one year after treatment termination. The combination treatment was associated with reduced resting heart rate compared with liraglutide alone. Changes in outcomes from the RAND 36-Item Health Survey are shown in Figure S5 and Table S8. Participants who previously received the combination treatment had improved scores of physical functioning, less limitations due to physical health, and energy/fatigue compared with liraglutide alone. Exercise alone was associated with improved energy and fatigue and pain scores compared with liraglutide.

One year after treatment termination, participants who had received exercise alone or in combination with liraglutide reported the highest levels of moderate-to-vigorous-intensity physical activity. More people who had received liraglutide without exercise reported no activity: median 150 min/week for placebo, 240 min/week for exercise, 30 min/week for liraglutide, and 225 min/week for the combination treatment (Fig. 5A). Measures of physical activity with accelerometers also indicated higher levels of physical activity in the exercise groups (Fig. 5C). Self-reported sitting and accelerometer-measured sedentary time was similar between the groups (Fig. 5B and D).

Discussion

In this study, we investigated whether exercise during obesity pharmacotherapy improved healthy weight

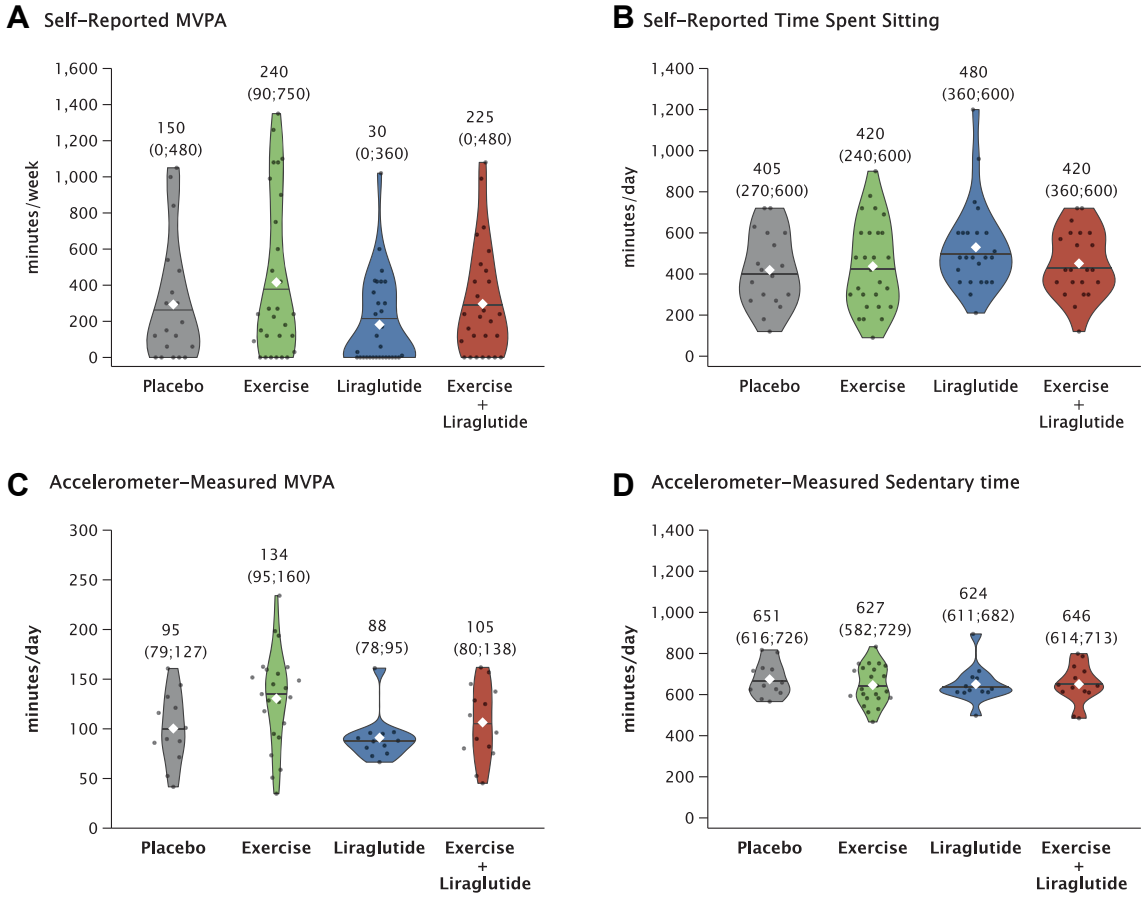

***Fig. 5:* Physical activity and sedentary time**. Violin plots of physical activity and sedentary time in the post-treatment study. Panel A shows the self-reported moderate-to-vigorous-intensity physical activity in the week leading up to post-treatment assessments (week 104). Panel B shows the self-reported daily sitting time in the week leading up to post-treatment assessments (week 104). Panel C shows the daily moderate-to-vigorous-intensity physical activity measured with accelerometers worn on the wrist in the week leading up to post-treatment assessments (week 104). Panel D shows the sedentary time measured from the accelerometers. The black lines indicate the medians, the white diamonds indicate the observed means, and the black dots indicate individual observations. Self-reported measures were calculated from the International Physical Activity Questionnaire.[32] Accelerometer-derived measures were calculated with the R-package GGIR.[29] *MVPA*, moderate-to-vigorous-intensity physical activity.

maintenance after one year of active treatment followed by one year in a real-world setting after treatment was terminated. One year after treatment termination, participants who had previously received combined supervised exercise and GLP-1 receptor agonist treatment had maintained weight loss and body-fat reduction compared with GLP-1 receptor agonist alone. More participants who had previously received combination treatment maintained a weight loss of at least 10% of initial body weight one year after treatment termination compared with participants who had received liraglutide alone or placebo. Weight regain during the one-year post-treatment phase was 6 kg larger for participants who had previously received liraglutide alone compared with participants who had previously received supervised exercise alone, despite similar initial weight loss. Collectively, these results indicate that the addition of supervised exercise during obesity pharmacotherapy improves maintenance of healthy body weight and body composition after treatment termination.

In the intervention phase of the S-LiTE study, weight loss was successfully maintained for one year with exercise and liraglutide as separate treatments, and the combination of both was the most effective strategy in terms of healthy body weight and fat reduction.[7] In the present study, approximately two-thirds of the initial weight loss had been regained one year after liraglutide treatment alone was stopped. This magnitude of regain with liraglutide alone is similar to that observed 52 weeks after a 68-week treatment phase with semaglutide 2.4 mg per week.[19] However, clinical obesity trials with off-medication phases have not previously assessed fat mass.[18,19,34,35] In our study, discontinuation of liraglutide alone was associated with a regain of 6.3 kg fat mass after one year, corresponding to a regain of more than 70% of the fat mass reduction after termination of liraglutide alone. In contrast, with liraglutide combined with exercise, after one year of habitual living after treatment termination, participants were 5.1 kg weight reduced compared with after termination of liraglutide alone. This difference resulted from a 2.7 kg larger weight reduction during active treatment and 2.5 kg less weight regain in the off-treatment period. The combination of liraglutide with exercise also led to lowered fat percentage, fat mass, and waist circumference compared with liraglutide alone, illustrating healthier body composition. A substantial larger proportion of participants who had exercised compared with non-exercise were able to sustain a weight loss of at least 10%, and greater, of initial body weight one year after treatment termination.

The analyses of exercise versus non-exercise groups showed that the improvements in body weight and body composition obtained with a one-year exercise intervention were maintained one year after the completion of the intervention. Conversely, the analyses contrasting liraglutide versus placebo groups showed that the benefits on body weight, body composition, and glucose levels obtained with liraglutide were lost one year after treatment. Therefore, our results show that supervised exercise, as a weight maintenance strategy, improves body weight and composition, which can be sustained after termination of the supervised exercise. In contrast, we found no indication of a sustained effect of liraglutide after the treatment had been terminated.

A possible explanation for the maintained benefits after exercise is that the participants remained more physically active on their own after the intervention. More participants who had exercised engaged in moderate- or vigorous-intensity physical activity in the week prior to the post-treatment assessments, compared to liraglutide alone, which was also confirmed in the questionnaires. Thus, people randomised to exercise may have had acquired exercise behaviours during the intervention and, therefore, were able to sustain higher physical activity levels after medication was stopped to minimise the otherwise insistent weight regain. This notion could also explain the observed improvements in resting heart rate and physical functioning after termination of combined exercise plus liraglutide compared with after termination of liraglutide alone. In the Finnish Diabetes Prevention Study, more participants in the lifestyle group than the control group remained physically active, as assessed by a self-reported questionnaire three years after the active intervention.[24] In adults aged +65 years, exercise-based interventions led to sustained increases in physical activity six months after interventions, but not after one year.[21] Thus, increases in physical activity may persist after controlled exercise interventions. Although the exercise program in our study was not specifically focused on maintaining habits after the intervention, a sustained effect on healthy weight was present one year after the intervention was completed. Despite the sustained weight and fat reduction after termination of combined exercise and liraglutide compared with after termination of liraglutide alone, some weight gain after treatment was not entirely prevented. Therefore, focused continued physical activity after the termination of pharmacotherapy is advisable for healthy weight maintenance. Future lifestyle-based treatments during obesity pharmacotherapy may further improve body weight and composition outcomes with an additional focus on strategies and tools to maintain healthy physical activity habits after termination of pharmacotherapy.

In our study, the weight regain resulting from one year of liraglutide treatment followed by one year off treatment exceeded the weight regain of the exercise and placebo treatments. GLP-1 receptor agonists induce weight loss primarily by appetite inhibition[5,6,36] and slowed gastric emptying,[37] and have been shown to improve eating behaviours, i.e., reduce uncontrolled and emotional eating and improve cognitive restraint.[6,38] When GLP-1 receptor agoinst treatment is stopped,

appetite inhibition and improved eating behaviours are lost, and the participants do not have any available means to counteract these changes, which is the likely cause for the observed rapid weight regain. This contrasts with physical activity interventions, where increased physical activity in principle can be continued in a real world-setting after intervention termination and, thus, treatments effects can be maintained.

The present study has several strengths. It is the first study to directly compare body weight changes after physical activity and obesity pharmaceutical interventions and investigate the combination of both. Body composition was assessed in addition to body weight using dual-energy X-ray absorptiometry to evaluate healthy weight. The inclusion of a one-year post-treatment phase with no active intervention reflects a real-world setting and is important in the evaluation of obesity treatments due to the relapsing nature of obesity. Weight regain often occurs after treatment termination, irrespective of whether the weight loss is obtained with medication or lifestyle-based interventions.[19,39] Given the many people who initiate obesity pharmacotherapy worldwide but also terminate treatment again,[14–17] off-treatment assessments are imperative to elucidate the real-world potential of pharmacotherapy and are clinically relevant. Therefore, we investigated the sustainability of exercise-based and pharmacology-based single or combination treatment for weight loss maintenance in a real-world situation. A total of 71% of the participants who had completed an active weight maintenance treatment (exercise, liraglutide, or the combination) participated in the post-treatment study. The sample size in the active treatment groups was thus sufficiently high to give indications of what happens in a real-world situation. Overall, the loss to follow-up rates in our study were similar to other post-intervention follow-up studies of exercise and long-term pharmacological interventions.[13,40,41]

The study also has limitations. Fewer participants from the placebo group participated in the post-treatment study. It is common in obesity pharmacotherapy trials that more people in the placebo group are lost to follow-up than in the active treatment group.[8,10,35] Here, we aimed to investigate and compare the sustainability of the different active weight loss maintenance treatments. For all treatment groups, those who attended the post-treatment study had a better mean treatment response during the active treatment than those who did not attend. However, in the statistical model, the repeated measurements recorded during the trial were used to estimate the missing values at the post-treatment assessment, thereby likely mitigating potential selection bias.

In summary, supervised exercise combined with obesity pharmacotherapy has the potential to prevent body weight and fat mass regain after treatment termination compared with obesity pharmacotherapy without exercise.

Contributors

SST, SBKJ, and SM contributed to the design of the post-treatment study. SBKJ, LMO, RMS, CRJ, JRL, and CJ contributed to data collection of the S-LITE study. SBKJ and LMO contributed to the practical conduction of the post-treatment study. SST, SBKJ, and MBB wrote the statistical analysis plan with contributions from CRJ, SM, BMS, and JJH. MBB performed the analyses of primary and secondary outcomes, and SBKJ performed the analyses of supportive outcomes. SBKJ and RMS processed accelerometer data. SBKJ and SST wrote the first draft of the manuscript. All authors contributed to subsequent drafts and interpretation of data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Data sharing statement

De-identified participant data that underlie the results reported in this article will be made available for research collaboration purposes upon request and approval of the requested use of data by the corresponding author and will require the completion of a data processing agreement.

Declaration of interests

RMS: family member owns Novo Nordisk stocks.

S.M.: *Advisory boards:* AstraZeneca; Boehringer Ingelheim; Eli Lilly; Merck Sharp & Dohme; Novo Nordisk; Sanofi Aventis. *Lecture fees:* AstraZeneca; Boehringer Ingelheim; Merck Sharp & Dohme; Novo Nordisk; Sanofi Aventis. *Research Grant Recipient*: Novo Nordisk, Boehringer-Ingelheim.

S.S.T.: *Research Grant and Lecture Fee Recipient*: Novo Nordisk.

J.J.H.: *Advisory board:* Novo Nordisk.

M.B.B.: *Research Grant* Novo Nordisk A/S, payment made to institution.

B.M.S.: Board member of Steno Diabetes Center Copenhagen. Board member of the Centre for Childhood Health, appointed by the Novo Nordisk Foundation.

Acknowledgements

The study was funded by the Novo Nordisk Foundation (NNF16OC0019968 and NNF15CC0018486) and Helsefonden (20-B-0389). The authors thank all who agreed to participate in the study. Novo Nordisk A/S supplied study medication (liraglutide and placebo pens). Cambridge Weight Plan supplied meal replacement products for the low-calorie diet.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102475.

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