Statistical Analysis Plan for clinical outcomes in the one-year follow-up of the S-LiTE study

Section 1: Administrative information

Title: **One-year follow-up of the *S-LiTE* randomized trial**

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This document is a supplement to the S-LiTE study protocol[1] and contains the statistical analysis plan for the article reporting the results of the 1-year follow-up of the S-LiTE study. This document follows the guidelines for content of statistical analysis plans in clinical trials.[2]

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Title: **One-year follow-up of the *S-LiTE* randomized trial**

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I hereby declare that I have reviewed and approved the Statistical Analysis Plan

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Section 2: Introduction

7 Background and Rationale

Substantial weight loss can be obtained through various treatment modalities for persons with obesity, but weight is regained gradually over time for the vast majority.[3] Reasons for this expected weight-regain include physiological responses to weight loss, i.e. decreased energy expenditure and increased hunger, and difficulty in maintaining good adherence to prescribed weight management intervention.[4]

Increasing physical activity is recommended to avoid weight regain.[5] Retrospective analyses of weight loss interventions have shown that individuals who are able to maintain weight loss are more active than those who regain weight.[6–8] However, evidence from randomized controlled trials on the benefits of exercise on weight maintenance is lacking.[9] Independent of significant weight reductions, exercise programs improve body composition by reducing fat mass while preserving lean mass.[10,11]

Liraglutide, a GLP-1 receptor agonist, is used in the treatment of obesity because it induces 4-6% weight loss[12,13] primarily by appetite inhibition.[14] Liraglutide has also been shown to maintain low-calorie diet–induced weight loss for at least one year.[15]

In our recently finished study, The S-LiTE Randomized Trial,[16] we tested the hypothesis that the combination of exercise and liraglutide would improve weight loss maintenance and body composition since the physiological response to weight loss with decreased energy expenditure is targeted with exercise and the increased appetite with liraglutide. We reported that, after an initial diet-induced weight loss of 13 kg, compared with placebo there was a significant benefit on body weight for exercise alone (−4.1 kg; 95%CI −7.8 to −0.4), for liraglutide alone (−6.8 kg; 95% CI, −10.4 to −3.1), and for the combination of both (−9.5 kg; 95% CI, −13.1 to −5.9). The combination treatment led to larger weight reduction than exercise alone (−5.4 kg; 95% CI, −9.0 to −1.7) and reduced fat percentage to a degree that was larger than exercise alone (−1.7 %-points; 95% CI, −3.2 to −0.2) and liraglutide alone (−1.9 %-points; 95% CI, −3.3 to −0.5). Therefore, we concluded that the combination of exercise and liraglutide treatment after diet-induced weight loss was more effective in improving healthy weight loss than either treatment alone.

Obesity is a chronic condition, and a challenge to any weight loss program is to maintain beneficial effects once the intervention is completed and the individuals are no longer in an active treatment regimen.

In off-drug follow-up trials of anti-obesity medications, switching to placebo from active medication is associated with gradual weight regain towards pre-intervention baseline.[17–19] On the other hand, exercise interventions represents a behavioral change that in principle can be continued by the participants on their own after the intervention is completed. For studies with an exercise intervention and post-trial follow-up, the results are not clear: some have reported sustained increases in physical activity levels evaluated 6-24 months post intervention,[20–24] whereas others have not found such sustained increase.[25–27] A synergistic resistance to obesity may be optainable between appetite inhibiting agents and exercise by lowering hypothalamic inflammation and insulin resistance.[28,29]

Whether weight loss and improved body composition obtained with either exercise, liraglutide, or the combination of both can be maintained after termination of the treatment program is unknown. Post-trial follow-up conducted after a longer period without supervision (e.g. one year) could answer whether intervention-induced health benefits persist in practice and thus elucidate the potential of implementing such treatment strategies.

8 Objectives

The overall objectives of this study are to investigate the maintenance of weight loss and improvements in body composition one year after the termination of treatment with liraglutide, exercise program, or the combination of both, in individuals with obesity.

Section 3: Study Methods

9 Trial design

The S-LiTE trial (acronym for 'Synergy effect of the appetite hormone GLP-1 (LiragluTide) and Exercise on maintenance of weight loss and health after a low-calorie diet') was an investigator-initiated, randomized, placebo-controlled, parallel group trial. The trial is registered at the European Clinical Trials Database (EudraCT Nr.: 2015-005585-32). A detailed description of the trial design has been published with the study protocol[1] and with the paper on primary and secondary outcome.[16] In brief, all participants underwent eight weeks with a low-calorie diet (LCD) (Cambridge Weight Plan, 800 kcal/day). Participants who lost at least 5 % of body weight were randomized to one of the four study groups: 52 weeks of treatment with 1) placebo, 2) exercise + placebo, 3) liraglutide, or 4) exercise + liraglutide.

Liraglutide or placebo: Liraglutide (3.0 mg) or volume-matched placebo was administrated once daily as subcutaneous injections. The starting dose was 0.6 mg with weekly increments of 0.6 mg until 3.0 mg was achieved. Participants who had unacceptable adverse effects at a given dose received the maximum dose at which they did not have such effects. Liraglutide/placebo treatment was terminated after 52 weeks (Visit 3).

Physical exercise: The exercise intervention was designed to meet the WHO global recommendations on physical activity for health of 150 minutes of moderate-intensity aerobic physical activity throughout the week or 75 minutes of vigorous-intensity aerobic physical activity throughout the week or an equivalent combination of moderate- and vigorous-intensity activity.[30] After an initial 6-week ramp-up phase, participants were encouraged to attend supervised group exercise sessions (30 minutes of vigorous-intensity, interval-based indoor cycling and 15 minutes of circuit training) two times per week and to perform moderate-to-vigorous–intensity exercise individually (mostly outdoor or indoor cycling, running, or brisk walking) two times per week. Participants not randomized to exercise were instructed to maintain habitual physical activity. At week 52 (Visit 3), participants were no longer enrolled in the exercise program.

Study visits

Test days took place before the initial weight loss phase (Visit 0, week -8), after initial weight loss (Visit 1, week 0), after 52 weeks of treatment (Visit 3), and one year after treatment was terminated (Visit 4). Weight consultations were performed weekly during the initial LCD phase and at week 1, 2, 3, 4, 9, 13, 17, 22, 26, 32, 39 and 46.

10 Randomization

After the initial eight-week LCD phase, participants were randomized after the test day (Visit 1) to one of the four study groups in a 1:1:1:1 ratio in accordance with a subject randomization list provided by Novo Nordisk. Assignment to study group was carried out by a qualified designated nurse not otherwise associated with the trial. Randomization was stratified by sex (male/female) and age (below/above 40 years).[16]

11 Sample size

All randomized participants from the original study were re-invited for this follow-up study. No sample size calculations were performed for this follow-up study. The sample size calculations for the original study are listed below:

Sample size calculation for total body weight:

The original sample size calculation for body weight (primary outcome):

Based on previous weight loss studies with liraglutide,[31,32] *we estimate the response within each treatment group to be normally distributed with a standard deviation of 5.5 kg. Thus, with 30 participants completing each study arm we will be able to detect a difference in delta of 4 kg between groups with a power of 0.8, assuming a two-sided α-level of 0.05. We will need 34 completers in each arm in order to attain a statistical power of 0.85 and 40 completers in each arm to attain a statistical power of 0.90. In our previous study, 10 % of participants who entered the initial LCD phase did not complete this phase.*[32] *With 222 recruited study participants and an expected dropout rate of 25 % after randomization, we expect to have at least 30 participants from each study arm to complete the trial*.

Sample size for total body fat percentage

The original sample size calculation for total body fat percentage (secondary outcome) were the following:

Sample size for secondary endpoint body composition was calculated in relation to total body fat percentage. Based on previous exercise trials[10,33–35] *the response within each treatment group was estimated to have a standard deviation of 2.1%. Thus, with 32 participants completing each study arm we will be able to detect a difference in delta body fat percentage of 1.5% between groups with a power of 0.8, assuming a two-sided α-level of 0.05. We will need 36 completers to attain a statistical power of 0.85. Sample size calculation for fat percentage was performed in relation to writing the SAP; after the intervention was started but prior to the termination of the intervention.*

The actual number of participants who attended outcome assessments at Visit 3 were higher than expected: 166 participants (85%) attended the visit for the assessment of the primary outcome at week 52. This included 40 of 48 (83%) in the exercise group, 41 of 49 (84%) in the liraglutide group, 45 of 49 (92%) in the combination group, and 40 of 49 (82%) in the placebo group.

12 Framework

See point 8.

13 Statistical interim analyses and stopping guidance

No interim analyses were planned and no guidelines for terminating the trial early was made.

14 Timing of final analyses

Results from Visit 1 to Visit 4 will be performed when the final participant has completed Visit 4.

15 Timing of outcome assessments

Body weight was measured at week -8 (Visit 0), -7, -6, -5, -4, -3, -2, -1, 0 (Visit 1), 1, 2, 4, 9, 13, 17, 22, 26, 39, 46, 52 (Visit 3), and 104 (Visit 4).

Body composition was measured at Visit 0, Visit 1, Visit 3, and Visit 4.
See point 26 for timing of descriptive/explorative outcome assessments.

Section 4: Statistical Principles

16-18 Confidence intervals and P values

P-values and 95% confidence intervals will be presented for comparisons (between and within group). 95% confidence intervals will be presented for estimated levels. A total of 12 comparisons will be performed between groups to evaluate the changes in the primary and secondary outcomes (6 for each outcome); all groups previously receiving active treatment will be compared with each other and with the placebo group. The Benjamini-Hochberg Procedure[36] will be used to control the false detection rate (FDR) for tests related to the primary and secondary outcomes. The overall accepted FDR will be set to 10%. Statistical significance will be claimed for tests with a FDR of 10% if the null hypothesis is rejected at the alpha level of 0.05 (two-sided). All other tests are per definition descriptive/exploratory and no definite inferences can be drawn based on these tests.

19-20 Adherence and protocol deviations and Analysis populations

Adherence will not be reported for the period following the active intervention (the follow-up period, Visit 3 to Visit 4). Those participants designated as per protocol (see below) during the active treatment period will likewise be designated as per procotol for the per protocol based supplementary analysis (see point 27).

Intention-to-treat (ITT) analysis set:
All participants analyzed as randomized.

Per Protocol (PP) analysis set:
All participants who completed the 52-week randomized treatment period with sufficient compliance to study medication and/or exercise protocol as defined by:

Study medication: Having administered 2.4 or 3.0 mg subcutaneous liraglutide/placebo for at least 75% of the intervention period (measured by self-reporting during the 12 visits from week 1 to 52 after up-titration).
Exercise: Sports watches with heart rate monitors were worn during all exercise sessions. Relative exercise intensity for each heart rate measurement was classified based on percentage of maximum heart rate (determined during a maximal incremental cycle ergometer test) accordingly: very light intensity (<57% of HR_{max}), light intensity (57-63% of HR_{max}), moderate intensity (64-76% HR_{max}), vigorous intensity (77-95% HR_{max}) and near-maximal to maximal intensity ($\geq$ 96% HR_{max}).[37] Exercise was averaged for all weeks after the ramp-up phase and until end-of-trial test day and exercise compliance was calculated as percentage of WHO's global recommendations on physical activity for health: *Adults aged 18–64 should do at least 150 minutes of moderate-intensity aerobic physical activity throughout the week or do at least 75 minutes of vigorous-intensity aerobic physical activity throughout the week or an equivalent combination of moderate- and vigorous-intensity activity.*[30] Thus, for example, one minute of moderate-intensity exercise accounted for 1/150 and one minute of vigorous- or near-maximal to maximal intensity exercise accounted for 1/75 of prescribed weekly exercise. Per protocol analysis set was defined as meeting at least 75% of global recommendations.

For participants to be included in the per protocol analysis:
a) Liraglutide group: Having administered 2.4 or 3.0 mg sc liraglutide for at least 75% of the intervention period.
b) Placebo group: Having administered 2.4 or 3.0 mg sc placebo for at least 75% of the intervention period.
c) Exercise + placebo group: Having administered 2.4 or 3.0 mg sc placebo for at least 75% of the intervention period and having met at least 75% of global recommendations on physical activity.
d) Exercise + liraglutide group: Having administered 2.4 or 3.0 mg sc liraglutide for at least 75% of the intervention period and having met at least 75% of global recommendations on physical activity.

Section 5: Trial Population

21 Screening data

Screening data will not be reported.

22 Eligibility

Inclusion and exclusion criteria for study participation has been described previously.[1,16] All participants who underwent randomization were eligible to attend the follow-up assessments (Visit 4).

23 Recruitment

The flow chart of the trial will follow the CONSORT guidelines and will include the number of participants who a) received oral information, b) were assessed for eligibility at prescreening, c) were included in the trial, d) attended first test day and initiated LCD, e) were withdrawn or excluded from the LCD phase, f) were randomized, g) were allocated to the four intervention groups, h) lost to follow-up during active treatment, i) discontinued the intervention, j) attended the test day after one year of treatment, k) attended the one-year post-intervention test day, l) lost to follow-up during the one-year follow-up period, and m) were included in the analysis.

24 Withdrawal/follow-up

The number/frequency of participants lost to follow-up (those not attending a weight measurement at Visit 4) will be provided for each group and for each time point. If possible, the reasons for participants not completing the trial will be given. Summary of baseline levels for variables reported in the baseline table, plus weight changes during the LCD and during active treatment, will be provided for completers and non-completers. Spaghetti plots will be used to visualize levels of the main outcome for completers and non-completers.

25 Baseline participant characteristics

The distribution of all outcomes included in baseline characteristics will be visually inspected using QQ-plots and histograms; those with a Gaussian distribution will be presented as means and standard deviations and those with a non-Gaussian distribution will be presented as medians plus 25^{th} and 75^{th} percentiles.
The following outcomes will be included in the baseline participant characteristics table for all participants combined at Visit 0, all participants combined at Visit 1 and participants divided by randomization group at Visit 1:

- Number of participants (men/women)
- Age (years)
- Weight (kg)
- BMI (kg/m^2)
- Waist circumference (cm)
- Total fat mass (kg)
- Total fat free mass (kg)
- Body fat percentage (%)
- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- HbA1c (mmol/mol)
- Fasting glucose (mmol/L)
- Cholesterol: total, LDL and HDL (mmol/L)
- Triglycerides (mmol/L)
- SF-36 (scoring of eight health concepts ranging from 0-100: physical functioning, role limitations due to physical health problems, role limitations due to personal or emotional problems, energy/fatigue, emotional well-being, social functioning, pain, and general health perception)

Section 6: Analysis

26 Outcome definitions

Primary outcome: Primary outcome is the change in total body weight (measured to the nearest 0.1 kg) from baseline (Visit 1) to end-of-treatment (Visit 4). A weight difference of 2.5-4.5 % body weight, obtained with liraglutide or semaglutide compared to placebo, have been associated with beneficial cardiovascular outcomes.[40,41] A weight difference of 1-5% of body weight obtained with exercise has been associated with beneficial cardiovascular disease risk factors[5,38] and prevention of diabetes.[39]
Thus, a difference in delta of 3-5% of total body weight has been defined as the minimal important difference. The definition for how the absolute size of the minimal important difference was defined in the SLiTE trial: *With a study population consisting of men and women (expected mean height of 170-174 cm based on previous lifestyle trials performed in Denmark[32,42,43] and a BMI range of 32-43 kg /m^2, a difference of 3-5% of total body weight will correspond to 4 kg.*

Secondary outcome: Secondary outcome body composition is defined as change in total body fat percentage (measured to the nearest 0.01 % in fasted state with dual-energy X-ray absorptiometry (DXA) scans) from Visit 1 to Visit 4. In most exercise interventions with aerobic exercise, almost exclusively fat mass is lost whereas lean mass is close to unchanged.[10,11,44,45] In weight loss studies with liraglutide, a combination of fat and lean mass is lost.[46,47] The clinically relevant effect size for changes in fat percentage is not well described or investigated. However, based on the results of previous exercise interventions,[10,48] a decrease in fat percentage equivalent of approximately 1.5 % seems to be physiologically relevant.

Descriptive/explorative outcomes:
Changes in total body weight and body fat percentage from Visit 0 to Visit 1, from Visit 1 to Visit 3, and from Visit 3 to Visit 4.

Change from Visit 1 to Visit 4:

- Body composition (fat free mass (kg) and fat mass (kg))
- Circulating biomarkers of metabolic regulation to evaluate metabolic health (fasting glucose (mmol/L and fasting insulin (pmol/L) for HOMA-IR , HbA1c (mmol/mol), waist circumference (cm), systolic and diastolic blood pressure (mmHg), lipids (total cholesterol, HDL, LDL, and triglycerides (mmol/L))
- Self-rated quality of life will be measured with the SF-36 questionnaire. Eight health concepts ranging from 0-100 will be scored: physical functioning, role limitations due to physical health problems, role limitations due to personal or emotional problems, energy/fatigue, emotional well-being, social functioning, pain, and general health perception.
- Use of medication (n, frequency)
- Determination of daily physical activity and sleep
- Systemic markers of immune-metabolism and oxidation
- Gene expression profile of circulating inflammatory cells
- Bone health
- Food preferences (Leeds Food Preferences Questionnaire, LFPQ)
- Questionnaires: Three-factor eating questionnaire (TFEQ), International Physical Activity Questionnaire (IPAQ), General self-efficacy scale (G-SES), and Pittsburgh Sleep Quality Index (PSQI)
- Plasma metabolomics and proteomics

27 Analysis methods

Analyses of primary and secondary outcome (except for the pre-planned sensitivity analyses) will be performed based on the intention-to-treat (ITT) principle. All continuous outcomes will be modelled using linear mixed effects models with the following fixed effects and interactions: Time (factorial), Treatment, Time (factorial)*Treatment, sex (female, male) and age group (<40 years, ≥40 years). The models will be specified with a restricted maximum likelihood estimation method, the Kenward-Roger degrees of freedom method, and a repeat on participant level (unstructured covariance structure). Model fit will be evaluated using graphical methods and if necessary, outcomes will be log-transformed. Estimated mean differences (CI95%) for changes between groups (main study effects), conditional means (CI95%), and within group changes (CI95%) will be extracted from the model. For log-transformed outcomes the results will be back-transformed and be presented as the ratio between estimated relative changes (CI95%), estimated conditional geometric means (CI95%) and within group relative changes (CI95%), respectively. Between group differences in changes will be null-hypothesis tested and presented with P-values.
The following predefined sensitivity analyses will be performed for the primary and secondary outcome; an additional ITT analysis with adjustment for initial weight loss, an ITT analysis using multiple imputation to assess effects of missing data (see also 28), and finally an analysis of per protocol completers.

The analysis of the primary and secondary outcome will be performed blinded to group allocation by a researcher (Martin Bæk Blond) that have not been involved in the execution of the trial. The statistical and clinical/physiological implications of the results will be evaluated by the research team before un-blinding.

28 Missing data

The number/frequency of missing values for the primary and secondary outcome in each group at each time point will be provided. In the primary analysis, missing data is handled implicitly by maximum likelihood estimation in the repeated measures regression model and missing data will be assumed to be missing at random. This is equivalent to making multiple imputations for each treatment group separately and estimates the treatment effect that would have been found had all subject completed their assigned treatment (efficacy estimate) under the missing at random assumption. In order to challenge the assumptions of the primary analysis we will perform a supplementary analysis based on datasets with multiple imputations of missing values in which it is assumed that the development in body weight among the participants from active treatment groups that are lost-to-follow-up will resemble the development in the placebo group rather than the development in the group to which they were randomized. Participants from the active treatment groups with missing values at Visit 4 will be pooled with the placebo group and using a Markov chain Monte Carlo method all missing values will be imputed to create 1000 new datasets, assuming a multivariate normal distribution for the data. The dataset used for the imputation will include all previous measurements for total body weight/fat percentage, age and sex. Subsequently, the imputed datasets will be analyzed using a mixed linear model including the same variables included in the main analysis and averaged estimates will be calculated. If the main outcome has been transformed to fit the statistical model used for the main analysis this transformation will be applied to the outcome prior to the imputation procedure.

29 Additional analyses

Not relevant

30 Harms

No harms will be reported for the post-intervention follow-up period.

31 Statistical software

R version 3.6.0 or newer version (The R Foundation for Statistical Computing, www.R-project.org) and SAS version 9.4 or newer version (SAS Institute, Cary, NC, USA).

References

1 Jensen SBK, Lundgren JR, Janus C, *et al.* Protocol for a randomised controlled trial of the combined effects of the GLP-1 receptor agonist liraglutide and exercise on maintenance of weight loss and health after a very low-calorie diet. *BMJ Open* 2019; **9**: e031431.

2 Gamble C, Krishan A, Stocken D, *et al.* Guidelines for the content of statistical analysis plans in clinical trials. *JAMA - J Am Med Assoc* 2017; **318**: 2337–43.

3 Nordmo M, Danielsen YS, Nordmo M. The challenge of keeping it off, a descriptive systematic review of high-quality, follow-up studies of obesity treatments. Obes Rev. 2020; **21**. DOI:10.1111/obr.12949.

4 Hall KD, Kahan S. Maintenance of Lost Weight and Long-Term Management of Obesity. Med Clin North Am. 2018; **102**: 183–97.

5 Donnelly JE, Blair SN, Jakicic JM, Manore MM, Rankin JW, Smith BK. Appropriate physical activity intervention strategies for weight loss and prevention of weight regain for adults. *Med Sci Sports Exerc* 2009; **41**: 459–71.

6 Jakicic JM, Marcus BH, Lang W, Janney C. Effect of Exercise on 24-Month Weight Loss Maintenance in Overweight Women. *Arch Intern Med* 2008; **168**: 1550.

7 Ewbank PP, Darga LL, Lucas CP. Physical Activity as a Predictor of Weight Maintenance in Previously Obese Subjects. *Obes Res* 1995; **3**: 257–63.

8 Unick JL, Gaussoin SA, Hill JO, *et al.* Objectively Assessed Physical Activity and Weight Loss Maintenance among Individuals Enrolled in a Lifestyle Intervention. *Obesity* 2017; **25**: 1903–9.

9 Beaulieu K, Blundell JE, Baak MA, *et al.* Effect of exercise training interventions on energy intake and appetite control in adults with overweight or obesity: A systematic review and meta-analysis. *Obes Rev* 2021; : e13251.

10 Willis LH, Slentz CA, Bateman LA, *et al.* Effects of aerobic and/or resistance training on body mass and fat mass in overweight or obese adults. *J Appl Physiol* 2012; **113**: 1831–7.

11 Foster-Schubert KE, Alfano CM, Duggan CR, *et al.* Effect of diet and exercise, alone or combined, on weight and body composition in overweight-to-obese postmenopausal women. *Obesity* 2012; **20**: 1628–38.

12 Pi-Sunyer X, Astrup A, Fujioka K, *et al.* A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management. *N Engl J Med* 2015; **373**: 11–22.

13 Davies MJ, Bergenstal R, Bode B, *et al.* Efficacy of liraglutide for weight loss among patients with type 2 diabetes: The SCALE diabetes randomized clinical trial. *JAMA - J Am Med Assoc* 2015; **314**: 687–99.

14 Van Can J, Sloth B, Jensen CB, Flint A, Blaak EE, Saris WHM. Effects of the once-daily GLP-1 analog liraglutide on gastric emptying, glycemic parameters, appetite and energy metabolism in obese, non-diabetic adults. *Int J Obes* 2014; **38**: 784–93.

15 Wadden TA, Hollander P, Klein S, *et al.* Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: The SCALE Maintenance randomized study. *Int J Obes* 2013; **37**: 1443–51.

16 Lundgren JR, Janus C, Jensen SBK, *et al.* Healthy Weight Loss Maintenance with Exercise, Liraglutide, or Both Combined. *N Engl J Med* 2021; **384**: 1719–30.

17 Smith SR, Weissman NJ, Anderson CM, *et al.* Multicenter, Placebo-Controlled Trial of Lorcaserin for Weight Management. *N Engl J Med* 2010; **363**: 245–56.

18 Rubino D, Abrahamsson N, Davies M, *et al.* Effect of Continued Weekly Subcutaneous Semaglutide vs Placebo on Weight Loss Maintenance in Adults with Overweight or Obesity: The STEP 4 Randomized Clinical Trial. *JAMA - J Am Med Assoc* 2021; **325**: 1414–25.

19 James WPT, Astrup A, Finer N, *et al.* Effect of sibutramine on weight maintenance after weight loss: A randomised trial. *Lancet* 2000; **356**: 2119–25.

20 Lindström J, Ilanne-Parikka P, Peltonen M, *et al.* Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study. *Lancet* 2006; **368**: 1673–9.

21 Hardcastle SJ, Taylor AH, Bailey MP, Harley RA, Hagger MS. Effectiveness of a motivational interviewing intervention on weight loss, physical activity and cardiovascular disease risk factors: a randomised controlled trial with a 12-month post-intervention follow-up. International Journal. *Int J Behav Nutr Phys Act* 2013; **10**: 1–16.

22 Andersen E, Burton NW, Anderssen SA. Physical activity levels six months after a randomised controlled physical activity intervention for Pakistani immigrant men living in Norway. *Int J Behav Nutr Phys Act* 2012; **9**.

23 Liu-Ambrose TYL, Khan KM, Eng JJ, Gillies GL, Lord SR, McKay HA. The beneficial effects of group-based exercises on fall risk profile and physical activity persist 1 year postintervention in older women with low bone mass: Follow-up after withdrawal of exercise. *J Am Geriatr Soc* 2005; **53**: 1767–73.

24 Hertogh EM, Vergouwe Y, Schuit AJ, *et al.* Changes after a 1-yr Exercise Program and Predictors of Maintenance. *Med Sci Sport Exerc* 2010; **42**: 886–92.

25 Skogstad M, Lunde LK, Ulvestad B, *et al.* The effect of a leisure time physical activity intervention delivered via a workplace: 15-month follow-up study. *Int J Environ Res Public Health* 2018; **15**: 1–13.

26 Henderson RM, Miller ME, Fielding RA, *et al.* Maintenance of Physical Function 1 Year after Exercise Intervention in At-Risk Older Adults: Follow-up from the LIFE Study. *Journals Gerontol - Ser A Biol Sci Med Sci* 2018; **73**: 688–94.

27 Aparicio-Ting FE, Farris M, Courneya KS, Schiller A, Friedenreich CM. Predictors of physical activity at 12month follow-up after a supervised exercise intervention in postmenopausal women. *Int J Behav Nutr Phys Act* 2015; **12**: 1–12.

28 Krawczewski Carhuatanta KA, Demuro G, Tschöp MH, Pfluger PT, Benoit SC, Obici S. Voluntary exercise improves high-fat diet-induced leptin resistance independent of adiposity. *Endocrinology* 2011; **152**: 2655–64.

29 Patterson CM, Dunn-Meynell AA, Levin BE. Three weeks of early-onset exercise prolongs obesity resistance in DIO rats after exercise cessation. *Am J Physiol - Regul Integr Comp Physiol* 2008; **294**: 290–301.

30 Bull FC, Al-Ansari SS, Biddle S, *et al.* World Health Organization 2020 guidelines on physical activity and sedentary behaviour. *Br J Sports Med* 2020; **54**: 1451–62.

31 Astrup A, Rössner S, Van Gaal L, *et al.* Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study. *Lancet* 2009; **374**: 1606–16.

32 Iepsen EW, Lundgren J, Dirksen C, *et al.* Treatment with a GLP-1 receptor agonist diminishes the decrease in free plasma leptin during maintenance of weight loss. *Int J Obes* 2015; **39**: 834–41.

33 Mensberg P, Nyby S, Jørgensen PG, *et al.* Near-normalization of glycaemic control with glucagon-like peptide-1 receptor agonist treatment combined with exercise in patients with type 2 diabetes. *Diabetes, Obes Metab* 2017; **19**: 172–80.

34 Skrypnik D, Bogdański P, Mądry E, *et al.* Effects of Endurance and Endurance Strength Training on Body Composition and Physical Capacity in Women with Abdominal Obesity. *Obes Facts* 2015; **8**: 175–87.

35 Slentz CA, Duscha BD, Johnson JL, *et al.* Effects of the Amount of Exercise on Body Weight, Body Composition, and Measures of Central Obesity: STRRIDE - A Randomized Controlled Study. *Arch Intern Med* 2004; **164**: 31–9.

36 Benjamini Y, Hochberg Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *J R Stat Soc Ser B* 1995; **57**: 289–300.

37 Garber CE, Blissmer B, Deschenes MR, *et al.* Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: Guidance for prescribing exercise. *Med Sci Sports Exerc* 2011; **43**: 1334–59.

38 Shaw K, Gennat H, O'Rourke P, Del Mar C. Exercise for overweight or obesity. *Cochrane Database Syst Rev* 2006. DOI:10.1002/14651858.CD003817.pub3.www.cochranelibrary.com.

39 Knowler WC, Barrett-Connor E, Fowler SE, *et al.* Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002; **346**: 393–403.

40 Marso SP, Daniels GH, Brown-Frandsen K, *et al.* Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med* 2016; **375**: 311–22.

41 Marso SP, Bain SC, Consoli A, *et al.* Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2016; **375**: 1834–44.

42 Blond MB, Rosenkilde M, Gram AS, *et al.* How does 6 months of active bike commuting or leisure-time exercise affect insulin sensitivity, cardiorespiratory fitness and intra-abdominal fat? A randomised controlled trial in individuals with overweight and obesity. *Br J Sports Med* 2019; **53**: 1183–92.

43 Iepsen EW, Zhang J, Thomsen HS, *et al.* Patients with Obesity Caused by Melanocortin-4 Receptor Mutations Can Be Treated with a Glucagon-like Peptide-1 Receptor Agonist. *Cell Metab* 2018; **28**: 23-32.e3.

44 Donnelly JE, Jacobsen DJ, Snyder Heelan K, Seip R, Smith S. The effects of 18 months of intermittent

vs continuous exercise on aerobic capacity, body weight and composition, and metabolic ®tness in previously sedentary, moderately obese females. 2000 www.nature.com/ijo (accessed Nov 12, 2019).

45 Nordby P, Auerbach PL, Rosenkilde M, *et al.* Endurance training per se increases metabolic health in young, moderately overweight men. *Obesity* 2012; **20**: 2202–12.

46 Jendle J, Nauck MA, Matthews DR, *et al.* Weight loss with liraglutide, a once-daily human glucagon-like peptide-1 analogue for type 2 diabetes treatment as monotherapy or added to metformin, is primarily as a result of a reduction in fat tissue. *Diabetes, Obes Metab* 2009; **11**: 1163–72.

47 Frøssing S, Nylander M, Chabanova E, *et al.* Effect of liraglutide on ectopic fat in polycystic ovary syndrome: A randomized clinical trial. *Diabetes, Obes Metab* 2018; **20**: 215–8.

48 Sigal RJ, Kenny GP, Boulé NG, *et al.* Effects of aerobic training, resistance training, or both on glycemic control in type 2 diabetes: A randomized trial. *Ann Intern Med* 2007; **147**: 357–69.