

ORIGINAL ARTICLE

Healthy Weight Loss Maintenance with Exercise, Liraglutide, or Both Combined

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ABSTRACT

BACKGROUND

Weight regain after weight loss is a major problem in the treatment of persons with obesity.

METHODS

In a randomized, head-to-head, placebo-controlled trial, we enrolled adults with obesity (body-mass index [the weight in kilograms divided by the square of the height in meters], 32 to 43) who did not have diabetes. After an 8-week low-calorie diet, participants were randomly assigned for 1 year to one of four strategies: a moderate-to-vigorous-intensity exercise program plus placebo (exercise group); treatment with liraglutide (3.0 mg per day) plus usual activity (liraglutide group); exercise program plus liraglutide therapy (combination group); or placebo plus usual activity (placebo group). End points with prespecified hypotheses were the change in body weight (primary end point) and the change in body-fat percentage (secondary end point) from randomization to the end of the treatment period in the intention-to-treat population. Prespecified metabolic health-related end points and safety were also assessed.

RESULTS

After the 8-week low-calorie diet, 195 participants had a mean decrease in body weight of 13.1 kg. At 1 year, all the active-treatment strategies led to greater weight loss than placebo: difference in the exercise group, -4.1 kg (95% confidence interval [CI], -7.8 to -0.4 ; $P=0.03$); in the liraglutide group, -6.8 kg (95% CI, -10.4 to -3.1 ; $P<0.001$); and in the combination group, -9.5 kg (95% CI, -13.1 to -5.9 ; $P<0.001$). The combination strategy led to greater weight loss than exercise (difference, -5.4 kg; 95% CI, -9.0 to -1.7 ; $P=0.004$) but not liraglutide (-2.7 kg; 95% CI, -6.3 to 0.8 ; $P=0.13$). The combination strategy decreased body-fat percentage by 3.9 percentage points, which was approximately twice the decrease in the exercise group (-1.7 percentage points; 95% CI, -3.2 to -0.2 ; $P=0.02$) and the liraglutide group (-1.9 percentage points; 95% CI, -3.3 to -0.5 ; $P=0.009$). Only the combination strategy was associated with improvements in the glycated hemoglobin level, insulin sensitivity, and cardiorespiratory fitness. Increased heart rate and cholelithiasis were observed more often in the liraglutide group than in the combination group.

CONCLUSIONS

A strategy combining exercise and liraglutide therapy improved healthy weight loss maintenance more than either treatment alone. (Funded by the Novo Nordisk Foundation and others; EudraCT number, 2015-005585-32; ClinicalTrials.gov number, NCT04122716.)

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THE PREVALENCE OF OBESITY IS INCREASING,¹ with detrimental effects on health.² Obesity is characterized by excess body fat and is associated with physical inactivity,³ which also impairs health and increases the risk of death.⁴ A decrease in body weight of 3 to 5% has been associated with reduced obesity-related risk factors, although a larger weight loss of more than 5 to 15% of the initial body weight is recommended for patients with coexisting conditions, morbid obesity, or both.^{2,5} Many patients have an initial large weight loss, but weight regain often occurs^{6,7} unless a structured weight-maintenance program is followed. Rapid weight regain may be due to a reduction in total energy expenditure, beyond that predicted from the loss of lean and fat mass,⁸ and to increased appetite.⁹⁻¹¹ Structured aerobic exercise programs increase energy expenditure and cardiorespiratory fitness while reducing fat mass and preserving or increasing lean mass.¹²⁻¹⁴ Diet management programs, including the use of low-calorie meal-replacement products, can sustain low-calorie diet-induced weight loss with a small weight regain.^{11,15-17} Furthermore, lifestyle interventions that encourage increased physical activity concurrent with calorie restriction have been shown to sustain moderate weight loss.^{18,19} However, the isolated benefits of exercise to prevent weight regain after weight loss is understudied.²⁰

Liraglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist, is used in the treatment of obesity because it induces weight loss²¹⁻²³ and maintains low-calorie diet-induced weight loss for at least 1 year,^{11,24} primarily by means of appetite inhibition.²⁵ Whether exercise, medication, or a combination strategy constitutes the more effective approach for maintaining healthy weight loss remains an open question. We investigated the efficacy of 1-year treatment with a moderate-to-vigorous-intensity exercise program, liraglutide at a dose of 3.0 mg per day, or the combination of exercise plus liraglutide, as compared with placebo, for healthy weight loss maintenance after weight loss induced by a low-calorie diet.

METHODS

TRIAL DESIGN AND OVERSIGHT

We conducted this investigator-initiated, randomized, head-to-head, placebo-controlled trial at Hvidovre Hospital and the University of Copenhagen, Denmark. Participants followed a low-

calorie diet of 800 kcal per day (Cambridge Weight Plan) for 8 weeks. All the participants who had a weight loss of at least 5% of their baseline body weight were randomly assigned, in a 1:1:1:1 ratio, to one of the following treatment strategies for 1 year: exercise plus placebo (exercise group), liraglutide plus usual activity (liraglutide group), exercise plus liraglutide (combination group), or placebo plus usual activity (placebo group). Randomization was stratified according to sex and age (<40 years vs. ≥40 years of age) (see Methods Section A in the Supplementary Appendix, available with the full text of this article at NEJM.org).

Participants, assessors, and investigators were unaware of the trial-group assignments with regard to liraglutide or placebo. To support the maintenance of weight loss after randomization, all the participants were to attend 12 individual consultations that included measurement of body weight and dietetic support complying with the dietetic recommendations for sustained weight loss from the Danish authorities (see Methods Section B in the Supplementary Appendix). The trial was approved by the local ethics committee and the Danish Medicines Agency and was conducted according to the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. All the participants provided written informed consent before the first trial visit.

Our primary trial report adheres to the CONSORT (Consolidated Standards of Reporting Trials) guidelines. The trial design has been published previously,²⁶ and the protocol, with the statistical analysis plan, is available at NEJM.org.

Eight of the authors designed the trial, and nine authors gathered data. Statistical analyses of hypothesis-based end points (change in body weight [primary] and body-fat percentage [secondary]) were performed in a blinded manner with regard to group assignment by a statistical assessor who is an author but who was not involved in the trial design and execution. Four of the authors analyzed other end points. All the authors had full access to all the data and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. The first four authors and the last author wrote the first draft of the manuscript, which all the authors edited and approved. All the authors agreed to submit the manuscript for publication.

Novo Nordisk supplied liraglutide and placebo injector pens, and Cambridge Weight Plan sup-

plied diet-replacement products for the low-calorie-diet phase. The funding partners did not influence or take part in the execution of the trial; in the collection, analysis, ownership, or interpretation of the data; or in the communication of the trial results.

PARTICIPANTS

Eligible participants were adults (18 to 65 years of age) with obesity, which was defined as a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of 32 to 43. Diabetes (type 1 or 2) was a major exclusion criterion. Full lists of the inclusion and exclusion criteria are provided in Table S1 of the Supplementary Appendix.

INTERVENTIONS

The exercise program was designed to meet the World Health Organization (WHO) recommendations on physical activity for health of a minimum of 150 minutes per week of moderate-intensity aerobic physical activity, or 75 minutes per week of vigorous-intensity aerobic physical activity, or an equivalent combination of both.²⁷ Each participant was assigned to an instructor (who had a bachelor's or master's degree in exercise physiology) who planned and monitored the individualized programs. After an initial 6-week ramp-up phase, participants were encouraged to attend supervised group exercise sessions (which involved 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 (which mostly involved outdoor or indoor cycling, running, or brisk walking) two times per week. Heart-rate monitors were worn at all exercise sessions to determine whether the requirement regarding weekly time spent at moderate or vigorous intensity was met.

The exercise program was structured but flexible, which meant that participants could substitute group exercise with individual exercise or vice versa; participants could also reduce exercise frequency if the duration was prolonged or the intensity was increased. Modifications were made in agreement between the participant and instructor if deemed necessary in order to reach the sufficient exercise volume (duration \times intensity). Adherence was based on the weekly exercise volume. A detailed program description is provided in Methods Section D in the Supplemen-

tary Appendix. Participants who were not randomly assigned to trial exercise (i.e., those in the placebo group or liraglutide group) were instructed to maintain usual physical activity.

Liraglutide (at a concentration of 6 mg per milliliter) or volume-matched placebo was injected subcutaneously, starting at a dose of 0.6 mg per day, with supervised weekly increments of 0.6 mg per day; the dose was intended to eventually reach 3.0 mg per day. Participants who had unacceptable adverse effects at a given dose received the maximum dose at which they did not have such effects. Participants remained enrolled in the trial if the use of liraglutide or placebo was discontinued (see Methods Section C in the Supplementary Appendix).

END POINTS

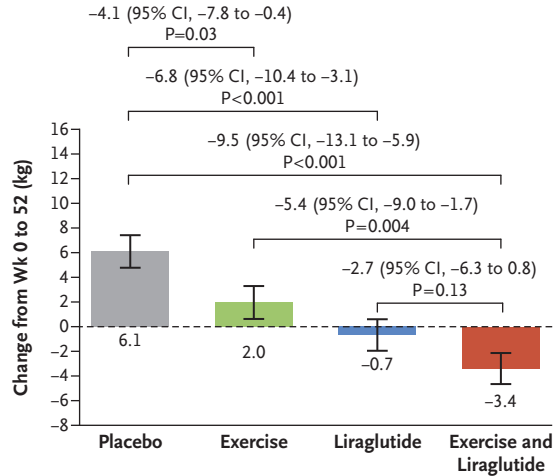
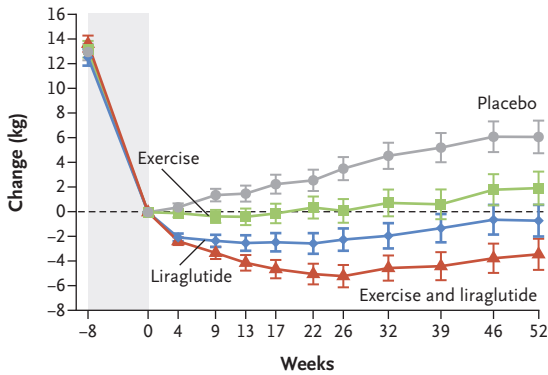
The primary end point was the change in body weight (in kilograms) from randomization to week 52. The secondary end point was the change in the percentage of body fat (calculated as the fat mass [in kilograms] divided by the body weight [in kilograms], times 100) from randomization to week 52. Body weight was measured before the prerandomization low-calorie diet was started, at randomization, and at weeks 1, 2, 4, 9, 13, 17, 22, 26, 32, 39, 46, and 52. The percentage of body fat was measured by means of dual-energy x-ray absorptiometry (Hologic Discovery) before the low-calorie diet was started, at randomization, and at week 52.

Prespecified metabolic health-related end points included changes from randomization to week 52 in fat mass, lean mass, cardiorespiratory fitness, glycated hemoglobin level, indexes of insulin resistance during fasting (liver insulin resistance, as assessed by the homeostatic model assessment of insulin resistance [HOMA-IR]) and during meal intake (whole-body insulin resistance, as assessed by the Matsuda index²⁸), lipid levels, quality of life, waist and hip circumferences, waist-to-hip ratio, blood pressure, and resting heart rate (see Methods Section G in the Supplementary Appendix). Adverse events and the dose of liraglutide or placebo were reported and registered at all visits.

STATISTICAL ANALYSIS

We estimated that a sample of 30 participants in each group would provide the trial with 80% power to detect a minimal clinically important difference in the primary end point, the change

A Change in Body Weight



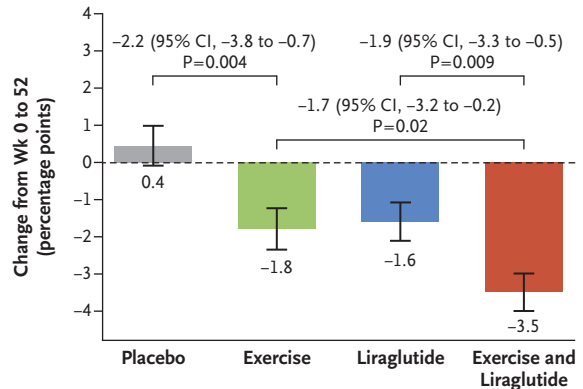
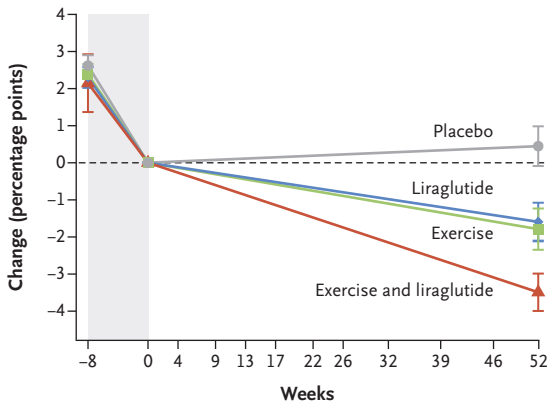
No. of Participants

215 195 187 183 181 178 178 175 171 169 168 166

No. Who Underwent Randomization
No. Who Completed Trial

Group	No. Who Underwent Randomization	No. Who Completed Trial
Placebo	49	40
Exercise	48	40
Liraglutide	49	41
Exercise and Liraglutide	49	45

B Change in Body-Fat Percentage



C Change in Body Weight from Wk -8 to Wk 52

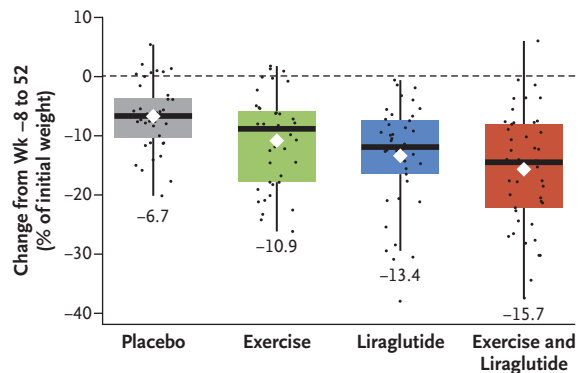
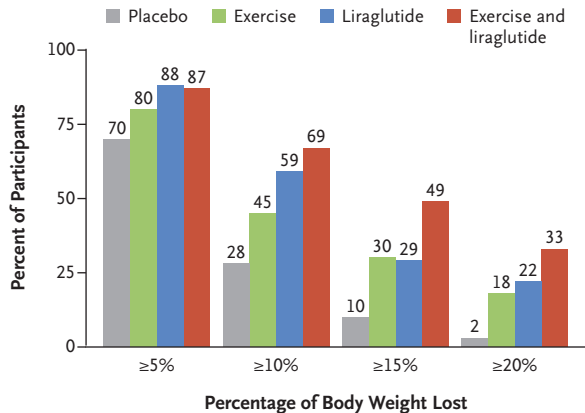


Figure 1 (facing page). Changes in Body Weight and Body-Fat Percentage during the Trial.

Shown are the mean changes in body weight (primary end point; Panel A) and body-fat percentage (secondary end point; Panel B) during a low-calorie diet (weeks -8 to 0, shaded area) and during 1 year of subsequent treatment (from randomization [week 0] to week 52). All the means were estimated from a repeated-measures linear regression model with time, group, sex, age, and a time-group interaction as explanatory variables in the intention-to-treat population. I bars indicate the standard error, and the dashed lines indicate baseline at randomization (week 0). The results from the prespecified hypotheses of changes in body weight and body-fat percentage from week 0 to 52 are shown in the bar charts as estimated mean differences with 95% confidence intervals. (See the Hypothesis: Analysis Results and Claims section in the Supplementary Appendix.) Panel C shows a bar chart of the percentages of participants in each trial group who had a total weight loss from baseline at enrollment (week -8) to the end of the trial (week 52) of at least 5%, 10%, 15%, and 20% of the initial body weight (left graph) and also shows a box plot of the percentage weight loss from baseline (dashed line) to the end of the trial in each group (right graph). In the box plot, the diamonds indicate means; the black horizontal bars medians; the tops and bottoms of the boxes the upper and lower quartiles, respectively; and the whiskers ± 1.5 times the interquartile range or the smallest or highest observation. Dots indicate individual observations.

in body weight, of 4.0 kg at an alpha level of 0.05.^{11,21} For the secondary end point, the change in body-fat percentage, we estimated that a sample of 32 participants in each group would provide the trial with 80% power to detect a minimal clinically important difference of 1.5 percentage points at an alpha level of 0.05.¹³ We anticipated that 68% of the participants would complete the trial (see item 11 in the statistical analysis plan, which is available with the protocol).

In accordance with the prespecified statistical analysis plan, eight hypotheses for the primary and secondary end points were tested hierarchically (see the Hypotheses: Analysis Results and Claims section in the Supplementary Appendix and items 8 and 16 through 18 in the statistical analysis plan). The analyses were performed in the intention-to-treat population.

End points were analyzed with the use of a repeated-measures linear regression model, which included time (factorial), trial group, sex, age group (<40 years vs. ≥ 40 years), and a time-group interaction as explanatory variables and a repeated effect for visit. A multivariate normal

error structure was assumed in the model. All missing data were assumed to be missing at random. Three prespecified supplementary analyses were performed regarding body weight and body-fat percentage — a per-protocol analysis (which excluded participants who had deviations from the protocol), an analysis with adjustment for initial weight loss during the low-calorie diet (to assess the effect of missing data by incorporating further information), and an analysis that used multiple imputations (under the assumption that participants who were lost to follow-up would have a response as if they received placebo, in order to challenge the assumption that data were missing at random) (see items 27 and 28 in the statistical analysis plan). Prespecified end points without hypotheses are reported as point estimates with 95% confidence intervals that were unadjusted for multiple testing, so definite inferences cannot be made regarding those end points.

RESULTS

TRIAL POPULATION

The trial was conducted from August 2016 through November 2019. A total of 215 participants initiated the low-calorie diet, of whom 195 had a weight loss of at least 5% of their baseline body weight; these 195 participants underwent randomization. A total of 166 participants (85%), including 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, attended the visit for the assessment of the primary end point at week 52 (Fig. 1A and Table S13). The reasons that participants missed the assessment visit are shown in Figure S1. The demographic characteristics of the participants at randomization were similar across the trial groups (Table S3).

LOW-CALORIE DIET

The characteristics of the participants before and after the low-calorie diet are shown in Table 1. During the 8-week low-calorie diet, the participants' body weight decreased by a mean of 13.1 kg (95% confidence interval [CI], 12.4 to 13.7), which was equivalent to a mean reduction in body weight of 12%. This decrease was accompanied by decreases in the body-fat percentage, waist circumference, waist-to-hip ratio, glycated

Table 1. Characteristics of the Participants before and after 8 Weeks of a Low-Calorie Diet.*

Characteristic	Before Low-Calorie Diet (N=215)	After Low-Calorie Diet, at Randomization (N=195)
Sex — no. (%)		
Male	80 (37)	71 (36)
Female	135 (63)	124 (64)
Age — yr	42±12	43±12
Body weight — kg	109.7±14.9	96.7±12.5
Body-mass index	37.0±2.9	32.6±2.9
Body-fat percentage — %	41.1±6.1	38.6±6.9
Fat mass — kg	44.9±7.2	37.7±7.2
Lean mass — kg	65.3±12.9	60.4±11.6
Waist circumference — cm	110.6±11.3	100.3±10.0
Hip circumference — cm	121.4±7.5	113.9±7.3
Waist-to-hip ratio	0.91±0.10	0.88±0.10
Cardiorespiratory fitness — ml/min/kg†	22.9±4.2	24.9±5.4
Glycated hemoglobin — mmol/mol	36±4	34±3
Blood pressure — mm Hg		
Systolic	132±16	122±13
Diastolic	86±10	79±8
Resting heart rate — beats/min	73±10	69±12
HOMA-IR‡	3.9±2.4	1.7±1.0
Matsuda index§	2.7±1.8	4.9±2.7
Cholesterol — mmol/liter		
Total	5.0±1.0	4.1±0.8
Low-density lipoprotein	3.1±0.8	2.5±0.8
High-density lipoprotein	1.3±0.3	1.1±0.3
Triglycerides — mmol/liter	1.5±0.9	1.1±0.4
RAND-36 score¶		
General health perception	71±16	79±15
Physical functioning	86±13	91±11
Emotional well-being	81±12	84±11

* Plus–minus values are observed means ±SD. Among the 215 enrolled participants who began the low-calorie diet, those who had a weight loss at 8 weeks of at least 5% of their baseline body weight (195 participants) underwent randomization. The estimated mean changes (with 95% confidence intervals) during the low-calorie diet are shown in Table S2. To convert the values for cholesterol to milligrams per deciliter, divide by 0.02586. To convert the values for triglycerides to milligrams per deciliter, divide by 0.01129.

† Cardiorespiratory fitness was assessed as the peak oxygen consumption (in milliliters of oxygen per minute per kilogram of body weight).

‡ The homeostatic model assessment of insulin resistance (HOMA-IR) was calculated as the fasting insulin level (in milliu-nits per milliliter) times the fasting glucose level (in millimoles per liter), divided by 22.5. The conversion factor that was used for insulin was that 1 μ U per milliliter was equal to 6.00 pmol per liter. The conversion factor that was used for glucose was that 1 mg per deciliter was equal to 0.05551 mmol per liter.

§ The Matsuda index was calculated as 10,000 divided by the square root of the following value: the fasting glucose level times the fasting insulin level times the mean glucose level times the mean insulin level.

¶ Scores on each domain of the RAND 36-Item Health Survey (RAND-36) range from 0 to 100, with higher scores indicating better health.

hemoglobin level, blood pressure, lipid levels, resting heart rate, and HOMA-IR. The Matsuda index, cardiorespiratory fitness, general health perception, physical functioning, and emotional well-being increased (Table S2).

WEIGHT LOSS MAINTENANCE AT 1 YEAR

Adherence to Interventions

The mean (\pm SD) weekly duration of exercise was 118 ± 74 minutes at an intensity of $78\pm 4\%$ of the maximum heart rate in the exercise group and 111 ± 73 minutes at an intensity of $79\pm 5\%$ of the maximum heart rate in the combination group, which corresponded to adherence of $119\pm 70\%$ and $113\pm 71\%$, respectively, of the WHO recommended exercise volume.²⁷ The mean exercise frequency was 2.5 times per week in the exercise group and 2.4 times per week in the combination group. In both groups, approximately one third of the exercise was performed during group sessions and the remaining exercise was performed individually, with a similar mean intensity in the group and individual exercise sessions (Table S7).

The mean dose of liraglutide was 2.8 ± 0.4 mg per day in the liraglutide group and 2.8 ± 0.7 mg per day in the combination group; the mean dose of volume-matched placebo was 2.6 ± 0.9 mg per day in the exercise group and 2.9 ± 0.4 mg per day in the placebo group. Details are provided in Table S8.

Body Weight and Body-Fat Percentage

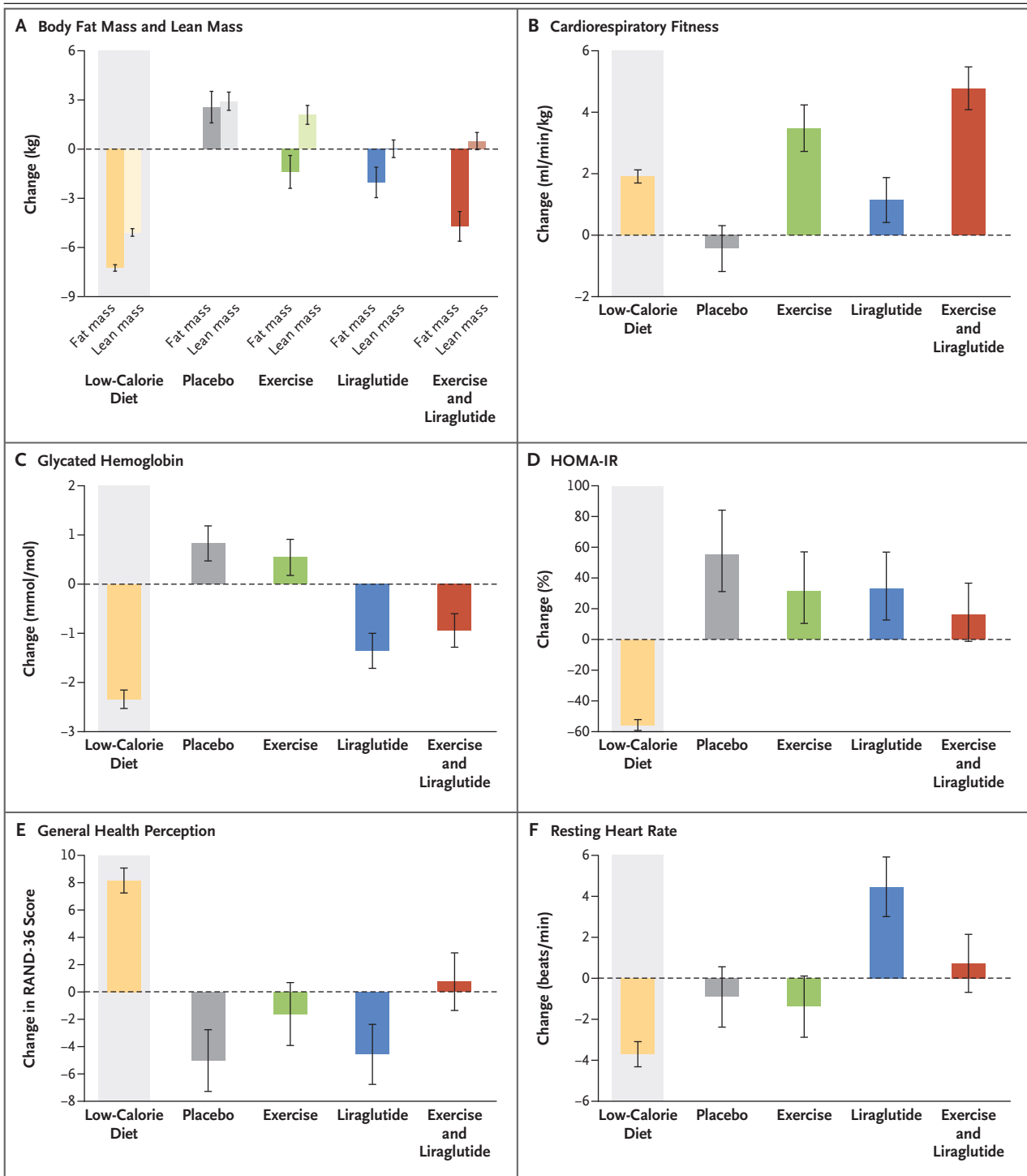
After the low-calorie diet, the participants' body weight decreased further by a mean of -3.4 kg in the combination group but increased by a mean of 6.1 kg in the placebo group, resulting in a treatment difference of -9.5 kg (95% CI, -13.1 to -5.9 ; $P<0.001$). The initial weight loss was maintained in the exercise group, with a treatment effect as compared with placebo of -4.1 kg (95% CI, -7.8 to -0.4 ; $P=0.03$). Liraglutide treatment also resulted in maintenance of the initial weight loss, with a treatment effect as compared with placebo of -6.8 kg (95% CI, -10.4 to -3.1 ; $P<0.001$). In the combination group, the treatment effect as compared with exercise was -5.4 kg (95% CI, -9.0 to -1.7 ; $P=0.004$) and the treatment effect as compared with liraglutide was -2.7 kg (95% CI, -6.3 to 0.8 ; $P=0.13$) (Fig. 1A and Table S4).

The percentages of participants in each group who had a total weight loss of at least 5%, at least 10%, at least 15%, and at least 20% of the baseline body weight are shown in Figure 1C. The mean total weight loss from before the low-calorie diet to the end of the trial was 15.7% of the baseline body weight in the combination group, 10.9% of the baseline weight in the exercise group, 13.4% of the baseline weight in the liraglutide group, and 6.7% of the baseline weight in the placebo group.

At 52 weeks, the reduction in the body-fat percentage was greater in the exercise group than in the placebo group, with a treatment effect of -2.2 percentage points (95% CI, -3.8 to -0.7 ; $P=0.004$); was greater in the liraglutide group than in the placebo group, with a treatment effect of -2.0 percentage points (95% CI, -3.5 to -0.6); and was greater in the combination group than in the placebo group, with a treatment effect of -3.9 percentage points (95% CI, -5.4 to -2.5). Thus, the body-fat percentage was further reduced in the combination group by -1.7 percentage points (95% CI, -3.2 to -0.2) as compared with the exercise group ($P=0.02$) and by -1.9 percentage points (95% CI, -3.3 to -0.5) as compared with the liraglutide group ($P=0.009$) (Fig. 1B and Table S4). The three supplementary analyses of the primary and secondary end points supported the results of the primary analysis (Tables S9 and S10).

Metabolic Health-Related End Points

All active treatments (i.e., those involving exercise, liraglutide treatment, or both) were associated with decreases in fat mass and waist circumference, as compared with increases in the placebo group, and the decreases were twice as large in the combination group as in the other groups (Fig. 2A and S2). Exercise was associated with increased lean mass. Exercise and the combination strategy were associated with increased cardiorespiratory fitness, which was not observed with placebo or liraglutide (Fig. 2B). Liraglutide treatment and the combination strategy were associated with reductions in the glycated hemoglobin level, as compared with an increase in the placebo group (Fig. 2C). Only the combination strategy was associated with reductions in the HOMA-IR and the waist-to-hip ratio and with increases in the Matsuda index and in



physical functioning, as compared with placebo (Fig. 2D). All active treatments were associated with maintained reductions in the systolic and diastolic blood pressures, which were not observed with placebo (Tables S5 and S6). Exercise

and the combination strategy were associated with maintenance of the initial improvements in general health perception and emotional well-being, which were not observed with placebo or liraglutide (Fig. 2E).

Figure 2 (facing page). Changes in Metabolic Health-Related Measures and Resting Heart Rate during the Trial.

Shown are the changes in various metabolic health-related factors such as body fat mass and lean mass (Panel A), cardiorespiratory fitness as assessed by peak oxygen consumption (Panel B), the glycated hemoglobin level (Panel C), the homeostatic model assessment of insulin resistance (HOMA-IR; Panel D), the participants' general health perception as assessed by the RAND 36-Item Health Survey (RAND-36) score (Panel E), and the resting heart rate (Panel F). The HOMA-IR was calculated as the fasting insulin level (in milliunits per milliliter) times the fasting glucose level (in millimoles per liter), divided by 22.5. RAND-36 scores range from 0 to 100, with higher scores indicating better health. Data are shown as the change from week -8 to week 0 (after the low-calorie diet [shaded area]) in all four groups combined and the change from week 0 to week 52 (after randomization) in the four individual trial groups. Values are estimated mean changes resulting from a repeated-measures linear regression model with time, group, sex, age, and a time-group interaction as explanatory variables in the intention-to-treat population. The estimated mean changes are presented with standard errors (I bars), except for the HOMA-IR data, which are presented as the geometric means of the percentage changes with 95% confidence intervals (I bars). Dashed lines indicate baseline, which was week -8 for the low-calorie diet and week 0 for the four randomized trial groups.

Safety

Adverse events that occurred in at least 10% of all participants, urinary tract infections, palpitations, and all serious adverse events are reported in Table 2; full lists of adverse events and serious adverse events are provided in Tables S11 and S12, respectively. Five participants (two receiving liraglutide and three receiving placebo) discontinued taking liraglutide or placebo because of adverse events. Gastrointestinal adverse events, decreased appetite, and dizziness were more frequently reported in the groups that received liraglutide (i.e., in the liraglutide group and combination group) than in the other two groups. Cholelithiasis as a serious adverse event and palpitations were reported more frequently in the liraglutide group than in the combination group. After 1 year, liraglutide treatment alone was associated with an increased resting heart rate; this finding was not observed with the combination strategy (Figs. 2F and S3). The incidence of other adverse events was similar among the trial groups.

DISCUSSION

In this randomized, head-to-head, placebo-controlled trial, we investigated exercise, liraglutide, and both treatments combined for healthy weight loss maintenance. All active-treatment groups decreased body weight and body-fat percentage after 1 year, as compared with the increases observed in the placebo group. The combined strategy reduced the body weight and body-fat percentage approximately twice as much as the single-treatment strategies did and was associated with additional health benefits, such as improvements in the glycated hemoglobin level, insulin sensitivity, cardiorespiratory fitness, physical functioning, and emotional well-being.

The initial low-calorie diet resulted in a mean body-weight reduction of 12% of the baseline body weight among the participants who underwent randomization. After 1 year, the combination of exercise and liraglutide therapy induced an additional reduction in body weight, resulting in a total weight loss of 16%. This is more than the total weight losses of approximately 10% that were obtained with 1-year diet-management programs after an initial low-calorie diet.^{11,15,16,29}

It is also more than the 1-year weight loss of 7 to 9% of the initial body weight that has been observed with concurrent intensive diet and physical activity programs.^{18,19} The total weight reduction was approximately similar to the 15% weight loss that was observed after 68 weeks of treatment with the GLP-1 receptor agonist semaglutide, administered subcutaneously at a dose of 2.4 mg once weekly as an adjunct to lifestyle change (currently not approved by any governmental medical agencies at this dose and for this indication).³⁰ In our trial, participants in the placebo group regained, on average, 6.1 kg, which was equivalent to 45% of the weight that they had initially lost; this weight regain was accompanied by deterioration in all associated metabolic health-related improvements. This result shows the critical importance of implementing structured treatment after weight loss, as compared with a strategy of just 12 individualized consultations regarding weight and diet, as provided in the current trial according to the recommendations of the Danish authorities for sustained weight loss.

Exercise alone led to maintenance of the ini-

Table 2. Adverse Events and Serious Adverse Events after Randomization.*

Event	All Participants (N = 195)	Placebo Group (N = 49)	Exercise Group (N = 48)	Liraglutide Group (N = 49)	Combination Group (N = 49)
	<i>number of participants (percent)</i>				
Any adverse event	175 (90)	42 (86)	39 (81)	49 (100)	45 (92)
Gastrointestinal adverse event	130 (67)	22 (45)	31 (65)	42 (86)	35 (71)
Serious adverse event†	16 (8)	2 (4)	4 (8)	6 (12)	4 (8)
Adverse event that led to the discontinuation of liraglutide or placebo	5 (3)	0	3 (6)	1 (2)	1 (2)
Adverse event that led to withdrawal from the trial	2 (1)	0	0	1 (2)	1 (2)
Adverse events that occurred in ≥10% of all participants					
Nausea	81 (42)	8 (16)	15 (31)	32 (65)	26 (53)
Upper respiratory tract infection	55 (28)	13 (27)	17 (35)	12 (24)	13 (27)
Abdominal pain	46 (24)	3 (6)	13 (27)	18 (37)	12 (24)
Influenza or influenza-like symptoms	40 (21)	8 (16)	8 (17)	11 (22)	13 (27)
Decreased appetite	40 (21)	2 (4)	4 (8)	18 (37)	16 (33)
Headache	40 (21)	9 (18)	10 (21)	10 (20)	11 (22)
Diarrhea	38 (19)	4 (8)	7 (15)	13 (27)	14 (29)
Constipation	34 (17)	6 (12)	7 (15)	9 (18)	12 (24)
Vomiting	34 (17)	2 (4)	6 (12)	11 (22)	15 (31)
Pyrexia	34 (17)	4 (8)	9 (19)	7 (14)	14 (29)
Dizziness	33 (17)	3 (6)	4 (8)	15 (31)	11 (22)
Fatigue	33 (17)	4 (8)	6 (12)	15 (31)	8 (16)
Flatulence or abdominal distention	22 (11)	5 (10)	4 (8)	5 (10)	8 (16)
Dyspepsia	19 (10)	0	1 (2)	9 (18)	9 (18)
Urinary tract infection	17 (9)	3 (6)	5 (10)	6 (12)	3 (6)
Palpitations	9 (5)	1 (2)	0	6 (12)	2 (4)

* Adverse events and serious adverse events from randomization through week 52 among all participants are included in the table and are presented with the preferred terms in the *Medical Dictionary for Regulatory Activities*, version 23.1. Specific adverse events reported here are those that occurred in at least 10% of all participants; in addition, given their importance, urinary tract infections and palpitations are reported. All the adverse events and serious adverse events are listed in Tables S11 and S12, respectively.

† The following serious adverse events were reported: in the placebo group, abdominal pain without verified reason (in one participant) and urosepsis (in one); in the exercise group, abdominal pain without verified reason (in two), ileus (in one), and autoimmune hepatitis (in one); in the liraglutide group, abdominal pain without verified reason (in one), acute cholelithiasis (in two), acute pancreatitis due to cholelithiasis (in one), appendicitis (in one), and gastroenteritis (in one); and in the combination group, abdominal pain without verified reason (in two), acute cholelithiasis (in one), and broken shoulder due to a road traffic accident (in one).

tial weight loss and further reduced body-fat percentage. Exercise (walking or resistance training) as a weight-loss maintenance strategy after diet-induced weight loss was previously reported as having a minor effect (<3 kg)³¹ or no effect.³² In contrast, the exercise program in this trial was predominantly of vigorous intensity, both at

group sessions and individual sessions (mostly cycling and running) and with high adherence to WHO recommendations regarding physical activity volume. This strategy was associated with improved cardiorespiratory fitness, increased lean mass, and prevention of a 4-kg regain of body fat.

Treatment with liraglutide alone resulted in maintenance of the initial weight loss, with a treatment effect as compared with placebo of -6.8 kg, which is similar to the results of previous studies,^{21,24} and was also associated with loss of fat mass. The combination of exercise and liraglutide treatment was associated with loss of fat mass and reduction in waist circumference that were approximately twice those observed with the single treatments, and it preserved lean mass.

Both the liraglutide group and the combination group had further reductions in the glycosylated hemoglobin level, which is generally considered to reduce the risk of new-onset diabetes.³³ By contrast, the exercise group and the combination group were observed to have increased the participants' cardiorespiratory fitness at a magnitude that has been associated with a decreased risk of cardiovascular disease and decreased all-cause mortality,³⁴ and these strategies also maintained improvements in general and emotional health.

In accordance with previous studies,^{21,22,24} we observed an increased heart rate with liraglutide alone. Increased heart rate is generally considered an adverse effect, associated with lower survival.³⁵ We did not observe an increased resting heart rate when exercise was combined with liraglutide, a finding that supports the health-promoting potential of this combination.

The percentage of participants who completed the trial was high in all the groups (82 to 92%) and was highest in the combination group, which shows that a combination of moderate-to-vigorous-intensity exercise and liraglutide treatment is feasible. Only the combined treatment was associated with improvements in insulin sensitivity and physical functioning as compared with placebo.

A major strength of this trial was the structured but flexible exercise program with rigorous monitoring of exercise adherence. Our trial showed that 1 year of mostly vigorous-intensity

exercise, performed approximately 2.4 times per week, as a weight-loss maintenance strategy was feasible in persons with obesity with a very low initial level of fitness. The finding that the 1-year trajectories with regard to body weight, waist-to-hip ratio, and adherence were stable in the exercising groups — in which participants had a loss of fat mass and increase in lean mass, along with improved emotional well-being — also support feasibility. Other strengths of our trial included the direct comparison of separate and combined effects of exercise and liraglutide and high-quality assessments of body composition and cardiorespiratory fitness in addition to body weight.

Limitations of the trial include the fact that our results may not be generalizable to older persons (>65 years of age), persons with greater obesity (BMI of >43), patients with coexisting conditions (e.g., type 2 diabetes), and persons who have low adherence to participation in a moderate-to-vigorous-intensity exercise program or who are limited in their ability to perform moderate-to-vigorous-intensity exercise.

In this trial involving persons with obesity, the combination of a moderate-to-vigorous-intensity exercise program and liraglutide treatment after diet-induced weight loss was more effective in improving healthy weight loss than either treatment alone.

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REFERENCES

1. Ward ZJ, Bleich SN, Cradock AL, et al. Projected U.S. state-level prevalence of adult obesity and severe obesity. *N Engl J Med* 2019;381:2440-50.
2. Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Obesity Society. *Circulation* 2014;129:Suppl 2:S102-S138.
3. Pietiläinen KH, Kaprio J, Borg P, et al. Physical inactivity and obesity: a vicious circle. *Obesity (Silver Spring)* 2008;16:409-14.
4. Stringhini S, Carmeli C, Jokela M, et al. Socioeconomic status and the 25 × 25 risk factors as determinants of premature mortality: a multicohort study and meta-analysis of 1.7 million men and women. *Lancet* 2017;389:1229-37.
5. Logue J, Thompson L, Romanes F, Wilson DC, Thompson J, Sattar N. Man-

- agement of obesity: summary of SIGN guideline. *BMJ* 2010;340:c154.
6. Purcell K, Sumithran P, Prendergast LA, Bouniu CJ, Delbridge E, Proietto J. The effect of rate of weight loss on long-term weight management: a randomised controlled trial. *Lancet Diabetes Endocrinol* 2014;2:954-62.
 7. van Baak MA, Mariman ECM. Mechanisms of weight regain after weight loss — the role of adipose tissue. *Nat Rev Endocrinol* 2019;15:274-87.
 8. Leibel RL, Rosenbaum M, Hirsch J. Changes in energy expenditure resulting from altered body weight. *N Engl J Med* 1995;332:621-8.
 9. Iepsen EW, Lundgren J, Holst JJ, Madsbad S, Torekov SS. Successful weight loss maintenance includes long-term increased meal responses of GLP-1 and PYY3-36. *Eur J Endocrinol* 2016;174:775-84.
 10. Sumithran P, Prendergast LA, Delbridge E, et al. Long-term persistence of hormonal adaptations to weight loss. *N Engl J Med* 2011;365:1597-604.
 11. 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 (Lond)* 2015;39:834-41.
 12. Church TS, Earnest CP, Skinner JS, Blair SN. Effects of different doses of physical activity on cardiorespiratory fitness among sedentary, overweight or obese postmenopausal women with elevated blood pressure: a randomized controlled trial. *JAMA* 2007;297:2081-91.
 13. 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* (1985) 2012;113:1831-7.
 14. Ross R, Dagnone D, Jones PJH, et al. Reduction in obesity and related comorbid conditions after diet-induced weight loss or exercise-induced weight loss in men: a randomized, controlled trial. *Ann Intern Med* 2000;133:92-103.
 15. Lean ME, Leslie WS, Barnes AC, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. *Lancet* 2018;391:541-51.
 16. Astbury NM, Aveyard P, Nickless A, et al. Doctor Referral of Overweight People to Low Energy total diet replacement Treatment (DROPLET): pragmatic randomised controlled trial. *BMJ* 2018;362: k3760.
 17. Lean MEJ, Leslie WS, Barnes AC, et al. Durability of a primary care-led weight-management intervention for remission of type 2 diabetes: 2-year results of the DiRECT open-label, cluster-randomised trial. *Lancet Diabetes Endocrinol* 2019;7: 344-55.
 18. The Look AHEAD Research Group. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med* 2013;369:145-54.
 19. 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.
 20. Foright RM, Presby DM, Sherk VD, et al. Is regular exercise an effective strategy for weight loss maintenance? *Physiol Behav* 2018;188:86-93.
 21. 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.
 22. 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.
 23. 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(1):23-32.e3.
 24. 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 (Lond)* 2013;37:1443-51.
 25. 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 (Lond)* 2014;38: 784-93.
 26. 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(11):e031431.
 27. 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.
 28. Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. *Diabetes Care* 1999;22:1462-70.
 29. Taheri S, Zaghoul H, Chagoury O, et al. Effect of intensive lifestyle intervention on bodyweight and glycaemia in early type 2 diabetes (DIADEM-I): an open-label, parallel-group, randomised controlled trial. *Lancet Diabetes Endocrinol* 2020;8:477-89.
 30. Wilding JPH, Batterham RL, Calanna S, et al. Once-weekly semaglutide in adults with overweight or obesity. *N Engl J Med* 2021;384:989.
 31. Fogelholm M, Kukkonen-Harjula K, Nenonen A, Pasanen M. Effects of walking training on weight maintenance after a very-low-energy diet in premenopausal obese women: a randomized controlled trial. *Arch Intern Med* 2000;160:2177-84.
 32. Borg P, Kukkonen-Harjula K, Fogelholm M, Pasanen M. Effects of walking or resistance training on weight loss maintenance in obese, middle-aged men: a randomized trial. *Int J Obes Relat Metab Disord* 2002;26:676-83.
 33. Diabetes Prevention Program Research Group. HbA1c as a predictor of diabetes and as an outcome in the Diabetes Prevention Program: a randomized clinical trial. *Diabetes Care* 2015;38:51-8.
 34. Ross R, Blair SN, Arena R, et al. Importance of assessing cardiorespiratory fitness in clinical practice: a case for fitness as a clinical vital sign: a scientific statement from the American Heart Association. *Circulation* 2016;134(24):e653-e699.
 35. Böhm M, Reil J-C, Deedwania P, Kim JB, Borer JS. Resting heart rate: risk indicator and emerging risk factor in cardiovascular disease. *Am J Med* 2015;128:219-28.

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