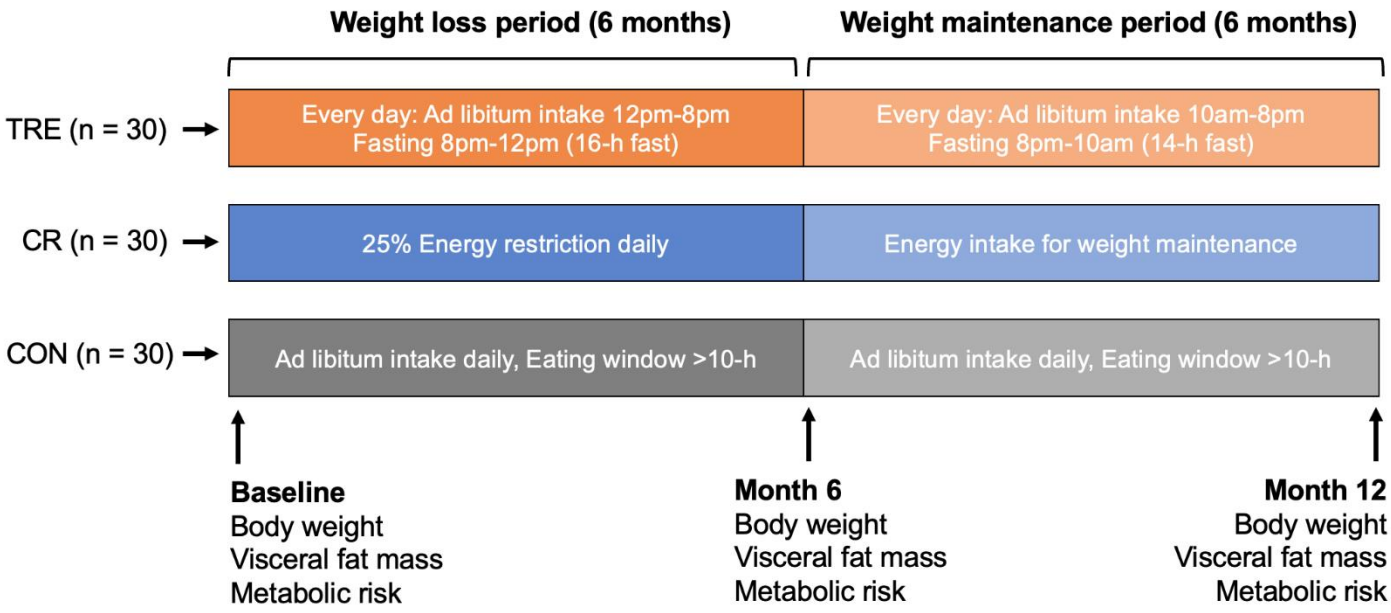
Supplementary Material*

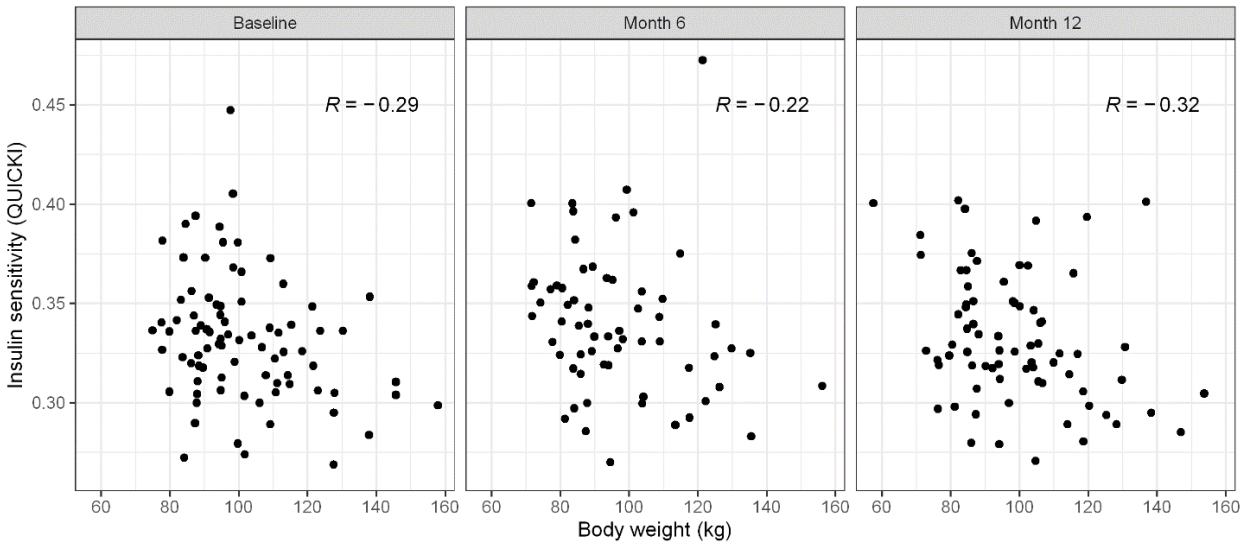
Lin S, Cienfuegos S, Ezpeleta M, et al. Time-restricted eating without calorie counting for weight loss in a racially diverse population. A randomized controlled trial. Ann Intern Med. 27 June 2023. [Epub ahead of print]. doi:10.7326/M23-0052

* This supplementary material was provided by the authors to give readers further details on their article. The material was not copyedited.

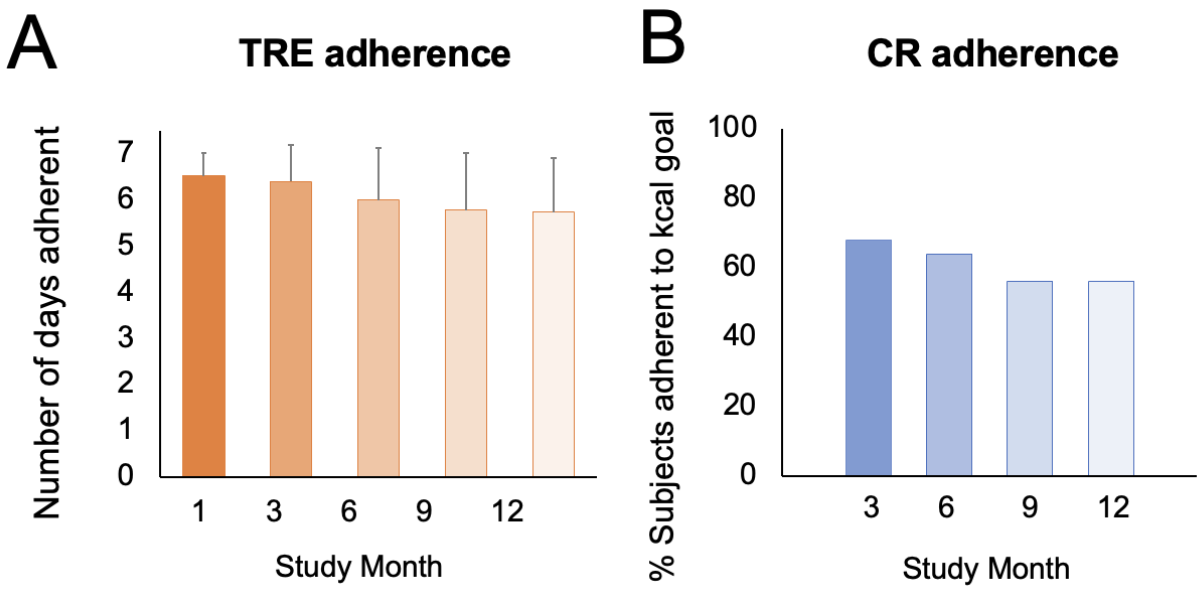
Supplement Figure 1. Experimental design



Supplement Figure 2. Correlation between body weight and insulin sensitivity



Supplement Figure 3. Adherence to the diet interventions



A. Adherence to the time restriction eating (TRE) intervention over 12 months. Data are expressed as mean (SD) days per week that participants reported being adherent with the 12:00 pm to 8:00 pm eating window; only observed values included. A total of 22/30 TRE participants returned all adherence logs. Adherence at month 1: 6.5 $\pm$ 0.5 days/week; month 3: 6.4 $\pm$ 0.8 days/week; month 6: 6.1 $\pm$ 1.2 days/week; month 9: 5.8 $\pm$ 1.3 days/week; month 12: 5.8 $\pm$ 1.2 days/week. **B.** Adherence to the daily calorie restriction (CR) intervention over 12 months. Data are expressed as the proportion of participants whose actual energy intake, determined via food records, was within 200 kcal of their prescribed daily energy goal; only observed values included A total of 17/30 CR participants returned all food records. Adherence at month 3: 68% participants adherent; month 6: 64% participants adherent; month 9: 56% participants adherent; month 12: 56% participants adherent.

Supplement Table 1. Baseline characteristics of all participants, completers, and dropouts

	All participants	Completers	All dropouts	Dropouts TRE	Dropouts CR	Dropouts Control
n	90	77	13	4	5	4
Age (y)	44 ± 11	44 ± 12	41 ± 8	46 ± 6	41 ± 11	36 ± 4
Sex						
Female	74 (82%)	66 (86%)	8 (62%)	4 (100%)	2 (40%)	2 (50%)
Male	16 (18%)	11 (14%)	5 (38%)	0 (0%)	3 (60%)	2 (50%)
Race or ethnic group						
Black	30 (33%)	27 (35%)	3 (23%)	2 (50%)	1 (20%)	0 (0%)
Asian	6 (7%)	5 (6%)	1 (8%)	0 (0%)	1 (20%)	0 (0%)
Hispanic	41 (46%)	35 (45%)	6 (46%)	2 (50%)	0 (0%)	4 (100%)
White	13 (14%)	10 (13%)	3 (23%)	0 (0%)	3 (60%)	0 (0%)
Body composition						
Body weight (kg)	101 ± 17	101 ± 17	105 ± 18	103 ± 6	110 ± 24	100 ± 20
Fat mass (kg)	47 ± 11	47 ± 11	51 ± 13	54 ± 9	52 ± 17	50 ± 9
Lean mass (kg)	50 ± 9	50 ± 9	51 ± 9	50 ± 5	53 ± 10	56 ± 14
Visceral fat mass (kg)	1.7 ± 0.7	1.6 ± 0.7	2.3 ± 0.8	2.0 ± 0.7	2.5 ± 0.8	2.2 ± 1.2
Waist circumference (cm)	110 ± 13	108 ± 12	117 ± 15	117 ± 13	117 ± 16	115 ± 25
Height (cm)	165 ± 8	165 ± 8	167 ± 7	162 ± 5	169 ± 11	168 ± 2
BMI (kg/m^2)	37 ± 5	37 ± 5	38 ± 6	39 ± 1	39 ± 9	36 ± 6
Bone parameters						
Bone mineral density (g/cm^2)	1.29 ± 0.13	1.29 ± 0.14	1.26 ± 0.09	1.28 ± 0.15	1.25 ± 0.06	1.26 ± 0.05
Bone mineral content (g)	2660 ± 420	2658 ± 461	2617 ± 253	2551 ± 168	2656 ± 358	2649 ± 136
Blood pressure, heart rate						
Systolic BP (mm Hg)	125 ± 15	124 ± 15	131 ± 13	135 ± 14	130 ± 10	129 ± 22
Diastolic BP (mm Hg)	84 ± 9	83 ± 9	89 ± 10	95 ± 6	87 ± 11	84 ± 14
Heart rate (bpm)	75 ± 13	74 ± 11	77 ± 19	75 ± 23	77 ± 20	80 ± 15
Plasma lipids						
Total cholesterol (mg/dl)	182 ± 33	182 ± 34	181 ± 25	187 ± 17	183 ± 29	--
LDL cholesterol (mg/dl)	106 ± 29	106 ± 30	108 ± 24	111 ± 14	111 ± 29	--
HDL cholesterol (mg/dl)	53 ± 13	52 ± 14	51 ± 11	54 ± 11	54 ± 9	--
Triglycerides (mg/dl)	113 ± 57	115 ± 58	104 ± 143	110 ± 29	88 ± 44	--
						--

Glucoregulatory factors						
Fasting glucose (mg/dl)	88 ± 12	88 ± 13	87 ± 8	83 ± 3	86 ± 8	--
Fasting insulin (µIU/mL)	15 ± 10	14 ± 10	16 ± 7	15 ± 6	15 ± 8	--
Insulin resistance (HOMA-IR)	3.3 ± 2.4	3.1 ± 2.4	3.4 ± 1.7	3.1 ± 1.3	3.2 ± 1.7	--
Insulin sensitivity (QUICKI)	0.33 ± 0.03	0.33 ± 0.03	0.33 ± 0.03	0.33 ± 0.02	0.33 ± 0.03	--
HbA1c (%)	5.5 ± 0.5	5.5 ± 0.5	5.4 ± 0.6	5.7 ± 1.0	5.1 ± 0.3	--

Data are expressed as mean (SD) unless otherwise indicated. Abbreviations: BP: Blood pressure; BMI: Body mass index, CR: Calorie restriction, HbA1c: Glycated hemoglobin; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; LDL, low-density lipoprotein; QUICKI: Quantitative insulin sensitivity check index, TRE: Time restricted eating.

Supplement Table 2. SI Units for change in fasting glucose, insulin, and plasma lipids from baseline and between intervention groups

Variables		Change from baseline (95% CI)			Difference between groups (95% CI)		
	N	Time restricted eating (TRE)	Daily calorie restriction (CR)	Control (CON)	TRE vs CR	TRE vs CON	CR vs CON
Secondary outcomes							
Fasting glucose (mmol/l)							
6 months	74	-0.09 (-0.36, 0.18)	-0.05 (-0.31, 0.22)	0.16 (-0.15, 0.47)	-0.05 (-0.42, 0.33)	-0.25 (-0.65, 0.15)	-0.21 (-0.61, 0.20)
12 months	74	0.16 (-0.06, 0.38)	0.32 (0.07, 0.58)	0.35 (0.09, 0.61)	-0.17 (-0.50, 0.16)	-0.19 (-0.52, 0.14)	-0.02 (-0.38, 0.33)
Fasting insulin (pmol/L)							
6 months	74	-17.34 (-36.66, 2.04)	-5.46 (-18.24, 7.26)	3.90 (-14.10, 21.84)	-11.82 (-34.44, 10.74)	-21.18 (-46.92, 4.50)	-9.36 (-30.84, 12.12)
12 months	74	-16.98 (-32.04, -1.98)	-0.72 (-13.32, 11.82)	8.64 (-13.92, 31.26)	-16.26 (-35.34, 2.88)	-25.62 (-52.08, 0.78)	-9.42 (-34.62, 15.78)
Total cholesterol (mmol/l)							
6 months	74	-0.03 (-0.22, 0.17)	-0.11 (-0.37, 0.15)	0.02 (-0.20, 0.23)	0.08 (-0.24, 0.40)	-0.04 (-0.33, 0.24)	-0.13 (-0.46, 0.21)
12 months	74	-0.04 (-0.25, 0.16)	-0.04 (-0.25, 0.17)	-0.02 (-0.19, 0.16)	0.00 (-0.29, 0.29)	-0.03 (-0.29, 0.24)	-0.03 (-0.29, 0.24)
LDL cholesterol (mmol/l)							
6 months	74	0.02 (-0.18, 0.22)	-0.16 (-0.40, 0.09)	0.03 (-0.14, 0.21)	0.17 (-0.13, 0.48)	-0.01 (-0.27, 0.24)	-0.19 (-0.48, 0.10)
12 months	74	-0.02 (-0.24, 0.19)	-0.03 (-0.19, 0.12)	0.06 (-0.12, 0.24)	0.01 (-0.25, 0.27)	-0.08 (-0.35, 0.19)	-0.10 (-0.33, 0.14)
HDL cholesterol (mmol/)							
6 months	74	-0.05 (-0.13, 0.04)	0.03 (-0.08, 0.13)	-0.02 (-0.07, 0.03)	-0.07 (-0.21, 0.06)	-0.03 (-0.12, 0.07)	0.05 (-0.07, 0.16)
12 months	74	-0.04 (-0.12, 0.04)	0.00 (-0.12, 0.11)	-0.07 (-0.14, -0.01)	-0.04 (-0.17, 0.10)	0.03 (-0.06, 0.13)	0.07 (-0.06, 0.20)
Triglycerides (mmol/l)							
6 months	74	0.00 (-0.25, 0.25)	0.08 (-0.06, 0.22)	-0.01 (-0.21, 0.20)	-0.08 (-0.36, 0.21)	0.01 (-0.31, 0.33)	0.08 (-0.16, 0.33)
12 months	74	0.04 (-0.12, 0.20)	0.00 (-0.15, 0.14)	0.00 (-0.20, 0.20)	0.04 (-0.17, 0.25)	0.04 (-0.21, 0.29)	0.00 (-0.24, 0.24)

Data were included for 90 participants; means were estimated using an intention-to-treat analysis using a linear mixed model. Error bars indicate 95% confidence intervals for each parameter from baseline by diet group. Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein. The widths of the confidence intervals have not been adjusted for multiplicity and should therefore not be used to reject or not reject treatment effects.

Supplement Table 3. Multiple imputation sensitivity analysis results

Variables		Difference between groups at month 12 (95% CI)		
	Baseline N	TRE vs CR	TRE vs CON	CR vs CON
Body weight (kg)	90	0.88 (-4.72, 6.48) p=0.75	-3.99 (-7.00, -0.99) p=0.01	-4.87 (-8.62, -1.13) p=0.01
Fat mass (kg)	88	0.33 (-4.06, 4.72)	-2.86 (-5.41, -0.32)	-3.20 (-6.66, 0.27)
Lean mass (kg)	88	0.27 (-1.53, 2.06)	-0.71 (-1.92, 0.50)	-0.98 (-2.38, 0.42)
Visceral fat mass (kg)	88	0.00 (-0.20, 0.21)	-0.10 (-0.27, 0.07)	-0.10 (-0.33, 0.12)
Waist circumference (cm)	88	-2.06 (-14.97, 10.85)	-4.67 (-7.93, -1.41)	-2.61 (-7.00, 1.78)
BMI (kg/m^2)	90	0.32 (-2.23, 2.87)	-1.51 (-2.61, -0.42)	-1.83 (-3.24, -0.42)
Bone mineral density (g/cm^2)	88	0.01 (-0.05, 0.07)	0.00 (-0.02, 0.02)	-0.01 (-0.03, 0.01)
Bone mineral content (g)	88	-7.57 (-218.43, 203.30)	9.26 (-55.63, 74.15)	16.82 (-55.68, 89.33)
Fasting glucose (mg/dl)	84	-2.33 (-17.66, 13.00)	-3.18 (-9.26, 2.89)	-0.85 (-7.36, 5.65)
Fasting insulin (µIU/mL)	84	-2.64 (-17.57, 12.29)	-4.11 (-8.70, 0.48)	-1.47 (-6.00, 3.07)
Insulin resistance (HOMA-IR)	84	-0.56 (-3.79, 2.66)	-0.98 (-2.12, 0.17)	-0.42 (-1.48, 0.65)
Insulin sensitivity (QUICKI)	84	0.01 (-0.07, 0.10)	0.02 (0.01, 0.04)	0.01 (-0.01, 0.02)
HbA1c (%)	84	-0.07 (-0.44, 0.30)	-0.08 (-0.26, 0.10)	-0.01 (-0.19, 0.16)
Systolic BP (mm Hg)	88	2.38 (-7.30, 12.07)	-1.76 (-8.81, 5.30)	-4.14 (-11.18, 2.90)
Diastolic BP (mm Hg)	88	-1.90 (-11.35, 7.55)	-3.45 (-8.31, 1.40)	-1.56 (-6.15, 3.03)
Heart rate (bpm)	88	-4.27 (-17.63, 9.09)	-0.74 (-7.12, 5.64)	3.53 (-2.96, 10.02)
Total cholesterol (mg/dl)	84	0.80 (-18.28, 19.88)	-0.69 (-11.85, 10.48)	-1.49 (-12.97, 10.00)
LDL cholesterol (mg/dl)	84	1.10 (-18.10, 20.31)	-3.16 (-14.18, 7.86)	-4.26 (-15.58, 7.05)
HDL cholesterol (mg/dl)	84	-0.66 (-13.39, 12.07)	1.19 (-2.91, 5.30)	1.85 (-3.20, 6.90)
Triglycerides (mg/dl)	84	1.26 (-60.99, 63.52)	4.73 (-18.78, 28.24)	3.47 (-19.42, 26.36)

Data were included for 90 participants; missing values of the outcome at non-baseline time points were imputed using multiple imputation by chained equations in these sensitivity analyses. Means were estimated using an intention-to-treat analysis using a linear mixed model. Error bars indicate 95% confidence intervals for each parameter from baseline by diet group. Abbreviations: BP: Blood pressure; CR: Calorie restriction, HbA1c: Glycated hemoglobin; HDL, high-density lipoprotein; HOMA, homeostasis model assessment of insulin resistance; LDL, low-density lipoprotein; QUICKI: Quantitative insulin sensitivity check index, TRE: Time restricted eating. The widths of the confidence intervals have not been adjusted for multiplicity and should therefore not be used to reject or not reject treatment effects.

Supplement Table 4. Adverse events during the intervention

	Time restricted eating (n =30)	Calorie restriction (n =30)	Control (n =30)
		No. (%) participants	
General adverse events			
Headache	16 (53)	18 (60)	19 (63)
Dizziness	7 (23)	9 (30)	10 (33)
Fatigue	15 (50)	14 (47)	18 (60)
Irritability	16 (53)	17 (57)	13 (43)
Halitosis	10 (33)	11 (37)	12 (40)
Dry mouth	13 (43)	16 (53)	16 (53)
Gastrointestinal adverse events			
Nausea	9 (30)	14 (47)	12 (40)
Vomiting	9 (30)	9 (30)	8 (27)
Diarrhea	13 (43)	11 (37)	15 (50)
Constipation	14 (47)	14 (47)	16 (53)

Data are expressed as the number of participants with at least one adverse event that occurred during the 12-month intervention. Participants may have experienced an adverse event at more than one time point. No significant differences between groups for occurrences of any adverse event.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3-4
	2b	Specific objectives or hypotheses	4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	NA
Participants	4a	Eligibility criteria for participants	5
	4b	Settings and locations where the data were collected	5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6-7
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	8
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	8-9
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	20
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	5

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	NA
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	8-10
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	8-10
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	Figure 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	Figure 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	5
	14b	Why the trial ended or was stopped	NA
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	All tables/figures
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Figure 2 Table 2 and 3
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Table S1
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	NA
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	Table S2
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	18-19
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	19
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	19
Other information			
Registration	23	Registration number and name of trial registry	2, 5
Protocol	24	Where the full trial protocol can be accessed, if available	5
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	10, 20

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

The causal quantities from the primary linear mixed effects model for body weight are the pairwise contrasts between the within-group contrasts from time 0 (baseline) to time 12. These quantities (estimands) correspond directly to parameters estimated in the model equation.

Notation and Convention

Let $A_i = TRE$ if participant i was assigned to the TRE group, $A_i = CR$ if participant i was assigned to the CR group, and $A_i = control$ if participant i was assigned to the control group. Let b_i be the random intercept for participant i.

Let time $t = \{0, 1, ..., 12\}$ be time in months since baseline. Let Y_{it} be body weight for participant i at time t. Let S be the 13x6 basis matrix corresponding to a cubic spline for time with knots placed at 3.5, 6.5, 9.5 months. By design, the row of S corresponding to baseline is the zero vector; that is, $S_{0,k} = 0$ for $k = 1, ..., 6$. The row of S corresponding to month 12 is $S_{12,6} = 1$ and $S_{12,k} = 0$ for $k = 1, ..., 5$.

Model and Estimands

The linear mixed effects model for body weight can be written as

$$E[Y_{it}] = \beta_0 + \beta_{TRE} I(A_i = TRE) + \beta_{CR} I(A_i = CR) + \left[\sum_{k=1}^{6} \beta_k S_{tk}\right] + \left[\sum_{k=1}^{6} \beta_{TRE,k} S_{tk} I(A_i = TRE)\right] + \left[\sum_{k=1}^{6} \beta_{CR,k} S_{tk} I(A_i = CR)\right] + b_i,$$

where $I(\cdot)$ is the indicator function such that $I(\cdot) = 1$ if the internal expression is true and is 0 otherwise.

The pairwise contrast comparing TRE to control is $\beta_{TRE,6}$, the contrast comparing CR to control is $\beta_{CR,6}$, and the contrast comparing TRE to CR is $\beta_{TRE,6} - \beta_{CR,6}$.