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Effects of 3 months of 10-h per-day time-restricted eating and 3 months of follow-up on bodyweight and cardiometabolic health in Danish individuals at high risk of type 2 diabetes: the RESET single-centre, parallel, superiority, open-label, randomised controlled trial

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Summary

Background Time-restricted eating (TRE) has been suggested to be a simple, feasible, and effective dietary strategy for individuals with overweight or obesity. We aimed to investigate the effects of 3 months of 10-h per-day TRE and 3 months of follow-up on bodyweight and cardiometabolic risk factors in individuals at high risk of type 2 diabetes.

Methods This was a single-centre, parallel, superiority, open-label randomised controlled clinical trial conducted at Steno Diabetes Center Copenhagen (Denmark). The inclusion criteria were age 30–70 years with either overweight (ie, BMI ≥25 kg/m²) and concomitant prediabetes (ie, glycated haemoglobin [HbA_{1c}] 39–47 mmol/mol) or obesity (ie, BMI ≥30 kg/m²) with or without prediabetes and a habitual self-reported eating window (eating and drinking [except for water]) of 12 h per day or more every day and of 14 h per day or more at least 1 day per week. Individuals were randomly assigned 1:1 to 3 months of habitual living (hereafter referred to as the control group) or TRE, which was a self-selected 10-h per-day eating window placed between 0600 h and 2000 h. Randomisation was done in blocks varying in size and was open for participants and research staff, but outcome assessors were masked during statistical analyses. The randomisation list was generated by an external statistician. The primary outcome was change in bodyweight, assessed after 3 months (12 weeks) of the intervention and after 3 months (13 weeks) of follow-up. Adverse events were reported and registered at study visits or if participants contacted study staff to report events between visits. This trial is registered on ClinicalTrials.gov (NCT03854656).

Findings Between March 12, 2019, and March 2, 2022, 100 participants (66 [66%] were female and 34 [34%] were male; median age 59 years [IQR 52–65]) were enrolled and randomly assigned (50 to each group). Of those 100, 46 (92%) in the TRE group and 46 (92%) in the control group completed the intervention period. After 3 months of the intervention, there was no difference in bodyweight between the TRE group and the control group (–0·8 kg, 95% CI –1·7 to 0·2; p=0·099). Being in the TRE group was not associated with a lower bodyweight compared with the control group after subsequent 3-month follow-up (–0·2 kg, –1·6 to 1·2). In the per-protocol analysis, participants who completed the intervention in the TRE group lost 1·0 kg (–1·9 to –0·0; p=0·040) bodyweight compared with the control group after 3 months of intervention, which was not maintained after the 3-month follow-up period (–0·4 kg, –1·8 to 1·0). During the trial and follow-up period, one participant in the TRE group reported a severe adverse event: development of a subcutaneous nodule and pain when the arm was in use. This side-effect was evaluated to be related to the trial procedures.

Interpretation 3 months of 10-h per-day TRE did not lead to clinically relevant effects on bodyweight in middle-aged to older individuals at high risk of type 2 diabetes.

Funding Novo Nordisk Foundation, Aalborg University, Helsefonden, and Innovation Fund Denmark.

Introduction

There is a strong need for feasible regimens that can be implemented to obtain and maintain a healthy bodyweight in individuals with overweight or obesity. Time-restricted eating (TRE) has been suggested as a simple, feasible, and effective dietary strategy in individuals with overweight or obesity.[1,2] TRE limits the time interval for food intake, typically to 12 h per day or less, with an extended overnight fast and, compared with classic dietary regimens, there are typically no dietary restrictions.[1]

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Research in context

Evidence before this study

On Feb 7, 2024, we searched PubMed for studies investigating time-restricted eating (TRE) in individuals with overweight, obesity, prediabetes, or type 2 diabetes published in English between database inception and March 12, 2019, the time of trial initiation, using the search terms "overweight" or "obesity" or "prediabetes" or "type 2 diabetes" AND "time-restricted eating" or "intermittent fasting" or "time-restricted feeding" AND "bodyweight" or "weight loss". Animal studies were excluded. Of 237 results, we identified three clinical trials. We searched the reference lists of the three trials and identified a further three relevant clinical trials. Of the six published trials, four were single-arm pilot studies with few participants and two were randomised controlled trials (RCTs) investigating TRE in combination with either a hypocaloric or a eucaloric or isocaloric diet. There were no previous RCTs investigating TRE in combination with no dietary or caloric restrictions in individuals with overweight and prediabetes or obesity and there were no RCTs including a follow-up period.

Added value of this study

Our trial is one of few RCTs investigating the effects of TRE on bodyweight and cardiometabolic health in individuals aged 32–70 years with overweight or obesity at high risk of type 2 diabetes and that has included a predefined follow-up period to investigate whether TRE and health effects are maintained after termination of the intervention. To our knowledge, our trial is one of the first TRE RCTs to include repeated continuous glucose monitoring. Our findings add to the scarce existing evidence from RCTs by showing that TRE compared with habitual living for 3 months did not lead to a significant reduction in bodyweight in middle-aged to older individuals despite a high adherence to the intervention.

Implications of all the available evidence

We cannot recommend 10-h TRE as a short-term strategy to obtain a clinically relevant weight loss in middle-aged or older individuals with overweight or obesity at high risk of type 2 diabetes. However, TRE is a simple and feasible lifestyle regimen and future long-term studies should investigate the effects of TRE in individuals with increased adiposity compared with participants in this trial and metabolic dysfunction (eg, type 2 diabetes).

Since 2015, several small studies have reported weight loss of approximately 1–4% and improvements in glucose regulation, blood lipid profile, and blood pressure in response to TRE with varying eating windows in individuals with overweight or obesity and high risk of type 2 diabetes.[1,3–5] However, many studies had few participants and some did not have a control group. Furthermore, some studies concluded on secondary or exploratory outcomes without considering the risk of false-positive findings. These shortcomings leave a need for large randomised controlled trials (RCTs) with follow-up to evaluate whether TRE results in long-term healthy bodyweight.

Proposed mechanisms by which TRE is thought to elicit positive effects on bodyweight and cardiometabolic health include alignment of food intake to circadian rhythms in metabolism, a spontaneous reduction in energy intake, and increased lipolysis and fat oxidation.[1] Due to the simplicity of TRE, individuals who follow TRE for a period might be compelled to continue the regimen after active treatment has been terminated. If so, this continuation could make TRE highly relevant in the treatment of obesity, as adherence to other lifestyle regimens is generally poor during long time periods.[6] In a 16-week pilot study of 10–12-h TRE, bodyweight was reduced in eight individuals with overweight or obesity and they expressed interest in continuing TRE after the intervention; weight loss was maintained at 1-year follow-up.[7] However, how much participants adhered to TRE during the follow-up period was uncertain. There is a need for large studies to assess the maintenance of TRE after an intervention.[8,9]

We aimed to investigate the effects of 3 months of 10-h TRE on bodyweight and cardiometabolic risk factors in individuals at high risk of type 2 diabetes and whether potential changes in bodyweight and cardiometabolic risk markers were maintained 3 months after completion of the intervention. We hypothesised that 3 months of TRE would induce clinically relevant weight loss and that weight loss would be maintained during the 3-month follow-up period.

See Online for appendix

Methods

Study design

The study design and methods have been published elsewhere.[10] Additional information is available in the protocol (appendix p 41) and on ClinicalTrials.gov (NCT03854656). The trial was a single-centre, parallel, superiority, open-label randomised controlled clinical trial conducted at Steno Diabetes Center Copenhagen (Copenhagen, Denmark). Participants received compensation for travel expenses. The Ethics Committee of the Capital Region of Denmark (H-18059188) and the Danish Data Protection Agency approved this trial, which was conducted in accordance with the Declaration of Helsinki.

Participants

Participants were recruited by advertisements in newspapers, webpages, pharmacies, general practitioners

clinics, Steno Diabetes Center Copenhagen, and from previous participants of other studies at Steno Diabetes Center Copenhagen. The inclusion criteria were age 30–70 years with either overweight (ie, BMI ≥25 kg/m²) and concomitant prediabetes (ie, glycated haemoglobin [HbA_{1c}] 39–47 mmol/mol) or obesity (ie, BMI ≥30 kg/m²) with or without prediabetes and a habitual self-reported eating and drinking (except for water) window of 12 h per day or more every day and of 14 h per day or more at least 1 day per week. The main exclusion criteria were shift work, diabetes, uncontrolled medical conditions, history of bariatric surgery, weight change (ie, >5 kg) within 3 months, and concomitant participation in other intervention studies. The full list of inclusion and exclusion criteria can be found elsewhere (appendix p 53).[10] Data on sex were self-reported, with the options of female or male. All participants provided oral and written consent before participation in the trial.

Randomisation and masking

Participants were enrolled by a medical doctor and a medical student, who were also involved in checking blood samples and registering adverse events but did not take part in the study visits. Individuals were randomly assigned 1:1 to 3 months of 10-h TRE or habitual living (hereafter referred to as the control group) after completion of screening and baseline testing at visit 1. Randomisation was done in blocks varying in size, which were unknown to the researchers. The randomisation list was generated by an external statistician who was otherwise not involved in the trial. When participants left the research facility at the test day on visit 1, they received a sleeve, fastened with a zip secured with a combination lock, that contained information about group allocation. On day 7, when all baseline assessments were completed, participants were provided with the code for the lock by an investigator (JSQ, HEP, or MMJ) to ensure that participants were masked to group allocation during the 7-day assessment period. Also on day 7, an investigator (JSQ, HEP, or MMJ) provided a detailed introduction to the specific group allocation by telephone. Randomisation was open for participants and research staff, but outcome assessors were masked during statistical analyses.

Procedures

Participants allocated to the TRE group were instructed to consume all foods and beverages (except water) within a self-selected 10-h per-day eating window placed between 0600 h and 2000 h for the 3-month (13 weeks) intervention. Participants were asked to maintain a stable eating window during the intervention period, preferably to start at least 2 h after habitual wake-up time and ending 3 h before habitual bedtime. Participants were advised to drink plain sparkling water outside the eating window if they needed something other than still water (eg, during social events). Participants in the control group were instructed to continue their habitual lifestyle during the 3-month intervention. Instructions to participants in both groups were given at the time of randomisation and no other instructions were given during the duration of the trial. Except for timing in the TRE group, there were no restrictions regarding food or drink intake and all participants in both groups were advised to follow the Danish Official Dietary Guidelines.[11] During the 3-month follow-up, there were no restrictions regarding food or drink intake and participants in the control group were allowed to follow TRE.

Participants were invited for test days at baseline (visit 1 at week –1), after 1·5 months (mid-intervention visit 2 at 6 weeks after visit 1), after 3 months of the intervention (visit 3 at 12 weeks after visit 1), and at 3-month follow-up (visit 4 at 13 weeks after visit 3) without active intervention. After test days at visit 1, visit 2, and visit 3, free-living continuous glucose monitoring (CGM) with IPro2 (Medtronic Denmark, Copenhagen, Denmark) was done simultaneously with measurement of physical activity by accelerometers (Axivity AX3, Newcastle upon Tyne, UK) for 7 consecutive days. Participants were asked to weigh and register food intake via pen and paper on 2 weekdays and 1 weekend day (appendix p 1). Participants were reminded to follow their group allocation (ie, control group or TRE group) during these periods at visit 2 (ie, the seventh intervention week) and visit 3 (ie, the thirteenth intervention week).

At the trial site during visits 1–4, height was measured with a stadiometer (Seca Vogel & Halke, Hamburg, Germany) and bodyweight was measured with a digital scale (Tanita BWB-620A, Amsterdam, Netherlands) when participants were wearing only light clothes (underwear and, in some cases, a light t-shirt). Waist circumference was measured at the midpoint between the lowest point of the lowest rib and the highest point of the iliac crest; hip circumference was measured at the point of the greater femoral trochanter. A mean of two repeated measurements of hip and waist circumference was used. If the two measurements differed by more than 3 cm, a third measurement was conducted and the mean of the two closest measurements was used. Body composition (ie, fat mass and fat-free mass) was measured with whole-body, dual-energy, x-ray absorptiometry (Discovery, Hologic, Bedford, MA, USA). At all visits, blood pressure and resting heart rate (ie, beats per min) were measured three times with 2-min intervals in between via a digital blood pressure monitor (UA-852, A&D Instruments, Abingdon, UK) after a minimum of 10 min rest, and the mean of the two lowest values of three consecutive measurements was used. Resting energy expenditure and substrate oxidation were measured for 30 min at visit 1 and visit 3 via indirect calorimetry and a ventilated hood (Vyntus CPX, CareFusion, Höchberg, Germany) with the participant resting in the supine position in a quiet room. Fasting blood samples were collected at all visits for assessment of HbA_{1c}, glucose, insulin, triglyceride, cholesterol,

alanine aminotransferase, and aspartate aminotransferase (appendix p 1). The test days at baseline (visit 1) and after 3 months of the intervention (visit 3) included a 4-h meal test with repeated blood sampling to assess postprandial glucose and insulin concentrations.

Self-reported sleep quality, bedtime, wake-up time, and sleep duration were assessed with the Pittsburgh Sleep Quality Index.[12] Sleep quality was expressed as the global score (0–21). A global score of more than 5 has been suggested as a sensitive measure of poor sleep quality.[12] Self-rated quality of life was assessed with Short Form-36.[13] The components of general health perception, physical functioning, and emotional wellbeing were evaluated and reported.

Participants were instructed to register time of initiating the first and terminating the last eating and drinking episode (except water) every day from the baseline visit (visit 1) to the follow-up visit (visit 4). Once per week, participants received an e-mail with a URL that led to an online form in which they were asked to register the time of first and last eating and drinking episodes for the preceding week. In the first week, participants in the control group were contacted by telephone if they restricted their eating window to less than their habitual 12 h per day or more. Participants in the TRE group were contacted if their eating window deviated from their self-selected 10-h window on 4 days or more. After the first week, participants were only contacted if they did not register their eating window.

To account for small variations in per-day eating window, participants in the TRE group were considered adherent if their eating window was less than 11 h per day.[10] Adherence to the intervention was defined as the percentage of days during the intervention in which the eating window was less than 11 h per day, starting less than 1 h before and ending less than 1 h after the 10-h self-selected eating window. Days for which a participant had not recorded an eating window were regarded as non-adherent days. Test days and other days on which participants, as per the study design, did not follow TRE (ie, if eating between 1900 and 2000 h the day before the test day) were excluded from the calculation of adherence for all participants. As per the study design, no other reasons for non-adherence were permitted. No adherence criteria for the participants in the control group were defined.

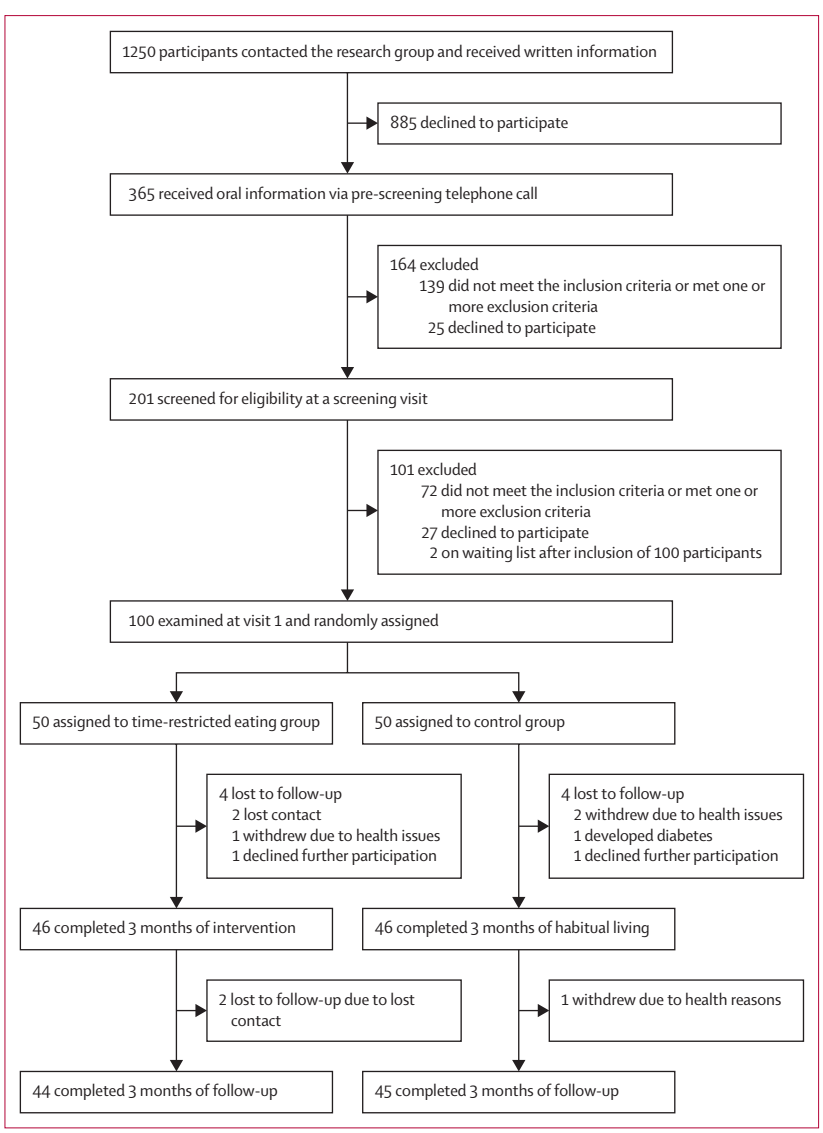

Figure 1: **Trial profile**

Outcomes

The primary outcome of change in bodyweight was assessed after 3 months (12 weeks) of the intervention (ie, at visit 3) and after 3 months (13 weeks) of follow-up (ie, at visit 4). All clinical examinations were conducted at Steno Diabetes Center Copenhagen. Participants arrived at about 0800 h after an approximate 12-h overnight fast (except water). All participants were instructed to eat something between 1900 h and 2000 h on the evening before a test day to minimise the potential acute effects of varying fasting duration on the outcomes of interest.[14,15] No alcohol consumption or strenuous physical activity were allowed for 48 h before testing. Participants were asked to avoid physically demanding transportation to the research facility.

Secondary outcomes were differences in changes in body fat mass, fat-free mass, total energy intake, HbA_{1c}, fasting plasma glucose, and fasting LDL cholesterol from baseline to end of the intervention (3 months) and during 3 months of follow-up. Energy intake was not included as a secondary outcome in the original protocol but was included in the trial registration and the statistical analysis plan, which were published before termination of the trial.

Adverse events were reported and registered at study visits or if participants contacted study staff to report events between visits.

Statistical analysis

The statistical analysis plan is available (appendix p 23). A weight loss of 2 kg (3%) during 3 months was assumed to be clinically relevant.[16] With an expected standard deviation of 3·1 kg for changes to bodyweight, at least 40 participants who completed the intervention were needed in each group to attain a statistical power of 0·8 (α 0·05). To allow for 20% drop-out, we included 50 participants in each of the two groups. To estimate the intention-to-treat effect of treatment assignment, we used a linear mixed model with fixed effects for treatment assignment, visit, and their interaction and a repeated effect at the participant level, with unstructured covariance matrix. The model was baseline-adjusted by putting all participants in the control group at visit 1 (before randomisation).[17] For several outcomes (bodyweight, BMI, waist circumference, waist-to-hip ratio, fat mass, fat-free mass, fat percentage, android-to-gynoid ratio, resting energy expenditure, and HDL cholesterol), the analysis was adjusted for sex to improve model fit, which was not defined in the statistical analysis plan. This process was done before assessing treatment effects. A per-protocol analysis was done for the primary outcome. Participants who completed the intervention in the TRE group were considered per-protocol if their adherence was 80% or more. All participants who completed the intervention period in the control group were considered per-protocol. For the primary outcome, a hierarchical testing procedure was used to control the false-positive rate; for the predefined secondary outcomes, a false-detection rate (FDR) correction ad modem Benjamini and Hochberg (ie, FDR <5%) was used.[18]

R version 3.6.0 and SAS version 9.4 were used for the analyses. The linear mixed model was Proc Mixed in SAS.

Role of the funding source

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

Results

Between March 12, 2019, and March 2, 2022, 1250 individuals contacted the research group and received written information about the study (figure 1). Of these 1250 individuals, 201 were screened for eligibility and 100 participants (66 [66%] female and 34 [34%] male) were enrolled and randomly assigned (50 to each group; figure 1). Overall median age was 59 years (IQR 52–65). Of those 100, 46 (92%) in the TRE group and 46 (92%) in the control group completed the intervention period. Three participants were lost during follow-up and testing (two in the TRE group and one in the control group; table 1; figure 1). Participants who were randomly assigned to the TRE group adhered to the intervention on 91% of the intervention days and 38 (83%)

	All participants (n=100)	Control group (n=50)	TRE group (n=50)
Sex			
Female	66 (66%)	34 (68%)	32 (64%)
Male	34 (34%)	16 (32%)	18 (36%)
Age, years	59 (52–65)	59 (52–65)	56 (52–64)
Self-reported ethnicity			
White	98 (98%)	49 (98%)	49 (98%)
Asian	1 (1%)	1 (2%)	0
Other*	1 (1%)	0	1 (2%)
Smoker status			
Yes occasionally but not on test days	4 (4%)	2 (4%)	2 (4%)
No	96 (96%)	48 (96%)	48 (96%)
Highest education			
Elementary school (aged 5–15 years)	6 (6%)	2 (4%)	4 (8%)
Higher education <5 years (aged >15 years)	71 (71%)	39 (78%)	32 (64%)
Higher education ≥5 years (aged >18 years)	20 (20%)	8 (16%)	12 (24%)
Other	1 (1%)	0	1 (2%)
Occupation			
Retired	23 (23%)	12 (24%)	11 (22%)
Unemployed	4 (4%)	0	4 (8%)
Employed or self-employed	64 (64%)	33 (66%)	31 (62%)
Other	7 (7%)	4 (8%)	3 (6%)
Living situation			
Living alone	23 (23%)	13 (26%)	10 (20%)
Children living at home	34 (34%)	17 (34%)	17 (34%)
Other	41 (41%)	19 (38%)	22 (44%)
Family members with diabetes†	32 (32%)	16 (32%)	16 (32%)
Family members with cardiovascular disease†	52 (52%)	26 (52%)	26 (52%)
Antihypertensives	23 (23%)	13 (26%)	10 (20%)
Lipid-lowering medication	6 (6%)	4 (8%)	2 (4%)
Anticoagulants	4 (4%)	2 (4%)	2 (4%)
Bodyweight, kg	99 (20)	99 (22)	98 (19)
Female participants	91·7 (17·5)	91·0 (17·6)	92·4 (17·6)
Male participants	112·2 (18·6)	116·3 (19·6)	108·6 (17·4)
BMI, kg/m²	33·9 (5·8)	33·9 (6·4)	33·8 (5·2)
Waist circumference of female participants, cm	104 (11)	103 (12)	104 (11)
Waist circumference of male participants, cm	116 (12)	117 (12)	116 (13)
Waist-to-hip ratio of female participants	0·89 (0·07)	0·89 (0·06)	0·89 (0·08)
Waist-to-hip ratio of male participants	1·02 (0·05)	1·01 (0·05)	1·03 (0·05)
Fat mass, kg	38·3 (34·3–44·0)	36·9 (33·8–44·1)	38·5 (34·4–43·3)
Fat-free mass of female participants, kg	51·5 (7·0)	52·0 (6·7)	51·0 (7·4)
Fat-free mass of male participants, kg	73·0 (8·2)	75·6 (8·3)	70·6 (7·5)
Fat percentage of female participants	44 (4)	43 (5)	45 (4)
Fat percentage of male participants	35 (5)	35 (6)	35 (5)
REE of female participants, kJ per day	6968 (1010)	6976 (1081)	6960 (947)

(Table 1 continues on next page)

	All participants (n=100)	Control group (n=50)	TRE group (n=50)
(Continued from previous page)			
REE of male participants, kJ per day	9344 (1349)	9909 (1404)	8845 (1106)
Daily eating duration, h	13·3 (12·3–14·2)	13·1 (11·9–14·0)	13·4 (12·7–14·4)
Energy intake of female participants, kJ per day	8264 (2078)	7853 (2010)	8715 (2090)
Energy intake of male participants, kJ per day	10 014 (2103)	10 740 (2316)	9370 (1708)
Systolic blood pressure, mm Hg	130 (123–144)	133 (124–145)	127 (122–141)
Diastolic blood pressure, mm Hg	85 (79–91)	86 (80–96)	84 (79–89)
HbA_{1c}, mmol/mol	38 (4)	39 (5)	37 (4)
Prediabetes			
HbA_{1c} 39–41 mmol/mol	29 (29%)	15 (30%)	14 (28%)
HbA_{1c} 42–47 mmol/mol	19 (19%)	12 (24%)	7 (14%)
Fasting glucose, mmol/L	5·7 (0·6)	5·8 (0·6)	5·7 (0·6)
Fasting insulin, pmol/L	77 (57–106)	82 (63–108)	71 (50–96)
CGM glucose, mmol/L	6·1 (0·5)	6·1 (0·5)	6·1 (0·4)
Total fasting cholesterol of female participants, mmol/L	5·7 (0·8)	5·6 (0·7)	5·7 (1·0)
Total fasting cholesterol of male participants, mmol/L	5·2 (1·0)	5·4 (1·1)	4·9 (0·8)
Fasting HDL-C of female participants, mmol/L	1·54 (0·32)	1·57 (0·33)	1·51 (0·31)
Fasting HDL-C of male participants, mmol/L	1·21 (0·22)	1·20 (0·14)	1·22 (0·27)
Fasting LDL-C of female participants, mmol/L	3·5 (0·8)	3·4 (0·6)	3·6 (0·9)
Fasting LDL-C of male participants, mmol/L	3·1 (0·7)	3·3 (0·7)	3·0 (0·7)
Fasting VLDL-C, mmol/L	0·68 (0·25)	0·70 (0·26)	0·67 (0·24)
Fasting triglyceride, mmol/L	1·54 (0·67)	1·60 (0·79)	1·47 (0·54)
Self-reported general health, SF36	75 (60–85)	75 (60–85)	70 (55–85)

Data are n (%), mean (SD), or median (IQR). Normally distributed data are presented as mean (SD) and non-normally distributed data are presented as median (IQR). CGM=continuous glucose monitoring. HbA_{1c}=glycated haemoglobin. HDL-C=HDL cholesterol. LDL-C=LDL cholesterol. REE=resting-energy expenditure. SF36=Short Form-36. TRE=time-restricted eating. VLDL-C=very LDL cholesterol. *Options were Arabic, Black, or Hispanic. †Mother, father, sister, or brother.

Table 1: **Baseline characteristics**

of 46 who completed the intervention were highly adherent (ie, were per-protocol participants who completed the intervention). Compared with baseline, participants in the TRE group consumed their first calories later in the day and consumed their last calories earlier in the day, which resulted in a median reduction of their habitual eating window by approximately 4 h per day with no major fluctuations during the intervention (figure 2; table 2). The changed timing of their eating window was corroborated by CGM data and weighted food records (figure 2). During the follow-up period, the reduction of the habitual eating window of participants in the TRE group attenuated and showed larger variations than during the intervention period, with only 13 (30%) of 44 participants being highly adherent.

After 3 months of the intervention, there was no difference in bodyweight between the TRE group and the control group (–0·8 kg, 95% CI –1·7 to 0·2; p=0·099; table 3). Few participants in the TRE group and the control group had a clinically relevant weight loss defined as 3% or more and 5% or more of their baseline bodyweight (figure 3; table 3). Being in the TRE group was not associated with a lower bodyweight compared with the control group after the subsequent 3-month follow-up period (–0·2 kg, 95% CI –1·6 to 1·2). The results of the per-protocol analysis showed that participants in the TRE group who were able to adhere to the intervention had a weight loss of 1·0 kg (95% CI –1·9 to –0·0; p=0·040) after 3 months of TRE compared with habitual living (appendix p 3).

3 months of TRE, but not habitual living, was associated with within-group reductions in bodyweight, fat mass, and HbA_{1c} (figure 3; table 3). However, there were no statistically significant changes in any of the secondary outcomes after adjustment for multiplicity (figure 3; table 3).

The explorative outcomes are presented in the appendix (p 4).

During the trial and follow-up period, one participant in the TRE group reported a severe adverse event: development of a subcutaneous nodule and pain when the arm was in use. This side-effect was evaluated to be related to the trial procedures. Three participants (one in the TRE group and two in the control group) had HbA_{1c} more than or equal to 48 mmol/mol and three participants (all in the TRE group) reported headache, migraine, and general discomfort between visits. These participants were referred to their general practitioner for further examination. Five participants (three in the TRE group and two in the control group) reported local pain in relation to blood sampling, fainting during the mixed meal test, patch rash, and mild gastrointestinal discomfort after test meal.

Discussion

3 months of 10-h TRE did not lead to clinically relevant weight loss or improvement in cardiometabolic health in individuals with overweight or obesity at high risk of type 2 diabetes. Small reductions in fat mass and HbA_{1c} were observed in response to TRE compared with the control group; however, these reductions were not statistically significant after adjustment for multiple testing. The trial had a high overall retention rate (92% during the intervention and 89% at follow-up) and adherence of 91% to TRE during the intervention and 45% during the follow-up period (table 2). The per-protocol analysis indicated that participants who were adherent to the intervention had a mean weight loss of 1·0 kg after 3 months of TRE, which was less than the predefined clinically relevant effect size. Future studies should investigate whether clinically relevant weight loss can be obtained if TRE is maintained in the long term.

Our results are consistent with the randomised clinical trial by Lowe and colleagues.[19] In their trial, individuals with overweight or obesity did not lose weight in response

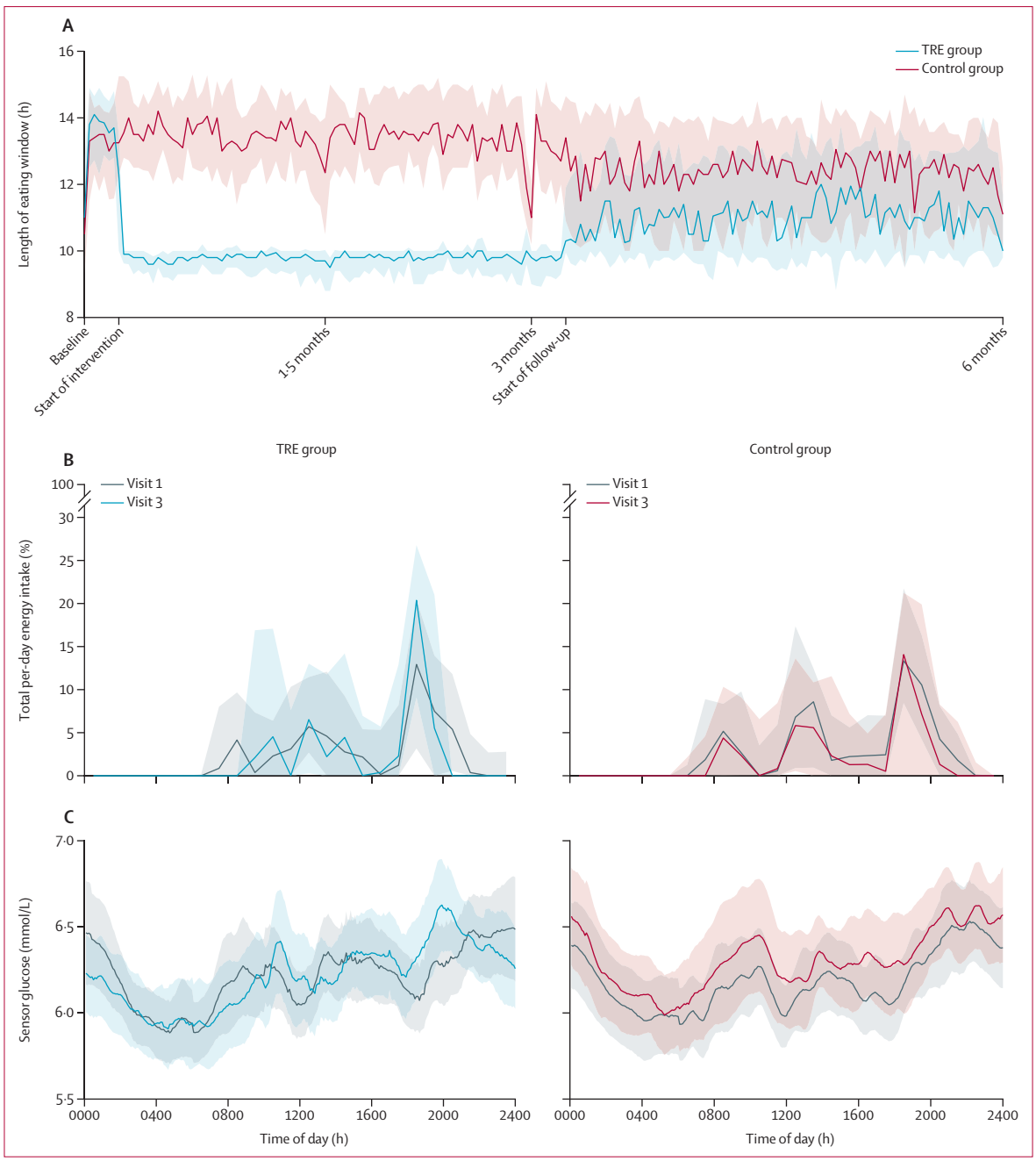

Figure 2: **Per-day eating window, energy intake, and sensor glucose**
(A) Median (IQR) per-day self-reported eating window of participants who completed the intervention. Trial duration was standardised to 26 weeks for all participants. (B) Median (IQR) of daily self-reported energy intake at baseline (visit 1) and during the last week of the intervention (visit 3) for participants who completed the intervention. (C) Mean (95% CI) sensor glucose measured by continuous glucose monitoring at baseline (visit 1) and during the last week of the intervention (visit 3) for participants who completed the intervention. TRE=time-restricted eating.

to 12 weeks of 8-h TRE compared with participants who kept consistent timing of three structured meals per day.[19] In a 2022 RCT of fire fighters working 24-h shifts, Manoogian and colleagues[20] observed that 12 weeks of 10-h TRE did not result in weight loss. A 2022 meta-analysis of 17 RCTs (all ≥4 weeks in duration) suggested that TRE of 12-h eating window or less led to modest reductions (approximately 1·5 kg) in bodyweight and fat mass.[21] Subgroup analyses of studies in which participants adhered to prescribed eating windows revealed no significant weight reduction in response to 12-h TRE but significant reductions in response to TRE interventions with an eating window of 10 h or less.[21] Few long-term TRE trials have been conducted. In a 2023 RCT of individuals

	Visits 1–3 of the control group (n=46)	Visits 1–3 of the TRE group (n=46)	Visits 3–4 of the control group (n=45)	Visits 3–4 of the TRE group (n=44)
Duration, days	83 (83 to 85)	83 (83 to 84)	91 (87 to 92)	91 (90 to 93)
First caloric event, time of day*	0730 h (0710 to 0850)	0950 h (0900 to 1010)	0810 h (0730 to 0930)	0900 h (0800 to 1000)
Change in timing of first caloric event, min*	–10 (–20 to 10)	100 (50 to 140)	20 (–10 to 370)	60 (10 to 100)
End of last caloric event, time of day*	2130 h (2030 to 2150)	1920 h (1900 to 2000)	2030 h (1950 to 2120)	2000 h (1910 to 2110)
Change in timing of last caloric event, min*	10 (–20 to 40)	–120 (–170 to –80)	–30 (–70 to 10)	–80 (–130 to –10)
Daily eating duration, min*	790 (770 to 860)	590 (570 to 600)	750 (660 to 820)	650 (580 to 750)
Difference in daily eating duration, min*	20 (–20 to 40)	–230 (–280 to –200)	–50 (–130 to 0)	–130 (–220 to –60)
Adherence to TRE, percentage of days†	4% (1 to 14)	91% (85 to 98)	14% (3 to 47)	45% (14 to 83)
Strict TRE‡	0	38 (83%)	5 (11%)	13 (30%)

Data are median (IQR) or n (%). Visits 1–3 was the 3-month intervention period. Visits 3–4 was the 3-month follow-up period. TRE=time-restricted eating. *Rounded to nearest 10-min interval. †Percentage of days with an eating window of <11 h. ‡Number of participants with an eating window of <11 h for 80% or more of the days in the given period.

Table 2: **Timing of energy intake and adherence**

with obesity, Lin and colleagues[22] observed that 6 months of 8-h TRE then 6 months of 10-h TRE led to a 4·6 kg reduction in bodyweight and a 2·8 kg reduction in fat mass compared with the control group. Another 2023 RCT by Pavlou and colleagues[23] that included individuals with obesity and type 2 diabetes showed that 6 months of 8-h TRE led to a 3·5 kg reduction in bodyweight and 2·5 kg reduction in fat mass compared with control individuals. Fat-free mass was unaltered in both trials. In this trial, we observed no change in fat-free mass but indications of reduced fat mass in those following TRE. This finding contrasts with the study by Lowe and colleagues,[19] in which a statistically significant loss of appendicular lean mass was observed after TRE in a subgroup who attended in-person testing.[19] However, the functional implications of the fat-free mass loss (1·8%) can be questioned.[24] Overall, more studies are needed before any conclusions on the effects of TRE on body composition can be made.

TRE in the current trial was associated with a reduction in HbA_{1c}; however, the change was small and not statistically significant after adjustment for multiplicity. This finding is in accordance with previous studies, in which HbA_{1c} did not change in response to 8–12 weeks of 4–10-h TRE in individuals with overweight or prediabetes.[19,25–27] In these studies, weight loss was either absent[19] or modest (approximately 3%),[25–27] which, as well as little potential for change with regards to baseline HbA_{1c}, might partly explain the lack of changes. Furthermore, in our trial, fasting plasma glucose did not change, which agrees with most previous studies[4,20] and could be explained by participants' relatively typical plasma glucose at baseline. Therefore, improvement in this outcome will be difficult.

In the RCT of fire fighters, participants had a baseline eating window of approximately 14 h per day, which was reduced to approximately 11 h per day in the TRE group. However, no difference in self-reported per-day energy intake between the TRE group and the control group was shown, which probably explains no weight loss in response to TRE.[20] In our trial, the eating window was reduced by about 4 h per day during TRE, with no major fluctuations during the intervention. However, we observed no difference in self-reported energy intake between the TRE group and the control group, possibly because the eating window was sufficiently long for the participants to consume the same number of calories as before the trial. Previous studies with no imposed concomitant calorie restriction indicated that TRE is associated with a 7–22% reduction in daily energy intake[1] and, accordingly, the amount of reduction in per-day eating window might affect the degree of energy deficit during TRE.[1,19,28] Consequently, the lack of significant weight loss and changes in cardiometabolic risk factors in our trial and previous randomised trials might be related to the reduction in the per-day eating window.[4] Therefore, whether the inclusion of participants with longer habitual eating windows would lead to improvements in bodyweight and cardiometabolic health is uncertain. Therefore, prescribing individualised reduction in per-day eating window duration on the basis of a participant's habitual eating window might be relevant. In our trial, 3 months of TRE was not associated with changes in physical activity, which is in accordance with findings from other TRE studies.[28]

Participants in our trial found TRE appealing due to the unrestricted dietary intake, but also found it socially challenging.[29,30] As participants were largely adherent to the TRE intervention, no changes in bodyweight imply that they compensated by increasing their energy intake within the per-day eating window. Furthermore, the data on food intake and CGM indicated that participants in the TRE group increased their energy or carbohydrate intake in the evening, close to the end of their eating window. This increase in food intake might be undesirable in terms of energy balance and glycaemia, especially in individuals with diabetes. Future TRE studies could potentially benefit from advising participants not to increase energy or carbohydrate intake in the evening and to consider recommending satiating foods (eg, high in dietary fibre), and supporting them to maintain these habits. A qualitative analysis including a subgroup of 17 participants included in the TRE group in our trial suggested that some participants occasionally ate more at mealtimes to manage potential hunger later in the evening, although they did not feel hungry.[29]

Adherence to TRE was roughly halved during follow-up compared with the intervention period. According to our qualitative analysis, most participants in this subgroup maintained elements of the intervention after the end of the first 3-month period.[30] Facilitators for maintenance

	Estimated mean (95% CI)	Within-group changes (95% CI)	Difference from control group (95% CI)	p value	FDR <5%
Weight, kg*					
Control group at baseline	101·8 (98·1 to 105·6)	..	..	..	..
Control group at 3 months	101·5 (97·7 to 105·3)	−0·4 (−1·0 to 0·3)	..	..	..
Control group at 6 months	101·0 (97·2 to 104·8)	−0·9 (−1·9 to 0·1)	..	..	..
TRE group at baseline	101·8 (98·1 to 105·6)	..	..	..	..
TRE group at 3 months	100·7 (96·9 to 104·5)	−1·2 (−1·8 to −0·5)	−0·8 (−1·7 to 0·2)	0·099	..
TRE group at 6 months	100·8 (97·0 to 104·5)	−1·1 (−2·1 to −0·1)	−0·2 (−1·6 to 1·2)	..	..
Fat mass, kg*					
Control group at baseline	40·7 (38·2 to 43·2)	..	..	..	..
Control group at 3 months	40·6 (38·1 to 43·2)	−0·1 (−0·6 to 0·4)	..	..	..
Control group at 6 months	39·9 (37·4 to 42·5)	−0·8 (−1·6 to −0·0)	..	..	..
TRE group at baseline	40·7 (38·2 to 43·2)	..	..	..	..
TRE group at 3 months	39·7 (37·1 to 42·2)	−1·0 (−1·5 to −0·6)	−1·0 (−1·6 to −0·3)	0·0067	No
TRE group at 6 months	39·1 (36·5 to 41·7)	−1·6 (−2·4 to −0·9)	−0·8 (−1·9 to 0·2)	0·13	No
Fat-free mass, kg*					
Control group at baseline	62·3 (60·7 to 63·8)	..	..	..	..
Control group at 3 months	62·1 (60·5 to 63·6)	−0·2 (−0·6 to 0·2)	..	..	..
Control group at 6 months	62·2 (60·6 to 63·8)	−0·1 (−0·7 to 0·5)	..	..	..
TRE group at baseline	62·3 (60·7 to 63·8)	..	..	..	..
TRE group at 3 months	62·1 (60·5 to 63·6)	−0·2 (−0·6 to 0·2)	0·0 (−0·6 to 0·6)	0·99	No
TRE group at 6 months	62·6 (60·9 to 64·2)	0·3 (−0·3 to 0·9)	0·4 (−0·5 to 1·2)	0·37	No
Energy intake, kJ per day					
Control group at baseline	8865 (8419 to 9312)	..	..	..	..
Control group at 3 months	7981 (7291 to 8671)	−884 (−1522 to −247)	..	..	..
TRE group at baseline	8865 (8419 to 9312)	..	..	..	..
TRE group at 3 months	8172 (7469 to 8876)	−693 (−1345 to −41)	192 (−702 to 1085)	0·67	No
HbA_{1c}, mmol/mol					
Control group at baseline	38 (37 to 39)	..	..	..	..
Control group at 3 months	38 (37 to 39)	0 (−0 to 1)	..	..	..
Control group at 6 months	38 (37 to 39)	0 (−1 to 1)	..	..	..
TRE group at baseline	38 (37 to 39)	..	..	..	..
TRE group at 3 months	37 (37 to 38)	−1 (−1 to −0)	−1 (−1 to −0)	0·024	No
TRE group at 6 months	38 (37 to 39)	−0 (−1 to 0)	−0 (−1 to 0)	0·32	No
Fasting glucose, mmol/L					
Control group at baseline	5·7 (5·6 to 5·8)	..	..	..	..
Control group at 3 months	5·7 (5·6 to 5·9)	0·0 (−0·1 to 0·1)	..	..	..
Control group at 6 months	5·9 (5·7 to 6·0)	0·1 (−0·0 to 0·3)	..	..	..
TRE group at baseline	5·7 (5·6 to 5·8)	..	..	..	..
TRE group at 3 months	5·7 (5·5 to 5·8)	−0·1 (−0·2 to 0·0)	−0·1 (−0·2 to 0·1)	0·21	No
TRE group at 6 months	5·8 (5·6 to 5·9)	0·0 (−0·1 to 0·2)	−0·1 (−0·3 to 0·1)	0·33	No
LDL-C, mmol/L					
Control group at baseline	3·4 (3·2 to 3·5)	..	..	..	..
Control group at 3 months	3·2 (3·0 to 3·4)	−0·1 (−0·3 to 0·0)	..	..	..
Control group at 6 months	3·2 (3·0 to 3·4)	−0·2 (−0·3 to −0·0)	..	..	..
TRE group at baseline	3·4 (3·2 to 3·5)	..	..	..	..
TRE group at 3 months	3·4 (3·1 to 3·6)	−0·0 (−0·2 to 0·2)	0·1 (−0·1 to 0·4)	0·30	No
TRE group at 6 months	3·2 (3·0 to 3·4)	−0·2 (−0·4 to −0·0)	−0·0 (−0·2 to 0·2)	0·96	No

Data are estimated means (95% CI) or baseline-corrected difference between groups (95% CI). Only the primary and predefined secondary outcomes were null-hypothesis tested; p values are given for these outcomes. FDR was calculated for secondary outcomes only. FDR=false-detection rate. HbA_{1c}=glycated haemoglobin. LDL-C=LDL cholesterol. TRE=time-restricted eating. *Adjusted for sex with female as the reference.

Table 3: **Estimated changes in primary and secondary outcomes during the intervention and follow-up periods**

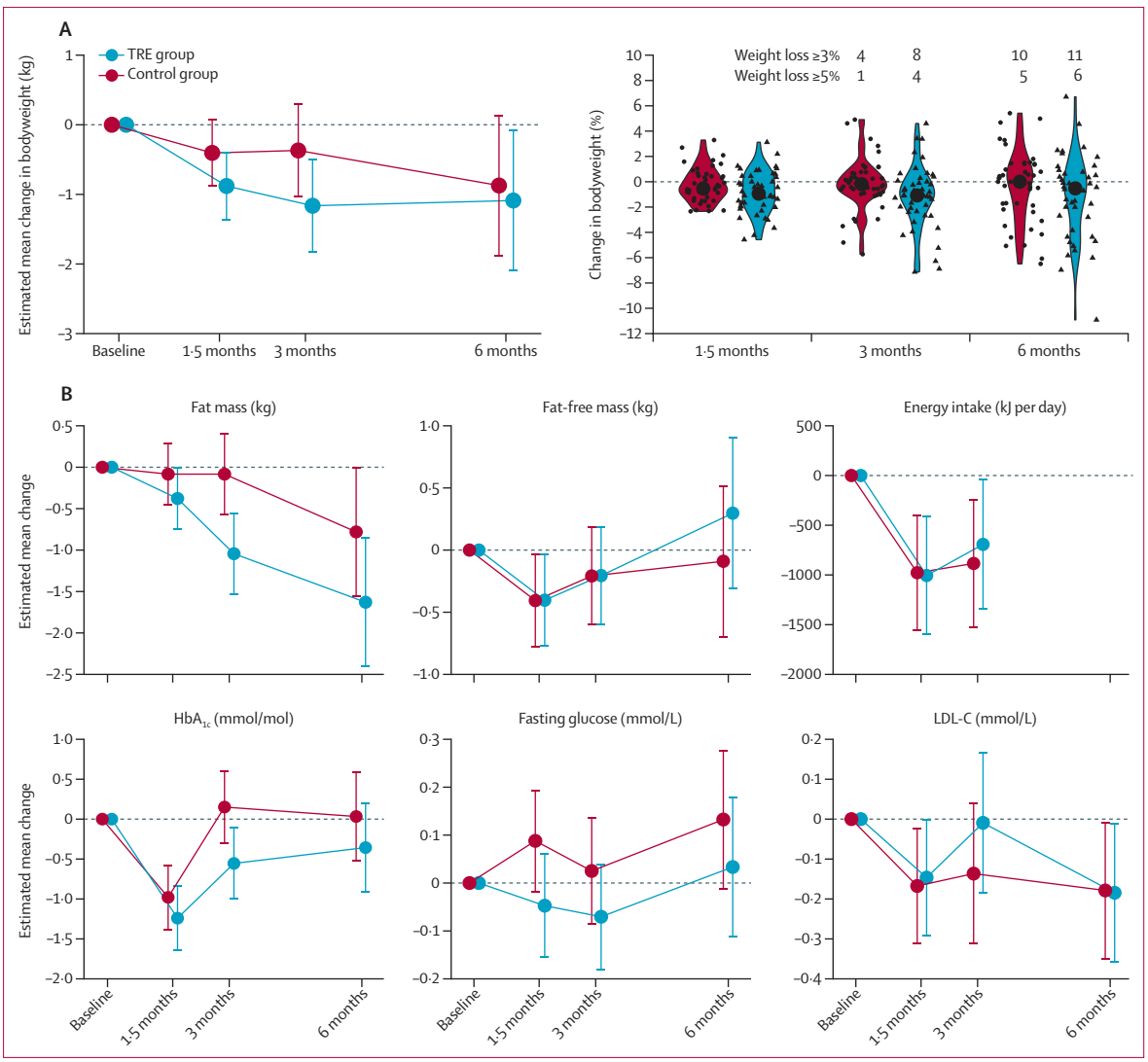

Figure 3: **Estimated mean changes in primary and secondary outcomes**
(A) Estimated mean change in the primary outcome (left; bars show 95% CI) and observed changes from baseline to the given visit for all participants who attended the visit; the numbers indicate the number of participants with ≥3% and ≥5% weight loss (right). (B) Estimated mean changes in secondary outcomes. Bars show 95% CI. HbA_{1c}=glycated haemoglobin. LDL-C=LDL cholesterol. TRE=time-restricted eating.

included consistent daily rhythms, regular meal patterns, and making flexible adjustments to TRE, whereas barriers included little social support, inconsistent per-day rhythms, and irregular meal patterns.[30] In a 2023 systematic review, we investigated the feasibility of TRE and observed that determinants of adherence to TRE included allowing intake of calorie-free beverages outside the eating window, provision of support, and individual influence on the timing of the eating window.[2] These findings emphasise the importance of including the target group in the design of a TRE intervention, as highlighted in our 2023 needs assessment analysis among individuals with type 2 diabetes.[31]

The strengths of this trial were the randomised controlled design with a predefined follow-up period. Furthermore, the trial had a high retention rate and high adherence to the intervention. However, the open-label feature of the study design is a limitation, but is inevitable in studies of lifestyle modifications. Another limitation of the study is that information on first and last meal intake (ie, per-day eating window) was obtained via self-report. Part of the study was done during the COVID-19 pandemic, with repeated lockdowns. However, according to our qualitative analysis in a subgroup of the TRE group, participants were able to follow TRE during this period.[32] Furthermore, this trial was conducted at a single centre in a European city and the study population was almost entirely White, both of which restrict the generalisability of the results. Overall, we interpret these findings to indicate that the trial has a high external validity.

In this RCT, 3 months of 10-h TRE did not induce clinically relevant effects on bodyweight or other clinical outcomes in middle-aged and older individuals at high risk of type 2 diabetes, despite high retention rate and high adherence. On the basis of our findings, we cannot recommend 10-h TRE as a short-term strategy to obtain weight loss and improve cardiometabolic health in the target group included in this trial. However, long-term studies of individuals with increased adiposity and metabolic dysfunction (eg, type 2 diabetes) are needed.

Contributors

JSQ and KF conceptualised and designed the study. HEP, MMJ, KKBC, NB, JS, NJWA, JJH, SST, DV, MEJ, SP, CB, GF, and MBB contributed to the design of the study. JSQ wrote the first draft of the manuscript. MBB and KF contributed to writing the manuscript. JSQ, HEP, MMJ, KKBC, TSE, SU, and KF collected data. HEP, MMJ, KKBC, TSE, MEN, and MBB analysed data. JSQ, MBB, and KF interpreted data. TSE and MBB accessed and verified the data. MBB did the statistical analysis. JSQ, HEP, MMJ, CB, JJH, SST, and KF obtained funding. All authors had full access to all the data in the study, reviewed and edited the manuscript, approved the final version of the manuscript, and had final responsibility for the decision to submit for publication.

Declaration of interests

JSQ has received funding for this study from the Novo Nordisk Foundation, Innovation Foundation, and Aalborg University; for other studies from Novo Nordisk; and travel grants from American Diabetes Association, European Association for the Study of Obesity, and Trygfonden Center for Physical Activity Research. HEP is currently employed by Novo Nordisk and is co-investigator on a project partly funded by the Novo Nordisk Foundation and Innovation Fund Denmark. SP is the author of the books *The Circadian Code* and *The Circadian Diabetes Code*, which advocate for time-restricted eating. DV is currently employed by Novo Nordisk and has received research grants from Bayer, Sanofi Aventis, Novo Nordisk, and Boehringer Ingelheim and holds shares in Novo Nordisk. SST has received research grants for a study drug and lecture fees from Novo Nordisk. KKBC is currently employed by Novo Nordisk; holds shares in Novo Nordisk; and was co-investigator on this project, for which her salary was covered by a grant from the Novo Nordisk Foundation. MEN has received research grants from Bayer. NJWA has received research grants from Novo Nordisk and Mercodia and has received speaker fees and fees as a member of the advisory board from Merck, Guidepoint, and Boehringer Ingelheim. JJH has received research grants from Novo Nordisk Foundation, Arla Foods, and European Research Council; consulting fees from Alphasights, Arix Bioscience, Eli Lilly, Structure Therapeutics USA, Zealand Pharma, Alcimed, Google Ventures Management, MSD Danmark, and Novo Nordisk; and support for presentations from Eli Lilly, Zealand Pharma, Novo Nordisk, and the Mayo Clinic. MEJ holds shares in Novo Nordisk. JS holds shares in Novo Nordisk. KF is currently employed by Novo Nordisk and has received research grants from Novo Nordisk, Unilever, and AstraZeneca and holds shares in Novo Nordisk and ChemoMetec. MMJ received funding from the Danish Association for the Study of Obesity; is a co-investigator on a project funded by Novo Nordisk; and was co-investigator on this project, for which her salary was covered by grants from the Novo Nordisk Foundation and Aalborg University. All other authors declare no competing interests.

Data sharing

Anonymised aggregated datasets generated during and analysed during this study are available from the corresponding author on reasonable request. Individual participant data cannot be shared as the informed consent signed by patients does not allow these data to be shared.

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