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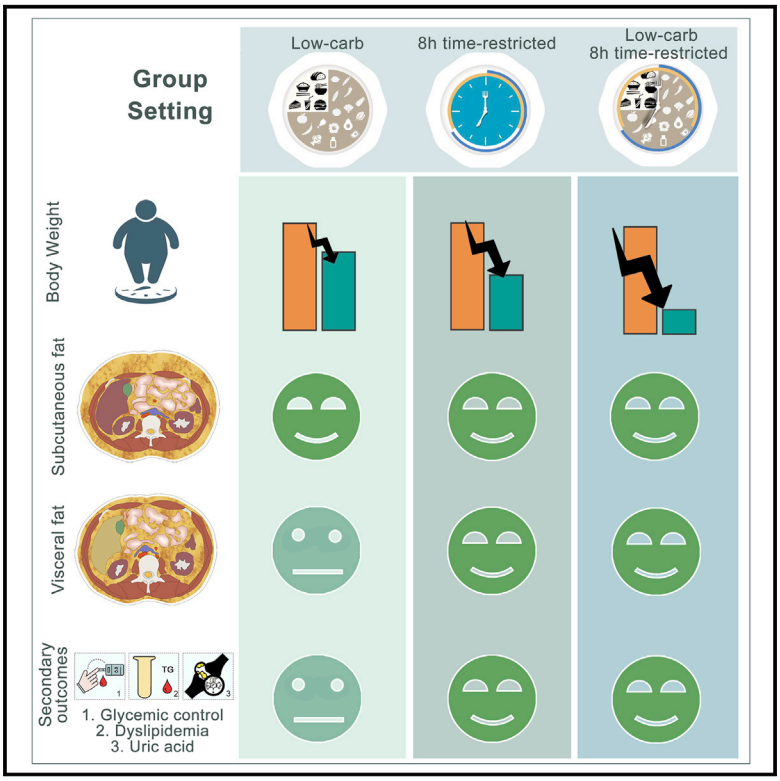
Time-restricted eating with or without low-carbohydrate diet reduces visceral fat and improves metabolic syndrome: A randomized trial

Graphical abstract



Highlights

- LCD, 8-h TRE, and their combination significantly reduce body weight and subcutaneous fat
- TRE yields more benefits on visceral obesity and cardiometabolic outcomes than LCD
- Combination intervention induces more weight loss compared with LCD or TRE alone

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In brief

He et al. determined the effects of LCD, 8-h TRE, and their combination on body weight and cardiometabolic outcomes in adults with MetS. Results imply that, without changing physical activity, 8-h TRE intervention with and without LCD can serve as an effective treatment for MetS.

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Time-restricted eating with or without low-carbohydrate diet reduces visceral fat and improves metabolic syndrome: A randomized trial

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SUMMARY

Overconsumption of carbohydrate-rich food combined with adverse eating patterns contributes to the increasing incidence of metabolic syndrome (MetS) in China. Therefore, we conducted a randomized trial to determine the effects of a low-carbohydrate diet (LCD), an 8-h time-restricted eating (TRE) schedule, and their combination on body weight and abdominal fat area (i.e., primary outcomes) and cardiometabolic outcomes in participants with MetS. Compared with baseline, all 3-month treatments significantly reduce body weight and subcutaneous fat area, but only TRE and combination treatment reduce visceral fat area (VFA), fasting blood glucose, uric acid (UA), and dyslipidemia. Furthermore, compared with changes of LCD, TRE and combination treatment further decrease body weight and VFA, while only combination treatment yields more benefits on glycemic control, UA, and dyslipidemia. In conclusion, without change of physical activity, an 8-h TRE with or without LCD can serve as an effective treatment for MetS (ClinicalTrials.gov: NCT04475822).

INTRODUCTION

Metabolic syndrome (MetS) is characterized by abdominal obesity, elevated blood pressure, and fasting blood glucose (FBG) as well as atherogenic dyslipidemia with high triglyceride (TG) and low high-density lipoprotein cholesterol (HDL-c) levels,[1,2] and it remarkably increases the risk of type 2 diabetes mellitus (T2DM) and cardiovascular diseases (CVD).[3] MetS has long been highly prevalent in Western countries and has steeply increased in the Chinese population over the past decades as well. Abdominal obesity is of central importance in the induction of metabolic dysfunctions including hypertension, hyperglycemia, atherogenic dyslipidemia, and release of proinflammatory cytokines by adipose tissue. Since 2004, the prevalence of general obesity in China has increased 3-fold, and abdominal obesity has increased by more than 50%; concomitantly, a rapid increase in the incidences of T2DM and CVD was also observed.[4,5] Since even mild body weight reduction can

ameliorate metabolic dysfunction,[6] the first line of therapy for MetS comprises lifestyle interventions including aggressive dietary adjustment to reduce body weight.[1,7] Nevertheless, long-term adherence to lifestyle intervention is always a challenge.

Among dietary interventions, low-carbohydrate diet (LCD) seems more ideal to induce weight loss in overweight individuals compared with low-fat diet,[8,9] as LCD generally exerts more rapid weight reduction with a greater loss in body fat and maintenance of lean mass.[9–11] LCD restricts carbohydrate consumption to <26% of energy intake (or <130 g carbohydrate/day) and does not contain specific carbohydrates, such as starch and sugar, while containing healthy fats and a moderate protein content.[10,12–14] The lower carbohydrate content of LCD is known to reduce insulin secretion, which promotes fat oxidation and lipolysis during negative energy balance.[10,15] In addition to LCD, time-restricted eating (TRE) has become increasingly popular in recent years for inducing clinically significant weight reduction and ameliorating metabolic disorders.[16–21] TRE is defined by intentionally restricting the times during the day when energy is consumed, confining the temporal window of food access to a specified number of hours each day, and fasting (water and tea without sugar or any artificial sweeteners are permitted) for the remainder of the day. Importantly, it is not necessary to monitor caloric intake in any way during the eating window. Chronic circadian disruption can aggravate the risk for components of MetS,[22–24] and TRE maintains a robust daily cycle of eating and fasting to support circadian rhythm.[25–28] One of the most popular regimens of TRE is 8-h TRE (also known as "the 16:8 diet"). There are specific regimens of TRE according to the timing of the eating window,[19] including early TRE (eTRE) that involves eating earlier in the day and late TRE (lTRE) that skips breakfast. Although both LCD and TRE have been demonstrated to be metabolically beneficial,[16,20,29] whether these 8-h TREs could exert a rapid weight reduction effect comparable to that of LCD in adults with MetS has not been assessed yet.

Despite being an underdeveloped and less prosperous part of the country, the prevalence of abdominal obesity in the Shaanxi province in Northwestern China is close to the national average of 31.5%,[30] and it can thus be regarded as a representative sample of China. In this region, regular eating habits include carbohydrate-rich staple foods, and an eating pattern of consuming three meals a day with late dinner and multiple snacks including a midnight snack is prevalent. In this study, we conducted a 3-month randomized clinical trial (RCT) to determine the effects of an LCD, TRE, and their combination on body weight, fat mass, and cardiometabolic outcomes in adults with MetS in Shaanxi, China. Furthermore, we allowed participants to choose freely between eTRE and lTRE, to keep their social eating pattern. We hypothesized that TRE effectively improves metabolic disease risk parameters without restricting carbohydrate consumption and that combination of TRE with LCD leads to additional metabolic benefits.

RESULTS

Participants

As illustrated in Figure 1, 290 participants were screened for this study, and 121 were excluded because they did not meet the inclusion criteria, had scheduling conflicts, or declined to participate. A total of 169 participants were randomized to receive intervention with LCD (group A; n = 56), TRE (group B; n = 57), or their combination (group C; n = 56), and after dropout of seven individuals, 162 individuals finally participated in the study. All participants met three or more MetS criteria at enrollment, and a minority (n = 62) of participants were on medication. This trial started with a 2-week weight stabilization and was followed by a 3-month intervention. At the end of the 3-month trial, 47 participants completed LCD, 44 completed TRE, and 44 completed their combination intervention. The main reason for dropout was scheduling conflicts. Table 1 and Table S1 show the baseline characteristics of the participants (n = 162). In this trial, we allowed participants to choose freely between two meal-eating windows for participants: 8 a.m. to 4 p.m. (eTRE) and 12 p.m. to 8 p.m. (lTRE), and we compared effects of two meal-eating windows using an exploratory analysis. In the TRE group, 38 participants (m/f 23/15) chose eTRE, and 17 participants (m/f 12/5) chose lTRE. In the combination group, 32 participants (m/f 22/10) chose eTRE, and 20 participants (m/f 15/5) chose lTRE. Table S2 shows the baseline characteristics of the eTRE and lTRE subgroups within the TRE and combination groups. At baseline, there were no significant differences in primary outcomes (i.e., body weight and abdominal fat area) or any secondary outcomes (i.e., body composition, glycemic control, plasma lipids, uric acid [UA], and blood pressure) between groups and subgroups. Table S3 clearly shows that participants receiving LCD or combination intervention had decreased intake of food containing high carbohydrates, such as rice, wheat flour, and pastry. Table S4 and Figure S1 show physical activity and daily step counts of participants, respectively, and demonstrate that participants maintained their usual physical activity throughout the study. Furthermore, participants with or without more than 50% dietary log records during the first 2 weeks of the intervention period showed similar responses to every treatment on primary outcomes after 3 months of intervention (Table S5).

LCD, TRE, and their combination reduce body weight in adults with MetS

As compared with baseline, after 3 months of intervention a significant reduction of body weight was observed in all three groups (Figures 2A and 2B), and only combination treatment induced a further reduction of body weight at month 3 compared with month 2 (Figure 2C and Table 2). Moreover, as shown in Table 2, combination treatment induced a higher reduction in body weight (−5.0 ± 0.4 kg) compared with either LCD (−2.2 ± 0.3 kg, $p < 0.001$) or TRE alone (−3.4 ± 0.4 kg, $p = 0.004$), and a significant difference in body weight reduction was also observed between LCD and TRE treatment ($p = 0.013$). Furthermore, both eTRE and lTRE alone or combined with LCD led to a sustained reduction of body weight as early as after 1 month, which persisted over 3 months (Table S6).

TRE, LCD, and their combination reduce subcutaneous fat, while only TRE with and without LCD reduces abdominal visceral fat

Abdominal fat is a pivotal risk factor and one of the drivers of the metabolic risk related to overweight and obesity.

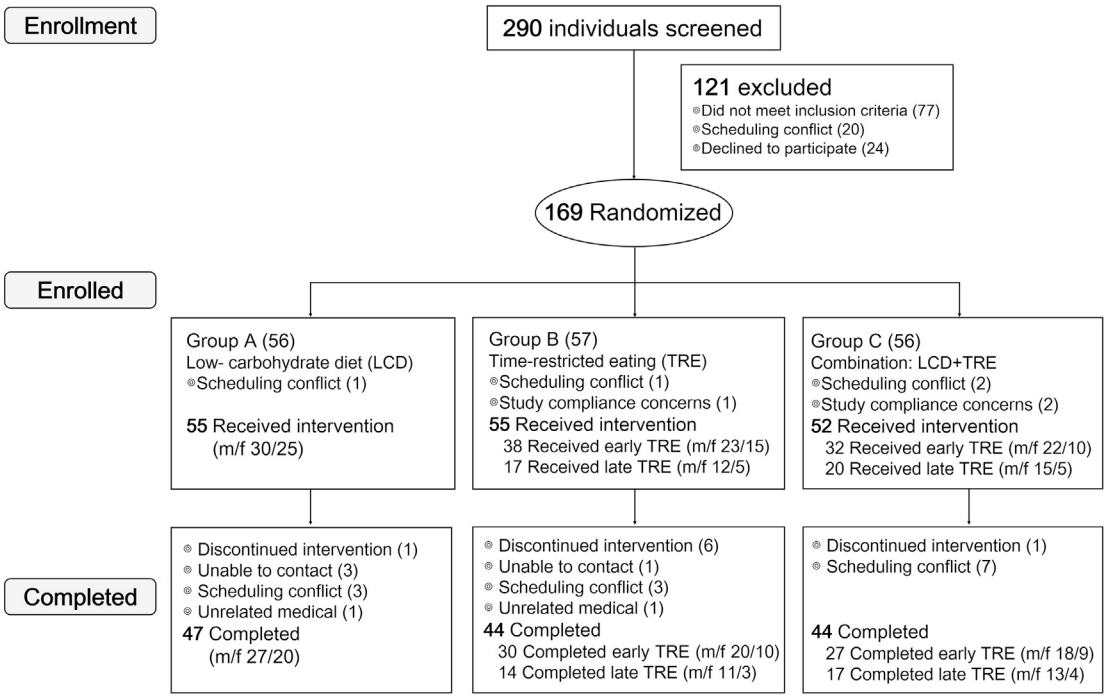

Figure 1. Trial profile

A total of 290 individuals were screened, and 77 were excluded because they did not meet one or more inclusion criteria. A total of 169 participants were randomized into the low-carbohydrate diet (LCD) group (n = 56), the 8-h time-restricted eating (TRE) group (n = 57), or the combination group (n = 56), and 162 participants received a diet intervention. During the 3 months of intervention, eight participants (LCD group, n = 1; TRE group, n = 6; combination group, n = 1) discontinued diet intervention due to lack of motivation or inability to stick to the diet. At the end of the 3-month trial, 47 participants (m/f 27/20) completed the LCD treatment, 44 participants (m/f 31/13) completed the TRE treatment (30 [m/f 20/10] completed early TRE, and 14 [11/3] completed late TRE), and 44 participants (m/f 31/13) completed the combination treatment (27 [m/f 18/9] completed early TRE, and 17 [13/4] completed late TRE).

Waist-to-hip ratio (WHR), an indicator of abdominal obesity, is more closely correlated to MetS than body mass index (BMI).[31,32] As compared with baseline, all three treatments induced a significant reduction of waist circumference, hip circumference, and body fat mass (Figures 2D, 2E, and 2F) after 3 months of intervention. Nevertheless, only TRE induced a more prominent reduction of WHR (−0.04 ± 0.01, Figure 2G and Table 2) compared with LCD (−0.01 ± 0.01, p = 0.023) and combination (−0.01 ± 0.01, p = 0.033), suggesting that TRE more effectively alleviates abdominal obesity than LCD.

Both abdominal visceral fat area (VFA) and abdominal subcutaneous fat area (SFA) play important but distinct roles in metabolic function. Thus, we further dissected the changes in these two fat depots using bioelectrical impedance analysis. Although after 3 months of intervention all three treatments induced similar reduction of SFA (Figure 2H), VFA was only decreased by TRE (−13 ± 5 cm^2) and combination treatment (−10 ± 3 cm^2, Figure 2I and Table 2). Compared with LCD (6 ± 5 cm^2), VFA was significantly reduced by both TRE (p = 0.009) and combination treatment (p = 0.016). Furthermore, as shown in Table S6, eTRE significantly reduced VFA and SFA, whereas lTRE did not, albeit that the change of VFA or SFA induced by eTRE and lTRE alone or combined with LCD did not differ.

TRE with and without LCD improves glycemic control

We next compared the effects of LCD, TRE, and their combination on glycemic control. In line with findings on abdominal VFA, TRE with or without LCD, but not LCD alone, significantly improved FBG and UA (Figures 3A and 3B and Table 2). Only combination treatment significantly decreased hemoglobin A1c (HbA1c) (Figure 3C and Table 2). In contrast, compared with baseline, all three treatments clearly improved fasting insulin levels (Figure 3D), C-peptide, homeostasis model assessment of insulin resistance (HOMA-IR), homeostatic model assessment of insulin sensitivity (HOMA-IS) (Figure 3E), and quantitative insulin-sensitivity check index (QUICKI) (Table 2). Notably, combination treatment caused more prominent changes on UA (combination: −51 ± 13 μmol/L, versus LCD: −17 ± 11 μmol/L, p = 0.039), HOMA-IR (combination: −2.16 [4.82], versus LCD: −1.15 [2.99], p = 0.049), HOMA-IS (combination: 0.10 [0.20], versus LCD: 0.03 [0.12], p = 0.042) and QUICKI (combination: 0.02 [0.03], versus LCD: 0.01 [0.02], p = 0.004) compared with LCD (Figures 3B and 3E and Table 2), indicating that the combination of LCD and TRE is most effective to combat cardiometabolic risk factors among the three interventions. Furthermore, we did not observe any significant differences in parameters related to glucose and insulin metabolism between eTRE and lTRE, whereas combined with LCD, eTRE displayed a further

Table 1. Baseline characteristics of participants

	LCD	TRE	Both	p value
Male/Female (total)	30/25 (55)	35/20 (55)	37/15 (52)	0.204
Age (years)	41.3 ± 1.4	43.0 ± 1.4	39.0 ± 1.2	0.106
Meal-eating window (hours)	10.6 ± 0.3	10.4 ± 0.3	10.7 ± 0.2	0.730
Daily carbohydrate intake (g)	324 ± 21	348 ± 16	361 ± 22	0.405
Weight (kg)	84.3 ± 2.2	84.7 ± 2.0	84.9 ± 1.8	0.979
BMI (kg/m^2)	29.3 ± 0.5	29.6 ±.5	29.0 ± 0.5	0.711
Waist circumference (cm)	96.1 ± 1.4	96.8 ± 1.2	94.7 ± 1.0	0.457
Hip circumference (cm)	105.1 ± 1.4	104.5 ± 0.9	103.7 ± 0.9	0.645
Waist-to-hip ratio (WHR)	0.92 ± 0.01	0.93 ± 0.01	0.91 ± 0.01	0.212
Body fat mass (kg)	33.9 ± 1.0	33.2 ± 0.9	32.7 ± 0.9	0.651
Body muscle mass (kg)	31.2 ± 1.0	31.6 ± 1.0	32.0 ± 0.8	0.818
Subcutaneous fat area (SFA, cm^2)	277 ± 11	270 ± 9	255 ± 9	0.307
Visceral fat area (VFA, cm^2)	92 ± 5	105 ± 5	96 ± 4	0.112
Hemoglobin A1c (HbA1c, %)	5.7 (0.6)	5.6 (0.6)	5.6 (0.8)	0.853
Fasting blood glucose (mmol/L)	5.10 (0.97)	5.05 (0.89)	5.07 (1.08)	0.763
Fasting insulin (mIU/L)	27.4 (24.7)	31.8 (24.8)	28.2 (17.7)	0.459
C-peptide (pg/mL)	1,608.8 ± 104.2	1,660.2 ± 100.1	1,651.7 ± 88.5	0.923
HOMA-IR	6.76 (9.68)	7.38 (5.90)	7.04 (6.67)	0.612
HOMA-IS	0.17 (0.17)	0.17 (0.19)	0.16 (0.12)	0.473
QUICKI	0.30 (0.04)	0.29 (0.03)	0.29 (0.03)	0.253
Uric acid (UA, μmol/L)	380 ± 13	384 ± 13	416 ± 16	0.144
Total cholesterol (mmol/L)	4.72 ± 0.14	4.76 ± 0.13	4.73 ± 0.13	0.978
LDL-c (mmol/L)	2.99 ± 0.13	3.01 ± 0.12	3.03 ± 0.12	0.974
Triglycerides (TG, mmol/L)	1.74 (1.52)	2.10 (1.55)	2.12 (2.56)	0.086
HDL-c (mmol/L)	1.13 ± 0.03	1.10 ± 0.03	1.04 ± 0.03	0.161
TG/HDL-c	1.58 (1.52)	1.84 (1.88)	2.02 (2.87)	0.044
Systolic blood pressure (mmHg)	130 ± 2	136 ± 2	131 ± 2	0.086
Diastolic blood pressure (mmHg)	82 ± 2	87 ± 2	84 ± 2	0.112

LCD, low-carbohydrate diet; TRE, time-restricted eating; Both, combination treatment; BMI, body mass index; HOMA-IR, homeostasis model assessment insulin resistance; HOMA-IS, homeostatic model assessment of insulin sensitivity; QUICKI, quantitative insulin-sensitivity check index; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol. All data are presented as the mean ± standard error of the mean (SEM) for normal distribution or median (interquartile range) for abnormal distribution. Differences between treatment arms (LCD, TRE, and both) were tested by one-way ANOVA or Kruskal-Wallis H test.

improvement of HOMA-IS (Table S6). As shown in Figures S2A and S2B, HOMA-IS and UA were significantly correlated with VFA but not with SFA.

TRE with and without LCD, but not LCD alone, improves dyslipidemia

LCD did not cause any significant differences in plasma levels of TG, HDL-c, or the ratio between TG and HDL-c (TG/HDL-c ratio) after 3 months of intervention (Figures 3F, 3G, and 3H and Table 2). In marked contrast, TRE with and without LCD significantly reduced TG level and TG/HDL-c ratio, and the change in TG and TG/HDL-c ratio was significantly different between LCD and combination treatment (TG: −0.15 [1.20] mmol/L versus −0.51 [2.01] mmol/L, p = 0.011; TG/HDL-c: −0.02 [1.20] versus −0.59 [2.13], p = 0.003). While TRE did not affect low-density lipoprotein cholesterol (LDL-c) levels, LCD with and without TRE even significantly increased LDL-c levels (Table 2). Moreover, we did not find any significant difference between eTRE and lTRE in the improvements of dyslipidemia (Table S6). In line with the prominent contribution of VFA to glycemic control, TG/HDL-c ratio was only significantly correlated with VFA, not SFA (Figure S2C). Taken together, while LCD adversely affects LDL-c, TRE improves the lipoprotein profile.

TRE with and without LCD, but not LCD alone, reduces diastolic blood pressure

Although none of the treatments had benefits on systolic blood pressure (SBP) (Figure 3I), diastolic blood pressure (DBP) was significantly reduced by combination treatment, but not by LCD and TRE alone (Figure 3J) after 3 months of intervention. Compared with changes of each group, no significant difference in DBP was observed among three treatments (Table 2). When combined with LCD, eTRE significantly reduced DBP, whereas lTRE did not (Table S3), albeit that eTRE did not induce a significantly different effect on DBP compared with

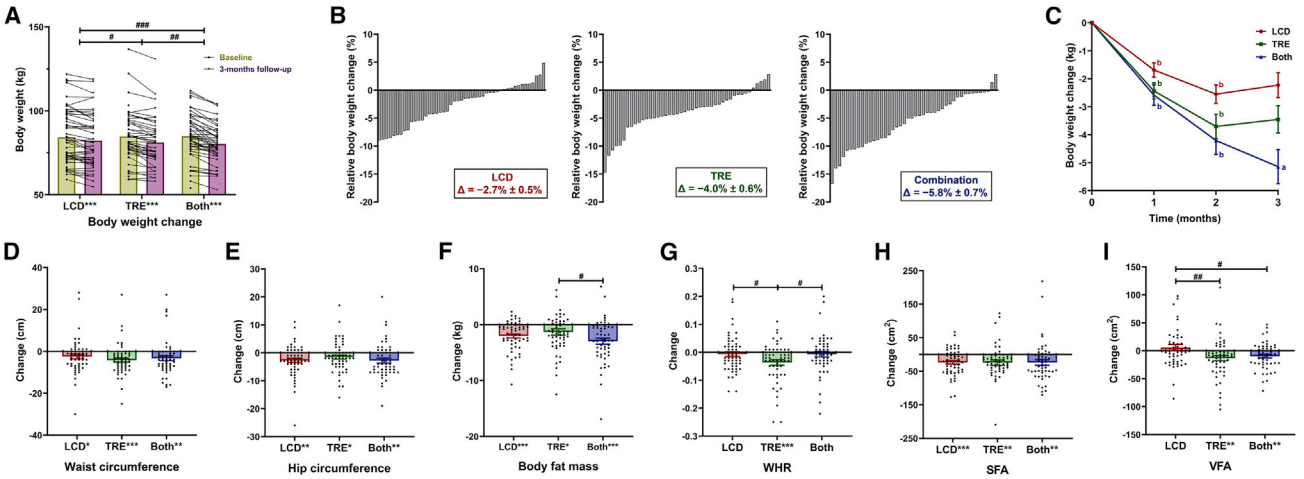

Figure 2. Body weight and body composition change

(A and B) Body weight change (A), relative body weight change (B) for the low-carbohydrate diet (LCD), 8-h time-restricted eating (TRE), and combination treatment (Both) groups during the 3-month intervention period.

(C–I) Mean decrease in (C) body weight after 1, 2, and 3 months among three groups. Change in (D) waist circumstance, (E) hip circumstance, (F) body fat mass, (G) waist-to-hip ratio (WHR), (H) subcutaneous fat area (SFA), (I) visceral fat area (VFA) among three groups after 3 months of the intervention.

For (A) and (D)–(I), analyses were conducted using all participants (intention-to-treat) using a linear mixed model with randomized dietary intervention as factor to correct for the correlations of repeated measurements on changes in body weight and using a multiple imputation approach for other missing data. Each black data point represents an individual participant (LCD, n = 55; TRE, n = 55; Both, n = 52). Change from baseline is presented as mean ± standard error of the mean (SEM). $^{\#}p < 0.05$, $^{\#\#}p < 0.01$, $^{\#\#\#}p < 0.001$: pairwise comparisons of change scores between the groups (e.g., TRE versus LCD, TRE versus Both, LCD versus Both) were evaluated by t test or Mann-Whitney U test. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$: significant differences shown at x axis compared with baseline (paired t test or paired Wilcoxon test). For (B), each column represents relative body weight change for each participant. For (C), change from baseline is presented as mean ± SEM, $^{a}p < 0.05$, $^{b}p < 0.001$: significant differences compared with 1 month before (paired t test).

ITRE. Both SBP and DBP strongly correlated to VFA but not SFA (Figure S2D).

Adverse events

No serious adverse events were observed. Approximately five adverse events were regarded as probably associated with the diet interventions, including constipation, dizziness, insomnia, dry mouth, and alopecia. The occurrence rate of adverse events was not significantly different among the three groups (Table 3). Independent of the diet intervention, two participants reported the exacerbation of lumbar disc herniation and lithangiuria requiring surgery during the 3-month intervention, which caused withdrawal from the trial.

Feasibility and acceptability

We also analyzed acceptability and feasibility of the interventions. As shown in Table 2, participants' self-reported compliance with their meal-eating window during the 8-h TRE intervention was on average 65.9 ± 3.0 days out of the 3-month intervention period, which was significantly more to adherence to LCD (55.5 ± 3.5 days; p = 0.024). In addition, adherence to eTRE was substantially less (61.4 ± 4.0 days) compared with ITRE (74.9 ± 2.7 days; p = 0.031, Table S6). Nonetheless, at the end of our study, 46 out of 47 participants (98%) in the LCD group and 43 out of 44 participants (98%) in the TRE group who completed the intervention period reported to be willing to continue. In contrast, only 36 out of 44 participants (82%) in the combination group reported to be willing to continue with the intervention, which was significantly lower compared with LCD (p = 0.010) and TRE (p = 0.014).

DISCUSSION

To our knowledge, this is the first clinical trial that directly compared the efficacy of weight loss and improvement of metabolic parameters of an LCD, 8-h TRE, and their combination in adults with MetS. We showed that although all three treatments significantly reduce body weight accompanied by a reduction in SFA, TRE yielded more benefits on abdominal visceral obesity and cardiometabolic outcomes and caused higher adherence to intervention compared with LCD. Moreover, both meal-eating windows of TRE (i.e., eTRE and ITRE) showed comparable beneficial effects on body weight, abdominal visceral fat, glucose metabolism, lipoprotein profile and blood pressure, as well as adherence. In addition, we observed that VFA, but not SFA, significantly correlated with several cardiometabolic parameters, including HOMA-IS, UA, the TG/HDL-c ratio, SBP, and DBP.

In this study, we have followed the ADA recommendation on the LCD, restricting subjects' carbohydrate intake to <130 g/day and demonstrated a slight but significant reduction in body weight (−2.2 kg; −2.7%) in adults with MetS over the course of 3 months without apparent adverse effects. Similarly, a previous clinical trial showed that LCD treatment of T2DM patients, i.e., 130 g/day carbohydrates without other specific restrictions, caused 1.6 kg body weight loss over 6 months[29] A 12-week randomized study also showed that LCD (<100 g carbohydrates/day) reduced body weight in type 1 diabetes

Table 2. Change in body composition and metabolic risk factors after 3 months intervention among participants

		LCD		TRE		Both		p value for pairwise comparison		
		N = 55	p value	N = 55	p value	N = 52	p value	LCD vs. TRE	LCD vs. Both	TRE vs. Both
Days of adherence (days)	–	55.5 ± 3.5	–	65.9 ± 3.0	–	57.7 ± 3.1	–	0.024	0.631	0.059
Willingness to continue the diet (n/total, %)	–	46/47 (98)	–	43/44 (98)	–	36/44 (82)	–	0.962	0.010	0.014
Meal-eating window (hours)	Follow-up	10.0 ± 0.3	–	6.5 ± 0.3	–	6.8 ± 0.3	–	–	–	–
	△	−0.6 ± 0.3	0.075	−3.9 ± 0.4	< 0.001	−3.9 ± 0.4	< 0.001	< 0.001	< 0.001	0.992
Daily carbohydrate intake (g)	Follow-up	149 ± 12	–	327 ± 15	–	140 ± 11	–	–	–	–
	△	−175 ± 22	< 0.001	−21 ± 14	0.137	−221 ± 20	< 0.001	< 0.001	0.125	< 0.001
Weight [a] (kg)	1 M Follow-up	83.0 ± 2.2	–	82.6 ± 2.1	–	82.1 ± 1.8	–	–	–	–
	1 M △	−1.7 ± 0.3	< 0.001	−2.4 ± 0.4	< 0.001	−2.6 ± 0.4	< 0.001	0.116	0.082	0.768
	2 M Follow-up	82.2 ± 2.2	–	81.4 ± 2.0	–	80.5 ± 1.8	–	–	–	–
	2 M △	−2.5 ± 0.3	< 0.001	−3.7 ± 0.4	< 0.001	−4.2 ± 0.4	< 0.001	0.015	0.002	0.347
	3 M Follow-up	82.3 ± 2.4	–	81.2 ± 2.2	–	80.2 ± 1.8	–	–	–	–
	3 M △	−2.2 ± 0.3	0.213	−3.4 ± 0.4	0.323	−5.0 ± 0.4	0.028	0.013	<0.001	0.004
BMI (kg/m^2)	Follow-up	28.3 ± 0.4	–	28.1 ± 0.4	–	27.2 ± 0.4	–	–	–	–
	△	−0.9 ± 0.2	< 0.001	−1.4 ± 0.3	< 0.001	−1.8 ± 0.2	< 0.001	0.098	0.003	0.280
Waist circumference (cm)	Follow-up	93.6 ± 1.6	–	92.7 ± 1.5	–	91.4 ± 1.4	–	–	–	–
	△	−2.4 ± 1.1	0.035	−4.2 ± 1.0	< 0.001	−3.3 ± 1.2	0.008	0.248	0.603	0.563
Hip circumference (cm)	Follow-up	102.3 ± 0.9	–	103.0 ± 0.9	–	100.9 ± 1.0	–	–	–	–
	△	−2.7 ± 0.8	0.001	−1.5 ± 0.7	0.046	−2.8 ± 0.9	0.002	0.263	0.945	0.267
Waist-to-hip ratio (WHR)	Follow-up	0.91 ± 0.01	–	0.90 ± 0.01	–	0.90 ± 0.01	–	–	–	–
	△	−0.01 ± 0.01	0.421	−0.04 ± 0.01	< 0.001	−0.01 ± 0.01	0.493	0.023	0.994	0.033
Body fat mass (kg)	Follow-up	31.9 ± 0.9	–	31.9 ± 0.9	–	29.8 ± 0.9	–	–	–	–
	△	−2.0 ± 0.4	< 0.001	−1.3 ± 0.6	0.028	−3.0 ± 0.5	< 0.001	0.301	0.103	0.041
Body muscle mass (kg)	Follow-up	31.3 ± 1.0	–	31.1 ± 0.9	–	31.5 ± 0.8	–	–	–	–
	△	0.1 ± 0.2	0.524	−0.5 ± 0.3	0.046	−0.5 ± 0.2	0.064	0.048	0.064	0.893
Subcutaneous fat area (SFA, cm^2)	Follow-up	253 ± 12	–	245 ± 10	–	231 ± 10	–	–	–	–
	△	−23 ± 5	< 0.001	−24 ± 8	0.003	−24 ± 8	0.006	0.927	0.988	0.949
Visceral fat area (VFA, cm^2)	Follow-up	98 ± 6	–	92 ± 5	–	86 ± 4	–	–	–	–
	△	6 ± 5	0.277	−13 ± 5	0.008	−10 ± 3	0.006	0.009	0.016	0.548
Hemoglobin A1c (HbA1c, %)	Follow-up	5.7 (0.6)	–	5.6 (0.6)	–	5.6 (0.7)	–	–	–	–
	△	0.0 (0.3)	0.404	0.0 (0.3)	0.385	−0.1 (0.4)	0.021	0.928	0.126	0.157
Fasting blood glucose (mmol/L)	Follow-up	5.22 (1.11)	–	4.76 (1.01)	–	5.01 (1.23)	–	–	–	–
	△	0.07 (0.81)	0.820	−0.18 (0.65)	0.024	−0.21 (0.96)	0.048	0.102	0.113	0.739
Fasting insulin (mIU/L)	Follow-up	23.7 (19.4)	–	26.5 (20.3)	–	18.2 (20.8)	–	–	–	–
	△	−3.1 (10.4)	< 0.001	−3.3 (12.7)	< 0.001	−5.5 (14.4)	< 0.001	0.394	0.319	0.781

(*Continued on next page*)

Table 2. ***Continued***

		LCD		TRE		Both		p value for pairwise comparison		
		N = 55	p value	N = 55	p value	N = 52	p value	LCD vs. TRE	LCD vs. Both	TRE vs. Both
C-peptide (pg/mL)	Follow-up	1,424.1 ± 85.2	–	1,416.3 ± 80.3	–	1,332.7 ± 71.0	–	–	–	–
	△	−184.6 ± 47.6	< 0.001	−243.9 ± 66.0	0.001	−319.1 ± 67.8	< 0.001	0.468	0.104	0.429
HOMA-IR	Follow-up	4.64 (4.70)	–	5.73 (4.39)	–	4.17 (4.41)	–	–	–	–
	△	−1.15 (2.99)	< 0.001	−1.04 (4.53)	< 0.001	−2.16 (4.82)	< 0.001	0.427	0.049	0.258
HOMA-IS	Follow-up	0.23 (0.29)	–	0.22 (0.42)	–	0.29 (0.21)	–	–	–	–
	△	0.03 (0.12)	< 0.001	0.04 (0.25)	< 0.001	0.10 (0.20)	< 0.001	0.421	0.042	0.245
QUICKI	Follow-up	0.31 (0.04)	–	0.30 (0.04)	–	0.31 (0.04)	–	–	–	–
	△	0.01 (0.02)	0.001	0.01 (0.03)	< 0.001	0.02 (0.03)	< 0.001	0.144	0.004	0.157
Uric acid (UA, μmol/L)	Follow-up	363 ± 14	–	345 ± 12	–	364 ± 12	–	–	–	–
	△	−17 ± 11	0.125	−40 ± 9	0.001	−51 ± 13	< 0.001	0.146	0.039	0.259
Total cholesterol (mmol/L)	Follow-up	4.91 ± 0.15	–	4.79 ± 0.14	–	4.87 ± 0.15	–	–	–	–
	△	0.19 ± 0.12	0.112	0.03 ± 0.17	0.866	0.14 ± 0.13	0.289	0.432	0.777	0.603
LDL-c (mmol/L)	Follow-up	3.27 ± 0.14	–	3.14 ± 0.14	–	3.33 ± 0.15	–	–	–	–
	△	0.28 ± 0.13	0.042	0.13 ± 0.14	0.343	0.30 ± 0.13	0.026	0.447	0.929	0.389
Triglycerides (TG, mmol/L)	Follow-up	1.30 (0.94)	–	1.60 (1.64)	–	1.40 (1.59)	–	–	–	–
	△	−0.15 (1.20)	0.052	−0.30 (1.36)	0.006	−0.51 (2.01)	< 0.001	0.363	0.011	0.160
HDL-c (mmol/L)	Follow-up	1.16 ± 0.03	–	1.13 ± 0.03	–	1.13 ± 0.03	–	–	–	–
	△	0.03 ± 0.03	0.288	0.02 ± 0.03	0.442	0.09 ± 0.02	< 0.001	0.869	0.136	0.109
TG/HDL-c	Follow-up	1.20 (1.20)	–	1.49 (1.54)	–	1.30 (1.33)	–	–	–	–
	△	−0.02 (1.20)	0.244	−0.30 (1.59)	0.024	−0.59 (2.13)	< 0.001	0.265	0.003	0.094
Systolic blood pressure (mmHg)	Follow-up	130 ± 3	–	137 ± 2	–	131 ± 2	–	–	–	–
	△	1 ± 2	0.770	1 ± 2	0.635	1 ± 2	0.719	0.923	0.979	0.914
Diastolic blood pressure (mmHg)	Follow-up	81 ± 2	–	85 ± 2	–	80 ± 2	–	–	–	–
	△	−1 ± 1	0.313	−2 ± 1	0.144	−5 ± 2	0.005	0.823	0.140	0.178

LCD, low-carbohydrate diet; TRE, time-restricted eating; Both, combination treatment; BMI, body mass index; HOMA-IR, homeostasis model assessment insulin resistance; HOMA-IS, homeostatic model assessment of insulin sensitivity; QUICKI, quantitative insulin-sensitivity check index; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol. All data were presented as mean ± standard error of the mean (SEM) for normally distributed variables or the median (interquartile range) for abnormal distribution. Change scores from baseline were represented by "Δ" in the table. Analyses were conducted using all participants (intention-to-treat), using a linear mixed model with randomized dietary intervention as factor to correct for the correlations of repeated measurements on changes in body weight, and using a multiple imputation approach for other missing data. After 3 months of intervention, pairwise comparisons of change scores between the groups (e.g., TRE vs. LCD, TRE vs. Both, LCD vs. Both) were evaluated by t test or Mann-Whitney U test. For weight [a]: significant differences compared with 1 month before (paired t test); for other parameters: significant differences compared with baseline (paired t test or paired Wilcoxon test).

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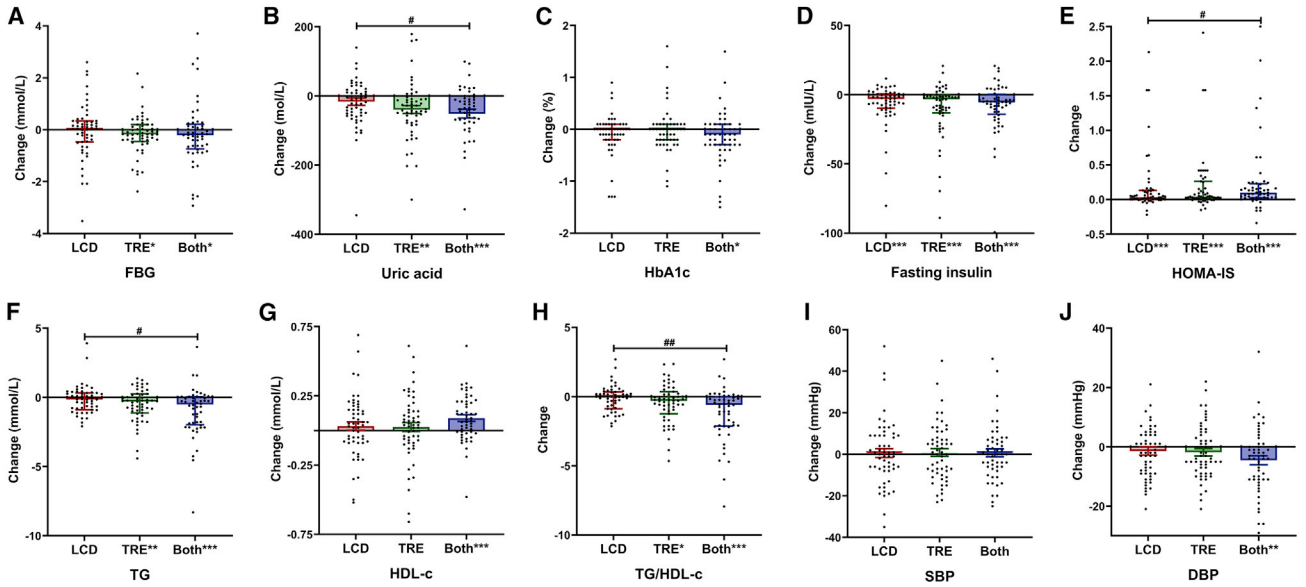

Figure 3. Change in metabolic factors among three groups

(A–J) Change in (A) fasting blood glucose (FBG), (B) uric acid, (C) hemoglobin A1c (HbA1c), (D) fasting insulin, (E) homeostasis model assessment-IS (HOMA-IS), (F) triglycerides (TG), (G) high-density lipoprotein cholesterol (HDL-c), (H) triglycerides/high-density lipoprotein cholesterol (TG/HDL-c), (I) systolic blood pressure (SBP), and (J) diastolic blood pressure (DBP) among the low-carbohydrate diet (LCD), 8-h time-restricted eating (TRE), and combination treatment (Both) groups after 3 months of the intervention. Analyses were conducted using all participants (intention-to-treat), using a multiple imputation approach for other missing data. Each black data point represents an individual participant (LCD, n = 55; TRE, n = 55; Both, n = 52). Change from baseline is presented as mean ± standard error of the mean (SEM) for normally distributed variables or the median (interquartile range) for abnormal distribution. $^{\#}p < 0.05$, $^{\#\#}p < 0.01$, $^{\#\#\#}p < 0.001$: pairwise comparisons of change scores between the groups (e.g., TRE versus LCD, TRE versus Both, LCD versus Both) were evaluated by t test or Mann-Whitney U test. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$: significant differences shown at x axis compared with baseline (paired t test or paired Wilcoxon test).

subjects by 2.0 kg.[33] In addition, the beneficial effects of very-low-carbohydrate ketogenic diets (VLCKD; < 50 g carbohydrates/day)[34] on body weight reduction have been assessed.[9,33,35,36] Samaha et al.[9] showed that severely obese subjects with MetS significantly lost body weight (−5.8 kg) after 6 months on a VLCKD (<30 g carbohydrates/day). Another 1-year clinical trial showed that a VLCKD (<40 g carbohydrates/day) intervention resulted in significant weight loss (−3.5 kg) in obese individuals without T2DM or CVD.[36] However, the efficacy and safety of VLCKD and adherence during long-term intervention are still under debate.[37] Besides, we found participants from Northwestern China showed a 10.6-h baseline meal-eating window, which was calculated by participants' self-report of average three meal times on 2-week recall. This baseline meal-eating window is comparable with the finding from a recent 1-year RCT study in Southern China,[38] which was 10.4-h baseline eating window that was calculated by daily dietary log, food photograph, and eating time. We further demonstrated that an 8-h TRE significantly reduces body weight in adults with MetS (−4.0%), independent of timing of TRE. Several previous clinical trials have evaluated the weight-reduction efficiency of TRE in individuals with MetS.[16,39,40] Wilkinson et al.[16] found that a 10-h TRE led to an approximately 3% weight reduction and improvements in cardiovascular risk parameters in individuals with MetS. A recent trial showed that 8-h TRE decreased body weight of obese individuals by 2.6% after 3 months[39] Nonetheless, in our study only the combination of LCD and TRE produced clinically significant weight loss,[41] i.e., a reduction of 5.8% from baseline over 3 months.

Our results showed that LCD decreased SFA without affecting VFA, while TRE and the combination treatment decreased SFA as well as VFA. Accumulating evidence indicates that visceral fat is crucially associated with many aspects of MetS, including hypertension, dyslipidemia, glucose intolerance, and insulin resistance, and it is more closely linked to inflammatory and oxidative stress biomarkers than subcutaneous fat.[42–44] Our results suggest that compared with LCD, TRE might yield more benefits on cardiometabolic outcomes in adults with MetS. Indeed, in our study, LCD intervention did not significantly decrease FBG levels but prominently reduced insulin levels and ameliorated insulin sensitivity, which are consistent with previous trials,[9,45] suggesting that LCD is more effective in lowering blood insulin levels and improving insulin sensitivity than in lowering blood glucose levels. This is likely explained by the fact that most studies were conducted with relatively healthy or overweight individuals but not individuals with T2DM, and not all participants in these studies had elevated FBG levels. In contrast, in our study, TRE intervention improved insulin levels as well as blood glucose levels, and furthermore, the combination of LCD and TRE significantly reduced fasting glucose, insulin, and HbA1c levels in MetS patients. In addition, compared with baseline, TRE with and without LCD reduced UA levels, while compared with changes among treatments, combination treatment caused more prominent reduction on UA. High UA is a strong and independent predictor of MetS and is associated

Table 3. Adverse effects among participants

	LCD N = 55	TRE N = 55	Both N = 52	p value
Adverse effects (number, n%)	–	–	–	0.232
Constipation	0 (0.0)	1 (1.8)	3 (5.8)	–
Dizziness	0 (0.0)	1 (1.8)	2 (5.8)	–
Insomnia	3 (5.5)	0 (0.0)	1 (1.9)	–
Dry mouth	1 (1.8)	0 (0.0)	1 (1.9)	–
Alopecia	0 (0.0)	0 (0.0)	1 (1.9)	–

LCD, low-carbohydrate diet; TRE, time-restricted eating; Both, combination treatment. Differences between treatment arms (LCD, TRE, and Both) were tested by Chi-square test.

with impaired fasting glucose and insulin resistance.[46–48] A recent 6-h TRE trial in overweight individuals with prediabetes revealed an improvement in insulin sensitivity and β cell responsiveness but no reduction in FBG.[19] Fasting might improve glycemic control as a result of metabolic switch from liver-derived glucose to adipose cell-derived ketones, occurring when switching from a fed to a fasted state, and it might induce ketoplasia, decrease fat accumulation, and increase insulin sensitivity.[20,49,50] However, further studies need to be performed in participants with elevated FBG, prediabetes, or T2DM to better define the effects of LCD versus TRE on glucose regulation. Whether TRE with or without LCD has independent effects on visceral fat and metabolic outcomes or is simply an epiphenomenon of greater weight loss could not be addressed in this study. It is noted that a previous RCT indicated that TRE that induced mild body weight reduction (~3%) without changing visceral fat mass was accompanied with improvements of insulin resistance and oxidative stress,[17] while another study showed that although there were no effects on body weight reduction, TRE could still improve those cardiometabolic parameters in prediabetic men.[19]

The effects of LCD and TRE on dyslipidemia are highly variable between studies.[19,39,51–55] We observed that LCD alone and combined with TRE adversely increased LDL-c after 3-month intervention, which is consistent with several studies showing that LCD increases cholesterol levels within the large LDL subfractions.[56,57] In this study, while TRE treatment did not impact HDL-c, TRE and combination treatment, but not LCD, significantly reduced plasma TG levels. In fact, TRE was generally reported not to affect HDL-c, although one study reported a minor improvement.[58] Yet, the effects of TRE on TG levels are still controversial. For instance, some TRE studies demonstrated a reduction in TG,[51,53] whereas others showed no significant effects.[19,39,51,52] In addition, we observed that TRE and combination treatment reduced the TG/HDL-c ratio, which could be partly due to reduced VFA by these treatments, but not by LCD alone. Indeed, VFA but not SFA strongly correlates with the TG/HDL-c ratio (Figure S2C). The TG/HDL-c ratio is a well-known predictor for CVD. A reduced TG/HDL-c ratio may be attributed to decreased cholesteryl ester transfer protein (CETP) activity, as CETP mediates the net transfer of CE from HDL to TG-rich lipoproteins in exchange for TG. Previous studies have demonstrated that weight loss induced by a very low calorie diet was correlated with reduced CETP concentration,[59] and CETP inhibition was associated with the improvement of visceral fat.[60] Therefore, TRE, with or without restricted carbohydrate consumption, could significantly improve visceral obesity and reduce TG level and TG/HDL-c ratio, as well as decrease CETP concentration.

In addition, only combination intervention significantly decreased blood pressure in our study. Generally, moderate (5%–10%) weight loss caused by interventions is expected to lead to larger reductions in SBP of 5 mmHg and DBP of 3 mmHg than that of mild (0–5%) weight loss over 6–12 months as shown in a systematic review and meta-analysis.[61] We observed that the mean reduction in DBP (5 mmHg) by combination intervention that produced a moderate weight loss of 5.8% was apparently higher and not accompanied by a reduction in SBP. It should be noted though that our study was not properly powered to observe a significant change in blood pressure, and larger studies are obviously needed to further address the effects of LCD and TRE on blood pressure in MetS patients.

In this study, eTRE shows greater effects on reducing abdominal fat area (both SFA and VFA) than lTRE, while eTRE and lTRE showed comparable benefits on body weight, glycemic control, dyslipidemia, and blood pressure. Nevertheless, participants were not randomly assigned to eTRE or lTRE, and sample sizes were relatively small, so the comparison of eTRE and lTRE was exploratory. Previous studies showed that both eTRE[19] and lTRE[17] improved multiple indicators of cardiovascular health. Sutton et al.[19] conducted a 5-week study comparing eTRE (6-h eating window before 3:00 p.m.) with a control condition (conventional 12-h eating window) and found better glycemic control and improvement of blood pressure by eTRE without significant body weight changes. Furthermore, Cienfuegos et al.[17] found that both 4- and 6-h lTRE caused mild body weight reduction (~3%) over 2 months when compared with the control. However, several studies on lTRE demonstrated conflicting results regarding body weight.[62,63] Moreover, the thermic effect of food, insulin sensitivity, and β cell function is better in early morning than night[64–66] because the body is optimized to ingesting food in early morning.[64–67] Thus, an 8 a.m. to 4 p.m. eating window may be applied as a more effective intervention to improve insulin sensitivity. Besides, lipids were also affected by meal timing, which might be due to an increase of fat oxidation in eTRE.[68] However, for participants who find it easier to skip breakfast than dinner, the latter being a more social meal in most cultures, a 12 p.m. to 8 p.m. eating window is an alternative. Thus, it is important to consider participants' individual schedule and personal preference and allow them to choose the suitable TRE eating window in order to increase efficacy and adherence.

Conclusions

In conclusion, compared with baseline, all three treatments after a 3-month intervention reduce body weight and SFA, as well as some cardiometabolic outcomes, including fasting insulin, C-peptide, and insulin sensitivity index, but only TRE, with and

without LCD, significantly reduces abdominal visceral fat, FBG, UA, TG, and TG/HDL-c ratio. More importantly, compared with changes of LCD, TRE and combination treatment further decrease body weight and VFA. Taken together, without changing physical activity, TRE with and without LCD significantly improves glycemic control, atherogenic dyslipidemia, and UA, thus largely improves metabolic disease risk, with TRE being superior over LCD with respect to reducing body weight and abdominal visceral obesity. Therefore, we anticipate that an 8-h TRE without and with LCD can serve as an effective intervention for MetS.

Limitations of the study

First, as is the case for all self-reported dietary intake data and because the daily dietary log was not compulsory, we cannot verify that the data reported by participants represent a complete record of their diet and asking participants to report adherence is subject to recall bias. In addition, the meal-eating window was calculated by participants' self-report of average meal times on 2-week recall without accounting for caloric consumption outside of three meals a day, so this method did not account for day-to-day variation of caloric consumption, and participants' true eating window is likely being underestimated. Second, except for the combination treatment, both the LCD and TRE treatments did not induce clinically significant weight reduction over 3 months. Longer-term trials are necessary to investigate whether LCD and TRE treatment alone can indeed produce 5% weight loss and lasting benefits to overall health. Third, the comparison of eTRE and lTRE was exploratory as participants were not randomly assigned to eTRE or lTRE and sample sizes were relatively small. Moreover, there were significantly more adherent days in the TRE group compared with LCD, and the absence of a control group is another limitation of this study. Last, only Chinese people living in the Shaanxi province were enrolled in this study, which warrants future validation of our findings in other race or ethnic groups.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.xcrm.2022.100777.

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AUTHOR CONTRIBUTIONS

M.H. and Y.-N.W. conducted the clinical trial, analyzed the data, and wrote the manuscript; B.S., C.-C.H., and P.C.N.R. designed the research and revised the manuscript; J.W., Q.L., M.L., H.G., Y.W., C.D., J.S., Y.Z., and Y.-W.W. assisted with the conduction of the clinical trial; B.Q., H.C., M.M., S.S., H.G., W.-X.Z., and X.G. conducted the investigation; Y.L., W.-Z.Z., M.Z., and Z.C. assisted with the statistical analysis. All authors helped interpret the data, revised the manuscript for critical content, and approved the final version of the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Critical commercial assays		
Human Metabolic Hormone Magnetic Bead Panel	Merck Millipore	Cat#HMHEMAG-34K
Software and algorithms		
GraphPad Prism version 8.0.2	GraphPad Software	https://www.graphpad.com/
R version 4.1.3	R-Project	https://cran.r-project.org/
Other		
Protease Inhibitor Cocktail	Sigma-Aldrich	Cat#P8340
Gliptins	Sigma-Aldrich	Cat#DPP4

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources and reagents should be directed to and will be fulfilled by the lead contact, Bingyin Shi (shibingy@126.com).

Materials availability

This study did not generate new unique reagents.

Data and code availability

- All data reported in this paper will be shared by the lead contact upon reasonable request.
- This paper does not report original code.
- Any additional information required to reanalyze the data reported in this work paper is available from the lead contact upon reasonable request.

EXPERIMENTAL MODEL AND SUBJECT DETAILS

Study design

We performed a randomized, open-label, single-center, clinical trial to evaluate the efficacy of weight loss and improvement of metabolic parameters of an LCD, TRE, and their combination, in adults with MetS. Participants were recruited from Xi'an between July 2020 and September 2020, and the trial was conducted from September 2020 to January 2021. This study was conducted with approval from the Institutional Review Board at the First Affiliated Hospital of Xi'an Jiaotong University, Shaanxi, China. This trial was registered as ClinicalTrials.gov, number NCT04475822.

Participants

Participants were recruited via emails, flyers, social media, and website advertisements and were diagnosed with metabolic syndrome.[2] All participants provided written informed consent.

Inclusion criteria

(1) Diagnosed with metabolic syndrome (i.e., more than 3 abnormal findings out of 5):
   a. Waist circumference $\geq$90 cm (men) or $\geq$80 cm (women).
   b. Elevated TG (use of medications for elevated TG is an alternate indicator) $\geq$ 150 mg/dL (1.7 mmol/L).
   c. Reduced HDL-c (use of medications for reduced HDL-c is an alternate indicator) < 40 mg/dL (1.0 mmol/L) in males <50 mg/dL (1.3 mmol/L) in females.
   d. Elevated blood pressure (use of hypoglycemic medications is an alternate indicator). SBP $\geq$130 and/or DBP $\geq$85 mmHg.
   e. Elevated FBG (used of hypoglycemic medications is an alternate indicator) $\geq$ 100 mg/dL (5.6 mmol/L).
(2) Age from 18 to 65 years.
(3) Stable weight (change $\leq$10% current body weight) for 3 months prior to the study.
(4) If participants were on hypoglycemic medications, hypotensive medications, lipid-lowering medications and cardiovascular medications, dose adjustment was not permitted during the 3-month intervention.

Exclusion criteria

1) Pregnant or breast-feeding.
2) Night shift workers.
3) History of major diseases or related diseases, such as inflammatory disease, rheumatologic disease, adrenal disease, malignancy, type 1 diabetes, cirrhosis, chronic kidney disease, acquired immunodeficiency syndrome, eating disorder, uncontrolled psychiatric disorder and major adverse cardiovascular event.
4) Current participate in other weight-management program, current on a prescribed diet for special disease or current on any drugs that effect appetite.
5) History of weight-loss surgery.

METHOD DETAILS

Randomisation and masking

Participants were randomized in a 1:1:1 ratio to an LCD group, TRE group, or combination group (before all baseline measurements). Block randomization was performed by a computer-generated random number list prepared by an investigator without clinical involvement in this trial. After obtaining the patient's consent, the research nurse telephoned a clinician who was independent of the recruitment process for allocation consignment.

Procedures

Before the intervention started, all participants were requested to maintain their usual diet and physical activity habits for weight stabilization in 2-week. During the 3-month intervention period, the LCD group was instructed to eat a low-carbohydrate diet (carbohydrates <130 g/day or <26% total energy, according to the ADA definition of 130 g/day as recommended minimum); a suggested food and menu list (Table S7) is provided in the supplemental information. The 8 h TRE group was instructed to consume all calories from 8 AM to 4 PM each day and fast from 4 PM to 8 AM, or to consume all calories from 12 PM to 8 PM each day and fast from 8 PM to 12 PM (16 h fast). During the 8 h meal eating windows, they could eat *ad libitum* without any restriction on the quantities and types of food, and the fasting guide is provided in the supplemental information. Likewise, the combination group was instructed to eat a LCD in the same 8 h meal eating windows as the TRE group. Furthermore, participants were not requested to calculate their caloric intake in 8 h meal eating window. In 16 h fasting window, participants were recommended to drink plenty of water and zero calorie beverages without artificial sweeteners, such as sparkling water and black tea.

The study was conducted with the internet hospital application (App) of the First Affiliated Hospital of Xi'an Jiaotong University, named ''Zhihui Hao Yiyuan'', which was a new approach to provide health services, outpatient service in particular, through the internet technology. Participants could contact clinicians at any time and any place though online communication and received diet guides and questionnaires through the App. All the participants were encouraged to write in a daily dietary log and note the time at which they ate with the use of the App, yet this was not compulsory. Clinicians checked participants' daily dietary log every day, and provided diet guidance in adjusting schemes for compliance based on participants' dietary interventions through the App. Raw data in Chinese version is available from the lead contact upon reasonable request. All participants were asked to maintain their usual physical activity throughout the study, which was evaluated by International Physical Activity Questionnaire (IPAQ) before and after 3-month intervention. All participants received our own custom-made sport bracelet, recording daily step counts that was connected with our App, and were encouraged to wear it during the 3-month intervention period.

Compliance with the dietary intervention was assessed for all participants every other week through a Food Frequency Questionnaire (FFQ), including days of adherence, meal eating window, and the amount, type and frequency of food intake (a blank copy of FFQ can be found as Data S1 in supplemental information). Compliance with diet was evaluated by the same dietician every other week. ''Daily carbohydrate intake'' was estimated by the same dietician, according to a previously defined method providing quantitative information on macronutrient composition of the diet consumed. ''Meal eating window'' was calculated by participants self-report on 2-week recall by FFQ. ''Days of adherence'' was assessed by participants self-reporting being compliant with their diet intervention during the 3-month intervention period. ''Willingness to continue the diet'' was evaluated by asking those who completed the intervention their willingness at the end of 3-month intervention.

Outcomes

The primary outcome of the study was changes in body weight and abdominal fat area. Secondary outcomes were changes in body composition, glycemic control, plasma lipids, UA and blood pressure.

Body weight was assessed every month at the research center with the participants without shoes and in light clothing using a digital scale (OMRON MEDICAL Beijing Co., Ltd. HNH-318) to the nearest 0.1 kg. Height was assessed during the screening visit using a wall-mounted stadiometer (OMRON MEDICAL Beijing Co., Ltd. HNH-318) to the nearest 0.1 cm. Abdominal fat area (VFA and SFA) was measured at baseline and after 3 months using bioelectrical impedance analysis (OMRON MEDICAL Beijing Co., Ltd. DUALSCAN, HDS-2000) to the nearest 1 cm^2. This approach has been proved to produce reliable measurements that correlate well with data obtained from computed tomography (CT).[69] Body composition (body fat mass and body muscle mass) was measured at baseline and month 3 using the direct segmental multifrequency bioelectrical impedance analysis method DSM-BIA (InBody H20) to the nearest 0.1 kg.

All blood collection was performed at the physical examination center of the First Affiliated Hospital of Xi'an Jiaotong University, after fasting overnight (i.e., from 20:00 on) at baseline and at month 3, between 7:40 and 9:00 am. Blood was centrifuged for 20 min at 1500 *g* and 4°C to separate plasma, then stored at −80°C until analysis. HbA1c was measured on an automatic HbA1c analyzer (TOSOH BIOSCIENCE, Inc.; HLC-723G8) to the nearest 0.1%. FBG, UA, total cholesterol, TG, HDL-c, and LDL-c were measured on an automatic biochemistry analyzer (HITACHI, Inc.; LAbOSPECT, 008AS) using standard reagents to the nearest 0.01 mmol/L, 1 μmol/L, 0.01 mmol/L, 0.01 mmol/L, 0.01 mmol/L and 0.01 mmol/L, respectively.

Fasting insulin and C-peptide were measured by immunoassay with fluorescent detection on a Luminex instrument (EMD Millipore Corporation; HMHEMAG-34K) to the nearest 0.1 pg/mL. Insulin resistance and insulin sensitivity were calculated using the homeostasis model assessment method by applying the following formula: [HOMA-IR = fasting insulin (mIU/L) × fasting glucose (mg/dL)/405], [HOMA-IS = 1/HOMA-IR]. QUICKI = 1/[log (fasting insulin level, in microunits per milliliter) + log (fasting glucose level, in milligrams per deciliter)].[70] Blood pressure was measured in triplicate using a digital automatic blood pressure (Omron HBP-9020, Kyoto, Japan) to the nearest 1 mmHg.

Adverse effects (constipation, dizziness, insomnia, dry mouth and alopecia) were assessed by a telephone interview at baseline and every other week during the 3-month intervention.

Statistical analysis

This study was powered to detect the primary outcome of percentage reduction in body weight. We estimated that the LCD-treated group (A) would lose 5% body weight and that the group treated with combination diet (C) would lose 10% of body weight after 3 months. The proposed reduction in body weight were determined on the basis of preliminary data obtained from dietary intervention studies.[17,58,71,72] We calculated that 78 participants (26 per group) would provide with greater than 80% power to detect a significant difference of 5% in body weight between the A and C groups at a significance level of 0.05 using a 2-tailed independent-samples t test. We estimated that dropout rate was 20%. Therefore, we decided to recruit 165 participants (55 per group) to increase our statistical power because our dropout rate might be higher than expected.

Statistical analyses were performed using R version 4.1.3. A two-tailed p value of less than 0.05 was considered statistically significant. Tests for normality were conducted. All data are presented as the mean ± SEM for normally distributed variables or median (interquartile range, IQR) for abnormally distributed variables. At baseline, differences between treatment arms (LCD, TRE and combination) were tested by one-way ANOVA or Kruskal-Wallis H test. Analyses were conducted in the intention-to-treat population, using a linear mixed model with randomized dietary intervention as a factor to correct for the correlations of repeated measurements on changes in body weight, and handled other missing data by multiple imputations with the use of the Markov chain Monte Carlo method. Change scores are represented by "Δ" in the results text. At month 3, pairwise comparisons of change scores from baseline between the groups (e.g., TRE vs. LCD, TRE vs. Combi, LCD vs. Combi) were evaluated by t test or Mann-Whitney U test. The significant difference between baseline and 3-month follow-up was measured by paired T test or Wilcoxon test in each group. Pearson and Spearman correlations were performed to assess the relationship between abdominal fat area and other metabolic risk factors.

The trial protocol can be found as Data S2 in supplemental information.

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Supplemental information

Time-restricted eating with or without low-carbohydrate diet reduces visceral fat and improves metabolic syndrome: A randomized trial

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Table S1. Baseline characteristics of participants

	LCD N = 55	TRE N = 55	Both N = 52	p value
Drug treatment (number, n%)				0.252
Hypotensive drugs	9 (16.4)	12 (21.8)	5 (9.6)	
Lipid-lowering drugs	2 (3.6)	4 (7.3)	0 (0.0)	
Urate-lowering drugs	3 (5.5)	3 (5.5)	5 (9.6)	
Oral hypoglycemic drugs	8 (14.5)	2 (3.6)	4 (7.7)	
Insulin	2 (3.6)	2 (3.6)	1 (1.9)	
Complicating metabolic disease (number, n%)				0.539
Hypertension	12 (21.8)	17 (30.9)	8 (15.4)	
Coronary heart disease	2 (3.6)	2 (3.6)	1 (1.9)	
Arthrolithiasis	4 (7.3)	3 (5.5)	6 (11.5)	
Type 2 diabetes	8 (14.5)	3 (5.5)	6 (11.5)	

LCD, low-carbohydrate diet; TRE, time-restricted eating; Both, combination treatment. Differences between treatment arms (LCD, TRE and Both) were tested by Chi-square test. Related to Table 1.

Table S2. Baseline characteristics of early TRE and late TRE subgroups

	TRE		p	Both		p
	eTRE (N = 38)	lTRE (N = 17)	value	eTRE (N = 32)	lTRE (N = 20)	value
Gender male/female	23/15	12/5	0.473	22/10	15/5	0.628
Age (years)	43.7 ± 1.6	41.6 ± 2.9	0.501	40.6 ± 1.6	36.5 ± 1.8	0.095
Meal eating window (hours)	10.3 ± 0.4	10.5 ± 0.4	0.824	10.9 ± 0.3	10.3 ± 0.4	0.118
Daily carbohydrate intake (g)	341 ± 18	365 ± 33	0.499	352 ± 29	375 ± 35	0.607
Weight (kg)	84.2 ± 2.4	85.7 ± 3.6	0.725	84.7 ± 2.3	85.0 ± 3.1	0.935
BMI (kg/m^2)	29.7 ± 0.5	29.2 ± 0.9	0.639	29.1 ± 0.6	28.8 ± 0.8	0.808
Waist circumference (cm)	96.8 ± 1.4	97.0 ± 2.6	0.930	94.8 ± 1.4	94.4 ± 1.5	0.819
Hip circumference (cm)	104.7 ± 1.2	104.1 ± 1.3	0.773	104.1 ± 1.3	104.1 ± 2.1	0.987
Waist-to-hip ratio (WHR)	0.93 ± 0.01	0.95 ± 0.02	0.462	0.91 ± 0.01	0.92 ± 0.02	0.611
Body fat mass (kg)	33.7 ± 1.1	32.3 ± 1.6	0.496	33.3 ± 1.0	31.8 ± 1.5	0.374
Body muscle mass (kg)	31.2 ± 1.1	32.6 ± 1.7	0.477	31.5 ± 1.1	32.7 ± 1.4	0.506
Subcutaneous fat area (SFA, cm^2)	270 ± 11	270 ± 19	0.990	256 ± 10	254 ± 18	0.902
Visceral fat area (VFA, cm^2)	102 ± 6	113 ± 8	0.321	97 ± 5	94 ± 7	0.681
Hemoglobin A1c (HbA1c, %)	5.6 (0.6)	5.7 (0.6)	0.784	5.6 (0.7)	5.6 (1.1)	0.445
Fasting blood glucose (mmol/L)	5.05 (1.16)	5.05 (0.69)	0.579	5.01 (1.05)	5.19 (1.66)	0.735
Fasting insulin (mIU/L)	27.8 (21.1)	32.8 (19.9)	0.344	27.0 (13.9)	30.6 (57.6)	0.337
C-peptide (pg/mL)	1696.1 ± 131.9	1580.0 ± 137.9	0.877	1570.7 ± 84.7	1781.4 ± 185.6	0.250
HOMA-IR	6.70 (6.55)	7.64 (6.58)	0.202	6.79 (4.05)	7.58 (14.00)	0.829
HOMA-IS	0.21 (0.23)	0.14 (0.12)	0.177	0.16 (0.10)	0.16 (0.17)	0.836
QUICKI	0.29 (0.04)	0.29 (0.02)	0.236	0.29 (0.03)	0.29 (0.05)	0.463
Uric acid (UA, μmol/L)	383 ± 15	387 ± 26	0.877	429 ± 23	395 ± 18	0.298
Total cholesterol (mmol/L)	4.67 ± 0.16	4.95 ± 0.20	0.309	4.82 ± 0.18	4.58 ± 0.19	0.384
LDL-c (mmol/L)	2.88 ± 0.14	3.28 ± 0.19	0.108	3.15 ± 0.17	2.85 ± 0.16	0.235
Triglycerides (TG, mmol/L)	2.10 (1.52)	2.31 (1.77)	0.439	1.92 (1.92)	2.43 (3.63)	0.776
HDL-c (mmol/L)	1.11 ± 0.04	1.08 ± 0.05	0.663	1.07 ± 0.04	1.01 ± 0.05	0.378
TG/HDL	1.77 (1.85)	2.24 (1.99)	0.412	1.89 (2.61)	2.32 (4.43)	0.749
Systolic blood pressure (mmHg)	136 ± 3	137 ± 4	0.857	132 ± 3	129 ± 4	0.558
Diastolic blood pressure (mmHg)	86 ± 2	89 ± 3	0.407	86 ± 2	81 ± 2	0.091

TRE, time-restricted eating; Both, combination treatment; eTRE, early TRE; lTRE, late TRE; BMI, body mass index; HOMA-IR, homeostasis model assessment insulin resistance; HOMA-IS, homeostatic model assessment of insulin sensitivity; QUICKI, quantitative insulin-sensitivity check index; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol. All data are presented as the mean ± standard error of the mean (SEM) for normal distribution or median (interquartile range) for abnormal distribution. Differences between the eTRE and lTRE subgroups were tested by two sample dependent T test or Mann-Whitney U test. Related to Table 1.

1 **Table S3. Food intake among participants who completed the intervention**

	LCD	TRE	Both	p value for pairwise comparison		
	N = 47	N = 44	N = 44	LCD vs. TRE	LCD vs. Both	TRE vs. Both
Staple food- rice						
Baseline	450 (400)	600 (750)	475 (563)			
Follow-up	200 (300)***	450 (550)	225 (388)***			
△	-250 (475)	0 (413)	-273 (700)	**0.002**	0.424	0.068
Staple food- wheat flour						
Baseline	600 (750)	700 (906)	750 (1088)			
Follow-up	200 (363)***	500 (400)*	150 (213)***			
△	-350 (800)	-100 (1019)	-575 (1050)	0.051	0.350	**0.005**
Staple food- coarse grain and field crop (corn, oat, sorghum, etc.)						
Baseline	150 (300)	50 (369)	100 (309)			
Follow-up	0 (150)**	0 (100)**	0 (94)***			
△	0 (200)	0 (338)	0 (250)	0.789	0.811	0.623
Staple food- tuber vegetable (potato, batata, yam, taro, etc.)						
Baseline	200 (300)	100 (275)	0 (169)			
Follow-up	50 (200)*	0 (150)	0 (150)			
△	-50 (200)	0 (100)	0 (144)	0.287	0.044	0.350
Staple food- starch and derived products (vermicelli, etc.)						
Baseline	0 (100)	0 (100)	50 (150)			
Follow-up	0 (50)	0 (100)	0 (100)			
△	0 (50)	0 (62)	0 (130)	0.664	0.467	0.351
Pastry- bread, cake, cookie, etc.						
Baseline	50 (200)	0 (100)	25 (150)			
Follow-up	0 (50)**	0 (138)	0 (0)**			
△	-50 (150)	0 (100)	0 (100)	**0.020**	0.864	**0.016**
Meat- pork, beef and lamb						
Baseline	350 (300)	350 (588)	350 (550)			
Follow-up	300 (300)	350 (588)	375 (838)**			
△	0 (350)	0 (388)	100 (438)	0.733	**0.006**	**0.004**
Meat- processed meat (bacon, sausage, etc.)						
Baseline	0 (50)	0 (8)	0 (15)			
Follow-up	0 (50)	0 (50)	0 (0)			
△	0 (25)	0 (0)	0 (0)	0.242	0.627	0.437
Meat- animal innards						
Baseline	0 (0)	0 (0)	0 (0)			
Follow-up	0 (0)	0 (0)	0 (0)			
△	0 (0)	0 (0)	0 (0)	0.120	0.883	0.161
Aquatic product- fish, crab, shrimp, shellfish, molluscs, etc.						
Baseline	50 (150)	100 (200)	0 (50)			
Follow-up	100 (200)	0 (150)*	0 (150)			
△	0 (150)	0 (100)	0 (100)	**0.011**	0.980	**0.009**
Poultry- chicken, duck, pigeon, etc.						

Baseline	100 (200)	50 (150)	0 (138)			
Follow-up	100 (263)	50 (200)	100 (200)			
△	0 (150)	0 (150)	0 (175)	0.358	0.763	0.254
Egg- hen's egg, duck's egg, preserved egg, salted egg, etc.						
Baseline	300 (150)	350 (475)	200 (200)			
Follow-up	350 (200)	350 (313)	290 (356)			
△	0 (325)	-25 (408)	0 (375)	0.178	0.978	0.235
Milk and milk products- milk, yogurt, etc.						
Baseline	540 (1260)	450 (1014)	600 (1038)			
Follow-up	700 (1400)	500 (838)	600 (928)			
△	0 (1200)	0 (434)	0 (838)	0.758	0.582	0.299
Milk and milk products- milk powder, cheese, etc.						
Baseline	0 (0)	0 (0)	0 (0)			
Follow-up	0 (0)	0 (0)	0 (0)			
△	0 (0)	0 (0)	0 (0)	0.607	0.262	0.642
Beans and legume products- soybean						
Baseline	0 (150)	0 (200)	0 (150)			
Follow-up	0 (250)	0 (100)	0 (100)			
△	0 (175)	0 (100)	0 (164)	0.171	0.763	0.160
Beans and legume products- tofu, soybean curd sheet, soybean curd slab and oily bean curd						
Baseline	100 (150)	100 (200)	33 (100)			
Follow-up	100 (225)	65 (281)	50 (150)			
△	0 (150)	0 (150)	0 (226)	0.438	0.345	0.806
Vegetables- dark vegetables						
Baseline	500 (1200)	650 (738)	613 (1100)			
Follow-up	600 (110)	600 (1113)	700 (1113)			
△	100 (725)	0 (998)	-18 (975)	0.570	0.247	0.613
Vegetables- light vegetables						
Baseline	350 (1200)	350 (1163)	350 (538)			
Follow-up	450 (850)	375 (813)	600 (675)			
△	0 (650)	-50 (653)	120 (838)	0.279	0.352	0.073
Phytocomycetes- mushrooms, seaweed, porphyra, etc.						
Baseline	50 (150)	50 (100)	50 (125)			
Follow-up	100 (225)	0 (100)	100 (200)*			
△	0 (105)	0 (100)	25 (150)	0.299	0.396	0.084
Fruits- apple, pear, peach, cherry, grapefruit, kiwifruit, etc.						
Baseline	350 (950)	350 (675)	450 (694)			
Follow-up	200 (400)*	300 (425)*	200 (388)**			
△	0 (500)	-75 (425)	-200 (613)	0.927	0.368	0.268
Fruits- mango, pineapple, etc.						
Baseline	0 (0)	0 (0)	0 (0)			
Follow-up	0 (0)	0 (0)	0 (0)			
△	0 (0)	0 (0)	0 (0)	0.824	0.734	0.576
Fruits- watermelon, etc.						

Baseline	0 (50)	0 (0)	0 (0)			
Follow-up	0 (0)	0 (0)	0 (0)			
△	0 (0)	0 (0)	0 (0)	0.658	0.238	0.105
Nuts- peanut, sunflower seed, walnut, pumpkin seed, etc.						
Baseline	35 (175)	0 (169)	50 (150)			
Follow-up	140 (300)	63 (150)	63 (200)			
△	0 (185)	0 (150)	0 (181)	0.404	0.275	0.799
Alcohol- low-alcohol liquor (≤38°)						
Baseline	0 (0)	0 (0)	0 (0)			
Follow-up	0 (0)	0 (0)	0 (0)			
△	0 (0)	0 (0)	0 (0)	0.680	0.171	0.100
Alcohol- high-alcohol liquor (＞38°)						
Baseline	0 (0)	0 (50)	0 (0)			
Follow-up	0 (0)	0 (50)	0 (0)			
△	0 (0)	0 (38)	0 (0)	0.321	0.408	0.876
Alcohol- beer						
Baseline	0 (0)	0 (0)	0 (0)			
Follow-up	0 (0)	0 (0)	0 (0)			
△	0 (0)	0 (0)	0 (0)	0.405	0.514	0.183
Alcohol- fruit wine						
Baseline	0 (0)	0 (0)	0 (0)			
Follow-up	0 (0)	0 (0)	0 (0)			
△	0 (0)	0 (0)	0 (0)	0.169	0.195	0.559

LCD, low-carbohydrate diet; TRE, time-restricted eating; Both, combination treatment. All data were presented as the median (interquartile range) for abnormal distribution. Analyses were conducted in participants who completed the intervention. Change scores from baseline were represented by "Δ" in the table. After 3 months of intervention, pairwise comparisons of change scores between the groups (e.g., TRE vs. LCD, TRE vs. Both, LCD vs. Both) were evaluated by Mann-Whitney U test. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$: significant differences compared with baseline (paired Wilcoxon test). Related to STAR Methods.

Table S4. Physical activity analysis among participants who completed the intervention

		LCD	TRE	Both
		N = 47	N = 44	N = 44
Intense physical activity time (h/week)	Baseline	0.0 (0.3)	0.0 (0.6)	0.0 (1.0)
	Follow-up	0.0 (0.8)	0.0 (0.5)	0.0 (0.8)
	△	0.0 (0.0)	0.0 (0.0)	0.0 (0.2)
Moderate physical activity time (h/week)	Baseline	0.0 (1.3)	0.0 (0.1)	0.0 (0.5)
	Follow-up	0.0 (1.0)	0.0 (0.0)	0.0 (1.0)
	△	0.0 (0.0)	0.0 (0.0)	0.0 (0.6)
Walking time (h/week)	Baseline	2.3 (3.8)	3.5 (4.0)	3.5 (3.6)
	Follow-up	2.5 (4.8)	2.5 (2.4)	2.6 (4.8)
	△	0.0 (2.3)	0.0 (3.2)	-0.5 (1.5)
Sitting time (h/week)	Baseline	35.0 (31.5)	28.6 (25.7)	33.8 (35.0)
	Follow-up	35.0 (25.7)	35.0 (25.7)	35.0 (34.4)
	△	0.0 (7.0)	0.0 (16.3)	0.0 (16.3)

LCD, low-carbohydrate diet; TRE, time-restricted eating Both, combination treatment. All data were presented as the median (interquartile range) for abnormal distribution. Analyses were conducted in participants who completed the intervention. Change scores from baseline were represented by "Δ" in the table. After 3 months of intervention, pairwise comparisons of baseline and change scores between the groups (e.g., TRE vs. LCD, TRE vs. Both, LCD vs. Both) were evaluated by Mann-Whitney U test. The significant difference as compared with baseline were evaluated by paired Wilcoxon test for each group. No significant difference was found either within each group or between groups. Related to STAR Methods.

Table S5. Change in primary outcomes between participants with or without more than 50% dietary log records

	LCD (N = 55)			TRE (N = 55)			Both (N = 52)		
	Records ≥ 50% (N = 19)	Records < 50% (N = 36)	p value	Records ≥ 50% (N = 19)	Records < 50% (N = 36)	p value	Records ≥ 50% (N = 23)	Records < 50% (N = 29)	p value
Days of dietary log (during the first 2 weeks)	14 (5)	1 (2)	<0.001	14 (4)	1 (2)	<0.001	14 (2)	0 (1)	<0.001
△ Weight (kg)	-2.2 ± 0.9	-2.3 ± 0.5	0.908	-3.1 ± 0.7	-3.7 ± 0.7	0.540	-5.4 ± 0.9	-4.9 ± 0.8	0.739
△ Visceral fat area (VFA, cm^2)	-7 ± 7	12 ± 7	0.089	-11 ± 4	-14 ± 7	0.738	-9 ± 5	-10 ± 5	0.842
△ Subcutaneous fat area (SFA, cm^2)	-29 ± 9	-21 ± 6	0.468	-24 ± 13	-24 ±10	0.994	-35 ± 7	-15 ± 13	0.235

LCD, low-carbohydrate diet; TRE, time-restricted eating; Both, combination treatment. During the first 2-week of intervention period, when participants were trained for diet schemes, daily dietary log was monitored, analyzed and clustered into two groups based on the record time more than 7 days (≥ 50%) or not (< 50%). All data were presented as mean ± standard error of the mean (SEM) for normally distributed variables or the median (interquartile range) for abnormal distribution (Days of dietary log). Change scores from baseline were represented by "Δ" in the table. Analyses were conducted using all participants (intention-to-treat), using a multiple imputation approach for missing data. After 3 months of intervention, pairwise comparisons of change scores between the valid and invalid record subgroups were evaluated by t test or Mann-Whitney U test. Related to STAR Methods.

Table S6. Change in body composition and metabolic risk markers after 3 months of the intervention between early TRE and late TRE subgroups.

		TRE		p value	Both		p value
		eTRE (N = 38)	lTRE (N = 17)		eTRE (N = 32)	lTRE (N = 20)	
Days of adherence (days)		61.4 ± 4.0	74.9 ± 2.7	**0.031**	57.0 ± 3.9	58.7 ± 5.3	0.798
Willingness to continue the diet (n/total, %)		29/30 (97)	14/14 (100)	0.490	20/27 (74)	16/17 (94)	0.093
Meal eating window (hours)	Follow-up	6.4 ± 0.4***	6.9 ± 0.3***		6.9 ± 0.5***	6.6 ± 0.5***	
	△	-4.0 ± 0.6	-3.6 ± 0.4	0.715	-4.0 ± 0.5	-3.7 ± 0.7	0.726
Daily carbohydrate intake (g)	Follow-up	315 ± 19	356 ± 26		144 ± 15***	133 ± 14***	
	△	-26 ±18	-9 ± 22	0.564	-207 ± 23	-243 ± 36	0.392
Weight (kg)	1 M Follow-up	81.6 ± 2.7[b]	85.7 ± 3.6[b]		81.5 ± 2.3[b]	83.1 ± 2.9[a]	
	1 M △	-2.4 ± 0.4	-2.5 ± 0.7	0.869	-3.1 ± 0.5	-1.9 ± 0.7	0.151
	2 M Follow-up	80.4 ± 2.6[a]	83.3 ± 3.2[a]		79.7 ± 2.2[b]	81.8 ± 2.9[b]	
	2 M △	-3.6 ± 0.4	-4.0 ± 0.7	0.599	-4.9± 0.5	-3.2 ± 0.7	**0.040**
	3 M Follow-up	79.9 ± 2.8	84.0 ± 3.5		78.9 ± 2.4	82.4 ± 2.6	
	3 M △	-3.3 ± 0.4	-3.7 ± 0.7	0.606	-5.6 ± 0.5	-4.2 ± 0.7	0.096
BMI (kg/m^2)	Follow-up	28.3 ± 0.5***	27.7 ± 0.5*		27.0 ± 0.6***	27.5 ± 0.7**	
	△	-1.4 ± 0.3	-1.6 ± 0.6	0.781	-2.1 ± 0.3	-1.4 ± 0.4	0.148
Waist circumference (cm)	Follow-up	91.7 ± 1.8***	94.9 ± 2.8		91.0 ± 1.9*	92.0 ± 1.8	
	△	-5.1 ± 1.1	-2.1 ± 2.1	0.167	-3.8 ± 1.5	-2.4 ± 1.9	0.558
Hip circumference (cm)	Follow-up	103.1 ± 1.1	102.9 ± 1.3		101.0 ± 1.4*	100.8 ± 1.5	
	△	-1.7 ± 0.9	-1.2 ± 1.2	0.796	-3.2 ± 1.2	-2.3 ± 1.2	0.621
Waist-to-hip ratio (WHR)	Follow-up	0.89 ± 0.01**	0.92 ± 0.02		0.90 ± 0.01	0.91 ± 0.02	

	△	-0.04 ± 0.01	-0.02 ± 0.02	0.380	-0.01 ± 0.01	-0.00 ± 0.01	0.838
Body fat mass (kg)	Follow-up	32.4 ± 1.1	30.8 ± 1.5		30.5 ± 1.1**	28.5 ± 1.6***	
	△	-1.3 ± 0.8	-1.4 ± 0.7	0.912	-2.8 ± 0.8	-3.2 ± 0.7	0.703
Body muscle mass (kg)	Follow-up	30.6 ± 1.0	32.3 ± 1.5		30.7 ± 1.0*	32.8 ± 1.2	
	△	-0.6 ± 0.3	-0.4 ± 0.3	0.674	-0.8 ± 0.3	0.1 ± 0.4	0.061
Subcutaneous fat area (SFA, cm^2)	Follow-up	251 ± 13*	232 ± 14		227 ± 13*	239 ± 18	
	△	-18 ± 7	-38 ± 21	0.256	-29 ± 11	-15 ± 13	0.394
Visceral fat area (VFA, cm^2)	Follow-up	88 ± 7*	101 ± 8		88 ± 6*	83 ± 7	
	△	-14 ± 6	-12 ± 8	0.872	-9 ± 4	-10 ± 6	0.856
Hemoglobin A1c (HbA1c, %)	Follow-up	5.5 (0.6)	5.6 (0.7)		5.6 (0.7)	5.5 (0.9)	
	△	0.0 (0.3)	-0.1 (0.4)	0.854	-0.1 (0.6)	-0.2 (0.4)	0.502
Fasting blood glucose (mmol/L)	Follow-up	4.77 (1.07)	4.76 (0.94)		4.83 (1.22)	5.23 (1.13)	
	△	-0.15 (1.02)	-0.22 (0.35)	0.863	-0.32 (0.95)	-0.15 (0.82)	0.457
Fasting insulin (mIU/L)	Follow-up	23.9 (21.0)***	29.9 (12.7)*		16.1 (13.4)**	26.4 (34.7)*	
	△	-3.5 (13.2)	-2.2 (13.6)	0.771	-5.3 (11.0)	-5.7 (24.6)	0.880
C-peptide (pg/mL)	Follow-up	1451.1 ± 108.2**	1338.5 ± 96.5		1185.5 ± 74.1***	1568.1 ± 127.1	
	△	-245.0 ± 77.5	-241.5 ± 128.4	0.981	-385.2 ± 76.2	-213.3 ± 126.4	0.221
HOMA-IR	Follow-up	4.68 (4.51)***	6.48 (4.67)**		3.76 (2.33)***	6.78 (5.72)	
	△	-0.84 (4.61)	-2.15 (4.99)	0.548	-2.40 (4.54)	-1.65 (7.53)	0.229
HOMA-IS	Follow-up	0.28 (0.51)***	0.18 (0.25)*		0.31 (0.23)***	0.24 (0.22)	
	△	0.05 (0.33)	0.03 (0.09)	0.629	0.14 (0.21)	0.04 (0.14)	**0.007**
QUICKI	Follow-up	0.31 (0.05)***	0.30 (0.03)*		0.32 (0.03)***	0.30 (0.04)	
	△	0.02 (0.03)	0.01 (0.02)	0.489	0.02 (0.01)	0.01 (0.04)	0.102
Uric acid (UA, μmol/L)	Follow-up	344 ± 16*	347 ± 16*		370 ± 17**	354 ± 18**	

	△	-39 ± 15	-40 ± 18	0.967	-58 ± 19	-41 ± 14	0.511
Total cholesterol (mmol/L)	Follow-up	4.56 ± 0.15	5.30 ± 0.27		4.93 ± 0.20	4.77 ± 0.22	
	△	-0.12 ± 0.21	0.35 ± 0.26	0.201	0.11 ± 0.13	0.19 ± 0.27	0.775
LDL-c (mmol/L)	Follow-up	2.89 ± 0.15	3.69 ± 0.25*		3.42 ± 0.19*	3.17 ± 0.23	
	△	0.01 ± 0.18	0.41 ± 0.19	0.180	0.28 ± 0.12	0.33 ± 0.28	0.847
Triglycerides (TG, mmol/L)	Follow-up	1.53 (1.65)*	1.98 (1.56)*		1.40 (1.25)**	1.30 (1.76)*	
	△	-0.39 (1.33)	-0.30 (1.38)	0.884	-0.51 (1.84)	-0.49 (2.28)	0.707
HDL-c (mmol/L)	Follow-up	1.14 ± 0.04	1.09 ± 0.05		1.15 ± 0.04*	1.13 ± 0.05*	
	△	0.03 ± 0.04	0.01 ± 0.04	0.723	0.07 ± 0.03	0.12 ± 0.04	0.327
TG/HDL-c	Follow-up	1.25 (1.63)	2.01 (1.29)		1.23 (1.08)***	1.63 (1.82)**	
	△	-0.31 (1.48)	-0.30 (2.06)	0.855	-0.54 (2.07)	-0.87 (2.64)	0.707
Systolic blood pressure (mmHg)	Follow-up	136 ± 2	139 ± 3		131 ± 3	132 ± 3	
	△	0 ± 2	2 ± 3	0.590	-1 ± 2	3 ± 3	0.367
Diastolic blood pressure (mmHg)	Follow-up	84 ± 2	88 ± 2		82 ± 2*	76 ± 2	
	△	-2 ± 2	-2 ± 2	0.895	-5 ± 2	-4 ± 2	0.873

TRE, time-restricted eating; Both, combination treatment; eTRE, early TRE; lTRE, late TRE; BMI, body mass index; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-IS, homeostatic model assessment of insulin sensitivity; QUICKI, quantitative insulin-sensitivity check index; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol. All data were presented as mean ± standard error of the mean (SEM) for normally distributed variables or the median (interquartile range) for abnormal distribution. Change scores from baseline were represented by "Δ" in the table. Analyses were conducted using all participants (intention-to-treat), using a linear mixed model with randomized dietary intervention as factor to correct for the correlations of repeated measurements on changes in body weight, and using a multiple imputation approach for other missing data. After 3 months of intervention, pairwise comparisons of change scores between the eTRE and lTRE subgroups were evaluated by t test or Mann-Whitney U test. $^{a}p < 0.05$, $^{b}p < 0.001$: significant differences compared with one month before (paired t test); *p < 0.05, **p < 0.01, ***p < 0.001: significant differences compared with baseline (paired t test or paired Wilcoxon test). Related to Table 2.

Table S7. Suggested Food and Menu List

Go/Green	**Vegetables:** Spinach, Cabbage, Red cabbage, Watercress, Lettuce, Stern lettuce, Bok choy, Coriander, Celery, Leeks, Bitter melon, Cucumber, Garlic, Ginger, Spring onions, Onion, Chili pepper, Green bell Pepper, Red bell pepper, Tomato, Eggplant, Cauliflower, Broccoli, Mushroom, Bean sprouts **Meat:** Pork, Lean meet, Bacon belly, Pig's Trotters , Pork liver, Spareribs, Beef, Mutton, Chicken, Shrimp, Fish **Soups:** excluding any staple food contained in the soup Egg & vegetable soup, Seaweed soup, Sweet & sour soup , Pork thick soup, Fish ball soup, Meat ball soup **Fruit and nuts:** Coconut, Avocado **Drinks:** Mineral water, Soda water **Local snacks:** excluding any staple food contained in the dish Vegetable stew with lamb ball, Casserole **Common vegetarian dishes:** Scrambled egg with tomato, Stir fried beancurd with sliced pork & pepper, Sauté eggplant with fish flavor, Sauté leek sprouts & eggs, Stir fried green bean, Stir fried bitter melon, Stir fried mixed greens, Stir fried Chinese broccoli, Sauté string bean **Common meat dishes:** Stir fried shredded pork with sweet and sour sauce, Sauté diced chicken with hot peppers, Sauté diced chicken with peanuts, Stir fried shrimps with bamboo shoots, Beef curry, Chicken curry, Braised common carp, Steamed fish, Braised prawns with soy sauce, Sauté pork in hot sauce, Braised pork with soy sauce, Boiled salted duck, Braised beef with brown sauce, Roast Beijing duck
Slow down /Yellow < 300 ml/day	**Vegetables: (< 50ml/meal, 150 ml/day)** Lima bean, Pea, Radish, Carrot, Lotus root, Yam, Sweet corn, Pump, Potato, Sweet potato **Staple food: (< 50 ml/meal, 150 ml/day)** Plain white rice, Fried rice with egg, Sweet potato congee, Rice porridge, Rice noodles **Fruits and nuts: (< 50 ml/meal, 100 ml/day)** Apple, Pear, Peach, Apricot, Orange, Lemon, Grape, Strawberry, Mulberry, Nectarine, Cherry, Watermelon, Papaya, Pomegranate, Persimmon, Guava, Kiwi, Lychee, Pomelo, Mangosteen, Longan, Pineapple, Banana, Mango, Durian, Date, Peanut, Chestnut **Drinks: (< 50 ml/meal, < 100 ml/day)** Soybean milk **Local Snack: < 50 ml/meal, < 150 ml/day)** Extra soft tofu, Cold steamed rice noodle, Mutton blood with rice noodles, Honey glutinous rice **Common meat dishes: (< 50 ml/meal, < 150 ml/day)** Pork fillets with sweet & sour sauce, Sauté chops with sweet & sour sauce, Crisp fried spareribs
Stop/Red	**Staple food:** Clay oven rolls, Fried bread stick, Steamed buns, Boiled dumplings, Steamed dumplings, Sliced noodles, Sesame paste noodles, Shredded pork & pickled mustard green noodles **Drinks:** Coffee with cream and sugar, Juice, Carbonated drinks, Milk shake, Milk tea **Local Snack:** Pot Sticker, Beef (lamb) stew of bread, Chinese bread stuffed with cooked pork, Buckwheat noodles with sesame dressing, Sweets, glutinous millet

Low carbohydrate diet guide:

- Avoid all sugars and sweeteners such as white sugar, brown sugar, honey, corn syrup, maple syrup
- Avoid all artificial sweeteners such as aspartame
- Limit all staple and starchy foods
- Use olive oil, suet, coconut oil, butter, lard, palm oil, tallow, tea seed oil for cooking.
- Avoid using vegetable seed oils such as canola oil for high heat cooking (cold press is acceptable)
- Avoid deep fried food
- Use konjac to replace staple and starchy food when possible

Time-restricted eating guide:

- Most people can fast for a medical procedure such as a fasting blood sugar test. Therefore, it is safe for most people not to eat for 16 hours
- When we are busy or occupied, we are less likely to feel hungry
- To eat at a certain time is a habit not a necessity

- Drink plenty of fluid

Recommended zero calorie beverages:
- Water, mineral water, sparkling water, tea, herbal tea
- Absolutely no sweetened drink, especially those with artificial sweeteners

Related to STAR Methods.

Supplemental figures

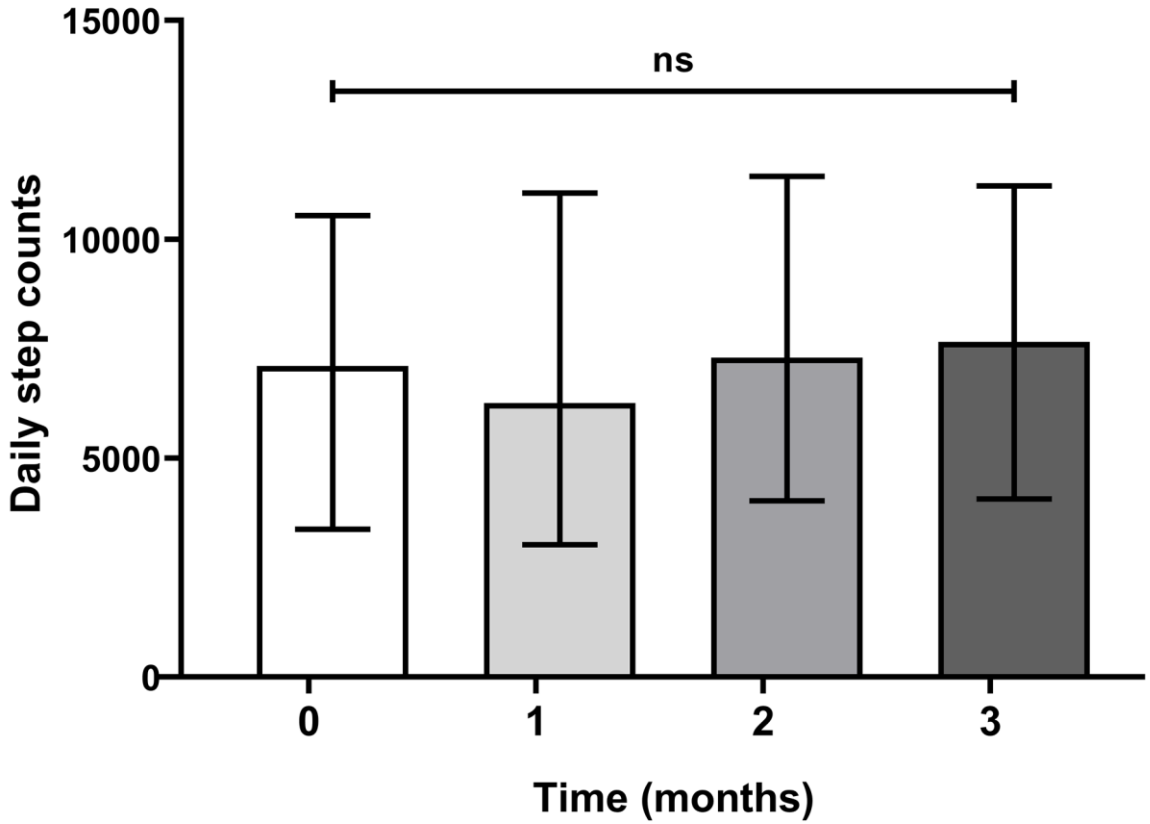

Figure S1. The daily step counts during the intervention period

Data from all participates (n = 162) are presented as median (interquartile range, IQR) for abnormally distributed variables. There were no significant differences between baseline, 1-month, 2-month, and 3-month follow-up, which were measured by Wilcoxon test. Related to STAR Methods.

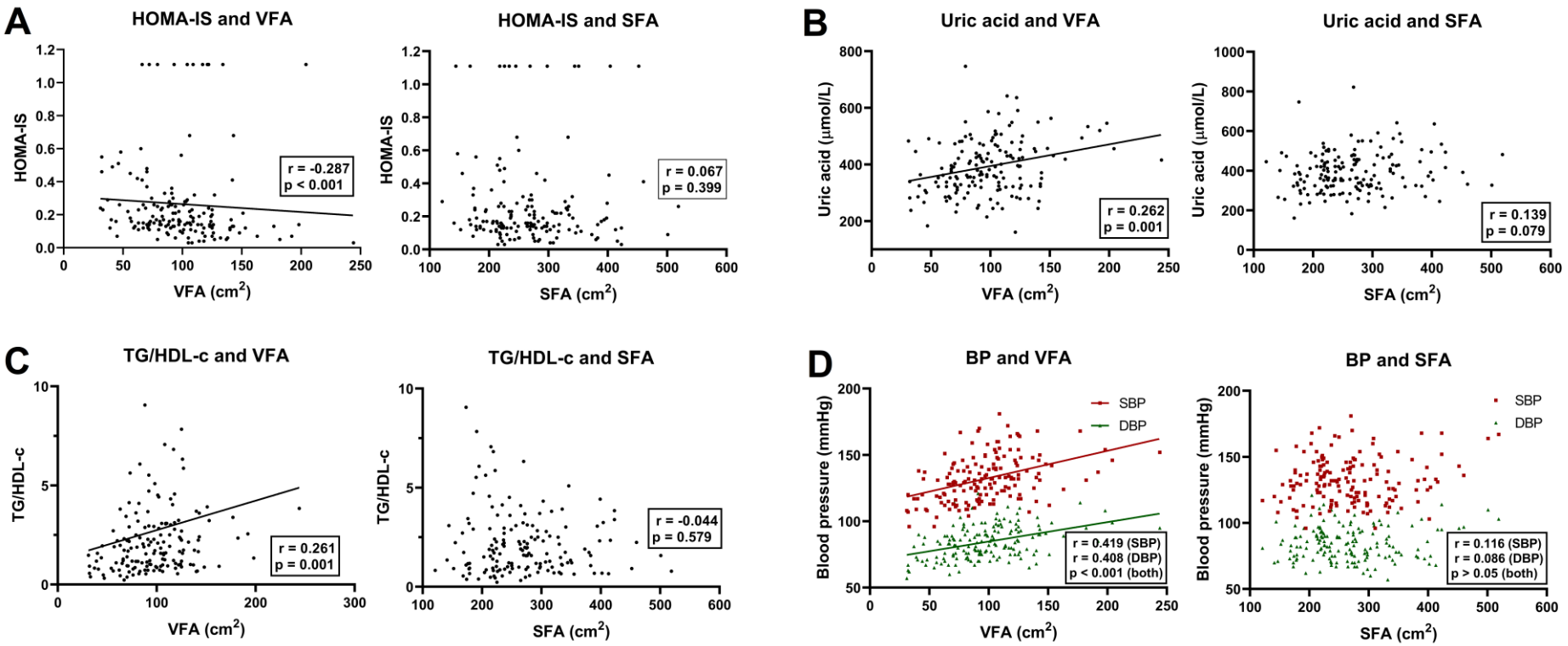

Figure S2. The correlation between metabolic factors and abdominal fat area

The correlation between baseline (A) homeostasis model assessment insulin sensitivity (HOMA-IS), (B) uric acid, (C) the ratio between triglycerides and high-density lipoprotein cholesterol (TG/HDL-c), (D) systolic and diastolic blood pressure (SBP and DBP), and abdominal fat area (visceral fat area, VFA; subcutaneous fat area, SFA). Pearson or Spearman correlations were performed to assess the relationship between abdominal fat area and other metabolic risk factors. Each data point represents an individual participant (n = 162). Related to Figure 3.

Data S1

Food Frequency Questionnaire (FFQ), related to STAR Methods

1. Days of adherence over the past two weeks: ___ days

2. Mean meal time over the past two weeks
First meal started at □□:□□
Second meal started at □□:□□ (leave a blank if skipped)
Third meal ended at □□:□□

3. Food frequency and quantity over the past two weeks
● Staple food
(1) How often and how much did you eat rice?
A Never
B ____ times a day, and ___ g each time.
C ____ times a week, and ___ g each time.
(2) How often and how much did you eat wheat flour?
A Never
B ____ times a day, and ___ g each time.
C ____ times a week, and ___ g each time.
(3) How often and how much did you eat coarse grain and field crop (corn, oat, sorghum, etc.)?
A Never
B ____ times a day, and ___ g each time.
C ____ times a week, and ___ g each time.
(4) How often and how much did you eat tuber vegetable (potato, batata, yam, taro, etc.)?
A Never
B ____ times a day, and ___ g each time.
C ____ times a week, and ___ g each time.
(5) How often and how much did you eat starch and derived products (vermicelli, etc.)?
A Never
B ____ times a day, and ___ g each time.
C ____ times a week, and ___ g each time.
● Pastry
(1) How often and how much did you eat bread, cake, cookie, etc.?
A Never
B ____ times a day, and ___ g each time.
C ____ times a week, and ___ g each time.
● Meat
(1) How often and how much did you eat pork, beef and lamb?
A Never
B ____ times a day, and ___ g each time.
C ____ times a week, and ___ g each time.
(2) How often and how much did you eat processed meat (bacon, sausage, etc.?
A Never
B ____ times a day, and ___ g each time.
C ____ times a week, and ___ g each time.
(3) How often and how much did you eat animal innards?
A Never
B ____ times a day, and ___ g each time.
C ____ times a week, and ___ g each time.
● Aquatic product
(1) How often and how much did you eat fish, crab, shrimp, shellfish, molluscs, etc.?
A Never
B ____ times a day, and ___ g each time.
C ____ times a week, and ___ g each time.

● Poultry
(1) How often and how much did you eat chicken, duck, pigeon, etc.?
A Never
B ____ times a day, and ___ g each time.
C ____ times a week, and ___ g each time.
● Egg
(1) How often and how much did you eat hen's egg, duck's egg, preserved egg, salted egg, etc.?
A Never
B ____ times a day, and ___ g each time.
C ____ times a week, and ___ g each time.
● Milk and milk products?
(1) How often and how much did you eat milk, yogurt, etc.?
A Never
B ____ times a day, and ___ ml each time.
C ____ times a week, and ___ ml each time.
(2) How often and how much did you eat milk powder, cheese, etc.?
A Never
B ____ times a day, and ___ ml each time.
C ____ times a week, and ___ ml each time.
● Beans and legume products
(1) How often and how much did you eat soybean?
A Never
B ____ times a day, and ___ g each time.
C ____ times a week, and ___ g each time.
(2) How often and how much did you eat tofu, soybean curd sheet, soybean curd slab and oily bean curd?
A Never
B ____ times a day, and ___ g each time.
C ____ times a week, and ___ g each time.
● Vegetables
(1) How often and how much did you eat dark vegetables?
A Never
B ____ times a day, and ___ g each time.
C ____ times a week, and ___ g each time.
(2) How often and how much did you eat light vegetables?
A Never
B ____ times a day, and ___ g each time.
C ____ times a week, and ___ g each time.
● Phytocomycetes
(1) How often and how much did you eat mushrooms, seaweed, porphyra, etc.?
A Never
B ____ times a day, and ___ g each time.
C ____ times a week, and ___ g each time.
● Fruits
(1) How often and how much did you eat apple, pear, peach, cherry, grapefruit, kiwifruit, etc.?
A Never
B ____ times a day, and ___ g each time.
C ____ times a week, and ___ g each time.
(2) How often and how much did you eat mango, pineapple, etc.?
A Never
B ____ times a day, and ___ g each time.
C ____ times a week, and ___ g each time.
(3) How often and how much did you eat watermelon, etc.?
A Never
B ____ times a day, and ___ g each time.

C ____ times a week, and ___ g each time.

● Nuts

(1) How often and how much did you eat peanut, sunflower seed, walnut, pumpkin seed, etc.?

A Never

B ____ times a day, and ___ g each time.

C ____ times a week, and ___ g each time.

● Alcohol

(1) How often and how much did you drink low-alcohol liquor (≤38%)?

A Never

B ____ times a day, and ___ ml each time.

C ____ times a week, and ___ ml each time.

(2) How often and how much did you drink high-alcohol liquor (>38%)?

A Never

B ____ times a day, and ___ ml each time.

C ____ times a week, and ___ ml each time.

(3) How often and how much did you drink beer?

A Never

B ____ times a day, and ___ ml each time.

C ____ times a week, and ___ ml each time.

(4) How often and how much did you drink yellow rice wine?

A Never

B ____ times a day, and ___ ml each time.

C ____ times a week, and ___ ml each time.

(5) How often and how much did you drink fruit wine?

A Never

B ____ times a day, and ___ ml each time.

C ____ times a week, and ___ ml each time.

Data S2

Trial protocol, related to STAR Methods

This is a randomized, open-label, single-centre, clinical trial to evaluate the weight loss efficacy and improvement of metabolic parameters by low-carbohydrate diet (LCD), time-restricted feeding (TRF), and their combination in adults with MetS. This study is conducted with approval from the Institutional Review Board at the First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China (No: XJTUAF2020LSK-003). The trial is registered as ClinicalTrials.gov, number NCT04475822.

Sample size calculation

The study is powered to detect the primary outcome of percentage reduction in body weight. For the sample size calculation, we estimate that the LCD-treated group (A) would lose 5% body weight and that the group treated with combination diet (C) would lose 10% body weight over 3 months. We calculate that n=26 participants per group would provide 80% power to detect a significant difference of 5% in body weight between the A and C groups by 3 month using a 2-tailed independent-samples t test with α=0.05. We anticipate a dropout rate of 20%. Thus, we initially aim to recruit 99 participants (n=33 per group), assuming that 78 participants (n=26 per group) would complete the trial. We finally decided to increase the number of recruits to 165 because of concerns about the high dropout, but also to increase the strength of statistics.

Recruitment

Participants are recruited between July 2020 and September 2020 from Xi'an via emails, flyers, social media, and website advertisements and are diagnosed with metabolic syndrome (using AHA/National Heart, Lung, and Blood Institute cutoff points for waist circumference). All participants should provide written informed consent.

Inclusion criteria

(1) Diagnosed with metabolic syndrome (i.e., more than 3 abnormal findings out of 5):

a. Waist circumference ≥ 90 cm (men) or ≥ 80 cm (women).

b. Elevated TG (use of medications for elevated TG is an alternate indicator) ≥ 150 mg/dL (1.7 mmol/L).

c. Reduced HDL-c (use of medications for reduced HDL-c is an alternate indicator) < 40 mg/dL (1.0 mmol/L) in males < 50 mg/dL (1.3 mmol/L) in females.

d. Elevated blood pressure (use of hypoglycemic medications is an alternate indicator). SBP ≥ 130 and/or DBP ≥ 85 mmHg.

e. Elevated FBG (used of hypoglycemic medications is an alternate indicator) ≥ 100 mg/dL (5.6 mmol/L).

(2) Age from 18 to 65 years.

(3) Stable weight (change ≤ 10% current body weight) for 3 months prior to the study.

(4) If participants were on hypoglycemic medications, hypotensive medications, lipid-lowering medications and cardiovascular medications, dose adjustment was not permitted during the 3-month intervention.

Exclusion criteria

1) Pregnant or breast-feeding.

2) Night shift workers.

3) History of major diseases or related diseases, such as inflammatory disease, rheumatologic disease, adrenal disease, malignancy, type 1 diabetes, cirrhosis, chronic kidney disease, acquired immunodeficiency syndrome, eating disorder, uncontrolled psychiatric disorder and major adverse cardiovascular event.

4) Current participate in other weight-management program, current on a prescribed diet for special disease or current on any drugs that effect appetite.

5) History of weight-loss surgery.

Randomisation and masking

Participants are randomly divided into LCD, TRF and a combination group at a ratio of 1:1:1 (the formal study is preceded by basic assessment and a two-week window period). Block randomization is performed by a computer-generated random number list prepared by an investigator with no clinical involvement in the trial. After the research nurse obtains the patient's consent, she telephones a clinician who is independent of the recruitment process for allocation consignment.

Procedures

Before commencing the study, all participants are asked to maintain a consistent diet, exercise and lifestyle during a two-week window period to keep their weight stable. During the 3-months intervention period, the LCD group is instructed to eat a low-carbohydrate diet (carbohydrates <130 g/day or <26% total energy, according to the ADA definition of 130 g/day as recommended minimum). The 8h TRF group is instructed to eat *ad libitum* from 8 am to 4 pm daily and fasting from 4 pm to 8 am or to eat *ad libitum* from 12 am to 8 pm daily and fasting from 8 pm to 12 am (16h fast). During the 8h feeding windows, there are no restrictions on the types or quantities of foods consumed, and the fasting guide is provided in the supplemental materials. Likewise, the combination group is instructed to eat a LCD in the same 8h feeding windows as the TRF group. Moreover, participants are not required to monitor their caloric intake during this *ad libitum* feeding period. During the fasting period, participants are encouraged to drink plenty of water and are permitted to consume energy-free beverages, such as black tea and sparkling water.

The study is conducted with the help of the internet hospital application (app) of the First Affiliated Hospital of Xi'an Jiaotong University, named "Smart Hospital", which is a new approach to provide health services, outpatient service in particular, through the internet technology. All participants could contact clinicians at any time and any place though online communication and receive diet guides and questionnaires through the app. According to a previously defined method providing quantitative information on macronutrient composition of the diet, compliance with the dietary intervention is evaluated by the same dietician every other week through diet questionnaires. All subjects are asked to maintain their usual physical activity throughout the study, which is supervised by our own custom-made sport bracelet.

Outcomes

The primary outcome of the study is change in body weight and abdominal fat area, and the secondary outcomes are body composition, glycemic control, plasma lipids, uric acid (UA), blood pressure and diet adherence.

Body weight is assessed every month at the research center with the participants without shoes and in light clothing using a digital scale (OMRON MEDICAL Beijing Co., Ltd. HNH-318) to the nearest 0.1 kg. Height is assessed during the screening visit using a wall-mounted stadiometer

(OMRON MEDICAL Beijing Co., Ltd. HNH-318) to the nearest 0.1 cm. Abdominal fat area (visceral fat area, VFA; subcutaneous fat area, SFA) is measured at baseline and after 3 months using bioelectrical impedance analysis (OMRON MEDICAL Beijing Co., Ltd. DUALSCAN, HDS-2000) to the nearest 1 cm^2, and body composition (body fat mass and body muscle mass) is measured at baseline and month 3 using the direct segmental multifrequency bioelectrical impedance analysis method DSM-BIA (InBody H20) to the nearest 0.1 kg.

Blood samples are collected after a 12h fast at week 1 (before starting the intervention) and at month 3, between 7:40 and 9:00 am. All blood draws are performed at the physical examination center of the First Affiliated Hospital of Xi'an Jiaotong University. Blood is centrifuged for 20 min at 520*g* and 4°C to separate plasma from red cells and stored at -80°C until analysis. Hemoglobin A1c (HbA1c) is measured on an automatic HbA1c analyzer (TOSOH BIOSCIENCE, Inc.; HLC-723G8) to the nearest 0.1%. FBG, UA, total cholesterol, TG, HDL-c, and LDL-c are measured on an automatic biochemistry analyzer (HITACHI, Inc.; LAbOSPECT, 008AS) using standard reagents to the nearest 0.01 mmol/L, 1 μmol/L, 0.01 mmol/L, 0.01 mmol/L, 0.01 mmol/L and 0.01 mmol/L, respectively.

Fasting insulin and C-peptide are measured by immunoassay with fluorescent detection on a Luminex instrument (EMD Millipore Corporation; HMHEMAG-34K) to the nearest 0.1 pg/mL. Insulin resistance (IR) and insulin sensitivity (IS) is calculated using the homeostasis model assessment (HOMA) method by applying the following formula: [HOMA-IR=fasting insulin (mIU/L) × fasting glucose (mg/dL)/405], [HOMA-IS=1/HOMA-IR]. Quantitative insulin-sensitivity check index (QUICKI)=1/[log (fasting insulin level, in microunits per milliliter) + log (fasting glucose level, in milligrams per deciliter)]. Blood pressure is measured in triplicate using a digital automatic blood pressure (Omron HBP-9020, Kyoto, Japan) to the nearest 1 mmHg with the participant in a seated position after a 10-min rest.

Neurological issues (dizziness, headache, fatigue, and irritability) and gastrointestinal issues (nausea, diarrhea, constipation, and dry mouth) are assessed by a telephone interview at baseline and every other week during the intervention period.

Statistical Analysis Plan

Statistical analyses are performed using SPSS v.25.0 for Windows. A two-tailed p value of less than 0.05 is considered statistically significant. Tests for normality are conducted. All data are presented as the mean ± standard deviation (SD) for normally distributed variables or median (interquartile range, IQR) for abnormally distributed variables. At baseline, differences between treatment arms (LCD, TRF and combination) are tested by one-way ANOVA or Kruskal-Wallis H test, with an LSD post hoc test (continuous variables) or McNemar test (categorical variables). Pearson and Spearman correlations are performed to assess the relationship between abdominal fat area and other metabolic risk factors. The significant difference between baseline and 3-month follow-up is measured by paired T test or Wilcoxon test in each group. At month 3, differences across treatment arms (LCD, TRF and combination) are evaluated as change scores (from baseline to month 3) using one-way ANOVA or Kruskal-Wallis H test, with an LSD post hoc test (continuous variables) or McNemar test (categorical variables).