

Randomized Control Trials

Effects of time-restricted eating and low-carbohydrate diet on psychosocial health and appetite in individuals with metabolic syndrome: A secondary analysis of a randomized controlled trial

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SUMMARY

Background & aims: Time-restricted eating (TRE) and low-carbohydrate diet (LCD) can improve multiple cardiometabolic parameters in patients with metabolic syndrome (MetS), but their effects on psychosocial health and satiety are unclear. In this study, we aimed to evaluate the effects of TRE, LCD, and their combination (TRE + LCD) on quality of life (QoL), sleep, mood, appetite, and metabolic hormones in patients with MetS.

Methods: This is a secondary analysis of a single-center, 3-month, open-label, randomized clinical trial investigating the effects of TRE, LCD, and TRE + LCD on weight and cardiometabolic parameters in individuals with MetS. This secondary analysis examined QoL, sleep, mood, and appetite using the Rand 36-Item Short Form (SF-36); Pittsburgh Sleep Quality Index (PSQI); Depression, Anxiety, and Stress Scale; and Eating Behavior Rating Scale, respectively, as well as measured levels of metabolic hormones including leptin, amylin, glucose-dependent insulinotropic polypeptide, glucagon-like peptide-1 (GLP-1), pancreatic polypeptide (PP), and peptide YY. Between-group comparisons were conducted via one-way ANOVAs and post hoc LSD tests for normally distributed variables or Kruskal–Wallis H tests and the Nemenyi test for abnormally distributed variables. $P < 0.017$ was considered significant in multiple comparisons following Bonferroni adjustment.

Results: A total of 162 participants (mean [SD] age, 41.2 [9.9] years; mean [SD] body mass index, 29.3 [3.4] kg/m²; 102 [63%] men) who started the intervention were analyzed. After 3 months, only the TRE group decreased GLP-1 levels (−0.9 [IQR, −1.9 to −0.3] pg/mL; $P = 0.002$), increased PP levels (8.9 [IQR, −7.6 to 71.8] pg/mL; $P = 0.011$), physical functioning in the SF-36 (5.2 [95% CI, 1.9 to 8.5]; $P = 0.001$), social functioning in the SF-36 (9.1 [95% CI, 2.5 to 15.6]; $P = 0.005$), role-physical in the SF-36 (24.1 [95% CI, 11.8 to 36.4]; $P < 0.001$), role-emotional in the SF-36 (22.4 [95% CI, 12.6 to 32.2]; $P < 0.001$), and sleep efficiency in the PSQI (0.29 [95% CI, 0.03 to 0.55]; $P = 0.021$). Compared with changes in LCD, TRE further increased general health in the SF-36 (9.7 [95% CI, 3.3 to 16.0]; $P = 0.006$). Relative to the changes of

Abbreviations: TRE, time-restricted eating; LCD, low-carbohydrate diet; QoL, quality of life; SF-36, Rand 36-Item Short Form; PSQI, Pittsburgh Sleep Quality Index; DASS-21, Depression, Anxiety, and Stress Scale; EBRs, Eating Behavior Rating Scale; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; PP, pancreatic polypeptide; PYY, peptide YY.

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TRE + LCD, TRE significantly increased role-emotional in the SF-36 (19.9 [95% CI 4.9 to 34.8]; $P = 0.006$). Changes in sleep quality, mood status, appetite, and metabolic hormones did not differ among three groups. Greater weight loss was associated with decreased leptin levels ($r = 0.538$), decreased amylin levels ($r = 0.294$), reduced total appetite scores ($r = 0.220$), and improved general health ($r = -0.253$) (all $P \leq 0.01$).

Conclusions: TRE, LCD, and TRE + LCD all could improve psychosocial health and reduce appetite. Notably, TRE yielded greater benefits in QoL compared with LCD or TRE + LCD in individuals with MetS.

Trial registration: [ClinicalTrials.gov](https://clinicaltrials.gov) Identifier: NCT04475822.

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1. Introduction

Characterized by abdominal obesity, insulin resistance, hypertension, and hyperlipidemia, metabolic syndrome (MetS) affects nearly one-quarter of the world's population, representing a pressing public health issue [1–3]. Time-restricted eating (TRE) and low-carbohydrate diet (LCD) have been confirmed as efficient strategies for weight loss that yield cardiometabolic benefits [4,5]. It is increasingly recognized that MetS not only predisposes individuals to type 2 diabetes mellitus (T2DM) and cardiovascular diseases but is also strongly associated with impaired psychosocial health and disrupted gut-brain axis. The effectiveness of interventions on perceived psychosocial health and appetite will directly affect patients' recognition, acceptance, and compliance of the treatment method, which can accordingly impact MetS management and long-term prognosis [6]. For this reason, psychosocial health and appetite may be important outcome measures for MetS management, in addition to body weight and cardiometabolic parameters.

Psychosocial factors play vital roles in the development of obesity and MetS. Individuals with MetS have impaired health-related quality of life (QoL) [7], psychiatric disorders [8], and sleep disturbance [9], which can be tested by multiple well-established self-report questionnaires, such as the Rand 36-Item Short Form (SF-36) for both physical and mental aspects of QoL [10], the Pittsburgh Sleep Quality Index (PSQI) for sleep quality [11], and the Depression, Anxiety, and Stress Scale (DASS-21) for mood status [12]. Weight loss after dietary intervention is strongly associated with improvements in the physical domains of QoL, while the effects on mental health remain ambiguous [13,14]. The effects of TRE and LCD on psychosocial health are controversial in limited previous studies; some studies observed significant improvements in QoL [15,16], sleep quality [17,18], and mood status [19,20], whereas others reported no changes in QoL [21,22], sleep quality [5,23], or mood [24,25].

In addition to impaired psychosocial health, individuals with MetS exhibit disruption of the hormonal gut-brain connection, resulting in increased appetite and uncontrollable eating behaviors [26], which can be assessed by the Eating Behavior Rating Scale (EBRS). Metabolic hormones consisting of both orexigenic and anorexigenic hormones are released from the gastrointestinal tract, pancreas and adipose tissue to regulate food intake behaviors. Orexigenic hormones such as ghrelin act as hunger signals to increase gut motility, while anorexigenic hormones including oxyntomodulin, peptide YY (PYY), glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), amylin, leptin and pancreatic polypeptide (PP) act as satiety signals to inhibit gastric emptying. These hormones have been recognized as the most important components of the gut-brain hormonal axis [27] and are linked with adverse mental health outcomes after bariatric surgery [28]. However, the effects of weight loss induced by TRE or LCD on subjective appetite and metabolic hormone levels differ

sharply [29–32], and the underlying mechanisms remain unclear. Furthermore, limitations existed in several trials that only assessed subject appetite lacking simultaneous evaluations of objective appetite biomarkers (metabolic hormones) [33,34].

We previously found that TRE, LCD, and TRE + LCD all resulted in significant improvements in body weight and cardiometabolic parameters after 3 months, and TRE with or without LCD exerted more benefits on body weight, visceral fat area (VFA), uric acid, and dyslipidemia [35]. In this secondary analysis, we aimed to evaluate the effects of TRE, LCD, and TRE + LCD on QoL, sleep, mood, and appetite (assessed by both self-report questionnaires and metabolic hormones), which are all important outcome measures in the management of MetS.

2. Method

2.1. Study design

This study is a secondary analysis of a single-center, 3-month, open-label, randomized clinical trial conducted at the First Affiliated Hospital of Xi'an Jiaotong University between October 2020 and January 2021. The detailed protocol and the primary results have been published previously [35]. This trial was approved by the Institutional Review Board of the First Affiliated Hospital of Xi'an Jiaotong University and registered at [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT04475822). All participants provided written informed consent.

2.2. Participants

Participants were recruited via emails, flyers, posters, social media, and website advertisements from July 2020 to September 2020. The inclusion and exclusion criteria were described in detail previously [35]. Briefly, participants were eligible if they were diagnosed with MetS [36], aged 18–65 years, and were at a weight stable period of more than 3 months. Individuals who were pregnant, breastfeeding, night shift workers, participating in other weight management programs, had a history of serious or related diseases, were using medications known to affect appetite, or had undergone weight-loss surgery were excluded.

2.3. Interventions

Details on the study procedure were published in the previous manuscript [35]. Participants were randomized to one of the following three groups. The TRE group was allowed to eat ad libitum (AL) within an 8-h window from 8 AM to 4 PM (the early TRE [eTRE] subgroup) or from 12 PM to 8 PM (the late TRE [lTRE] subgroup). The LCD group consumed a reduced-carbohydrate diet (carbohydrates <130 g/day or <26% of total energy) without a

limitation on eating time. The TRE + LCD group consumed a carbohydrate-restricted diet within only an 8-h window each day. Participants in the TRE and TRE + LCD groups could choose whether they wanted to be in the eTRE or ITRE subgroups. One-on-one dietary guidance and questionnaires were provided through an online medical application (Zhihui Hao Yiyuan). All participants were instructed not to alter their physical activity or medication doses until the end of the intervention.

2.4. Measurements and outcomes

Self-report questionnaire data and metabolic hormone levels were assessed at baseline and 3 months. The complete questionnaires were provided as supplements. QoL was evaluated with SF-36 [10], which consists of eight subscales encompassing mental aspects (role limitations due to emotional problems [role-emotional], vitality, social functioning, and mental health) and physical aspects (physical functioning, role limitations due to physical problems [role-physical], bodily pain, and general health). Scores range from 0 to 100, and higher scores reflect better QoL, with a mean score of 50 as a normative value for all items.

Participants' sleep quality was evaluated with PSQI [11], a validated and standardized 19-item questionnaire, including seven categories that assess different aspects of sleep (all with a score range of 0–3): subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, daytime dysfunction, and use of sleep medications. Total sleep scores range from 0 to 21. Lower scores indicate better sleep quality, with a score >5 suggesting significant sleep difficulties.

DASS-21 was used to assess the psychiatric symptoms of participants, including depression, anxiety, and stress levels. The DASS-21 is a self-reported 21-item questionnaire with 3 subscales, each composed of 7 items; items are rated on a scale ranging from 0 to 3 (0 = never, 1 = sometimes, 2 = frequently, and 3 = always) [12]. Lower DASS-21 scores indicate better mood status, and the normal range was 0–9 for depression, 0–7 for anxiety, and 0–14 for stress.

Subjective appetite was assessed with EBRS, established by Eli Lilly and Company to evaluate subjective appetite and eating behavior. It consists of 9 items: overeating behavior, hunger, indulgence in food, fullness, appetite, the desire for something sweet, the desire for something greasy, satiety, and unstoppable eating behaviors. Items are rated on the following scale: 0 = none, 1 = rarely, 2 = sometimes, 3 = frequently, and 4 = very. Lower total appetite scores indicate lower subjective appetite.

Venous blood samples (5 mL) were collected in anticoagulant tubes after a whole-night fast (from 8 PM on) before and after the intervention, and were centrifuged for 20 min at 1500 g and 4 °C to separate the plasma and stored at –80 °C before assessment. Levels of metabolic hormones were measured once by immunofluorescence assay on a Luminex instrument (EMD Millipore Corporation; HMHEMAG-34K), including leptin, amylin, GIP, GLP-1, PP, and PYY.

2.5. Statistical analysis

Participants who started an intervention were included in the intention-to-treat analysis. Missing data were handled by multiple imputations with the use of the Markov chain Monte Carlo method. Data are shown as the mean (95% confidence intervals) unless otherwise noted. Differences in baseline data among three groups were detected with chi-square tests for categorical variables, one-way ANOVAs for normally distributed variables or Kruskal–Wallis H tests for abnormally distributed variables. Within-group evaluations of changes in outcome variables were performed with paired t tests for normally distributed variables or paired Wilcoxon tests

for abnormally distributed variables. Between-group comparisons of changes in outcome variables were conducted via one-way ANOVAs and post hoc LSD tests for normally distributed variables or Kruskal–Wallis H tests and the Nemenyi test for abnormally distributed variables. Between-subgroup comparisons were performed with independent-sample t tests for normally distributed variables or Mann–Whitney U tests for abnormally distributed variables. Pearson's correlation for normally distributed variables or Spearman's correlation for abnormally distributed variables was analyzed in those who completed interventions to assess the correlation between changes in weight and abdominal fat area and changes in psychosocial outcome variables. A two-tailed $P < 0.05$ indicated a statistically significant difference, except the α was set at 0.017 in the multiple comparisons following Bonferroni correction to reduce type 1 errors. Statistical analysis was performed using the R version 4.1.3.

3. Results

3.1. Characteristics of participants

Fig. 1 shows the flow of participants throughout the trial. Of the 290 individuals screened, 121 were excluded, and the 169 remaining individuals were randomly assigned to the TRE group ($n = 57$), LCD group ($n = 56$), or TRE + LCD group ($n = 56$). In total, 162 participants began the interventions (55 in the TRE group, 55 in the LCD group, and 52 in the TRE + LCD group), and 135 participants ultimately completed the trial (44 in the TRE group, 47 in the LCD group, and 44 in the TRE + LCD group). The baseline characteristics were similar among the three intervention arms, except that the LCD group exhibited higher feelings of appetite and fullness (Table 1). At baseline, the majority of aspects of QoL (6/8) were above 50, except the health transition and general health. Three aspects of mood status were all within the normal range and the total sleep score was slightly increased.

Supplementary Table 1 shows the comparison between 135 participants who completed 3-month trials and 27 patients who dropped out after starting the intervention. Participants who completed the interventions had better QoL (higher health transition, role-emotional, and mental health scores), better sleep quality (lower use of sleep medications scores), and better mood (lower depression and stress scores) than those who withdrew from the interventions. Supplementary Table 2 shows the baseline comparisons between the eTRE and ITRE subgroups.

3.2. Quality of life

At the three-month follow-up, all three interventions increased health transition, general health, mental health, and vitality scores as compared with their corresponding baseline values. Only the TRE group significantly increased physical functioning (5.2 [95% CI, 1.9 to 8.5]; $P = 0.001$), social functioning (9.1 [95% CI, 2.5 to 15.6]; $P = 0.005$), role-physical (24.1 [95% CI, 11.8 to 36.4]; $P < 0.001$), and role-emotional (22.4 [95% CI, 12.6 to 32.2]; $P < 0.001$). Notably, TRE produced greater improvements in general health than the LCD group (9.7 [95% CI, 3.3 to 16.0]; $P = 0.006$) and induced greater increases in role-emotional scores than TRE + LCD (19.9 [95% CI 4.9 to 34.8]; $P = 0.006$) group. Bodily pain was not included in this analysis due to the missing data (Table 2). Increases in general health were associated with greater reductions in body weight ($r = -0.253$, $P = 0.003$) and VFA ($r = -0.240$, $P = 0.005$) (Supplementary Fig. 1). The eTRE and ITRE subgroups in the TRE or TRE + LCD groups exhibited comparable improvements in QoL (Supplementary Table 3).

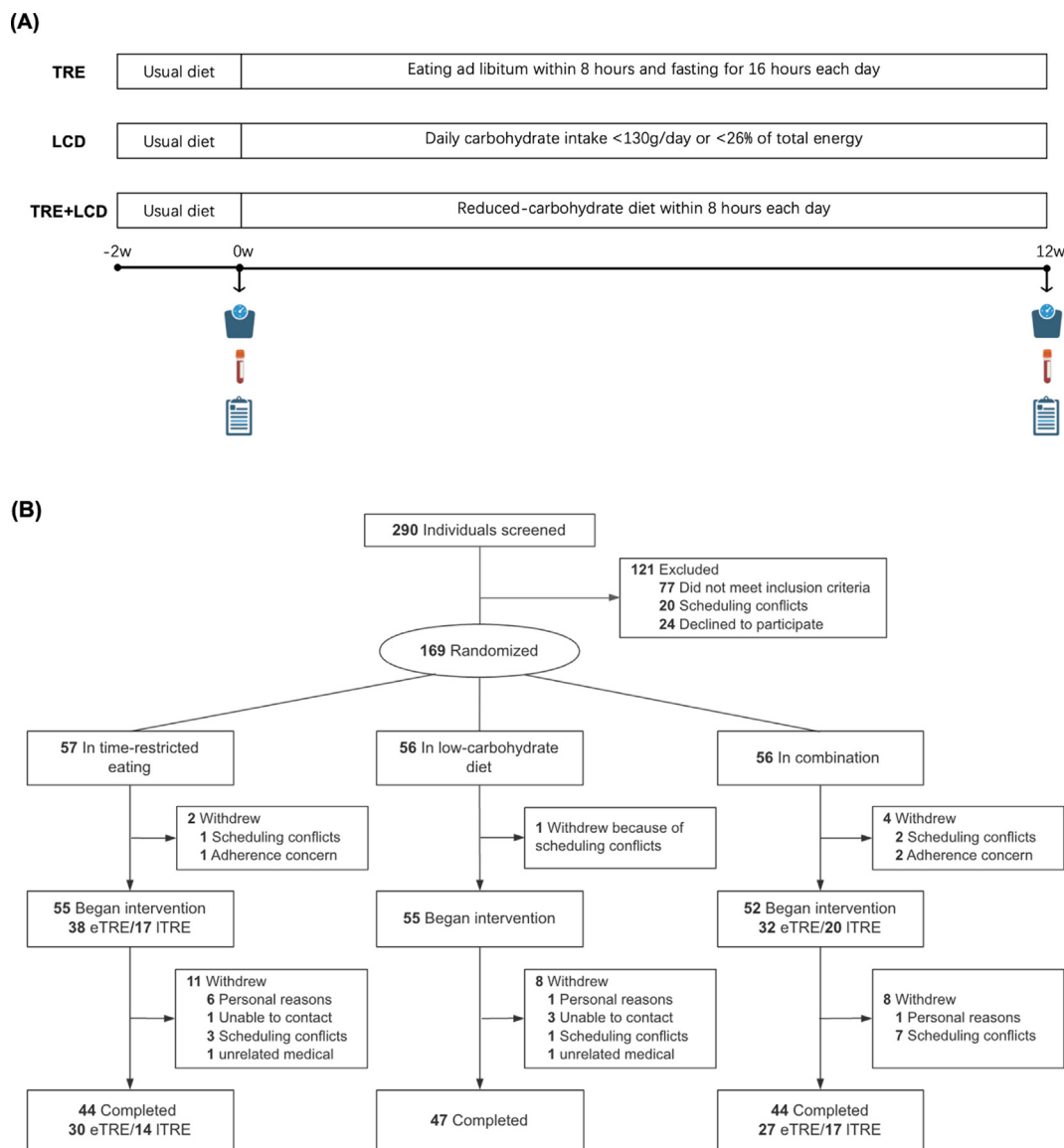


Fig. 1. Flow diagram of study procedures. Abbreviations: TRE, time-restricted eating; LCD, low-carbohydrate diet; eTRE, early time-restricted eating; ITRE, late time-restricted eating.

3.3. Sleep quality

After 3 months, only TRE led to a significant increase in habitual sleep efficiency (0.29 [95% CI, 0.03 to 0.55]; $P = 0.021$). Daytime dysfunction was decreased in both the TRE (-0.49 [95% CI, -0.70 to -0.28], $P < 0.001$) and TRE + LCD (-0.31 [95% CI, -0.50 to -0.11], $P = 0.005$) groups. There were no significant differences in other subscales of the sleep quality (Table 2). In the TRE group, ITRE improved habitual sleep efficiency to a greater extent than eTRE (0.69 [95% CI, 0.15 to 1.22]; $P = 0.022$). No significant difference in other domains of PSQI was observed between eTRE and ITRE (Supplementary Table 3).

3.4. Mood status

In the three aspects of mood, as compared with baseline, only the stress level was decreased in the TRE (-2.2 [95% CI, -3.5 to -0.7], $P = 0.003$) and LCD (-2.9 [95% CI, -4.4 to -1.3], $P < 0.001$) groups after 3 months. There were no significant differences in changes in depression, anxiety or stress scores among the three

interventions (Table 2) as well as between eTRE and ITRE subgroups in TRE or TRE + LCD groups (Supplementary Table 3).

3.5. Subjective appetite

Relative to baseline, all three interventions led to a significant reduction in overeating behavior and total appetite scores. Both the LCD and TRE + LCD groups decreased feelings of hunger, indulgence in food and fullness, and only the LCD group decreased feelings of appetite (-0.5 [95% CI, -0.8 to -0.2]; $P = 0.004$), the desire for something sweet (-0.3 [95% CI, -0.5 to -0.0]; $P = 0.028$) and the desire for something greasy (-0.4 [95% CI, -0.6 to -0.1]; $P = 0.005$). Satiety remained unchanged in all three groups. There were no significant differences in changes in appetite among the three groups (Table 3). Reductions in total appetite scores were positively correlated with weight loss ($r = 0.220$, $P = 0.010$; Supplementary Fig. 1). No significant differences in subjective appetite were observed between the eTRE and ITRE subgroups in either the TRE or TRE + LCD groups (Supplementary Table 3).

Table 1
Baseline characteristics of the participants.

	Mean (SD) ^a			p value
	TRE	LCD	TRE + LCD	
Age, y	43.0 (10.4)	41.3 (10.2)	39.0 (8.6)	0.106
Sex, No. (%)				0.204
Male	35 (64)	30 (55)	37 (71)	
Female	20 (36)	25 (45)	15 (29)	
Weight, kg	84.7 (14.6)	84.3 (16.4)	84.9 (13.2)	0.979
Body mass index, kg/m ²	29.6 (3.4)	29.3 (3.5)	29.0 (3.5)	0.711
Eating window, hours	10.6 (2.1)	10.4 (2.4)	10.7 (1.5)	0.730
Daily carbohydrate intake, g	324 (154)	348 (120)	361 (158)	0.405
Quality of Life (SF-36)^b				
Health transition	44.1 (23.1)	42.3 (23.5)	47.6 (19.3)	0.334
General health	49.3 (20.0)	52.2 (22.4)	49.6 (18.8)	0.723
Mental health	66.3 (19.8)	66.1 (22.8)	64.7 (19.4)	0.803
Vitality	65.7 (18.5)	64.9 (19.9)	63.0 (17.7)	0.778
Physical functioning	86.0 (11.8)	86.6 (11.3)	87.2 (12.3)	0.714
Social functioning	79.4 (22.2)	83.2 (19.2)	83.1 (19.6)	0.576
Role-physical	66.4 (44.4)	77.3 (35.4)	79.3 (33.8)	0.426
Role-emotional	57.6 (43.7)	70.9 (39.6)	73.1 (39.1)	0.086
Sleep (PSQI)				
Subjective sleep quality	1.05 (0.71)	1.09 (0.82)	1.06 (0.83)	0.919
Sleep latency	1.04 (0.96)	1.11 (0.79)	1.13 (1.07)	0.800
Sleep duration	0.91 (0.48)	1.02 (0.56)	1.00 (0.63)	0.570
Habitual sleep efficiency	0.33 (0.72)	0.55 (0.86)	0.38 (0.75)	0.221
Sleep disturbance	1.27 (0.59)	1.36 (0.56)	1.42 (0.61)	0.268
Use of sleep medications	0.09 (0.40)	0.05 (0.30)	0.06 (0.42)	0.641
Daytime dysfunction	1.89 (0.79)	1.85 (0.85)	1.73 (0.69)	0.607
Total sleep scores	6.58 (3.02)	7.04 (3.08)	6.79 (3.07)	0.760
Mood (DASS-21)				
Depression	6.7 (7.8)	6.5 (7.9)	6.5 (8.5)	0.917
Anxiety	6.5 (6.8)	6.0 (4.9)	6.3 (5.9)	0.966
Stress	10.7 (9.0)	9.4 (7.3)	8.5 (8.1)	0.413
Subjective Appetite (EBRS)				
Overeating	1.9 (0.8)	2.2 (0.7)	2.0 (0.8)	0.096
Total appetite scores	16.4 (5.6)	18.3 (4.4)	16.5 (4.8)	0.074
Hunger	1.9 (0.8)	2.0 (0.8)	2.0 (0.8)	0.574
Indulge in food	1.6 (1.1)	1.8 (0.9)	1.4 (0.9)	0.085
Fullness	1.7 (0.9)	2.2 (1.0)	2.0 (0.9)	0.041
Appetite	3.0 (0.8)	3.3 (0.7)	2.9 (0.8)	0.042
Desire to sweet	1.6 (1.2)	1.8 (1.0)	1.5 (1.3)	0.340
Desire to greasy	1.4 (1.0)	1.7 (0.9)	1.5 (1.0)	0.182
Satiety	2.3 (0.8)	2.3 (0.6)	2.2 (0.7)	0.914
Unstoppable eating behaviors	0.9 (1.0)	1.0 (1.1)	1.0 (0.9)	0.691
Metabolic Hormones				
Leptin, Median (IQR), pg/mL	4384.0 (4010.0)	4863.0 (4582.0)	4515.5 (4101.5)	0.395
Amylin, Median (IQR), pg/mL	15.6 (14.4)	16.9 (23.2)	12.5 (20.4)	0.604
GIP, Median (IQR), pg/mL	79.4 (65.9)	74.0 (47.7)	81.3 (41.7)	0.979
GLP-1, Median (IQR), pg/mL	5.4 (7.0)	6.8 (10.8)	6.2 (6.6)	0.095
PP, Median (IQR), pg/mL	46.6 (45.0)	54.0 (65.1)	53.9 (61.3)	0.830
Peptide YY, pg/mL	19.0 (29.3)	21.9 (43.6)	9.5 (11.5)	0.477

Abbreviations: TRE, time-restricted eating; LCD, low-carbohydrate diet; SF-36, Rand 36-Item Short Form; PSQI, Pittsburgh Sleep Quality Index; DASS-21, The Depression Anxiety Stress Scale; EBRS, Eating Behavior Rating Scale; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; PP, pancreatic polypeptide; SD, standard deviation; IQR, interquartile range.

^a Unless otherwise indicated, data are expressed as mean (SD). Differences in baseline data among three groups were detected with chi-square tests for categorical variables, one-way ANOVAs for normally distributed variables or Kruskal–Wallis H tests for abnormally distributed variables. Significant p values were italic.

^b Means the bodily pain aspect of quality of life is not reported due to missing data.

3.6. Metabolic hormones

After the 3-month intervention, all three groups reduced leptin and amylin levels, and did not change GIP levels. Only the TRE group decreased GLP-1 levels (−0.9 [IQR, −1.9 to −0.3] pg/mL; $P = 0.002$) and increased PP levels (8.9 [IQR, −7.6 to 71.8] pg/mL; $P = 0.011$). No significant differences were observed in changes in metabolic hormones among the three interventions (Table 3). Correlation analysis revealed that reductions in leptin and amylin levels were positively related to weight loss ($r = 0.538$, $P < 0.001$; $r = 0.294$, $P = 0.001$, respectively). Decreases in amylin levels were also associated with reductions in the VFA ($r = 0.258$, $P = 0.003$) and insulin levels ($r = 0.560$, $P < 0.001$) (Supplementary Fig. 1).

Both the eTRE and lTRE subgroups of either the TRE or TRE + LCD group led to comparable improvements in metabolic hormones (Supplementary Table 3).

4. Discussion

In this secondary analysis, we found that 3-month interventions of TRE, LCD, and TRE + LCD all improved QoL, appetite, and metabolic hormones, as compared with LCD with or without TRE, TRE significantly increased role-emotional and general health scores. Greater weight loss was associated with greater increases in general health scores and greater reductions in amylin, leptin, and total appetite scores. To our knowledge, this is the first study to

Table 2
Effects of diets on quality of life, sleep, and mood.

	Participant group, mean change from baseline (95% CI) ^a			Between-group comparison ^b			
	TRE (n = 55)	LCD (n = 55)	TRE + LCD (n = 52)	P value	TRE vs. LCD	TRE vs. TRE + LCD	LCD vs. TRE + LCD
Quality of life (SF-36)^c							
Health transition	20.0 (12.9–27.1)***	18.6 (10.3–27.0)***	20.7 (14.1–27.2)***	0.924	0.792	0.898	0.698
General health	18.4 (14.2–22.6)***	8.7 (3.9–13.6)**	13.1 (7.2–18.9)***	0.023	0.006	0.134	0.220
Mental health	4.9 (0.1–9.8)*	5.8 (1.8–9.9)**	5.1 (0.7–9.4)*	0.955	0.779	0.967	0.814
Vitality	6.4 (1.9–10.8)**	4.7 (0.7–8.7)*	6.8 (1.8–11.8)**	0.783	0.601	0.884	0.509
Physical functioning	5.2 (1.9–8.5)**	0.7 (–1.7 to 3.2)	0.4 (–2.9 to 3.7)	0.046	0.038	0.028	0.874
Social functioning	9.1 (2.5–15.6)**	3.0 (–1.6 to 7.7)	4.5 (–1.4 to 10.3)	0.291	0.132	0.259	0.720
Role-physical	24.1 (11.8–36.4)***	8.6 (–0.6 to 17.9)	7.2 (–2.5 to 16.9)	0.044	0.037	0.025	0.849
Role-emotional	22.4 (12.6–32.2)***	6.7 (–2.1 to 15.4)	2.6 (–9.0 to 14.2)	0.014	0.026	0.006	0.566
Sleep (PSQI)							
Subjective sleep quality	0.11 (–0.05 to 0.27)	–0.09 (–0.28 to 0.10)	–0.06 (–0.24 to 0.13)	0.237	0.113	0.192	0.794
Sleep latency	–0.11 (–0.36 to 0.14)	–0.04 (–0.24 to 0.17)	–0.04 (–0.27 to 0.19)	0.875	0.649	0.663	0.990
Sleep duration	0.09 (–0.08 to 0.26)	0.04 (–0.15 to 0.22)	0.13 (–0.06 to 0.33)	0.747	0.668	0.735	0.447
Habitual sleep efficiency	0.29 (0.03–0.55)*	0.11 (–0.17 to 0.39)	0.15 (–0.08 to 0.39)	0.585	0.320	0.460	0.809
Sleep disturbances	–0.07 (–0.23 to 0.08)	–0.09 (–0.22 to 0.04)	–0.13 (–0.27 to 0.00)	0.817	0.854	0.536	0.662
Use of sleep medications	–0.02 (–0.10 to 0.06)	–0.04 (–0.09 to 0.01)	0.00 (0.00–0.00)	0.666	0.648	0.653	0.368
Daytime dysfunction	–0.49 (–0.70 to –0.28)***	–0.18 (–0.39 to 0.03)	–0.31 (–0.50 to –0.11)**	0.102	0.034	0.212	0.391
Total sleep scores	–0.20 (–0.93 to 0.53)	–0.31 (–1.07 to 0.45)	–0.19 (–0.75 to 0.36)	0.965	0.822	0.988	0.812
Mood (DASS-21)							
Depression	–0.8 (–2.5 to 1.0)	–0.5 (–2.0 to 0.9)	–0.2 (–2.0 to 1.6)	0.902	0.826	0.813	0.651
Anxiety	–0.3 (–1.7 to 1.0)	–0.5 (–1.7 to 0.7)	–0.8 (–2.3 to 0.6)	0.857	0.845	0.721	0.583
Stress	–2.2 (–3.5 to –0.7)**	–2.9 (–4.4 to –1.3)***	–0.9 (–2.6 to 0.8)	0.191	0.480	0.071	0.265

Abbreviations: CI, confidence interval; TRE, time-restricted eating; LCD, low-carbohydrate diet; SF-36, Rand 36-Item Short Form; PSQI, Pittsburgh Sleep Quality Index; DASS-21, The Depression Anxiety Stress Scale.

^a Within-group evaluations of changes in outcome variables were performed with paired t tests for normally distributed variables or paired Wilcoxon tests for abnormally distributed variables. *p < 0.05, **p < 0.01, ***p < 0.001: significant differences compared with baseline (paired t test).

^b Between-group comparisons were conducted using one-way ANOVAs and post hoc LSD tests for normally distributed variables or Kruskal–Wallis H tests and the Nemenyi test for abnormally distributed variables. P < 0.05 were italic and P < 0.017 were bolded.

^c Means the bodily pain aspect of quality of life is not reported due to missing data.

Table 3
Effects of diets on subjective appetite and metabolic hormones.

	Participant group, mean change from baseline (95% CI) ^a			Between-group comparison ^b			
	TRE (n = 55)	LCD (n = 55)	TRE + LCD (n = 52)	P value	TRE vs. LCD	TRE vs. TRE + LCD	LCD vs. TRE + LCD
Subjective Appetite (EBRS)							
Overeating	–0.5 (–0.8 to –0.2)**	–0.7 (–1.0 to –0.5)***	–0.6 (–0.8 to –0.3)***	0.520	0.264	0.736	0.445
Total appetite scores	–1.9 (–3.3 to –0.5)**	–3.5 (–4.7 to –2.2)***	–2.8 (–4.0 to –1.6)***	0.220	0.084	0.325	0.466
Hunger	–0.1 (–0.3 to 0.2)	–0.4 (–0.6 to –0.1)**	–0.3 (–0.6 to –0.0)*	0.247	0.107	0.238	0.680
Indulge in food	–0.3 (–0.6 to 0.1)	–0.5 (–0.7 to –0.2)**	–0.3 (–0.6 to –0.0)*	0.570	0.321	0.868	0.417
Fullness	–0.3 (–0.7 to 0.0)	–0.6 (–0.9 to –0.3)***	–0.7 (–1.0 to –0.4)***	0.160	0.226	0.059	0.484
Appetite	–0.2 (–0.4 to 0.1)	–0.5 (–0.8 to –0.2)**	–0.0 (–0.3 to 0.3)	0.064	0.113	0.464	0.022
Desire to sweet	–0.1 (–0.5 to 0.2)	–0.3 (–0.5 to –0.0)*	–0.2 (–0.5 to 0.1)	0.808	0.535	0.894	0.632
Desire to greasy	–0.1 (–0.4 to 0.1)	–0.4 (–0.6 to –0.1)**	–0.2 (–0.5 to 0.1)	0.434	0.202	0.649	0.421
Satiety	–0.3 (–0.6 to 0.0)	–0.1 (–0.3 to 0.1)	–0.1 (–0.4 to 0.2)	0.510	0.287	0.357	0.898
Unstoppable eating behaviors	–0.0 (–0.3 to 0.3)	–0.1 (–0.4 to 0.1)	–0.4 (–0.7 to –0.1)**	0.141	0.512	0.052	0.191
Metabolic Hormones							
Leptin, Median (IQR), pg/mL	–1567.0 (–3263.0 to –86.0)***	–705.0 (–2141.0 to 65.0)***	–1200.0 (–3458.6 to 369.0)***	0.514	0.498	0.939	0.719
Amylin, Median (IQR), pg/mL	–3.7 (–6.7 to 0.0)***	–2.4 (–11.0 to 0.0)***	–3.1 (–12.2 to 0.3)**	0.930	0.994	0.928	0.962
GIP, Median (IQR), pg/mL	5.0 (–19.0 to 23.3)	–0.4 (–15.7 to 12.6)	–11.0 (–40.1 to 13.1)	0.298	0.894	0.282	0.531
GLP-1, Median (IQR), pg/mL	–0.9 (–1.9 to –0.3)**	–0.3 (–2.7 to 1.3)	–0.7 (–3.3 to 1.2)	0.939	0.935	0.993	0.971
PP, Median (IQR), pg/mL	8.9 (–7.6 to 71.8)*	3.7 (–23.4 to 32.7)	–1.2 (–26.1 to 21.8)	0.120	0.283	0.122	0.887
Peptide YY, pg/mL	1.1 (–5.0 to 7.1)	0.1 (–7.2 to 7.4)	9.6 (3.7–15.6)*	0.028	0.996	0.058	0.047

Abbreviations: CI, confidence interval; TRE, time-restricted eating; LCD, low-carbohydrate diet; EBRS, Eating Behavior Rating Scale. GIP, glucose-dependent insulintropic polypeptide; GLP-1, glucagon-like peptide-1; PP, pancreatic polypeptide; IQR, interquartile range.

^a Within-group evaluations of changes in outcome variables were performed with paired t tests for normally distributed variables or paired Wilcoxon tests for abnormally distributed variables. *p < 0.05, **p < 0.01, ***p < 0.001: significant differences compared with baseline (paired t test or paired Wilcoxon test).

^b Between-group comparisons were conducted using one-way ANOVAs and post hoc LSD tests for normally distributed variables or Kruskal–Wallis H tests and the Nemenyi test for abnormally distributed variables, P < 0.05 were italic.

explore the effects of TRE, LCD, and their combination on psychosocial health and appetite in patients with MetS.

We observed that 3-month TRE significantly improved all domains of QoL, especially role-emotional and general health relative to either LCD or TRE + LCD. Our findings are in agreement with previous studies showing that TRE improved several domains of QoL [16,37], while to date no study has shown all domains of QoL were improved after TRE. We also first revealed the greater improvement of TRE in role-emotional and general health levels in the field of dietary intervention. Inconsistent with our findings, other TRE interventions with shorter duration failed to significantly improve domains of QoL [21,38]. Guldbrand et al. found that physical functioning was improved after 12 months (but not after 6 months) on an LCD (20% energy from carbohydrates) in patients with T2DM [39], which suggests that the moderate intervention period and carbohydrate restriction may account for our findings of few improvements in QoL in the LCD group; further studies are warranted to investigate the effects of LCD with longer intervention period and varying degrees of daily carb intake.

Available studies assessing the effects of dietary interventions on sleep and mood are limited. In this study, we showed TRE significantly improved sleep efficiency and daytime dysfunction after 3 months, which may be attributed to the benefits of TRE on the circadian rhythm [40]. The failure to find a change in other domains of sleep quality in the TRE group is consistent with previous studies in individuals with MetS [5], T2DM [38], and obesity [41]. Overall, the 3-month intervention of 8h TRE could ameliorate several aspects of sleep quality to some extent in individuals with MetS. In contrast, we did not find significant changes in mood in all three groups compared with baseline, despite the reduction in stress in the TRE and LCD groups, which might be due to the limited variability of the normal baseline data and moderate intervention duration. The failure to find changes in depression and anxiety is consistent with previous studies in overweight or obese individuals with or without T2DM after TRE [25,38] or LCD [42,43], but inconsistent with one other study that showed depression was significantly improved in adults with obesity after 14-week eTRE combined with energy restriction (ER) than only ER [19]. We speculated that selection bias may influence the results because individuals with psychiatric disorders are less likely to participate in intensive weight-loss interventions.

We observed that multiple domains of subjective appetite scores were decreased in both the LCD and TRE + LCD groups, partly owing to the reduced daily intake of carbohydrates, which were previously reported to be positively associated with feelings of hunger [44]. It should be noted that the appetite score measured by the questionnaire had limited reliability owing to its subjectivity, thus the objective biomarkers of appetite (levels of metabolic hormones) were assessed in the present study.

Consistent with other TRE [45] or LCD [42] studies, we observed that all three groups decreased leptin and amylin levels after 3 months, the positive correlation between changes in leptin and amylin levels and weight loss could partially explain this phenomenon (Supplementary Fig. 1A and B). As adiposity signals, leptin and amylin may increase in obese individuals. Leptin resistance, which co-existed with elevated leptin levels [46], could be improved once the leptin levels decrease to restore hypothalamic leptin sensitivity and enhance insulin sensitivity [47]. Common in patients with obesity and prediabetes, hyperamylinemia is tightly associated with glucose and lipid metabolic abnormalities [48], contributing to cardiac myocyte injury and neurological deficits [49,50]. Co-secreted with insulin in pancreatic β cells, amylin was decreased after all three interventions seemingly with changes in insulin [35], in line with the positive correlation between changes in amylin and reductions in insulin (Supplementary Fig. 1H).

In this study, PP levels increased only in TRE group relative to baseline, inconsistent with one other study reporting increased fasting PP levels after 12-week LCD [51]. In humans, intravenous infusion of PP could decrease appetite and food intake for 24 h [52], thus, we speculate that TRE could inhibit longer-time appetite by increasing PP levels. However, studies investigating the effects of TRE on PP levels were sparse, further trials are needed to confirm our findings. Interestingly, in line with findings from other TRE studies [29,32,53], we showed GLP-1 levels were decreased after 3 months of TRE, which may be attributed to the prominent reduction in leptin which stimulates GLP-1 secretion [54]. Moreover, we observed that TRE + LCD significantly increased PYY levels, while TRE and LCD did not. Yet, the effects of TRE on PYY levels are still unclear. One study found increased PYY concentration in the evening [29], while others showed no significant changes [32] or decreased fasting PYY [55]. However, the intervention durations were relatively short and varied among studies investigating the effects of TRE on PYY, warranting further studies to investigate the longer-term effects of TRE and LCD on metabolic hormones.

In this study, the eTRE and lTRE interventions led to comparable improvements in QoL, sleep, mood, and appetite, except for a greater increase in habitual sleep efficiency in lTRE of TRE. Consistent with our results, Xie et al. reported no significant differences in changes in sleep quality, subjective appetite, and leptin levels among eTRE (eating between 6 AM and 3 PM), lTRE (eating between 11 AM and 8 PM), and control groups of healthy adults without obesity after 5 weeks [56]. Similarly, a 7-day randomized crossover trial showed no significant differences in changes in amylin, GLP-1, GIP, and PYY levels between the eTRE (eating from 8 AM to 5 PM) and lTRE groups (eating from 12 PM to 9 PM) [32]. Further randomized trials to compare the effects of eTRE and lTRE on psychosocial health and appetite are needed.

4.1. Strengths and limitations

The key strengths of this trial include its use of well-established questionnaires to assess psychosocial health, a combination of subjective and objective measures of appetite (i.e. questionnaire scores and metabolic hormone levels, respectively), and the data obtained from a randomized clinical trial. However, there are some limitations. First, metabolic hormone levels were assessed only in the fasting state, lacking levels after consuming a test meal to explore postprandial responses. Further studies should measure both pre- and postprandial levels of metabolic hormones. Moreover, to enhance adherence, the eTRE and lTRE interventions were not randomly assigned, as participants selected subgroups on their own, which impaired the reliability of the analytical results. Nonetheless, the subgroup analysis is still meaningful as it represents a preliminary exploration of the effects of eTRE and lTRE interventions on psychosocial health and appetite in MetS patients. Further large-scale studies that randomly assign participants to eTRE or lTRE groups are needed. Additionally, the absence of bodily pain from SF-36 limits the integrity of the data. To date, the reported effects of TRE and LCD on bodily pain varied among studies; some found improvement [39,57], while some did not [15,16]. Further studies are needed to verify the effects of TRE and LCD on bodily pain.

5. Conclusion

We conclude that TRE, LCD, and TRE + LCD all improved QoL, appetite, and metabolic hormone levels. Compared with LCD or TRE + LCD, TRE led to greater increases in role emotional and general health scores. Our results emphasize the importance of paying attention to perceived psychosocial health and appetite and monitoring these variables during the management of MetS. Our

findings also suggest that TRE is superior to LCD or TRE + LCD in managing MetS regarding its greater benefits on QoL, which may be attributed in part to its type of restriction, but the proper time window needs more studies to confirm. Further long-term studies are needed to confirm and compare the effects of TRE and LCD on psychosocial health in individuals with MetS or other metabolic disorders.

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Conflict of interest

The authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.clnu.2024.08.029>.

References

- [1] Cohen RV, Drager LF, Petry TBZ, Santos RD. Metabolic health in Brazil: trends and challenges. *Lancet Diabetes Endocrinol* 2020;8(12):937–8.
- [2] Aguilar M, Bhuket T, Torres S, Liu B, Wong RJ. Prevalence of the metabolic syndrome in the United States, 2003–2012. *JAMA* 2015;313(19):1973–4.
- [3] Zuo H, Shi Z, Hu X, Wu M, Guo Z, Hussain A. Prevalence of metabolic syndrome and factors associated with its components in Chinese adults. *Metabolism* 2009;58(8):1102–8.
- [4] Hansen CD, Gram-Kampmann EM, Hansen JK, Hugger MB, Madsen BS, Jensen JM, et al. Effect of calorie-unrestricted low-carbohydrate, high-fat diet versus high-carbohydrate, low-fat diet on type 2 diabetes and nonalcoholic fatty liver disease : a randomized controlled trial. *Ann Intern Med* 2023;176(1):10–21.
- [5] Wilkinson MJ, Manoogian ENC, Zadourian A, Lo H, Fakhouri S, Shoghi A, et al. Ten-hour time-restricted eating reduces weight, blood pressure, and atherogenic lipids in patients with metabolic syndrome. *Cell Metabol* 2020;31(1):92–104.e5.
- [6] Chopra S, Ranjan P, Malhotra A, Sarkar S, Kumari A, Kalojiya GS, et al. Identification of instruments for evaluation of behavioural and psychological parameters associated with obesity management: a systematic review with narrative synthesis of the findings. *Diabetes Metabol Syndr* 2022;16(1):102350.
- [7] Ford ES, Li C. Metabolic syndrome and health-related quality of life among U.S. adults. *Ann Epidemiol* 2008;18(3):165–71.
- [8] Vassou C, Georgousopoulou EN, Chrysoshoou C, Yannakoulia M, Pitsavos C, Cropley M, et al. Psychological factors in relation to the 10-year incidence of metabolic syndrome: the ATTICA epidemiological study (2002–2012). *Nutr Metabol Cardiovasc Dis* 2022;32(9):2195–203.
- [9] Qian Y, Xu H, Wang Y, Yi H, Guan J, Yin S. Obstructive sleep apnea predicts risk of metabolic syndrome independently of obesity: a meta-analysis. *Arch Med Sci* 2016;12(5):1077–87.
- [10] Ware Jr JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30(6):473–83.
- [11] Buysse DJ, Reynolds 3rd CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatr Res* 1989;28(2):193–213.
- [12] Lovibond PF, Lovibond SH. The structure of negative emotional states: comparison of the depression anxiety stress scales (DASS) with the beck depression and anxiety inventories. *Behav Res Ther* 1995;33(3):335–43.
- [13] Warkentin LM, Das D, Majumdar SR, Johnson JA, Padwal RS. The effect of weight loss on health-related quality of life: systematic review and meta-analysis of randomized trials. *Obes Rev* 2014;15(3):169–82.
- [14] Kroes M, Osei-Assibey G, Baker-Searle R, Huang J. Impact of weight change on quality of life in adults with overweight/obesity in the United States: a systematic review. *Curr Med Res Opin* 2016;32(3):485–508.
- [15] Jensen NJ, Wodschow HZ, Skytte MJ, Samkani A, Astrup A, Frystyk J, et al. Weight-loss induced by carbohydrate restriction does not negatively affect health-related quality of life and cognition in people with type 2 diabetes: a randomised controlled trial. *Clin Nutr* 2022;41(7):1605–12.
- [16] Crose A, Alvear A, Singroy S, Wang Q, Manoogian E, Panda S, et al. Time-restricted eating improves quality of life measures in overweight humans. *Nutrients* 2021;13(5).
- [17] Kesztyűs D, Fuchs M, Cermak P, Kesztyűs T. Associations of time-restricted eating with health-related quality of life and sleep in adults: a secondary analysis of two pre-post pilot studies. *BMC Nutr* 2020;6(1):76.
- [18] Yamada S, Inoue G, Ooyane H, Nishikawa H. Changes in body weight, dysglycemia, and dyslipidemia after moderately low-carbohydrate diet education (LOCABO challenge program) among workers in Japan. *Diabetes Metab Syndr* 2021;14:2863–70.
- [19] Jamshed H, Steger FL, Bryan DR, Richman JS, Warriner AH, Hanick CJ, et al. Effectiveness of early time-restricted eating for weight loss, fat loss, and cardiometabolic health in adults with obesity: a randomized clinical trial. *JAMA Intern Med* 2022;182(9):953–62.
- [20] Field R, Pourkazemi F, Rooney K. Effects of a low-carbohydrate ketogenic diet on reported pain, blood biomarkers and quality of life in patients with chronic pain: a pilot randomized clinical trial. *Pain Med* 2022;23(2):326–38.
- [21] Anton SD, Lee SA, Donahoo WT, McLaren C, Manini T, Leeuwenburgh C, et al. The effects of time restricted feeding on overweight, older adults: a pilot study. *Nutrients* 2019;11(7).
- [22] Kleissl-Muir S, Owen A, Rasmussen B, Zinn C, Driscoll A. Effects of a low carbohydrate diet on heart failure symptoms and quality of life in patients with diabetic cardiomyopathy: a randomised controlled trial pilot study. *Nutr Metabol Cardiovasc Dis* 2023;33(12):2455–63.
- [23] Kalam F, Gabel K, Cienfuegos S, Ezpeleta M, Wiseman E, Varady KA. Alternate day fasting combined with a low carbohydrate diet: effect on sleep quality, duration, insomnia severity and risk of obstructive sleep apnea in adults with obesity. *Nutrients* 2021;13(1).
- [24] Dietrich DM, Kerr-Gaffney J, Hockey M, Marx W, Ruusunen A, Young AH, et al. Efficacy of low carbohydrate and ketogenic diets in treating mood and anxiety disorders: systematic review and implications for clinical practice. *BJPsych Open* 2023;9(3):e70.
- [25] Lin S, Cienfuegos S, Ezpeleta M, Pavlou V, Chakos K, McStay M, et al. Effect of time-restricted eating versus daily calorie restriction on mood and quality of life in adults with obesity. *Nutrients* 2023;15(20).
- [26] Holst JJ. Glucagon and other proglucagon-derived peptides in the pathogenesis of obesity. *Front Nutr* 2022;9:964406.
- [27] Chaudhri OB, Salem V, Murphy KG, Bloom SR. Gastrointestinal satiety signals. *Annu Rev Physiol* 2008;70:239–55.
- [28] Brown RM, Guerrero-Hreins E, Brown WA, le Roux CW, Sumithran P. Potential gut-brain mechanisms behind adverse mental health outcomes of bariatric surgery. *Nat Rev Endocrinol* 2021;17(9):549–59.
- [29] Ravussin E, Beyl RA, Poggiogalle E, Hsia DS, Peterson CM. Early time-restricted feeding reduces appetite and increases fat oxidation but does not affect energy expenditure in humans. *Obesity* 2019;27(8):1244–54.

- [30] Di Rosa C, Lattanzi G, Taylor SF, Manfrini S, Khazrai YM. Very low calorie ketogenic diets in overweight and obesity treatment: effects on anthropometric parameters, body composition, satiety, lipid profile and microbiota. *Obes Res Clin Pract* 2020;14(6):491–503.
- [31] Hu T, Yao L, Reynolds K, Niu T, Li S, Whelton P, et al. The effects of a low-carbohydrate diet on appetite: a randomized controlled trial. *Nutr Metabol Cardiovasc Dis* 2016;26(6):476–88.
- [32] Hutchison AT, Regmi P, Manoogian ENC, Fleischer JG, Wittert GA, Panda S, et al. Time-restricted feeding improves glucose tolerance in men at risk for type 2 diabetes: a randomized crossover trial. *Obesity* 2019;27(5):724–32.
- [33] Struik NA, Brinkworth GD, Thompson CH, Buckley JD, Wittert G, Luscombe-Marsh ND. Very low and higher carbohydrate diets promote differential appetite responses in adults with type 2 diabetes: a randomized trial. *J Nutr* 2020;150(4):800–5.
- [34] Steger FL, Jamshed H, Martin CK, Richman JS, Bryan DR, Hanick CJ, et al. Impact of early time-restricted eating on diet quality, meal frequency, appetite, and eating behaviors: a randomized trial. *Obesity* 2023;31(Suppl 1):127–38. Suppl 1.
- [35] He M, Wang J, Liang Q, Li M, Guo H, Wang Y, et al. Time-restricted eating with or without low-carbohydrate diet reduces visceral fat and improves metabolic syndrome: a randomized trial. *Cell Rep Med* 2022;3(10):100777.
- [36] Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the international diabetes federation task force on epidemiology and prevention; national heart, lung, and blood institute; American heart association; world heart federation; international atherosclerosis society; and international association for the study of obesity. *Circulation* 2009;120(16):1640–5.
- [37] Schroder JD, Falquetto H, Mânica A, Zanini D, de Oliveira T, de Sá CA, et al. Effects of time-restricted feeding in weight loss, metabolic syndrome and cardiovascular risk in obese women. *J Transl Med* 2021;19(1):3.
- [38] Parr EB, Devlin BL, Lim KHC, Moresi LNZ, Geils C, Brennan L, et al. Time-restricted eating as a nutrition strategy for individuals with type 2 diabetes: a feasibility study. *Nutrients* 2020;12(11).
- [39] Guldbrand H, Lindström T, Dizdar B, Bunjaku B, Östgren CJ, Nystrom FH, et al. Randomization to a low-carbohydrate diet advice improves health related quality of life compared with a low-fat diet at similar weight-loss in Type 2 diabetes mellitus. *Diabetes Res Clin Pract* 2014;106(2):221–7.
- [40] Longo VD, Panda S. Fasting, circadian rhythms, and time-restricted feeding in healthy lifespan. *Cell Metabol* 2016;23(6):1048–59.
- [41] Gabel K, Hoddy KK, Burgess HJ, Varady KA. Effect of 8-h time-restricted feeding on sleep quality and duration in adults with obesity. *Appl Physiol Nutr Metabol* 2019;44(8):903–6.
- [42] Kackley ML, Brownlow ML, Buga A, Crabtree CD, Sapper TN, O'Connor A, et al. The effects of a 6-week controlled, hypocaloric ketogenic diet, with and without exogenous ketone salts, on cognitive performance and mood states in overweight and obese adults. *Front Neurosci* 2022;16:971144.
- [43] Varae H, Darand M, Hassanizadeh S, Hosseinzadeh M. Effect of low-carbohydrate diet on depression and anxiety: a systematic review and meta-analysis of controlled trials. *J Affect Disord* 2023;325:206–14.
- [44] Zhu R, Larsen TM, Poppitt SD, Silvestre MP, Fogelholm M, Jalo E, et al. Associations of quantity and quality of carbohydrate sources with subjective appetite sensations during 3-year weight-loss maintenance: results from the PREVIEW intervention study. *Clin Nutr* 2022;41(1):219–30.
- [45] Moro T, Tinsley G, Bianco A, Marcolin G, Pacelli QF, Battaglia G, et al. Effects of eight weeks of time-restricted feeding (16/8) on basal metabolism, maximal strength, body composition, inflammation, and cardiovascular risk factors in resistance-trained males. *J Transl Med* 2016;14(1):290.
- [46] Cui H, López M, Rahmouni K. The cellular and molecular bases of leptin and ghrelin resistance in obesity. *Nat Rev Endocrinol* 2017;13(6):338–51.
- [47] Zhao S, Zhu Y, Schultz RD, Li N, He Z, Zhang Z, et al. Partial leptin reduction as an insulin sensitization and weight loss strategy. *Cell Metabol* 2019;30(4):706. 19.e6.
- [48] Reinehr T, de Sousa G, Niklowitz P, Roth CL. Amylin and its relation to insulin and lipids in obese children before and after weight loss. *Obesity* 2007;15(8):2006–11.
- [49] Despa S, Margulies KB, Chen L, Knowlton AA, Havel PJ, Taegtmeier H, et al. Hyperamylinemia contributes to cardiac dysfunction in obesity and diabetes: a study in humans and rats. *Circ Res* 2012;110(4):598–608.
- [50] Srodulski S, Sharma S, Bachstetter AB, Brelsfoard JM, Pascual C, Xie XS, et al. Neuroinflammation and neurologic deficits in diabetes linked to brain accumulation of amylin. *Mol Neurodegener* 2014;9:30.
- [51] Jensen DE, Ngou K, Baxter KA, Cardinal JW, King NA, Ware RS, et al. Fasting gut hormone levels change with modest weight loss in obese adolescents. *Pediatr Obes* 2015;10(5):380–7.
- [52] Batterham RL, Le Roux CW, Cohen MA, Park AJ, Ellis SM, Patterson M, et al. Pancreatic polypeptide reduces appetite and food intake in humans. *J Clin Endocrinol Metab* 2003;88(8):3989–92.
- [53] Zouhal H, Bagheri R, Triki R, Saeidi A, Wong A, Hackney AC, et al. Effects of Ramadan intermittent fasting on gut hormones and body composition in males with obesity. *Int J Environ Res Publ Health* 2020;17(15).
- [54] Tacad DKM, Tovar AP, Richardson CE, Horn WF, Krishnan GP, Keim NL, et al. Satiety associated with calorie restriction and time-restricted feeding: peripheral hormones. *Adv Nutr* 2022;13(3):792–820.
- [55] Sutton EF, Beyl R, Early KS, Cefalu WT, Ravussin E, Peterson CM. Early time-restricted feeding improves insulin sensitivity, blood pressure, and oxidative stress even without weight loss in men with prediabetes. *Cell Metabol* 2018;27(6):1212. 21.e3.
- [56] Xie Z, Sun Y, Ye Y, Hu D, Zhang H, He Z, et al. Randomized controlled trial for time-restricted eating in healthy volunteers without obesity. *Nat Commun* 2022;13(1):1003.
- [57] Kämmerer U, Klement RJ, Joos FT, Sütterlin M, Reuss-Borst M. Low carb and ketogenic diets increase quality of life, physical performance, body composition, and metabolic health of women with breast cancer. *Nutrients* 2021;13(3).