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Effect of 5:2 Regimens: Energy-Restricted Diet or Low-Volume High-Intensity Interval Training Combined With Resistance Exercise on Glycemic Control and Cardiometabolic Health in Adults With Overweight/Obesity and Type 2 Diabetes—A Three-Arm Randomized Controlled Trial

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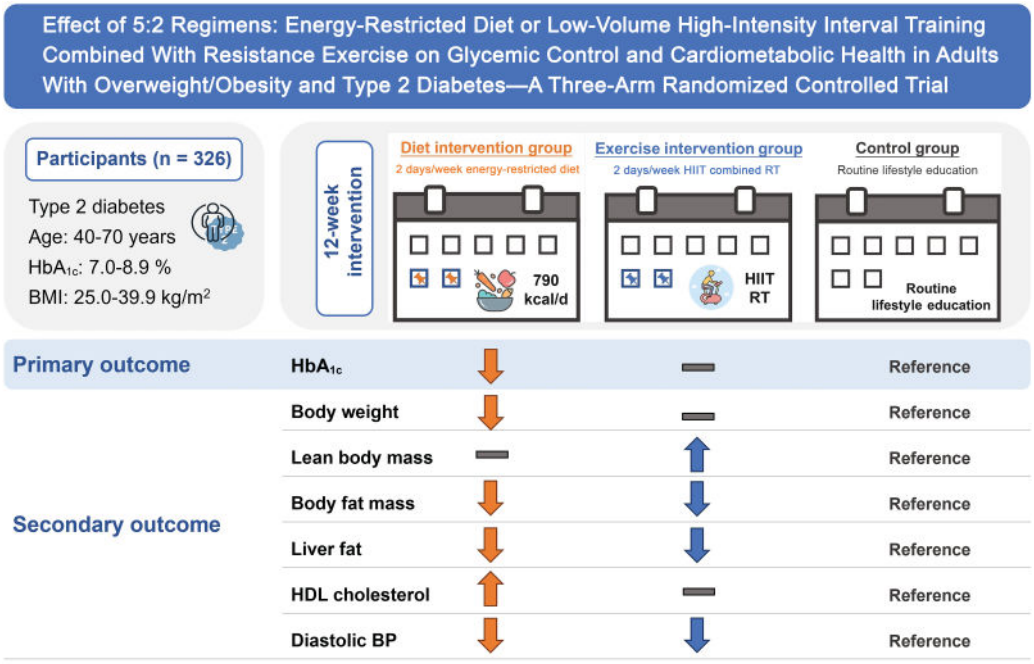

BP, blood pressure; HIIT, high-intensity interval training; RT, resistance training.

ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  A 5:2 regimen of diet or exercise intervention may offer an alternative option to accommodate work-life rhythms, but its efficacy on glycemic control has rarely been studied.
- **What is the specific question we wanted to answer?**
  Does the 5:2 diet or exercise intervention exert favorable effects on glycemic control and cardiometabolic health compared with routine lifestyle education among adults with overweight/obesity and type 2 diabetes?
- **What did we find?**
  The 5:2 diet intervention improved glycemic control, body composition, and several cardiometabolic parameters; the exercise regimen also improved body composition but inadequately improved glycemic control.
- **What are the implications of our findings?**
  These findings suggest that a medically supervised 5:2 energy-restricted diet could serve as an alternative strategy for improving glycemic control.

Effect of 5:2 Regimens: Energy-Restricted Diet or Low-Volume High-Intensity Interval Training Combined With Resistance Exercise on Glycemic Control and Cardiometabolic Health in Adults With Overweight/Obesity and Type 2 Diabetes—A Three-Arm Randomized Controlled Trial

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OBJECTIVE

We aimed to examine the effects of a 5:2 regimens diet (2 days per week of energy restriction by formula diet) or an exercise (2 days per week of high-intensity interval training and resistance training) intervention compared with routine lifestyle education (control) on glycemic control and cardiometabolic health among adults with overweight/obesity and type 2 diabetes.

RESEARCH DESIGN AND METHODS

This two-center, open-label, three-arm, parallel-group, randomized controlled trial recruited 326 participants with overweight/obesity and type 2 diabetes and randomized them into 12 weeks of diet intervention (n = 109), exercise intervention (n = 108), or lifestyle education (control) (n = 109). The primary outcome was the change of glycemic control measured as glycated hemoglobin (HbA_{1c}) between the diet or exercise intervention groups and the control group after the 12-week intervention.

RESULTS

The diet intervention significantly reduced HbA_{1c} level (%) after the 12-week intervention (−0.72, 95% CI −0.95 to −0.48) compared with the control group (−0.37, 95% CI −0.60 to −0.15) (diet vs. control −0.34, 95% CI −0.58 to −0.11, P = 0.007). The reduction in HbA_{1c} level in the exercise intervention group (−0.46, 95% CI −0.70 to −0.23) did not significantly differ from the control group (exercise vs. control −0.09, 95% CI −0.32 to 0.15, P = 0.47). The exercise intervention group was superior in maintaining lean body mass. Both diet and exercise interventions induced improvements in adiposity and hepatic steatosis.

CONCLUSIONS

These findings suggest that the medically supervised 5:2 energy-restricted diet could provide an alternative strategy for improving glycemic control and that the exercise regimen could improve body composition, although it inadequately improved glycemic control.

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Diabetes poses a significant public health issue that needs effective and cost-efficient glycemic control strategies (1). Lifestyle intervention involving dietary modification and enhanced physical activity serves as a first-line treatment for type 2 diabetes. Daily calorie restriction leading to substantial weight loss has been proven to improve glycemic control and induce diabetes remission (2,3). However, these approaches typically involve a rigorous continuous caloric restriction, which significantly impacts daily life and proves challenging to adhere to, particularly for the working-age population without severe obesity (4). Lifestyle interventions that are flexible to work-life rhythms could enhance compliance.

The 5:2 diet, a periodic fasting regimen involving a very-low-calorie diet for 2 days per week and a regular diet for the remaining 5 days (5), has presented a comparable effect to continuous energy restriction on the reduction of glycated hemoglobin (HbA_{1c}) in type 2 diabetes, although results were inconsistent and limited by small sample sizes (6–9). The efficacy of the 5:2 diet challenges the existing paradigm of lifestyle intervention where sustained behavior change is required. Approaches where people are required to modify their behaviors intensely but intermittently may allow a more convenient and efficacious way to achieve metabolic benefits.

Similarly, observational studies demonstrated the benefits of a weekend warrior physical activity pattern characterized as doing all exercise on 1 or 2 days of the week (10). Since lack of time is one of the most cited barriers to regular physical activity, the amount of aerobic and resistance training (RT) recommended by guidelines may be burdensome for individuals with not a lot of free time (11,12). Early evidence from small-scale studies suggests that as little as 4 min of high-intensity interval training (HIIT) at a low volume may reduce HbA_{1c} (13–16), although others have not corroborated these findings (17,18). The combined approach of low-volume HIIT and RT could offer a comprehensive, time-efficient exercise strategy (19); nonetheless, its efficacy for glycemic control has rarely been studied.

Both the 5:2 diet and low-volume HIIT combined with RT have shown potential as practical strategies, which are time efficient and flexible to work-life rhythms. Thus, we designed a study, the first of its kind as a randomized controlled trial, to examine the effects of 2 days per week energy-restricted diet or low-volume HIIT combined with RT intervention undertaken on 2 days of the week (5:2 regimen) compared with routine lifestyle education (control) on glycemic control, as well as body composition, liver fat content, and cardiometabolic parameters, among adults with overweight/obesity and type 2 diabetes.

RESEARCH DESIGN AND METHODS

Study Design and Participants

The Intermittent Intensive Diet and Enhanced Physical Activity on Glycemic Control in Newly Diagnosed Type 2 Diabetes Study (IDEATE) was a two-center, open-label, three-arm, parallel-group, randomized controlled trial. Participants were randomized 1:1:1 to one of three arms: diet intervention (2 days per week energy-restricted diet), exercise intervention (2 days per week low-volume HIIT combined with RT), and control (routine lifestyle education). The study consisted of a 12-week intervention and a 36-week postintervention follow-up observation. The primary outcome was the difference in the change of glycemic control measured as HbA_{1c} between the diet or exercise intervention groups and the control group after a 12-week intervention. The secondary outcomes included changes in other glycemic metrics, body weight, body composition, liver fat content, serum lipids, and blood pressure (BP). The study was approved by the ethical review committee of Ruijin Hospital (Ruijin-2018-174) and registered prospectively at ClinicalTrials.gov (NCT03839667).

The prescreening of potential participants started in January 2019 at the Third People's Hospital of Datong and Shanghai Songnan Health Community Center. Potentially eligible participants were identified by the clinical primary care team from electronic medical records or were referred by medical clinics. Participants were initially asked about their age, disease history, etc., via a simple categorical questionnaire, and once written consent was provided, the final eligibility of participants was established before randomization. Eligible participants were aged 40–70 years, reported a diagnosis of type 2 diabetes within the prior 2 years, and had a BMI of 25.0–39.9 kg/m^2 and an HbA_{1c} ranging from 7.0 to 8.9%. Individuals were excluded if they had type 1 diabetes or received insulin treatment; had a cardiovascular event in the previous 6 months; had uncontrolled hypertension; reported currently completing >75 min of high-intensity exercise or 150 min of moderate-intensity exercise per week; reported a high alcohol intake; had an active foot ulcer; had impaired liver function or renal function; had a history of food allergies or bariatric surgery; were currently pregnant, breastfeeding, or planning a pregnancy; or had other conditions not eligible for the trial. The study's design is described in detail in the study protocol (Supplementary Material).

Intervention

Diet Intervention

The diet intervention group received 12 weeks of a 5:2 diet comprising a restricted energy intake of 790 kcal per day on 2 days per week (mostly consecutive) and a regular diet on the remaining 5 days. Energy restriction was induced with a total diet replacement phase using a low-energy formula diet (~25% of energy from protein, ~55% from carbohydrates, and ~20% from fat; Chiatai Qingchunbao Pharmaceutical Co., Ltd., Hangzhou, China). The dietitian evaluated adherence and discussed the improvement plan with participants through telephone or WeChat instant messaging weekly, together with face-to-face education monthly. Consumption of food besides the formula diet was defined as having less adherence.

Exercise Intervention

The exercise intervention group completed 12 weeks of twice-weekly (mostly nonconsecutive) supervised exercise at the health care centers, consisting of a single bout of 4 min of HIIT at 85–90% of age-predicted heart rate maximum with a 5-min warm-up and 5-min cooldown and four machine-based resistance exercises involving two sets of 8–12 repetitions at 80% of 1-repetition maximum. HIIT was undertaken using a cycle ergometer, and resistance exercise was undertaken using a comprehensive strength machine. Heart rate was monitored with a Bluetooth heart rate chest strap (GEONAUTE), and the intensity of RT was recorded for each region (shoulders, chest, back, and anterior chain [thigh]). Adherence to the exercise intervention protocol was defined as completing sessions with HIIT at ≥85% heart rate maximum and RT at 80% of one-repetition maximum. During the

coronavirus 2019 (COVID-19) pandemic, participants allocated to the exercise intervention completed HIIT or RT sessions at home, including cycle ergometer, treadmill, or running in place and strength training without equipment, with supervision by physicians through real-time audio or video meetings.

Lifestyle Education

Routine lifestyle education was performed in the same manner for all intervention and control groups by physicians masked to the randomization and consisted of instructions on healthy diet and exercise per the Guidelines for the Prevention and Treatment of Type 2 Diabetes in China (20). The physicians offered lifestyle advice to the participants through telephone or WeChat weekly, together with face-to-face education monthly.

Antihyperglycemic Medication Management

During the 12-week intervention, participants were asked to maintain their medication type, dosage, or frequency, unless certain conditions arose. Sulfonylureas were omitted on days of energy restriction. If any glucose readings were <4 mmol/L or >20 mmol/L or fasting blood glucose levels >10 mmol/L, participants were advised to contact physicians for potential medication changes. During the intervention and follow-up phases, physicians who were masked to the study group made decisions about patients' antihyperglycemic medication. Medication dosages were recorded at every visit, and the medication effect score (MES) was used to quantify changes (21).

OUTCOMES

Glycemic Control

We evaluated glycemic control by blood sampling at all visits, including baseline (before intervention) and weeks 4, 12 (after intervention, assessment of primary outcome), 24, 36, and 48. All fasting blood collection was performed at the physical examination center, refraining from the intervention for at least 48 h to avoid the interference of acute response to energy restriction or exercise. Then, participants underwent a standard oral glucose tolerance test (OGTT), and blood was sampled at 30 min and 120 min for postload plasma glucose (PPG). Plasma glucose concentrations were analyzed using a glucose oxidase or hexokinase method, and HbA_{1c} was determined through high-performance liquid chromatography (Bio-Rad, Hercules, CA) within 2 h after blood sample collection. Glucose area under the curve (AUC) was calculated as 1/2 (fasting plasma glucose [FPG] + 30-min PPG) × 30 min/h + 1/2 (30-min PPG + 120-min PPG) × 90 min/h (22,23). Fasting serum samples were shipped by air on dry ice to the study central laboratory at the Shanghai Institute of Endocrine and Metabolic Disease to measure the lipids profile and insulin (Atellica Solution; Siemens Healthineers). Insulin resistance (IR) was calculated using the HOMA method: HOMA-IR = fasting insulin (μIU/mL) × fasting glucose (mmol/L) / 22.5.

Body Composition

Trained study nurses measured body weight, height, and waist circumference. BMI was calculated as body weight in kilograms divided by height in meters squared. Waist circumference was measured at the level of the umbilicus with the patient in the standing position. We used bioelectrical impedance analysis (H-Key350, Beijing Seehigher Technology Co., Ltd., Beijing, China) to estimate body fat mass, body fat percentage, and lean body mass.

Liver Fat Content

Liver fat content was measured and quantified by abdominal MRI-proton density fat fraction (PDFF) examination using a 3.0-T MRI scanner (Ingenia; Philips Healthcare). Fat-water separation images of the liver were acquired using a mDIXON-Quant sequence. The mDIXON-Quant is a 3-dimensional fast field echo sequence and uses multiple acquired echoes to generate water, fat, T2*, and fat fraction images synthesized from the water-fat images. Nine circular regions of interest (ROIs) corresponding to the Couinaud liver segments on the MRI-PDFF maps were analyzed. Each ROI had an area of 3 cm^2 and was placed near the center of each segment while avoiding major vessels, liver edges, and artifacts. The PDFF in each of the nine ROIs was recorded, and the PDFF value across the entire liver was reported as the mean of the PDFF values of all nine ROIs. The technician performing the MRI-PDFF measurements was masked to participant group assignment.

Cardiometabolic Parameters

BP measurements were obtained using an automated electronic device (Omron Model HEM-752 Fuzzy; Omron, Tokyo, Japan). HDL cholesterol, LDL cholesterol, and triglycerides were measured at the central laboratory using enzymatic methods with an autoanalyzer (cobas c 701; Roche, Mannheim, Germany).

Statistical Analysis

We calculated that 324 participants (108 per group) would provide 90% power to detect a significant difference of -0.5% in HbA_{1c} (SD 1.0%) between the diet or exercise intervention and control group, which was based on a two-tailed independent-samples *t* test with a significance level of 0.05 and a predicted dropout rate of 20%. The estimations were derived from the effect estimated by previous studies of the 5:2 diet or structured exercise training for 12 weeks in participants with type 2 diabetes, which were also in line with a clinically significant change in HbA_{1c} recommended by the American Diabetes Association (6,24,25). Finally, 326 participants were recruited. Randomization was conducted with a 1:1:1 ratio on the stratification of three factors: study center, sex (men vs. women), and age-group (<65 vs. ≥ 65 years). Block randomization was done with block sizes of six using an independent online computerized randomization system. The staff responsible for allocation were masked to the block sizes.

Data were analyzed according to participants' randomization assignment (intention to treat). Multiple imputations for missing data in the multivariable analyses were conducted using the Markov chain Monte Carlo method. Supplementary Table 1 shows the number (percent) of missing data for multiple imputation. A linear mixed model was conducted to assess time, group, and time × group effects for each continuous outcome using PROC MIXED of SAS statistical software to obtain point estimates and 95% CIs of the treatment effects and to test for differences between the diet or exercise intervention and control intervention by the interaction terms (time × group), with adjustments for study center, sex, and age, which are the stratification factors in the randomization. MES, HOMA-IR, liver fat content, and triglyceride outcomes were log-transformed for the analysis and reported on the original scale using the equation (10^β − 1) × x0,

where ^β is the estimate or interval limit and x0 is the baseline sample mean. The categorical outcomes, including the proportion of diabetes remission and incidence of severe adverse events or adverse events across groups, were analyzed using χ^2 test and logistic regression analysis. Bonferroni adjustment was applied for the primary outcome to protect against false-positive findings due to multiple comparisons of three groups. No multiple test adjustments were performed for secondary outcomes, so such analyses should be interpreted as exploratory. We used SAS 9.4 and R version 4.1.1 software for statistical analyses. All reported *P* values were nominal. Statistical significance was set as a two-tailed $P < 0.05$.

RESULTS

As shown in Fig. 1, a total of 440 individuals were initially enrolled for prescreening. Of these participants, 114 were excluded for not meeting eligibility criteria, declining participation, or withdrawing their consent. Consequently, 326 participants were randomized to the diet intervention group (*n* = 109), exercise intervention group (*n* = 108), or control group (*n* = 109). Finally, 301 (92.33%) completed the intervention and the 12-week assessment of primary outcome until June 2021. Baseline characteristics were similar between participants who completed the interventions and those who dropped out (Supplementary Table 2). Supplementary Table 3 summarizes the baseline sample characteristics: 116 women and 210 men, mean (SD) age 52.65 (8.13) years, mean (SD) HbA_{1c} level 7.63% (0.85%) (59.88 [9.27] mmol/mol), and mean (SD) BMI 27.71 (2.61) kg/m^2. No significant differences existed across groups for baseline characteristics, including the proportion of participants taking antihyperglycemic medication and the level of MES (Supplementary Tables 3 and 4). Figure 2*A* presents the proportion of participants who were considered adherent to their intervention per week. After the 12-week intervention period, 98 diet group participants and 81 exercise group participants were adherent for ≥80% of the whole intervention, and 105 control group participants completed the education session; these participants were considered compliant and included in the per-protocol population.

Primary Outcome

Following the intention-to-treat principle, all randomized individuals were included. Participants in the diet intervention group experienced a greater decrease in HbA_{1c} level (%) after the 12-week intervention (−0.72, 95% CI −0.95 to −0.48) compared with the control group (−0.37, 95% CI −0.60 to −0.15) (diet vs. control −0.34, 95% CI −0.58 to −0.11, *P* = 0.007). The reduction in HbA_{1c} level in the exercise intervention group (−0.46, 95% CI −0.70 to −0.23) did not significantly differ from the control group (exercise vs. control −0.09, 95% CI −0.32 to 0.15, *P* = 0.47) (Table 1). Among the 301 patients who underwent the 12-week assessment, the proportion and degree of reduction in HbA_{1c} were more significant in the diet intervention group than in the control group (Fig. 2*C*).

Secondary Outcome

Diabetes was in remission in 20 (19.42%) participants in the diet intervention group, 11 (11.83%) in the exercise intervention group, and 11 (10.48%) in the control group, which was defined as $HbA_{1c} < 6.5\%$ without antihyperglycemic medication after the intervention. Compared with the control group, the diet intervention, but not the exercise intervention, increased the likelihood of diabetes remission (diet vs. control adjusted odds ratio 3.60 [95% CI 1.40–9.25, *P* = 0.008]; exercise vs. control adjusted odds ratio 1.42 [95% CI 0.51–3.95, *P* = 0.52]) (Fig. 2*D*).

In the intention-to-treat analysis for other glycemic metrics, glucose AUC during OGTT and OGTT 30-min PPG improved in the diet intervention group compared with the control group (diet vs. control: glucose AUC [mmol · min/L] −84.77 [95% CI −160.13 to −9.42, *P* = 0.028]; OGTT 30-min PPG [mmol/L] −1.16 [95% CI −1.74 to −0.57, *P* = 0.0001]), but not in the exercise intervention group. There were no significant differences between interventions and control in MES, FPG, OGTT 120-min PPG, and HOMA-IR ($P > 0.05$) (Table 1).

During the 12-week intervention, significant reductions in self-monitoring body weight were observed across all three groups, with the diet intervention group showing the most pronounced effect (Fig. 2*B*). A reduction in body weight became evident after 4 weeks of intervention in the diet group (Fig. 3*B*). After the 12-week intervention, the diet intervention achieved significantly greater reductions in body weight (kg) compared with the control group (diet vs. control −1.94 [95% CI −2.70 to −1.19, $P < 0.0001$], exercise vs. control −0.48 [95% CI −1.24 to 0.28, *P* = 0.21]), which was also observed for BMI and waist circumference. The exercise intervention exhibited a superior effect on preserving lean body mass (kg) compared with the control group (diet vs. control 0.29 [95% CI −0.70 to 1.27, *P* = 0.57], exercise vs. control 1.08 [95% CI 0.05 to 2.10, *P* = 0.039]). Both diet and exercise interventions induced greater reduction in body fat mass and fat-to-lean mass ratio compared with the control group. There were notable reductions in liver fat content (%) after diet and exercise interventions (diet vs. control −2.31 [95% CI −3.07 to −1.47, $P < 0.0001$], exercise vs. control −1.27 [95% CI −2.14 to −0.30, *P* = 0.012]). Favorable changes in HDL cholesterol were observed in the diet intervention group but not in the exercise group. Both diet and exercise interventions significantly reduced diastolic BP. No significant alterations were detected in LDL cholesterol, triglycerides, or systolic BP (Table 1).

Supplementary Table 5 shows that no serious adverse events occurred in the diet or exercise intervention groups, with only one serious event reported in the control group (hospitalization due to a nasal polypectomy). The occurrence of serious adverse events or adverse events was evenly distributed across all groups.

Sensitivity Analysis

We excluded 16 participants who changed their antihyperglycemic medication during the intervention (Supplementary Table 6), and similar results were obtained (Supplementary Table 7). We confirmed the results in the per-protocol population and further detected a significantly reduced FPG, OGTT 120-min PPG, and HOMA-IR in the diet intervention group (Supplementary Table 8). After excluding 15 participants who received modified exercise intervention and 1 who withdrew because of an inability to train at home during the COVID-19 pandemic, the effect of the exercise intervention was not substantially changed (Supplementary Table 9).

Postintervention Follow-up Assessment

After the intervention, we continued to monitor the HbA_{1c} and body weight every 12 weeks to identify the sustainability of the intervention effects. Compared with

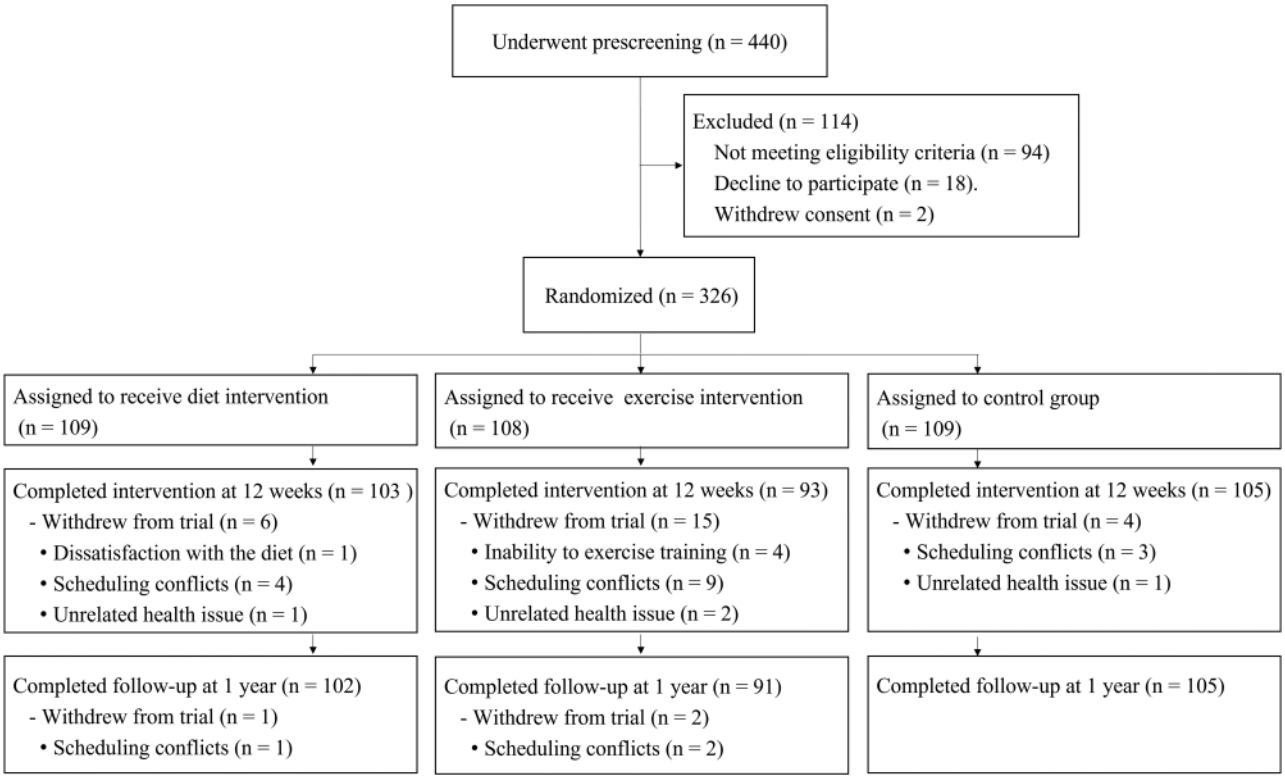

Figure 1—Study participant flowchart.

baseline, the diet and exercise interventions continued to significantly enhance glycemic control and body weight during the postintervention follow-up period. However, no significant differences in HbA_{1c} were detected between the interventions and control (Fig. 3*A*). The diet intervention continued to show sustained weight loss until week 36, after which the trend converged (Fig. 3*B*). Similar trends were obtained in the per-protocol population (Supplementary Fig. 1). After excluding participants who altered their antihyperglycemic medication, the effects on body weight caused by the diet intervention were sustained by week 48 (Supplementary Fig. 2).

CONCLUSIONS

To our knowledge, this randomized controlled trial is the first to investigate the effects of energy-restricted diet or low-volume HIIT combined with RT (5:2 regimen) on glycemic control in adults with overweight/obesity and type 2 diabetes. Our findings suggest that the 5:2 energy-restricted diet intervention improved glycemic control, body composition, and cardiometabolic parameters compared with routine lifestyle education. Despite observing favorable effects on body composition, including significant reductions in adiposity and liver fat content and superior maintenance of lean body mass, the exercise intervention did not significantly decrease HbA_{1c} compared with routine lifestyle education.

The current study is the largest trial to date to examine the effect of a 5:2 diet on glycemic control in patients with type 2 diabetes, aligning with prior smaller-scale studies (6–8,26,27). For instance, Corley et al. (26) reported a 0.6–0.7% absolute reduction of HbA_{1c} from baseline after 12 weeks of a 5:2 diet. Furthermore, our study identified a significant decrease in peak glucose after 30 min of OGTT following the diet intervention, suggesting potential improvements in early-phase β-cell responsiveness (22), which also led to a significant reduction in glucose AUC during the 120-min OGTT, thereby reducing the overall blood glucose burden (23). Participants in the diet intervention were significantly more likely to achieve diabetes remission, with a prevalence rate of 19.42% compared with the control group at 10.48%. Although the remission rate induced by the 5:2 diet intervention was relatively lower than that of other studies implementing rigorous and continuous caloric restriction and greater weight losses, such as the Diabetes Remission Clinical Trial (DiRECT) with a prevalence of 46% (2), it was comparable to the prevalence of 11.5% observed in the Look AHEAD (Action for Health in Diabetes) study, which also implemented a combined physical activity and diet program (28). It is worth noting that previous trials were predominantly conducted in western populations with severe obesity, most of which had a mean BMI >35 kg/m^2. Our study distinguishes itself by extending the evidence for the equivalent effectiveness of a 5:2 diet in improving glycemic control in diabetes with overweight or mild obesity, a nonnegligible proportion of the people with diabetes in Asia (29). As conducted in our study, it should be emphasized that the 5:2 diet be performed under medical supervision regarding appropriate adjustment of hypoglycemic drugs and monitoring of blood glucose.

On the other hand, the low-volume HIIT and RT intervention failed to induce improvements in glycemic control compared with routine lifestyle education. Among previous trials, only one study involving 80 patients investigated the effects of combined HIIT and RT, reporting no appreciable benefits in HbA_{1c} levels (30). According to a meta-analysis involving 32 randomized

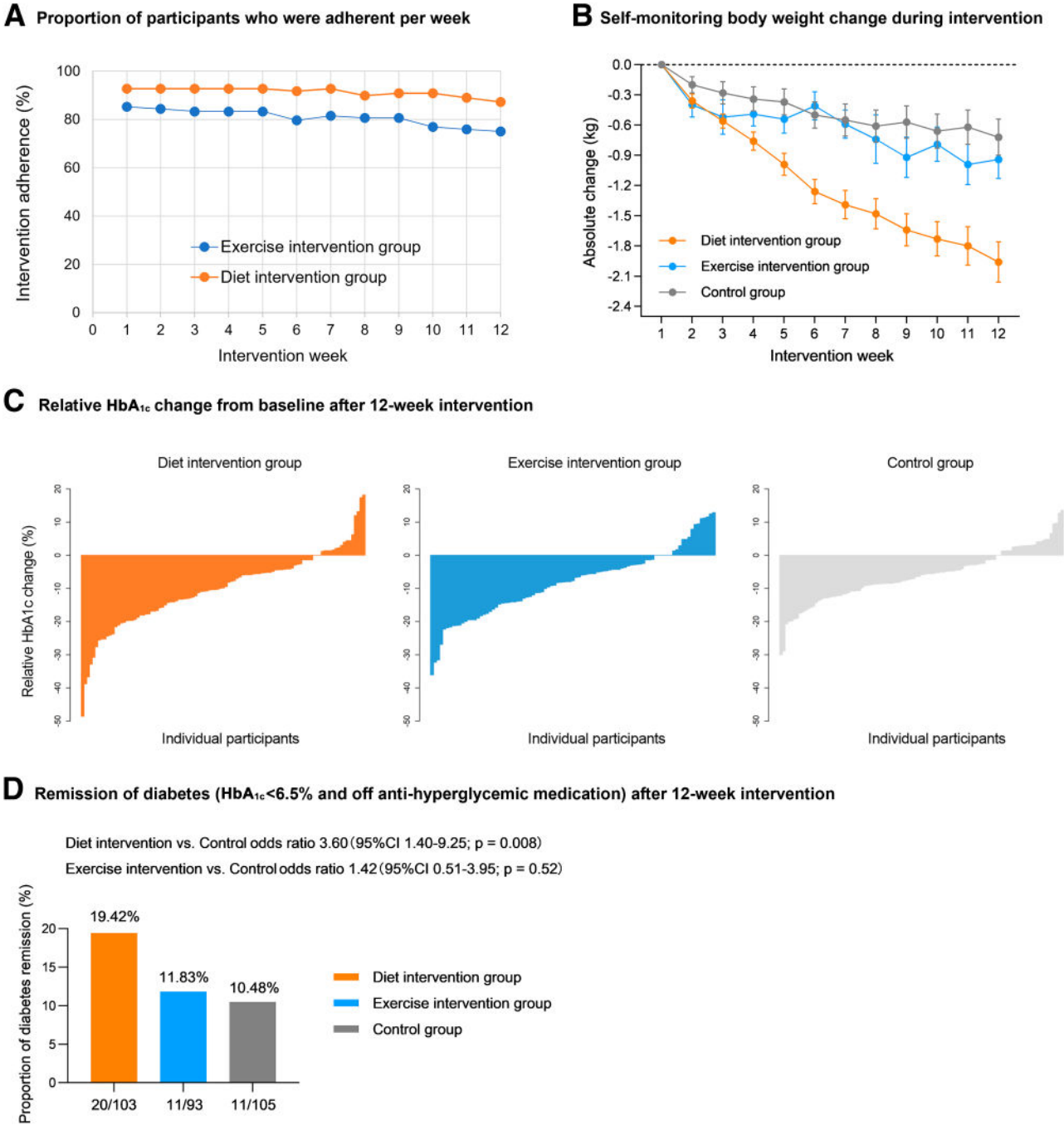

Figure 2—Adherence to intervention, body weight change, and glycemic control during the 12-week intervention period. *A*: Proportion of participants who were considered adherent to the diet and exercise intervention protocol per week. *B*: Absolute change of self-monitored body weight per week. Bars indicate mean ± SE. *C*: Individual data of relative HbA_{1c} change (%) from baseline after intervention among participants who underwent randomization and had a 12-week assessment. *D*: Proportion of diabetes remissions after the 12-week intervention and the multivariable-adjusted odds ratios of diabetes remission for the diet or exercise intervention compared with the control group among patients who underwent randomization and had a 12-week assessment. Odds ratios were adjusted for age at recruitment, sex, study center, baseline HbA_{1c}, and baseline MES of antihyperglycemic medication.

controlled trials, HIIT intervention reduced HbA_{1c} by 0.34% (31). In the current study, participants experienced a −0.46% (95% CI −0.70% to −0.23%) absolute decrease in HbA_{1c} after a 12-week low-volume HIIT combined with RT. It is worth noting that participants in the control group also made substantial improvements in glycemic control, possibly because of their participation in exercise and diet guidance as part of routine lifestyle education. Our results aligned with a prior meta-analysis involving 47 trials evaluating the efficacy of structured exercise training or physical activity advice to lower HbA_{1c} levels, which showed that aerobic exercise plus RT and only physical activity plus dietary advice resulted in HbA_{1c} reductions of 0.51% and 0.58%, respectively (24).

Even so, our study suggests that both a 5:2 diet regimen and low-volume HIIT

Table 1—Intention-to-treat analysis for the effects of intervention on primary and secondary outcomes

	Change (95% CI) within-group (12 weeks − 0 weeks)			Comparison between groups (12 weeks − 0 weeks)			
				Diet vs. control		Exercise vs. control	
	Diet intervention	Exercise intervention	Control	Difference (95% CI)	*P*	Difference (95% CI)	*P*
Primary outcome (change after 12-week intervention)							
HbA_{1c}							
%	−0.72 (−0.95 to −0.48)	−0.46 (−0.70 to −0.23)	−0.37 (−0.60 to −0.15)	−0.34 (−0.58 to −0.11)	0.007	−0.09 (−0.32 to 0.15)	0.47
mmol/mol	−7.83 (−10.41 to −5.25)	−5.02 (−7.57 to −2.47)	−4.07 (−6.53 to −1.60)	−3.77 (−6.30 to −1.23)	0.007	−0.95 (−3.52 to 1.61)	0.47
Secondary outcome (change after 12-week intervention)							
Glucose metabolism							
MES	0.02 (−0.03, 0.09)	0.09 (0.02 to 0.17)	0.03 (−0.02 to 0.10)	−0.01 (−0.06 to 0.05)	0.77	0.05 (−0.01 to 0.13)	0.11
Glucose AUC (mmol · min/L)	−135.06 (−212.93 to −57.19)	−28.44 (−102.31 to 45.44)	−50.29 (−123.54 to 22.97)	−84.77 (−160.13 to −9.42)	0.028	21.85 (−53.41 to 97.11)	0.57
FPG (mmol/L)	−0.72 (−1.16 to −0.28)	−0.23 (−0.64 to 0.19)	−0.38 (−0.78 to 0.03)	−0.34 (−0.76 to 0.07)	0.11	0.15 (−0.27 to 0.57)	0.48
OGTT							
30-min PPG (mmol/L)	−1.11 (−1.71 to −0.52)	−0.25 (−0.84 to 0.33)	0.04 (−0.54 to 0.62)	−1.16 (−1.74 to −0.57)	0.0001	−0.30 (−0.89 to 0.30)	0.33
120-min PPG (mmol/L)	−1.55 (−2.52, −0.58)	−0.74 (−1.68 to 0.21)	−0.85 (−1.79 to 0.08)	−0.70 (−1.65 to 0.26)	0.15	0.12 (−0.86 to 1.10)	0.81
HOMA-IR	0.03 (−0.66 to 0.87)	0.55 (−0.22 to 1.48)	0.71 (−0.06 to 1.63)	−0.57 (−1.14 to 0.11)	0.094	−0.13 (−0.78 to 0.64)	0.71
Body composition							
Body weight (kg)	−2.56 (−3.40 to −1.72)	−1.10 (−1.92 to −0.28)	−0.62 (−1.37 to 0.14)	−1.94 (−2.70 to −1.19)	< 0.0001	−0.48 (−1.24 to 0.28)	0.21
BMI (kg/m^2)	−0.95 (−1.26 to −0.65)	−0.41 (−0.71 to −0.11)	−0.25 (−0.52 to 0.03)	−0.71 (−0.98 to −0.44)	< 0.0001	−0.16 (−0.44 to 0.11)	0.25
Waist circumference (cm)	−2.74 (−4.39 to −1.09)	−1.87 (−3.53 to −0.21)	−1.05 (−2.62 to 0.52)	−1.69 (−3.29 to −0.09)	0.038	−0.82 (−2.49 to 0.86)	0.34
Lean body mass (kg)	−1.32 (−2.78 to 0.15)	−0.52 (−1.90 to 0.86)	−1.60 (−3.04 to −0.15)	0.29 (−0.70 to 1.27)	0.57	1.08 (0.05 to 2.10)	0.039
Body fat mass (kg)	−1.34 (−2.42 to −0.27)	−1.14 (−2.28 to 0.001)	0.48 (−0.65 to 1.60)	−1.82 (−2.66 to −0.98)	<0.0001	−1.62 (−2.57 to −0.66)	0.001
Fat-to-lean mass ratio (%)	−1.84 (−4.82 to 1.14)	−2.01 (−5.04 to 1.02)	2.16 (−0.89 to 5.21)	−4.00 (−6.20 to −1.80)	0.0004	−4.17 (−6.66 to −1.68)	0.001
Liver fat (%) (MRI-PDFF)	−3.43 (−4.07 to −2.71)	−2.55 (−3.28 to −1.74)	−1.48 (−2.32 to −0.54)	−2.31 (−3.07 to −1.47)	<0.0001	−1.27 (−2.14 to −0.30)	0.012
Cardiometabolic parameters							
HDL cholesterol (mmol/L)	0.11 (0.07 to 0.16)	0.09 (0.04 to 0.13)	0.07 (0.03 to 0.11)	0.05 (0.003 to 0.09)	0.037	0.02 (−0.03 to 0.06)	0.45
LDL cholesterol (mmol/L)	0.13 (−0.04 to 0.30)	0.17 (0.005 to 0.34)	0.15 (−0.01 to 0.32)	−0.02 (−0.19 to 0.15)	0.80	0.02 (−0.14 to 0.19)	0.78
Triglycerides (mmol/L)	−0.69 (−0.97 to −0.36)	−0.57 (−0.88 to −0.22)	−0.67 (−0.95 to −0.35)	−0.03 (−0.39 to 0.40)	0.89	0.13 (−0.31 to 0.66)	0.59
Systolic BP (mmHg)	−1.04 (−4.89 to 2.82)	−0.84 (−4.57 to 2.88)	2.25 (−1.51 to 6.01)	−3.29 (−7.13 to 0.55)	0.093	−3.10 (−6.92 to 0.72)	0.11
Diastolic BP (mmHg)	−1.87 (−4.26 to 0.52)	−1.74 (−4.09 to 0.60)	0.74 (−1.58 to 3.07)	−2.61 (−4.98 to −0.24)	0.031	−2.48 (−4.89 to −0.07)	0.043

Data are included for 326 participants according to the intention-to-treat principle after multiple imputations and presented as the estimates and corresponding 95% CIs for within-group changes and between-group differences after intervention. *P* values for the difference between intervention and control group (group × time) were analyzed for the diet intervention group and exercise intervention group, respectively. Data were analyzed using a linear mixed model with repeated measures to test intervention effects, adjusting for age at recruitment, sex, and study center.

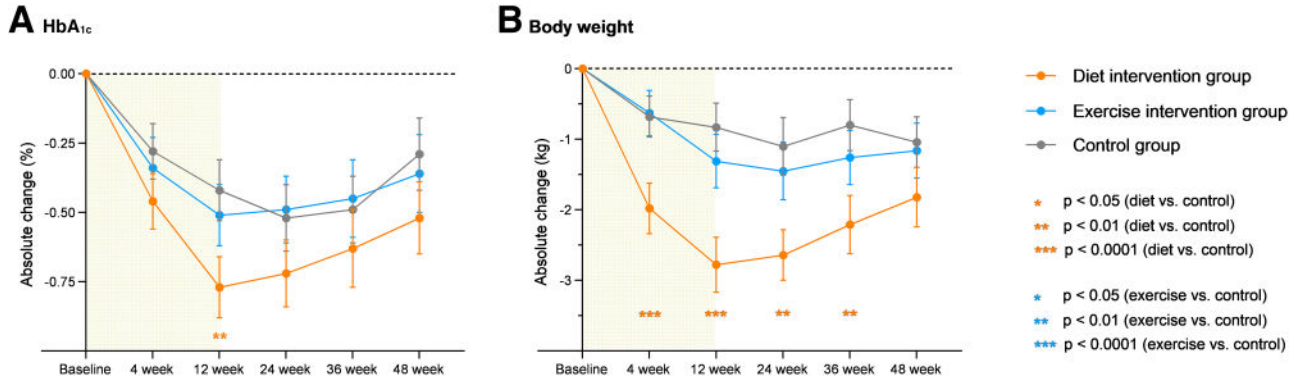

Figure 3—Intention-to-treat analysis for the changes of HbA_{1c} and body weight according to groups during the 12-week intervention and 36-week postintervention follow-up period. Data were included for 326 participants according to the intention-to-treat principle after multiple imputations. *A*: HbA_{1c}. *B*: Body weight. Bars indicated mean ± SE from baseline to each visit for each group. The shaded area represents the intervention period. *P* values for the difference between the intervention and the control group (group × time) were analyzed for the diet intervention group and exercise intervention group, respectively. Data were analyzed using a linear mixed model with repeated measures to test intervention effects, adjusting for age at recruitment, sex, and study center.

combined with RT intervention could induce improvements in body composition and hepatic steatosis for type 2 diabetes. Our low-volume exercise intervention did not induce significant weight loss, which was consistent with the literature, but showed a superior effect of maintaining lean body mass compared with the control intervention (32). Currently, the efficacy of HIIT on body composition remains controversial. HIIT was reported to reduce body fat, visceral fat, or liver fat in several small-scale studies (13,18,33) but not in other studies (34,35). A meta-analysis involving 47 trials concluded that low-volume HIIT is not superior to nonexercise control for improving body composition measures of body fat mass (36). Our study is the first to detect the effect of low-volume HIIT combined with RT on reducing body adiposity and liver fat content, as well as its unique benefits on maintaining lean body mass during fat loss compared with the control intervention.

In essence, while the 5:2 diet and exercise interventions can lead to positive changes in body composition, exercise training alone only resulted in a slight increase in weekly energy expenditure. Conversely, the diet intervention group experienced a greater energy deficit with a more pronounced metabolic benefit (37). In addition, since we observed a higher compliance of the supervised home exercise during the COVID-19 pandemic (93%), it might be deduced that the exercise intervention requiring individuals to travel to a supervised exercise center and possibly creating scheduling conflicts resulted in lower compliance, limiting its effectiveness to some extent. Recently, randomized controlled trials investigating the effect of an intermittent fasting diet, HIIT, or combined intervention on glycemic control and body composition in adults with normal glucose demonstrated that only combined diet and exercise interventions resulted in improved glycemic control or liver fat content, not isolated diet or exercise interventions alone (18,35). A recent four-arm randomized trial in 82 patients with newly diagnosed type 2 diabetes also found that adding an exercise intervention to diet-induced weight loss improves glucose-stimulated β-cell function (38). In our study, we chose not to combine interventions because of concerns about the potential safety issues of simultaneous calorie restriction and exercise training on intervention days based on the 5:2 regimen design. Given the benefits of exercise in maintaining lean body mass detected in our study, future trials are warranted to explore whether aperiodic fasting combined with low-volume HIIT and RT is an effective and safe option for people with diabetes under continuous blood glucose monitoring.

We also found that the diet intervention failed to show significant durability in improving HbA_{1c} compared with routine lifestyle education, despite significant within-group improvements from baseline to the 1-year mark. In contrast, the effect on body weight was significantly maintained after the intervention, suggesting the potential for sustained benefits on body weight from short-term interventions. This pattern aligns with a previous meta-analysis that found that long-term interventions are associated with significant diabetes risk reduction, while short-term interventions are more effective in weight loss because of metabolic adaptation and poor compliance with long-term interventions (39,40).

Our trial does have several limitations. First, our study population only included type 2 diabetes diagnosed within the past 2 years with an HbA_{1c} ranging from 7.0 to 8.9%, limiting the application to patients with a longer duration and poorer glycemic control. Because of safety concerns, our study focused on newly diagnosed type 2 diabetes with relatively preserved β-cell function and did not include patients with insulin treatment or with an $HbA_{1c} \geq 9.0\%$ who would be recommended to consider insulin treatment by several leading guidelines (41). Second, we assessed body composition using bioelectrical impedance analysis, which is less accurate than DEXA. Third, we relied on finger-prick tests to monitor blood glucose levels, potentially underestimating both hyperglycemic and hypoglycemic episodes. Finally, we did not collect information on whether the participants maintained the diet or exercise regimen in the postintervention follow-up period.

In conclusion, our study demonstrates that a short-term 5:2 energy-restricted diet could significantly improve glycemic control, body composition, and several cardiometabolic parameters. Despite no significant benefit on glycemic control, the exercise protocol improved body adiposity and hepatic steatosis and showed superior effects in maintaining lean body mass. These findings challenge the current

paradigm of lifestyle intervention in which frequent behavioral change is required to see improvements in metabolic health. Our study suggests that a medically supervised 5:2 energy-restricted diet could serve as an alternative strategy for improving glycemic control. Further research is warranted to explore the effect of the 5:2 regimen with a combination of diet and exercise.

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