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Complete List of Authors:	Wang, Xi; Hospital of Chengdu Office of People's Government of Tibetan Autonomous Region, Endocrinology department Wang, Suyuan; Hospital of Chengdu Office of People's Government of Tibetan Autonomous Region, Endocrinology department Zhang, Chenghui; Hospital of Chengdu Office of People's Government of Tibetan Autonomous Region, Endocrinology department Lerman, Lilach; Mayo Clinic, Division of Nephrology and Hypertension; Lerman, Amir; Mayo Clinic College of Medicine, Department of Cardiovascular Medicine Lin, Weihua; Hangzhou MetaWell Technology Co., CEO Zhang, Xiaoyong; Hangzhou MetaWell Technology Co., Research and Development Department Zhong, Lingyu; Hospital of Chengdu Office of People's Government of Tibetan Autonomous Region, .Clinical nutrition department Guo, Yanhong; Hospital of Chengdu Office of People's Government of Tibetan Autonomous Region, Endocrinology department Lopez-Jimenez, Francisco; Mayo Clinic, Division of Cardiovascular Diseases Wu, Yunhong; Hospital of Chengdu Office of People's Government of Tibetan Autonomous Region, Endocrinology department
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An Internet-Based Platform with a Low-Calorie Dietary Intervention Involving Prepackaged Food for Weight Loss for Overweight People in China: Rationale and Design

Wang Xi[1] Wang Suyuan[1] Zhang Chenghui[1] Zhong Lingyu[2] Lilach O. Lerman[3] Amir Lerman[4] Lin Welhua[5] Zhang Xiaoyong[5] Guo yanhong[1] Francisco Lopez-Jimenez [4] Wu Yunhong[1i]

1. Endocrinology department, Hospital of Chengdu Office of People's Government of Tibetan Autonomous Region, Chengdu, China

2.Clinical nutrition department, Hospital of Chengdu Office of People's Government of Tibetan Autonomous Region, Chengdu, China

3. Division of Nephrology and Hypertension, Department of Internal Medicine, Mayo Clinic, Rochester, MN, USA

4. Department of Cardiovascular Medicine, Mayo Clinic, Rochester, MN, USA

5. Hangzhou MetaWell Technology Co., Hangzhou, China

Abstract

Introduction: Obesity affects human health and quality of life around the world. A calorie-restricted diet with high-intensity consultation provided through the internet could be an effective way to lose weight.

Method and analysis: This is an open-label, randomized controlled trial. A total of 220 overweight and obese adults aged 18 to 70 meeting the inclusion criteria will be enrolled in the program and assigned to the control group (n=110) or trial group (n=110). The trial group will be enrolled in the MetaWell program, which is a weight loss program using diet replacement products, wireless scales and a mobile phone app. Participants in the control group will receive paper material

[i] Correspondence to:

Dr. Wu Yunhong: wu_yunhong@qq.com

Dr. Francisco Lopez-Jimenez: lopez@mayo.edu

containing a sample diet for weight loss (1200 kcal/day for females and 1500 kcal/day for males). The follow-up period will be 1 year, and measurements will take place at 3 months, 6 months and 12 months. DXA and abdominal CT will be performed to measure the percentage of body fat and the areas of visceral fat and subcutaneous fat, along with a number of cardiometabolic measurements. The primary outcome of this study is the mid- and long-term effectiveness of the MetaWell program, evaluated by the change in the BMI of participants. A mixed-effects model will be used to compare the changes in BMI and body fat between the two groups.

Ethics and dissemination: This study was approved by the ethics committee of Hospital of Chengdu Office of People's Government of Tibetan Autonomous Region and registered on Chinese clinical trial registry (ChiCTR1900021630)

Strengths and limitations of this study:

The first study to evaluate the weight loss from a weight loss program combining a mobile phone app, diet replacement product, wireless scale and high-intensity guidance from professionals.

Using DXA and QCT to accurately evaluate changes in body fat, visceral adipose tissue and subcutaneous adipose tissue of participants.

The follow-up period is not long enough to observe the long-term affect of this weight loss program.

Introduction

Obesity has become a public health problem affecting human health worldwide in recent years. According to the WHO, more than 1.9 billion adults worldwide were overweight in 2016, nearly tripling since 1975 [1]. Obesity is not only associated with a poorer health-related quality of life, including physical impairments such as back pain [2], but is also closely related to an elevated risk of cardiovascular diseases, diabetes, hypertension, and thus elevated mortality. In China, the Chinese Residents Nutrition and Chronic Disease Status Report 2015 revealed that the prevalence of overweight and obesity was 30.15% and 11.9%, respectively [3]. The economic burden caused by overweight and obesity in China in 2010 alone was estimated to be 12.97 billion USD [2].

Dietary intervention is a commonly used strategy to lose weight, and guidelines for the management of overweight and obese adults recommend a calorie-restricted diet. This diet pattern limits daily energy intake to 1200-1500 kcal/day for women and 1500-1800 kcal/day for

men and can provide an energy gap of more than 500 kcal/day [4]. Despite changing diet patterns, an in-person, high-intensity consultation provided by a trained practitioner is also crucial for the effectiveness and safety of a weight loss program. However, in middle-income countries such as China, a high-intensity and face-to-face consultation is not practical. Along with the development of information technology, commercial programs providing individualized feedback through the internet to help patients lose weight have emerged. Evidence has shown that long-distance, internet-based, and high-intensity intervention is also effective [4]. A meta-analysis of internet-delivered interventions providing personalized feedback for obese adults revealed that compared to participants without personized feedback, those receiving internet-delivered personalized feedback lost 2.13 kg more weight [5]. The weight loss effect of various dietary interventions or food replacement programs has been well studied, although they include face-to-face interventions or human contact in the process [6-8]. However, evidence from randomized trials combining Internet-delivery programs enhanced with monitoring body weight using electronic scales is scarce. Furthermore, to our knowledge, there have been no trials testing the effectiveness of an online intervention that includes food replacement and remote weight monitoring.

The MetaWell program (Weijian Technologies Inc., Hangzhou, China) is a commercial weightloss program in China that is integrated with prepackaged food, online guidance and a wireless home scale and has proven to be effective in a previous retrospective study. The results showed that at 120 days after the initiation of the program, 62.7% of participants had lost at least 5% of their initial weight [9]. However, further investigations of the effect of this kind of intervention on body composition, fat distribution, and improvement of metabolic problems, such as abnormal blood pressure and insulin resistance, still need to be investigated.

In this study, we will conduct a randomized controlled trial to determine how this practitioner-guided, mobile internet-based, and low-energy dietary intervention would affect body weight, body composition, and body fat and improve metabolic health in overweight and obese Chinese populations and the safety profile of this program.

This study was approved by the ethics committee of Hospital of Chengdu Office of People's Government of Tibetan Autonomous Region and registered on Chinese clinical trial registry (ChiCTR1900021630)

Methods and analysis

Overview of study design

This program is a single-center, open-label, randomized controlled trial using a modified crossover design. The aim of this study is mainly to explore how effective the MetaWell program will be for weight loss, fat loss and distribution and for changes in cardiometabolic parameters. A total of 220 people aged 18 to 75 years living in Chengdu city, Sichuan Province, China, will be enrolled and randomly assigned 1:1 to the trial group or control group. The follow-up period will be 1 year. The flowchart and schedule of this study is shown in Fig. 1 and Table 1.

Recruitment

Potential participants from the community will be invited to be screened through the use of advertisements, and participants intending to join this program would have a prior consultation through telephone or WeChat. Then, an appointment would be made for the initial screening of eligibility criteria and baseline measurements. The inclusion and exclusion criteria are listed below.

Inclusion criteria: Participant age between 18 and 70 years old and BMI ≥25 kg/m^2, with at least one condition listed below: history of hypertension or either systolic blood pressure>120 or diastolic blood pressure>80 mmHg; abdominal circumference >96 cm (90 cm for women) fasting triglycerides>1.69 mmol/L; history of type 2 diabetes mellitus managed with lifestyle (not on insulin or oral medications) or fasting blood glucose >5.6 mmol/L; HDL cholesterol <1.04 mmol/L (1.3 mmol/L for women).

Exclusion criteria: Participants with one or more conditions listed below are not suitable for participation in this program and will be excluded: history of coronary artery disease diabetes mellitus managed with insulin or any oral hypoglycemic pill for diabetes; glucose intolerance or fasting glucose≥8 mmol/L; congestive heart failure; familial hypercholesterolemia, including familial hypertriglyceridemia, fasting low-density lipoprotein (LDL) cholesterol >160 mg/dL, fasting triglycerides > 600 mg/dL, and current use of lipid-lowering agents; history of hypothyroidism, Cushing's syndrome, eating disorders, gout in the past six months, confirmed episodes of hypoglycemia, pregnancy, advanced liver disease, renal insufficiency, or any other major chronic medical condition; and smokers who plan to quit smoking in the following 12 months. Subjects with hypertension will be included only if they take <3 antihypertensive medications, have not had changes in the dose of their blood pressure medications in the last month, and have systolic blood pressure <160 and diastolic blood pressure <100. People who cannot use smartphones will be excluded.

Sample size

We hypothesize that the absolute difference in weight loss between the trial group and the control group will be at least 5% of their baseline weight, and 100 participants per group will provide 80% power to detect this difference with an alpha error of 0.05. The sample size will be 110 participants per group considering an estimated 10% attrition rate.

Randomization

We will use stratified randomization by blood pressure values or history of hypertension, where 66 participants with either history of hypertension or either a systolic blood pressure above 120 mmHg or a diastolic blood pressure above 80 mmHg will be randomly assigned to the trial group and control group 1:1, while the remaining 154 participants will also be assigned to each group 1:1. This will allow us to have enough people with elevated blood pressure values for a prespecified subgroup analysis and to have the study groups evenly distributed. A list of randomization numbers will be generated using R, and the allocation result will be sealed in an envelope. When participants finish the baseline measurement, the randomization envelope will

be unsealed by the practitioners responsible for participant allocation.

Interventions

Metawell program： The MetaWell program is a remote weight loss program that consists of a free mobile application combined with a wireless home scale, customized nutrition program and weight management coach (Fig. 2). Once enrolled in the program, participants will receive advice from the weight management coach certified by MetaWell and up to three MetaWell biscuits daily along with a selection of healthy recipes (such as seaweed soup, skimmed milk, spiced beef, grains, vegetables, etc.). In the meantime, participants are instructed to measure their weight and urinary ketone on a daily basis, and weight management coach measures, monitors and evaluates their body fat parameters as well as ketone production to adjust the program and meal plan accordingly to make sure the program is effective and safe.

Study design： This study has a modified crossover design, where participants randomized to the intervention group will receive the MetaWell program for the first six months. Then, they will be told only to monitor their weight and follow a healthy diet for the next six months. The participants randomized to the control group will receive general diet education for the first six months (more details provided later in this report), and then they will be enrolled in the MetaWell program for the next six months. This design is considered a modified crossover design because patients randomized to the intervention group for the first 6 months, when crossing to the control phase, will benefit from the experience and knowledge received following the MetaWell program, in addition to the anticipated motivation gained after experiencing significant weight loss during the first 6 months. Thus, the principles applicable to a crossover design may not apply entirely to this study, as it is anticipated there will be a residual effect of the main intervention after crossing over at month 6. The sample diet plan for participants in the control group is listed in Table 2.

Trial group： Following randomization, the participants will be enrolled in the MetaWell program (Weijian Technologies Inc., Hangzhou, China). This program is a mobile internet-based weight loss program combined with a wireless home scale and diet intervention using a prepackaged food product named Yufit biscuit (Weijian Technologies Inc., Hangzhou, China). The program will contain three stages: (1) weight loss stage (0-3 months), (2) continued weight loss transitioning into weight maintenance stage (3-6 months), and (3) weight monitoring stage (6-12 months)

Weight loss stage (0-3 months): Once participants are assigned to the trial group, an app will be downloaded on their mobile phones, and the home scale, urine ketone testing strip and Yufit biscuit will be provided to them. They will be told how to use their scale to monitor the change in their body weight and fat, and then they will be randomly assigned to a certain practitioner. The participants will be required to monitor their body composition and urine ketone levels using a scale and test strip every day, respectively, and their data will be uploaded to their mobile phone and transmitted to their coach. These coaches are trained by the MetaWell group, and most of them have medical backgrounds. Then, guidance on how to make adjustments to their diet will be given through the app. Their coach will make necessary adjustments to participants' daily diet

based on their health condition, such as urine ketone, hypoglycemia and the speed of weight loss. Usually, the daily energy intake will be 800-1200 kcal/day. **Weight maintenance stage (3-6 months):** After 3 months, the Yufit biscuit will no longer be used routinely in the diet. However, participants will still be told to monitor their weight and upload data. When obvious weight regain is detected, the practitioner will initiate a 2-3 day weight loss intervention using the same protocol used in the weight loss stage to maintain the participant's body weight. **Weight monitoring stage (6-12 months):** After 6 months, no further guidance will be provided from the practitioner, but the participants will still be told to keep monitoring their body weight every week and keep their body weight by themselves.

Control group： A printed education material will be given to participants, containing general guidance on a routine diet and a sample diet for weight loss (1500 kcal/day for men and 1200 kcal/day for women). Face-to-face education will take place only once, and then participants will be told to follow this diet to lose weight and to monitor their weight and urine ketone levels once a week. Every participant in this group will be told that they should contact us if their urine ketone becomes positive, and we will review their recent diet and then give them advice on how to adjust their diet.

After 6 months, the participants in the control group will be enrolled in the MetaWell program, including a 3-month stage of weight loss and a 3-month stage of weight maintenance as described in detail in the previous section.

Outcomes

The primary outcome of our study is to test the mid- and long-term effectiveness of the MetaWell program for weight loss in overweight or obese people. The amount of weight loss will be defined as the change in participants' BMI during the whole follow-up period.

There are five secondary outcomes in our study: The proportion of participants achieving a 5% loss of body weight; considering that a decrease in body weight is not equal to a loss of body fat, we will also investigate the change in total body fat; as visceral adipose tissue is closely related to obesity patients' health, we also want to know how our intervention will change the distribution of abdominal visceral adipose tissue and subcutaneous adipose tissue; the improvement of systemic inflammation reflected by high-sensitivity C-reactive protein (hs-CRP) before and after intervention; and the mid- and long-term effectiveness of the MetaWell program to improve systemic blood pressure, abdominal, blood glucose and blood lipids.

The safety outcomes of our study are as follows: changes in serum vitamin levels and changes in liver and renal function.

Assessment and follow-up

To investigate the weight loss effect of our intervention, as well as other secondary aims, a set of assessments will be conducted. Eligible individuals who meet the criteria and consent to participate in the clinical trial will have a baseline assessment, and follow-up assessments will take place at 3, 6, 9 and 12 months after enrollment. The summary of follow-ups is listed in Table 1.

To ensure the quality and reliability of our data, all follow-up measurements will be

performed by a nurse who is specially trained by our team or qualified lab.

Baseline information: All participants will fill out a questionnaire collecting their sociodemographic and medical information, including their age, sex, medical and surgical history in baseline assessments.

Anthropometry: At baseline and during every follow-up assessment, body weight will be measured to assess the weight loss effect or the regain of body weight after our dietary intervention is over. An electronic scale will be used to carry out this measurement. All participants will be told to take off their shoes and greatcoat before weighting. The body height will be recorded to the nearest 0.1 cm and 0.1 kg for recording body weight. To ensure the accuracy of measurement, the scale will be calibrated using a 20 kg standard weight every month. Waist and hip circumference will also be measured during every assessment. This measurement will be carried out by two nurses trained by our program crew. Waist circumference will be measured approximately 3 cm above navel, and hip circumference will be measured on the widest part of their hip. All participants will be told to keep their arms down and relax while measuring. BMI and waist-hip ratio will be calculated.

Blood tests: At every follow-up visit, an approximately 30 mL fasting blood sample will be taken from every participant using vacuum tubes, including procoagulation tubes, for various blood tests listed below:

1) Liver function, renal function blood lipids, and CRP: Elevated alanine aminotransferase (ALT) is the most commonly used biomarker of liver dysfunction. Considering the close relationship between obesity and nonalcoholic fatty liver (NAFLD) and that bariatric surgery can improve NAFLD in obese patients with weight loss [10], we decided to measure the liver function of participants at every follow-up. In addition to NAFLD, hyperuricacidemia, hyperlipidemia and body inflammation are closely linked to overweight and obesity. To investigate whether these symptoms will improve with weight loss, we conducted a test on renal function and blood lipids at every follow-up to observe the changes in ALT, urine acidity and blood lipids during our program.

2) Blood glucose and insulin levels: Obese patients are more vulnerable to glucose intolerance [11]. Although for the safety of our participants, we will not enroll any diabetic patients in our program, we will still assess how well the weight loss program improves insulin resistance for our participants. Therefore, fasting blood glucose and insulin levels will be measured, and HOMA2-IR will be calculated using the HOMA2 calculator [12]. The change in HOMA2-IR will be analyzed.

3) Hemoglobin and vitamin levels: the safety assessment of a weight loss program is crucial, and there are many reports on the side effects of weight loss surgery [13,14]. The most common symptoms are vitamin deficiency and anemia. However, we do not know during dietary intervention whether a lack of nutrition intake will occur and cause similar side effects. Therefore, we will assess the hemoglobin level and vitamin (VA, Vb6, Vb12, 25-(OH)-D) levels during our program.

Questionnaires: To analyze the impact of our weight loss program on general life quality, physical activity and lifestyle, we will administer a set of questionnaires at every follow-up assessment. The SF-36 is a commonly used questionnaire to assess quality of life and has been

validated in the Chinese population [15-17]. To assess changes in physical activity and self-efficiency, the IPAQ [18] and Weight Efficacy Lifestyle (WEL) short form questionnaire [19] will be employed.

Considering that the feeling of hunger may have an important impact on the adherence and feelings of participants, we used a visual analog scale (VAS) scale to investigate the feeling of hunger at different timepoints before and after each meal for every participant.

Dietary assessment: Reports show that many obese individuals enrolled in previous weight loss programs will regain their weight one or two years after intervention. We hypothesize that the reason is because these programs failed to change their dietary pattern. Therefore, we plan to conduct dietary assessments at baseline and 6 months after enrollment to determine whether our program can change the dietary patterns of participants and the relationship between this change and weight regain. We used 24-h dietary recall and short food frequency questionnaires (FFQs) in our study. Twenty-four-hour dietary recall is the standard method for performing diet investigations and is widely used worldwide [20-22], and the FFQ we used is designed to perform nutritional investigations in Chengdu city [23].

Body composition: The main goal of weight loss is to reduce the amount of body fat. Therefore, to investigate the effect of our weight loss program on body fat, DXA will be employed using the GE Lunar Prodigy scanner [24] to assess body composition. The total body fat, leg and upper body fat will be measured, and the percentage of body fat will be calculated.

Visceral adipose tissue is closely related to various symptoms, such as hypertriglyceridemia [25], cardiovascular diseases [26] or metabolic syndrome [27]. Considering the impact of visceral adipose tissue on human health, we will investigate changes in VAS with weight loss. We will use 16-slice spiral CT (TOSHIBA aquilion 16, Japan) to scan and analyze a slice between L2/L3 to evaluate the amount of visceral fat and subcutaneous fat in each participant using QCTPRO software [28]. DXA will be performed at baseline, 6 months and 12 months, while CT will be performed only at baseline and 6 months. We will also measure the skinfold thickness of the triceps, subscapular crest and iliac crest at every follow-up assessment [29].

24-h blood pressure monitoring: Participants will be required to undergo 24-h blood pressure monitoring at baseline and at the 6-month follow-up using a Welch Allyn ABPM 6100/7100 blood pressure monitor. The average blood pressure during the daytime and night will be recorded, as well as the standard deviation of blood pressure.

Adverse events: The expected adverse events included hypoglycemia, menstrual disorder, constipation and dizziness for our weight loss intervention. All participants will be asked if they have experienced these side effects mentioned above during every follow-up. All adverse events will be recorded.

Data management

We collect the paper case report forms and report of each measurement as the original data of participants, then these data will be entered into an electronic data collection system. Every month, the missing data, outliers and other types of wrong entered data will be screened and reported in a monthly meeting of main research group members. We'll check the raw material of any suspectable data and correct the wrong entered data. When the enrollment is finished, a brief report will be given on the data distribution of two groups to check the efficient of randomization.

Statistical analysis

Analysis of primary and secondary outcomes: the intention-to-treat dataset will be used to analyze the primary and secondary outcomes by an independent statistician group. The change in participants' BMI, as the primary outcome, and amount of body fat, abdominal visceral adipose tissue hs-CRP, as the secondary outcome, will be analyzed using a mixed-effects model, the fixed effects will include different intervention groups, and random effects will include such as repeat measurement on the same participant and the individual differences among participants. The proportion of participants losing 10% of their initial weight will be analyzed using cox regression, Kaplan-Meller survival curve and log-rank test. The data in the 6th month will be considered as the main result, so the change of all outcomes measurement between baseline and 6 months follow-up will be analyzed. The different of change of measurement will be tested using t-test or chi-square test.

Adjustment: baseline BMI, gender and age of participants will be adjusted. Both adjusted and un-adjusted analysis will be performed, and the adjusted result will be considered as the main result.

Comparison of baseline characteristics: after the enrollment of participants is finished, a comparison of the baseline characteristics between two random groups will be performed, and the T-test and chi-square test will be used.

Missing values: missing values will be implemented using multiple imputation, both datasets, before and after imputation will be analyzed, and the result of after imputation data will be considered as the main result.

Statistical description and software: the distribution of continuous, normally distributed data will be presented using the mean and standard deviation, and other continuous data will be presented using the median and IQR. All analyses will be performed on R v3.5, and the p value, 95% CI, together with the different effects between two interventions will be reported. A difference with a P value less than 0.05 will be considered statistically significant.

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research

Discussion

This program will be carried out to determine the effect on body weight and composition of

an internet-based, low-carbohydrate dietary intervention, as well as the benefit to general metabolic health. Although this kind of program is widely used in some developed countries, it has emerged in China in recent years, and few related studies can be found. In our plan, the use of DXA and quantitative computed tomography (QCT) can provide much more detailed and accurate data on the change in body fat during the intervention, which can help us achieve a better understanding of the benefits a low-carbohydrate diet can confer to obese patients.

In recent years, many studies have investigated the effect of diverse dietary interventions on weight loss and concluded that patient adherence is the most important factor. A prepackaged diet replacement product can provide a much easier plan to follow. The use of an internet-based platform allows professional practitioners to monitor patient status, have high-intensity contact with patients and modify their weight loss plan in time without requiring patients to go to certain organizations very often. We believe these advantages can improve patient adherence and, hence, improve the outcomes compared to traditional weight loss programs.

The final purpose of losing weight is to reduce the amount of body fat and improve health and quality of life. Considering that the loss of body weight can result from the loss of water, lean mass or body fat, simply monitoring the change in body weight cannot prove that this program can lead to the improvement of body fat and health conditions. Therefore, monitoring the change in fat is essential in our study. Bioimpedance spectrum analysis (BIA) is the most commonly used method to measure the amount and percentage of body fat, but the study shows that compared to BIA, DXA is much more accurate in measuring body fat.

To the best of our knowledge, this is the first study to evaluate the weight loss from a weight loss program combining a mobile phone app, diet replacement product, wireless scale and high-intensity guidance from professionals. Moreover, we used DXA and QCT to accurately evaluate changes in body fat, visceral adipose tissue and subcutaneous adipose tissue. These are highlights of our study. However, this study still has some limitations. First, it is reported that many participants enrolled in previous weight loss programs will regain most of their weight within years. Considering that the follow-up period is 1 year, we cannot fully analyze the regain of weight regain of our participants. Second, the follow-up period of 1 year is also not enough to assess the long-term benefit of this weight loss program, such as the reduction in cardiovascular events, the reduction in diabetes onset, etc. Therefore, we will consider having a prolonged follow-up for 2 to 3 years for those participants who agreed to stay in our program so we can observe the long-term effect of our program.

Ethics and dissemination

This study is conformed to the Declaration of Helsinki and have been approved by the ethics committee of Hospital of Chengdu Office of People's Government of Tibetan Autonomous Region and registered on Chinese clinical trial registry (ChiCTR1900021630). Before sign the consent, all participants will be well informed about the benefit, risk of join this program.

Contributorship statement

WX,WYH,LOL,AL and FLJ designed this study, WX, WYH and ZCH are the medical supervisor of this study, responsible for participants enrolling. WSY is responsible for randomization, data collection and management and drafted of this manuscript. WX, ZCH, WYH and FLJ reviewed and revised this manuscript. LWH and ZXY are the main coordinator of this study.

Competing interests

ZXY and LWH are working for MetaWell company.

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Data sharing statement

We can share the deidentified data. Any researchers in need can contact our corresponding author (Dr. Wu). Research data are allowed to use if the sharing requirements meet the relevant provisions made by Chinese government.

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Table 1 Schedule of study

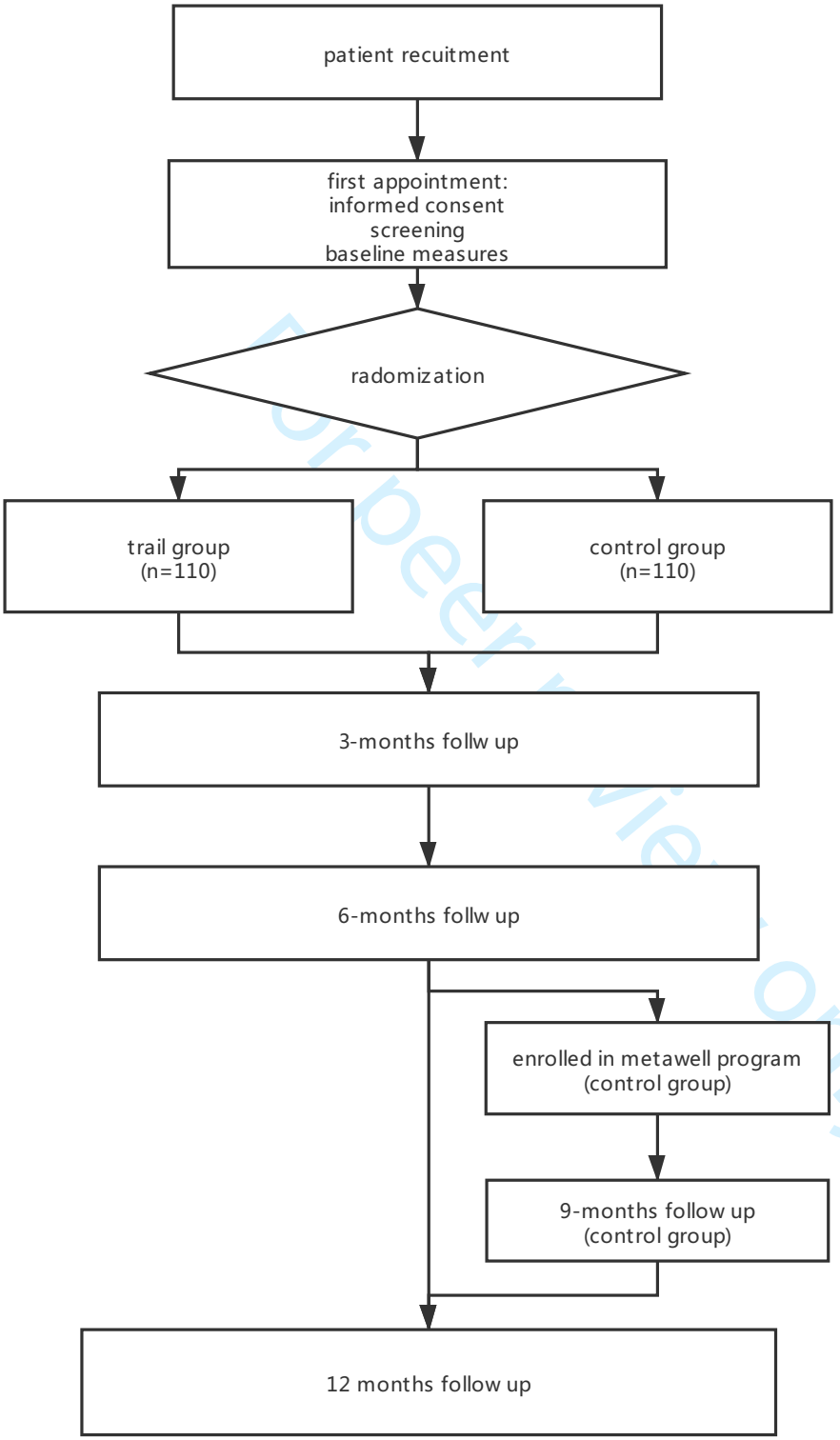
TIME POINT	Baseline	3 months	6 months	9 months	12 months
ENROLMENT:					
Eligibility screen	X				
Informed consent	X				
Allocation	X				
INTERVENTIONS:					
Metawell interventio program: n group	→	→	→		

Traditional diet guide:	control group			→	
	intervention group				
	control group	→			
ASSESSMENTS					
Anthropometry	X	X	X	X	X
Blood tests	X	X	X	X	X
Vitamin level	X		X		X
Questionnaires	X	X	X	X	X
Dietary assessment	X		X		
CT	X		X		
DEXA	X		X		X
24h blood pressure monitor	X		X		

Table 2 Diet sample for participants in the control group

male	female
breakfast	
Egg/meat 60 g	Egg/meat 60 g
Cereal 50 g	Fruit 100 g
Milk 250 mL	Milk 250 mL
lunch	
Egg/meat 50-75 g	Egg/meat 50 g
Cereal 75 g	Cereal 50 g

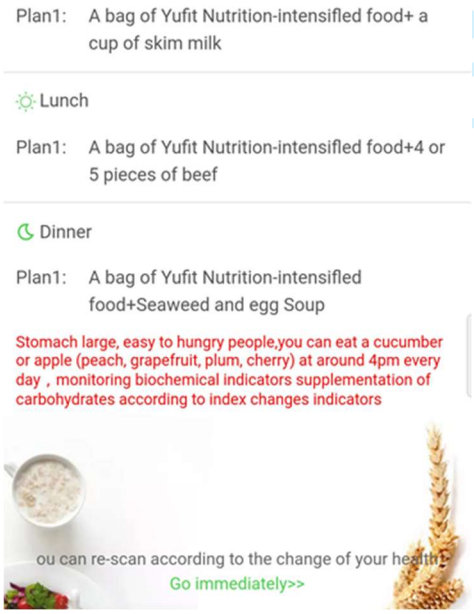
Vegetable 250 g	Vegetable 250 g
dinner	
Egg/meat 50-75 g	Egg/meat 50 g
Cereal 75 g	Cereal 50 g
Vegetable 250 g	Vegetable 250 g
others	
Fruit 200 g/d	Nuts/soybeans 75-100 g/week
Nuts/soybeans 100 g/week	Salt≤6 g/d, oil 15 g
Salt≤6 g/d, oil 25 g	



a.


MetaWell Weight Loss Application
MetaWell HealthyWeight Loss Program
Customized Nutrition Program
Weight Management Coach

b.


16:59
64
Healthy Recipes
Medium Speed
Low Speed
Breakfast
Plan1: A bag of Yufit Nutrition-intensifled food+ a cup of skim milk
Lunch
Plan1: A bag of Yufit Nutrition-intensifled food+4 or 5 pieces of beef
Dinner
Plan1: A bag of Yufit Nutrition-intensifled food+Seaweed and egg Soup
Stomach large, easy to hungry people,you can eat a cucumber or apple (peach, grapefruit, plum, cherry) at around 4pm every day , monitoring biochemical indicators supplementation of carbohydrates according to index changes indicators
ou can re-scan according to the change of your health
Go immediately>>

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	2b	Page 3
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An Internet-Based Platform with a Low-Calorie Dietary Intervention Involving Prepackaged Food for Weight Loss for Overweight and Obese People in China: protocol for a randomized trial

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An Internet-Based Platform with a Low-Calorie Dietary Intervention Involving Prepackaged Food for Weight Loss for Overweight and Obese People in China: protocol for a randomized trial

Wang Xi[1] Wang Suyuan[1] Zhang Chenghui[1] Zhong Linyu[2] Lilach O. Lerman[3] Amir Lerman[4] Guo yanhong[1] Francisco Lopez-Jimenez [4i] Wu Yunhong[1i]

1. Endocrinology department, Hospital of Chengdu Office of People's Government of Tibetan Autonomous Region, Chengdu, China

2. Clinical nutrition department, Hospital of Chengdu Office of People's Government of Tibetan Autonomous Region, Chengdu, China

3. Division of Nephrology and Hypertension, Department of Internal Medicine, Mayo Clinic, Rochester, MN, USA

4. Department of Cardiovascular Medicine, Mayo Clinic, Rochester, MN, USA

Abstract

Introduction: Obesity affects human health and quality of life around the world. A calorie-restricted diet with high-intensity consultation provided through the internet could be an effective way to lose weight. The objective of this study is to test the weight loss effect of a practitioner-guided, mobile internet-based, and low-energy dietary intervention on overweight and obese Chinese populations.

Method and analysis: This is an open-label, randomized controlled trial. A total of 220 overweight and obese adults aged 18 to 70 y meeting the inclusion criteria will be enrolled in the program and assigned to the control group (n=110) or trial group (n=110). The trial group will be enrolled in the MetaWell program, a weight loss program using diet replacement products, wireless scales, and a mobile phone app. Participants in the control group will receive paper material containing a sample diet for weight loss (1200 kcal/day for females and 1500 kcal/day for males). The follow-up period will be one year, and measurements will occur at three months, six months, and 12 months. DXA and abdominal CT will be performed to measure the percentage of body fat and the areas of visceral fat and subcutaneous fat, along with several cardiometabolic

[i] Correspondence to:

Dr. Wu Yunhong: wu_yunhong@163.com

Dr. Francisco Lopez-Jimenez: lopez@mayo.edu

measurements. The primary outcome of this study is the mid-and long-term effectiveness of the MetaWell program, evaluated by the change in the BMI of participants. A mixed-effects model will be used to compare BMI and body fat changes between the two groups.

Ethics and dissemination: The recruitment advertisement will be send through official accounts using Wechat. This study was approved by the ethics committee of the Hospital of Chengdu Office of People's Government of Tibetan Autonomous Region and registered on the Chinese clinical trial registry (ChiCTR1900021630)

Strengths and limitations of this study:

The first study evaluates the weight loss from a weight loss program combining a mobile phone app, diet replacement product, wireless scale, and high-intensity guidance from professionals.

We are using DXA and QCT to accurately evaluate changes in body fat, visceral adipose tissue, and subcutaneous adipose tissue of participants.

The follow-up period is not long enough to observe the long-term effect of this weight loss program.

Introduction

Obesity has become a public health problem affecting human health worldwide in recent years. According to the WHO, more than 1.9 billion adults worldwide were overweight in 2016, nearly tripling since 1975 [1]. Obesity is not only associated with a poorer health-related quality of life, including physical impairments such as back pain [2], but is also closely related to an elevated risk of cardiovascular diseases, diabetes, hypertension, and thus elevated mortality. In China, the Chinese Residents Nutrition and Chronic Disease Status Report 2015 revealed that the prevalence of overweight and obesity was 30.15% and 11.9%, respectively [3]. The economic burden caused by overweight and obesity in China in 2010 alone was estimated to be 12.97 billion USD [2].

Dietary intervention is a commonly used strategy to lose weight, and guidelines for managing overweight and obese adults recommend a calorie-restricted diet. This diet pattern limits daily energy intake to 1200-1500 kcal/day for women and 1500-1800 kcal/day for men and can provide an energy gap of more than 500 kcal/day [4]. Despite changing diet patterns, an in-person, high-intensity consultation provided by a trained practitioner is crucial for a weight loss program[5]. However, in middle-income countries such as China, a high-intensity and face-to-face consultation is not practical. Along with developing information technology, commercial programs providing individualized feedback through the internet to help patients lose weight have emerged. Evidence has shown that long-distance, internet-based, and high-intensity intervention is also effective [4]. A meta-analysis of internet-delivered interventions providing personalized feedback for obese adults revealed that those receiving internet-delivered personalized feedback lost 2.13 kg more weight [6]. The weight loss effect of various dietary interventions or food replacement programs has been well studied, although they include face-to-face interventions or human contact in the

process [6-9]. However, evidence from randomized trials combining Internet-delivery programs enhanced with monitoring body weight using electronic scales is scarce. Furthermore, to our knowledge, there have been no trials testing the effectiveness of an online intervention that includes food replacement and remote weight monitoring.

The MetaWell program (Weijian Technologies Inc., Hangzhou, China) is a commercial weight loss program in China that is integrated with prepackaged food, online guidance, and a wireless home scale and has proven effective in a previous retrospective study. The results showed that at 120 days after the program's initiation, 62.7% of participants had lost at least 5% of their initial weight [10]. However, further investigations of the effect of this kind of intervention on body composition, fat distribution, and improvement of metabolic problems, such as abnormal blood pressure and insulin resistance, still need to be investigated.

This study will conduct a randomized controlled trial to determine how the practitioner-guided, mobile internet-based, and low-energy dietary intervention would affect overweight and obese Chinese populations on body weight, body composition, body fat, and metabolic profiles. And it will demonstrate the safety profile of this program.

This study was approved by the ethics committee of the Hospital of Chengdu Office of People's Government of Tibetan Autonomous Region and registered on the Chinese clinical trial registry (ChiCTR1900021630). We will start the trial on 11th April 2019.

Methods and analysis

Overview of study design

This program is a single-center, open-label, randomized controlled trial. This study explores how effective the MetaWell program will be for weight loss, fat loss, distribution, and cardiometabolic parameters changes. A total of 220 people aged 18 to 75 years living in Chengdu city, Sichuan Province, China, will be enrolled and randomly assigned 1:1 to the trial and control groups. The follow-up period will be one year. The flowchart and schedule of this study is shown in Fig. 1 and Table 1.

Recruitment and informed consent

We will push advertisements of recruiting participant containing our contact information through various Wechat official account. Overweight and obese people who are willing to attend our study will contact us, Then, we will make an appointment. A trained research nurse will inform participants about detailed information about this study. After informed consent is signed, the initial screening of eligibility criteria and baseline measurements will be performed. The inclusion and exclusion criteria are listed below.

Inclusion criteria: Participant's age was between 18 and 70 years old and 25 $\leqslant$BMI $<$40 kg/m^2, with at least one condition listed below: history of hypertension or either systolic blood pressure>120 or diastolic blood pressure>80 mmHg; abdominal circumference >96 cm (90 cm for women) fasting triglycerides>1.69 mmol/L; history of type 2 diabetes mellitus managed with lifestyle (not on insulin or oral medications) or fasting blood glucose >5.6 mmol/L; HDL cholesterol

<1.04 mmol/L (1.3 mmol/L for women).

Exclusion criteria: Participants with one or more conditions listed below are not suitable for participation in this program and will be excluded: history of coronary artery disease diabetes mellitus managed with insulin or any oral hypoglycemic pill for diabetes; glucose intolerance or fasting glucose≥ 8 mmol/L; congestive heart failure; familial hypercholesterolemia, including familial hypertriglyceridemia, fasting low-density lipoprotein (LDL) cholesterol >4.2 mmol/L; fasting triglycerides > 6.8 mmol/L, and current use of lipid-lowering agents; history of hypothyroidism, Cushing's syndrome, eating disorders, gout in the past six months, confirmed episodes of hypoglycemia, pregnancy, advanced liver disease, renal insufficiency, or any other major chronic medical condition; and smokers who plan to quit smoking in the following 12 months. Subjects with hypertension will be included only if they take <3 antihypertensive medications, have not had changes in the dose of their blood pressure medications in the last month, and have systolic blood pressure <160 mmHg and diastolic blood pressure <100 mmHg. People who cannot use smartphones will be excluded.

Sample size

According to DROPLET study[7], we hypothesize that the absolute difference in weight loss between the trial group and the control group will be at least 4 kg of weight, the standard deviation was 9 kg. So 100 participants per group will provide more than 90% power to detect this difference with an alpha error of 0.05. The sample size will be 110 participants per group considering an estimated 10% attrition rate.

Randomization

All participants will be randomly assigned to the trial group and control group 1:1. A list of randomization numbers will be generated using R, and the allocation result will be sealed in an opaque envelope. When participants finish the baseline measurement, the randomization envelope will be unsealed by the practitioners responsible for participant allocation.

Interventions

Metawell program： The MetaWell program is a remote weight loss program that consists of a free mobile application combined with a wireless home scale, customized nutrition program, and weight management coach (Fig. 2). Once enrolled in the program, participants will receive advice from the weight management coach certified by MetaWell and up to three MetaWell biscuits daily, along with a selection of healthy recipes (such as seaweed soup, skimmed milk, spiced beef, grains, vegetables, etc.). The nutritional information of biscuits is listed in table 2. In the meantime, participants are instructed to measure their weight and urinary ketone daily, and weight management coach measures, monitors, and evaluates their body fat parameters and ketone production to adjust the program and meal plan accordingly to make sure the program is effective and safe.

Study design： This study is two-arms parallel design with an extended follow-up period.

Participants will be randomly assigned into intervention or control group. They will receive Metawell program or general diet education. The intervention and follow up period will be six months. Then for ethical purpose, the participants in control group will also receive Metawell program, and an extended follow up will take place in the 9th (only for participants in control group) and 12th month after enrollment.

Trial group： After randomization, the participants will be enrolled in the MetaWell program (Weijian Technologies Inc., Hangzhou, China). This program will contain three stages: (1) weight loss stage (0-3 months), (2) continued weight loss transitioning into weight maintenance stage (3-6 months), and (3) extended follow up stage (6-12 months)

Weight loss stage (0-3 months): Once participants are assigned to the trial group, an app will be downloaded on their mobile phones, and the home scale, urine ketone testing strip and Yufit biscuit will be provided to them. They will be told how to use their scale to monitor the change in their body weight and fat, and then they will be randomly assigned to a particular practitioner. The participants will be required to monitor their body composition and urine ketone levels using a scale and test strip every day, respectively. Their data will be uploaded to their mobile phone and transmitted to their coach. The MetaWell group trains these coaches, and all of them have medical backgrounds. Then, coaches will give them guidance on how to adjust their diet through the app. Their coaches will also make necessary adjustments to participants' daily diet based on their health condition, such as urine ketone, hypoglycemia, and the speed of weight loss. Usually, the daily energy intake will be 800-1200 kcal/day. **Weight maintenance stage (3-6 months):** After 3 months, the Yufit biscuits will no longer be used routinely in the diet. However, participants will still be told to monitor their weight and upload data. When noticeable weight regain is detected, the practitioner will initiate a 2–3-day weight loss intervention using the same protocol used in the weight-loss stage to maintain the participant's body weight. **Extended follow up stage (6-12 months):** After 6 months, coaches will not provide advice, but will ask participants to monitor their body weight every week and maintain their body weight by themselves.

Control group： A printed education material will be given to participants, containing general guidance on a routine diet and a sample diet for weight loss (1500 kcal/day for men and 1200 kcal/day for women),the detail of this sample diet is listed in table 3. Face-to-face education will occur only once, and then participants will be told to follow this diet to lose weight and monitor their weight and urine ketone levels once a week. Every participant in this group will be told that they should contact us if their urine ketone becomes positive, and we will review their recent diet and then advise on how to adjust their diet.

After 6 months, the participants in the control group will be enrolled in the MetaWell program, including a 3-month stage of weight loss and a 3-month stage of weight maintenance as described in detail in the previous section.

Outcomes

The primary outcome of our study is to test the effectiveness of the MetaWell program for weight loss in overweight or obese people. The amount of weight loss will be defined as the change in participants' BMI by the sixth month

There are four secondary outcomes in our study: 1) The proportion of participants achieving a 5% loss of body weight; 2) considering that a decrease in body weight is not equal to a loss of body fat, we will also investigate the change in total body fat; as visceral adipose tissue is closely related to obesity patients' health, we also want to know how our intervention will change the distribution of abdominal visceral adipose tissue and subcutaneous adipose tissue; 3) the improvement of systemic inflammation reflected by high-sensitivity C-reactive protein (hs-CRP) before and after the intervention; 4) the mid-and long-term effectiveness of the MetaWell program to improve systemic blood pressure, abdominal, blood glucose and blood lipids.

The exploratory outcomes of our study is the weight loss effect of MetaWell program in 1 year for participants in intervention group.

The safety outcomes of our study are as follows: changes in serum vitamin levels and changes in liver and renal function.

Assessment and follow-up

Eligible individuals who meet the criteria and consent to participate in the clinical trial will have a baseline assessment, and follow-up assessments will occur at 3, 6, 9, and 12 months after enrollment. The summary of follow-ups is listed in Table 1. The interventions of each group will be masked in the data given to the assessor to avoid bias.

To ensure the data's quality and reliability, all follow-up measurements will be performed by a nurse who is specially trained by our team or qualified lab.

Baseline information: All participants will fill out a questionnaire collecting their sociodemographic and medical information, including their age, sex, medical and surgical history in baseline assessments.

Anthropometry: At baseline and during every follow-up assessment, bodyweight will be measured to assess the weight change. An ultrasonic height-weight scale (DHM-200, Dinghengkeji, Hennan China) will be used to carry out this measurement. All participants will be asked to take off their shoes and greatcoat before weighting. The body height will be recorded to the nearest 0.1 cm and 0.1 kg for recording body weight. To ensure the accuracy of measurement, the scale will be calibrated using a 20 kg standard weight every month. Waist and hip circumference will also be measured during every assessment. This measurement will be carried out by two nurses trained by our program crew. Waist circumference will be measured approximately 3 cm above the navel, and hip circumference will be measured on the widest part of their hip. All participants will be told to keep their arms down and relax while measuring. BMI and waist-hip ratio will be calculated.

Blood tests: At every follow-up visit, an approximately 30 mL fasting blood sample will be taken from every participant using vacuum tubes, including procoagulation tubes, for various blood tests listed below:

1) Liver function, renal function, blood lipids, and CRP: Elevated alanine aminotransferase (ALT) is the most used biomarker of liver dysfunction. Considering the close relationship between obesity and nonalcoholic fatty liver (NAFLD) and that bariatric surgery can improve NAFLD in obese

patients with weight loss [11], we decided to measure the liver function of participants at every follow-up. In addition to NAFLD, hyperuricacidemia, hyperlipidemia, and body inflammation are closely linked to overweight and obesity. To investigate whether these symptoms will improve with weight loss, we conducted a test on renal function and blood lipids at every follow-up to observe the changes in ALT, urine acidity, and blood lipids during our program.

2) Blood glucose and insulin levels: Obese patients are more vulnerable to glucose intolerance [12]. Although we will not enroll any diabetic patients in our program, we will still assess how well the weight loss program improves insulin resistance for our participants. Therefore, fasting blood glucose and insulin levels will be measured, and HOMA2-IR will be calculated using the HOMA2 calculator [13]. The change in HOMA2-IR will be analyzed.

3) Hemoglobin and vitamin levels: the safety assessment of a weight loss program is crucial, and there are many reports on the side effects of weight loss surgery [14,15]. The most common symptoms are vitamin deficiency and anemia. However, we do not know whether a lack of nutrition intake will occur during the dietary intervention and cause similar side effects. Therefore, we will assess the hemoglobin level and vitamin (VA, Vb6, Vb12, 25-(OH)-D) levels during our program.

Questionnaires: To analyze the impact of our weight loss program on general life quality, physical activity, and lifestyle, we will administer a set of questionnaires at every follow-up assessment. The SF-36 is a commonly used questionnaire to assess the quality of life and has been validated in the Chinese population [16-18]. T For assessing changes in physical activity and self-efficiency, the IPAQ [19] and Weight Efficacy Lifestyle (WEL) short form questionnaire will be employed[20].

Considering that the feeling of hunger may have an important impact on the adherence and feelings of participants, we used a visual analog scale (VAS) scale to investigate the feeling of hunger at different timepoints before and after each meal for every participant.

Dietary assessment: Reports show that many obese individuals enrolled in previous weight loss programs will regain their weight one or two years after intervention. We hypothesize that the reason is that these programs failed to change their dietary pattern. Therefore, we plan to conduct dietary assessments at baseline and 6 months after enrollment to determine whether our program can change the dietary patterns of participants and the relationship between this change and weight regain. We used 24-h dietary recall and short food frequency questionnaires (FFQs) in our study. Twenty-four-hour dietary recall is the standard method for performing diet investigations and is widely used worldwide [21-23]. The FFQ we used is designed to conduct nutritional investigations in Chengdu city [24].

Body composition: The main goal of weight loss is to reduce the amount of body fat. Therefore, to investigate the effect of our weight loss program on body fat, DXA will be employed using the GE Lunar Prodigy scanner [25] to assess body composition. The total body fat, leg and upper body fat will be measured, and the percentage of body fat will be calculated.

Visceral adipose tissue is closely related to various symptoms, such as hypertriglyceridemia [26], cardiovascular diseases [27] or metabolic syndrome [28]. Considering the impact of visceral adipose tissue on human health, we will investigate changes in VAT with weight loss. We will use

16-slice spiral CT (TOSHIBA aquilion 16, Japan) to scan and analyze a slice between L2/L3 to evaluate the amount of visceral fat and subcutaneous fat in each participant using QCTPRO software [29]. DXA will be performed at baseline, 6 months, and 12 months, while CT will be performed only at baseline and 6 months. We will also measure the skinfold thickness of the triceps, subscapular crest, and iliac crest at every follow-up assessment [30].

24-h blood pressure monitoring: Participants will be required to undergo 24-h blood pressure monitoring at baseline and the 6-month follow-up using a Welch Allyn ABPM 6100/7100 blood pressure monitor. The average blood pressure during the daytime and night will be recorded, as well as the standard deviation of blood pressure.

Adverse events: The expected adverse events included hypoglycemia, menstrual disorder, constipation, and dizziness for our weight loss intervention. All participants will be asked if they have experienced these side effects mentioned above during every follow-up. All adverse events will be recorded.

Data management

We collect the paper case report forms and report of each measurement as the original data of participants. Then we will enter these data into an electronic data collection system. Every month, the missing data, outliers, and other types of wrong entered data will be screened and reported in a monthly meeting of main research group members. We'll check the raw material of any suspectable data and correct the incorrectly entered data. When the enrollment is finished, a brief report will be given on the data distribution of two groups to check the efficiency of randomization.

Statistical analysis

Analysis of primary and secondary outcomes: the intention-to-treat dataset will be used to analyze the primary and secondary outcomes by an independent statistician group. The change in participants' BMI, as the primary outcome, and amount of body fat, abdominal visceral adipose tissue hs-CRP, as the secondary outcome, will be analyzed using a mixed-effects model, the fixed effects will include different intervention groups, and random effects will include such as repeat measurement on the same participant and the individual differences among participants. The proportion of participants losing 10% of their initial weight will be analyzed using cox regression, Kaplan-Meller survival curve and log-rank test. The data in the 6^{th} month will be considered as the main result, so the change of all outcomes measurement between baseline and 6 months follow-up will be analyzed. The difference of change will be tested using t-test or chi-square test.

Adjustment: baseline BMI, gender age and IPAQ score of participants will be adjusted. Both adjusted and un-adjusted analysis will be performed, and the adjusted result will be considered as the main result.

Comparison of baseline characteristics: after the enrollment of participants is finished, a comparison of the baseline characteristics between two random groups will be performed, and the T-test and chi-square test will be used.

Sensitivity analysis: the difference in change of body weight for participants in control group

using different method will be analyzed using t-test to confirm the effect of Metawell program.

Missing values: missing values will be implemented using multiple imputation, both datasets, before and after imputation will be analyzed, and the result of after imputation data will be considered as the main result.

Statistical description and software: the distribution of continuous, normally distributed data will be presented using the mean and standard deviation, and other continuous data will be presented using the median and IQR. All analyses will be performed on R v3.5, and the p value, 95% CI, together with the different effects between two interventions will be reported. A difference with a P value less than 0.05 will be considered statistically significant.

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Discussion

This internet-based, low-carbohydrate dietary intervention program will be carried out to determine the effect on body weight and composition and the benefit to general metabolic health. Although this kind of program is widely used in some developed countries, it has emerged in China in recent years, and we can find few related studies. In our plan, DXA and quantitative computed tomography (QCT) can provide much more detailed and accurate data on the change in body fat during the intervention, which can help us achieve a better understanding of the benefits a low-carbohydrate diet can confer to obese patients.

In recent years, many studies have investigated the effect of diverse dietary interventions on weight loss and concluded that patient adherence is the most crucial factor. A pre-packaged diet replacement product can provide a much easier plan to follow. The use of an internet-based platform allows professional practitioners to monitor patient status, have high-intensity contact with patients, and modify their weight loss plan in time without requiring patients to go to specific organizations very often. We believe these advantages can improve patient adherence and improve outcomes compared to traditional weight loss programs.

The final purpose of losing weight is to reduce body fat and improve health and quality of life. Considering that the loss of body weight can result from the loss of water, lean mass, or body fat, simply monitoring the change in body weight cannot prove that this program can improve body fat and health conditions. Therefore, tracking the change in fat is essential in our study. Bioimpedance spectrum analysis (BIA) is the most used method to measure the amount and percentage of body fat. Still, the study shows that DXA is much more accurate in measuring body fat compared to BIA.

To the best of our knowledge, this is the first study to evaluate the weight loss from a weight loss program combining a mobile phone app, diet replacement product, wireless scale, and high-intensity guidance from professionals. Moreover, we used DXA and QCT to accurately evaluate changes in body fat, visceral adipose tissue, and subcutaneous adipose tissue. These are highlights

of our study. However, this study still has some limitations. First, it is reported that many participants enrolled in previous weight loss programs will regain most of their weight within years. The follow-up period will be one year, and we cannot thoroughly analyze the regain of weight regain of our participants. Second, the follow-up period of 1 year is also not enough to assess the long-term benefit of this weight loss program, such as reducing cardiovascular events, reducing diabetes onset, etc. Therefore, we will consider having a prolonged follow-up for 2 to 3 years for those participants who agreed to stay in our program so we can observe the long-term effect of our program.

Ethics and dissemination

This study is conformed to the Declaration of Helsinki and have been approved by the ethics committee of Hospital of Chengdu Office of People's Government of Tibetan Autonomous Region and registered on Chinese clinical trial registry (ChiCTR1900021630). Before sign the consent, all participants will be well informed about the benefit, risk of join this program.

Contributorship statement

WX, WYH, LOL, AL, and FLJ designed this study. WX, WYH, GYH and ZCH are the medical supervisor of this study, responsible for participants enrolling. WSY is responsible for the randomization, data collection, management, and drafting of this manuscript. WX, ZCH, WYH, ZLY and FLJ reviewed and revised this manuscript.

Competing interests and funding

This study is fully funded by Weijian Technologies Inc.

Data sharing statement

We can share the deidentified data. Any researchers in need can contact our corresponding author (Dr. Wu). Research data are allowed to use if the sharing requirements meet the relevant provisions made by Chinese government .

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Table 2 Nutritional information of Yufit biscuit

Ingredients:	**Nutrition Facts**		
Wheat Flour, Soybean Protein Flour, Soybean Oil, Eggs, Powdered Sugar, Lentinula Edodes, Black Fungus, Hericium Erinaceus, Grifola Frondosa, Bamboo Fungus, Seaweed,	Items	Per 100g	NRV%
	Energy	1792kJ	21%
	Protein	10.2g	17%
	Fat	16.1g	27%
	-Trans Fat	0g	

Cassia, Kumb, Emblica, Bran, Starch, Salt, Retinyl Acetate (Vitamin A), Thiamine Hydrochloride (Vitamin B1), Riboflavin (Vitamin B2), Pyridoxine Hydrochloride (Vitamin B6), Niacin, Folic Acid, Ferrous Sulfate, Calcium Carbonate, Zinc Gluconate, Sodium Selenite.	Carbohydrate	53.4g	18%
	Dietary Fiber	14.4g	58%
	Sodium	315mg	16%
	Vitamin A	13mgRE	2%
	Vitamin B1	0.46mg	33%
	Vitamin B2	0.88mg	63%
	Vitamin B6	0.43mg	31%
	Folic Acid	105mgDFE	26%
	Calcium	300mg	38%
	Iron	4.6mg	31%
	Zinc	1.61mg	11%

Table 1 Schedule of study

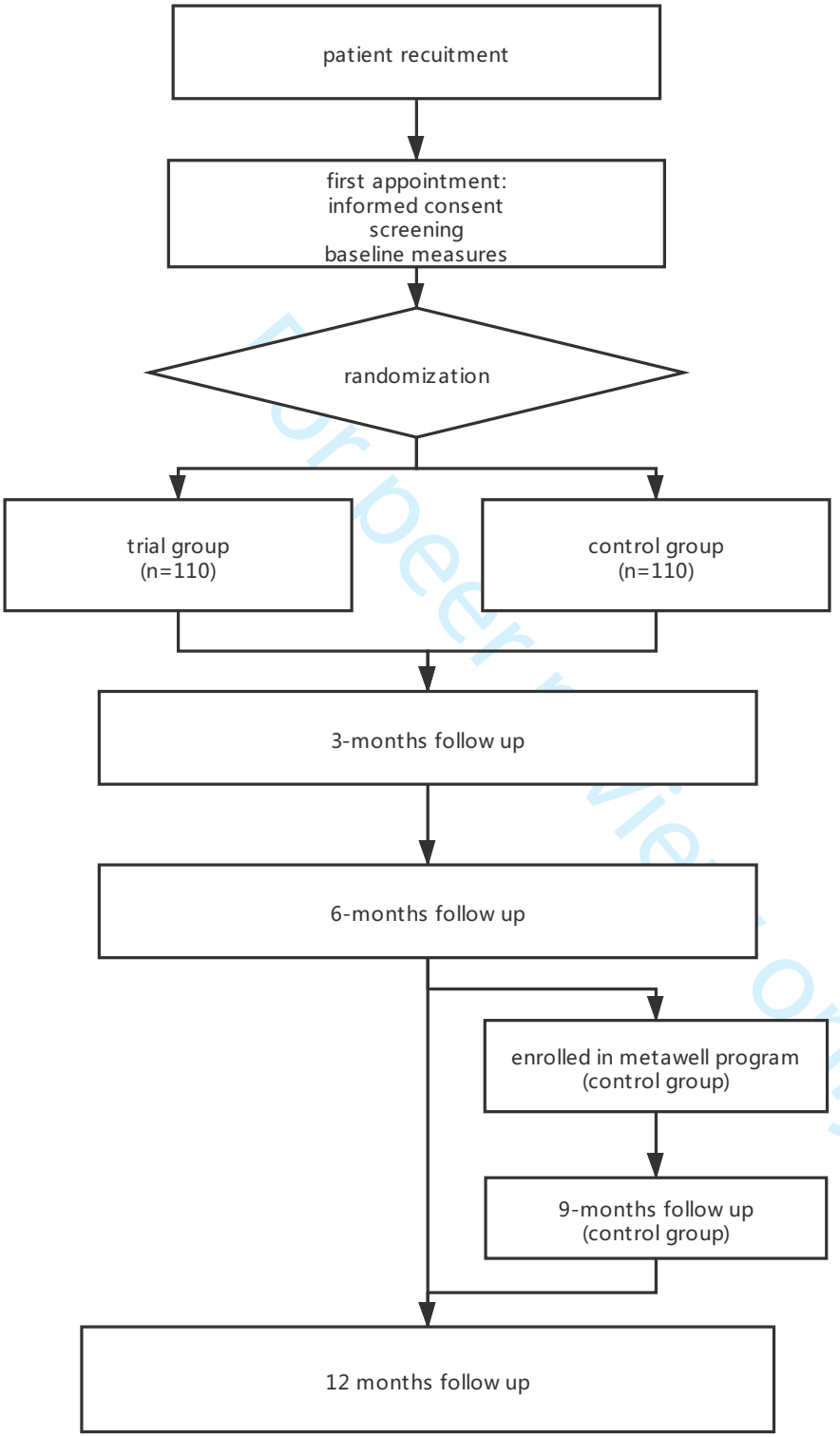
TIME POINT	Baseline	3 months	6 months	9 months	12 months
ENROLMENT:					
Eligibility screen	X				
Informed consent	X				
Allocation	X				
INTERVENTIONS:					
Metawell interventio program: n group	→	→	→		

Traditional diet guide: control group					
	→	→	→	→	→
Traditional diet guide: intervention group					
Traditional diet guide: control group					
	→	→	→		
ASSESSMENTS					
Anthropometry	X	X	X	X	X
Blood tests	X	X	X	X	X
Vitamin level	X		X		X
Questionnaires	X	X	X	X	X
Dietary assessment	X		X		
CT	X		X		
DEXA	X		X		X
24h blood pressure monitor	X		X		

Table 3 Diet sample for participants in the control group

male	female
breakfast	
Egg/meat 60 g	Egg/meat 60 g
Cereal 50 g	Fruit 100 g
Milk 250 mL	Milk 250 mL
lunch	
Egg/meat 50-75 g	Egg/meat 50 g
Cereal 75 g	Cereal 50 g

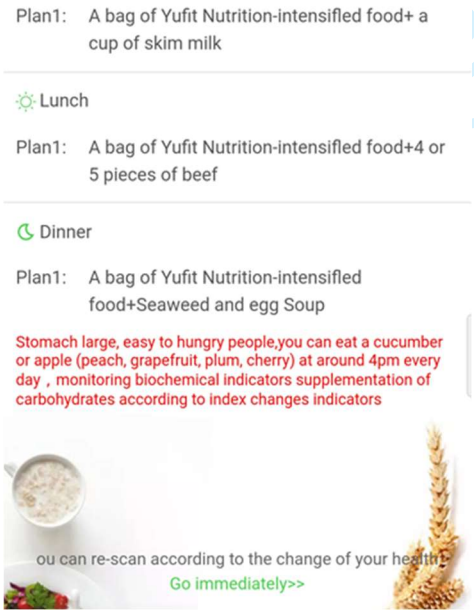
Vegetable 250 g	Vegetable 250 g
dinner	
Egg/meat 50-75 g	Egg/meat 50 g
Cereal 75 g	Cereal 50 g
Vegetable 250 g	Vegetable 250 g
others	
Fruit 200 g/d	Nuts/soybeans 75-100 g/week
Nuts/soybeans 100 g/week	Salt≤6 g/d, oil 15 g
Salt≤6 g/d, oil 25 g	



a.


MetaWell Weight Loss Application
MetaWell HealthyWeight Loss Program
Customized Nutrition Program
Weight Management Coach

b.


16:59
64
Healthy Recipes
Medium Speed
Low Speed
Breakfast
Plan1: A bag of Yufit Nutrition-intensifled food+ a cup of skim milk
Lunch
Plan1: A bag of Yufit Nutrition-intensifled food+4 or 5 pieces of beef
Dinner
Plan1: A bag of Yufit Nutrition-intensifled food+Seaweed and egg Soup
Stomach large, easy to hungry people,you can eat a cucumber or apple (peach, grapefruit, plum, cherry) at around 4pm every day , monitoring biochemical indicators supplementation of carbohydrates according to index changes indicators
ou can re-scan according to the change of your health
Go immediately>>

Section/item	ItemNo	Description	Related content in manuscript
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 2
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 3
	2b	All items from the World Health Organization Trial Registration Data Set	Page 3
Protocol version	3	Date and version identifier	NA
Funding	4	Sources and types of financial, material, and other support	Page 9
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Page 11
	5b	Name and contact information for the trial sponsor	Page 18

	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	NA
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Page 2
	6b	Explanation for choice of comparators	Page 2
Objectives	7	Specific objectives or hypotheses	Page 2

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Page 3
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Page 3
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Page 3
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page 4-5
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Page 4-5

	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Page 4-5
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Page 6
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Page 15(Table 2)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Page 4

Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Page 4

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Page 4
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Page 4
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Page 4

Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Page 6-8
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	NA

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Page 9
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Page 8
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Page 8
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Page 8
Methods: Monitoring			

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	NA
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Page 8
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page 3
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	NA
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Pate 3
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	NA
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 10

Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	NA
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	NA
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NA

Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

BMJ Open

An Internet-Based Platform for a Low-Calorie Dietary Intervention Involving Prepackaged Food for Weight Loss in Overweight and Obese Individuals in China: Protocol for a Randomized Controlled Trial

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Keywords:	Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Clinical trials < THERAPEUTICS, NUTRITION & DIETETICS

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An Internet-Based Platform for a Low-Calorie Dietary Intervention Involving Prepackaged Food for Weight Loss in Overweight and Obese Individuals in China: Protocol for a Randomized Controlled Trial

Wang Xi[1], Wang Suyuan[1], Zhang Chenghui[1], Zhong Linyu[2], Lilach O. Lerman[3], Amir Lerman[4], Guo Yanhong[1], Francisco Lopez-Jimenez[4*], Wu Yunhong[1*]

[1] Endocrinology Department, Hospital of Chengdu Office of People's Government of Tibetan Autonomous Region, Chengdu, China

[2] Clinical Nutrition Department, Hospital of Chengdu Office of People's Government of Tibetan Autonomous Region, Chengdu, China

[3] Division of Nephrology and Hypertension, Department of Internal Medicine, Mayo Clinic, Rochester, MN, USA

[4] Department of Cardiovascular Medicine, Mayo Clinic, Rochester, MN, USA

* Correspondence to: No.20 Ximianqiao Cross Street, Sichuan, China
Dr. Wu Yunhong: wu_yunhong@163.com

Dr. Francisco Lopez-Jimenez: lopez@mayo.edu

Word count: 3814

ABSTRACT

Introduction: Obesity is a global health issue that impacts quality of life. A calorie-restricted diet with high-intensity consultation provided via the Internet may be an effective way to lose weight. The objective of this study was to assess the effectiveness of a practitioner-guided, mobile internet-based low-energy dietary intervention in overweight and obese populations in China.

Methods and analysis: This open-label randomised controlled trial enrolled 220 overweight and obese adults aged 18 to 70 years who met the inclusion criteria. Participants were assigned to the control group (n=110) or trial group (n=110). The trial group will be enrolled in the MetaWell program, a weight loss program using diet replacement products, wireless scales, and a mobile phone app. Participants in the control group will receive paper material containing a sample diet for weight loss. The follow-up period will be 1 year, and measurements will occur at 3, 6, and 12 months. Dual-emission X-ray absorptiometry (DXA) and abdominal quantitative computed tomography (QCT) will be performed to estimate the percentage of overall body fat and areas of visceral and subcutaneous fat, alongside several cardiometabolic measurements. The primary outcome of this study is the change in BMI at 6 months after enrolment. A mixed-effects model will be used to compare BMI and body fat changes between the two groups.

Ethics and dissemination: This study was approved by the ethics committee of the Hospital of Chengdu Office of the People's Government of the Tibetan Autonomous Region. Advertisements for recruitment will be sent via official accounts using WeChat. The results will be disseminated via publications in academic journals and our clinic. Our study group will maintain contact with the participants to inform them of the study findings.

Trial registration: This study was registered in the Chinese Clinical Trial Registry (ChiCTR1900021630) by March 02, 2019

Article summary

Strengths and limitations of the study

- To the best of our knowledge, this is the first study to evaluate the effectiveness of a program combining a mobile phone app, diet replacement product, wireless scale, and high-intensity guidance from professionals for weight loss in overweight and obese individuals
- For more precise results, this study will use DXA to evaluate body fat, unlike most studies that use bioimpedance spectrum analysis to evaluate the amount of body fat, which may underestimate the body fat of participants.
- Since the effects of subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) on health are different, we will use QCT to evaluate the changes in SAT and VAT during the intervention period.
- The follow-up period may be insufficient to observe the long-term effects of this weight loss program.

INTRODUCTION

Obesity has become a global public health issue in recent years. According to the WHO, more than 1.9 billion adults worldwide were overweight in 2016, a number which has nearly tripled since 1975.[1] Obesity is associated with a poorer health-related quality of life, including physical impairments such as back pain,[2] as well as an elevated risk of cardiovascular diseases, diabetes, hypertension, and elevated mortality. In China, the Chinese Residents Nutrition and Chronic Disease Status Report 2015 revealed that the prevalence of overweight and obesity was 30.15% and 11.9%, respectively.[3] The economic burden caused by overweight and obesity in China in 2010 alone was estimated to be 12.97 billion USD.[2]

Dietary interventions are a commonly used strategy for weight loss. Guidelines for managing overweight and obese adults recommend a calorie-restricted diet that limits daily energy intake to 1200-1500 kcal/day for women and 1500-1800 kcal/day for men, thereby providing an energy deficit exceeding 500 kcal/day.[4] Despite modification of dietary patterns, in-person high-intensity consultations provided by a trained practitioner can significantly promote the effectiveness of a weight loss program.[5] However, in middle-income countries such as China, high-intensity face-to-face consultations are impractical. With the development of information technology, commercial programs that provide individualised feedback via the Internet to help patients lose weight have emerged. Evidence suggests that long-distance, internet-based high-intensity interventions are effective.[4] A meta-analysis of Internet-delivered interventions providing personalised feedback for obese adults revealed that those receiving Internet-delivered personalised feedback lost 2.13 kg more weight.[6] The effectiveness of various dietary interventions and food replacement programs for weight loss are well-documented, although they involve face-to-face interventions or human contact.[6-9] However, evidence from randomised trials combining Internet-delivered programs enhanced by monitoring of body weight using electronic scales is scarce. Furthermore, to the best of our knowledge, no trials to date have assessed the effectiveness of an online intervention that includes food replacement and remote weight monitoring.

The MetaWell program (Weijian Technologies Inc., Hangzhou, China) is a commercial weight loss program in China that integrates prepackaged food, online guidance, and a wireless home scale and has been proven to be effective in a previous retrospective study. The results demonstrated that at 120 days after program initiation, 62.7% of participants had lost at least 5% of their initial weight.[10] However, further investigations of the effects of this type of intervention on body composition, fat distribution, and improvements in metabolic issues, such as abnormal blood pressure and insulin resistance, warrant further investigation.

We will conduct a randomised controlled trial to determine the effects of a practitioner-guided, mobile internet-based low-energy dietary intervention on body weight, body composition, body fat, and metabolic profiles in overweight and obese Chinese populations. Further, we aim to evaluate the safety profile of the program. This trial was commenced on 11 April 2019.

METHODS AND ANALYSIS

Overview of study design

This trial is a single-centre, open-label, randomised controlled trial that aims to explore the effects of the MetaWell program on weight loss, fat loss distribution, and cardiometabolic parameters. A total of 220 individuals aged 18 to 75 years living in Chengdu city, Sichuan Province, China, will be enrolled and randomly assigned at a 1:1 ratio to the intervention and control groups. This study uses a two-arm parallel design with an extended follow-up period of 1 year. The flowchart and schedule of this study are presented in Fig. 1 and Table 1. Participants will receive a Metawell program or general diet education. The intervention and follow-up periods will be 6 months. For ethical purposes, the participants in the control group will also receive the Metawell program, and an extended follow-up will be conducted during the 9th (only for participants in the control group) and 12th month after enrolment.

Table 1. Study schedule

TIME POINT	Baseline	3 months	6 months	9 months	12 months
ENROLMENT:					
Eligibility screen	X				
Informed consent	X				
Allocation	X				
INTERVENTIONS:					
Metawell program: Intervention group	→	→			
Metawell program: Control group			→	→	
Traditional diet guide: Intervention group					
Traditional diet guide: Control group	→	→			
ASSESSMENTS					
Anthropometry	X	X	X	X	X
Blood tests	X	X	X	X	X
Vitamin level	X		X		X
Questionnaires	X	X	X	X	X
Dietary assessment	X		X		
CT	X		X		
DXA	X		X		X

24-h blood pressure monitor	X		X		

Recruitment and informed consent

We will disseminate advertisements containing our contact information to recruit participants via various social media platforms through their official account on an instant messaging app (WeChat). Appointments will be made with overweight and obese individuals who are willing to participate in our study. A trained research nurse will provide the participants with detailed information about this study. After informed consent is signed, the initial screening for eligibility criteria and baseline measurements will be performed. The inclusion and exclusion criteria are as follows:

Inclusion criteria: Participant's age is between 18 and 70 years old and 25 ≤ BMI < 40 kg/m^2, with at least one condition from the following list: history of hypertension, systolic blood pressure > 120 mmHg or diastolic blood pressure > 80 mmHg; abdominal circumference > 96 cm for men and > 90 cm for women; fasting triglycerides > 1.69 mmol/L; history of type 2 diabetes mellitus managed with lifestyle (not on insulin or oral medications) or fasting blood glucose > 5.6 mmol/L; HDL cholesterol < 1.04 mmol/L for men and < 1.3 mmol/L for women.

Exclusion criteria: Participants with one or more conditions listed below are considered unsuitable for participation in the program and will be excluded: history of coronary artery disease; diabetes mellitus managed with insulin or any oral hypoglycaemic pill for diabetes; glucose intolerance or fasting glucose ≥ 8 mmol/L; congestive heart failure; familial hypercholesterolemia, including familial hypertriglyceridemia; fasting low-density lipoprotein (LDL) cholesterol > 4.2 mmol/L; fasting triglycerides > 6.8 mmol/L; current use of lipid-lowering agents; history of hypothyroidism, Cushing's syndrome, eating disorders, and/or gout in the past 6 months; confirmed episodes of hypoglycaemia, pregnancy, advanced liver disease, renal insufficiency, or any other major chronic medical condition; and smokers who

plan to quit smoking in the following 12 months. Participants with hypertension will be included only if they take < 3 antihypertensive medications, do not change the dose of their blood pressure medications in the preceding month, and have systolic blood pressure < 160 mmHg and diastolic blood pressure < 100 mmHg. Individuals who are unable to use smartphones will be excluded.

Sample size

Based on the DROPLET study,[7] we hypothesised that the absolute difference in weight loss between the trial and control groups will be at least 4 kg in weight, with a standard deviation of 9 kg. Therefore, 100 participants per group will provide more than 90% power to detect this difference with an alpha error of 0.05. The required sample size was determined to be 110 participants per group, considering an estimated 10% attrition rate.

Randomisation

All participants will be randomly assigned to the trial or control groups at a 1:1 ratio. A list of randomisation numbers will be generated using R, and the allocation results will be sealed in an opaque envelope. After completion of baseline measurements, the randomisation envelope will be unsealed by the practitioners responsible for participant allocation.

Interventions

The MetaWell program is a remote weight loss program that consists of a free mobile application combined with a wireless home scale, customised nutrition program, and weight management coach (Fig. 2). Once enrolled in the program, participants will receive advice from the weight management coach certified by MetaWell and up to three MetaWell biscuits daily, along with a selection of healthy recipes (such as seaweed soup, skimmed milk, spiced beef, grains, vegetables, etc.). The nutritional information of the biscuits is presented in Table 2. Participants are required to measure their weight and urinary ketones daily. The weight management coach will

measure, monitor, and evaluate participants' body fat parameters and ketone production to adjust the program and meal plan accordingly to ensure that the program is effective and safe.

Table 2. Nutritional information of Yufit biscuits

Ingredients:	**Nutrition Facts**		
Wheat Flour, Soybean Protein Flour, Soybean Oil, Eggs, Powdered Sugar, Lentinula Edodes, Black Fungus, Hericium Erinaceus, Grifola Frondosa, Bamboo Fungus, Seaweed, Cassia, Kumb, Emblica, Bran, Starch, Salt, Retinyl Acetate (Vitamin A), Thiamine Hydrochloride (Vitamin B1), Riboflavin (Vitamin B2), Pyridoxine Hydrochloride (Vitamin B6), Niacin, Folic Acid, Ferrous Sulfate, Calcium Carbonate, Zinc Gluconate, Sodium Selenite.	Items	Per 100 g	NRV%
	Energy	1792 kJ	21%
	Protein	10.2 g	17%
	Fat	16.1 g	27%
	-Trans Fat	0 g	
	Carbohydrate	53.4 g	18%
	Dietary Fibre	14.4 g	58%
	Sodium	315 mg	16%
	Vitamin A	13 mg RE	2%
	Vitamin B1	0.46 mg	33%
	Vitamin B2	0.88 mg	63%
	Vitamin B6	0.43 mg	31%
	Folic Acid	105 mg	26%
	Calcium	300 mg	38%
	Iron	4.6 mg	31%
	Zinc	1.61 mg	11%

Trial group

After randomisation, the participants will be enrolled in the MetaWell program (Weijian Technologies Inc., Hangzhou, China). The program comprises three stages: (1) weight loss stage (0-3 months), (2) continued weight loss transitioning to a weight

maintenance stage (3-6 months), and (3) extended follow-up stage (6-12 months)

Weight loss stage (0-3 months)

After being assigned to the trial group, participants will download an app on their mobile phones and will be provided with a home scale, urine ketone testing strip, and Yufit biscuits. Participants will be instructed on how to use the scale to monitor changes in body weight and fat. Participants will be randomly assigned to a particular practitioner. Participants will be required to monitor their body composition and urine ketone levels using a scale and test strip daily. Data will be uploaded to their mobile phones and transmitted to their practitioners. All practitioners have medical backgrounds and are trained by the MetaWell group. Practitioners will provide guidance on required dietary adjustments via the app and will make necessary adjustments to the participants' daily diet based on their health condition, such as urine ketones, hypoglycaemia, and rate of weight loss. The daily energy intake is typically 800-1200 kcal/day.

Weight maintenance stage (3-6 months)

After 3 months, the Yufit biscuits will no longer be used routinely in the diet. Participants will still be required to monitor their weight and upload the data. When noticeable weight regain is detected, the practitioner will initiate a 2- to 3-day weight loss intervention using the same protocol as that in the weight-loss stage to maintain the participant's body weight.

Extended follow-up stage (6-12 months)

After 6 months, practitioners will not provide advice but will instruct participants to monitor their body weight weekly and maintain their body weight autonomously.

Control group

Printed educational material containing general guidance on a routine diet and sample diet for weight loss (1500 kcal/day for men and 1200 kcal/day for women) will be

provided to participants. Details are provided in Table 3. Face-to-face education will occur only once, and participants will be instructed to follow this diet to lose weight and monitor their weight and urine ketone levels once a week. If their urine ketones become positive, participants will be informed to contact the study organisers. Their recent diet will be reviewed and advice on relevant dietary adjustments will be provided.

After 6 months, participants in the control group will be enrolled in the MetaWell program, including a 3-month weight loss stage and 3-month weight maintenance stage, as described above.

Table 3. Diet sample for participants in the control group

Men	Women
Breakfast	
Egg/meat 60 g	Egg/meat 60 g
Cereal 50 g	Fruit 100 g
Milk 250 mL	Milk 250 mL
Lunch	
Egg/meat 50-75 g	Egg/meat 50 g
Cereal 75 g	Cereal 50 g
Vegetable 250 g	Vegetable 250 g
Dinner	
Egg/meat 50-75 g	Egg/meat 50 g
Cereal 75 g	Cereal 50 g
Vegetable 250 g	Vegetable 250 g
Others	
Fruit 200 g/d	Nuts/soybeans 75-100 g/week
Nuts/soybeans 100 g/week	Salt ≤ 6 g/d, oil 15 g
Salt ≤ 6 g/d, oil 25 g	

Outcomes

The primary outcome of this study is the between-group difference in the change in participants' BMI after 6 months of follow-up. The study has four secondary outcomes: 1) proportion of participants losing 5% of their body weight; 2) changes in total body fat and distribution of abdominal visceral adipose tissue and subcutaneous adipose tissue given that visceral adipose tissue is closely associated with health in obese patients and a decrease in body weight is not equal to a loss in body fat; 3) changes in systemic inflammation reflected by high-sensitivity C-reactive protein (hs-CRP) pre- and post-intervention; and 4) mid-and long-term effectiveness of the MetaWell program for improving systemic blood pressure, abdominal obesity, blood glucose, and blood lipids.

The exploratory outcome of our study is the weight loss effect of the MetaWell program at 1 year for participants in the intervention group. The safety outcomes of our study are changes in serum vitamin levels and changes in liver and renal function.

Assessment and follow-up

Eligible individuals who meet the criteria and consent to participate in the clinical trial will undergo a baseline assessment. Follow-up assessments will be performed at 3, 6, 9, and 12 months after enrolment. A summary of the follow-up assessments is presented in Table 1. Group interventions will be masked in the data provided to the assessor to avoid bias. To ensure the quality and reliability of the data, all follow-up measurements will be performed by a nurse who is specially trained by our team or qualified lab.

Baseline information

All participants will complete a questionnaire on sociodemographic and medical information, including age, sex, and medical and surgical history in baseline assessments.

Anthropometry

At baseline and during every follow-up assessment, body weight will be measured to assess weight changes. Measurements will be performed with an ultrasonic height-weight scale (DHM-200, Dinghengkeji, Hennan, China). Participants will be weighed barefoot and without greatcoats. Body height and weight will be recorded to the nearest 0.1 cm and 0.1 kg, respectively. To ensure measurement accuracy, the scale will be calibrated using a 20 kg standard weight every month. Waist and hip circumferences will be measured at every assessment. Measurements will be performed by two nurses trained by our study group. Waist and hip circumferences will be measured approximately 3 cm above the navel and at the widest part of the hip, respectively. Participants will be instructed to keep their arms down and relax during measurements. BMI and waist-to-hip ratio will be calculated.

Blood tests

At every follow-up visit, a 30-mL fasting blood sample will be collected from each participant using vacuum tubes, including procoagulation tubes, for various blood tests listed below:

1) Liver function, renal function, blood lipids, and CRP: Elevated alanine aminotransferase (ALT) is the most commonly used biomarker of liver dysfunction. Given the association between obesity and non-alcoholic fatty liver (NAFLD) and based on reports that bariatric surgery can improve NAFLD in obese patients with weight loss,[11] we will measure the liver function of participants at every follow-up. In addition to NAFLD, hyperuricemia, hyperlipidaemia, and body inflammation are closely linked to overweight and obesity. To investigate whether these symptoms will improve with weight loss, we will assess renal function and blood lipids at every follow-up to observe changes in ALT, urine acidity, and blood lipids during the program.

2) Blood glucose and insulin levels: Obese patients are more vulnerable to glucose intolerance.[12] Although diabetic patients will not be enrolled in our program, the effects of the weight loss program on insulin resistance in participants will be measured. Fasting blood glucose and insulin levels will be measured. HOMA2-IR will

be calculated using the HOMA2 calculator,[13] and changes in HOMA2-IR will be analysed.

3) Haemoglobin and vitamin levels: Safety assessments of weight loss programs are crucial, and there are many reports on the side effects of weight loss surgery.[14,15] The most common symptoms are vitamin deficiency and anaemia. However, it remains unclear whether dietary interventions are associated with a lack of nutritional intake and similar side effects. Therefore, we will assess levels of haemoglobin and vitamins A, B6, B12, and 25-(OH)-D during the program.

Questionnaires

To analyse the impact of our weight loss program on general quality of life, physical activity, and lifestyle, a set of questionnaires will be administered at every follow-up assessment. The SF-36 is a commonly used questionnaire to assess quality of life and has been validated in the Chinese population.[16-18] To assess changes in physical activity and self-efficiency, the IPAQ [19] and Weight Efficacy Lifestyle (WEL) short-form questionnaire will be employed.[20]

Given that the feeling of hunger may impact the adherence and feelings of participants, a visual analogue scale (VAS) will be used to investigate the feeling of hunger at different time points before and after each meal in each participant.

Dietary assessment

Obese individuals enrolled in weight loss programs tend to regain their weight 1 or 2 years post-intervention.[21] We hypothesise that this could be due to the failure of the programs to change dietary patterns. Therefore, we plan to conduct dietary assessments at baseline and 6 months after enrolment to determine whether our program alters the dietary patterns of participants and to examine the relationship between dietary changes and weight regain. A 24-h dietary recall, which is the standard method for performing dietary investigations and is widely used globally,[22-24] and short food frequency questionnaires (FFQs) will be used. The FFQ used in this study was designed to conduct nutritional investigations in Chengdu City.[25]

Body composition

The main goal of weight loss is to reduce the amount of body fat. Therefore, to investigate the effect of our weight loss program on body fat, DXA will be performed using the GE Lunar Prodigy scanner[26] to assess body composition. Total body fat, leg fat, and upper body fat will be measured. The percentage of body fat will be calculated.

Visceral adipose tissue is closely associated with various symptoms, including hypertriglyceridemia,[27] cardiovascular diseases[28] or metabolic syndrome.[29] Considering the impact of visceral adipose tissue on human health, we will investigate changes in visceral adipose tissue with weight loss. We will use 16-slice spiral CT (TOSHIBA Aquilion 16, Japan) to scan and analyse slices between L2/L3 to evaluate the amount of visceral fat and subcutaneous fat in each participant using QCTPRO software.[30] DXA will be performed at baseline, 6 months, and 12 months. CT will be performed at baseline and 6 months. We will also measure the skinfold thickness of the triceps, subscapular crest, and iliac crest at every follow-up assessment.[31]

24-h blood pressure monitoring

Participants will be required to undergo 24-h blood pressure monitoring at baseline and 6-month follow-up using a Welch Allyn ABPM 6100/7100 blood pressure monitor. Average and standard deviation of blood pressure during the daytime and at night will be recorded.

Adverse events

Expected adverse events of the weight loss intervention include hypoglycaemia, menstrual disorder, constipation, and dizziness. At every follow-up, participants will be asked if they have experienced the aforementioned side effects. All adverse events will be recorded.

Data management

Paper case report forms and reports of each measurement will be collected as original data. These data will be entered into an electronic data collection system. Every month, the missing data, outliers, and other types of incorrectly entered data will be screened and reported in a monthly meeting of the main research group members. We will assess the raw material of any suspicious data and amend any incorrectly entered data. Upon conclusion of enrolment, a brief report on the data distribution of the two groups will be prepared to assess the efficiency of randomisation.

Statistical analysis

Analysis of primary and secondary outcomes

The intention-to-treat dataset will be used to analyse the primary and secondary outcomes performed by an independent statistician group. Changes in participants' BMI (primary outcome) and the amount of body fat, abdominal visceral adipose tissue, and hs-CRP (secondary outcomes) will be analysed using a mixed-effects model, which includes different intervention groups. Random effects will include repeat measurements on the same participant and individual differences among participants. The proportion of participants who lose 5% of their initial weight will be analysed using Cox regression, Kaplan-Meier survival curves, and log-rank test. The data at 6 months will be considered as the main result. Changes in all outcome measurements between baseline and at 6-month follow-up will be analysed. Differences in changes will be assessed using a t-test or chi-square test.

Adjustment

Baseline BMI, sex, age, and IPAQ scores of participants will be adjusted. Both adjusted and unadjusted analyses will be performed, and the adjusted result will be considered as the main result.

Comparison of baseline characteristics

After the enrolment of participants is completed, baseline characteristics will be compared between two groups using a t-test and chi-square test.

Sensitivity analysis

The differences in body weight changes of participants in the control group will be analysed using a t-test to confirm the effects of the Metawell program.

Missing values

Missing values will be implemented using multiple imputation. Both pre- and post-imputation datasets will be analysed. The results of post-imputation data will be considered as the main result.

Statistical description and software

The distribution of continuous, normally distributed data will be presented as means and standard deviation. Other continuous data will be presented as medians and IQR. All analyses will be performed using R v3.5. P-values, 95% CIs, and the different effects of the two interventions will be reported. Differences will be considered statistically significant at $P < 0.05$.

Patient and Public Involvement

Patients and the public were not involved in the design, conduct, reporting, or dissemination of our research.

ETHICS AND DISSEMINATION

This study conforms to the Declaration of Helsinki. The study has been approved by the ethics committee of the Hospital of Chengdu Office of People's Government of Tibetan Autonomous Region（Reference ID for ethics approval: 2019-01） and is registered in the Chinese Clinical Trial Registry (ChiCTR1900021630). Before signing consent forms, participants will be well informed about the benefits and risks of participating in this program. The trial was commenced on 11 April 2019.

There are two main audiences of this research: the overweight/obese population in China and professionals working in the weight loss field. The results of our study will be disseminated via publications in academic journals and our clinic. Our study group

will maintain contact with participants to inform them of the study findings.

Discussion

This study aims to examine the effectiveness of an internet-based, low-carbohydrate dietary intervention program for improving body weight, body composition, and general metabolic health. Although similar types of programs have been performed in developed countries, there is a paucity of similar studies in China. In our study, DXA and QCT will provide more detailed and accurate data on changes in body fat during the intervention, which may clarify the benefits of a low-carbohydrate diet in obese patients.

In recent years, the effects of diverse dietary interventions on weight loss have been extensively examined. The findings indicate that patient adherence is the most crucial factor. A pre-packaged diet replacement product provides a much easier plan to follow. The use of an Internet-based platform allows professional practitioners to monitor patient status, have high-intensity contact with patients, and modify their weight loss plan in real time without the need for patients to attend specific facilities. These advantages may improve patient adherence and improve outcomes compared to traditional weight loss programs.

The main purpose of losing weight is to reduce body fat and improve health and quality of life. Given that weight loss can be due to loss of water, lean mass, or body fat, simply observing a reduction in body weight does not necessarily indicate a reduction in body fat and improvements in health outcomes. Accordingly, a key feature of our study is the ability to track changes in body fat. Bioimpedance spectrum analysis (BIA) is the most commonly used method for estimating the amount and percentage of body fat. However, one study reported that BIA overestimated total body lean mass in 93% of participants and underestimated total body fat mass in 90% of participants.[32] In this regard, DXA is a more accurate measure of body fat compared to BIA.

To the best of our knowledge, this is the first study to evaluate weight loss resulting from a weight loss program combining a mobile phone app, diet replacement product,

wireless scale, and high-intensity guidance from professionals. Moreover, we will employ DXA and QCT to accurately evaluate changes in body fat, visceral adipose tissue, and subcutaneous adipose tissue. Nevertheless, this study has several limitations. First, participants enrolled in previous loss programs tend to regain most of their weight within years. As the follow-up period is 1 year, we will be unable to thoroughly analyse weight regain in our participants. Second, the follow-up period of 1 year is also insufficient to assess the long-term benefits of this weight loss program, such as reduced risk of cardiovascular events and diabetes onset. Therefore, we will consider a prolonged follow-up period of 2 to 3 years for participants that agree to stay in our program in order to observe the long-term effects of our program.

Contributorship statement

WX, WYH, LOL, AL, and FLJ designed the study. WX, WYH, GYH, and ZCH are the medical supervisors of this study and are responsible for enrolling participants. WSY is responsible for the randomisation, data collection, management, and drafting of this manuscript. WX, ZCH, WYH, ZLY, and FLJ reviewed and revised the manuscript.

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Competing Interests

Weijian Technologies Inc. has funded this study.

Data availability statement

Deidentified data may be shared. Any researchers in need of the data may contact the corresponding author (Dr. Wu). Research data may be used if the sharing requirements meet the relevant provisions of the Chinese government.

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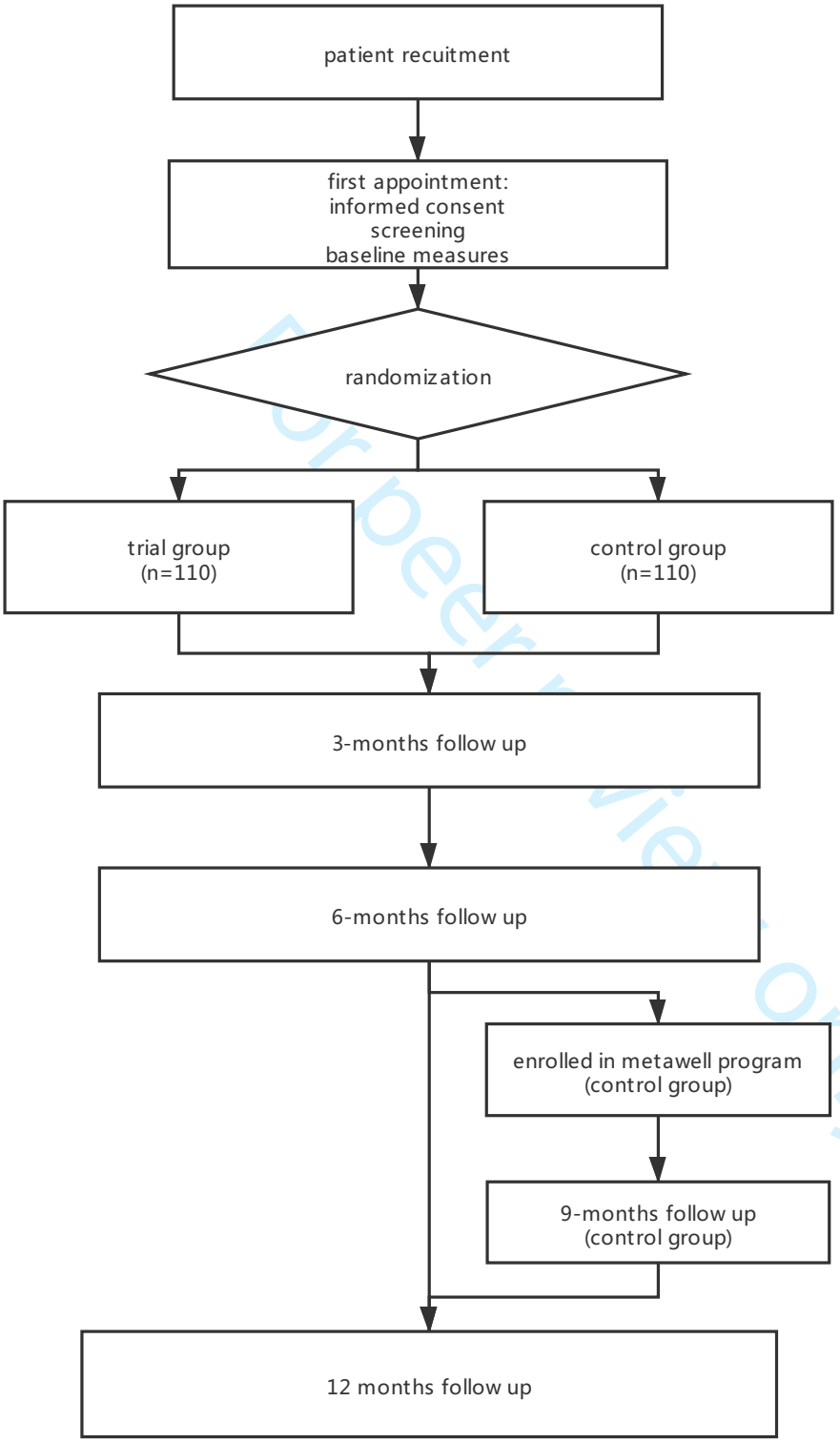
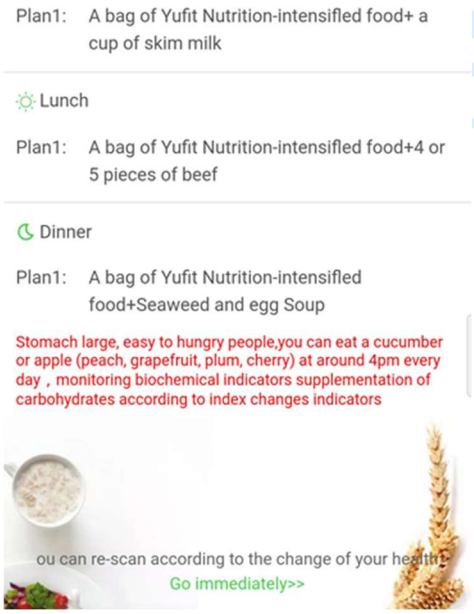


a.


MetaWell Weight Loss Application
MetaWell HealthyWeight Loss Program
Weight Management Coach
Customized Nutrition Program

b.


16:59
64
Healthy Recipes
Medium Speed
Low Speed
Breakfast
Plan1: A bag of Yufit Nutrition-intensifled food+ a cup of skim milk
Lunch
Plan1: A bag of Yufit Nutrition-intensifled food+4 or 5 pieces of beef
Dinner
Plan1: A bag of Yufit Nutrition-intensifled food+Seaweed and egg Soup
Stomach large, easy to hungry people,you can eat a cucumber or apple (peach, grapefruit, plum, cherry) at around 4pm every day , monitoring biochemical indicators supplementation of carbohydrates according to index changes indicators
ou can re-scan according to the change of your health
Go immediately>>

Section/item	ItemNo	Description	Related content in manuscript
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 2
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 3
	2b	All items from the World Health Organization Trial Registration Data Set	Page 3
Protocol version	3	Date and version identifier	NA
Funding	4	Sources and types of financial, material, and other support	Page 9
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Page 11
	5b	Name and contact information for the trial sponsor	Page 18

	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	NA
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Page 2
	6b	Explanation for choice of comparators	Page 2
Objectives	7	Specific objectives or hypotheses	Page 2

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Page 3
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Page 3
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Page 3
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page 4-5
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Page 4-5

	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Page 4-5
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Page 6
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Page 15(Table 2)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Page 4

Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Page 4

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Page 4
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Page 4
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Page 4

Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Page 6-8
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	NA

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Page 9
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Page 8
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Page 8
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Page 8

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	NA
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Page 8
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page 3
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	NA
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Pate 3
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	NA
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 10

Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	NA
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	NA
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NA

Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable