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Effect and Safety of Electroacupuncture on Weight Loss in Obese Patients with Prediabetes: Study Protocol of a Randomised Controlled Trial

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Abstract

Introduction: Obesity has been identified as a significant risk factor for several chronic conditions, including diabetes, tumors, and cardiovascular disease, and has been associated with increased mortality rates. Despite the well-established clinical practice of electroacupuncture (EA) as a potential treatment option for obesity, its efficacy remains questionable, primarily due to the paucity of empirical evidence supporting its therapeutic benefits.

Methods and analysis: The present study aims to investigate the efficacy and safety of electroacupuncture (EA) for weight loss in obese individuals with prediabetes, using a randomized, placebo-controlled clinical trial design. A total of 256 eligible patients will be randomly assigned to one of two groups: EA (comprising EA therapy with health education) or Sham Acupuncture (SA) (comprising superficial acupuncture treatment with health education). The intervention will be administered three times per week for the initial 12 weeks, twice per week for the subsequent eight weeks, and once per week for the final four weeks, with a 24-week follow-up period. The primary outcome measure will be the percentage of patients who achieve a reduction of 10% or more in their body weight at week 24. Secondary outcome measures will include changes in body weight and BMI, blood test results, data collected by the body composition analyzer, size of adipose tissue scanned by magnetic resonance imaging of the abdomen, and the impact of weight on Quality of Life (IWQOL-Lite), The Three-Factor Eating Questionnaire-R21 (TFEQ-R21), and the Food Craving Questionnaire

(FCQ-T). The Treatment Emergent Symptom Scale (TESS) will be employed to monitor every adverse reaction from baseline to follow-up.

Ethics and dissemination: This trial has received ethical clearance from the Ethics Committee of Shanghai Municipal Hospital of Traditional Chinese Medicine under the registration number 2021SHL-KY-74. All participants will provide their written informed consent prior to their enrolment. The findings of this investigation will be disseminated through peer-reviewed publications and scholarly conferences.

Trial registration: ClinicalTrials.gov ID: NCT05237089; Pre-results

Keywords: obesity, prediabetes, electroacupuncture, weight loss, randomized controlled trial

Introduction

Obesity is a chronic metabolic disorder characterized by excessive accumulation of adipose tissue, typically resulting from an energy imbalance between calorie intake and expenditure. It is defined by a body mass index (BMI) of 30 or more, reflecting a high level of obesity [1, 2]. Epidemiological evidence has consistently shown that obesity is a significant risk factor for a variety of adverse health outcomes, including cardiovascular disease, diabetes mellitus and various types of cancer [3].

In 2015, high BMI was estimated to be responsible for approximately 4 million deaths worldwide, accounting for 7.1% of all deaths. 41% of these deaths were attributed to cardiovascular disease, followed by diabetes mellitus [4]. Notably, the prevalence of obesity and associated comorbidities has increased worldwide, and China currently has the highest proportion of obese and diabetic patients worldwide .

The treatment and prevention of obesity are complex and multifaceted challenges that require innovative and effective strategies. Weight loss through lifestyle changes (e.g., diet and exercise) is the most important intervention in the treatment of obesity. In individuals with prediabetes and obesity, losing 10% or more of their body weight has been shown to be extremely effective in preventing the onset of type 2 diabetes [5]. Therefore, the development of novel approaches to treat and prevent obesity is a crucial public health priority that requires further research and investment.

Maintaining a healthy lifestyle that includes healthy eating habits, regular physical activity, and effective stress management can facilitate healthy weight management [6–

8]. However, sustaining lifestyle changes over the long term can prove challenging, in part due to the fast pace of modern life. Therefore, some individuals may consider alternative strategies such as weight loss medications or surgery.

Weight-loss drugs or diet pills can suppress appetite and increase energy expenditure, but they can also interfere with digestive and absorption functions, leading to side effects such as nausea, vomiting, constipation, dizziness, and dry mouth. In addition, there is evidence that long-term use of these drugs may increase the risk of cardiovascular disease or mental illness [9, 10].

Surgical procedures for weight loss, such as gastric bypass or gastric sleeve surgery, have the potential for significant benefits, but also carry significant risks. Complications such as excessive bleeding, infection, acid reflux and intestinal obstruction are possible [11]. Therefore, the decision to undergo surgery should be based on a careful assessment of the risks and benefits under the guidance of a qualified healthcare professional.

In summary, while alternative weight loss strategies can be effective in some cases, they come with significant risks and limitations. Therefore, promoting and maintaining a healthy lifestyle that includes regular physical activity, healthy eating habits, and managing stress remains the most effective and sustainable approach to healthy weight management.

Electroacupuncture (EA) is an innovative form of traditional Chinese acupuncture that incorporates electrical impulses to enhance the therapeutic effects of acupuncture. EA has emerged as an alternative therapy for obesity. Previous studies have

demonstrated its superiority over sham acupuncture in reducing body mass index (BMI), body weight, body fat mass, waist-to-hip ratio (WHR), triglyceride (TG) and total cholesterol (TC) levels [12, 13]. The mechanism of action of EA in suppressing appetite and promoting lipid metabolism is believed to be due to activation of the sympathetic nervous system [14]. Furthermore, EA has been shown to improve glycemic control and insulin sensitivity in patients with type 2 diabetes mellitus, thereby possibly preventing the development of diabetes and its complications [15, 16].

To investigate the impact of EA on the treatment of obese patients with prediabetes and to address some of the limitations of previous studies, we designed a randomized controlled trial (RCT) with an adequate follow-up period. The study will evaluate the effectiveness of EA treatment in weight loss and diabetes prevention using subjective and objective measures while minimizing the placebo effect through the use of an appropriate sham acupuncture (SA) method. Our findings can inform the development of optimal acupuncture treatment protocols for obesity and prediabetes, providing valuable insights for healthcare professionals, policy makers and the general public.

Methods/design

Hypothesis

The main objective of this study is to evaluate the efficacy of electroacupuncture (EA) versus sham acupuncture (SA) treatment in the treatment of obesity and prediabetes in a randomized controlled trial. Our hypothesis is that EA will be superior to SA in promoting weight loss and preventing the onset of diabetes in obese patients with

prediabetes. By providing conclusive evidence on the effectiveness of EA treatment, this study may help inform clinical practice and guide the development of more effective treatment strategies for this growing public health problem.

Study design

This study protocol describes a single-site, randomized, patient-evaluator-blinded, placebo-controlled clinical study designed to evaluate the efficacy and safety of electroacupuncture (EA) for weight loss in obese patients with prediabetes. The study will be conducted at the Acupuncture Department of the Shanghai Municipal Hospital of Traditional Chinese Medicine and will include 256 eligible participants who will be randomly assigned to either the EA or sham acupuncture (SA) treatment group. After a one-week baseline assessment, the study intervention will continue for 48 weeks, with three treatment sessions per week for the first 12 weeks, followed by two sessions per week for the next 8 weeks and once per week for the last 4 weeks. Assessments of patient outcomes will be conducted during both the intervention period (weeks 8, 16, and 24) and the follow-up period (weeks 32, 40, and 48). All participants give a voluntary declaration of consent and sign a written declaration of consent. The study process is shown in Figure 1 and the timeline for registration, intervention, and assessment is shown in Table 1. Compliance with the Consolidated Standards for Study Reporting (CONSORT) and the Standards for Reporting of Interventions in Clinical Trials in Acupuncture (STRICTA) will be maintained throughout the trial [17].

Sample size calculation

The sample size calculation for this study was based on the proportion of patients

achieving weight loss of 10% or more of their body weight, with the assumption that EA treatment would be more effective than SA treatment. Previous research conducted in this area has shown that the proportion of patients achieving this level of weight loss is 26% in the EA group and 11% in the SA group, as shown in a previous randomized controlled trial (RCT) [18] . Sample size calculations were performed using PASS 15.0 software (NCSS. LLC, Utah, USA) which revealed that each group would require 102 cases to achieve a Type I error rate of 0.025 (one-sided) and a power of 80% to reach. With a dropout rate of 20%, a total of 256 cases were required, with 128 cases allocated to each treatment group.

Subject recruitment and randomization

Patients are recruited via WeChat advertisements and hospital banners. Initial screening is conducted through telephone or in-person consultations. Eligible patients are provided with comprehensive information about the study's objectives, methods, and potential benefits and risks. They are also requested to complete a set of standardized questionnaires during their initial in-person visit to assess their eligibility for the trial. Upon confirmation of eligibility, patients are invited to participate in the study and sign a written informed consent form before the intervention begins.

Inclusion Criteria

Eligibility criteria for study participants include the following:

Enrollment criteria for study participants encompass the following:

(1) male or female individuals between 18 and 65 years of age;

(2) participants with a body mass index (BMI) of 24.0 kg/m^2;

(3) Participants with a hemoglobin A1c (HbA1c) value between 5.7% and 6.4% or a fasting plasma glucose value between 6.1 mmol/L and <7.0 mmol/L or a 2-hour Post-exercise plasma glucose level (oral glucose tolerance). test) between 7.8 mmol/L and <11.1 mmol/L;

(4) participants who have maintained a stable weight within 4 kg for the three months prior to study commencement;

(5) Participants who provide their voluntary consent by signing a written consent form.

Exclusion Criteria

Exclusion criteria for study participants are as follows: (1) patients with secondary obesity induced by drugs or neuroendocrine-metabolic disorders (such as hypothalamic disease and hypopituitarism); (2) patients diagnosed with type 1 or type 2 diabetes; (3) patients who are taking medications that may interfere with the study outcomes; (4) patients with a score of >18 on the 17-item Hamilton Depression Scale (HDRS-17); (5) patients with severe ulcers, abscesses, or skin infections in the local acupuncture area; (6) patients with severe cardiac, cerebral, pulmonary, hepatic, renal, hematological, or other serious medical conditions; (7) participants who have participated in other clinical trials within the last month; and (8) pregnant or lactating women.

Randomization and allocation concealment

Participant allocation will be accomplished through a process of randomization employing block sizes of 4, 6, and 8. Stratification will be based on three criteria: (1) participant BMI; (2) gender; and (3) age. Eligible participants will be randomly assigned to either the EA or SA group at a 1:1 ratio, utilizing computer-generated

random sequences. Distribution cards will be generated and enclosed in opaque, sealed envelopes. Participants will receive envelopes sequentially according to the order of enrollment from an independent researcher, and envelopes will be opened by an acupuncturist prior to treatment. All randomization procedures will be executed at a central office by researchers not associated with intervention, evaluation, or data collection. Throughout the trial, the study sponsor will maintain records of the randomization results .

Blinding and researcher shielding

This study will employ a patient-evaluator blinded approach. Participants will be informed, during the screening process, of their equal chance of receiving either conventional electroacupuncture (EA) treatment or superficial acupuncture (SA). Patients will be treated in the supine position, with a specialized shield positioned over the chest to prevent any movement or manipulation during treatment. Treatment sessions, whether EA or SA, will be conducted in a secluded environment with private communication between patients disallowed to ensure the proper implementation of blinding procedures. Acupuncturists will be the only individuals informed of the participants' allocation. All researchers will undergo pre-study training and follow strict segregation of duties policies throughout the study.

Intervention

During the intervention period, patients in both the conventional electroacupuncture (EA) treatment and superficial acupuncture (SA) groups will undergo 56 treatment sessions. The interventions will be administered three times per week, every other day,

for the initial 12 weeks. Subsequently, the interventions will be given twice per week, on Mondays and Fridays, for an additional 8 weeks, and once per week during the final 4 weeks. The duration of each session will be 30 minutes. To ensure patient comfort and safety, the treatment room temperature must remain above 25°C. Additionally, all patients will receive identical health education brochures detailing the benefits of personalized lifestyle practices during the 24-week intervention period.

EA group

In the EA group, patients will receive authentic acupuncture treatment combined with low-frequency pulse electrical stimulation. The acupuncture treatment will involve the use of disposable sterile stainless-steel needles (Wuxi Jiajian Medical Device Co., LTD, China), with a diameter of either 0.25mm*40mm or 0.30mm*75mm, applied to the main and combined acupoints. The acupuncturists will manipulate the needles by lifting-thrusting or twirling to achieve the De-qi sensation. The main acupoints will include Shangwan (CV13), Zhongwan (CV12), Jianli (CV11), Xiawan (CV10), bilateral Quchi (LI11), Hegu (LI4), Liangmen (ST21), Tianshu (ST25), Daheng (SP15), Fujie (SP14), Shuidao (ST28), Zusanli (ST36), Fenglong (ST40), Wailing (ST26), and Guilai (ST29). The combined acupoints will include bilateral Shangjuxu (ST37), Neiting (ST44), Yinlingquan (SP9), Shuifen (CV9), Qihai (CV6), and Guanyuan (CV4). The acupuncturists will use all main acupoints and select the combined acupoints based on the patients' unique patterns at each treatment session. The electrodes of the EA apparatus (Type G6805-2B, Shanghai Huayi Medical Instrument Co., LTD, China) will be connected to the needles at the bilateral ST21, ST25, and SP15 acupoints. The EA

stimulation will be continuous wave type, with a frequency of 3 Hz, and an intensity of 4-5 mA, adjusted based on the endurance of each patient. The details of the acupoints and EA parameters are presented in Table 2.

SA group

In the SA group, participants will receive superficial acupuncture treatment applied to the same main acupoints as those used in the EA group. Sterile disposable stainless-steel needles with a diameter of 0.22*0.25mm will be used, and the De-qi sensation will not be intentionally achieved. The electrodes of the EA apparatus will be connected to the needles at the bilateral ST21, ST25, and SP15 acupoints as in the EA group. However, the electric wires will be intentionally broken inside the apparatus, and no current output will be applied during the treatment. This will ensure that the patients in the SA group do not receive active electroacupuncture treatment, while still receiving a similar needling experience .

Health education

The health management brochure will be disseminated to all participants upon enrollment, and health education sessions will be conducted either online or offline at weeks 8, 16, and 24, with a duration of approximately 60 minutes each. The researchers will offer personalized advice on healthy lifestyle practices tailored to each individual patient's characteristics, with no imposed restrictions on their dietary habits or physical activity levels.

Outcome measures

The primary outcome of this study is the proportion of patients who have lost 10%

or more of their initial body weight at week 24 in both groups. Secondary outcomes include changes in body weight, body mass index (BMI), blood test results, abdominal magnetic resonance imaging (MRI) measurements of fat tissue size, data collected from the body composition analyzer, and scores on the Impact of Weight on Quality of Life (IWQOL-Lite), the Three-Factor Eating Questionnaire-R21 (TFEQ-R21), and the Food Craving Questionnaire (FCQ-T). All adverse effects will be assessed using the Treatment Emergent Symptom Scale (TESS) from baseline to the follow-up period.

Body weight and BMI will be calculated at baseline, week 8, week 16, week 24, week 32, week 40, and week 48, and IWQOL-Lite, TFEQ-R21, and FCQ-T scores will also be collected at these time points. Blood tests will be performed at baseline and week 24, while the body composition analyzer and abdominal MRI scan will be conducted at baseline and week 24. A detailed schedule of assessments can be found in Table 1.

Primary outcome measure

The primary objective of this study is to assess the proportion of participants who achieved a weight loss of 10% or more of their baseline body weight at the end of the intervention period (week 24) and compare this outcome between the treatment groups. Previous research suggests that a weight loss of 5% to 15% in obese individuals can lead to significant improvements in glucose control and reduce the risk of type 2 diabetes and its associated complications [19]. As such, the 10% weight loss threshold is an important clinical marker of success in weight management interventions.

Secondary outcome measures

Obesity level

Changes in body weight are a crucial factor in the pathogenesis of diabetes [20]. To assess this variable, we will calculate the mean difference in body weight of the subjects during the intervention and follow-up periods compared to baseline measurements. The body mass index (BMI) is a widely used statistical tool that estimates body fat in relation to a person's height and weight. It is determined by dividing the weight of an individual in kilograms by the square of their height in meters. The National Institutes of Health employs BMI as a means to classify individuals as underweight, normal weight, overweight, or obese. We will supplement our analysis with data from the Inbody 770 non-invasive body composition analyzer (Biospace Inc. Dba Inbody, California, USA), which uses bioelectrical impedance analysis to determine high-density body composition, including body fat mass, skeletal muscle mass, body fat percentage, and basal metabolic rate at baseline and at the conclusion of the study period, which is week 24. Body fat mass provides an insight into the quantity of body fat contributing to weight, including subcutaneous and visceral deposits. Skeletal muscle mass, on the other hand, is a proxy for the amount of muscle tissue that can be stimulated and developed through exercise. Furthermore, the muscle-fat analysis furnishes information on whether the patient has a harmonious distribution of skeletal muscle mass and body fat mass concerning their weight. Notably, body fat percentage is a superior indicator of the risk of obesity compared to BMI [21]. Finally, basal metabolic rate represents the number of calories a person requires to sustain basic bodily functions. Collaboration between individuals and dietitians is crucial for developing nutritional plans that facilitate the attainment of desired body composition

objectives [22]. Metabolic diseases, such as obesity, diabetes, and metabolic syndrome, are often correlated with high levels of subcutaneous abdominal fat, pancreas fat, and liver fat. Quantitative assessments of the size of abdominal adipose tissues and the intra-abdominal to subcutaneous adipose tissue ratio can be accomplished using an abdominal MRI scan. This non-invasive imaging technique permits precise and accurate measurements of adiposity within the upper abdomen and the flat umbilical layer, offering valuable information on risk factors for metabolic diseases.

Glucolipid metabolism

We will access the blood test of glucose and lipid metabolism to find out the differences between patients in two groups. Patients must abstain from food and water twice on the evening before the blood test, after 10 p.m., and at baseline and week 24. It is the blood glucose concentration, including fasting plasma glucose (FPG), which reflects the secretory function of the islet cell and 2-hour postprandial blood glucose (2hPG), reflecting the reserve function of the islet cell [23] . HbA1c levels of 5.5% indicate the presence of insulin resistance, while levels of 6.5% indicate the occurrence of diabetes[24]. Insulin resistance is commonly assessed using the homeostasis model assessment of insulin resistance (HOMA-IR). This index increases in severity as insulin resistance becomes more pronounced [25]. HOMA-IR is calculated by multiplying fasting plasma insulin (FPI) by fasting plasma glucose (FPG), and dividing the product by the constant 22.5 [26]. Blood lipids, including low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), and triglycerides (TG), can reflect the body's lipid metabolism. Elevated LDL-C levels in

obese patients increase the risk of cardiovascular disease, and may also serve as a predictor of diabetes [27].

Questionnaires

The present study utilized three standardized self-report questionnaires to assess the quality of life and eating behaviors of individuals with obesity. The first questionnaire, IWQOL-Lite, consists of 31 items and evaluates five dimensions of quality of life, namely physical functioning, self-esteem, sex life, public stress, and work [28]. The second questionnaire, TFEQ-R21, assesses three aspects of eating behavior, including emotional eating (eating in response to negative emotions), uncontrolled eating (eating in response to food exposure or hunger), and cognitive restraint (deliberate attempt to limit eating). Scores range from 0 to 100, with higher scores indicating greater levels of eating behavior [29]. The third questionnaire, FCQ-T, comprises 39 items grouped into nine subscales that assess food cravings, including intentions and plans about eating, expectation of positive reinforcement that eating may produce, expectation of alleviation of negative states and feelings as a result of eating, lack of control over eating, thoughts or preoccupation with food, cravings as a physiological state, emotions that may be experienced before or during cravings or while eating, cues that can trigger cravings, and guilt about cravings and/or giving in [30]. These standardized questionnaires are widely used and have been validated for measuring quality of life and eating behaviors in individuals with obesity, providing valuable insights into the impact of obesity on daily living.

Adverse Events

Acupuncture is a widely used complementary therapy for various conditions. Despite its potential benefits, it may also cause adverse events (AEs) that need to be carefully monitored and recorded. Common AEs associated with acupuncture include bleeding, fainting, subcutaneous hematoma, and severe pain. The acupuncturists responsible for the treatment will evaluate these AEs based on their severity and document their incidence. The grading system for severity of AEs consists of three levels: grade 1 for mild, grade 2 for moderate, and grade 3 for severe or medically significant. The incidence of AEs will be expressed as the number of AEs per number of acupuncture sessions, calculated as a percentage.

In addition, any diseases or events that may be affected by acupuncture treatment or that may affect the efficacy of the treatment, such as cold, fever, abdominal pain, diarrhea, and constipation, will be recorded by the Treatment Emergent Symptom Scale (TESS) in the case report form. The TESS will also document the resolution of these events. By doing so, the study can obtain a comprehensive understanding of the potential AEs and their severity associated with acupuncture treatment, as well as any confounding factors that may influence the outcome.

Statistical analysis

Analyses were conducted on the intention-to-treat (ITT) population, which included all participants who received at least one treatment. To address missing data, multiple imputation was utilized, assuming a specific distribution of values at each time point calculated by the R software. Linear mixed effects models were employed for analysis, utilizing IBM SPSS Statistics for Windows (version 24.0; IBM Corp, Armonk, NY,

USA).

For comparison of measurement data between the groups at baseline and follow-up, the t-test was employed, while the rank sum test was utilized for ranked data, and the chi-square test for categorical data. All statistical analyses employed two-tailed tests at a level of significance of 5%. Results were primarily presented as mean ± standard deviation (SD).

Ethics and clinical trial registration

All practitioners of acupuncture in this study are licensed acupuncturists with 3-5 years of clinical experience in the department of acupuncture and moxibustion at Shanghai Municipal Hospital of Traditional Chinese Medicine. To ensure the quality of the study, all practitioners undergo clinical training before the intervention, including standard procedures for both real and sham acupuncture.

This randomized controlled trial has been approved by the Ethics Committee of Shanghai Municipal Hospital of Traditional Chinese Medicine (2021SHL-KY-74) on November 19th, 2021, and is registered with ClinicalTrials.gov (NCT05237089). Before participating in the trial, all patients are required to sign a written informed consent.

An independent Data and Safety Monitoring Board (DSMB) has been established to supervise the trial and ensure its integrity. The DSMB consists of three experts in the field, namely Professor Lixing Lao, a specialist in clinical trials of acupuncture and president of Virginia University of Integrative Medicine; Dr. Xianyu Tang, a specialist in diabetes and chief of the endocrinology department at Guangdong Provincial

Hospital of Traditional Chinese Medicine; and Dr. Ruiping Wang, a specialist in statistics and director of the clinical research center at Shanghai Skin Disease Hospital. The DSMB monitors the progress of the trial, examines collected data, and controls for bias. Its members are authorized to supervise the process at any time and may raise objections directly or even halt the trial in the event of serious adverse events until the problem has been resolved.

The results of this study will be disseminated through peer-reviewed academic journals or presented at academic conferences.

Patient and public involvement

Prior to the design phase of the trial, the researchers consulted obese patients, with or without abnormal glucose metabolism, in the department of acupuncture. The suggested treatment frequency, duration, and follow-up period of the study were informed by endocrinologists and epidemiologists. Eligible participants will be recruited from the outpatient clinics at the Shanghai Municipal Hospital of Traditional Chinese Medicine. Patients who participated in the consultation process for the trial design will be excluded from recruitment. Upon completion of the trial, a manuscript will be written for publication in a scholarly journal, which will provide a comprehensive account of the results. Additionally, a brief summary of the findings, written in plain language, will be distributed to all participants. The burden of intervention will not be assessed by participants themselves.

Discussion

Obesity is rapidly emerging as a preeminent health hazard, poised to supplant smoking as the second most prevalent risk factor for numerous diseases [31]. Recent decades have witnessed a dramatic surge in the prevalence of obesity, with nearly half (48.5%) of obese adults exhibiting prediabetes or diabetes. The World Health Organization reports that obesity significantly elevates the risk of developing type 2 diabetes, underscoring the gravity of the global obesity pandemic [32]. Mitigating the comorbidities associated with obesity mandates weight loss, yet current treatment modalities are limited in their efficacy. Bariatric surgery, while efficacious, is available to only a minority of patients and poses serious complications [33]. Alternative therapies remain suboptimal, and further research is necessary to develop more effective interventions. Acupuncture therapy is a popular non-pharmacological alternative treatment for obesity due to its demonstrated efficacy and safety. Previous randomized controlled trials (RCTs) have focused primarily on acupuncture for simple obesity, neglecting comorbid symptoms of obesity, such as abnormal glucose metabolism. Given that abnormal glucose metabolism is the most common complication of obesity, it is essential to develop a sensible acupuncture treatment protocol that can address both weight loss and improve abnormal glucose metabolism. However, there is a significant lack of comparable RCTs investigating acupuncture for the treatment of abnormal glucose metabolism in obese patients with a large sample size and a long follow-up period.

Therefore, this study proposes a protocol for an RCT to examine the effectiveness and safety of electroacupuncture (EA) in treating obesity and abnormal glucose

metabolism. The study aims to address the existing limitations of previous clinical studies on acupuncture, including illogical design, imperfect blinding methods, and practical difficulties in practical application. In order to eliminate possible placebo effects of EA treatment, the sham acupuncture method will be employed, which uses thinner and shorter needles to deliver flat acupuncture on the same main acupuncture points. The fundamental principle of Traditional Chinese Medicine (TCM), 'treatment based on syndrome differentiation,' will guide the selection of acupoints for the treatment of obesity based on dialectical classification.

The trial will also incorporate a more prolonged follow-up period to explore the sustained effects of acupuncture on obesity and ascertain the duration of such effects. Furthermore, this trial aims to address two key technical issues, namely the application of sham electroacupuncture and patient compliance. To ensure the appropriate administration of sham acupuncture, all acupuncturists will receive extensive training before the commencement of the trial. Additionally, researchers will educate patients on medical knowledge to promote overall health and wellness, as good compliance is crucial for the successful completion of the trial.

The primary objective of this clinical trial is to assess the efficacy of EA treatment in reducing weight among obese patients, regulating their blood glucose and metabolism, and improving their quality of life. By conducting this trial, we aim to provide reliable scientific evidence for the clinical application of acupuncture in weight management and blood glucose control. In conclusion, by addressing the technical issues of sham acupuncture and patient compliance, this trial seeks to demonstrate the

potential benefits of EA treatment for weight management and blood glucose control, with significant implications for the clinical application of acupuncture in improving overall health outcomes.

Trial status

This trial is now recruiting participants.

Competing interests statement

The authors declare that they have no competing interests.

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Author contributions

SFX is the main researcher who provided the conception and designed the study. XY is the co-researcher who contributed to the design of the study and critical revision of the manuscript. XYL contributed to the design of the protocol, and writing of the manuscript. JJL and CFH contributed to the manuscript draft. BJL and FL contributed

to the design of the interventions. JYL, XLZ and SSL contributed to the statistical design and the design of the randomization method. YQM is the project manager and contributed to the revision of the manuscript. All authors read and approved the final manuscript.

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Figure legends

Figure 1 Flowchart of the trial

Table legends

Table 1 Schedule of enrolment, intervention, and assessments

Table 2 Treatment methods of electroacupuncture and acupoints

Table 1： Schedule of enrollment, intervention, and assessments

	Baseline	Treatment phase			Follow-up phase		
	Week 0	Week 8	Week 16	Week 24	Week 32	Week 40	Week 48
Patients							
Enrollment	×						
Signed informed consent	×						
Medical history	×						
Randomization	×						
Intervention		×	×	×			
Outcome measures							
BMI	×	×	×	×	×	×	×
Blood glucose	×			×			
HbA1c	×			×			
HOMA-IR	×			×			
Blood lipid	×			×			
Body composition analysis	×			×			
Abdominal MRI	×			×			
IWQOL-Lite	×	×	×	×	×	×	×
TFEQ-R21	×	×	×	×	×	×	×
FCQ-T	×	×	×	×	×	×	×
Blinding		×	×	×			

TESS	×	×	×	×	×	×	×
Patients' compliance		×	×	×	×	×	×

Abbreviations:

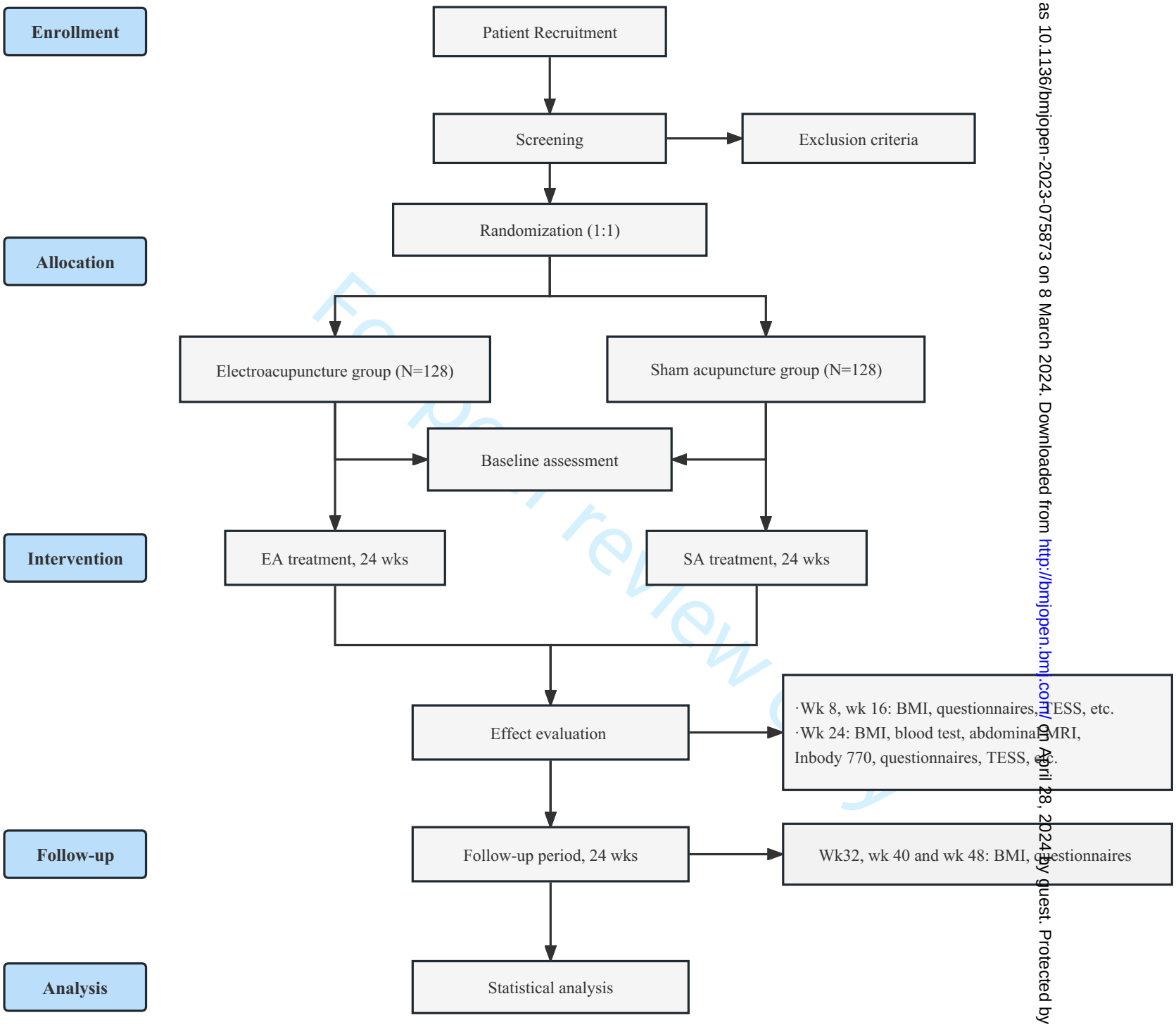
BMI: Body Mass Index; HbA1c: Hemoglobin A1c; MRI: Magnetic Resonance Imaging; IWQOL-Lite: Impact of Weight on Quality of Life; TESS: Treatment Emergent Symptom Scale; HOMA-IR: Insulin Resistance Index; TFEQ-R21: 21-item Three-Factor Eating Questionnaire; FCQ-T: Food Craving Questionnaire;

Table 2: Treatment methods of electroacupuncture and acupoints

	EA group	SA group
Main acupoints	CV13, CV12, CV11, CV10, LI11, LI4, ST21, ST25, SP15, SP14, ST28, ST36, ST40, ST26, and ST29.	CV13, CV12, CV11, CV10, LI11, LI4, ST21, ST25, SP15, SP14, ST28, ST36, ST40, ST26, and ST29.
Combined acupoints	ST37, ST44, SP9, CV9, CV6, and CV4	None
Needle type	Steel needles, 0.25*40mm at acupoints in the limbs, and 0.30*75mm at acupoints in the abdomen	Steel needles, 0.22*25mm at all acupoints
Needle sensation	With *de-qi* sensation	Without *de-qi* sensation
Electrical stimulation	Bilateral ST21, ST25, and SP15, with continuous wave, 3Hz frequency, and 4-5 mA current	Bilateral ST21, ST25, and SP15, with no current.

Abbreviations:

EA: Electroacupuncture; SA: Sham acupuncture; CV: Conception Vessel; LI: Large intestine meridian; ST: Stomach meridian; SP: Spleen meridian; CV13: Shangwan; CV12: Zhongwan; CV11: Jianli; CV10: Xiawan; LI11: Quchi; LI4: Hegu; ST21: Liangmen; ST25: Tianshu; SP15: Daheng; SP14: Fujie; ST28: Shuidao; ST36: Zusanli; ST40: Fenglong; ST26: Wailing; ST29: Guilai; ST37: Shangjuxu; ST44: Neiting; SP9: Yinlingquan; CV9: Shuifen; CV6: Qihai; CV4: Guanyuan.



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Strengths and limitations

- This is a single-center, randomized, and controlled clinical trial with a large sample size, and a long intervention and follow-up period to observe the effects of acupuncture on losing weight among obese patients with comorbid prediabetes.
- Changes on the body weight, glucolipid metabolism, body composition as well as the adverse events will be comprehensively evaluated to explore the effect of real and sham acupuncture treatment on weight loss.
- Acupuncture treatment based on 'syndrome differentiation' will be applied during the intervention period and it will provide more pragmatic evidence.
- Acupuncturists can't be blinded to the group assignment because of the treatment operations.
- Patients with prediabetes may progress to diabetes during the trial.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 4
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	No
Funding	4	Sources and types of financial, material, and other support	Page 23
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Page 1
	5b	Name and contact information for the trial sponsor	Page 1
	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	Page 23
	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)	Page 19

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 4
	6b	Explanation for choice of comparators	Page 4
Objectives	7	Specific objectives or hypotheses	Page 6
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 7
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 7
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 8-9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page 11
	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 11-12
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Page 11-12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Page 11-12
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 13-18
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 7 (Fig. 1)

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 8
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Page 8
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 10
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 10
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Page 19-20
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Page 10
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Page 10
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 13-17
	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	Page 18

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 19
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 18
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Page 18
	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 18
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	Page 19
	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	Page 19
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 17-18
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Page 19
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page 18-19
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)	Page 18-19

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 19-20
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Page 19-20
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	Page 19-20
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 22
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	Page 23
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	Page 12-13
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	Page 19-20
	31b	Authorship eligibility guidelines and any intended use of professional writers	Page 19-20
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Page 19-20
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Page 7
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	Page 13-17

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Effect and Safety of Electroacupuncture on Weight Loss in Obese Patients with Prediabetes: Study Protocol of a Randomised Controlled Trial

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Keywords:	Obesity, Randomized Controlled Trial, DIABETES & ENDOCRINOLOGY

Effect and Safety of Electroacupuncture on Weight Loss in Obese Patients with Prediabetes: Study Protocol of a Randomised Controlled Trial

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Abstract

Introduction: Obesity has been identified as a significant risk factor for several chronic conditions, including diabetes, tumors, and cardiovascular disease, and has been associated with increased mortality rates. Despite the well-established clinical practice of electroacupuncture (EA) as a potential treatment option for obesity, its efficacy remains questionable, primarily due to the paucity of empirical evidence supporting its therapeutic benefits.

Methods and analysis: The present study aims to investigate the efficacy and safety of electroacupuncture (EA) for weight loss in obese individuals with prediabetes, using a randomized, placebo-controlled clinical trial design. A total of 256 eligible patients will be randomly assigned to one of two groups: EA (comprising EA treatment with health education) or superficial acupuncture (SA) (comprising SA treatment with health education). The intervention will be administered three times per week for the initial 12 weeks, twice per week for the subsequent eight weeks, and once per week for the final four weeks, with a 24-week follow-up period. The primary outcome measure will be the percentage of patients who achieve a reduction of 10% or more in their body weight at week 24. Secondary outcome measures will include changes in body weight and BMI, blood test results, data collected by the body composition analyzer, size of adipose tissue scanned by magnetic resonance imaging of the abdomen, and the impact of weight on Quality of Life (IWQOL-Lite), The Three-Factor Eating Questionnaire-R21 (TFEQ-R21), and the Food Craving Questionnaire (FCQ-T). The Treatment Emergent Symptom Scale (TESS) will be employed to monitor every adverse reaction from baseline to follow-up.

Ethics and dissemination: This trial has received ethical clearance from the Ethics Committee of Shanghai Municipal Hospital of Traditional Chinese Medicine under the registration number 2021SHL-KY-74. All participants will provide their written informed consent prior to their enrolment. The findings of this investigation will be disseminated through peer-reviewed publications and scholarly conferences.

Trial registration: ClinicalTrials.gov ID: NCT05237089; Pre-results

Keywords: obesity, prediabetes, electroacupuncture, weight loss, randomized controlled trial

Strengths and Limitations

- Objective outcomes will be comprehensively evaluated to explore the effect of electroacupuncture on weight loss and glucose metabolism.
- Acupuncture based on 'syndrome differentiation' will be applied to provide more pragmatic evidence.
- Acupuncturists can't be blinded to the group assignment because of the acupuncture operations.
- Patients with prediabetes may progress to diabetes during the trial.
- Patients' varying degrees of lifestyle modification may influence the results of the trial to some extent.

Introduction

Obesity is a chronic metabolic disorder characterized by excessive accumulation of adipose tissue. It is defined by a body mass index (BMI) of 30 or more, reflecting a high level of obesity [1,2]. Epidemiological evidence has consistently shown that obesity is a significant risk factor for a variety of adverse health outcomes, including cardiovascular disease, diabetes mellitus and various types of cancer [3]. Notably, China currently has the highest proportion of obese and diabetic patients worldwide [4].

In individuals with prediabetes and obesity, losing 10% or more of their body weight has been shown to be extremely effective in preventing the onset of type 2 diabetes [5]. Maintaining a healthy lifestyle that includes healthy eating habits, regular physical activity, and effective stress management can facilitate healthy weight management [6-8]. However, sustaining lifestyle changes over the long term can prove challenging. Therefore, some individuals may consider alternative strategies such as weight loss medications or surgery.

Weight-loss drugs can suppress appetite and increase energy expenditure, but they can also interfere with digestive and absorption functions, leading to side effects such as nausea, vomiting, constipation, dizziness, and dry mouth. Evidence suggests that long-term use of these drugs may increase the risk of cardiovascular disease and mental illness [9, 10]. Surgical procedures for weight loss, have the potential for significant benefits, but also carry significant risks. Complications such as excessive bleeding, infection, acid reflux and intestinal obstruction are possible [11].

Electroacupuncture (EA) is an innovative form of traditional Chinese acupuncture that incorporates electrical impulses to enhance the therapeutic effects. EA has emerged as an

alternative therapy for obesity. Previous studies have demonstrated its superiority over lifestyle advice or sham acupuncture in reducing BMI, body weight, body fat mass, waist-to-hip ratio (WHR), triglyceride (TG) and total cholesterol (TC) levels [12]. EA has also been shown to improve glycemic control and insulin sensitivity in patients with type 2 diabetes mellitus, thereby possibly preventing the development of diabetes and its complications [13, 14].

To investigate the impact of EA on the treatment of obese patients with prediabetes and to address some of the limitations of previous studies, we designed a randomized controlled trial (RCT) with an adequate follow-up period. The study will evaluate the effectiveness of EA treatment in weight loss and diabetes prevention using subjective and objective measures while minimizing the placebo effect through the use of an appropriate superficial acupuncture (SA) method. Our findings can inform the development of optimal acupuncture treatment protocols for obesity and prediabetes, providing valuable insights for healthcare professionals, policy makers and the general public.

Methods/design

Hypothesis

The main objective of this study is to evaluate the efficacy of EA versus SA treatment in the treatment of obesity and prediabetes in a randomized controlled trial. Our hypothesis is that EA will be superior to SA in promoting weight loss and preventing the onset of diabetes in obese patients with prediabetes. By providing conclusive evidence on the effectiveness of EA treatment, this study may help inform clinical practice and guide the development of more effective treatment strategies for this growing public health problem.

Study design

This study protocol describes a single-site, randomized, patient-assessor-blinded, and placebo-controlled clinical study designed to evaluate the efficacy and safety of EA for weight loss in obese patients with prediabetes. The study will be conducted at the Acupuncture Department of the Shanghai Municipal Hospital of Traditional Chinese Medicine, recruiting 256 participants who will be randomly assigned to either the EA or SA treatment group. After a one-week baseline assessment, the study intervention will continue for 24 weeks, with a 16-week follow-up period. Assessments of patient outcomes will be conducted during the intervention period (weeks 8, 16, and 24) and the follow-up period (weeks 32, 40, and 48). The study process is shown in Figure 1 and the timeline for registration, intervention, and assessment is shown in Table 1. We started the study on September, 2022 and planned to finish the recruitment at the end of 2024, and the whole trial might be finished on December, 2026. Compliance with the Consolidated Standards for Study Reporting (CONSORT) and the Standards for Reporting of Interventions in Clinical Trials in Acupuncture (STRICTA) will be maintained throughout the trial [15].

Sample size calculation

The sample size calculation for this study was based on the proportion of patients achieving weight loss of 10% or more of their body weight, with the assumption that EA treatment would be more effective than SA treatment. Previous research conducted in this area has shown that the proportion of patients achieving this level of weight loss is 26% in the EA group and 11% in the SA group, as shown in a previous RCT [16]. Sample size calculations were performed using PASS 15.0 software (NCSS. LLC, Utah, USA) which revealed that each group would

require 102 cases to achieve a Type I error rate of 0.025 (one-sided) and a power of 80% to reach. With a dropout rate of 20%, a total of 256 cases were required, with 128 cases allocated to each group.

Subject recruitment and randomization

Patients are recruited via WeChat advertisements and hospital banners. Screening is conducted through telephone or in-person consultations. Eligible patients are provided with comprehensive information about the study's objectives, methods, and potential benefits and risks. They are also requested to complete a set of questionnaires during their initial visit to assess their eligibility for the trial. Upon confirmation of eligibility, patients are invited to participate in the study and sign a written informed consent form before the intervention begins.

Inclusion Criteria

Enrollment criteria for study participants encompass the following:

(1) male or female individuals between 18 and 65 years of age;

(2) participants with a BMI of $\geqslant$24.0 kg/m^2;

(3) participants with a hemoglobin A1c (HbA1c) value between 5.7% and 6.4% or a fasting plasma glucose value between 6.1 mmol/L and <7.0 mmol/L or a 2-hour postprandial plasma glucose level (oral glucose tolerance test) between 7.8 mmol/L and <11.1 mmol/L;

(4) participants who have maintained a stable weight within 4 kg for the three months prior to study commencement;

(5) participants who provide their voluntary consent by signing a written consent form.

Exclusion Criteria

Exclusion criteria for study participants are as follows:

(1) participants with secondary obesity induced by drugs or neuroendocrine-metabolic disorders (such as hypothalamic disease and hypopituitarism);

(2) participants diagnosed with type 1 or type 2 diabetes;

(3) participants who are taking medications that may interfere with the study outcomes (which cause weight loss, such as liraglutide or semaglutide; or that may cause weight gain, such as dexamethasone);

(4) participants with a score of >18 on the 17-item Hamilton Depression Scale (HDRS-17);

(5) participants with severe ulcers, abscesses, or skin infections in the local acupuncture area;

(6) participants with severe cardiac, cerebral, pulmonary, hepatic, renal, hematological, or other serious medical conditions;

(7) participants who have participated in other clinical trials within the last month;

(8) pregnant or lactating women.

Randomization and allocation concealment

Participant allocation will be accomplished through a process of randomization employing random block sizes of 4, 6, and 8. Stratification will be based on three criteria: (1) BMI; (2) gender; and (3) age. Eligible participants will be randomly assigned to either the EA or SA group at a 1:1 ratio, utilizing computer-generated random sequences. Distribution cards will be generated and enclosed in opaque, sealed envelopes. Participants will receive envelopes sequentially according to the order of enrollment from an independent researcher, and envelopes will be opened by an acupuncturist prior to treatment. All randomization procedures will be executed at a central office by researchers not associated with intervention, evaluation, or data collection. Throughout the trial, the study sponsor will maintain records of the

randomization results.

Blinding and researcher shielding

This study will employ a patient-assessor-blinded approach. Participants will be informed, during the screening process, of their equal chance of receiving either conventional EA or SA treatment. Patients will be treated in the supine position, with a specialized shield positioned over the chest to prevent movement during treatment. All treatment sessions will be conducted in a secluded environment without private communication between patients to ensure the implementation of blinding procedures. Acupuncturists will be the only individuals informed of the participants' allocation. All researchers will undergo pre-study training and follow strict segregation of duties policies throughout the study.

Intervention

During the intervention period, patients in both EA and SA groups will undergo 56 treatment sessions. The interventions will be administered three times per week, every other day, for the initial 12 weeks. Subsequently, the interventions will be given twice per week, on Mondays and Fridays, for an additional 8 weeks, and once per week during the final 4 weeks. The duration of each session will be 30 minutes. To ensure patient comfort and safety, the treatment room temperature must remain above 25°C. Additionally, all patients will receive identical health education brochures detailing the benefits of personalized lifestyle practices during the 24-week intervention period.

EA group

In the EA group, patients will receive authentic acupuncture treatment combined with low-frequency pulse electrical stimulation. The acupuncture treatment will involve the use of

disposable sterile stainless-steel needles (Wuxi Jiajian Medical Device Co., LTD, China), with a diameter of either 0.25mm*40mm or 0.30mm*75mm at acupoints in different parts of the bodies. The acupuncturists will manipulate the needles by lifting-thrusting or twirling to achieve the De-qi sensation. The acupuncturists will use the main acupoints and choose the combined acupoints based on the syndrome differentiation during each session of the treatment. The main acupoints will include Shangwan (CV13), Zhongwan (CV12), Jianli (CV11), Xiawan (CV10), bilateral Quchi (LI11), Hegu (LI4), Liangmen (ST21), Tianshu (ST25), Daheng (SP15), Fujie (SP14), Shuidao (ST28), Zusanli (ST36), Fenglong (ST40), Wailing (ST26), and Guilai (ST29). The combined acupoints will include bilateral Shangjuxu (ST37), Neiting (ST44), Yinlingquan (SP9), Shuifen (CV9), Qihai (CV6), and Guanyuan (CV4). The electrodes of the EA apparatus (Type G6805-2B, Shanghai Huayi Medical Instrument Co., LTD, China) will be connected to the needles at the bilateral ST21, ST25, and SP15 acupoints. The EA stimulation will be continuous wave type, with a frequency of 3 Hz, and an intensity of 4-5 mA, adjusted based on the endurance of each patient. The details of the acupoints and EA parameters are presented in Table 2.

SA group

In the SA group, participants will receive superficial acupuncture treatment applied to the same main acupoints as those used in the EA group, while no combined acupoints will be used for intervention. Sterile disposable stainless-steel needles with a diameter of 0.22*0.25mm will be inserted into the skin for about 2-3mm in depth, and no De-qi sensation will be intentionally achieved. The electrodes of the EA apparatus will be connected to the needles at the bilateral ST21, ST25, and SP15 acupoints as well. However, the electric wires will be intentionally

broken inside the apparatus, without current output during the treatment.

Health education

The health management brochure will be disseminated to all participants upon enrollment, and health education sessions will be conducted either online or offline at weeks 8, 16, and 24, with a duration of approximately 60 minutes each. The researchers will offer personalized advice on healthy lifestyle practices tailored to each individual patient's characteristics, with no imposed restrictions on their dietary habits or physical activity levels.

Outcome measures

The primary outcome of this study is the proportion of patients who have lost 10% or more of their initial body weight at week 24 in both groups. Secondary outcomes include changes in body weight, BMI, blood test results, abdominal magnetic resonance imaging (MRI) measurements of fat tissue size, data collected from the body composition analyzer, and scores on the Impact of Weight on Quality of Life (IWQOL-Lite), the Three-Factor Eating Questionnaire-R21 (TFEQ-R21), and the Food Craving Questionnaire (FCQ-T). All adverse effects will be assessed using the Treatment Emergent Symptom Scale (TESS) from baseline to the follow-up period.

Body weight and BMI will be calculated at baseline, week 8, week 16, week 24, week 32, week 40, and week 48, and IWQOL-Lite, TFEQ-R21, and FCQ-T scores will also be collected at these time points. Blood tests will be performed at baseline and week 24, while the body composition analyzer and abdominal MRI scan will be conducted at baseline and week 24. A detailed schedule of assessments can be found in Table 1.

Primary outcome measure

The primary objective of this study is to assess the proportion of participants who achieved a weight loss of 10% or more of their baseline body weight at the end of the intervention period (week 24) and compare the between-group difference. Previous research suggests that a weight loss of 5% to 15% in obese individuals can lead to significant improvements in glucose control and reduce the risk of type 2 diabetes and its associated complications [17]. As such, the 10% weight loss threshold is an important clinical marker of success in weight management interventions.

Secondary outcome measures

Obesity level

We will calculate the mean difference in body weight of the subjects during the intervention and follow-up periods compared to baseline measurements. The BMI can estimate body fat in relation to a person's height and weight. It is determined by dividing the weight of an individual in kilograms by the square of their height in meters. We will supplement our analysis with data from the Inbody 770 non-invasive body composition analyzer (Biospace Inc. Dba Inbody, California, USA), which uses bioelectrical impedance analysis to determine high-density body composition, including body fat mass, skeletal muscle mass, body fat percentage, and basal metabolic rate at baseline and at week 24. Body fat mass provides an insight into the quantity of body fat contributing to weight, including subcutaneous and visceral deposits. Skeletal muscle mass is a proxy for the amount of muscle tissue that can be stimulated and developed through exercise. Furthermore, the muscle-fat analysis furnishes information on whether the patient has a harmonious distribution of skeletal muscle mass and body fat mass concerning their weight. Body fat percentage might be a superior indicator of the risk of obesity compared

to BMI [18], and basal metabolic rate represents the number of calories a person requires to sustain basic bodily functions. Quantitative assessments of the size of abdominal adipose tissues and the intra-abdominal to subcutaneous adipose tissue ratio can be accomplished using an abdominal MRI scan.

Glucolipid metabolism

We will access the blood test of glucose and lipid metabolism to find out the differences between patients in two groups. Patients must abstain from food and water twice on the evening before the blood test, after 10 p.m., and at baseline and week 24. It is the blood glucose concentration, including fasting plasma glucose (FPG), which reflects the secretory function of the islet cell and 2-hour postprandial blood glucose (2hPG), reflecting the reserve function of the islet cell [19]. HbA1c levels of 5.5% indicate the presence of insulin resistance, while levels of 6.5% indicate the occurrence of diabetes [20]. Insulin resistance is commonly assessed using the homeostasis model assessment of insulin resistance (HOMA-IR). This index increases in severity as insulin resistance becomes more pronounced [21]. HOMA-IR is calculated by multiplying fasting plasma insulin (FPI) by fasting plasma glucose (FPG), and dividing the product by the constant 22.5 [22]. Blood lipids, including low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), and triglycerides (TG), can reflect the body's lipid metabolism. Elevated LDL-C levels in obese patients increase the risk of cardiovascular disease, and may also serve as a predictor of diabetes[23].

Questionnaires

The present study utilized three standardized self-report questionnaires to assess the quality of

life and eating behaviors of individuals with obesity. IWQOL-Lite consists of 31 items and evaluates five dimensions of quality of life, namely physical functioning, self-esteem, sex life, public stress, and work [24]. TFEQ-R21 assesses three aspects of eating behavior, including emotional eating (eating in response to negative emotions), uncontrolled eating (eating in response to food exposure or hunger), and cognitive restraint (deliberate attempt to limit eating). Scores range from 0 to 100, with higher scores indicating greater levels of eating behavior [25]. FCQ-T comprises 39 items grouped into nine subscales that assess food cravings, including intentions and plans about eating, expectation of positive reinforcement that eating may produce, expectation of alleviation of negative states and feelings as a result of eating, lack of control over eating, thoughts or preoccupation with food, cravings as a physiological state, emotions that may be experienced before or during cravings or while eating, cues that can trigger cravings, and guilt about cravings and/or giving in [26]. These questionnaires are widely used and have been validated for measuring quality of life and eating behaviors in individuals with obesity, providing valuable insights into the impact of obesity on daily living.

Adverse Events

Common AEs associated with acupuncture include bleeding, fainting, subcutaneous hematoma, and severe pain. The acupuncturists responsible for the treatment will evaluate these AEs based on their severity and document their incidence. The grading system for severity of AEs consists of three levels: grade 1 for mild, grade 2 for moderate, and grade 3 for severe or medically significant. The incidence of AEs will be expressed as the number of AEs per number of acupuncture sessions, calculated as a percentage.

In addition, any diseases or events that may be affected by acupuncture treatment or that may

affect the efficacy of the treatment, such as cold, fever, abdominal pain, diarrhea, and constipation, will be recorded by the TESS in the case report form. The TESS will also document the resolution of these events. By doing so, the study can obtain a comprehensive understanding of the potential AEs and their severity associated with acupuncture treatment, as well as any confounding factors that may influence the outcome.

Statistical analysis

Analyses were conducted on the intention-to-treat (ITT) population, which included all participants who received at least one treatment. To address missing data, multiple imputation was utilized, assuming a specific distribution of values at each time point calculated by the R software. Linear mixed effects models were employed for analysis, utilizing IBM SPSS Statistics for Windows (version 24.0; IBM Corp, Armonk, NY, USA).

For comparison of measurement data between the groups at baseline and follow-up, the t-test was employed, while the rank sum test was utilized for ranked data, and the chi-square test for categorical data. All statistical analyses employed two-tailed tests at a level of significance of 5%. Results were primarily presented as mean ± standard deviation (SD).

Ethics and clinical trial registration

All practitioners of acupuncture in this study are licensed acupuncturists with 3-5 years of clinical experience in the department of acupuncture and moxibustion at Shanghai Municipal Hospital of Traditional Chinese Medicine. To ensure the quality of the study, all practitioners undergo clinical training before the intervention.

This randomized controlled trial has been approved by the Ethics Committee of Shanghai Municipal Hospital of Traditional Chinese Medicine (2021SHL-KY-74) on November 19th,

2021, and is registered with ClinicalTrials.gov (NCT05237089). Before participating in the trial, all patients are required to sign a written informed consent.

An independent Data and Safety Monitoring Board (DSMB) has been established, including three experts in the field, namely Professor Lixing Lao, a specialist in clinical trials of acupuncture therapy; Chief Xianyu Tang, a specialist in diabetes; and Director Ruiping Wang, a specialist in statistics. The DSMB monitors the progress of the trial, examines collected data, and controls for bias. The members are authorized to supervise the process at any time and may raise objections directly or even halt the trial in the event of serious adverse events until the problem has been resolved.

Patient and public involvement

Prior to the design phase of the trial, the researchers consulted obese patients, with or without abnormal glucose metabolism, in the outpatients of the acupuncture department. The suggested treatment frequency, duration, and follow-up period of the study were informed by endocrinologists and epidemiologists. Eligible participants will be recruited from Shanghai Municipal Hospital of Traditional Chinese Medicine. Patients who participated in the consultation process for the trial design will be excluded. Upon completion of the trial, a manuscript with a comprehensive account of the results will be written for publication in a scholarly journal. Additionally, a brief summary of the findings, written in plain language, will be distributed to all participants.

Discussion

Recent decades have witnessed a dramatic surge in the prevalence of obesity, with nearly half

(48.5%) of obese adults exhibiting prediabetes or diabetes. The World Health Organization reports that obesity significantly elevates the risk of developing type 2 diabetes, underscoring the gravity of the global obesity pandemic [27]. Mitigating the comorbidities associated with obesity mandates weight loss, yet current treatment modalities are limited in their efficacy. Bariatric surgery, while efficacious, is available to only a minority of patients and poses serious complications [28]. Alternative therapies remain suboptimal, and further research is necessary to develop more effective interventions.

Acupuncture therapy is a popular non-pharmacological alternative treatment for obesity due to its demonstrated efficacy and safety. Previous RCTs have focused primarily on acupuncture for simple obesity, neglecting comorbid symptoms of obesity, such as abnormal glucose metabolism. Researches showed that acupuncture could regulate insulin secretion by regulating the neuroendocrine pathway [29,30]. and regulate glucose and lipid metabolism of insulin target organs (eg, liver, adipose tissue, and skeletal muscle). Acupuncture can improve insulin resistance through the modulation of adipocytokines to promote glucose and lipids metabolism and increase energy consumption [31]. However, there is a significant lack of comparable RCTs investigating acupuncture for the treatment of abnormal glucose metabolism in obese patients with a large sample size and a long follow-up period.

Therefore, this study proposes a protocol for an RCT to examine the effectiveness and safety of EA in treating obesity and abnormal glucose metabolism. The study aims to address the existing limitations of previous clinical studies on acupuncture, including illogical design, imperfect blinding methods, and other difficulties in practical application. The trial will incorporate a more prolonged follow-up period to explore the sustained effects of acupuncture

on obesity and ascertain the duration of such effects. In order to eliminate possible placebo effects of EA treatment as well as to ensure the success of the blinding method, the SA method will be employed as control, which uses thinner and shorter needles to deliver flat acupuncture on the same main acupoints. In this trial, the acupoints for treatment are mainly located in the abdomen, where the acupoints from the Stomach, Kidney, and Spleen meridians and the Conception Vessel are close to each other. And thus, it is hard to use the needling at the non-acupoints as the sham acupuncture method to treat the obese patients. In the previous studies, the results showed that "superficial acupuncture" is not more effective than the acupuncture at non-acupoints or placebo acupuncture with sham acupuncture devices for the treatment of knee osteoarthritis [32]. Besides, a RCT in neck pain patients showed that neither nonacupoint shallow puncture nor nonpenetration had a significant therapeutic effect. Interestingly, the nonacupoint shallow puncture produced even less placebo response than nonpenetration acupuncture [33]. The fundamental principle of Traditional Chinese Medicine (TCM), 'treatment based on syndrome differentiation,' will guide the selection of acupoints for the treatment of obesity based on dialectical classification.

This trial aims to address two key technical issues, namely the application of the SA treatment and patients' compliance. To ensure the appropriate administration of SA, all acupuncturists will receive extensive training before the commencement of the trial. Additionally, researchers will educate patients on medical knowledge to promote overall health and wellness, as good compliance is crucial for the successful completion of the trial.

The primary objective of this clinical trial is to assess the efficacy of EA treatment in reducing weight among obese patients, regulating their blood glucose and metabolism, and

improving their quality of life. By conducting this trial, we aim to provide reliable scientific evidence for the clinical application of acupuncture in weight management and blood glucose control.

Trial status

This trial is now recruiting participants.

Competing interests statement

The authors declare that they have no competing interests.

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Author contributions

SFX is the main researcher who provided the conception and designed the study. XY is the co-researcher who contributed to the design of the study and critical revision of the manuscript. XYL contributed to the design of the protocol, and writing of the manuscript. JJL and CFH contributed to the manuscript draft. BJL and FL contributed to the design of the interventions.

JYL, XLZ and SSL contributed to the statistical design and the design of the randomization method. YQM is the project manager and contributed to the revision of the manuscript. All authors read and approved the final manuscript.

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Figure legends

Figure 1 Flowchart of the trial

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1 **Table legends**

2 Table 1 Schedule of enrolment, intervention, and assessments

3 Table 2 Treatment methods of electroacupuncture and acupoints

4

Table 1: Schedule of enrollment, intervention, and assessments

	Baseline	Treatment phase			Follow-up phase		
	Week	Week	Week	Week	Week	Week	Week
	0	8	16	24	32	40	48
Patients							
Enrollment	×						
Signed informed consent	×						
Medical history	×						
Randomization	×						
Intervention		×	×	×			
Outcome measures							
BMI	×	×	×	×	×	×	×
Blood glucose	×			×			
HbA1c	×			×			
HOMA-IR	×			×			
Blood lipid	×			×			
Body composition analysis	×			×			
Abdominal MRI	×			×			
IWQOL-Lite	×	×	×	×	×	×	×
TFEQ-R21	×	×	×	×	×	×	×
FCQ-T	×	×	×	×	×	×	×
Blinding		×	×	×			

TESS	×	×	×	×	×	×	×
Patients' compliance		×	×	×	×	×	×

Abbreviations:

BMI: Body Mass Index; HbA1c: Hemoglobin A1c; MRI: Magnetic Resonance Imaging; IWQOL-Lite: Impact of Weight on Quality of Life; TESS: Treatment Emergent Symptom Scale; HOMA-IR: Insulin Resistance Index; TFEQ-R21: 21-item Three-Factor Eating Questionnaire; FCQ-T: Food Craving Questionnaire;

Table 2: Treatment methods of electroacupuncture and acupoints

	EA group	SA group
Main acupoints	CV13, CV12, CV11, CV10, LI11, LI4, ST21, ST25, SP15, SP14, ST28, ST36, ST40, ST26, and ST29.	CV13, CV12, CV11, CV10, LI11, LI4, ST21, ST25, SP15, SP14, ST28, ST36, ST40, ST26, and ST29.
Combined acupoints	ST37, ST44, SP9, CV9, CV6, and CV4	None
Needle type	Steel needles, 0.25*40mm at acupoints in the limbs, and 0.30*75mm at acupoints in the abdomen	Steel needles, 0.22*25mm at all acupoints
Needle sensation	With *de-qi* sensation	Without *de-qi* sensation
Electrical stimulation	Bilateral ST21, ST25, and SP15, with continuous wave, 3Hz frequency, and 4-5 mA current	Bilateral ST21, ST25, and SP15, with no current.

Abbreviations:

EA: Electroacupuncture; SA: Superficial acupuncture; CV: Conception Vessel; LI: Large intestine meridian; ST: Stomach meridian; SP: Spleen meridian; CV13: Shangwan; CV12: Zhongwan; CV11: Jianli; CV10: Xiawan; LI11: Quchi; LI4: Hegu; ST21: Liangmen; ST25: Tianshu; SP15: Daheng; SP14: Fujie; ST28: Shuidao; ST36: Zusanli; ST40: Fenglong; ST26: Wailing; ST29: Guilai; ST37: Shangjuxu; ST44: Neiting; SP9: Yinlingquan; CV9: Shuifen; CV6: Qihai; CV4: Guanyuan.

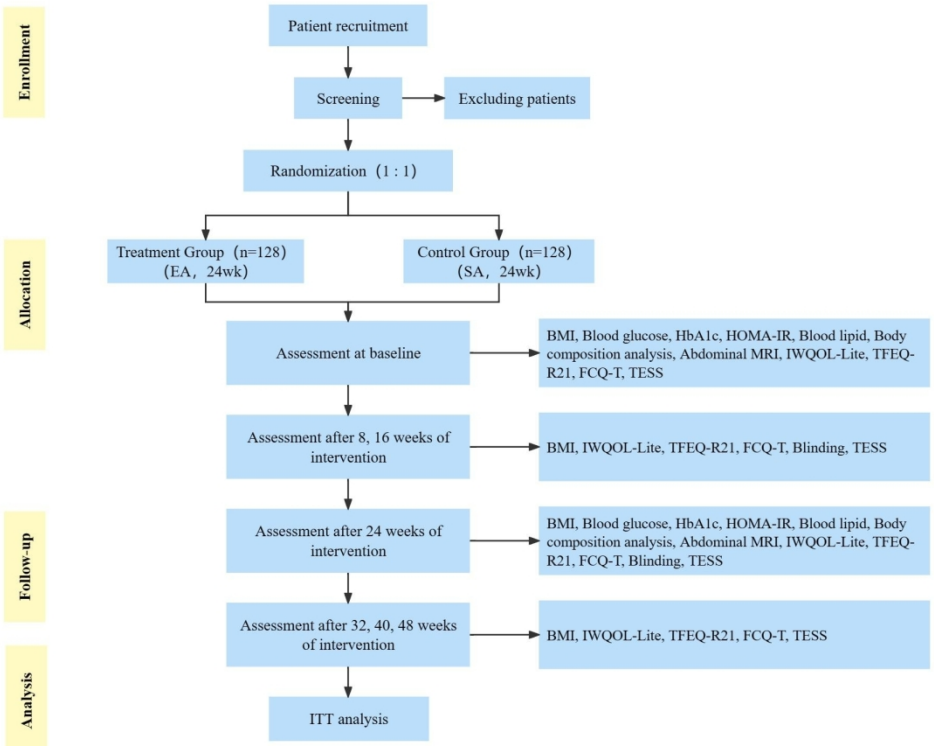

Figure 1 Flowchart of the trial

404x324mm (120 x 120 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 4
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	No
Funding	4	Sources and types of financial, material, and other support	Page 23
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Page 1
	5b	Name and contact information for the trial sponsor	Page 1
	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	Page 23
	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)	Page 19

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 4
	6b	Explanation for choice of comparators	Page 4
Objectives	7	Specific objectives or hypotheses	Page 6
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 7
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 7
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 8-9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page 11
	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 11-12
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Page 11-12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Page 11-12
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 13-18
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 7 (Fig. 1)

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 8
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Page 8
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 10
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 10
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Page 19-20
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Page 10
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Page 10
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 13-17
	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	Page 18

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 19
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 18
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Page 18
	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 18
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	Page 19
	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	Page 19
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 17-18
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Page 19
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page 18-19
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)	Page 18-19

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 19-20
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Page 19-20
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	Page 19-20
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 22
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	Page 23
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	Page 12-13
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	Page 19-20
	31b	Authorship eligibility guidelines and any intended use of professional writers	Page 19-20
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Page 19-20
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Page 7
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	Page 13-17

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Effect and Safety of Electroacupuncture on Weight Loss in Obese Patients with Prediabetes: Study Protocol of a Randomised Controlled Trial

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Effect and Safety of Electroacupuncture on Weight Loss in Obese Patients with Prediabetes: Study Protocol of a Randomised Controlled Trial

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Abstract

Introduction: Obesity has been identified as a significant risk factor for several chronic conditions, including diabetes, tumors, and cardiovascular disease, and has been associated with increased mortality rates. Despite the well-established clinical practice of electroacupuncture (EA) as a potential treatment option for obesity, its efficacy remains questionable, primarily due to the paucity of empirical evidence supporting its therapeutic benefits.

Methods and analysis: The present study aims to investigate the efficacy and safety of electroacupuncture (EA) for weight loss in obese individuals with prediabetes, using a randomized, placebo-controlled clinical trial design. A total of 256 eligible patients will be randomly assigned to one of two groups: EA (comprising EA treatment with health education) or superficial acupuncture (SA) (comprising SA treatment with health education). The intervention will be administered three times per week for the initial 12 weeks, twice per week for the subsequent eight weeks, and once per week for the final four weeks, with a 24-week follow-up period. The primary outcome measure will be the percentage of patients who achieve a reduction of 10% or more in their body weight at week 24. Secondary outcome measures will include changes in body weight and BMI, blood test results, data collected by the body composition analyzer, size of adipose tissue scanned by magnetic resonance imaging of the abdomen, and the impact of weight on Quality of Life (IWQOL-Lite), The Three-Factor Eating Questionnaire-R21 (TFEQ-R21), and the Food Craving Questionnaire (FCQ-T). The Treatment Emergent Symptom Scale (TESS) will be employed to monitor every adverse reaction from baseline to follow-up.

Ethics and dissemination: This trial has received ethical clearance from the Ethics Committee of Shanghai Municipal Hospital of Traditional Chinese Medicine under the registration number 2021SHL-KY-74. All participants will provide their written informed consent prior to their enrolment. The findings of this investigation will be disseminated through peer-reviewed publications and scholarly conferences.

Trial registration: ClinicalTrials.gov ID: NCT05237089; Pre-results

Keywords: obesity, prediabetes, electroacupuncture, weight loss, randomized controlled trial

Strengths and Limitations

- This is a single-center, randomized, and controlled clinical trial with a large sample size, and a long intervention and follow-up period.
- Objective outcomes including the body weight, glucolipid metabolism and body composition，as well as the adverse events will be comprehensively evaluated.
- Acupuncture treatment based on "syndrome differentiation" will be applied and will provide more pragmatic evidence.
- Acupuncturists can’t be blinded to the group assignment because of the acupuncture treatment operations.
- Superficial acupuncture will be used as the control method, which may cause some therapeutic effects.

Introduction

Obesity is a chronic metabolic disorder characterized by excessive accumulation of adipose tissue. It is defined by a body mass index (BMI) of 30 or more, reflecting a high level of obesity [1,2]. Epidemiological evidence has consistently shown that obesity is a significant risk factor for a variety of adverse health outcomes, including cardiovascular disease, diabetes mellitus and various types of cancer [3]. Notably, China currently has the highest proportion of obese and diabetic patients worldwide [4].

In individuals with prediabetes and obesity, losing 10% or more of their body weight has been shown to be extremely effective in preventing the onset of type 2 diabetes [5]. Maintaining a healthy lifestyle that includes healthy eating habits, regular physical activity, and effective stress management can facilitate healthy weight management [6-8]. However, sustaining lifestyle changes over the long term can prove challenging. Therefore, some individuals may consider alternative strategies such as weight loss medications or surgery.

Weight-loss drugs can suppress appetite and increase energy expenditure, but they can also interfere with digestive and absorption functions, leading to side effects such as nausea, vomiting, constipation, dizziness, and dry mouth. Evidence suggests that long-term use of these drugs may increase the risk of cardiovascular disease and mental illness [9, 10]. Surgical procedures for weight loss, have the potential for significant benefits, but also carry significant risks. Complications such as excessive bleeding, infection, acid reflux and intestinal obstruction are possible [11].

Electroacupuncture (EA) is an innovative form of traditional Chinese acupuncture that incorporates electrical impulses to enhance the therapeutic effects. EA has emerged as an

alternative therapy for obesity. Previous studies have demonstrated its superiority over lifestyle advice or sham acupuncture in reducing BMI, body weight, body fat mass, waist-to-hip ratio (WHR), triglyceride (TG) and total cholesterol (TC) levels [12]. EA has also been shown to improve glycemic control and insulin sensitivity in patients with type 2 diabetes mellitus, thereby possibly preventing the development of diabetes and its complications [13, 14].

To investigate the impact of EA on the treatment of obese patients with prediabetes and to address some of the limitations of previous studies, we designed a randomized controlled trial (RCT) with an adequate follow-up period. The study will evaluate the effectiveness of EA treatment in weight loss and diabetes prevention using subjective and objective measures while minimizing the placebo effect with an appropriate superficial acupuncture (SA) method. Our findings can inform the development of optimal acupuncture treatment protocols for obesity and prediabetes, providing valuable insights for healthcare professionals, policy makers and the public.

Methods/design

Hypothesis

The main objective of this study is to evaluate the efficacy of EA versus SA treatment in the treatment of obesity and prediabetes in a randomized controlled trial. Our hypothesis is that EA will be superior to SA in promoting weight loss and preventing the onset of diabetes in obese patients with prediabetes. By providing conclusive evidence on the effectiveness of EA treatment, this study may help inform clinical practice and guide the development of more effective treatment strategies for this growing public health problem.

Study design

This study protocol describes a single-site, randomized, patient-assessor-blinded, and placebo-controlled clinical study designed to evaluate the efficacy and safety of EA for weight loss in obese patients with prediabetes. The study will be conducted at the Acupuncture Department of the Shanghai Municipal Hospital of Traditional Chinese Medicine, recruiting 256 participants who will be randomly assigned to either the EA or SA treatment group. After a one-week baseline assessment, the study intervention will continue for 24 weeks, with a 16-week follow-up period. Assessments of patient outcomes will be conducted during the intervention period (weeks 8, 16, and 24) and the follow-up period (weeks 32, 40, and 48). The study process is shown in Figure 1 and the timeline for registration, intervention, and assessment is shown in Table 1. We started the study on September, 2022 and planned to finish the recruitment at the end of 2024, and the whole trial might be finished on December, 2026. Compliance with the Consolidated Standards for Study Reporting (CONSORT) and the Standards for Reporting of Interventions in Clinical Trials in Acupuncture (STRICTA) will be maintained throughout the trial [15].

Sample size calculation

The sample size calculation for this study was based on the proportion of patients achieving weight loss of 10% or more of their body weight, with the assumption that EA treatment would be more effective than SA treatment. Previous research conducted in this area has shown that the proportion of patients achieving this level of weight loss is 26% in the EA group and 11% in the SA group, as shown in a previous RCT [16]. Sample size calculations were performed using PASS 15.0 software (NCSS. LLC, Utah, USA) which revealed that each group would

require 102 cases to achieve a Type I error rate of 0.025 (one-sided) and a power of 80% to reach. With a dropout rate of 20%, a total of 256 cases were required, with 128 cases allocated to each group.

Subject recruitment and randomization

Patients are recruited via WeChat advertisements and hospital banners. Screening is conducted through telephone or in-person consultations. Eligible patients are provided with comprehensive information about the study's objectives, methods, and potential benefits and risks. They are also requested to complete a set of questionnaires during their initial visit to assess their eligibility for the trial. Upon confirmation of eligibility, patients are invited to participate in the study and sign a written informed consent form (seen in Supplement 1) before the intervention begins.

Inclusion Criteria

Enrollment criteria for study participants encompass the following:

(1) male or female individuals between 18 and 65 years of age;

(2) participants with a BMI of $\geqslant$24.0 kg/m^2;

(3) participants with a hemoglobin A1c (HbA1c) value between 5.7% and 6.4% or a fasting plasma glucose value between 6.1 mmol/L and <7.0 mmol/L or a 2-hour postprandial plasma glucose level (oral glucose tolerance test) between 7.8 mmol/L and <11.1 mmol/L;

(4) participants who have maintained a stable weight within 4 kg for the three months prior to study commencement;

(5) participants who provide their voluntary consent by signing a written consent form.

Exclusion Criteria

Exclusion criteria for study participants are as follows:

(1) participants with secondary obesity induced by drugs or neuroendocrine-metabolic disorders (such as hypothalamic disease and hypopituitarism);

(2) participants diagnosed with type 1 or type 2 diabetes;

(3) participants who are taking medications that may interfere with the study outcomes (which cause weight loss, such as liraglutide or semaglutide; or that may cause weight gain, such as dexamethasone);

(4) participants with a score of >18 on the 17-item Hamilton Depression Scale (HDRS-17);

(5) participants with severe ulcers, abscesses, or skin infections in the local acupuncture area;

(6) participants with severe cardiac, cerebral, pulmonary, hepatic, renal, hematological, or other serious medical conditions;

(7) participants who have participated in other clinical trials within the last month;

(8) pregnant or lactating women.

Randomization and allocation concealment

Participant allocation will be accomplished through a process of randomization employing random block sizes of 4, 6, and 8. Stratification will be based on three criteria: (1) BMI; (2) gender; and (3) age. Eligible participants will be randomly assigned to either the EA or SA group at a 1:1 ratio, utilizing computer-generated random sequences. Distribution cards will be generated and enclosed in opaque, sealed envelopes. Participants will receive envelopes sequentially according to the order of enrollment from an independent researcher, and envelopes will be opened by an acupuncturist prior to treatment. All randomization procedures will be executed at a central office by researchers not associated with intervention, evaluation,

or data collection. Throughout the trial, the study sponsor will maintain records of the randomization results.

Blinding and researcher shielding

This study will employ a patient-assessor-blinded approach. Participants will be informed, during the screening process, of their equal chance of receiving either conventional EA or SA treatment. Patients will be treated in the supine position, with a specialized shield positioned over the chest to prevent movement during treatment. All treatment sessions will be conducted in a secluded environment without private communication between patients to ensure the implementation of blinding procedures. Acupuncturists will be the only individuals informed of the participants' allocation. All researchers will undergo pre-study training and follow strict segregation of duties policies throughout the study.

Intervention

During the intervention period, patients in both EA and SA groups will undergo 56 treatment sessions. The interventions will be administered three times per week, every other day, for the initial 12 weeks. Subsequently, the interventions will be given twice per week, on Mondays and Fridays, for an additional 8 weeks, and once per week during the final 4 weeks. The duration of each session will be 30 minutes. To ensure patient comfort and safety, the treatment room temperature must remain above 25°C. Additionally, all patients will receive identical health education brochures detailing the benefits of personalized lifestyle practices during the 24-week intervention period.

EA group

In the EA group, patients will receive authentic acupuncture treatment combined with low-

frequency pulse electrical stimulation. The acupuncture treatment will involve the use of disposable sterile stainless-steel needles (Wuxi Jiajian Medical Device Co., LTD, China), with a diameter of either 0.25mm*40mm or 0.30mm*75mm at acupoints in different parts of the bodies. The acupuncturists will manipulate the needles by lifting-thrusting or twirling to achieve the De-qi sensation. The acupuncturists will use the main acupoints and choose the combined acupoints based on the syndrome differentiation during each session of the treatment. The main acupoints will include Shangwan (CV13), Zhongwan (CV12), Jianli (CV11), Xiawan (CV10), bilateral Quchi (LI11), Hegu (LI4), Liangmen (ST21), Tianshu (ST25), Daheng (SP15), Fujie (SP14), Shuidao (ST28), Zusanli (ST36), Fenglong (ST40), Wailing (ST26), and Guilai (ST29). The combined acupoints will include bilateral Shangjuxu (ST37), Neiting (ST44), Yinlingquan (SP9), Shuifen (CV9), Qihai (CV6), and Guanyuan (CV4). The electrodes of the EA apparatus (Type G6805-2B, Shanghai Huayi Medical Instrument Co., LTD, China) will be connected to the needles at the bilateral ST21, ST25, and SP15 acupoints. The EA stimulation will be continuous wave type, with a frequency of 3 Hz, and an intensity of 4-5 mA, adjusted based on the endurance of each patient. The details of the acupoints and EA parameters are presented in Table 2.

SA group

In the SA group, participants will receive superficial acupuncture treatment applied to the same main acupoints as those used in the EA group, while no combined acupoints will be used for intervention. Sterile disposable stainless-steel needles with a diameter of 0.22*0.25mm will be inserted into the skin for about 2-3mm in depth, and no De-qi sensation will be intentionally achieved. The electrodes of the EA apparatus will be connected to the needles at the bilateral

ST21, ST25, and SP15 acupoints as well. However, the electric wires will be intentionally broken inside the apparatus, without current output during the treatment.

Health education

The health management brochure will be disseminated to all participants upon enrollment, and health education sessions will be conducted either online or offline at weeks 8, 16, and 24, with a duration of approximately 60 minutes each. The researchers will offer personalized advice on healthy lifestyle practices tailored to each individual patient's characteristics, with no imposed restrictions on their dietary habits or physical activity levels.

Outcome measures

The primary outcome of this study is the proportion of patients who have lost 10% or more of their initial body weight at week 24 in both groups. Secondary outcomes include changes in body weight, BMI, blood test results, abdominal magnetic resonance imaging (MRI) measurements of fat tissue size, data collected from the body composition analyzer, and scores on the Impact of Weight on Quality of Life (IWQOL-Lite), the Three-Factor Eating Questionnaire-R21 (TFEQ-R21), and the Food Craving Questionnaire (FCQ-T). All adverse effects will be assessed using the Treatment Emergent Symptom Scale (TESS) from baseline to the follow-up period.

Body weight and BMI will be calculated at baseline, week 8, week 16, week 24, week 32, week 40, and week 48, and IWQOL-Lite, TFEQ-R21, and FCQ-T scores will also be collected at these time points. Blood tests will be performed at baseline and week 24, while the body composition analyzer and abdominal MRI scan will be conducted at baseline and week 24. A detailed schedule of assessments can be found in Table 1.

Primary outcome measure

The primary objective of this study is to assess the proportion of participants who achieved a weight loss of 10% or more of their baseline body weight at the end of the intervention period (week 24) and compare the between-group difference. Previous research suggests that a weight loss of 5% to 15% in obese individuals can lead to significant improvements in glucose control and reduce the risk of type 2 diabetes and its associated complications [17]. As such, the 10% weight loss threshold is an important clinical marker of success in weight management interventions.

Secondary outcome measures

Obesity level

We will calculate the mean difference in body weight of the subjects during the intervention and follow-up periods compared to baseline measurements. The BMI can estimate body fat in relation to a person's height and weight. It is determined by dividing the weight of an individual in kilograms by the square of their height in meters. We will supplement our analysis with data from the Inbody 770 non-invasive body composition analyzer (Biospace Inc. Dba Inbody, California, USA), which uses bioelectrical impedance analysis to determine high-density body composition, including body fat mass, skeletal muscle mass, body fat percentage, and basal metabolic rate at baseline and at week 24. Body fat mass provides an insight into the quantity of body fat contributing to weight, including subcutaneous and visceral deposits. Skeletal muscle mass is a proxy for the amount of muscle tissue that can be stimulated and developed through exercise. Furthermore, the muscle-fat analysis furnishes information on whether the patient has a harmonious distribution of skeletal muscle mass and body fat mass concerning

their weight. Body fat percentage might be a superior indicator of the risk of obesity compared to BMI [18], and basal metabolic rate represents the number of calories a person requires to sustain basic bodily functions. Quantitative assessments of the size of abdominal adipose tissues and the intra-abdominal to subcutaneous adipose tissue ratio can be accomplished using an abdominal MRI scan.

Glucolipid metabolism

We will access the blood test of glucose and lipid metabolism to find out the differences between patients in two groups. Patients must abstain from food and water twice on the evening before the blood test, after 10 p.m., and at baseline and week 24. It is the blood glucose concentration, including fasting plasma glucose (FPG), which reflects the secretory function of the islet cell and 2-hour postprandial blood glucose (2hPG), reflecting the reserve function of the islet cell [19]. HbA1c levels of 5.5% indicate the presence of insulin resistance, while levels of 6.5% indicate the occurrence of diabetes [20]. Insulin resistance is commonly assessed using the homeostasis model assessment of insulin resistance (HOMA-IR). This index increases in severity as insulin resistance becomes more pronounced [21]. HOMA-IR is calculated by multiplying fasting plasma insulin (FPI) by fasting plasma glucose (FPG), and dividing the product by the constant 22.5 [22]. Blood lipids, including low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), and triglycerides (TG), can reflect the body's lipid metabolism. Elevated LDL-C levels in obese patients increase the risk of cardiovascular disease, and may also serve as a predictor of diabetes [23].

Questionnaires

The present study utilized three standardized self-report questionnaires to assess the quality of life and eating behaviors of individuals with obesity. IWQOL-Lite consists of 31 items and evaluates five dimensions of quality of life, namely physical functioning, self-esteem, sex life, public stress, and work [24]. TFEQ-R21 assesses three aspects of eating behavior, including emotional eating (eating in response to negative emotions), uncontrolled eating (eating in response to food exposure or hunger), and cognitive restraint (deliberate attempt to limit eating). Scores range from 0 to 100, with higher scores indicating greater levels of eating behavior [25]. FCQ-T comprises 39 items grouped into nine subscales that assess food cravings, including intentions and plans about eating, expectation of positive reinforcement that eating may produce, expectation of alleviation of negative states and feelings as a result of eating, lack of control over eating, thoughts or preoccupation with food, cravings as a physiological state, emotions that may be experienced before or during cravings or while eating, cues that can trigger cravings, and guilt about cravings and/or giving in [26]. These questionnaires are widely used and have been validated for measuring quality of life and eating behaviors in individuals with obesity, providing valuable insights into the impact of obesity on daily living.

Adverse Events

Common AEs associated with acupuncture include bleeding, fainting, subcutaneous hematoma, and severe pain. The acupuncturists responsible for the treatment will evaluate these AEs based on their severity and document their incidence. The grading system for severity of AEs consists of three levels: grade 1 for mild, grade 2 for moderate, and grade 3 for severe or medically significant. The incidence of AEs will be expressed as the number of AEs per number of acupuncture sessions, calculated as a percentage.

In addition, any diseases or events that may be affected by acupuncture treatment or that may affect the efficacy of the treatment, such as cold, fever, abdominal pain, diarrhea, and constipation, will be recorded by the TESS in the case report form. The TESS will also document the resolution of these events. By doing so, the study can obtain a comprehensive understanding of the potential AEs and their severity associated with acupuncture treatment, as well as any confounding factors that may influence the outcome.

Statistical analysis

Analyses were conducted on the intention-to-treat (ITT) population, which included all participants who received at least one treatment. To address missing data, multiple imputation was utilized, assuming a specific distribution of values at each time point calculated by the R software. Linear mixed effects models were employed for analysis, utilizing IBM SPSS Statistics for Windows (version 24.0; IBM Corp, Armonk, NY, USA).

For comparison of measurement data between the groups at baseline and follow-up, the t-test was employed, while the rank sum test was utilized for ranked data, and the chi-square test for categorical data. All statistical analyses employed two-tailed tests at a level of significance of 5%. Results were primarily presented as mean ± standard deviation (SD).

Ethics and clinical trial registration

All practitioners of acupuncture in this study are licensed acupuncturists with 3-5 years of clinical experience in the department of acupuncture and moxibustion at Shanghai Municipal Hospital of Traditional Chinese Medicine. To ensure the quality of the study, all practitioners undergo clinical training before the intervention.

This randomized controlled trial has been approved by the Ethics Committee of Shanghai

Municipal Hospital of Traditional Chinese Medicine (2021SHL-KY-74) on November 19th, 2021, and is registered with ClinicalTrials.gov (NCT05237089). Before participating in the trial, all patients are required to sign a written informed consent.

An independent Data and Safety Monitoring Board (DSMB) has been established, including three experts in the field, namely Professor Lixing Lao, a specialist in clinical trials of acupuncture therapy; Chief Xianyu Tang, a specialist in diabetes; and Director Ruiping Wang, a specialist in statistics. The DSMB monitors the progress of the trial, examines collected data, and controls for bias. The members are authorized to supervise the process at any time and may raise objections directly or even halt the trial in the event of serious adverse events until the problem has been resolved.

Patient and public involvement

Prior to the design phase of the trial, the researchers consulted obese patients, with or without abnormal glucose metabolism, in the outpatients of the acupuncture department. The suggested treatment frequency, duration, and follow-up period of the study were informed by endocrinologists and epidemiologists. Eligible participants will be recruited from Shanghai Municipal Hospital of Traditional Chinese Medicine. Patients who participated in the consultation process for the trial design will be excluded. Upon completion of the trial, a manuscript with a comprehensive account of the results will be written for publication in a scholarly journal. Additionally, a summary of the findings, written in plain language, will be distributed to all participants.

Discussion

Recent decades have witnessed a dramatic surge in the prevalence of obesity, with nearly half (48.5%) of obese adults exhibiting prediabetes or diabetes. The World Health Organization reports that obesity significantly elevates the risk of developing type 2 diabetes, underscoring the gravity of the global obesity pandemic [27]. Mitigating the comorbidities associated with obesity mandates weight loss, yet current treatment modalities are limited in their efficacy. Bariatric surgery, while efficacious, is available to only a minority of patients and poses serious complications [28]. Alternative therapies remain suboptimal, and further research is necessary to develop more effective interventions.

Acupuncture therapy is a popular non-pharmacological alternative treatment for obesity due to its demonstrated efficacy and safety. Previous RCTs have focused primarily on acupuncture for simple obesity, neglecting comorbid symptoms of obesity, such as abnormal glucose metabolism. Researches showed that acupuncture could regulate insulin secretion by regulating the neuroendocrine pathway [29,30]. and regulate glucose and lipid metabolism of insulin target organs (eg, liver, adipose tissue, and skeletal muscle). Acupuncture can improve insulin resistance through the modulation of adipocytokines to promote glucose and lipids metabolism and increase energy consumption [31]. However, there is a significant lack of comparable RCTs investigating acupuncture for the treatment of abnormal glucose metabolism in obese patients with a large sample size and a long follow-up period.

Therefore, this study proposes a protocol for an RCT to examine the effectiveness and safety of EA in treating obesity and abnormal glucose metabolism. The study aims to address the existing limitations of previous clinical studies on acupuncture, including illogical design, imperfect blinding methods, and other difficulties in practical application. The trial will

incorporate a more prolonged follow-up period to explore the sustained effects of acupuncture on obesity and ascertain the duration of such effects.

To eliminate possible placebo effects of EA treatment as well as to ensure the success of the blinding method, the SA method will be employed as control, which uses thinner and shorter needles inserting at the same main acupoints as the EA group. The fundamental principle of Traditional Chinese Medicine, 'treatment based on syndrome differentiation,' will guide the selection of acupoints for the treatment of obesity based on dialectical classification. The acupoints chosen for treatment are mainly located in the abdomen, where the acupoints from the Stomach, Kidney, and Spleen meridians and the Conception Vessel are closely located to each other. And thus, it is hard to use the needling at the non-acupoints as the sham acupuncture method to treat the obese patients. In the previous studies, the results showed that superficial acupuncture is not more effective than the acupuncture at non-acupoints or placebo acupuncture with sham acupuncture devices for the treatment of knee osteoarthritis [32]. Besides, a RCT in neck pain patients showed that neither non-acupoint shallow puncture nor non-penetration had a significant therapeutic effect. Interestingly, the non-acupoint shallow puncture produced even less placebo response than non-penetration acupuncture [33].

This trial aims to address two key technical issues, namely the application of the SA treatment and patients' compliance. To ensure the appropriate administration of SA, all acupuncturists will receive extensive training before the commencement of the trial. Additionally, researchers will educate patients on medical knowledge to promote overall health and wellness, as good compliance is crucial for the successful completion of the trial.

There are some limitations of this study. First, the acupuncturists can't be blinded to the

group assignment because of the EA treatment operations. To minimize deviations, the acupuncturists will strictly adhere the task separation principal and will be asked to avoid communication about the therapeutic effect with the participants. Secondly, superficial acupuncture applied in the control group is a kind of conventional acupuncture treatment and it will produce little effect for acupoints in the abdomen in this trial. To ensure patients' blindness to the group assignment and to reduce the dropout rate during such a long intervention period, we decide to insert the needles into the skin as control, with only about 2-3mm in depth. Besides, patients with prediabetes may progress to diabetes during the trial. We will focus on the patients' symptomatic changes when assessing the primary outcome and will provide free EA treatment sessions to patients in the control group after the end of the follow-up period.

The primary objective of this clinical trial is to assess the efficacy of EA treatment in reducing weight among obese patients, regulating their blood glucose and metabolism, and improving their quality of life. By conducting this trial, we aim to provide reliable scientific evidence for the clinical application of acupuncture in weight management and blood glucose control.

Trial status

This trial is now recruiting participants.

Competing interests statement

The authors declare that they have no competing interests.

Acknowledgement

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Author contributions

SFX is the main researcher who provided the conception and designed the study. XY is the co-researcher who contributed to the design of the study and critical revision of the manuscript. XYL contributed to the design of the protocol, and writing of the manuscript. JJL and CFH contributed to the manuscript draft. BJL and FL contributed to the design of the interventions. JYL, XLZ and SSL contributed to the statistical design and the design of the randomization method. YQM is the project manager and contributed to the revision of the manuscript. All authors read and approved the final manuscript.

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Figure legends

Figure 1 Flowchart of the trial

Table legends

Table 1 Schedule of enrolment, intervention, and assessments

Table 2 Treatment methods of electroacupuncture and acupoints

Supplementary Material

Supplement 1 Informed consent form

Table 1： Schedule of enrollment, intervention, and assessments

	Baseline	Treatment phase			Follow-up phase		
	Week	Week	Week	Week	Week	Week	Week
	0	8	16	24	32	40	48
Patients							
Enrollment	×						
Signed informed consent	×						
Medical history	×						
Randomization	×						
Intervention		×	×	×			
Outcome measures							
BMI	×	×	×	×	×	×	×
Blood glucose	×			×			
HbA1c	×			×			
HOMA-IR	×			×			
Blood lipid	×			×			
Body composition analysis	×			×			
Abdominal MRI	×			×			
IWQOL-Lite	×	×	×	×	×	×	×
TFEQ-R21	×	×	×	×	×	×	×
FCQ-T	×	×	×	×	×	×	×
Blinding		×	×	×			

TESS	×	×	×	×	×	×	×
Patients' compliance		×	×	×	×	×	×

Abbreviations:

BMI: Body Mass Index; HbA1c: Hemoglobin A1c; MRI: Magnetic Resonance Imaging; IWQOL-Lite: Impact of Weight on Quality of Life; TESS: Treatment Emergent Symptom Scale; HOMA-IR: Insulin Resistance Index; TFEQ-R21: 21-item Three-Factor Eating Questionnaire; FCQ-T: Food Craving Questionnaire;

Table 2: Treatment methods of electroacupuncture and acupoints

	EA group	SA group
Main acupoints	CV13, CV12, CV11, CV10, LI11, LI4, ST21, ST25, SP15, SP14, ST28, ST36, ST40, ST26, and ST29.	CV13, CV12, CV11, CV10, LI11, LI4, ST21, ST25, SP15, SP14, ST28, ST36, ST40, ST26, and ST29.
Combined acupoints	ST37, ST44, SP9, CV9, CV6, and CV4	None
Needle type	Steel needles, 0.25*40mm at acupoints in the limbs, and 0.30*75mm at acupoints in the abdomen	Steel needles, 0.22*25mm at all acupoints
Needle sensation	With *de-qi* sensation	Without *de-qi* sensation
Electrical stimulation	Bilateral ST21, ST25, and SP15, with continuous wave, 3Hz frequency, and 4-5 mA current	Bilateral ST21, ST25, and SP15, with no current.

Abbreviations:

EA: Electroacupuncture; SA: Superficial acupuncture; CV: Conception Vessel; LI: Large intestine meridian; ST: Stomach meridian; SP: Spleen meridian; CV13: Shangwan; CV12: Zhongwan; CV11: Jianli; CV10: Xiawan; LI11: Quchi; LI4: Hegu; ST21: Liangmen; ST25: Tianshu; SP15: Daheng; SP14: Fujie; ST28: Shuidao; ST36: Zusanli; ST40: Fenglong; ST26: Wailing; ST29: Guilai; ST37: Shangjuxu; ST44: Neiting; SP9: Yinlingquan; CV9: Shuifen; CV6: Qihai; CV4: Guanyuan.

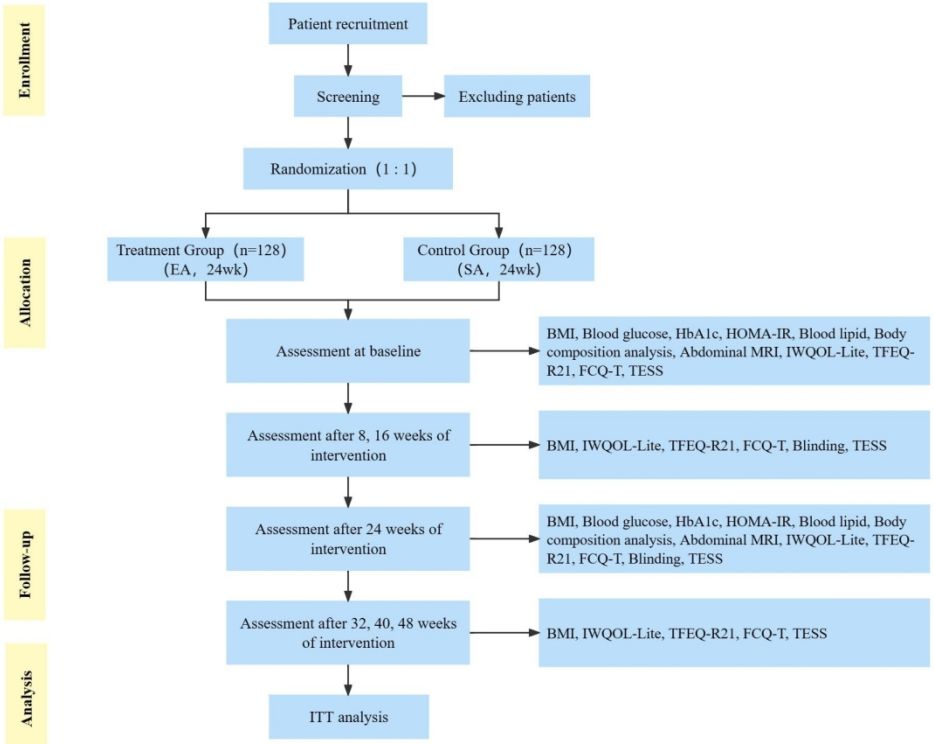

Figure 1 Flowchart of the trial

404x324mm (120 x 120 DPI)

Informed Consent Form

Dear patients:

You're invited to participate in a clinical trial of electroacupuncture on weight loss in obese patients with prediabetes. Please read the following content carefully before you decide to participate in this study or not. It may help you have an acquaintance with the study, including the research purpose, as well as benefits, risks, and discomfort after participating in the study. You can also discuss with your family and friends, or ask your doctor to explain it and to help you make decision.

Research Background

China currently has the highest proportion of obese and diabetic patients worldwide, leading to substantial social and medical burdens. Disrupted glucose metabolism in obese individuals, particularly when comorbid with diabetes, poses greater health risks than obesity alone. It is imperative to identify an effective and safe approach that concurrently addresses weight loss and enhances glucose metabolism in the treatment of obesity complicated by abnormal glucose regulation. Researches have demonstrated the potential of electroacupuncture therapy in reducing weight, lowering lipid levels, and ameliorating insulin resistance. This study utilizes rigorous high-quality randomized controlled trials to assess the clinical efficacy of electroacupuncture in promoting weight loss and improving glucose metabolism. The outcomes of this research are pivotal for developing optimized electroacupuncture treatment protocols tailored for obesity, offering essential support for the wider clinical implementation and promotion of electroacupuncture in the management of obesity.

The design of this research project adheres to the ethical principles protecting the rights and interests of the participants, in accordance with relevant laws and regulations of China and ethical guidelines including the Helsinki Declaration.

Requirements for Participation in the Study

Upon meeting the inclusion criteria and consenting to participate, the trial will proceed as below:

①Participants will be randomly assigned to two groups: the electroacupuncture group, incorporating pulse electrical stimulation based on traditional acupuncture methods, and the superficial acupuncture group, utilizing an acupuncture treatment with mild pain and minimal stimulation. Both groups will receive clinical treatment and observation over a 48-week period.

②Blood samples will be collected before treatment, at the 12th week during treatment, and at the 24th week after treatment. Body composition analysis and abdominal magnetic resonance imaging will be conducted before the start and after the completion of the treatment. Throughout the treatment process, assessments will be made using various relevant scales, including those measuring quality of life and appetite.

③Follow-up assessments, conducted within six months after the treatment's completion, will comprehensively evaluate the clinical efficacy of acupuncture treatment for patients.

Participation Benefits

Participating in this clinical trial offers potential benefits for your health. Participants will receive complimentary acupuncture treatment, health education, and regular assessments focused on glucose and lipid metabolism-related indicators.

Risks and Protection Measures for Participation

It is important to note the potential risks associated with participation. Adverse reactions to acupuncture, such as pain, bleeding and hematoma at the needle site, or fainting, could occur during the trial, leading to discomfort. If you experience any of these reactions, please promptly inform your acupuncturist and the clinical researcher. They will take immediate measures to address your discomfort and ensure the safety.

Costs of Participation

All treatments provided are entirely free of charge. Additionally, participants may receive a transportation allowance (500 RMB for each person) based on your completion of the trial.

Is Personal Information Kept Confidential?

The personal information provided for this research will be documented in the case report form. All data from the original medical records, including personal information and laboratory test reports, will be kept strictly confidential in compliance with legal regulations. Participants' names will be replaced by initials in Pinyin and an assigned number during the trial to ensure anonymity. In research summaries, articles, and public publications, participants will be identified solely by their initials in Pinyin and the assigned study number, if required.

The Ethics Committee or the project funding department may access participant data for the study when required by regulations. However, they are strictly prohibited from using this data for any purposes other than the study or disclosing it to other organizations without participants' permission.

How to Obtain More Information?

You are free to ask any questions related to this trial at any time.

Your doctor will provide you with their contact number to address your inquiries.

Your doctor will promptly notify you if there is any important new information during the trial that may affect your willingness to continue participating in the study.

Voluntary Participation and Withdrawal from the Study

Participation in this study is entirely voluntary and depends on your willingness.

You may refuse to participate in this study or withdraw from this study at any time during the study. If you choose to withdraw from this study, your benefits will not be affected and you will not be discriminated against or retaliated against for doing so. Your doctor or researcher may terminate your participation in this trial at any point in your best interest. Upon withdrawal, you may discuss your treatment options, and if necessary, undergo laboratory tests and physical examinations. Failure to comply will not lead to discrimination or retaliation.

We hope that if you choose to participate, you will complete the entire trial process.

What to Do Now?

It is up to you to decide whether to take part in this pilot study. You can discuss your decision with your family or friends. Before you make the decision to participate in the trial, ask your doctor as many questions as you can until you fully understand this trial study.

Ethical Committee

If you have any questions or need to inquire with someone other than the researchers or applicants, please consult the Ethics Committee of Shanghai Municipal Hospital of Traditional Chinese Medicine.

Contact Number: 021-56639828 **Contact Person:** Li Ling

Thank you for reviewing the aforementioned information. If you opt to participate in this clinical study, please inform your doctor, who will oversee all aspects related to the trial on your behalf.

Kindly provide your signature below. This informed consent form is duplicated for your records. Please keep this copy.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 4
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	No
Funding	4	Sources and types of financial, material, and other support	Page 23
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Page 1
	5b	Name and contact information for the trial sponsor	Page 1
	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	Page 23
	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)	Page 19

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 4
	6b	Explanation for choice of comparators	Page 4
Objectives	7	Specific objectives or hypotheses	Page 6
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 7
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 7
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 8-9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page 11
	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 11-12
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Page 11-12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Page 11-12
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 13-18
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 7 (Fig. 1)

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 8
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Page 8
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 10
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 10
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Page 19-20
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Page 10
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Page 10
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 13-17
	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	Page 18

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 19
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 18
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Page 18
	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 18
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	Page 19
	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	Page 19
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 17-18
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Page 19
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page 18-19
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)	Page 18-19

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 19-20
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Page 19-20
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	Page 19-20
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 22
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	Page 23
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	Page 12-13
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	Page 19-20
	31b	Authorship eligibility guidelines and any intended use of professional writers	Page 19-20
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Page 19-20
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Page 7
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	Page 13-17

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.