Diabetes, Metabolic Syndrome and Obesity

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STUDY PROTOCOL

Investigating the Microbiota-Gut-Brain Axis Mechanisms of Transcutaneous Auricular Vagus Nerve Stimulation in Patients with Obesity: A Study Protocol for a Randomized Controlled Trial

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Background: Obesity is a common metabolic disorder affecting nearly one-third of the global population. Emerging evidence indicates that the microbiota-gut-brain axis plays a key role in the pathogenesis of obesity. Transcutaneous auricular vagus nerve stimulation (taVNS), a non-invasive neuromodulation technique, may modulate brain function and gut microbiota via vagal pathways. This study aims to evaluate the short-term efficacy of taVNS in reducing body weight in patients with obesity and to explore its underlying mechanisms by assessing changes in neural activity and gut microbial composition.

Methods: This single-center, randomized controlled trial will enroll 74 patients with obesity, who will be randomized in a 1:1 ratio to receive either taVNS (electrical stimulation delivered to the left cymba conchae) or sham taVNS (stimulation at the tail of the helix). The primary outcome will be the percentage change in body weight from baseline to Week 12. Secondary outcomes will include anthropometric measures such as changes in body mass index (BMI), waist circumference, hip circumference, body fat percentage, and visceral fat area. Clinical evaluations will be conducted using validated instruments, including the Impact of Weight on Quality of Life-Lite (IWQOL-Lite), Perceived Stress Scale (PSS), Hamilton Depression Rating Scale (HAMD), Dutch Eating Behavior Questionnaire (DEBQ), International Physical Activity Questionnaire (IPAQ), and the Fatigue Scale-14 (FS-14). To investigate modulation of the microbiota–gut–brain (MGB) axis, assessments will include serum brain–gut peptides, gut microbiota composition, and functional magnetic resonance imaging (fMRI). Adverse events will also be systematically monitored throughout the study period.

Discussion: This study will preliminarily validate the clinical efficacy of taVNS for obesity. And by integrating measures such as gut peptides, microbiota profiling, and brain imaging, it seeks to link therapeutic effects with microbiota-gut-brain axis modulation. The findings may support taVNS as a safe, non-pharmacological approach for obesity management and inform future neuromodulation-based strategies.

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Keywords: obesity, transcutaneous auricular vagus nerve stimulation, randomized controlled trial, microbiota-gut-brain axis, fMRI, gut microbiota

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Introduction

Obesity is a chronic metabolic disorder resulting from abnormal or excessive accumulation of adipose tissue.[1] It has emerged as a major global public health challenge due to its rapidly increasing prevalence and its strong association with numerous comorbidities.[2] By 2021, an estimated 2.11 billion adults worldwide were classified as overweight or obese, with China reporting the highest number at 402 million. Projections indicate that by 2050, the global population aged over 25 with overweight or obesity will surge to 3.8 billion.[3] In addition to its direct impact on individuals' quality of life, obesity is also a major contributor to various disorders, including type 2 diabetes, hypertension, metabolic syndrome, asthma, and obstructive sleep apnea, all of which pose substantial risks to health.[4]

The current management of obesity relies on five primary strategies: behavioral interventions, nutritional therapy, physical activity, pharmacotherapy, and bariatric procedures.[4] Nutrition and physical activity demand high self-discipline and sustained efforts over at least six months to achieve significant improvements in body weight control.[5,6] Pharmacological treatments have advanced in recent years, with drugs such as semaglutide, tirzepatide, and orlistat approved by the US Food and Drug Administration (FDA).[4] Simultaneously, 2 bariatric endoscopic procedures, including intragastric balloons and endoscopic sleeve gastroplasty, have also received FDA approval.[4] However, despite these advances, no country has successfully curbed the growing prevalence of obesity. As such, more targeted and effective interventions are urgently needed to address this escalating health crisis.[3]

Recent evidence highlights the pivotal role of the microbiota-gut-brain (MGB) axis in regulating metabolic homeostasis and the development of obesity. For instance, Resting-state fMRI evidence suggests that tryptophan-derived indoles from gut microbiota modulate hedonic food intake by influencing neural activity within core regions of the brain's reward circuitry.[7] Preclinical studies suggest that the gut microbiota communicates with the brain via the release of neuroactive metabolites, thereby modulating host feeding behaviors.[8] It is now well-established that the MGB axis is involved in regulating food intake, glucose metabolism, and gastrointestinal motility. Disruptions in any component of this axis may contribute to metabolic disorders, including obesity.[9,10] This mechanistic insight has laid the theoretical foundation for developing gut-targeted anti-obesity strategies, including probiotics, prebiotics, and gut peptides[9,11] which has also prompted growing scientific interest in other pathways involved in gut-brain communication. Among these pathways, the vagus nerve has emerged as a crucial bidirectional conduit between the gut and the brain. It integrates mechanical and hormonal signals from the gastrointestinal tract and plays a central role in appetite regulation and energy homeostasis, making it a promising target for neuromodulatory interventions in obesity treatment.[9,12]

Transcutaneous auricular vagus nerve stimulation (taVNS) is a non-invasive neuromodulation technique that stimulates the auricular vagus nerve to influence brain function. Preclinical studies have shown that taVNS can reduce body weight and visceral fat in diet-induced obese rats, potentially through mechanisms related to enhanced lipolysis.[13] Similarly, taVNS has been reported to decrease body weight and improve hyperglycemia in Zucker Diabetic Fatty rats.[14,15] In preliminary human studies, short-term taVNS was found to increase preferences for low-fat foods, potentially reducing total caloric intake.[16] In addition, several studies have evaluated the clinical efficacy of auricular acupuncture in treating obesity and found that it can effectively reduce body weight and waist circumference in patients.[17,18] The selected acupoints are primarily located in the cymba concha, which corresponds to the auricular branch of the vagus nerve—indicating that auricular acupuncture in the cymba concha essentially stimulates the vagal branch.[19] These findings offer a scientific rationale for exploring taVNS as a promising intervention for obesity.

To the best of our knowledge, no study has comprehensively described the clinical outcomes of taVNS in the treatment of obesity, nor its interactions with brain function and the gut microbiota. Therefore, this randomized controlled trial aims to preliminarily explore whether taVNS can reduce body weight in patients with obesity by modulating the gut-brain axis.

Methods

Study Design

This study will be conducted at Hubei Provincial Hospital of Traditional Chinese Medicine. This study aims to evaluate the hypothesis that taVNS can reduce the weight in patients with obesity. All qualified participants will be assessed and followed up. A total of 74 consented patients with obesity will be enrolled in the study and randomly assigned in a 1:1 ratio to either the

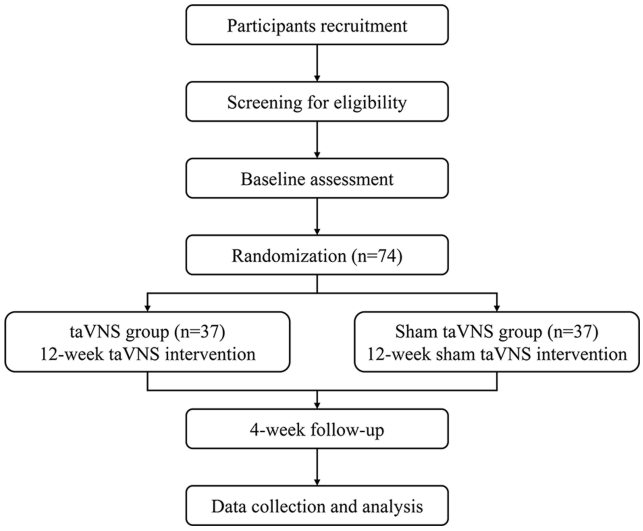

Figure 1 Flowchart of the study. Notes: CONSORT figure adapted from Schulz KF, Altman DG, Moher D. CONSORT 2010 Statement: Updated Guidelines for Reporting Parallel Group Randomised Trials. PLoS Med. 2010;7(3): e1000251. Copyright: © 2010 Schulz et al. Creative Commons Attribution License.[20]

taVNS group or the sham taVNS group. Figure 1 shows the study flow chart and the schedule is outlined in Table 1. The protocol adhered to the guidelines outlined in the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)[21] and the results will adhere to the Consolidated Standards of Reporting Trials (CONSORT).[22]

Participants and Eligibility Criteria

This study is being conducted at Hubei Provincial Hospital of Traditional Chinese Medicine. Patients meeting the eligibility criteria were consecutively enrolled from April 1, 2025. The inclusion and exclusion criteria are as follows:

Inclusion Criteria

(1) Meet the diagnostic criteria of obesity (BMI ≥28.0 kg/m^2).
(2) Age 18–50 years old right-handed.
(3) Senior high school or above can cooperate to complete the questionnaire.
(4) No metal implants claustrophobia and other contraindications to MRI examination.

Table 1 Schedule of Enrollment, Interventions and Assessments

Visit Timepoint	Enrollment	Baseline	Treatment			Follow-Up
	1 Week −1	2 Week 0	3 Week 4	4 Week 8	5 Week 12	6 Week 16
Eligibility screening	X					
Informed consent	X					
Demographic Characteristics	X					
Body composition		X	X	X	X	X
Clinical scale assessment		X			X	
Brain-gut peptide		X			X	
Gut microbiota		X			X	
fMRI acquisition		X			X	
Compliance of taVNS			X	X	X	
Blinding of taVNS					X	

Abbreviations: fMRI, functional magnetic resonance imaging; taVNS, transcutaneous auricular vagus nerve stimulation.

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(5) ECG results were normal.
(6) Not taking any drugs that may affect intestinal microbes in the past 3 months.
(7) Sign the informed consent form and voluntarily participate in the project.

Exclusion Criteria

(1) Secondary obesity caused by hypothyroidism Cushing's syndrome hyper Adreno-cortical function polycystic ovary syndrome etc.
(2) Using any drugs or substances that may significantly affect body weight within the past 3 months (eg, corticosteroids, antipsychotics, amphetamines).
(3) Surgical or device intervention with a history of obesity or planned surgery within 6 months.
(4) Have received within 3 months or are receiving weight-loss treatment including medications and organized weight-loss training camps.
(5) Weight change > 5 kg within 3 months.
(6) With mental disorders or previous history of schizophrenia depression somatization disorder history of suicidal behavior or diagnosed with eating disorders or long-term use of antipsychotic drugs.
(7) With serious diseases of the heart lung brain liver or kidney (including but not limited to persistent renal or hepatic insufficiency congestive heart failure unstable angina pectoris myocardial infarction or stroke within the past six months) or hematopoietic system diseases progressive malignant tumors or other serious wasting diseases.
(8) Magnetic resonance imaging showed cerebral vascular disease epilepsy tumor or other organic lesions.
(9) Mini-Mental State Examination score indicating cognitive impairment.
(10) Pregnant breastfeeding or planning to become pregnant in the next six months.
(11) Participated in other clinical trials within six months.
(12) Ear skin infection damage and other reasons not suitable for taVNS.
(13) Received taVNS intervention within the past 3 months.
(14) Other reasons: According to the investigator's judgment the subjects were unlikely to comply with the protocol or were not suitable for any reason such as frequent and long-time travel.

Recruitment and Screening

Patients with obesity are recruited consecutively from outpatient clinics, inpatient wards, hospital advertisements, and physician referrals. Recruitment and intervention are coordinated by Professor Zhongyu Zhou, the Principal Investigator, together with a multidisciplinary team of internists and acupuncturists. All team members have more than five years of clinical and research experience and have received Good Clinical Practice (GCP) training. The objectives, interventions, and potential risks and benefits of the study are explained to each patient and their families, and written informed consent is obtained before enrollment (Supplementary Material 1), and participants are informed of their right to withdraw at any time. Baseline demographic information (eg age, sex), medical history, and personal history are collected prior to randomization.

Sample Size

Based on our previous clinical observations, 12 weeks of taVNS intervention led to an average weight loss of 6%. We anticipate approximately 3.8% reduction in sham taVNS group. Assuming a standard deviation (SD) of 3.3%, a total of 58 subjects is required to achieve at least 80% power to detect the superiority of taVNS while maintaining a one-sided alpha level of 0.05. Considering a 20% dropout rate, the final sample size was determined to be 74 subjects, with 37 participants in each group.

Randomization and Blinding

In this study, an independent programmer generated the randomization sequence using SPSS 24.0, ensuring no contact with participants. The sequence was securely stored in sealed, opaque envelopes. After baseline assessments, eligible patients were randomly assigned to either the taVNS group (receiving real treatment) or the sham taVNS group

(receiving sham treatment) according to the sequence. Blinded researchers will distribute the corresponding treatment devices to participants based on the numbers on the envelopes. The devices are identical in appearance, with the only difference being the conductive placement between the two groups.

Intervention Description

Each participant in both groups received lifestyle instruction as basic intervention. And the detailed instructions can be found in Supplementary Material 2.

Following the methodology of previous studies,[23–25] in the taVNS group, a specially designed silicone clip will be applied to the left cymba conchae, where vagus nerve projection density is highest (100%). While sham taVNS are located at the left tail of the helix (outer ear margin midpoint), where there is no vagus nerve distribution. The stimulation parameters are the same: intermittent waves (5 seconds OFF and 15 seconds ON at 20 Hz), with a pulse width of 0.2 ms. The electrical stimulation intensity will be gradually increased from zero until the participant experiences a "tingling" sensation on the auricle (usually 1 mA to 2.5 mA). Participants will be trained by researchers on how to use the device, ensuring their familiarity with its use. Meanwhile, the electronic operation manual provided to patients, along with the evaluation of device usage at each clinic visit, will ensure the proper and standardized use of the treatment device throughout the treatment period. The patients will take the device home and will be instructed to use it regularly for 12 weeks, once daily for 30 minutes, 6 times per week.

Outcome Measures

Primary Outcomes

Percentage change in body weight from baseline to Week 12.

Secondary Outcomes

Body Composition Assessments

Body composition outcomes include BMI, waist circumference (WC), hip circumference (HC), body fat percentage (BF%), and visceral fat area (VFA). BF% and VFA are measured using bioelectrical impedance analysis (BIA) with InBody 770.[26]

Clinical Scale Assessments

Quality of life will be evaluated by impact of weight on quality of life (IWQOL-Lite).[27] Perceived Stress Scales (PSS)[28] and Hamilton Depression Rating Scale (HAMD)[29] will be used to assess the psychological function. Dutch Eating Behaviour Questionnaire (DEBQ),[30] international physical activity questionnaire (IPAQ)[31] and fatigue scale-14 (FS-14)[32] will be used to evaluate eating behavior, physical activity and fatigue, respectively.

Brain-Gut Peptides

Fasting venous blood samples will be collected from all participants before and after treatment to determine serum concentrations of GLP-1, Nesfatin-1, CCK, OXM, and Ghrelin.

Gut Microbiota collection

Stool samples will be collected from the middle portion of the feces at the hospital and immediately placed into 10 mL centrifuge tubes for storage at −80°C. Microbial DNA will be extracted from the samples, followed by 16S rRNA gene amplicon sequencing using a shotgun sequencing approach. In addition, fecal metabolomic fingerprinting will be performed to characterize the metabolic profiles across different patient groups.

fMRI Acquisition

fMRI data were acquired using a Siemens Skyra 3.0 Tesla MRI scanner equipped with an 8-channel head coil at our hospital. Each participant underwent a high-resolution 3D T1-weighted structural scan, followed by BOLD-fMRI. The scanning parameters are as follows:

T1-weight scan: acquisition time = 280 s matrix = 256 × 256 × 176 slices, repetition time (TR) = 2000ms, echo time (TE) =2.23ms, flip angle = 8°, field of view (FOV) = 240 × 240× 240, voxel size = 0.9 × 0.9 × 0.9 mm.

fMRI scan: acquisition time = 488 s matrix = 64 × 64 × 36 slices, TR = 2000 ms, TE = 30 ms, dynamic scans = 240, flip angle = 90°, FOV = 224 mm×224 mm× 224 mm, voxel size = 3.5 mm ×3.5 mm× 4.0mm

During the entire scanning session, participants wore noise-reducing earplugs and were instructed to remain still, keep their eyes open, avoid falling asleep, and refrain from engaging in any specific thoughts. Meanwhile, a T2-weighted scan was performed to exclude any intracranial lesions.

For these outcomes, body composition assessments and clinical scale assessments will be measured at week 0, 4, 8, 12. Brain-gut peptides, gut microbiota and fMRI will be evaluated at week 0 and 12.

Safety Assessment

According to previous study[33,34] and our clinical experience, most common taVNS-related adverse events include local skin irritation, pain, and skin infection. All adverse events that occur during the study will be record and properly handled. In case of serious adverse events (SAEs), research personnel shall take all necessary measures to ensure patient safety. In addition, SAEs will be reported, managed, and followed up according to GCP principles. They must be reported to the Ethics Committee of Hubei Provincial Hospital of Traditional Chinese Medicine within 24 hours, which holds the authority to terminate the trial if necessary.

Participant Retention, Adherence and Sustainability

The research team will make every effort to facilitate participants' adherence to the study protocol and ensure completion of the full treatment course. To maximize participant retention and minimize loss to follow-up, the following measures will be implemented:

(1) Participants will be required to maintain treatment logs and record dietary and physical activity behaviors throughout the intervention period.
(2) Weekly follow-up communication will be conducted via telephone or WeChat to ensure accurate use of taVNS or sham-taVNS devices.
(3) Participants will be scheduled for outpatient visits every four weeks for standardized body composition assessments, which will contribute to improved adherence and reduced dropout rates.

Analytical Approach and Data Management

We will collect and analyze relevant data from all enrolled participants. Descriptive statistics will be used to summarize baseline characteristics. The Kolmogorov–Smirnov test will be performed to assess the normality of continuous variables. For normally distributed quantitative data, results will be presented as mean ± standard deviation (SD), and intergroup comparisons will be conducted using the independent samples *t*-test. For non-normally distributed quantitative data, results will be presented as median and interquartile range (IQR), and the Mann–Whitney *U*-test will be used for group comparisons. In addition, qualitative variables will be presented as proportions (%), and intergroup differences will be compared using the chi-square test or Fisher's exact test, as appropriate. The effects of the outcome measures will be evaluated using linear mixed-effects multilevel models.[35] Both intention-to-treat analyses and per-protocol analyses will be executed. The last observation carried forward approach will be employed to impute missing data, and potential confounding variables will be controlled. Statistical significance will be determined at a two-sided p-value threshold of <0.05. All statistical analyses will be conducted using R software.

fMRI data will be processed using MATLAB R2022b, in conjunction with the Statistical Parametric Mapping software (SPM12) and the Data Processing Assistant for Resting-State fMRI (DPARSF) toolbox.[36] Preprocessing steps will include slice timing, realignment, spatial normalization, smoothing, linear trend removal, and temporal bandpass filtering. Seed-based functional connectivity (FC) analysis will be employed to evaluate the intervention effects of taVNS.

Hypothalamus will be defined as the primary region of interest (ROI).[37] The mean BOLD time series within the hypothalamic ROI will be extracted, and voxel-wise Pearson correlation analyses will be conducted to assess the temporal correlation between the seed region and all other voxels across the brain. These correlation coefficients will represent the strength of FC between the seed region and the rest of the brain. To improve the normality of the data for subsequent statistical analyses, Fisher's r-to-z transformation will be applied to the correlation maps.

Patient and Public Involvement

No patient or public was involved in designing, conducting, reporting or disseminating plans for the research.

Ethics and Dissemination

The study is a single center, double blind, randomized controlled trial, which has been approved by the Ethics Committee of Hubei Provincial Hospital of Traditional Chinese Medicine (HBZY2024-C53-01). The study has been registered in International Traditional Medicine Clinical Trial Registry at 9 October, 2024 (ITMCTR2024000518). The findings of this trial will be presented in a peer-reviewed journal.

Discussion

Obesity is not only a metabolic disorder, but increasing evidence suggests that it may also be associated with cognitive impairments.[38,39] These neurobehavioral traits may predispose individuals to impulsive eating and excessive intake of high-calorie foods, thereby exacerbating weight gain. As a result, neuromodulation-based interventions have emerged as a promising new strategy for obesity management.

Among neuromodulation strategies for obesity, vagus nerve stimulation and blockade differ notably in their mechanisms. Vagal blockade devices typically apply high-frequency stimulation (~5000 Hz) to abdominal vagal branches to disrupt neural signaling, thereby reducing hunger perception and food intake.[40,41] In contrast, vagal stimulation devices use low-frequency input to activate afferent fibers, which has been associated with enhanced satiety signaling.[42] In our study, taVNS delivers low-frequency (20 Hz) intermittent stimulation to the auricular branch of the vagus nerve, which consists primarily of afferent fibers projecting to brain regions involved in autonomic regulation. Mechanistically, taVNS aligns more closely with afferent stimulation approaches than with signal-blocking strategies.

Moreover, compared with implantable systems, taVNS is a non-invasive approach that may offer advantages in terms of safety, accessibility, and cost. These characteristics could support its feasibility for long-term obesity management, especially in broader populations where non-invasive interventions may be more acceptable By systematically evaluating taVNS through multimodal endpoints, this study aims to provide preliminary mechanistic and clinical evidence for its potential role in obesity treatment.

Although this protocol paper does not yet include efficacy data, its design is based on prior preclinical and preliminary clinical evidence suggesting that vagus nerve modulation may influence metabolic regulation and eating behaviors. However, the underlying mechanisms remain poorly understood. Our study addresses this gap by incorporating multi-dimensional outcome measures. By examining changes in brain activity and evaluating gut microbiota profiles, this study seeks to elucidate how taVNS may influence key regulatory pathways within the MGB axis. Publishing this protocol enhances research transparency, invites peer feedback, and supports the development of safe, non-invasive neuromodulation strategies for obesity management.

This study has certain limitations. Firstly, it is a single-center study conducted in China, which may limit the generalizability of the findings to broader populations. Nevertheless, the study is designed with methodological rigor and standardized procedures to ensure the highest possible research quality. Second, the relatively short follow-up period limits our ability to assess the long-term effects of taVNS. This is consistent with the study's primary aim, which is to evaluate the short-term efficacy and mechanistic signals of taVNS in the treatment of obesity.

In summary, this trial aims to explore how taVNS modulates brain activity and the microbiota-gut-brain axis in obesity. The findings are expected to provide preliminary mechanistic evidence and inform the development of safe, non-invasive, mechanism-based interventions for obesity management.

Data Sharing Statement

As this paper describes a study protocol, no datasets have been generated or analyzed yet. Data generated during the study will be made available upon reasonable request following publication of the trial results, subject to ethical approval and participant confidentiality.

Ethical Approval

The study protocol and informed consent form was approved by the Ethics Committee of Hubei Provincial Hospital of Traditional Chinese Medicine.

Author Contributions

Xia Chen, Weiqing Kong, and Yang Song contributed equally to this work and shared first authorship. Conceptualization: Xia Chen, Weiqing Kong, Chengwei Fu. Data curation: Chengwei Fu. Formal analysis: Chengwei Fu. Funding acquisition: Zhongyu Zhou. Investigation: Yang Song, Zhi Liu, Yanji Zhang, Wei Huang. Methodology: Xia Chen, Weiqing Kong. Project administration: Chengwei Fu, Zhongyu Zhou. Resources: Yang Song, Wei Huang. Software: Chengwei Fu, Wei Huang, Zhongyu Zhou. Supervision: Chengwei Fu, Zhongyu Zhou. Validation: Wei Huang, Zhi Liu. Visualization: Xia Chen, Yanji Zhang, Chengwei Fu. Writing -original draft: Xia Chen, Yanji Zhang, Chengwei Fu. Writing-review & editing: Chengwei Fu, Zhongyu Zhou. Xia Chen, Weiqing Kong, and Yang Song contributed equally to this work. All authors took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors have no conflicts of interest to declare.

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