Trials

STUDY PROTOCOL

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Efficacy and safety of levothyroxine monotherapy in lowering the risk of cardiovascular disease in older adults with subclinical hypothyroidism: research protocols of a multicenter, open-label, randomized controlled trial

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Abstract

Objective This multicenter, open-label, randomized controlled trial (RCT) aims to assess the efficacy and safety of levothyroxine monotherapy in lowering the risk of cardiovascular disease (CVD) in untreated older adults with subclinical hypothyroidism (SCH) who are diagnosed according to population-specific TSH reference values.

Methods A total of 254 patients with SCH who meet the diagnostic criteria will be recruited, and the baseline clinical data of the patients will be collected. Then, a total of 127 patients will be randomly divided into each of the treatment and control groups, and the treatment group will receive daily levothyroxine doses (Merck Euthyrox® levothyroxine 50 mcg tablet). Specifically, 50 μg of levothyroxine per day will be administered to patients in the treatment group (or 25 μg to patients with a body weight < 50 kg) for at least 48 weeks to maintain thyroid-stimulating hormone (TSH) levels within the normal range. The participants in the control group will be subjected only to thyroid status evaluation, and the results will be recorded. The participants will complete five visits before and after the start of the trial, and differences in the change in carotid intima–media thickness (CIMT), maximum mean change in plaque burden, and changes in lipid profiles, bone mineral densities, and incidences of fatal and nonfatal cardiovascular events between the initial visit and the last follow-up visit will be evaluated via vascular ultrasound.

Discussion We will explicitly address whether levothyroxine replacement therapy provides cardiovascular benefits for older adults with subclinical hypothyroidism.

Clinical trial registration ClinicalTrials.gov, No. ChiCTR2400092634. Registered on 30 November 2024. Recruitment for this study began on December 1, 2024, and continues until at least until November 30, 2025.

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Introduction

Subclinical hypothyroidism (SCH) occurs when the level of TSH exceeds the normal reference range but the level of free thyroxine (FT4) remains within the normal reference range [1]. In China, more than 50% of older adults suffer from thyroid diseases. SCH commonly affects elderly individuals, and it associated with various atypical clinical manifestations, such as fatigue, cognitive function decline, and osteoporosis. SCH can even cause life-threatening cardiovascular disease (CVD) or death [2]. Elevated TSH levels greatly increase the risk of CVD by promoting atherosclerosis of the vascular endothelium via the action of macrophages [3]. Inoue et al. reported that CVD mediates the causal relationship between SCH and all-cause mortality [4]. A meta-analysis revealed that SCH patients with serum TSH levels higher than 10.0 mU/L have a significantly increased risk of CVD [5]. In contrast, a cohort study with an average follow-up time of 11.2 years reported no relationship between TSH levels and CVD [6]. Razvi et al. reanalyzed the Whickham survey data and reported an association between incident ischemic heart disease (IHD) events and IHD-related mortality in patients with SCH over 20 years of follow-up. Subsequent cohort studies revealed that levothyroxine treatment can reduce all-cause mortality rates [7]. However, in another historical cohort study, the risk of all-cause mortality among patients who were treated with levothyroxine did not significantly increase compared with that among patients who were not treated with levothyroxine [8]. A recent meta-analysis demonstrated that older adults with SCH do not benefit from the use of levothyroxine monotherapy to lower the risk of CVD [9]. Therefore, the correlation between SCH and CVD and the exact efficacy of levothyroxine monotherapy in lowering the risk of CVD by reducing TSH levels to levels within the normal reference range remain largely unclear. The Thyroid Hormone Therapy for Older Adults with Subclinical Hypothyroidism (TRUST) trial is a randomized controlled trial (RCT) involving untreated older adults with SCH who were initially treated with levothyroxine [10]. However, owing to the small sample size and short-term follow-up, the potential of levothyroxine to reduce the risk of CVD in this population remains unclear. Another study nested within the TRUST trial has examined the average carotid intima–media thickness (CIMT), but the effect of treating SCH on improving cardiovascular outcomes remains uncertain [11].

Considering that physiological serum TSH levels of elderly individuals are elevated, the laboratory reference range of TSH levels that is used to diagnose SCH in this population should be modified according to age [12]. Our research team consistently revealed an age-dependent increase in the upper limit of TSH levels in older Chinese adults (≥ 65 years) from iodine-adequate areas [13]. Moreover, in previous studies, small numbers of healthy older adults were included in the SCH cohorts because the reference range of TSH levels was not modified according to age, leading to potential biases. Recent clinical evidence suggests that the 1-year change in CIMT is a surrogate marker for the risk of CVD, allowing for a significantly reduced sample size in research studies [14]. This clinical evidence allowed the association between the effects of treatments on CIMT progression and the reduction in risk of CVD to be quantified through a large-scale meta-analysis. Across all interventions, each 10 μm/year reduction in CIMT resulted in a relative risk of CVD of 0.91. The present multicenter, open-label RCT is designed to assess the efficacy and safety of levothyroxine monotherapy in lowering the risk of CVD in untreated older adults with SCH, and the mean change in CIMT between the first and last follow-up visits is the primary outcome.

Methods

Trial design

This is a multicenter, open-label RCT involving older adults (≥ 65 years) with untreated SCH from three medical institutions in Jiangsu Province, China. All the participants will receive 48 weeks of follow-up. In accordance with the Declaration of Helsinki, this clinical trial is approved by the ethics committees of the Affiliated Suqian Hospital of Xuzhou Medical University and the Affiliated Nanjing University of Chinese Medicine Nanjing Integrated Traditional Chinese and Western Medicine Hospital. This clinical trial was registered on the Chinese Clinical Trial Registry website (No. ChiCTR2400092634) on November 30, 2024. The subjects will be recruited by physicians from the aforementioned medical centers during outpatient visits or hospitalization periods. The SPIRIT checklist is provided in Additional file 1.

Participants

Older adults with SCH will be recruited from the three medical institutions beginning in December 2024. SCH will be diagnosed on the basis of the age-specific reference range of TSH levels that was determined in our previous study (65–69 years, 0.65–5.51 mIU/L; 70–79 years, 0.85–5.89 mIU/L; and ≥ 80 years, 0.78–6.70 mIU/L) [13].

The major inclusion criteria are older adults ≥ 65 years; at least two measurements of serum TSH levels higher than the upper limit with a period of 3 months or longer; free thyroxine (FT4) levels within the normal range; and written informed consent provided.

The exclusion criteria are a history of treatment with levothyroxine, antithyroid drugs, amiodarone, or lithium

preparations within the past 3 months; a history of thyroid surgery or radioactive iodine exposure within the past 12 months; heart failure graded according to the New York Heart Association (NYHA) classification IV; cognitive dysfunction; hospitalization due to major illness or elective surgery within the past 3 months; a history of acute coronary syndrome (e.g., myocardial infarction, unstable angina) within the past 3 months; untreated adrenal insufficiency or adrenal gland dysfunction; acute infections, severe liver and kidney dysfunction, and tumors; and participation in ongoing RCTs or clinical trials for testing drugs.

Randomization

The participants will be randomly allocated to the levothyroxine group or the control group at a ratio of 1:1. Randomization will be performed using block randomization, with four strata: baseline medical institution, gender (male or female), age (65–69 years, 70–79 years, or ≥ 80 years), and starting dose. The randomization process will be conducted by the Electronic Data Capture (EDC) system. The random allocation sequence will be implemented by data managers, independent of the investigators and subjects. The EDC and randomization system will be implemented by an independent party, namely, Hangzhou Transwarp Technology Co., Ltd.

Interventions

Participants in the levothyroxine group will receive daily levothyroxine doses (Merck Euthyrox® levothyroxine 50 mcg tablet) before breakfast, starting at a dose of 50 μg (or 25 μg for patients with a body weight < 50 kg), for 4 weeks. Participants in the control group will be subjected only to thyroid testing.

Following the 4-week randomization, dose adjustments will be made on the basis of three possible changes in serum TSH levels:

(1) TSH < 0.4 mIU/L: the levothyroxine dose will be reduced to 25 μg in participants with a starting dose of 50 μg and levothyroxine will be discontinued in participants with a starting dose of 25 μg; serum TSH levels will be measured again 4 weeks later, and participants with consistent results of TSH < 0.4 mIU/L will be withdrawn from the clinical trial.
(2) TSH 0.4–4.2 mIU/L: no change in the daily levothyroxine dose will be made, and serum TSH levels will be measured again 4 weeks later; additionally, participants will be reviewed at 12, 24, and 48 weeks.
(3) TSH ≥ 4.2 mIU/L: the levothyroxine dose will be increased by 25 μg; additionally, serum TSH levels will be measured again every 4 weeks until they decrease to 4.2 mIU/L or lower.

Vascular ultrasound

Two experienced investigators will be independently responsible for measuring CIMT at the first visit, at 24 weeks, and at the last visit by carotid ultrasound on the basis of the current measurement guidelines [15]. All the CIMT assessments will be conducted jointly by a team of 2 throughout the study. Briefly, a linear array probe (4–18 MHz) will be used to capture images of the distal wall of the bilateral common carotid arteries. Imaging data from 0–10 mm proximal to the carotid plaque and 10 mm from the end-diastole confirmed by the 3-lead electrocardiogram will be collected. The average and maximum CIMT, in mm and to two decimal places, will be measured with automated ultrasound edge-tracking software on the EPIQ 7® Ultrasound system. Additionally, plaque burden will be assessed by imaging examinations of the carotid, internal, and external arteries and the carotid bulb. Plaques are defined as focal structures that invade the arterial lumen of at least 0.5 mm or 50% of the surrounding CIMT or that demonstrate a thickness of > 1.5 mm, as measured from the intima–lumen interface to the media–adventitia interface. The maximum thickness of the largest plaques will be measured to one decimal place on longitudinal and cross-sectional images. A flow chart of the study is provided in Fig. 1.

Bone mineral density (BMD)

BMD will be assessed at the lumbar spine (L1–L4) and left femoral neck using DXA (Hologic® Horizon A), with daily calibration per the manufacturer's protocol. Scans will be analyzed by ISCD-certified technicians who are blinded to the clinical data. *T*-scores will be derived from the NHANES III reference.

Strategies to improve treatment adherence

Short Message Service (SMS) and email reminders will be sent every 2 weeks to increase participant retention throughout the 48-week follow-up period. Additionally, we will incorporate patient-centric measures (e.g., flexible scheduling, transportation support, or incentives where ethically approved) to reduce the likelihood of dropout. Drug compliance will be assessed by the "pill count" method, which involves comparing the number of doses remaining with the number of doses that should remain. All the patients will be instructed to bring the remaining levothyroxine tablets to each scheduled visit during the clinical follow-up period. Examiners will count the number of remaining pills and calculate drug compliance. If any discrepancy is present, researchers will record the reason for the

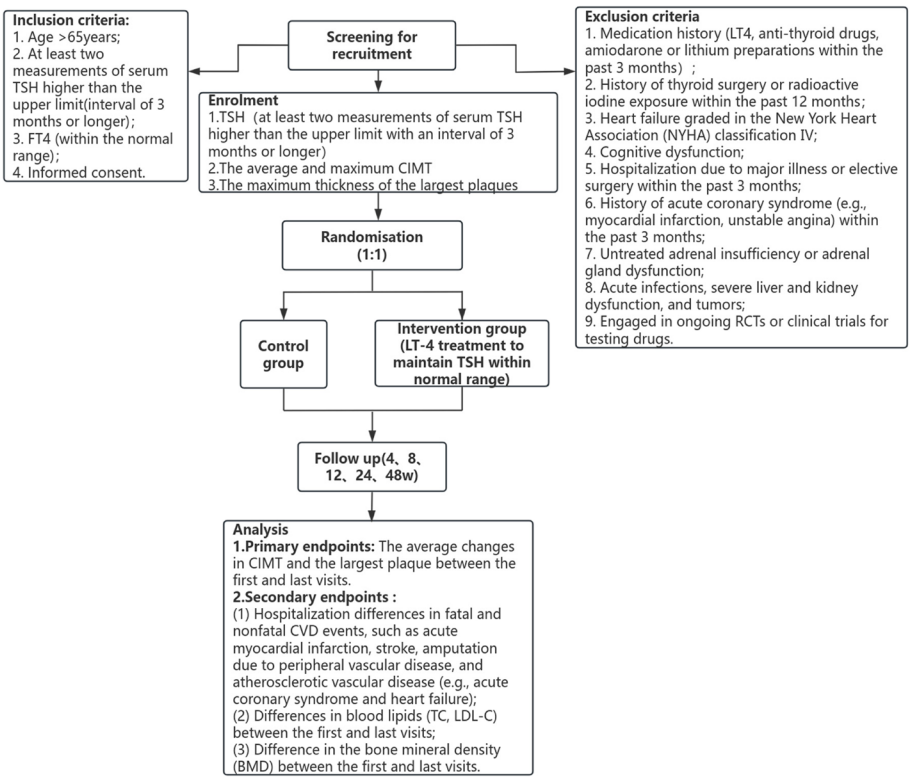

Fig. 1 Study flowchart. CIMT, carotid intima–media thickness

difference. Overall medication compliance should be at least 80% or more during the trial. Subjects who do not satisfy this criterion will be excluded from the analysis.

Provisions for post-trial care

After the study, the participants will return to their usual care. If the intervention proves superior, it may be adopted as the standard treatment at our institution. Any adverse events that are reported during the study will be promptly addressed and managed.

Clinical endpoints

The primary endpoints consist of the average changes in CIMT and the largest plaque between the first and last visits. The secondary endpoints are as follows: (1) differences in hospitalization for fatal and nonfatal CVD events, such as acute myocardial infarction, stroke, amputation due to peripheral vascular disease, and atherosclerotic vascular disease (e.g., acute coronary syndrome and heart failure); (2) differences in blood lipid (TC, LDL-C) levels between the first and last visits; and (3) differences in bone mineral density (BMD) between the first and last visits.

Concealment mechanism

To ensure concealment, block sizes will not be disclosed. Moreover, EDC will not release the outcome of the randomization until the patient has been included and baseline measurements have been completed. The randomization lists will remain undisclosed for the investigators until the end of the trial. However, a hard copy of the randomization list will be available in case of system failure and the need for emergency unblinding.

Follow-up

Follow-up visits will be conducted at 4, 8, 12, 24, and 48 weeks using the case report form (CRF). The schedule for visits and evaluation of the subjects is shown in Table 1. If a participant misses an appointment, the researcher will contact them by telephone and SMS.

Data management

This is an investigator-initiated, multicenter, open-label RCT. Data administrators, independent of the investigators and participants, will be responsible for data management. The outcome assessors will be blinded to blood testing results and instrumental examination findings in this study. The investigators and participants will not be

Table 1 Schedule of assessments

Steps	Projects	Screening randomization		Follow-up				
	No. of visit	**0**	**1**	**2**	**3**	**4**	**5**	**6**
	Weeks	**− 12 to − 4**	**0**	**4**	**8**	**12**	**24**	**48**
1	Informed consent	×						
2	Inclusion/exclusion criteria	×						
3 Clinical data	Basic data		×					
	Randomization		×					
	Concomitant medication		×					
	Concomitant illness		×					
4 Examination	TSH		×	×	×	×	×	×
	Vascular ultrasound		×				×	×
	BMD		×					×
	Blood lipids (TC, LDL-C)		×					×
5	Adverse events	×	×	×	×	×	×	×
6	Deviation from the protocol	×	×	×	×	×	×	×

TSH, thyroid-stimulating hormone; *BMD*, bone mineral density; *TC*, total cholesterol; *LDL-C*, low-density lipoprotein cholesterol

blinded. If incidental findings occur, they will be reported to the Institutional Review Board (IRB) and the principal investigator. The dose will be adjusted by the investigator according to the TSH level.

The data will be recorded in a database. An electronic data management system will be used for data collection and entry. Briefly, data administrators will collect clinical data from the electronic case report form (ECRF) and review and verify the data accuracy and integrity during scheduled visits. All the data management procedures will be recorded. Ultimately, complete clinical data will be exported after the clinical trial. To ensure data confidentiality, each participant will be assigned a unique code at the time of selection for data analysis. Only the study team will have access to the participants' authorized data, which will be securely stored in a file linked to an institutional email. The data will be shared within 6 months after the end of the experiment. Random missing data will be handled by multiple imputation using chained equations (MICEs) with 50 iterations, incorporating baseline scores and adherence patterns.

Dissemination polity: reproducible research

The study protocol, data, and results will be made available by the corresponding author upon request.

Statistical analysis

Statistical analysis will be performed using SPSS 26.0 by statisticians on our research team.

The primary endpoint, namely, CIMT progression, will be considered clinically significant if the change in this value is ≥ 0.1 mm/year ($p < 0.05$). For changes in BMD, a reduction of $\geq 3\%$ at the lumbar spine (DXA scan) will be considered clinically relevant. Statistical significance will be defined as $p < 0.01$ due to secondary endpoint multiplicity; changes in lipid profiles will be considered clinically significant if they meet the following thresholds: LDL-C: increase/decrease $\geq 10\%$ from baseline (or absolute change ≥ 0.5 mmol/L); HDL-C: increase/decrease ≥ 0.2 mmol/L; and TG: increase/decrease ≥ 0.3 mmol/L (or $\geq 15\%$ from baseline).

All the statistical analyses will be performed on an intent-to-treat (ITT) basis. Therefore, participants will be analyzed in the randomly allocated group, regardless of the actual treatment regimen and deviation. After adjusting for stratification variables (site, sex, and starting levothyroxine dose) in linear regression, primary endpoints will be compared with calculations of the absolute difference and corresponding 95% confidence interval (CI).

Continuous variables will be expressed as the infinite number, mean ± standard deviation, and median (interquartile range) of observations and missing values. Categorical data will be expressed as the number and percentage of observations and missing values in each category. All the baseline and follow-up measurements will be analyzed at each follow-up visit. Continuous variables with a normal distribution will be compared by the independent sample *t*-test; otherwise, they will be compared by the Wilcoxon rank test. Categorical variables will be compared by the two-sided likelihood ratio test for chi-square or Fisher's exact test.

Sample size calculation

The sample size will be determined by a two-sided test for an α of 0.05, a statistical power of 80%, and a randomization ratio of 1:1 on the basis of the change in the mean CIMT at the end of the 48-week period. A meta-analysis involving relevant RCTs reported a mean change in the 12-month CIMT of 10 μm [14]. Therefore, a minimum of 230 participants, with 115 participants per group, is essential to achieve at least a 10-μm reduction in CIMT after 48 weeks of observation. Allowing for a 10% dropout rate, 254 participants will eventually be included.

Comorbidity assessment

The preintervention comorbidity assessment will include the following:

(1) Systematic screening using the Charlson Comorbidity Index (CCI) with a threshold score ≤ 2
(2) Verification through baseline medication reconciliation
(3) Collection of data about medical history using standardized questionnaires

Nutritional status assessment

All the participants in this study will undergo comprehensive dietary and lifestyle assessments. Interventions targeting unhealthy CVD-related habits will be implemented with follow-up monitoring to control potential confounding factors. Previous studies have demonstrated that lifestyle factors have no significant effect on thyroid function, whereas dietary iodine status serves as the key determinant. Therefore, we will measure the urinary iodine-to-creatinine ratio in all the subjects. Preliminary data indicate that this region is iodine-sufficient, with the population maintaining a balanced iodine nutritional status.

Plans for the collection and storage of biological samples in this trial/future use

Participants will provide blood samples throughout the study. All the collected samples will be analyzed and stored in the clinical pathology laboratory at the Affiliated Suqian Hospital of Xuzhou Medical University. After the completion of the required analyses, the samples will be disposed of and destroyed in accordance with established protocols.

Definitions of completion and withdrawal of the clinical trial

Completion of the clinical trial is defined as the time at which the last participant finishes the required visits during the 48 weeks and has received all necessary treatments and examinations to provide all the necessary data related to the primary and secondary endpoints. The operational criterion for classifying lost-to-follow-up participants as being unwilling to continue study visits is failure to respond to any attempts to contact (3 phone calls + 2 SMS messages) within a 2-week window. All the attempts will be documented in the CRF with timestamps.

All the participants will be allowed to stop participating in the clinical trial at any time point. Those who refuse to participate in follow-up visits will be withdrawn. Investigators may terminate participation only for the following predefined reasons: (1) new diagnosis of clinically significant comorbidities (e.g., myocardial infarction, malignancy); (2) grade ≥ 3 adverse events per Common Terminology Criteria for Adverse Events (CTCAE); (3) protocol violations that affect safety assessments; and (4) participant withdrawal of consent. All the termination decisions will require documented justification and must be reviewed by the IRB. An eligible alternative will be recruited during the defined recruitment period.

Safety protection and adverse event reporting

The IRB, which includes three endocrinologists who are not involved in the present clinical trial, will be responsible for ensuring safety protection, monitoring adverse events, and assessing endpoints. Adverse events will be graded according to the CTCAE version 5.0 (National Cancer Institute, 2017), which is based on severity (grade 1–5, ranging from mild to death) and relationship to the intervention (unrelated/unlikely/possible/probable/definite). For grade ≥ 3 adverse events, the intervention will be immediately suspended, and the principal investigator and IRB will be notified within 24 h. All adverse events that are reported by participants or determined by investigators from randomization to the last visit, including severe heart failure, malignant arrhythmias, myocardial infarction, stroke, severe hepatic and renal insufficiency, sudden death, and hyperthyroid crisis, will be recorded in the CRF. Additionally, an independent data and safety monitoring committee (DSMB) will be composed of endocrinologists and a biostatistician, all of whom are not participating in the trial, following the applicable regulatory guidelines. The DSMB will review the safety data from this study and make recommendations on the basis of safety analyses of serious adverse events, protocol deviations, and follow-up reports. The DSMB will be responsible for recommending to the Executive Committee that the study be modified or stopping if there are any safety or compliance issues.

Dissemination policy: trial results

The information for this study will be published in the clinicaltrials.gov registry.

Discussion

This is the first multicenter, open-label RCT aiming to assess the efficacy and safety of levothyroxine monotherapy in lowering the risk of CVD in older adults with SCH who are diagnosed on the basis of the age-specific reference range of TSH levels. Moreover, major adverse cardiovascular events (MACEs), blood lipid levels, and BMD will be evaluated. The reason for including BMD as a secondary endpoint is that a study involving 122 patients with subclinical hypothyroidism and 153 healthy controls demonstrated a significantly greater incidence of bone loss in the SCH group [16].

Sufficient evidence shows that in iodine-adequate areas, physiological levels of TSH increase with age. The Third National Health and Nutrition Examination Survey reported that in individuals aged 30–39 years, the 97.5 percentile reference value of serum TSH levels increases by 0.3 mIU/L for every 10 years of age [17]. Zhai et al. established a reference range of TSH levels from 0.75 to 8.86 mIU/L in older adults >65 years from Chinese iodine-adequate areas [12]. According to the new cutoff value for elderly individuals, the prevalence of SCH in older people is far lower than the previously determined prevalence when the reference range of TSH levels for adults was used (3.3% vs. 19.87%). Therefore, an age-specific laboratory reference range of TSH levels is of clinical significance for accurately identifying SCH among older adults. Currently, the TRUST trial is the largest RCT to explore the clinical benefits of levothyroxine monotherapy in older adults with SCH. However, the lower limit of TSH levels in the diagnosis of SCH had not been modified by age, resulting in the potential for misdiagnosis [10]. Serum TSH levels are also influenced by previous and current iodine nutritional status [18, 19]. Moreover, SCH is not a stable pathological condition, and 46% of SCH patients with serum TSH levels lower than 7 mIU/L can have their TSH levels return to a normal range within 2 years [20]. Through cluster sampling in iodine-adequate areas in China, the present study provides a specific reference range for TSH levels in older adults. All the participants will be tested for thyroid function twice, with a minimal interval of 3 months, thus ensuring the accurate identification of SCH in older adults.

CVD events in most clinical trials are generally defined as myocardial infarction, stroke, revascularization surgery (e.g., coronary or carotid revascularization), or fatal cardiovascular disease [21]. Owing to the small sample size, more labor and economic costs are required for longer follow-up to achieve the primary endpoint of CVD events. Similarly, in the TRUST trial, a greatly reduced sample size from 3000 to 737 directly hindered the clinical assessment of CVD risk. A subsequent 1-year follow-up report based on the TRUST trial revealed that levothyroxine treatment does not improve the left ventricular ejection fraction of SCH patients with acute myocardial infarction [22]. Accumulating evidence suggests that CIMT is an effective alternative to CVD events in the evaluation of SCH. A meta-analysis involving 119 RCTs demonstrated that a change in CIMT can predict a decreased risk of CVD [14]. A decrease in CIMT of 10, 20, 30, and 40 μm per year results in relative risks of 0.84 (0.75–0.93), 0.76 (0.67–0.85), 0.69 (0.59–0.79), and 0.63 (0.52–0.74), respectively. With changes in CIMT as the endpoint, the required sample size is only 5.5% of that needed to achieve CVD events. With a primary endpoint of a 10-μm reduction in CIMT over 1 year, this study will assess whether levothyroxine therapy lowers CVD risk in elderly patients with SCH. As the first trial using age-specific TSH thresholds and CVD outcomes in this population, we would expect to address questions that were not answered in the TRUST trial, which is highly feasible.

There are some limitations in this clinical trial. First, subgroup analyses will not be performed because of the small sample size. This limitation may affect the results in two key ways: (1) biological variability: previous literature suggests potential gender differences in the pharmacokinetics of levothyroxine (higher clearance rates in men [23]), which could theoretically influence treatment efficacy. Our aggregated results might obscure such differential effects. (2) Ethnic considerations: variations in cardiovascular risk profiles across different ethnic groups (higher stroke risk in Asian populations [24]) raise the possibility that the cardiovascular effects of levothyroxine could vary across ethnic groups. Second, all the participants will be older Chinese adults, and our conclusions will need to be further validated in other patients of other ethnicities. Third, while our exclusion criteria will increase internal validity by minimizing confounding effects from severe comorbidities, this may affect generalizability to the wider population.

Overall, an accurate recognition of older adults with SCH who are diagnosed according to the age-specific reference range of TSH levels minimizes selection bias in our study. For the first time, we will assess the role of levothyroxine in decreasing the risk of CVD in older adults with SCH who reside in iodine-adequate areas in China, with the primary endpoint of a 1-year change in CIMT. Our findings are expected to provide scientific guidance for the precise diagnosis and treatment of SCH in older adults.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13063-025-08857-z.

Additional file 1. SPIRIT checklist.

Additional file 2. Informed consent.

Acknowledgements
Not applicable.

Trial status
Recruitment for this study began on December 1, 2024, and continues until at least November 30, 2025. Version 1.0 dated 31 January 2025.

Authors' contributions
All the authors contributed to refinement of the study protocol and approved the final manuscript. Authorship is based on substantial contributions to research conception or design, writing or revising manuscripts, and final approval of upcoming editions.

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This work was supported by the Suqian Key Research and Development Program (S202413). The study design, data collection, statistical analysis, or publications are not influenced by the sponsors and are the exclusive responsibility of the investigators.

Data availability
The data underlying this article will be shared upon reasonable request to the corresponding authors.

Declarations

Ethics approval and consent to participate
The study will follow the tenets of the Declaration of Helsinki, and the protocol was approved by the ethics committees of the Affiliated Suqian Hospital of Xuzhou Medical University and the Affiliated Nanjing University of Chinese Medicine Nanjing Integrated Traditional Chinese and Western Medicine Hospital (No. ChiCTR2400092634) on November 30, 2024. Informed consent will be obtained from all the participants. Informed consent procedures will be stratified by cognitive status: participants with MMSE scores ≥ 25 will provide autonomous consent, whereas those with scores < 25 will require consent from legally authorized representatives per institutional protocols. Any changes to the protocol resulting from data revision will be communicated to the Research Ethics Committee, and approval for the modifications will be obtained before implementing any adjustments to the study. Additionally, significant changes to the study protocol will require reconsent from participants.

Consent for publication
Not applicable.

Competing interests
The authors declare that there are no conflicts of interest that could be perceived as prejudicing the impartiality of this work.

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