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Effect of home-based and remotely supervised combined exercise and cognitive intervention on older adults with mild cognitive impairment (COGITO): study protocol for a randomised controlled trial

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ABSTRACT

Introduction Mild cognitive impairment (MCI) is an intermediate phase between normal cognitive ageing and dementia and poses a serious threat to public health worldwide; however, it might be reversible, representing the best opportunity for secondary prevention against serious cognitive impairment. As a non-pharmacological intervention for those patients, interventions that combine physical exercise and cognitive training, whether delivered simultaneously or sequentially, may have superior effects on various cognitive domains, including global cognition, memory, executive function and attention. The supportive evidence remains incomplete. This study aims to assess the effectiveness of a combined exercise and cognitive intervention in Chinese older adults with mild cognitive impairment (COGITO), empowered by digital therapy and guided by the Health Action Process Model and the Theory of Planned Behaviour (HAPA-TPB theory) in a home-based setting.

Methods and analysis This study is a randomised controlled, assessor-blinded multi-centre study. Four parallel groups will include a total of 160 patients, receiving either a combined exercise and cognitive intervention, an isolated exercise intervention, an isolated cognitive intervention or only health education. These interventions will be conducted at least twice a week for 50 min each session, over 3 months. All interventions will be delivered at home and remotely monitored through RehabApp and Mini-programme, along with an arm-worn heart rate telemetry device. Specifically, supervisors will receive participants' real-time training diaries, heart rates or other online monitoring data and then provide weekly telephone calls and monthly home visits to encourage participants to complete their tasks and address any difficulties based on their training information. Eligible participants are community-dwelling patients with no regular exercise habit and diagnosed with MCI. The primary outcome is cognitive function assessed by the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) and Community Screening Instrument for Dementia (CSI-D), with baseline and three follow-up assessments. Secondary outcomes include quality of life, physical fitness, sleep quality, intrinsic capacity, frailty, social support, adherence, cost-effectiveness and cost-benefit.

Ethics and dissemination The study was approved by the Institutional Review Board of Peking University. Research findings will be presented to stakeholders and published in peer-reviewed journals and at provincial, national and international conferences.

Trial registration number ChiCTR2300073900.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The combined exercise and cognitive intervention in Chinese older adults with mild cognitive impairment (COGITO) programme prioritizes combined exercise and cognitive interventions, employing telerehabilitation-based approaches for older adults with mild cognitive impairement in a home-based setting under remote supervision.
⇒ Strategies grounded in the integration of the Health Action Process Model and the Theory of Planned Behaviour (HAPA-TPB theory) theory will be used to improve adherence to this COGITO intervention programme.
⇒ The study will incorporate extensive process evaluation components.
⇒ Participants will be recruited from diverse provinces in China to ensure high representativeness.
⇒ One possible limitation might be the reach of the COGITO intervention since it is only applicable to participants with the support of family or caregivers and access to the internet or digital devices.

INTRODUCTION

In 2021, over 55 million older adults worldwide suffered from dementia with forecasts reaching 78 million by 2030, posing a serious

threat to global public health.[1] However, current medications only slow disease progression, failing to cure dementia. Mild cognitive impairment (MCI) is an intermediate phase between normal ageing-associated cognitive deterioration and dementia. 5–20% of people with MCI develop dementia per year, and almost two-thirds of those who develop dementia had MCI prior to cognitive changes.[2] In China, approximately 15.5% of older adults aged 60 years or older have MCI, representing 38.77 million people,[3] and approximately 6% of older adults with MCI progress to dementia annually.[4] Thus, intervention targeting MCI patients might help reduce the conversion from MCI to dementia. According to the WHO, it is vital to take global action against cognitive decline and dementia and encourage governments worldwide to focus on prevention, disease-modifying therapies and improving healthcare services. Therefore, additional intervention strategies like non-pharmacological intervention are needed to enhance older adults' quality of life and prevent MCI's progression to dementia, given that pharmacological treatment for MCI is limited and may introduce undesirable side effects.

Recent research suggests that interventions combining both physical exercise and cognitive training, whether delivered simultaneously or sequentially, may have superior effects on various cognitive domains, including global cognition, memory, executive function and attention as a non-pharmacological intervention trend for MCI patients. Physical exercise has shown promise in improving cognitive function in patients with MCI,[5] which may be attributed to elevated cerebral metabolism, cerebral blood flow and brain-derived neurotrophic factor, supporting brain plasticity and angiogenesis in the hippocampus.[6–9] Similarly, cognitive training, such as domain-specific cognitive stimulation, has also demonstrated significant effectiveness in global cognition, naming and episodic verbal memory.[10 11] However, most of these interventions are based on institutional settings, which may incur substantial financial burdens related to expenses such as space, staff and transportation. In contrast, home-based interventions have gained popularity as a cost-effective alternative due to their flexible scheduling, reduced space requirements and lower cost, which can also help maintain the delivery of healthcare services to patients. Nevertheless, older adults with MCI may struggle with adherence to home-based interventions, particularly when the interventions should be maintained over extended periods to achieve full benefits, and the absence of professional guidance further complicates this challenge. Hence, using telehealth technologies for home-based interventions and remote supervision is essential to address these issues with the benefits of cost reduction, improved accessibility and enhanced adherence in individuals with cognitive impairment.

Despite the potential benefits, there remains a lack of well-established intervention strategies in the field. Notably, our systematic review[12] identified that only a limited number of studies have investigated remotely supervised combined exercise and cognitive interventions in older adults with MCI from their homes.[13–19] Specifically, we identified seven relevant studies, and among these studies, only a randomised controlled trial (RCT) conducted by Michele Callisaya *et al* in Australia encountered challenges in meeting the planned sample size due to COVID-19 restrictions, and while it did not report a significant improvement in cognitive function, qualitative interviews revealed that older adults subjectively perceived memory enhancements. In addition, other studies are ongoing RCT protocols, uncontrolled or nonrandomised research or pilot, varying in efficacy due to factors such as sample sizes, low compliance and different inclusion criteria of MCI. Furthermore, considering the majority of individuals with MCI reside in their homes and there is a growing awareness of dementia prevention, an increasing number of older adults are engaging in activities like exercise and playing cards to enhance their overall health, thanks to the widespread dissemination of dementia knowledge. However, these activities often lack a well-defined strategy and systematic approach, making them less targeted and effective.

Therefore, our goal is to develop a home-based, remotely supervised combined exercise and cognitive intervention programme for Chinese older adults with MCI (COGITO) and validate its effectiveness in preventing dementia and addressing some of the aforementioned shortcomings. Compared with other studies investigating the combined effects of exercise and cognitive training interventions,[20] our COGITO programme will offer novel insights through its theoretical grounding in behavioural change theories, a focus on home-based telerehabilitation and robust process evaluation measures. Specifically, first, the COGITO intervention will be designed under the guidance of the HAPA-TPB theory, aiming to facilitate adherence to exercise-cognitive training and to guide the development of a mobile app for remote intervention. Second, the implementation of the COGITO programme will adopt a home-based telerehabilitation approach. In comparison to traditional group-based rehabilitation therapies in clinical settings, this approach will offer greater flexibility in scheduling, require minimal spatial resources and entail lower implementation costs. Home-based rehabilitation will enhance intervention continuity and participant adherence during pandemic outbreaks, home quarantines and periods of medical resource shortages.[21] Third, an extensive process evaluation component will be incorporated, entailing thorough assessment and monitoring of various intervention aspects, thus enhancing our understanding of implementation quality and the potential impact on study outcomes.

This paper outlines the research protocol of the COGITO programme, a multi-centre parallel RCT with assessor-blinded evaluations. The proposed study aims to determine whether a combined exercise and cognitive intervention, which is empowered by digital therapy and guided by the HAPA-TPB theory,[22 23] will improve global cognition relative to active or sham controls in older

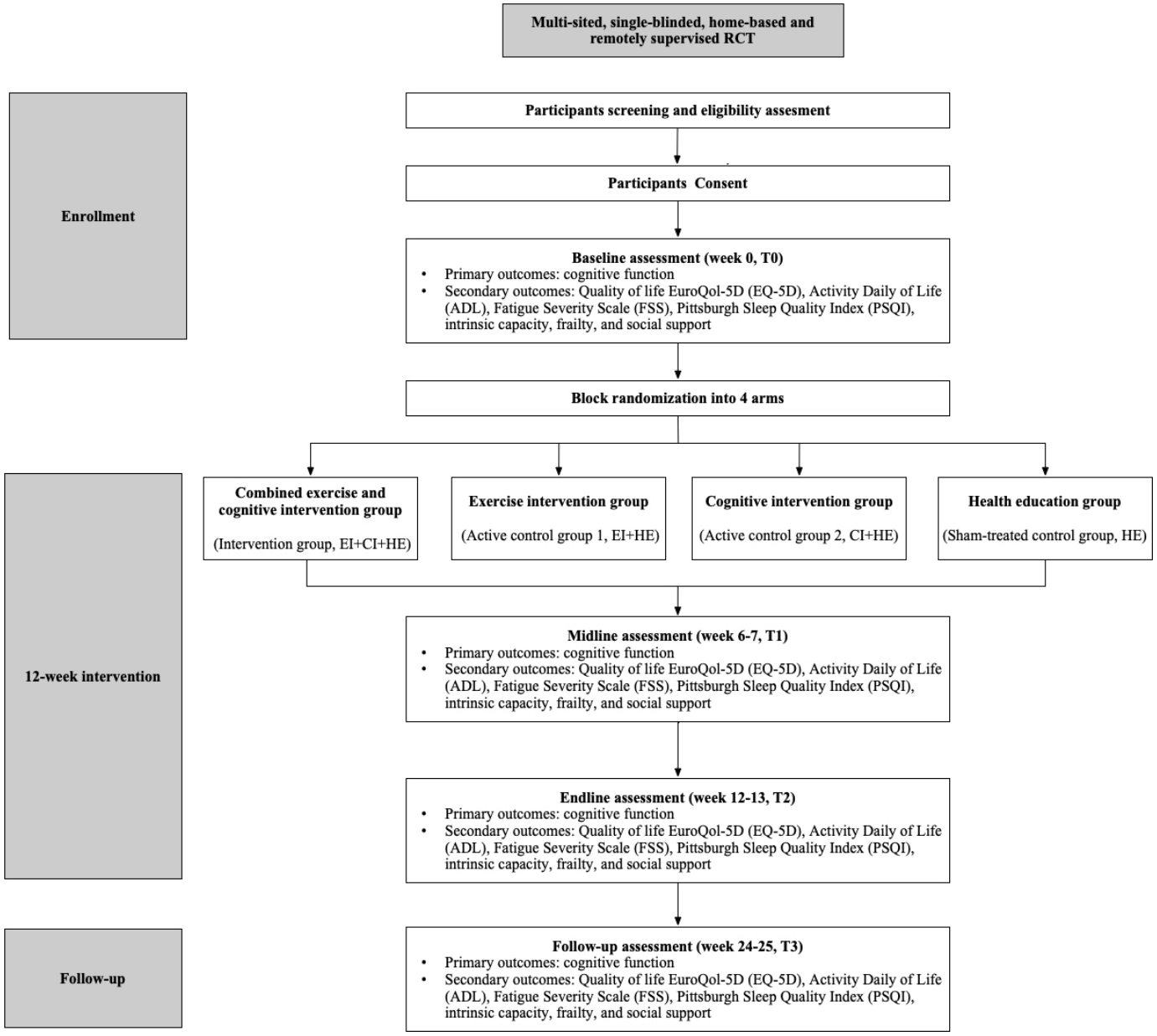

Figure 1 Study design and timeline of the procedures.

adults with MCI in a home-based setting with remote supervision in China.

METHODS AND ANALYSIS

Study design

The COGITO study is a randomised controlled, single-blinded study to be performed in four centres in China (figure 1). Block randomisation by four will be used to allocate enrolled participants into one of four arms, with 40 participants in each arm. Participants will be randomly assigned to the intervention group (combined exercise (EI) and cognitive intervention (CI) and health education (HE)), an active control group (either isolated exercise intervention or cognitive intervention and health education) or a passive control group (health education) according to a 1:1:1:1 allocation ratio. Assessors responsible for performing the baseline (week 0), midline (week 6–7), endline (week 12–13) and follow-up assessments (immediately after the 24–25 week intervention period) will be blinded to allocation. The COGITO programme will be delivered to participants' homes and will be accessible using two intervention techniques: the COGITO Mini-programme and RehabApp. Engagement will be encouraged via weekly telephone monitoring and monthly home visits to enhance compliance. Our study is scheduled to commence on 1 August 2023 and conclude on 31 December 2025. Recruitment began in April 2024 and is anticipated to conclude by December 2024. Data analysis is planned to commence in June 2025 following the completion of interventions and in September 2025 after the collection of follow-up data. The analysis is expected to be completed by December 2025. The latest

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Diagnosed with mild cognitive impairment (MCI) as Petersen criteria (memory complaint, preferably corroborated by an informant; objective memory impairment; normal general cognitive function; intact activities of daily living; not demented[49 50] by using the Functional Activities Questionnaire (FAQ) with a score of <6 indicating normal activities of daily living, the Community Screening Instrument for Dementia (CSI-D) with a score of <29.5 suggested relatively intact overall cognitive function,[30] the Geriatric Depression Scale (GDS) within the range of 2–3 and Clinical Dementia Rating (CDR) with a CDR ≤0.5 indicated relatively intact overall cognitive function.[51]	Medical history: ► With psychiatric disease comorbidities, including major depressive disorders, intellectual disability and bipolar disorder. ► With neurological disorder comorbidities. ► With neurologic or orthopaedic comorbidities impeding safe resistance training (eg, severe joint pain, osteoporosis). ► With cardiovascular comorbidities (known heart murmur, heart attack, heart surgery, cardiac catheterization or coronary angioplasty, pacemaker/implantable cardiac defibrillator/rhythm disturbance, heart valve disease, heart failure, heart transplantation, congenital heart disease). ► With poorly controlled hypertension, diabetes and renal diseases (such as nephritis, acute renal failure, kidney stones, renal cysts, etc.). ► Other conditions interfering with completing cognitive assessments, cognitive intervention and exercise intervention.
No regular exercise habit (ie, excluding at least 3 days per week, 30 min per day, planned, systematic moderate-intensity physical activity, lasting for at least 3 months).	Signs and symptoms that fail to meet the exercise preparticipation health screening recommendations: ► Chest discomfort with exertion. ► Unreasonable breathlessness. ► Dizziness, fainting, blackouts. ► Ankle swelling. ► Unpleasant awareness of a forceful, rapid or irregular heart rate. ► Burning or cramping sensations in lower legs when walking short distances.
With good visual, hearing and language abilities to read Chinese (not illiterate) and able to perform simple smartphone operations.	Medication: ► Use of beta-blockers and/or anti-psychotics such as metoprolol, bisoprolol, atenolol, propranolol, carvedilol, etc. (sleeping medications are not considered exclusion criteria).
Aged between 60 and 75 years.	Currently participating in any other intervention programme.
Community-dwelling participants.	
Able to walk independently for at least 5 min.	
Has access to smartphone or internet at home.	
With family/caregiver support.	
Able to complete the examinations, intervention and follow-up procedures to fulfil study requirements and participants or authorised representatives able to provide written informed consent.	

protocol (version 2.0) was dated 30 March 2024. Figure 1 presents a diagram of the overall study design and timeline of the procedures outlined in online supplemental appendix A.

Patient and public involvement

None.

Study population

Included participants will be community-dwelling older adults aged between 60 and 75 years, with no regular exercise habits. A regular exercise habit is defined as engaging in planned, structured moderate-intensity physical activity on at least 3 days per week, with each session lasting for a minimum of 30 min, for at least the last 3 months.[24] Additional inclusion and exclusion criteria are detailed in table 1.

Recruitment and setting

The trial will take place in four different locations across diverse provinces in China, including Kunming in Yunnan Province (a southern city), Hangzhou in Zhejiang Province (an eastern city), Yinchuan in Ning Xia Autonomous Region (a western city) and Dalian in Liaoning Province (a northern city). This geographical distribution ensures highly representative participant recruitment from diverse backgrounds. This approach enhances the likelihood of producing results that can be effectively extrapolated to broader populations. Participants will be recruited through Kunming Psychiatric

Hospital, Hangzhou Seventh People's Hospital, Ningxia Ning-An Hospital and Dalian Seventh People's Hospital. Given the challenge of recruiting individuals with MCI, a multi-channel approach including advertisements, posters, text messages, etc., will be employed for participant recruitment.[25] The recruitment process of the trial is as follows: (a) primary care physicians from four hospitals will identify potential participants who meet the inclusion criteria by verifying ages between 60 and 75 years and community-dwelling seniors with a sedentary lifestyle; (b) the Thoven Cognitive Self-Assessment (TCSA)[26] or clinical experience will be applied to screen potential participants with cognitive decline; (c) participants will be further screened based on the inclusion and exclusion criteria; and (d) eligible participants will then be invited to undergo final in-person assessments of MCI based on Petersen criteria, using an online questionnaire administrated by physicians or nurses. Informed consent will be signed at enrollment (see online supplemental appendix B). If no exclusion criteria are met during in-person assessments, participants will be included, and insurance purchase and baseline measurements will be performed.

Randomisation and blinding

Within 2weeks after the baseline assessments are performed, eligible participants will be randomly assigned to one of the four groups in a 1:1:1:1 randomisation ratio (block size 10) using a computer-generated random sequence. The groups are as follows: the combined exercise and cognitive intervention group (intervention group, EI+CI+HE), isolated exercise intervention group (active control group 1, EI+HE), isolated cognitive intervention group (active control group 2, CI+HE),or health education group (sham-treated control group, HE). Randomisation will be performed by a member of the research team who is not involved in the assessments or data analysis. Allocation will only be revealed after the baseline assessment. Participants will be informed of their allocation after randomisation but will not be aware of the details of the four allocation possibilities. All assessors will be blinded to the allocation, and participants will be requested not to disclose allocation to assessors at any time during the study. Any instances of participants appearing to be unblinded during follow-up assessments will be diligently recorded, and another assessor will be assigned to continue the assessment next time.

Measurements

Assessments will be performed at the baseline phase (week 0, T0), intermediate phase (week 6–7, T1), endline phase at the completion of the intervention (week 12–13, T2) and follow-up phase (week 24–25, T3). Each assessment will start at the same time of the day and will follow the same sequence to minimise the differences between participants. All tests and questionnaires are described in table 2 and detailed below.

Primary outcome measures

The primary outcome will be global cognitive function, which will be assessed by the Alzheimer's Disease Assessment Scale-Cognitive and Community Screening Instrument for Dementia. ADAS-Cog and CSI-D are the most widely used and validated clinical rating scales for MCI, which are sensitive to changes in clinical status. The ADAS-Cog questionnaire consists of a series of tasks and questions that measure various cognitive domains (memory, language, orientation, attention and other cognitive functions), including tasks of word recall, naming objects and fingers, following commands, constructional praxis, ideational praxis, orientation, word recognition, remembering test directions, spoken language, comprehension and word-finding difficulty.[27] This standardised and comprehensive assessment aims to help clinicians and researchers monitor cognitive changes over time and track the progression of cognitive decline in participants. Cognitive function will also be assessed using the CSI-D, which combines culturally sensitive cognitive testing, involving a 32-item cognitive test administered to the participant and a 26-item informant interview about the participant's daily functioning and general health. These elements are integrated into a predictive algorithm that has demonstrated robust cross-cultural measurement properties in the 10/66 Dementia Research Group study sites.[28] The CSI-D generates three summary scores: cognitive score (COGSCORE), an item-weighted total score from the participant's cognitive test; informant score (RELSCORE), an unweighted total score from the informant interview; and discriminant function score (DFSCORE), a weighted combination of COGSCORE and RELSCORE. COGSCORE and DFSCORE have validated cut-off points for identifying probable and possible cases of dementia.[29 30]

Secondary outcome measures

Several secondary outcomes will include Quality of life EuroQol-5D-5L (EQ-5D-5L),[31] Activity Daily of Life (ADL), Pittsburgh Sleep Quality Index (PSQI),[32 33] intrinsic capacity,[30] frailty,[34] social support[35] and intervention cost and benefit, which have been validated among Chinese older adults. Six intrinsic capacities will be evaluated, including cognitive capacity using CSI-D COGSCORE, vitality using Mini Nutritional Assessment Short-Form (MNA-SF), locomotion using Short Physical Performance Battery (SPPB), psychological status using Patient Health Questionnaire (PHQ-9) and sensory using self-reported vision and hearing questions, which are in accordance with the WHO ICOPE guidance on comprehensive assessment. Frailty will be assessed using the Frailty Phenotype (FP) and International Physical Activity Questionnaire-Short Form (IPAQ-SF) while social support will be assessed by the Lubben Social Network Scale (LSNS). Intervention costs will cover research and development expenses for training materials, including chest-worn heart rate telemetry devices and resistance bands, and personnel training fees

Table 2 Summary of outcome measures and assessment instruments

Outcome	Assessment instrument	Week 0 (baseline)	Week 6 (intermediate)	Week 12 (endline)	Week 24 (follow-up)
Primary outcome					
Cognitive function	ADAS-Cog	+	+	+	+
	CSI-D	+	+	+	+
Secondary outcome					
	ADL	+	+	+	+
	EQ-5D-5L	+	+	+	+
	PSQI	+	+	+	+
Intrinsic capacity	MNA-SF	+	+	+	+
	SPPB	+	+	+	+
	PHQ-9	+	+	+	+
	Sensory: vision and hearing	+	+	+	+
Frailty	FP	+	+	+	+
	IPAQ-SF	+	+	+	+
Social support	LSNS	+	+	+	+
Healthcare utilisation and cost	Number of outpatient and inpatient visits	+		+	
	Outpatient, inpatient and self-medication costs	+		+	
Process evaluation					
Eligibility and recruitment	Retention rate and reasons for withdrawal	+	+	+	+
Intervention acceptability	Participants' training logs, online monitoring data, supervisory documents, adherence records automatically collected through RehabApp and COGITO programme and satisfaction surveys conducted through qualitative interviews	+	+	+	+
Outcome acceptability	Outcome questionnaire completion rate	+	+	+	+
Intervention sustainability	Participants' continuing training logs and qualitative interviews				+
Adverse events	Adverse events	+	+	+	+
Cost-effectiveness	The indicator is the incremental cost-effectiveness ratio (ICER), which is defined as the difference in intervention costs between the intervention and control groups divided by the difference in intervention outcomes between the two groups.				
Cost-benefit	The indicator is the benefit-cost ratio (BCR), which is calculated as the present value of total benefits divided by the present value of total costs.				

ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive; ADL, Activity Daily of Life; CSI-D, Community Screening Instrument for Dementia; EQ-5D-5L, EuroQol-5D-5L; FP, Frailty Phenotype; IPAQ-SF, International Physical Activity Questionnaire--Short Form; LSNS, Lubben Social Network Scale; MNA-SF, Mini Nutritional Assessment Short-Form; PHQ-9, Patient Health Questionnaire; PSQI, Pittsburgh Sleep Quality Index; SPPB, Short Physical Performance Battery.

including wages of training and supervision of clinicians, nurses and therapists. Other costs related to non-health consequences will include time cost (patient and caregiver time based on the number of attended intervention sessions combined with information on the net income of participants), informal care cost (based on the monetary valuation of the time invested by the participant's caregiver) and additional transportation costs. The intervention benefit will consider healthcare utilisation and costs in the past 2 weeks. Healthcare utilisation will be measured by the number of outpatient and inpatient visits, and healthcare costs will include outpatient, inpatient and self-medication costs. All of the above information will be collected via questionnaires at both baseline and follow-up surveys.

Process evaluation

To evaluate the quality of intervention implementation and its potential impact on study outcomes, a comprehensive process evaluation will be conducted, encompassing various aspects.[36]

Eligibility and recruitment

Eligibility and recruitment will be documented by recording rates of eligibility and recruitment, retention rate and reasons for withdrawal.

Intervention acceptability

Data on intervention acceptability will be collected from participants' training logs, online monitoring data, supervisory documents, adherence records and satisfaction surveys conducted through qualitative interviews. Adherence will be assessed based on several criteria, including the number of dropouts, training frequency across all groups, total time exercised and total time spent in cognition training, as collected in RehabApp and COGITO programme, respectively. Dropouts will be defined as having an average training frequency of ≤2 times per week over 3 weeks, an average training frequency of ≤1 time per week for 2 consecutive weeks, or no training sessions within 1 week observation period. Exceptions will be made if participants are unable to participate for 1–2 weeks due to treatment or other reasons but subsequently resume full participation. Dropped-out participants will be encouraged to complete the follow-up measurements.

Outcome acceptability

Outcome acceptability will be assessed by rates of outcome questionnaire completion at baseline, 6 weeks and 12 weeks.

Intervention sustainability

Maintenance of the intervention over 6 months will be assessed through participants' continuing training logs and qualitative interviews.

Adverse events

Adverse events, including falls, fractures, muscle strains, cardiovascular exacerbations, or any worsening of underlying diseases or new-onset musculoskeletal, cardiovascular or metabolic abnormalities, may occur. Participants can report adverse events at any time during the study. Participants required to exercise will receive a prompt from RehabApp after each session and will be asked about adverse events during weekly telephone supervision. These events will be documented in the electronic database with prompt notification to responsible authorities in case of serious adverse events. Withdrawal from the study will not be necessary if the injury does not exacerbate the participant's condition and if adequate rest and treatment following the injury do not impact subsequent intervention.

Intervention

The total duration of the COGITO programme will be 12 weeks, with a frequency of at least twice a week, regardless of group allocation. At the end of the 12 week programme, participants will be encouraged to maintain their engagement until 6 months. This programme will be delivered individually at home and will be accessible using two intervention techniques: COGITO Mini-programme and RehabApp. All participants will be remotely supervised via weekly telephone monitoring and monthly home visits to increase compliance. The intervention is described in detail in the TiDIER format[37] (see online supplemental appendix C), and the intervention contents are presented in table 3.

Combined exercise and cognitive intervention and health education (intervention group)

The development of the intervention proceeded as follows: initially, based on literature and theoretical research, we developed an integrated theory of the Health Action Process Model and the Theory of Planned Behaviour, aiming to facilitate adherence and construct a COGITO remote training intervention technical package and plan suitable for older adults with MCI, guided by the HAPA-TPB theory and a complex intervention development framework.[38 39] The initial exercise intervention programme was designed based on the existing exercise intervention prescriptions and in accordance with the principles of frequency, intensity, time, type of exercise, volume and progression (FITT-VP) exercise prescription.[40] The cognitive training component had been previously developed and applied in the Chinese population but had not yet undergone validation in empirical studies. Second, we conducted two rounds of Delphi expert consultation in April 2023, distributing questionnaires via email or in paper form to gather feedback from 20 experts in cognitive impairment diagnosis and treatment, nursing, management and geriatric exercise rehabilitation. This iterative process aimed to revise and optimise the intervention plan to align with the FITT-VP framework and meet the needs of Chinese older adults with MCI in a remote home-based setting. Third, following the initial development phase, we proceeded with a 2 week pilot to further refine the intervention in August 2023.

In the intervention group of combined exercise and cognitive training, the duration will be 50 min (30 min of exercise intervention and 20 min of cognitive intervention), enhanced with telemonitoring through weekly telephone calls and monthly home visits. Participants will take part in a supervised home exercise programme involving a combination of the following activity types: a warm-up routine, aerobic training, resistance training, mind-body training and a cool-down routine, delivered through a smartphone application called RehabApp and monitored with an arm-worn heart rate telemetry device. Participants will be instructed to do aerobic and intensity exercises for 40 min within a predetermined heart rate zone, based on the heart rate reserve (HRR), calculated with the Karvonen method; the upper bound is set at 64–76% of HRR, and the Rate of Perceived Exertion is recommended at 5–6 with medium intensity.[41] The core exercises and activities encompass aerobic training (ie, shoulder exercises, hip abduction or extension and thigh raising), resistance training (ie, squats and twists exercise) and mind-body training (ie, marching while sitting and attention task, marching in place and attention inhibition

Table 3 Description of the preliminary combined exercise and cognitive intervention outline

	Description	Intervention content
Exercise intervention (EI)		
Warm-up (10 min)	A warm-up includes a range of stretch exercises, such as stretching arms, back and trunk and stretching hamstrings and calves.	Stretching arms and back.
		Stretching the trunk.
		Knee-straightening exercise.
		Stretching the hamstrings.
Aerobic training (15 min)	Aerobic training involves shoulder exercises, hip abduction or extensions and thighs raising.	Hip extension and shoulder raising.
		Hip abduction and shoulder raising.
		Thighs raising and shoulder exercise.
		Bilateral arm flexion movements.
Resistance training (15 min)	Resistance training involves squats, twists exercise	Standing/seated resistance band pulldown (Y→W).
		Standing/Sitting resistance band pulldown (Y→T).
		Squats.
		Twists exercise.
Mind-body training (6 min)	Mind-body training comprises marching while sitting and attention task and marching in place and attention inhibition task.	Marching while sitting or standing and simultaneously completing attention and inhibition task: Specifically, participants are instructed to step and clap their hands on multiples of three while counting the number of steps, or to stop counting aloud at that time on multiples of three (3, 6, 9…).
Cool-down (10 min)	A cool-down includes self-massage, breathing, stretching, walking and other relaxing exercises.	
Cognitive intervention (CI)		
Memory (4 min)	Memorise and identify targets to enhance memory abilities and reduce the risk of age-related cognitive decline or other neurological disorders.	Memorise and identify the teapots.
		Memorise and identify locations where the groundhogs appear.
Executive function (6 min)	Determine the object's category and make a decision to effectively enhance ability to handle multiple tasks simultaneously and elevate levels of executive functioning.	Determine whether the falling object is a fruit or a vegetable.
		Eradicate harmful substances and safeguard the brain.
Attention (4 min)	Focus on targets and select the same target numbers or objects to enhance sustained attention and reaction speed.	Select the balloons with the same target number.
		Purchase the corresponding items based on the shopping list.
Sensory (5 min)	Enhance perception of length/distance or spatial orientation perception and reduce the risk of age-related cognitive decline or other neurological disorders.	Cut suitable lengths of tree trunks to build bridges and help monkeys cross the river.
		Determine whether the approaching palm is a left palm or a right palm.
Health education (HE)		
	Participants will receive cognitive health education consistent with public health recommendations (eg, knowing more about mild cognitive impairment and healthy lifestyle promotion).	

task). In addition, participants will be advised to warm up before exercising and perform cool-down exercises after the session.

The cognitive intervention, including the type of cognitive tasks, frequency and time, will be optimised to meet the needs of older adults with MCI in the context of remote home training after expert consultations. Multimodal and multidomain training targeting memory, executive function, attention, speed of information processing and sensory functions will be based on a literature review. Cognitive games will be delivered through the COGITO Mini-programme, including a combination of the following cognitive activities: memory (eg, memorise and identify targets to enhance memory abilities and reduce the risk of age-related cognitive decline or other neurological disorders), executive function

(eg, determine the object's category and make decisions to effectively handle multiple tasks simultaneously and elevate levels of executive functioning), attention (eg, focus on targets and select same target numbers or objects to enhance sustained attention and reaction speed) and sensory training (enhance the perception of length/distance or spatial orientation perception and reduce the risk of age-related cognitive decline or other neurological disorders). Third, participants will also receive information brochures and cognitive health education consistent with public health recommendations during training sessions or the intervention phase.

Exercise intervention and health education (active control group)

The active control condition is designed to ascertain whether the combined exercise and cognitive intervention is significantly superior to either isolated intervention in terms of primary and secondary outcomes. The active control group 1 (EI+HE) will include both exercise training and health education, with the exercise training aligning with the five components outlined in table 3, and the duration of each session will be 30 min (see online supplemental appendix C).

Cognitive intervention and health education (active control group)

In the active control group 2 (CI+HE), participants will engage in cognitive games and receive health education, and the cognitive training component will consist of the eight cognitive games outlined in table 3 covering four dimensions: memory, executive function, attention and sensory, with a target duration of 20 min (see online supplemental appendix C).

Health education (passive control group)

Participants in the passive control group will receive information brochures and educational instructions during training sessions or the intervention phase.

Training procedure

Training for participants will be provided collaboratively by researchers and intervention providers at local centres. First, local intervention providers will receive comprehensive training materials, including instructional manuals for supervision and assessment sessions introducing the purpose of the intervention, the overall instruction plan and intervention precautions. Additionally, they will undergo two training sessions led by researchers before commencing participant training. Second, participants will be provided with materials, including 'How to' guides and recorded videos demonstrating the operation of the two intervention techniques (COGITO Mini-programme and RehabApp), as well as detailed exercise videos introducing the exercise training sessions. They will also receive an instruction manual and a health education manual covering various topics related to cognitive health. Moreover, participants will gain access to virtual groups and blogs for peer support, personalised schedules for intervention activities and reminders and personalised physical activity or cognitive training diaries to monitor progress against recommended weekly targets. To ensure all enrolled participants receive adequate training, intervention providers will conduct offline training sessions at the centre, integrating the first intervention with intervention training. During these sessions, intervention providers will ask participants and their family members to watch demonstration videos of COGITO intervention instructions and precautions, as well as operational videos of the two intervention techniques. Hands-on demonstrations will be conducted for using Bluetooth heart rate armbands and elastic bands, and assistance will be provided to instal and activate the COGITO Mini-programme and RehabApp accounts. Additional details are provided in online supplemental appendix C.

Sample size estimation

The sample size calculation is based on the effect sizes (ES) for the primary outcome of ADAS-COG, which were calculated based on two previous RCT studies using mean and SD,[42 43] resulting in an effect size of 0.54.[20] Assuming a 5% risk of type 1 error (α), 80% power, 3 group allocation and accounting for a 20% dropout rate, a minimum of 146 participants will be required. We aim to recruit 40 per arm for a total of 160 participants, allocating them randomly across four groups (1:1:1:1 ratio). The sample size was calculated using PASS 2021.v21.0.3.

Strategies to support home-based and supervised intervention empowered by digital therapy based on HAPA-TPB theory

To improve adherence to this intervention programme, strategies grounded in the integration of the HAPA-TPB theory will be used, which has been shown to better elucidate the cognitive underpinnings of exercise and cognition training among older adults with varying degrees of cognitive impairment. Considering the weakened intention-behaviour relationship among MCI patients, the HAPA-TPB theory could help bridge the gap in this study. More specifically, the home-based and remote supervision plan, which aims to promote effectiveness and adherence to combined exercise and cognitive interventions, comprises the following key components: (a) to facilitate intention formation for health behaviour change through improving task self-efficacy, outcome expectancy, attitude, subjective norm and social support; (b) to promote the adoption of health behaviour by fostering maintenance self-efficacy, and action planning and coping planning act as mediators between intentions and behaviour; and (c) to ensure the maintenance of the behaviour through enhancing both maintenance and recovery of self-efficacy. More details of the behavioural change techniques and how they are incorporated into the exercise and cognitive intervention programme are shown in online supplemental appendix D.

Guided by this theory, interventions will be remotely supervised using telehealth technologies. All supervision and motivational strategies will be delivered through coaching and motivational apps called COGITO Mini-programme and RehabApp. Participants will be required

to wear a heart rate telemetry device on one arm during exercise. Throughout the home-based combined exercise and cognitive intervention, the app will offer exercise-cognitive training prescriptions and guidance, health information and community support, all of which are intended to enhance participants' perceptions of training and compliance. Additionally, the digital devices will record all participants' exercise training heart rates or adverse events and cognitive training scores. These will help participants track progress, and supervisors will receive real-time feedback for better training supervision and effectiveness. Moreover, supervisors will telephone the participants once a week and will pay monthly home visits to prompt them to fulfil their tasks and solve difficulties based on their training records.

Participant timeline

The overall trial duration per participant is six months (24 weeks). Data analysis will commence once after all participants have completed the 12 week intervention and the 6 month follow-up interviews (see online supplemental appendix A).

Data collection and management

The COGITO programme follows Good Clinical Practice (GCP) guidelines for RCTs. Prior to data collection, the research team will review the standard operating procedures (SOP) protocol manual. Each participant will be assigned a unique ID account, consisting of a regional code and the last four digits of their identity card. Moreover, assessors from all centres will receive standardised training, conducting evaluations alongside experienced assessors on at least two individuals with MCI for consistency in assessment across different centres. All content, including screening, weekly telephone calls, and monthly home visits, will be audio-recorded to verify the delivery of the intervention as planned, except for refusals. Each centre will be required to provide weekly progress updates through shared documents, with monthly meetings held to review progress and address issues. Additionally, several local coordinators, who are not directly involved in the study, will be assigned to closely monitor and facilitate the recruitment and study progress of the trial in each centre. Any instances of protocol deviations will be documented. All data and information from this study will only be used for research purposes. Personal data will be kept strictly confidential, and no personal information will be reported. The findings of this trial will be reported according to the revised CONSORT guidelines. The protocol is written following the SPIRIT reporting guidelines[44] and in the TiDIER format[37] (see online supplemental appendices E–G).

Statistical analysis plan

Statistical analyses will be undertaken according to a statistical analysis plan. All statistical tests will be two-tailed, with a significance level set at $p<0.05$. All analyses will be conducted using STATA SE 17.0 or a later version if available.

Summary of baseline data and flow of participants

A CONSORT diagram will be used to illustrate participant flow throughout the study. Descriptive statistics for demographic and baseline characteristics by four groups and overall will be provided with means and SD or medians and interquartile ranges (IQR), where appropriate, for continuous characteristics and numbers and percentages for categorical variables. Descriptive summaries will similarly be provided for each outcome variable at baseline, 6 weeks, 12 weeks and 6 months, where applicable by group and overall. Participants who are lost to follow-up will be compared using chi-square tests and t-tests to assess the potential bias.

Analysis of the primary outcome

The primary analysis will follow an intention-to-treat (ITT) strategy, utilising Last Observation Carried Forward (LOCF) for handling missing data. Exploratory analyses will also be conducted using per-protocol analyses for all outcomes, including all participants adhering to the specified intervention protocol with baseline and 12 week outcome data available to assess optimal efficacy under ideal conditions. The primary outcome of the ADAS-COG and CSI-D will be analysed using Difference in Difference (DID) to compare the cognitive changes over time between the combined intervention and control groups, both before and after the intervention, aiming to identify the significance and effect sizes of the combined training arms. Additionally, we will employ an ANCOVA model to analyse the primary outcomes at 6 weeks, 12 weeks, and 6 months, using baseline cognitive scores and age as covariates. If statistically significant between-group differences are observed, Tukey's multiple comparisons will be used to identify specific significant pairwise differences. Within-group comparisons will also be conducted using a paired t-test.

Analysis of the secondary outcome

Secondary outcomes at 6 weeks, 12 weeks and 6 months will be analysed using ANCOVA mixed models, considering time, group interactions, baseline values of variables and age as covariates.

Interim analyses

An interim analysis will be conducted after data entry for baseline and 12-week-visits. Primary and selected secondary outcomes will be analysed following the same methods as the main analyses. The purpose of interim analysis is to facilitate early dissemination of results for the study's primary outcome.

Process evaluation

Descriptive statistics will assess feasibility outcomes and the results will be presented as mean and SD, median and IQR or numbers and percentages, as appropriate (ie, eligibility and recruitment, intervention acceptability,

outcome acceptability, intervention sustainability and adverse events).

Health economic analyses

Cost-effectiveness analysis will be conducted from a societal perspective, integrating costs and outcomes to calculate the Incremental Cost-Effectiveness Ratio (ICER) and a cost-benefit analysis will be performed using the Benefit-Cost Ratio (BCR) as the metric. Further details can be found in table 2.

Analysis of interview data

Qualitative analysis will be conducted through in-depth interviews with stakeholders at each of the four centres following the intervention, including participants, their family caregivers, local coordinators, and supervisors. All stakeholders will be invited to participate in interviews until either 10 interviewees per site are reached or data saturation were secured.[45] Those who agree to participate will provide oral consent prior to the interview. Interview questions will be designed using the Consolidated Framework for Implementation Research (CFIR) framework, employing their Interview Guide Tool.[46 47] All interviews will be audio-recorded and transcribed verbatim. The transcripts will be imported into NVivo 14 for thematic coding and management. Data triangulation will be achieved through investigator triangulation with parallel coding, and data source triangulation from different roles within the COGITO programme.[48] Thematic analysis will proceed in a deductive approach, guided by the CFIR framework.

DISCUSSION

In this section, we present the rationale and design of the COGITO study, and the RCT aims to provide evidence for the efficacy of combined exercise and cognitive intervention for older adults with MCI in the context of home-based and remotely supervision.

Previous studies have suggested a positive effect of remotely supervised combined exercise and cognitive interventions on several cognitive function domains in MCI patients. However, home-based combined exercise and cognitive intervention for Chinese older adults with MCI under remote monitoring in mainland China is limited. The COGITO programme is therefore timely and has the potential to inform best practices with insight into the effects of combined exercise with cognitive training to improve cognition and will also directly reveal its feasibility for implementation in a real-life home-based environment in China empowered by digital therapy and HAPA-TPB theory. The COGITO programme will also help to overcome traditional institution-based rehabilitation limitations by reducing the overall cost and lowering the barrier for patients to engage in intervention at home. Additionally, in contrast to previous home-based interventions, the COGITO programme entails several novelties to improve motivation and compliance. First, the addition of digital therapy based on HAPA-TPB theory has not been used before in MCI patients to stimulate their compliance in a home-based intervention. Second, we have added aspects of support, using immediate visualisation of intervention results and progress, weekly phone calls and monthly home visits by a medical professional, as well as support from the participant's family and friends. Third, two active control arms are designed to increase compliance and minimise drop-out rates in two of the control arms. Our study also has several limitations. First, one possible limitation might be the reach of the COGITO programme since it is only applicable for participants with support of family or caregiver and access to the internet or digital devices. Second, there is no patient and public involvement planned for our study. Third, the participants will not be blinded due to the characteristics of the exercise and cognitive intervention. Furthermore, the design of multicentre research with a sample size of 160 participants allows quicker recruitment, diverse population coverage, and increased generalizability. Moreover, such intervention programmes will provide high-level evidence for the feasibility and scalability, and results from this study will contribute to clinical practice or evidence base that community health workers and social workers can use to enhance health capacity and access to high-quality services for MCI intervention in places with scarce specialist resources.

ETHICS AND DISSEMINATION

This study is conducted in compliance with International Conference on Harmonisation of GCP and all applicable regulatory requirements. COGITO has undergone review and approval from the Institutional Review Board of Peking University (#IRB00001052-23037), and its trial registration number is ChiCTR2300073900. All participants will complete an informed consent process at enrollment. Research findings will be disseminated through publication in peer-reviewed journals and presentations to local stakeholders, as well as at provincial, national and international conferences or forums. Adhering to the International Committee of Medical Journal Editors' standards, the authorship of publications resulting from this study should accurately represent the academic contribution of individuals involved in designing and implementing the trial, analysing the data and preparing the manuscript.

Data availability statement

Access to de-identified data may be granted to interested parties 12 months after the publication of the principal paper addressing primary research questions, upon request via email to the responsible person (luoyanan@bjmu.edu.cn).

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Contributors YL and ZL conceived the study and initiated the study design. YL wrote the grant proposals. CH assisted in the study design and drafted the first version of the protocol. TCT assisted in the sample size calculation, the plan for the statistical analysis and the review of the protocol. JZ, CG, JS, JH and XX provided expertise in trial design, including clinical diagnosis, fieldwork and data collection. YD, GL, BG and XN reviewed and edited the protocol. XL reviewed the qualitative approach of this protocol and did the thorough language check through the manuscript. YL, the guarantor, accepts full responsibility for the work and/or the conduct of the study, had access to the data and made the final decision to submit for publication. All authors contributed to the refinement of the study protocol and approved the final manuscript.

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Patient consent for publication Not applicable.

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