STUDY PROTOCOL

Effects of an Exercise Snacking Intervention on Cognitive Function in Patients With Mild Cognitive Impairment: A Nationwide Multicenter Randomized Controlled Trial

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Signature Page

We have read and approved the protocol described in this document and agree with its contents.

Confidentiality Statement: Study records will be kept confidential in accordance with applicable laws and regulations. Names, identification numbers, addresses, telephone numbers, and other directly identifying information will not be disclosed unless required by law. Each participant will be assigned a unique study identification code. Identifying information and the code key will be securely maintained at Peking University. Participant identities will not be disclosed in scientific meetings, publications, or other dissemination of study findings. Authorized regulatory authorities and the Peking University Biomedical Ethics Committee may review study records as required.

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Protocol Synopsis

Item	Description
Objective	To evaluate the effects of a Baduanjin-based exercise snacking intervention, compared with usual health education, on global cognitive function, selected cognitive domains, physical function, psychological health, intervention adherence, and peripheral biomarkers in adults with mild cognitive impairment (MCI).
Design	Nationwide multicenter, parallel-group, randomized controlled exercise intervention trial.
Population	Adults aged 51–80 years recruited from neurology departments who meet the protocol-defined criteria for mild cognitive impairment and can safely participate in light-to-moderate intensity physical activity.
Study Centers	Peking University Third Hospital; Peking University Sixth Hospital; The First Affiliated Hospital of Zhengzhou University; The First Hospital of Jilin University.
Sample Size	240 participants; 1:1 allocation (120 intervention, 120 control).
Intervention	Usual health education plus Baduanjin-based exercise snacks, generally 5–8 minutes per bout, five times per day, with progression to an approximately 11-minute complete Baduanjin routine. Target intensity: 45%–55% HRmax or RPE 2–3.
Control	Usual health education, including educational materials on MCI/brain health and one online health lecture per month.
Intensive Intervention Period	24 weeks (approximately 6 months).
Follow-up	Follow-up through Week 96 (approximately 24 months).
Primary Outcome	Change in Montreal Cognitive Assessment (MoCA) total score.
Other Outcomes	Physical function and fitness, depression/anxiety/insomnia, adherence and acceptability, fasting glucose/lipids, BDNF, IL-6, and adverse events.
Primary Analysis Principle	Intention-to-treat, using longitudinal models appropriate to outcome type and prespecified sensitivity analyses.

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1. Background

Mild cognitive impairment (MCI) represents an important transitional stage between normal aging and dementia. Amnestic MCI (aMCI) is associated with an elevated risk of progression to Alzheimer's disease (AD). Sedentary behavior has been associated with adverse brain structural and functional changes, including reduced medial temporal lobe integrity, impaired cerebral hemodynamics, and poorer cognitive performance. Prolonged uninterrupted sitting may adversely affect metabolic and cognitive health even among individuals who otherwise engage in some physical activity.

Regularly interrupting sedentary time with brief bouts of physical activity may provide a practical strategy for older adults. "Exercise snacks" divide daily physical activity into multiple short bouts rather than requiring a single prolonged exercise session. This approach may be easier to integrate into everyday life and may improve adherence among older adults and people with MCI. Brief activity bouts can acutely increase heart rate, blood flow, and metabolic demand and may improve cardiometabolic health.

This study uses Baduanjin, a traditional Chinese mind–body exercise characterized by low-impact, coordinated movements, as the principal exercise-snacking modality. The Xiangdong Health application and WeChat-based reminders are used to support instruction, self-monitoring, adherence, and behavioral

reinforcement. The study therefore evaluates a low-cost, low-threshold, scalable non-pharmacological strategy intended to interrupt sedentary behavior and support cognitive health.

2. Objectives

2.1 Primary Objective

To evaluate whether a Baduanjin-based exercise snacking intervention, compared with usual health education, improves cognitive function as measured by the Montreal Cognitive Assessment (MoCA) in patients with mild cognitive impairment.

2.2 Secondary Objectives

- To evaluate effects on the severity of cognitive impairment and selected cognitive domains, including memory and executive function.
- To evaluate effects on physical function and fitness and on symptoms of depression, anxiety, and insomnia.
- To evaluate intervention adherence and acceptability and to characterize changes in daily behavior patterns.
- To assess changes in fasting glucose and lipid metabolism, brain-derived neurotrophic factor (BDNF), and the inflammatory marker interleukin-6 (IL-6).

3. Study Design

This is a multicenter, parallel-group randomized controlled trial. A total of 240 participants will be randomized in a 1:1 ratio to the comprehensive intervention group or the usual health education control group.

3.1 Study Population

Participants will be recruited from neurology departments at participating hospitals. All candidates must satisfy all inclusion criteria and none of the exclusion criteria.

3.1.1 Inclusion Criteria

Category	Criterion
Age	51–80 years, inclusive.
Clinical diagnosis	Meets the protocol-defined NIA-AA core clinical criteria for probable amnestic mild cognitive impairment (aMCI).
Subjective complaint	Progressive memory decline lasting >6 months, reported by the participant and/or an informant and confirmed by a study neurologist.
Objective impairment	Impairment in 1–2 cognitive domains, including the memory domain, on standardized neuropsychological assessment. Global cognition is assessed with MoCA; protocol eligibility uses a MoCA total score of 18–26. Plasma p-tau is used as an auxiliary measure as specified in the source protocol; discordant cases are reviewed by two attending neurologists.
Preserved function	Cognitive impairment has not resulted in clear functional dependence; instrumental activities of daily living are normal or only mildly reduced.
Non-dementia	Does not meet diagnostic criteria for any type of dementia.

Smartphone capability	Able to independently operate a smartphone and complete online check-ins, questionnaires, and other digital study tasks.
Physical capability	Able to walk independently without assistance and has no absolute contraindication to exercise based on the Physical Activity Readiness Questionnaire and/or physician assessment.
Consent and follow-up	Provides written informed consent; primary caregiver, if applicable, is informed and supportive; willing and able to complete the planned 24-month follow-up and study assessments.
Medication	Cognition-related medications are permitted if the dose has been stable for at least 1 month before screening. Other medications that may influence cognition are recorded. Medication initiation, discontinuation, and dose changes are documented throughout follow-up.

3.1.2 Exclusion Criteria

- Meets clinical diagnostic criteria for Alzheimer's disease dementia or another type of dementia.
- Cognitive impairment is primarily attributable to another clearly identified cause, including major neurodegenerative disease (e.g., Parkinson's disease, Huntington's disease, progressive supranuclear palsy, multiple sclerosis), severe psychiatric illness (e.g., schizophrenia, bipolar disorder, major depressive episode with psychotic features), or relevant uncontrolled systemic disease (e.g., uncontrolled thyroid dysfunction or vitamin B12 deficiency).
- Acute cardiovascular or cerebrovascular event within the previous 6 months, including myocardial infarction, unstable angina, stroke, or transient ischemic attack.
- New York Heart Association class III–IV heart failure.
- Poorly controlled hypertension, defined in the protocol as resting blood pressure ≥180/110 mmHg.
- Poorly controlled diabetes mellitus, defined in the protocol as HbA1c >9.0%.
- Severe musculoskeletal disease preventing continuous walking for >100 m, severe respiratory disease, or malignancy with expected survival <2 years.
- Severe visual or hearing impairment that prevents completion of study assessments despite usual corrective devices.
- High fall risk: ≥2 unprovoked falls in the previous year, SPPB balance-item score of 0 (unable to stand with feet together), or routine use of a walking aid or wheelchair.
- Current participation in another clinical study likely to affect cognition or physical activity.
- Plans to reside outside the study catchment area for >3 months during the next 24 months.
- Any other condition judged by the investigator to compromise safety, data integrity, or adherence.

3.2 Randomization and Blinding

3.2.1 Randomization

Randomization will use stratified block randomization with a 1:1 allocation ratio. The source protocol specifies age strata of 51–60, 61–70, and 71–80 years and sex as stratification factors. Block sizes of 4 or 6 will be randomly alternated and concealed from study implementation personnel. An independent statistician will generate the randomization sequence in R, and allocation concealment will be implemented through a central randomization system.

3.2.2 Blinding

Because of the behavioral nature of the intervention, participants and intervention providers cannot be blinded. Outcome assessors, including neuropsychological and physical-function assessors, data managers, and final statistical analysts will remain blinded to treatment allocation. Study materials and datasets used for assessment and analysis will identify participants by unique study ID without displaying group assignment.

3.3 Interventions

3.3.1 Comprehensive Intervention Group

Participants will receive all usual health education components plus the exercise-snacking intervention.

Component	Protocol
Digital support	Installation and use of the Xiangdong Health app. Daily health-status self-assessment is completed before exercise as specified in the protocol.
Reminder schedule	Five prespecified reminders distributed across the day: approximately 08:30, 10:00, 13:30, 17:30, and 20:30, delivered through the participant WeChat group.
Exercise content	Baduanjin-based exercise snacks incorporating the eight traditional movements: Two Hands Hold up the Heavens; Drawing the Bow to Shoot the Hawk; Separate Heaven and Earth; Wise Owl Gazes Backward; Sway the Head and Shake the Tail; Two Hands Hold the Feet; Clench the Fists and Glare Fiercely; Bouncing on the Toes.
Progression	During Weeks 1–4, participants complete short Baduanjin exercise-snack sessions (approximately 5–8 minutes/session) with video/photo check-in. Thereafter, an approximately 11-minute continuous Baduanjin routine is added while retaining the fragmented exercise-snacking approach.
Intensity	Light-to-moderate intensity; target 45%–55% HRmax or RPE 2–3 as defined in the source protocol.
Duration	Individual movements approximately 1–2 minutes; exercise-snack sessions approximately 5–8 minutes; complete Baduanjin routine approximately 11 minutes.
Daily target	Five successful check-ins per day. A successful check-in requires completion of the prescribed exercise followed by recording in the app.
Adherence monitoring	App check-in records, WeChat support, weekly telephone/WeChat contact, and monthly online group meetings.
Safety	Gradual initiation, low-impact movement options, individualized adjustment when needed, caregiver/supervisor support when applicable, and ongoing monitoring by exercise-science and clinical staff.

3.3.2 Usual Health Education Group (Control)

Participants receive educational materials related to MCI and brain health and one online educational session each month, covering topics such as brain-health practices, psychological health, and sleep management.

3.3.3 Intervention Period

The intensive intervention period is 24 weeks. After the intensive phase, active goal setting and proactive intervention support cease and participants enter naturalistic follow-up.

3.4 Follow-up Schedule

Assessment	Baseline	Week 12	Week 24	Week 36	Week 48	Week 60	Week 96
Informed consent / screening	X						
Demographics / medical history	X						
MoCA	X	X	X	X	X	X	X
HAMD / ISI / HAMA	X	X	X	X	X	X	X
SPPB / grip strength	X		X		X	X	X
Intervention adherence		X	X	X	X		
Blood sampling	X		X				
Adverse-event monitoring	X	X	X	X	X	X	X

3.5 Biospecimen Management

3.5.1 Blood Samples

Fasting venous blood will be collected at baseline and Week 24 by qualified nursing staff at participating centers. The source protocol specifies approximately 10 mL per collection after an overnight fast, including EDTA anticoagulant tubes for plasma and a serum separator/clot-activator tube for serum. Samples will be centrifuged promptly; required clinical biochemical tests will be performed locally, and remaining aliquots will be transported under controlled low-temperature conditions to the Peking University Third Hospital biobank.

Samples will be labeled with unique barcodes and linked only to coded study identifiers. The code key will be maintained separately by authorized personnel. Samples and information will be tested and processed domestically and will be used only for prespecified study analyses. The protocol states that retained biospecimens will be destroyed according to applicable procedures after the defined retention period.

3.6 Study Outcomes

3.6.1 Primary Outcome

Change in global cognitive function measured by the Montreal Cognitive Assessment (MoCA) total score. The principal intervention comparison is based on longitudinal change from baseline, with the Week 24 assessment representing the end of the intensive intervention period.

3.6.2 Secondary and Process Outcomes

Domain	Outcome / Method
Physical function	Dominant-hand grip strength; Short Physical Performance Battery (SPPB); blood pressure monitoring as specified in

	the protocol.
Depressive symptoms	Hamilton Depression Rating Scale (HAMD) total score.
Insomnia	Insomnia Severity Index (ISI) total score.
Anxiety	Hamilton Anxiety Rating Scale (HAMA) total score.
Behavior/process	Daily exercise-snack adherence rate and intervention acceptability questionnaire score; app/WeChat records.
Metabolic biomarkers	Fasting total cholesterol, triglycerides, LDL-C, HDL-C, and fasting plasma glucose.
Neurotrophic/inflammatory biomarkers	Serum BDNF and IL-6 using validated commercial ELISA methods.
Safety	Incidence and severity of adverse events (AEs) and serious adverse events (SAEs), including falls, musculoskeletal injury, cardiovascular symptoms, hypoglycemia, dizziness/fatigue, and sleep disturbance.

3.7 Sample Size

The planned sample size is 240 participants, with 120 participants assigned to each group. The study protocol uses this total enrollment target for the multicenter trial. Sample-size assumptions and calculations should be interpreted exactly as documented in the approved source protocol and statistical analysis plan.

4. Data Management

4.1 Data Entry

Study data will be recorded using standardized case report forms and/or the designated electronic system. Data entry and verification procedures will be standardized across centers, with double-entry or independent verification for key variables as specified in the protocol.

4.2 Data Verification and Quality Control

Data completeness, logical consistency, range checks, source-data consistency, and protocol deviations will be reviewed. Queries will be resolved before database lock. Staff will receive standardized training in assessment and data-recording procedures.

4.3 Data Security and Confidentiality

Paper records will be stored in secure locations with controlled access. Electronic data will use coded study identifiers, role-based access, password protection, and regular backup. Direct identifiers will be stored separately from analytic datasets.

5. Statistical Analysis

5.1 General Principles

The primary analysis will follow the intention-to-treat principle. Statistical tests will generally be two-sided, and effect estimates will be reported with appropriate confidence intervals. Baseline characteristics will be summarized by treatment group using methods appropriate to variable type.

5.2 Data Preprocessing

The protocol specifies use of the interquartile-range method to identify potential outliers, standardized processing of relevant variables where appropriate, and database verification before analysis.

5.3 Outcome Analysis

Longitudinal continuous outcomes, including MoCA, will be analyzed using repeated-measures approaches and/or linear mixed-effects models, incorporating treatment group, time, and the group-by-time interaction, with appropriate adjustment for baseline covariates and multicenter structure. Generalized linear models or generalized linear mixed models will be used for non-normally distributed or categorical outcomes as appropriate.

5.4 Missing Data

Multiple imputation will be used for missing data when appropriate. Sensitivity analyses will assess robustness under alternative assumptions, including analyses of complete cases and approaches addressing departures from missing-at-random assumptions.

5.5 Prespecified Subgroup Analyses

Subgroup	Definition / Approach
Baseline cognitive severity	Protocol-defined MoCA categories; interaction between intervention group and baseline MoCA subgroup.
Intervention adherence	High adherence: average completion rate >80%; low adherence: ≤80%; used to explore dose-response patterns.
Baseline physical activity	Low versus moderate/high activity according to the protocol-defined physical activity assessment.
Age	51–60, 61–70, and 71–80 years; intervention-by-age-group interaction.

5.6 Statistical Software

Data management and analysis will use EpiData 3.1, SPSS 26.0 and/or R 4.2.0. Relevant R packages specified in the protocol include dplyr, tidyr, tableone, lme4/nlme, glmmTMB, coxme, mice, lmerTest, and ggplot2. GraphPad Prism 9 may be used for publication-quality figures.

6. Safety Evaluation

6.1 Main Risks

Potential exercise-related adverse events include muscle strain, joint pain, falls, and very rare cardiovascular events such as acute myocardial infarction, malignant arrhythmia, or sudden cardiac death. Information-security risks include unauthorized disclosure of personal health information.

6.2 Risk Management

Participants will undergo pre-exercise safety screening and receive exercise-safety education. Exercise movements are designed to minimize fall risk and allow progressive adaptation. Clinical trial insurance will be purchased as specified in the protocol. Regular follow-up will actively inquire about adverse events.

6.3 Adverse Event Reporting

All adverse events will be documented, assessed, managed, and followed. The protocol requires serious adverse events to be reported promptly, including notification within 24 hours and subsequent written reporting according to applicable ethics and institutional requirements.

7. Protection of Research Participants

The study may not begin before the protocol and informed consent materials have been reviewed and approved by the Peking University Biomedical Ethics Committee. Protocol amendments will be implemented only after required review and approval, except where immediate changes are necessary to eliminate an apparent hazard to participants, in which case the change will be implemented and reported promptly.

Before enrollment, investigators will provide written and verbal explanations of the study background, purpose, procedures, potential benefits, risks, compensation, injury-related arrangements, and the right to withdraw. Written informed consent will be obtained from each participant or legally authorized representative as applicable.

7.1 Withdrawal / Discontinuation Criteria

- Poor adherence that meets the protocol-defined discontinuation threshold.
- Termination of the study by the ethics committee.
- Participant request to withdraw or inability to complete required assessments.
- Major protocol violation.
- An injury during the intervention that materially affects the participant’s ability to be physically active.
- A serious adverse event for which continued participation is judged by the investigator to pose substantial risk.

7.2 Participant Compensation

The protocol provides compensation for costs associated with participation, including meals during on-site visits and transportation reimbursement according to the approved study standard. Compensation for completed visits is not contingent on completion of the entire study.

8. Study Management

8.1 Protocol Amendments

Any protocol modification will be submitted to the Peking University Biomedical Ethics Committee and implemented only after approval, unless immediate implementation is required to protect participants from an apparent hazard.

8.2 Quality Management

The principal investigator will designate monitors to conduct periodic oversight. Study sites will maintain accurate source records and documentation of protocol implementation and amendments. Investigators and assessors will receive standardized training, and consistency of inclusion/exclusion criteria and outcome assessment will be emphasized across centers.

8.3 Early Termination

- Identification of a serious safety problem.

- Major flaws in the protocol or severe implementation deviations that prevent valid evaluation of the intervention.
- Termination requested by the applicant/sponsor or required by an administrative or regulatory authority.

9. Study Timeline

Phase	Time	Main Activities
Preparation	Weeks 0–12	Recruitment and screening; informed consent; baseline demographic, cognitive, physical, psychological and biospecimen assessments; randomization.
Intensive intervention	Approximately Weeks 13–24	Intervention training and implementation; weekly adherence support; interim safety/adherence assessments.
Post-intervention follow-up	Weeks 25–96	Follow-up cognitive, physical, psychological and behavioral assessments at protocol-specified time points; long-term endpoint at Week 96.
Data analysis / dissemination	Protocol-defined project period	Database cleaning and lock; primary and secondary analyses; sensitivity/subgroup analyses; preparation of scientific manuscripts and final report.

10. Collaborating Institutions

- Lead institution: Peking University School of Public Health – overall study design, data coordination, statistical support, and app-related technical support.
- Peking University Third Hospital, Department of Neurology – participant recruitment/assessment and study collaboration; biobank functions as specified in the protocol.
- Peking University Sixth Hospital, Department of Neurology – participant recruitment and neuropsychological assessment support.
- The First Affiliated Hospital of Zhengzhou University, Department of Neurology – participant recruitment and assessment.
- The First Hospital of Jilin University, Department of Neurology – participant recruitment and assessment.
- Department/Unit of Physical Education and Health at Peking University – exercise-snacking program design and safety guidance.

11. Publication of Study Results

Study results are expected to be disseminated through peer-reviewed scientific publications. Personally identifiable participant information will not be disclosed in publications or presentations.

12. Study Budget

Budget Item	Basis	Estimated Amount (CNY)
Outcome-assessment personnel at study centers	4 centers × 2 visits × 1 assessor; CNY 200/person-visit	1,600
Blood collection consumables	240 participants × 2 blood collections; CNY 3.4/person-visit	1,632
Nursing personnel for blood collection	4 centers × 2 visits × 1 nurse; CNY 200/person-visit	1,600
Participant transportation / breakfast support	Protocol-defined participant compensation	14,400
Clinical trial insurance	240 participants × CNY 60/person	14,400
Cold-chain biospecimen transport	Zhengzhou and Jilin centers; 4 shipments × CNY 500	2,000
Fasting lipids and glucose	240 participants × 2 assessments; protocol unit cost	7,200
IL-6 assay	Subset of 48 participants × 2 assessments; ELISA	1,500
BDNF assay	Subset of 48 participants × 2 assessments; ELISA	3,000
Total	Self-funded study	37,732

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