Trial Protocol*

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Note: the research protocol was approved by the IRB at the Oregon Research Institute, dated 9/12/2024

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*This study protocol has been developed and presented by the authors to provide readers with additional information about the trial reported in their article. The material was not copyedited.

Supplement 1: Trial Protocol

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Trial Protocol Synopsis

Protocol title	Cognitively enhanced tai ji quan training to improve global cognitive function and lower dual-task costs during walking in older adults with mild cognitive impairment: A randomized clinical trial
Principal investigator	Fuzhong Li, Ph.D. Oregon Research Institute 3800 Sports Way Springfield, OR 97477 E-mail: fuzhongl@ori.org
Study design	The design is a prospective, assessor-blinded, 3-arm parallel group, randomized clinical trial with a 1:1:1 allocation ratio
Study duration	5 years
Conditions or focus of study	Mild cognitive impairment
Primary aim	To determine whether a cognitively enhanced tai ji quan training intervention, in comparison to a standard tai ji quan intervention and an exercise stretching control, is more effective, at 24 weeks, in improving global cognitive function and dual-task walking performance among community-dwelling older adults with mild cognitive impairment (MCI).
Secondary aim	To determine whether the effect resulting from the acute intervention phase can be sustained 24 weeks after training stopped.
Setting	Community residential homes across the United States
Population and eligibility criteria	Population: community-dwelling older adults with MCI. *Inclusion criteria*: (a) being 65 years or older; (b) having a reported memory decline (by the participant and/or an informant); (c) having a diagnosis of MCI by a global score of ≤0.5 on the Clinical Dementia Rating (range: 0-3); (d) showing no diagnosis of dementia or significant cognitive impairment, as indicated by a score of ≥24 on the Mini Mental State Evaluation (MMSE, range: 0-30) *Exclusion criteria*: (a) having no medical clearance from a healthcare provider; (b) having participated in structured (class-based, instructor-led) rigorous activities or muscle-strengthening activities (>2 times a week for >15 minutes per session) in the past 3 months; (c) showing clinically significant depression (>4 on the Geriatric Depression Scale; range: 0-15); (d) having any physical condition that would preclude participation in moderate-intensity exercise; and (e) being unwilling to commit to the duration of the intervention or accept group assignment.
Intervention	*Cognitively enhanced tai ji quan*: A tai ji quan intervention with explicitly integrated cognitive training exercises, conducted twice weekly, for 60 minutes per session for a total of 24 weeks. Tai ji quan training exercises include repeated practice of (a) symmetrical postural forms/movements synchronized with breathing, (b) controlled displacement (weight-shifting) of the body's center of mass over the base of support, (c) dynamic eye-hand movements during whole-body motion, (d) multidirectional (anterior-posterior and medial-lateral) stepping, and (e) rotational ankle sway and self-induced reactive postural recovery actions. These dynamic exercises are superimposed, concomitantly, with a mix of interactive, cognitively stimulating, dual-task practices that challenge attention control, working memory, verbalization, response inhibition, processing speed, dual tasking, task

	switching/prioritization, and spatial orientation and postural awareness. *Standard tai ji quan*: A conventional tai ji quan intervention, conducted twice weekly, for 60 minutes per session for a total of 24 weeks. Training exercises include practice of tai ji quan forms with synchronized breathing, supplemented by a set of mini-therapeutic exercises. Specifically, the training involves repeated practice of (a) symmetrical, coordinated, trunk-driven tai ji quan form movements, (b) controlled displacement (weight-shifting) of the body's center of mass over varying sizes of the base of support, (c) dynamic eye-hand movements during whole-body motion, and (d) multidirectional (anterior-posterior and medial-lateral) stepping. As a balance-based training program, movement practices emphasize a dynamic interplay of stabilizing and self-induced destabilizing postural actions and balance exercises that target mobility, stability limits, and sensory integration. *Stretching exercise*: A stretching exercise intervention, conducted twice weekly, for 60 minutes per session for a total of 24 weeks. Exercises consist of breathing, stretching, and relaxation. The core exercises encompass a variety of light and static stretches for joints and muscles, performed in a seated or standing position, that involve the upper body (arms, neck, upper back, shoulder, back, and chest), lower extremities (quadriceps, hamstrings/calfs, and hips), and gentle and slow trunk rotations. Also included are intermittent light walking, deep abdominal breathing exercises that emphasize inhaling and exhaling to maximum capacity, and progressive relaxation of major muscle groups.
Duration of intervention	The intervention lasts 24 weeks
Primary efficacy endpoints	The trial has the following two a priori specified co-primary endpoints at 24 weeks post-randomization: 1. change in the Montreal Cognitive Function measure (MoCA; score range: 0 to 30) 2. change in dual-task cost (difference in walking speed [seconds] between performance conducted under single-task and dual-task conditions)
Secondary outcomes	The trial has the following secondary outcomes at 24 weeks post-randomization: 1. change in CDR Sum of Boxes scores (score range: 0 to 18) 2. change in Trail Making Test B (seconds) 3. change in Category Fluency for Animals (number of animal names recalled) 4. change in Forward Digit Span (score range: 1 to 16) 5. change in Backward Digit Span (score range: 1 to 16) 6. change in Timed Up&Go test (seconds) 7. change in 30-second chair stand test (number of times) 8. change in 4-stage balance test (score range: 0 to 4)
Tertiary outcomes	The trial has the following tertiary outcomes at 24 weeks post-randomization

	1. change in Everyday Cognition (score range: 1 to 4) 2. change in Geriatric Depression Scale score (score range: 0 to 15) 3. change in Pittsburgh Sleep Quality Index global score (score range: 0 to 21) 4. change in EuroQol EQ-D5 utility score (score range: -1 to 1)
Covariates	There are no pre-specified covariates for the primary and secondary endpoints.
Follow-up schedule	16 weeks (mid point), 24 weeks (intervention termination), 48 weeks (post-intervention follow-up)
Masking	Outcome assessors, data analysts
Number of subjects	The target sample size is 315 participants to provide 80% power to detect a medium-size difference in mean MoCA change of 1.5 points between the cognitively enhanced tai ji quan and the standard tai ji quan groups and a large-size difference of 3 points between the cognitively enhanced tai ji quan and the stretching control groups at 24 weeks.
Statistical analysis	The effect of the intervention on the primary endpoints will be evaluated using the intention-to-treat approach, in which participants are grouped according to randomization assignment. To compare change in outcome measures among the three intervention groups at 6 months, we will analyze a 3 (Group) by 3 (Time) mixed-effects model with repeated measures on the second factor (i.e., outcome measures assessed at baseline, 4 months, and 6 months). In the presence of a Group by Time interaction effect, pre-specified follow-up pair-wise comparisons will be performed to determine between-group differences (indicated below). Secondary outcomes will be similarly analyzed. Results from primary analyses will be presented as the difference in mean MoCA and dual-task performance between the cognitively enhanced tai ji quan and standard tai ji quan groups and between the cognitively enhanced tai ji quan and the stretching exercise control, with a Bonferroni-adjusted 2-tailed significance level of .0125 for each of the two primary outcomes and a 98.75% confidence interval.
Interim analysis	No interim analyses for efficacy or futility. However, interim monitoring is performed with a focus on subject accrual, intervention fidelity, protocol adherence, data completeness and quality, and intervention safety and analysis.

Study Background and Rationale

Mild cognitive impairment (MCI) is an intermediate stage between the common phenomenon of cognitive decline with aging and the more pronounced decline of dementia due to Alzheimer's disease (AD).[1,2] Approximately 16%-20% of adults over age 65 have MCI,[3] exposing these individuals to a higher risk of developing AD. Estimates show that more than 30% of individuals with MCI progress to developing dementia related to AD within 5 years.[4,5] These data call for an increased effort and demand to develop and test effective cognitive health care strategies that can prevent cognitive decline and slow the progression of MCI to AD.

Exercise plays an important protective role in preserving cognitive function or mitigating the progression of cognitive impairment for older adults with MCI.[6-8] Among various exercise modalities, tai ji quan represents one of the promising mind-body integrative therapeutics for promoting brain health.[9] However, studies examining the clinical impact of tai ji quan on influencing MCI remain insufficient to inform evidence-based recommendations due to (a) the limited number of rigorously designed studies and (b) the lack of explicit integration of a cognitive training component that could further boost its cognitive benefit. As a result, it is difficult to synthesize research findings and confirm the clinical merit or public health impact of tai ji quan in promoting and preserving cognitive function in people with cognitive impairment, including MCI.

Study Aims

Primary Aim. The primary aim of this study is to determine the effectiveness of a cognitively enhanced tai ji quan exercise intervention, compared to a standard tai ji quan intervention and an exercise stretching control, in improving cognitive function and dual-task walking ability among community-dwelling older adults with MCI. On the basis of preliminary results,[10-12] the primary hypothesis is that during a 6-month intervention, participants receiving enhanced tai ji quan training, compared to participants receiving either a standard tai ji quan intervention or stretching exercise control, will show greater improvement in the primary outcome measures of global cognitive function and dual-task walking ability. Secondary outcomes include cognitive impairment and domain-specific cognitive function and physical performance measures.

Secondary Aim. The secondary aim of this study is to evaluate how well the intervention effects in the cognitively enhanced tai ji quan intervention group will persist long-term. Specifically, we will examine whether group differences in primary and secondary outcomes will remain for 6 months after the end of the supervised interventions.

Study Design and Methodologies
***Original In-Person Intervention Protocol* (dated August 1, 2019)**

Study design and setting

We plan to conduct a prospective, assessor-blinded, 3-arm randomized parallel trial (with a 1:1:1 allocation ratio), in which the cognitively enhanced tai ji quan intervention will be evaluated against a standard tai ji quan intervention and a stretching exercise control. Enrolled participants will participate in a 60-minute exercise session, twice weekly for 24 weeks.

The trial will be conducted in local community settings, including senior centers, community centers, churches, outpatient medical clinics, or non-profit organizations.

The trial reporting will follow the general guidelines described in the Consolidated Standards of Reporting Trials (CONSORT).

Trial registration

ClinicalTrials.gov number: NCT04070703: Released August 28, 2019

Trial protocol approval

The in-person trial protocol was fully reviewed and approved by the Institute Review Board (IRB) of Oregon Research Institute. The protocol also will receive an annual IRB review during each year of the project. A Safety Officer, approved by the National Institute on Aging (NIA), will review and approve the study protocol, oversee the safety and scientific integrity of the study, and receive annual updates on the progress made on the various aspects of the project activity. Informed consent will be obtained from all participants.

Study population

The study targets older adults (age 65 and older) with clinically diagnosed MCI per Petersen criteria and criteria established by the National Institute on Aging—Alzheimer Association workgroup.[13,14] Potential eligible participants will be drawn from community-living older adult residents living in the state of Oregon who meet the following eligibility inclusion and exclusion criteria:

Inclusion:

- having complaint about memory loss, reported by the participant and corroborated by an informant (spouse, partner, or caregiver)
- having no or questionable dementia, i.e., scoring ≤0.5 on the Clinical Dementia Rating (CDR)[15] (confirmed via participant and informant interviews)
- showing no major cognitive impairment, i.e., scoring ≥24 on Mini-Mental State Examination (MMSE)[16]
- showing no major difficulties in performing activities of daily living

Exclusion:

- having medical conditions likely to compromise survival, such as metastatic cancer, or render the participant unable to engage in physical activity, such as severe cardiac failure
- showing significant depression symptoms (scoring <4 on the Geriatric Depression Scale [GDS])[17]
- participating in structured rigorous activities or muscle-strengthening activities (>2 times a week for >15 minutes per session) in the past 3 months
- incapable of exercising safely, as determined by a healthcare provider
- unwilling to be randomly assigned to an intervention condition and complete the 24-week intervention and 6-month follow-up
- having no medical clearance to participate

Criteria for premature withdrawal

Enrolled participants will be informed in the study consent form that they are free to withdraw their participation from the study at any time without any consequences. Although all three exercise interventions involve minimal risk (per the federal regulations at §46.102(j))[18] for injury or musculoskeletal pain or discomfort, we do not anticipate that there will be any requirement for a premature withdrawal. Our trial primary analysis will be intention-to-treat with all randomized participants who give full consent to the study.

Recruitment sources and procedures

Recruitment strategies to identify potential study participants include promotions at local senior/community centers, meal sites, offices of healthcare professionals and medical clinics, targeted mass mailings, organizational websites, and local newspaper advertisements. To reduce potential expectation bias, participants will be informed that the study compares three different exercises and that they will be assigned to one of these exercise groups at random.

To ascertain eligibility, a research assistant will make an initial telephone contact with those who respond to the study promotion. This initial prescreen telephone contact will determine basic eligibility set forth under the recruitment inclusion and exclusion criteria. Potentially, individuals who meet initial inclusion criteria will be scheduled for a 2-hour in-office visit at our research office, where the remainder

of the screening work (i.e., CDR, MMSE) will be completed, along with baseline assessment if the participant is qualified.

Randomization, allocation, concealment, and blinding

Eligible participants will be randomized to 1 of the 3 intervention groups with an allocation of 1:1:1 through a permuted block randomization with a block size of 3 or 6 to prevent anticipation of assignment to the study condition. Concealment of allocation will be implemented. The project data analyst will use computer software (nQuery) to generate a randomization schedule, which will be kept in a sealed envelope. On the day of the assignment, a research assistant will assign qualified individuals to intervention groups. The allocation sequence assigns individuals in the order that they were scheduled for baseline assessment. Randomization will occur after informed consent is obtained and baseline assessments have been completed.

Project data analysts will be blinded to group allocation. All study assessors who collect study outcome measures will also be blinded to the main study design and group allocation. Blinding will be strictly maintained by emphasizing to assessors the importance of minimizing assessment bias and regular checking of the blinding status. Efforts will be also made to maintain separation between the study assessors and research assistants who deal with administrative activities and class safety monitoring, and between study assessors and class instructors who deliver the intervention classes. Because of the nature of the interventions, study participants and interventionists will not be masked to group allocation. Participants will be instructed not to reveal their group status to the assessment staff at any time during follow-up.

Intervention

The intervention for the trial consists of three exercise modalities: (a) cognitively enhanced tai ji quan, (b) standard tai ji quan, and (c) stretching exercise. Each is described below. The protocol, which is specified in detail via a teaching manual, requires that each intervention be implemented, by a qualified interventionist, twice weekly, for 60 minutes per session for a total of 24 weeks (6 months).

Cognitively enhanced tai ji quan

The basic exercise routine entailed in this intervention consists primarily of an 8-form tai chi quan routine, derived from the well-established Tai Ji Quan: Moving for Better Balance (TJQMBB) protocol.[10,19] The training protocol includes preparatory (warm-up) exercises; an average of 50 minutes of core exercise that involves learning, practicing, and repeating the 8 forms (in the order listed below); and a brief cool down exercise that involves walking-the-forms and light breathing.

- (1) "*Move a Ball*," (2) "*Part Wild Horse's Mane*," (3) "*Repulse Monkey*," (4) "*Brush Knees*," (5) "*Fair Lady Works the Shuttles*," (6) "*Grasp Peacock's Tail*," (7) "*Single Whip*," and (8) "*Waving Hands like Clouds*."

The protocol involves two phases: (a) learning and practicing tai ji quan forms (weeks 1 through 15) and (b) exercising tai ji quan form movements concomitantly with integration of cognitively enhancing and stimulating tasks (weeks 16 through 24). During the learning phase, exercise focuses on practicing (a) symmetrical and coordinated postural movements synchronized with breathing, (b) controlled displacement (weight-shifting) of the body's center of mass over the base of support, (c) dynamic eye-head movements during motion, (d) multidirectional (anterior-posterior and medial-lateral) stepping, and (e) rotational ankle sway and self-induced reactive postural recovery actions. During the integrated exercise period, practices are superimposed by a set of interactive, cognitively stimulating, dual-task activities that exercise attention control, working memory, verbalization, response inhibition, processing speed, dual tasking, task switching/prioritization, and spatial orientation and postural awareness.

The key principles of integration of tai ji quan and cognitive exercises in this intervention are summarized in the box shown below.

Targeted cognitive domains	Concurrent tai ji quan and superimposed cognitive tasks	Practice examples
Attention control (selective attention, rapid attention switching, divided attention)	Forms practiced with varied or differential instructional cueing or with a posturally-challenging stance	Practicing forms with visual cueing only or with verbal cueing only; practicing forms in a narrow stance (e.g., a semi-tandem stance); practicing in response to correct form instructions while ignoring incorrect (interfering) instructions or practicing rapid attention-switching between two out-of-sequence forms
Working memory	Forms practiced with recall or retrieval of forms from either a sequenced or out-of-sequence order	Recalling and performing a set of tai ji quan forms from the sequenced order (e.g., performing 2 or 3 forms BEFORE or AFTER *Fair Lady Works the Shuttle*) or out of sequence (e.g., Performing *Brush Knee* followed quickly by *Single Whip* and/or *Part Wild Horse's Mane*)
Verbalization	Saying the form names and associated movement steps involved out loud	Following the instructor, reciting step-by-step movement instructions for a form or saying the name of each form being practiced
Response inhibition	Responding only to correct instructional cueing while ignoring other non-relevant verbal or visual instructional cueing	Practicing "Simon Says" game by responding to correct form instructions for exercises (e.g., "Simon Says *Brush Knees*") while suppressing interfering (non-Simon Says) instructional form (i.e., *Brush Knees*).
Processing speed	Responding to randomly called-out forms	Performing tai ji quan forms called out randomly, by the instructor, from the 8-form routine during walking/stepping
Task switching	Practicing deviations from pre-specified sequence order or format	Forms practiced with (a) side-switching (i.e., alternating between lateral and bilateral sides), (b) switching between odd and even orders in the forms sequence (i.e., practicing forms 1, 3, 5, and 7 followed by forms 2, 4, 6, and 8), or (c) sequence direction switch (i.e., practicing the sequence forward as ordered and backward (in reverse order))
Dual tasking	Practicing a form concurrently with a cognitive (verbal) task without task prioritization	Practicing a form in synchronization with a word-spelling or number-counting task
Task prioritization	Practicing a form concurrently with a cognitive task, with an emphasis on the performance of the form	Practicing a form (primary task) while reciting numbers or phrases backward continuously (secondary task)
Spatial orientation and postural awareness	Practicing forms with change in direction and size of base of support	Practicing a set of forms with (a) steps taken in multiple directions or (b) a narrow stance (e.g., feet close together) or semi-tandem stance

A sample session (Week 15) of this training protocol is shown at the end of this Intervention section.

Exercise intensity. Exercise intensity will be closely monitored throughout the intervention period. Specifically, during the 1st month, participants will be instructed to exercise physically at a level

characterized as being "Light" (equivalent to 2-3 on the Borg CR10® 1-10 scale [1 being "Very Light Activity" and 10 being "Maximum Effort Activity"]). In the 2nd month, participants will then proceed to a "Light to Moderate" level (equivalent to 3-4 on the scale). In the 4th-6th months, practice will be maintained at a "Moderate" level (equivalent to 4-6 on the scale). Exercise intensity will be evaluated on a weekly basis by the class instructor.

Standard tai ji quan

The standard tai ji quan intervention serves as an active concurrent neuromuscular control in this study. As in the cognitively enhanced tai ji quan group, participants in this group will receive an adapted version of Tai Ji Quan: Moving for Better Balance (known as TJQMBB),[10,19] which includes the identical 8 forms of training. The training protocol requires that each session begin with a set of preparatory exercises, followed by approximately 50 minutes of core training involving learning and practicing, with repetition, single forms, or a series of pre-ordered forms. Each session ends with a simple set of walking-the-forms and breathing exercises.

The intervention follows a traditional tai ji quan training approach, where the instructor plays a dominant and leading role in teaching (with clear verbal and visual instructions) and practicing, without instructor-participant interaction during exercise. Accordingly, the training involves primarily teaching participants, via both verbal and visual cues, tai ji quan forms and movements through repeated practice. Specific tai ji quan training activities include controlled, self-initiated tai ji quan–based postural movements with synchronized breathing, including center-of-gravity displacement using a dynamic interplay of stabilizing and self-induced destabilizing postural actions involving unilateral weight-bearing and weight-shifting movements, trunk and pelvic rotation, ankle sway, multidirectional stepping, and coordinated eye-head-hand movements. The training is progressive, with learning and practicing taking place during the first 15 weeks and repeated practice with variations thereafter. The exercise is accompanied by sets of therapeutic and functional tai ji quan–based exercises involving ankle sway, sit-to-stand, sensory compensation, turning, and stepping exercises that target mobility, stability limits, and sensory integration.

A sample session (Week 15) of this training protocol is shown at the end of this Intervention section.

Exercise intensity. Exercise intensity will be identical to that in the cognitively enhanced intervention and will be closely controlled and monitored throughout the intervention period by the class instructors.

Stretching exercise

The rationale for using stretching exercise is to provide participants with a low-intensity exercise program that contains identical social interaction, enjoyment, and physical activity (i.e., by traveling to and from the intervention locations), as well as changes in lifestyle secondary to study participation, that are inherent components in the other two tai ji quan-based exercise interventions, without providing comparable cognitive-physical exercise training benefits.

The program consists of breathing, stretching, and relaxation, with the majority of activities performed in a seated position.[10,20] Each session begins with a set of warm-up exercises (10 minutes) such as stretching the arms, neck, shoulder and back, hips, thighs, and legs; ankle and trunk rotation; and light walking. The core part of the training session consists of exercises that encompass a variety of combined stretches (seated and standing) involving the upper body (arms, neck, upper back, shoulder, back, and chest), lower extremities (quadriceps, hamstrings/calves, and hips), and gentle and slow trunk rotations. Also included are abdominal breathing exercises that emphasize inhaling and exhaling to maximum capacity, as well as progressive relaxation of major muscle groups.

A sample session (Week 15) of this training protocol is shown at the end of this Intervention section.

Exercise intensity. Exercise intensity in this group will be kept at a "Light" level (2-3 on the Borg CR10® scale) throughout the 24-week intervention period.

Week 15: Sessions 29 and 30 (Cognitively Enhanced Tai Ji Quan)

Preparatory exercises (≈ 10 min)

- in a hip-width stance, moving the trunk, with a ball motion, in a figure 8 pattern: ≈ **2 min**
- in a hip-width stance, waving hands (in the form of *Waving Hands like Clouds*) side to side: ≈ **2 min**
- in a bow stance, weight shifting with *Part Wild Horse's Mane*, *Brush Knees,* and *Fair Lady Works the Shuttle*: ≈ **2 min** (both sides)
- walking with *Waving Hands like Clouds*, *Part Wild Horse's Mane* or *Brush Knees*, and *Repulse Monkey*: ≈ **2 min**

Core practice (≈ 50 min)

- practicing Forms 2 through 7: **1 set**
- practicing Forms 2 through 7 without verbal instructions: **1 set**
- practicing Forms 7 through 2 (reverse): **1 set**
- **learning and practicing Form 8:** *Single Whip* (Note: start this practice with a demo of the Form)
  - standing: **5 sets**
  - in a bow stance: **5 sets**
  - moving: **5 sets**
- practicing Forms 2 through 8 (including *Single Whip*): **3 sets**
- **Integrative exercise: double- or single-sided forms switching**
  - in a forward sequence (i.e., Forms 2 through 8): **2 reps**
  - in a reverse sequence (i.e., Forms 8 through 2): **2 reps**
- **Integrative exercise: finger-tapping and word-spelling with *Single Whip* (b): 3 sets each**
  - *Single Whip* with the dominant hand whipping while finger-tapping and spelling the word "exercising" both forward and backward
  - *Single Whip* with the dominant hand whipping while finger-tapping and spelling the word "practicing" both forward and backward
- **Integrative exercise: stepping and balancing with *Grasp Peacock's Tail*: 3 sets**
  - practice in the order of: (1) *Grasp Peacock's Tail* in a bow stance (left and right), (2) *Grasp Peacock's Tail* with the front foot stepping forward (left and right), and (3) *Grasp Peacock's Tail* with the rear foot stepping forward.
    Note: calling out each move of *Grasp Peacock's Tail* (i.e., Ward-off, Pull, Press, Push) and ending the 2nd and 3rd practices with a single leg kick while saying slowly "***hold up***" "***hold tight***" and "***hold steady***"
- **Integrative exercise: single-leg standing and word-spelling with *Brush Knees***
  - in a bow stance, *Brush Knees* and single leg kick while naming 3 states in the US
  - in a bow stance, *Brush Knees* and single leg kick while naming 3 states starting with the letter M
  - in a bow stance, *Brush Knees* and single leg kick with the spelling of the word "*practice*" backward
- walking exercise with "Simon Says" forms in **Step 3**: ≈ **5 min**

Winding-down

- walking forward with a mix of *Part Wild Horse's Mane*, *Brush Knees*, and *Fair Lady Works the Shuttle*, sideways with *Waving Hands like Clouds*, and backward with *Repulse Monkey*, ending with breathing exercise in standing position

Week 15: Sessions 29 and 30 (Standard Tai Ji Quan)

Preparatory exercises (≈ 10 min)

- in a hip-width stance, moving the trunk, with a ball motion, in a figure 8 pattern: ≈ **2 min**
- in a hip-width stance, waving hands (in the form of *Waving Hands like Clouds*) side to side: ≈ **2 min**
- in a bow stance, weight shifting with *Part Wild Horse's Mane*, *Brush Knees,* and *Fair Lady Works the Shuttle*: ≈ **2 min** (both sides)
- walking with *Waving Hands like Clouds*, *Part Wild Horse's Mane* or *Brush Knees*, and *Repulse Monkey*: ≈ **2 min**

Core practice (≈ 50 min)

- **Mini exercise: sit to stand with *Part Wild Horse's Mane* and stand to sit with *Repulse Monkey***
  - practicing momentum-based sit-to-stand with *Part Wild Horse's Mane* and controlled stand-to-sit with *Repulse Monkey*: **3 sets**
- Forms practice
  - seated: practicing forward forms of *Part Wild Horse's Mane*, *Brush Knees*, *Fair Lady Works the Shuttle*, *Grasp Peacock's Tail*, *Waving Hands like Clouds*: **2 reps** on each side
  - seated: *Grasp Peacock's Tail with buttocks off chair on each move*: **3 reps** on each side
  - moving Forms 2 through 7: **2 sets**
- **learning and practicing Form 8:** *Single Whip* (Note: start this practice with a demo of the Form)
  - standing: **5 sets**
  - in a bow stance: **5 sets**
  - moving: **5 sets**
- moving Forms 2 through 8 (including *Single Whip*): **2 sets**
- **Mini exercise: weight shifting, stepping, and balancing with *Grasp Peacock's Tail*: 3 sets**
  - practicing this exercise in the order of: (1) *Grasp Peacock's Tail* in a bow stance (left and right), (2) *Grasp Peacock's Tail* with the front foot stepping forward (left and right), and (3) *Grasp Peacock's Tail* with the rear foot stepping forward and, after the last Push, add striking ears with fists followed by a gentle single leg kick (left and right)
- **Mini exercise: forms up and around a chair**
  - *Part Horse's Mane* to get up, *Waving Hands* to get to the side (away from the chair), *Repulse Monkey* to get to the back of the chair, *Waving Hands* to get across the chair (to the other side of the chair), *Brush Knees* forward toward the front of the chair, *Waving Hands* to align with the chair (in front), and *Repulse Monkey* to sit down: **3 sets**
- moving Forms 2 through 8 (including *Single Whip*): **2 sets**

Winding-down

- walking forward with a mix of *Part Wild Horse's Mane*, *Brush Knees*, and *Fair Lady Works the Shuttle*, sideways with *Waving Hands like Clouds*, and backward with *Repulse Monkey*, ending with breathing exercise in standing position

Week 15: Sessions 29 and 30 (Stretching Exercise)

Preparatory exercises (≈ 10 min)

Seated:

- breathing: encourage gentle, slow, and deep diaphragmatic breathing to allow for deeper, fuller breaths
- lightly marching in place with breathing and relaxed joints and muscles
- light stretching involving arms and neck, shoulder and back, and thighs and legs, ankle and trunk rotation
- light walking around chair or in a circle

Core exercise (≈ 48 min)

Stretches in chair (≈ 15 min)

- a variety of muscle stretching and flexibility exercises including, but not limited to:
  - neck stretch (including neck retraction, head drop, side bend, rotation, flexion, shoulder blade pull), chest stretch, chest and arm stretch, shoulder stretch, upper and lower back stretch, back and buttock stretch, seated groin stretch
  - seated marches with a focus on stabilizing the core and varying range of motion and pace in stepping and/or lifting
- light walking around chair or in a circle: **3 circles**

Stretches in standing position (with or without a chair) (≈ 15 min)

- a variety of lower-extremity muscle stretching and flexibility exercises that include:
  - quadriceps (thigh) stretch, hamstring stretch, calf stretch, ankle pivoting, circling, and stretch
- light walking around chair or in a circle: **3 circles**

Stretches in chair (≈ 10 min)

- a variety of lower-extremity muscle stretching and flexibility exercises that include:
  - quadriceps (thigh) stretch, hamstring stretch, calf stretch, ankle pivoting, circling, and stretch

Stretches while moving around (≈ 8 min)

- a variety of upper- and lower-extremity and trunk stretching exercises in standing position, which may involve slow bending (forward, sideways), reaching (arm forward or upward, or sideways), and turning (one half-circle – 180 degrees)

Instructions: pay attention to the following:

- range of motion (ROM): slow progression from 50% to 80%-90% ROM
- repetitions: 3 reps of each stretch and held to the point of mild tension for 5 seconds
- rotation: if an exercise involves a rotation, repeat 3 times on each side
- circle: if an exercise involves circling (e.g., ankle), repeat 3 times
- breathe naturally throughout the stretch

Winding-down (≈ 2 min)

- Seated or standing: light breathing and relaxing (meditative, verbal cued whole body) exercises – may repeat some of the warm-up exercises

Adverse events monitoring

Throughout the study period, both intervention- and non-intervention-related adverse events will be closely monitored and recorded by research staff and adjudicated by the Principal Investigator of the study. We will classify adverse events in three categories: Mild, Moderate, and Serious. Similarly, for all events observed or reported in this study, we will further classify them into three categories in relation to the intervention: Unrelated, Possible, or Definite. The following section describes the classification and categorization of our study adverse events. Per our IRB protocol, any serious adverse events will be reported to the IRB and the project Safety Officer within 48 hours of the reported incident.

Adverse Event and Serious Adverse Event Collection Process

The project defines Adverse Events and Serious Adverse Events as follows:

Definition of Adverse Events may include the following:

- Any musculoskeletal pain or discomfort, including lower back pain, ankle/muscle soreness or pain, or a fall without needing medical attention
- Any event that requires medical treatment but is not an immediate life-threatening condition (e.g., eye surgery or a medical procedure)

Definition of Serious Adverse Events are undesirable experiences associated with the prescribed exercise interventions in this project. Serious Adverse Events may include the following:

- Death
- Falls that result in a serious injury that requires immediate medical attention
- Prolonged hospitalization
- Important medical or life-threatening events such as a heart attack that require treatment in an emergency room
- Events that cause persistent or significant disability or incapacity

Classification of Adverse Events

This project will classify any adverse events observed during the 6-month active exercise intervention period into the following three categories:

- Mild: events that require no medical treatment or are non-life threatening
- Moderate: events that require medical treatment but are not immediate life-threatening conditions
- Serious: events that result in death or are life threatening and require medical treatment, including prolonged hospitalization or significant disability/incapacity

Relatedness

For all events observed or reported, the project will further classify them into three categories in relation to the intervention:

- Not related: an event that is reported but not directly related to participation in the intervention
- Possibly related: an event that is observed during an exercise class that is considered likely to be associated with participation
- Definitely related: an event that is observed or reported during an exercise class and is considered directly related to participation.

Adverse Events and Serious Adverse Event (SAE) Reporting Process

We will carefully monitor for unexpected adverse events, as well as the expected outcomes, that participants experience during each online exercise session and outcome assessment, whether or not the events or outcomes are directly related to the study intervention. All symptoms reported by the study participants will be tabulated in a checklist format and recorded by a designated research assistant. When an adverse event is identified, the staff member will report it directly to the Principal Investigator (PI). An Adverse Event Report Form will immediately be completed, filed, and reported to PI.

The PI will be directly responsible for monitoring and documentation of adverse events during the implementation of all prescribed exercise sessions across the three study conditions. Once the project is implemented, any activities (during a class session or during an assessment session) resulting in participant distress or discomfort, exercise-related side effects, injuries, or falls will be reported immediately to the PI, who will, upon consultation with other members of the team, take appropriate action. This will include consultation with the team's medical expert. The PI will report such incidents immediately to the IRB Chair at ORI. Summary reports of adverse events, and any subsequent IRB action taken as a result of such events, will be routinely provided to the NIA PO and the NIA-appointed Safety Officer.

For each event observed or reported, regardless of setting where the event takes place (i.e., at home or during exercise classes), a designated research assistant will contact the participant within 3 working days, via a telephone call, to ascertain detailed information related to the event. During this phone contact, information about date/time, location, nature of the event, symptoms experienced, and any measures taken for the event will be collected and documented. If necessary, the informant for the study participant will be contacted to verify the information provided by the participant. The recorded event, along with a detailed description, will be tabulated in a checklist format and entered into the project's Adverse Event Log. It will be shared immediately with the PI, who will report, within 3 working days, to the IRB, NIA-appointed Safety Officer, and Project Officer at NIA.

The following summarizes the reporting procedure to be implemented in this project:

- Expedited reporting: All SAEs (including expected and related or possibly related) observed during the active study period will be reported to local IRB and Safety Officer within 3 working days.
- Routine reporting: All events will be included in routine reports.

Fidelity of intervention delivery

A standardized intervention protocol and a process evaluation checklist, developed via prior trials,[10] will be implemented. These measures focus primarily on intervention fidelity and involve issues such as (a) interventionist qualifications and training, (b) teaching quality of the individual forms/movements or routine in each session, (c) exercise intensity and consistency in training dosage across different sites, and (d) weekly class attendance checking and monitoring. The evaluation will be conducted monthly by either an authorized research team member or an instructor, per guidelines specified in an established fidelity checklist.[10] In evaluating the item in (b), high intervention fidelity will be considered achieved if at least 95% of the mandatory components (overall completion of pre-specified activities, quality of verbal and visual instructions, emphasis of core training points, session completion time) are fully or partially delivered in each session.

Attention control across intervention groups

Participants assigned to each of the three intervention groups will receive the same amount of contact time from class interventionists and research staff. Specifically, 48 exercise sessions are planned for each exercise program in the study. Assessment time at each assessment time point will be constant (i.e., around 2.5 hours per visit). Unless there are special circumstances (e.g., participants experience an adverse event or illness), there will be no additional contact time with the project instructors or staff.

Trial interventionists

The community exercise instructors who deliver all three exercise interventions will be trained per our previously established criteria.[10] These trial interventionists will be trained by the Principal Investigator initially via an 8-hour training and orientation workshop, during which detailed instructions about the specifics of program delivery, practice safety, and teaching requirements will be provided. In-service training will be provided on a monthly basis and when needed as determined by the investigators.

These trial interventionists will also be asked to maintain the confidentiality of the study participants in their classes.

Trial outcome assessors

All research outcome assessors will complete a computer-based training course through Oregon Research Institute, an educational requirement for all researchers who conduct or support research involving human subjects. This will be completed during the project start-up period before data collection. In addition, these assessors will complete an online training on the clinical administration of cognitive-based measures (i.e., CDR, MoCA) and receive training from the Principal Investigator on established assessment procedures related to all study outcome measures including self-reports and performance-based measures.

Intervention adherence and attrition

The overall intervention adherence (i.e., exercise class attendance) rate is defined as the sum of the total number of participants attending divided by the maximum number of 48 sessions planned, multiplied by 100, during the 6 months of active intervention. For the trial, we will strive for an adherence rate of ≥75%. Accordingly, class attendance across the three study conditions will be closely monitored on a weekly basis. As an adherence procedure, participants who miss two consecutive sessions will be contacted by phone to ascertain the reason(s) for their absences and to encourage them to return.

Unavoidable drop-outs, from causes such as death, onset of severe illness, changes in health conditions, or other medical complications, are anticipated during the course of our active intervention. Based on our prior trial records,[10] we estimate a 15% intervention dropout rate for the overall study (i.e., 15% of the total enrolled participants will withdraw from or stop attending assigned exercise classes).

Study retention

Study retention is defined as participants who voluntarily provide primary outcome data regardless of intervention participation status. For the trial study, we have planned an overall study retention rate of 85%. To accomplish this goal, planned measures will be taken to ensure that as many participants as possible, including dropouts, attend each scheduled in-person assessment visit at our research facilities. Our proactive methods will include frequent telephone and e-mail contacts with subjects who miss scheduled data assessment appointments.

Study Outcome Measures and Procedures

Assessment schedule

The primary measures of global cognitive function and dual-task gait performance ability and other specified secondary and tertiary outcome measures will be assessed at baseline (before randomization), 4 months (midpoint), and 6 months (intervention termination). The repeated data collection will be performed by outcome assessors who have gone through a training process to familiarize themselves with the assessment protocol. All assessors will be blinded to group allocation.

Primary endpoints

Primary efficacy endpoints for the trial are changes in global cognitive function and cost of dual-task gait performance at 6 months from baseline.

Global cognitive function will be assessed by the Montreal Cognitive Assessment (MoCA),[21] which measures cognitive function of multiple domains (attention/concentration, executive functions, short-term memory, language, visuospatial abilities, orientation to time and place). The MoCA will be administered to the study participants by trained study assessors at baseline, 4 months, and 6 months. MoCA has a total score that ranges from 0 to 30, with higher scores representing better cognitive functioning. One point is added to the total scores for participants who received less than 12 years of education. To avoid potential practice effect associated with the repeated measures, we will use a different version at each of the three assessment time points (Note: Version 8.1 at baseline, Version 8.2 at 4 months, Version 8.3 at 6 months [Version 8.1 is repeated at 12 months]).

Dual-task cost will be assessed via an Instrumental Timed Up&Go (*i*TUG) gait performance (APDM, Inc.) in which the participant is asked to stand up from a chair, walk a 6-m walkway at normal pace (3 m toward a line, turn, and 3 m toward the chair), turn around, and sit down on the chair, with no cognitive task (single-task walking). The participant is then asked to perform the same procedure with a concurrent cognitive task (counting backward by 3s, starting with an odd number, e.g., 81).[12] The total walking duration (in seconds) during both 6-meter walks, at normal pace, will be recorded. These tests will be administered by trained study assessors at baseline, 4 months, and 6 months. Using the score ascertained from each walk, a dual-task cost measure is estimated using the following formula:

(1) Dual-task walking $cost_{baseline}$ = (dual-task walking – single-task walking) / single-task walking x 100

(2) Dual-task walking $cost_{6\_months}$ = (dual-task walking – single-task walking) / single-task walking x 100

(3) Change (Δ) in dual-task walking cost = dual-task walking $cost_{6\_months}$ – dual-task walking $cost_{baseline}$

Scores derived from formula 3 above will be used for efficacy, for which positive values indicate deteriorated performance in dual-task walking (i.e., dual-task walking cost), whereas negative values represent an improvement in dual-task walking performance with respect to single-task walking performance (i.e., dual-task walking benefit).

Secondary outcomes

Our key secondary outcome is change in cognitive impairment. Other secondary outcome measures include changes in domain-specific cognitive function and physical performance, from baseline. The operationalization of each outcome is described below.

Clinical Dementia Rating

The Clinical Dementia Rating (CDR) scale[15] uses a semi-structured interview with both the participant and a reliable informant (usually a spouse or adult child) to rate six domains of cognitive and functional performance: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. Each domain is rated according to one of five levels of impairment: 0 = none, 0.5 = questionable, 1 = mild, 2 = moderate, and 3 = severe (Note: the personal care item is scored on a 4-point scale without a 0.5 rating available). A global CDR score is then assigned according to published rules to indicate the presence or absence of dementia, and, when present, its severity. A CDR test score of 0 indicates no dementia and scores of 0.5, 1, 2, and 3 indicate very mild, mild, moderate, and severe dementia, respectively. This measure will be administered by the outcome assessors who have received training on CDR administration (https://knightadrc.wustl.edu/cdr/cdr.htm).

As a key secondary outcome in this trial, a CDR sum of box (CDR-SB) score, a validated outcome measure used in clinical trials of Alzheimer's disease,[22] will be obtained by summing each of the domain box scores, with scores ranging from 0 to 18 (higher scores indicating great impairment in cognition and function).

Paper-and-pencil cognitive battery tests

This set of tests includes cognitive domains of attention, processing speed, visuospatial ability, executive function, verbal fluency, and memory. Each is described below.

Trail Making Test (TMT) (Parts A and B) (attention, executive function). The TMT consists of two parts (A and B).[23] Part A, which has little executive input, requires the participant to use a pencil to connect a series of numbered circles arrayed randomly on a sheet of paper. In part B, which tests cognitive flexibility and stresses central executive processes of task-set inhibition, the participant connects numbers and letters in an alternating progressive sequence, 1 to A, 2 to B, 3 to C, and so on. For parts A and B, scoring is expressed in terms of the time (in seconds) to completion. In order to measure central executive functioning, the difference in time taken to complete Part B versus Part A is calculated, with smaller difference scores indicating better executive function.

Stroop Color and Word Test. The Stroop Color and Word Test[24] will be used to assess the executive aspects of attention control, information processing speed, selective attention, cognitive flexibility, and executive function in terms of the ability to inhibit a usual response in favor of an unusual response. The test consists of speeded trials of Word Reading, Color Naming, and Color-Word Interference and assigns a score for each trial based on the number of words read or colors named in 45 seconds. Upon completion of the test, the number of items correctly named in 45 seconds in each condition is calculated (i.e., W, C, CW), and this is followed by calculating the predicted CW score (Pcw) using the following formula:

$$Pcw = 45/\{((45 \times W) + (45 \times C))/(W \times C)\}$$

Or equivalent to:

$$Pcw = (W \times C)/(W + C)$$

The Pcw value is subtracted from the actual number of items correctly named in the incongruous condition (CW) (i.e., IG = CW − Pcw). This procedure results in an interference score (IG) based on the performance on both W and C conditions. Thus, a negative IG value represents a pathological ability to inhibit cognitive interference, whereas a lower score represents greater difficulty in inhibiting cognitive interference.

Category Fluency for Animals. This is a test that assesses verbal fluency and executive function.[25] The participant is asked to generate the names of as many animals as possible in 60 seconds.

Block Design Test. As a subset of the Wechsler Adult Intelligence Scale (WAIS-IV),[26] the Block Design Test provides a measure of visuospatial ability. The participant is asked to use his/her hand to arrange blocks that have various color patterns on different sides to match a pattern according to a presented model as accurately and quickly as possible. Though the items in the test can be scored both by accuracy in matching the pattern and by speed in completing each item, in this study we will score the test by speed measured in seconds.

Digit Symbol Coding. As another subset of WAIS-IV,[26] Digit Symbol Coding measures processing speed. The participant is given a piece of paper with nine symbols (on the bottom line) corresponding to 9 digits (on the top line) and 27 digits on the next seven lines. Next, on the same piece of paper are eight rows of digits with empty spaces below them. The participant is asked to fill in as many corresponding symbols as possible in 120 seconds. The total score is the number of correctly drawn symbols (possible scores, 0-135) within the time limit allocated, with higher scores indicating better processing speed.

Digit Span (Forward and Backward) Test. As a third subset of WAIS-IV,[26] this test involves evaluation of two main components: attention span and working memory. The participant is verbally presented with a series of digits (e.g., 6, 2, 9, 7) at a rate of one digit per second and is required to repeat them verbatim. If the participant succeeds, he/she is given a longer list (e.g., 5, 3, 8, 1, 6). The number of digits increases by one until the participant consecutively fails two trials of the same digit span length. The length of the longest list a person can remember is that person's digit span. This test contains two separate tasks. In the "Forward Digit-Span," the participant is asked to repeat the digits in the given called order. In the "Backward Digit-Span," the participant is required to repeat the digits in reverse. The participant receives 1 point for each correct answer. The maximum number of points in the entire test is 32. To minimize a learning effect, different lists of numbers are given to the participants in each of the four testing occasions.

Computerized cognitive battery tests

To augment our paper-and-pencil measures, we will also employ Cogstate (cogstate.com), a set of customized, computerized tasks taxing verbal learning, including (a) International Shopping List Task plus a recall (the number of correct responses is used as the unit of measurement); (b) attention (Identification [speed of performance]); (c) working memory (One Back Task [speed of performance]); (d) visual recognition memory/attention (One Card Learning Task [accuracy of performance]); and (e) executive function (Groton Maze Learning Task [accuracy of performance]). These assessments are performed on a desktop computer and administered according to guidelines. The test session takes about 45 minutes to complete, with a practice before every task. Similar to the paper-and-pencil tests, a composite cognitive score will be calculated from these computerized cognitive tests.

Physical Performance

Functional Reach. In an upright standing position, this measure (measured in inches) assesses the maximal distance the participant can reach forward, beyond arm's length, while maintaining a fixed based of support in the standing position.[27]

Short Physical Performance Battery (SPPB). This measure includes (1) increasingly challenging standing balance tasks (side-by-side stand, semi-tandem stance, tandem stance), (2) a 4-meter walk (gait velocity) at normal pace, and (3) repeated chair stands (leg strength).[28] A single SPPB measure is used, with the scale score ranging from 0 points (worst physical function) to 12 points (best physical function).

Timed Up&Go (TUG) test. The TUG measure[29] is recorded in seconds (the time taken by an individual to stand up from a standard armless chair, walk a distance of 3 meters, turn, walk back to the chair, and sit down).

Covariates

There are no pre-specified covariates in this study.

Tertiary measures

These measures include the (a) Everyday Cognition scale,[30] (b) Pittsburgh Sleep Quality Index,[31] (c) Geriatric Depression Scale,[17] and (d) EuroQol EQ-5D for health-related quality of life.[32] These measures, described below, are included in a paper survey completed by participants.

Everyday Cognition. This is assessed using the brief version of the informant-based Everyday Cognition questionnaire,[30] which will be completed by the informant of the participant. In people with MCI, the measure assesses a participant's ability to perform everyday tasks in the following areas: memory, language, visuospatial abilities, planning, organization, and divided attention. The average will be derived from the mean average of all responses (range from 1 to 4), with higher scores indicating greater impairment in everyday functional cognitive ability.

Pittsburgh Sleep Quality Index (PSQI). The PSQI[31] includes seven indices: subjective quality, latency (i.e., time needed to fall asleep), duration (i.e., number of hours of actual sleep per night), efficiency (i.e., total sleep time divided by time in bed, converted to a score of 0-3), sleep disturbances (e.g., waking up in the middle of the night and the like), use of sleeping medication, and daytime dysfunction (e.g., having difficulty staying awake during the day). Each of the component scores ranges from 0 to 3, with the PSQI global score ranging from 0 to 21 points, with higher scores indicating poorer sleep quality.

Geriatric Depression Scale. The 15-item version of the scale[17] will be used to assess depressive symptoms. The score for the measure ranges from 0 to 15. A score of 0 to 4 is considered to be within the normal range, 5 to 9 indicates mild depression, and a score of 10 or more indicates moderate to severe depression.

EuroQol EQ-5D. The EQ-5D[32] assesses health status in five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each domain is measured at three levels: no problems (coded as 1), some problems (2), and extreme problems (3). An EQ-5D utility score at baseline and 6 months for each participant will be calculated based on the U.S. population-based (preference-weighted)

health index scores on a scale ranging from less than 0 (worst health state) to 1.0 (best or perfect health state).[33]

Assessment of intervention adherence

Intervention classes will be closely monitored by research staff throughout the study period. Session-by-session attendance of the study participants will be recorded by research staff, regardless of participants' participation status, and this information on exercise adherence rate will be used as an indicator of intervention adherence across the three intervention groups. For each intervention group, there will be a total of 48 exercise classes to be completed over the 24-week intervention period. Accordingly, the average intervention adherence rate will be calculated as follows: number of intervention sessions attended during the 24 weeks divided by total number of sessions prescribed for the study, reported as a percentage.

Baseline measures

At baseline, demographic and other information about age, sex, ethnicity/race, income, education, living arrangements, medical conditions, health status, habitual physical activity,[34] and residence location will be collected via a survey questionnaire. Body weight, assessed by a medical scale, and height, measured by with a ruler fixed on a wall, will also be ascertained. These data will be used to describe study population characteristics at baseline.

Statistical Analysis Plan (SAP)

Study aims

The study has the following primary and secondary aims.

Primary aim

To determine whether a cognitively enhanced tai ji quan intervention, in comparison to a standard tai ji quan intervention and an exercise stretching control, is more effective in improving global cognitive function and dual-task walking performance among community-dwelling older adults with MCI.

Primary hypothesis: We hypothesize that, at 6 months, cognitively enhanced tai ji quan training will result in greater gains in the primary outcomes of global cognition and dual-task gait performance than either standard tai ji quan or stretching control.

Secondary aim

To determine whether the effect resulting from the acute intervention phase can be sustained 24 weeks after training stopped.

Secondary hypothesis: We hypothesize that compared with standard tai ji quan or stretching control, participants in the cognitively enhanced tai ji quan training will retain their intervention gains in the primary outcomes of global cognition and dual-task gait performance at 12 months (post-intervention) follow-up. We also hypothesize that cognitively enhanced tai ji quan training will continue to be superior to either standard tai ji quan or stretching control, at 12-month follow-up, in terms of sustaining the training effect on slowing disease progression to dementia, as indexed by the continued improvement in the mean CDR-SB score from baseline.

Study design

This study is designed as a prospective, assessor-blinded, 3-arm parallel group, randomized clinical trial with a 1:1:1 allocation ratio. The primary co-outcome measures are global cognition function and dual-task walking costs. The target sample size is 315 participants, enrolled from local communities. The goal is to detect, with 80% power, 1.5 points in MoCA between the cognitively enhanced tai ji quan and the standard tai ji quan groups and 3 points between the cognitively enhanced tai ji quan and the stretching control groups at 24 weeks. The study will consist of a 6-month acute intervention phase (designed for addressing the primary aim) followed a 6-month maintenance phase (for addressing the secondary aim).

Outcomes

Table 1 below describes the study's primary, secondary, and tertiary outcomes, source of data, and follow-up schedule.

	Measure	Data source	Follow-up schedule
Primary outcome			
Global cognition	Montreal Cognitive Function measure (MoCA; score range: 0 to 30)	Assessment conducted by assessors	4 months, 6 months, and 12 months
Dual-task walking costs	Difference between single- and dual-task gait speed (expressed in percentage)	Assessment conducted by assessors	4 months, 6 months, and 12 months
Secondary outcome			

Cognition and function	Clinical Dementia Rating Sum of Boxes score (range: 0 to 18)	Interviews with participants and informants conducted by assessors	4 months, 6 months, and 12 months
Executive function	Trail Making Test (B) (measured in seconds)	Cognitive assessment conducted by assessors	4 months, 6 months, and 12 months
Attention and memory	Category Fluency (number of animal names recalled)	Cognitive assessment conducted by assessors	4 months, 6 months, and 12 months
Attention	Forward Digit Span (range: 1 to 16)	Cognitive assessment conducted by assessors	4 months, 6 months, and 12 months
Memory	Backward Digit Span (range: 1 to 16)	Cognitive assessment conducted by assessors	4 months, 6 months, and 12 months
Mobility	Timed Up&Go (measured in seconds)	Physical assessment conducted by assessors	4 months, 6 months, and 12 months
Lower-extremity strength	30-second chair stand test (number of times)	Physical assessment conducted by assessors	4 months, 6 months, and 12 months
Static balance	4-stage balance test (range: 0 to 4)	Physical assessment conducted by assessors	4 months, 6 months, and 12 months
Tertiary outcome			
Everyday cognitive function	Everyday Cognition Scale (range: 1 to 4)	Informant-rated questionnaire	4 months, 6 months, and 12 months
Depressive symptoms	Geriatric Depression Scale (range: 0 to 15)	Survey completed by participants	4 months, 6 months, and 12 months
Sleep quality	Pittsburgh Sleep Quality Index (range: 0 to 21)	Survey completed by participants	4 months, 6 months, and 12 months
Quality of life	EuroQol EQ-5D (range: -1 to 1)	Survey completed by participants	4 months, 6 months, and 12 months

Randomization

Method of randomization

Eligible participants will be randomized to one of the three intervention groups with an allocation of 1:1:1 through a permuted block randomization method with a block size of 3 or 6 to prevent anticipation of assignment to the study group. The project data analyst, who will not be involved in the recruitment of participants, will use computer software (nQuery, version 4.0, Statistical Solutions Ltd) to generate a randomization schedule, which will be kept in a sealed envelope. No one else on the project will be

involved in generating the randomization. The schedule will be released by the data team to a research assistant before each wave of recruitment is scheduled. On the day of the assignment, the research assistant will assign qualified individuals to the intervention groups. The allocation sequence assigns individuals in the order that they were scheduled for baseline assessment. Randomization will occur after informed consent is obtained and baseline assessments have been completed.

Allocation concealment

To control for selection bias, all study assessors who collect study outcome measures will be blinded to the main study design and group allocation. Blinding will be strictly maintained by emphasizing to assessors the importance of minimizing assessment bias and by random checking of the blinding status. Efforts will be also made to maintain separation between the study assessors and research assistants who deal with administrative activities and class safety monitoring, and between study assessors and class instructors who deliver the intervention classes. Because of the nature of the interventions, study participants and interventionists will not be masked to group allocation. Participants will be instructed not to reveal their group status to the assessment staff at any time during follow-up.

Statistical interim analyses and stopping guidance

None. However, annual data and safety information related to the project will be presented to the project Safety Officer appointed by the funding agency. The Safety Officer will determine whether any interim statistical analyses will be necessary and whether data collection continues on the basis of the project progression on subject recruitment, study assessment, or intervention adherence.

The following describes our pre-specified data analysis plan. Data will be coded to maintain group allocation blinding during analysis.

Descriptive analyses

- *Trial flow*. Information on the number of individuals screened, excluded, and qualified per the study eligibility criteria and assigned to the intervention, as well as the follow-up status, at each assessment time point will be presented in a figure in accordance with the CONSORT guidelines.
- *Comparability of intervention groups*
  - Baseline characteristics of the study population will be summarized by intervention group using summary statistics (e.g., mean, standard deviation, range, frequencies, or percentages) for continuous variables and frequency or percentages for categorical variables. Median IQRs will be calculated for variables that are not normally distributed.
  - Participants' characteristics ascertained at baseline will be compared across intervention groups using independent samples or Wilcoxon rank sum tests, as appropriate, for continuous variables and a chi-square or Fisher's exact tests, as appropriate, for categorical variables. Although no significant differences are expected due to the randomized intervention assignment and the relatively large sample size, any variables found to be significantly different will be noted and accounted for, by controlling for them as covariates in supplements to the main analyses.
- *Time-specific and change scores*. Scores at each follow-up and change in mean scores from baseline at 24 weeks, by intervention group, for all outcome measures will be calculated and presented.
- *Intervention adherence, attrition, and retention*. Class attendance data will be calculated as the average number of scheduled intervention sessions (48 total) attended by participants across intervention groups. Study attrition and retention rates will also be calculated and reported, by intervention group, as the number of participants who completed the 24-week intervention and those who completed all scheduled study follow-up assessments.

Analysis populations

Efficacy analyses. The effect of intervention on the co-primary study outcomes will be evaluated using an intention-to-treat approach in which participants will be analyzed according to randomization assignment. A modified intention-to-treat analysis will be conducted that includes all participants who have undergone randomization and have completed all study follow-up assessments, regardless of their participation adherence status. Finally, a per-protocol analysis will include participants in the intention-to-treat population who have an overall class attendance rate of ≥75% (out of the total planned 48 intervention class sessions) of their assigned exercise intervention.[10]

Co-primary endpoint analyses

To test the *Primary hypothesis*, we plan to use a generalized linear mixed model with random intercepts and fixed treatment effects for the primary outcomes. Specifically, we will determine the intervention effect through an analysis of a 3 (Group) by 3 (Time) mixed-effects model with repeated measures (follow-up time point) on the second factor (i.e., outcome measures assessed at baseline, 4 months [mid-point], and 6 months [intervention termination]).

In the presence of a Group by Time interaction effect, follow-up pair-wise comparisons, using independent t tests, will be performed to identify a priori specified between-group differences. Specifically, we will determine the intervention effect of cognitively enhanced tai ji quan for change in MoCA and costs of dual task in gait performance from baseline to 24 weeks by making a comparison between cognitively enhanced tai ji quan and standard tai ji quan and between cognitively enhanced tai ji quan and stretching exercise.

Level of statistical significance and confidence intervals. Our primary outcome analyses will be 2-sided with an adjusted significance level of <0.0125 (0.05 / 4 comparisons) and a 98.75% confidence interval (CI). For each group, both estimated means and their corresponding standard error of estimates at each assessment point will be presented. In presenting between-group differences, mean differences with CIs will be presented. SPSS "MIXED" function will be used in analyzing our primary outcomes.

Secondary and tertiary outcome analyses

A similar analytic approach will also be applied to all secondary and tertiary (continuous) outcome variables described in Table 1. All study outcomes are expected to follow a normal distribution. In the case of deviation from normality, generalized estimating equations will be used to assess the effect of intervention over time. No Bonferroni correction will be made to account for multiple comparisons.

Level of statistical significance and confidence intervals. All tests and CIs will be 2-sided, and statistical significance will be defined as a P value of <0.05. For each group, we will report both estimated means and their corresponding standard error of estimates at each assessment point. In presenting between-group differences at 24 weeks, estimated mean differences with CIs will be presented.

Analyses on examining intervention durability at 48-week follow-up

We will use the same analytic strategy outlined in our primary and secondary outcome analyses, with the exception of CDR-SB (described in detail below), to examine whether the intervention effects will persist 24 weeks after the end of the 24-week supervised interventions (*Secondary hypothesis*).

With the longitudinal data, we will test the hypothesis that the rate of improvement over time in the mean CDR-SB score, at 24-week post-intervention follow-up, will be greater in the cognitively enhanced tai ji quan group compared with the other two exercise groups. To test this hypothesis, we will use the latent growth curve modeling approach,[35] with maximum-likelihood estimation, analyzing the rate of change in the mean CDR-SB score defined by the four measurement time points: baseline, 16 weeks (mid intervention assessment), 24 weeks (end of intervention assessment), and 48 weeks (24 weeks post intervention follow-up).

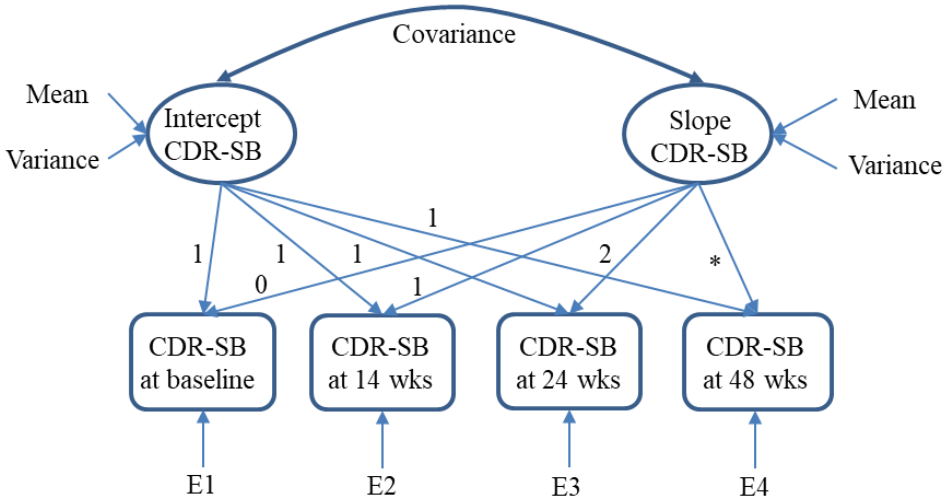
Accordingly, we will operationalize our basic growth curve model with two latent growth factors: Intercept (defining the initial level of CDR-SB – baseline) and Slope (defining the rate of change over the course of the 48-week study period), with each factor being defined by the four time-specific CDR-SB

measures. A schematic representation of the planned latent growth model to be evaluated for each intervention group is shown in Figure 1. The factor loadings for the Intercept factor will be fixed with a constant value of 1 for all measurement points whereas the loadings for the Slope factor, defining the rate of change over time, will be fixed at 0 for CDR-SB at baseline, 1 for CDR-SB at 16 weeks, 2 for CDR-SB at 24 weeks, and * for CDR-SB at 48 weeks (where * indicating an undefined, free estimate at 48 weeks). All other model parameters to be estimated include latent Intercept mean and its variance, latent Slope mean and its variance, the correlation between Intercept and Slope (covariance), and error variance for each of the four time-specific measurements (shown as E's). The model estimation will include all available data derived from the trial, hence, an intent-to-treat approach.

The model estimation of change in CDR-SB will involve two steps. First, we will estimate an unconditional latent growth model (i.e., without the group predictor [e.g., cognitively enhanced tai ji quan group vs standard tai ji quan group]). This unconditional growth curve model allows us to examine the overall pattern of change in the CDR-SB score over time. Next, a group predictor (as a binary variable [1=cognitively enhanced tai ji quan group and 2=standard tai ji quan group]) is added to the model parameterization. By regressing the Slope factor on to the predictor of the group variable, this model will examine the pre-specified intervention effect of the cognitively enhanced tai ji quan training, compared with each of other two active groups, individually, on the rate of change in cognitive functioning trajectories. The schematic representation of this second latent growth model with the group, as a predictor, is shown Figure 2 (next page). For reporting purposes, we will present (a) latent slope mean for each group and (b) the regression coefficient relating group and the latent slope (with 95% CI). A negative slope mean for CDR-SB will indicate an improvement in cognitive functioning and, therefore, a lowering of the disease progression, whereas a positive mean slope will indicate deterioration in cognitive functioning.

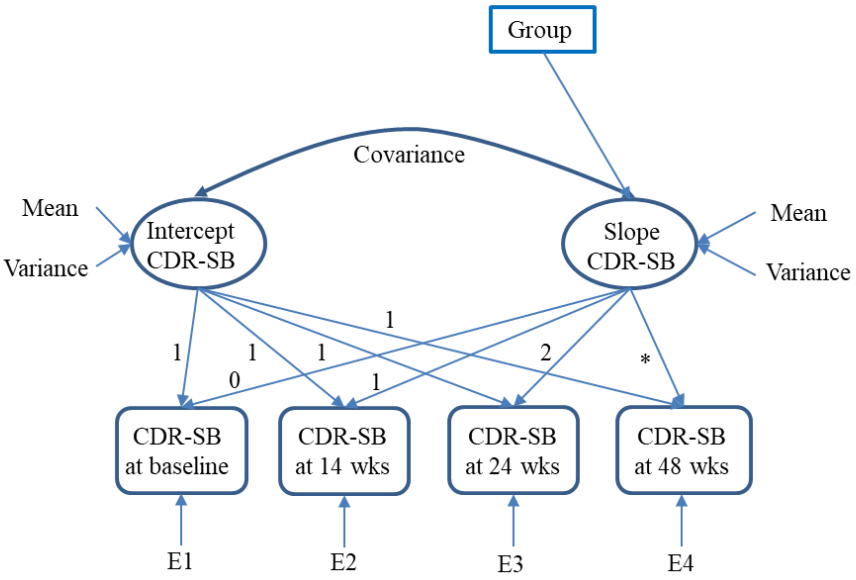
A statistically significant regression coefficient indicates the difference in the rate of CDR-SB progression. All tests and CIs will be 2-sided, and statistical significance will be defined as a P value of <0.05. The planned statistical analyses on change in CDR-SB will be performed in *Mplus* statistical software version 8.2 (Muthén & Muthén).

Figure 1. Latent growth curve model (intercept and slope) of change in CDR-SB over the 48-week study period



Note:
Intercept: defines the CDR-SB score at baseline
Slope: defines change or progression in the CDR-SB score from baseline to 48 weeks
*indicating an undefined, freely estimated loading at 48 weeks
Values in the squared box indicates observed value at each measurement time point
E1 through E4 represent measurement error at each measurement time point

Figure 2. Latent growth (intercept and slope) model for examining intervention effect on CDR-SB over the 48-week study period



Note: Group is a binary variable involving a comparison between cognitively enhanced tai ji quan and standard tai ji quan or cognitively enhanced tai ji quan and stretching exercise.

Post-hoc exploratory analyses

No pre-specified post-hoc exploratory analyses are planned.

Subgroup analyses

In light of the findings reported in prior studies,[36,37] we also plan to conduct a series of subgroup analyses. Specifically, using a three-way interaction model that involves factors of Group, Time, and Subgroup, we will examine whether the expected between-group differences in the two primary outcomes are associated with pre-specified subgroups that include sex (1 = men, 2 = women), age (1 = 65-74, 2 = 75-84, 3 = 85+ years old), and level of education (1 = high school diploma or lower, 2 = college degree or higher). We are aware of the fact that these subgroup analyses are not powered statistically, and we will therefore interpret any statistically significant results with caution. All subgroup analyses are based on an alpha level of <0.05.

Power estimation for primary outcomes

This study is powered to detect a mean difference in change in the primary outcomes of MoCA and motor-cognitive dual-task gait performance between (a) the cognitively enhanced tai ji quan intervention and a standard tai ji quan intervention operationalized by TJQMBB,[10] and (b) the cognitively enhanced tai ji quan intervention and a non-tai ji quan control condition – stretching – at 6 months, among older adults with MCI. We estimated the magnitude of the effect size (difference score divided by its pooled standard deviation) that is detectable with at least 80% power using a 2-sided 0.05-level test. We expect that participants in the cognitively enhanced tai ji quan intervention would experience a clinically meaningful improvement of at least 1 score unit in MoCA and a 10% reduction in dual-task costs on gait performance speed between the enhanced tai ji quan intervention and each of the two comparison arms. The following details the parameters used and results of our power analyses for each of the two primary outcomes.

MoCA. Assuming two (pre and post) repeated measurements and a between-level correlation of 0.7, the planned sample size of 267 participants would provide >80% power to detect a medium-size difference (Cohen d = 0.4) in mean MoCA change of 1.5 points (SD = 3.5) between the cognitively enhanced tai ji quan and the standard tai ji quan groups and a large-size difference (Cohen d = 0.8) of 3 points (SD = 3.5) between the cognitively enhanced tai ji quan and the stretching control groups at 6 months. No minimal clinically important difference (MCID) in MoCA has been established in the physical exercise literature, but our target estimate is close to that of 1.22 points established for the stroke patient population.[38]

Dual-task gait performance. Using the same assumptions, at 6 months, we estimated a 10% reduction in dual-task walking costs between the cognitively enhanced tai ji quan and standard tai ji quan interventions and a 20% reduction between cognitively enhanced tai ji quan and stretching interventions. At the time of developing this research proposal, no MCID for reduction in costs in dual-task performance in gait is available. The target estimates calculated in this trial were inferred from our prior completed studies.[10,12]

Taking into account a conservative 15% loss during the 6-month active intervention period, a total of 315 participants was planned for the study.

Treatment of noncompliance and missing data

All enrolled study participants will be followed until the trial period ends, whether or not the participant is still receiving or complying with the intervention. Primary endpoint analyses will be conducted according to the original randomization scheme in an intention-to-treat approach. We will use a multiple imputation data method for missing data. We plan to perform 10 sets of imputations. Variables without missing data to be used for prediction of imputed values on the study variables will include baseline measures of age, sex, level of education, MMSE, number of chronic conditions, and depression. The imputed data will be submitted to the same analytic model (i.e., linear mixed model) as the non-imputed observed data, and the results of each analytic model will be pooled across the 10 imputed data

sets. The secondary outcome analyses will also be conducted using the multiple imputation method described above. Tertiary outcome analysis will be conducted with observed data without imputation.

Interim analysis

We do not plan to perform any interim analyses for efficacy or futility. Instead, we will conduct interim monitoring performance with a focus on subject accrual, protocol adherence, intervention fidelity, data completeness and quality control, and intervention safety and analysis. Each is described below.

Subject accrual

We plan to conduct 10 staggered recruitment and enrollment waves, with approximately 35 participants planned at each wave, over 3.5 years of the 5-year project life. Each recruitment wave will be closely monitored at monthly staff meetings, with presentation of recruitment charts, to ensure we achieve our enrollment target. The accrual rate will be reviewed annually by research staff and will be reported to ORI IRB and the project Safety Officer appointed by NIA.

Protocol adherence

The overall intervention adherence (i.e., exercise class attendance) rate is defined as the sum of the total number of participants attending divided by the maximum number of 48 sessions planned, multiplied by 100, during the 6 months of active intervention. For the trial, the target adherence rate is ≥75%. Class attendance across the three study conditions will be closely monitored on a weekly basis by research staff and reviewed on a monthly basis by key personnel of the project. Participants who miss two consecutive sessions will be contacted by phone to ascertain the reason(s) for their absences and to encourage them to return.

Intervention fidelity

Intervention fidelity will focus primarily on issues such as (a) interventionist qualifications and training, (b) teaching quality of the individual forms/movements or routine in each session, (c) exercise intensity and consistency in training dosage across different sites, and (d) weekly class attendance checking and monitoring. The evaluation will be conducted monthly by either an authorized research team member or an instructor, per guidelines specified in an established fidelity checklist.[10] In evaluating the item in (b), high intervention fidelity will be considered achieved if at least 95% of the mandatory components (overall completion of pre-specified activities, quality of verbal and visual instructions, emphasis of core training points, session completion time) are fully or partially delivered in each session. Deviations related to intervention delivery protocol will be captured on a protocol deviation form and be entered into a project database for evaluation by the research staff and Principal Investigator. Prompt action will be taken by the Principal Investigator to remedy any problems and deviations identified.

Data completeness and quality control

Data completion refers to the study measurement ascertainment status from all enrolled study participants. The project strives to collect study outcome measures on every participant at each scheduled time point (baseline, 4 months, 6 months, and 12 months), regardless of his/her intervention participation status. As specified in the protocol for the study, we have planned an overall study retention rate of 85% (i.e., having primary and secondary outcome measures available on 85% of the enrolled participants and their informants). To accomplish this goal, planned measures will be taken to ensure that as many participants as possible, including dropouts, attend each scheduled in-person assessment visit at our research facilities. Our proactive methods will include frequent telephone and e-mail contacts with subjects who miss scheduled data assessment appointments. The planned completion of data ascertainment at each follow-up time point is described in the Table 2 below.

Table 2. Projected completion of data ascertainment on study outcome measures at each measurement time point

Measure\Time point	4 months	6 months	12 months
Primary	95%	90%	85%
Secondary	95%	90%	85%
Tertiary	95%	90%	85%

Outcome measures ascertained will be closely checked and verified for accuracy and completeness via a rigorous data checking and reviewing process implemented by the trial analyst(s) who will be blinded to group allocation. Specifically, data quality and accuracy will be assured via the following steps.

- All assessment data (i.e., surveys, semi-interviews, observational assessments) will be double checked for errors (e.g., out-of-range data, missing data, and accuracy) by research assistants before they are entered into a database.
- Raw data will be entered twice via an existing data entry module.
- All entered data will be subject to a process that checks for accuracy and consistency and will be verified by the project statistician. In the event that data entry errors are discovered, additional charts will be randomly selected for internal review.
- Raw data entry, cleaning, coding, manipulation, verification, and merging from all four time points (baseline, 4 months, 6 months, and 12 months) of assessment will be completed within 5 days after each follow-up.
- Charts and plots will be presented to the study's statistician and Principal Investigator every three months for quality assurance.

In addition, deviations related to outcome assessment and data ascertainment protocols will be captured on a protocol deviation form and be entered into a project database for review and evaluation by the research team and Principal Investigator during quality assurance meetings, which will be held on either a monthly or quarterly basis. Prompt action will be taken by the Principal Investigator and team's statistician to remedy any problems and deviations identified, and they will perform follow-up evaluations of actions taken, if necessary.

Intervention safety and analysis

Throughout the study period, both intervention- and non-intervention-related adverse events will be closely monitored and recorded by research staff and adjudicated by the Principal Investigator. We will classify adverse events in three categories: Mild (i.e., events that require no medical treatment or are not life threatening), Moderate (i.e., events that require medical treatment but are not immediate life-threatening conditions), and Serious (i.e., events that result in death or are life threatening and require medical treatment, including hospitalization, or significant disability/incapacity). For all events observed or reported, we will further classify them into three categories in relation to the intervention: Unrelated (an event that is reported but not directly related to participation in the intervention), Possible (an event that is observed during a class and that is considered likely to be associated with participation), or Definite (an event that is observed or reported during a class and is considered directly related to participation).

Per our IRB protocol, any serious adverse events that we have collected during the entire course of intervention will be reported to the IRB and the project Safety Officer within 48 hours of the reported incident. This will also include unanticipated issues such as prolonged hospitalizations and deaths. Safety analysis will involve tabulating the occurrence of adverse events, including Serious adverse events (deaths and hospitalizations) and unanticipated problems/issues among the three groups. Given the low risk of the trial, no inferential statistical tests are planned for safety.

Statistical software

Statistical analyses will be performed with the use of Stata software (version 17, Stata Corp), SPSS software (version 25, SPSS), and Mplus software (version 8.4, Muthén & Muthén).

Programming plan

All statistical programs used to generate the study results and unidentifiable data will made available upon reasonable request to the PI of this project.

Data Management

All data collected (self-reports, interviews, recorded study outcome performance ratings or scores) from the project will first be stored in locked filing cabinets in a designated area inside the ORI office building and, after review for completeness and accuracy, will be entered into a secure, password-protected ORI computer network database to be established by the data team staff. Only authorized project staff conducting this project will have full access to the data collected. Participants and informants' responses to the project surveys, interviews, and other forms of data will be coded with a unique numeric identification code. Only designated project staff will have the key to the file cabinets or password to the database and will have access to the data only for status checking or data verification purposes. An Excel data system will be created to track the subjects' status related to recruitment, enrollment, intervention participation, and follow-up assessment. For all raw data, a system file will be created, using the SPSS statistical software, that merges various subsets of data for final analyses. A periodic security check on the data files will be conducted under the supervision of project's statistician. Only the designated data analyst, project biostatistician, and PI will have access to the raw data and analyses.

Timing of Statistical Analysis

To address the primary aim of the study, preliminary and main statistical analyses and evaluation of the trial primary and secondary outcome measures specified in this protocol will begin immediately upon completing the last study participant follow-up at 6 months. To address the secondary aim of the study, analyses and evaluation of trial data will begin immediately upon completing the last study participant follow-up at 12 months.

Adverse Events Reporting

The following summarizes the procedures that will be followed by the investigative team when a participant experiences an adverse event (during the entire course of the study project):

1. The participant will be encouraged to call ORI's research staff at 541-484-2123 or 855-434-1548 (toll free).
2. ORI's staff will file an incident report and immediately report the event to the Principal Investigator (Fuzhong Li, Ph.D.).
3. The Principal Investigator will inform ORI's IRB administrator (Kathryn@ori.org) and project Safety Officer appointed by NIA of the incident within 48 hours.
4. The incident report will be sent to the Project Officer at NIA and filed in the project database.
5. An ORI staff member will conduct a follow-up contact with the participant within 5 working days to reassess the situation and report back to the Principal Investigator.

Annual Progress Reports

Annual review and progress reports of this trial will be submitted to (a) the Institute Review Board of the Oregon Research Institute and (b) the Safety Officer approved by the NIA. The report will include the following information on data and safety monitoring:

1. Overall summary of the project progress
2. Recruitment and enrollment status
3. Intervention participation status
4. Data ascertainment status
5. Participant safety, including detailed information on intervention and non-intervention-related adverse events

Dissemination Plan

In compliance with the funding agency's (National Institutes of Health, NIH) policy on the dissemination of NIH-funded clinical trial information, we will publish our research findings in scientific journals. Trial participants will be provided with a summary of our findings in the form of a newsletter.

Trial Funding

This trial is funded by the National Institute on Aging (R01AG059546), National Institutes of Health.

Trial Protocol Approval by the Institute Review Board

The original in-person trial protocol was approved on January 23, 2019, by the Institute Review Board of Oregon Research Institute (IRB Registration No. 00000278). The protocol also received (or will receive) an annual review during each project year. A Data Safety Monitoring Officer, approved by the National Institute on Aging, reviewed and approved the study protocol, will oversee the study, and received (or will receive) annual updates.

***Modified Study Protocol* due to the COVID-19 pandemic (dated March 20, 2022)**

Background

On March 15, 2020, due to the widespread nature of the COVID-19 pandemic and for the safety and wellbeing of trial participants and project staff, the in-person study trial protocol (see above), approved by ORI's IRB and with notification given to the funding agency, was completely suspended. At the time of the suspension, we had a total of 28 participants who were 3 months into the active intervention.

Upon IRB approval, on March 30, 2020, all research activities were resumed by moving the trial activities online, delivered at home through Zoom videoconferencing. The decision to switch from in-person to online delivery was made by the investigative team based on (a) the need to adapt to the COVID-19 pandemic situation in order to continue the project, (b) pilot data on the safety of conducting the project through home-based online classes, and (c) the feasibility of ascertaining study outcome measures via videoconferencing.

Trial Modifications

To move the trial forward using an online telehealth approach, it was necessary for the investigative team to make important modifications to our original study protocol outlined previously. These modifications included the following six areas:

1. subject recruitment
2. setting
3. interventions
4. outcome measures
5. assessment
6. data analysis

These modifications, which are described in detail below and are reported in accordance with the current guidelines for completed trials modified due to the COVID-19 pandemic and other extenuating cirumstances,[39] were approved by ORI's IRB on April 2020 and were fully pilot evaluated for feasibility and safety, with results shown in two published studies, one in 2021[40] and one in 2022.[41] No alternations were made to the trial timeline, trial design, or target population (including eligibility criteria and sample size).

1. Modifications made to subject recruitment

Between March and June 2020, due to COVID-19-related restrictions on in-person contacts, all activities related to recruitment were moved online via telephone and Zoom (HIPAA-compliant) videoconferencing. (Note: All modified recruitment activities remained HIPAA compliant). Specific modifications made to study recruitment are described below.

Study promotion to identify participants. Our modified recruitment methods involved mainly (a) mass mailing, (b) social media, (c) word of mouth (by telephone or e-mail communications), and (d) digital advisement. Because the online delivery platform of our intervention was no longer constrained by geographic region, we expanded our study sampling area from the originally planned recruitment area in the state of Oregon to include other cities and towns throughout the continental United States (U.S.), as described below.

Study recruitment areas. For the purpose of enhancing generalizability, we purposely focused our recruitment efforts on four geographic regions (Northeast, Midwest, South, and West) in the U.S. and included states that had a high proportion of the population aged 65 years and older (i.e., Maine, Florida, West Virginia, Vermont, Montana). Following the identification of our recruitment regions, special attention was given to targeting counties and cities within each state that, per the US Census Bureau, had the highest index scores on Racial and Ethnic Diversity (www.census.gov/library/stories/state-by-state.html).

Study recruitment procedure. The modified subject contact procedure involved the following:

1. The study recruiter made a return phone call to those who responded to our study promotions. During these calls, a prescreening was conducted with respect to eligibility related to age and memory.
2. Those potential participants who met the initial entry criteria were further screened, via Zoom conferencing, for eligibility, including CDR (both participants and informants) and MMSE.
3. Those who met all eligibility criteria were immediately scheduled for a baseline assessment via Zoom. The assessment was completed by an outcome assessor who was blinded to group allocation.
4. Each participant received an e-mail with a secure (password-protected) ORI Zoom link on the assessment day.
5. On the assessment day, the assessor:
    a. initiated a phone call
    b. described the assessment protocols
    c. visually checked the home environment
    d. conducted the assessment per the protocol

    The assessment was completed by an outcome assessor who was blinded to group allocation.
6. Those who met the study eligibility criteria, signed the study consent form, and completed baseline assessment were randomized into one of the three interventions.

2. Modifications made to intervention setting

The originally planned community-based intervention delivery approach was replaced by hosting the intervention classes online via videoconferencing using Zoom. This switch from in-person class delivery mode to a home-based online delivery mode allowed us to both effectively and efficiently resume our intervention while maintaining the interactive features of in-person, instructor-led training in a face-to-face social context.

3. Modifications made to interventions

Prior to resuming the intervention classes, appropriate modifications were made to fit the online videoconferencing delivery method. While the original in-person exercise protocol was used for each intervention group, some minor practical modifications were made to fit the interventions in a home situation. The home-based videoconferencing protocol included the following:

1. Participants received an ORI-initiated Zoom link sent via e-mail, and the exercises were done at home.
2. Instructors delivered the exercise classes from our ORI research facility.
3. Virtual class sessions were delivered twice per week, as originally planned.
4. Each exercise class session was closely supervised and monitored by the project staff for safety and compliance.

4. Modifications made to outcome measures

Removal of planned outcome measures. To accommodate the online assessment environment, we had to remove a number of the secondary measures that were planned via the in-person assessment protocol. Removal of the following measures from the assessment protocol were approved by ORI's IRB (dated May 5, 2020):

(a) all computerized cognitive measures (One Card Learning, Block Design, Identification, International Shipping List, and One Back)
(b) Stroop test
(c) Digit Symbol coding
(d) the lab-based *i*TUG (6-meter walk) test involving walking under single-task and dual-task conditions

Modifications to other outcome measures. To accommodate the outcome assessment conducted in a virtual (home) environment, modifications were made to some of the other cognitive and physical performance measures. Details for each are described below. Modifications to the measures were approved by ORI's IRB. These modified measures were pilot evaluated, and results from these evaluations have been published.[40,41]

Montreal Cognitive Assessment (MoCA). In the Visuospatial/Executive section of the MoCA, participants were asked to verbally connect each letter to the corresponding number for the Trail Making task and draw both the object (e.g., cube) and clock on a piece of paper. After they completed the task, participants were asked to show the drawing to the assessor for evaluation. In completing the "Read list of letters" task in the Attention section, the letter-tapping task was replaced by asking participants to count the number of A's in the list.

Trail-Making B (TMT-B). Due to remote operation, this measure was administered verbally. Specifically, the hand-drawing task was replaced by asking participants to verbally recite numbers of letters out loud, alternating between numbers and letters (i.e., 1-A-2-B-3-C, etc.). The study assessor recorded the time needed to complete the task.

Timed Up&Go (TUG). Before each walk, participants were asked to measure or estimate a 10-foot (3-meter) distance away from a table or device (PC or iPad) (see the detail below). The remaining test procedure followed the in-person assessment protocol, that is, participants were asked to (a) stand up from a chair, (b) walk (10 feet forward) at a normal pace to an imaginary straight line on the floor, (c) turn, (d) walk back (10 feet) to the chair, and (e) sit down. The same protocol was applied for the walk under a dual-task condition, where participants were asked to walk while performing an arithmetic task (i.e., starting at the number 81 and sequentially subtracting 3 from the resulting number). No specific verbal instructions were given for prioritization of one of the walking tasks during the dual-task walking trial.

Instructions. Prior to each of the scheduled assessments, participants were informed, by an e-mail, to prepare the following for the upcoming TUG assessment:

a. a measuring tape
b. a piece of paper
c. a standard height chair (without wheels)
d. an open home space of at least 12 feet in length (of which 10 feet will be measured on the floor for the walk test)
e. regular footwear

On the day of the assessment, participants were asked to (a) confirm the 10-foot walkway, (b) place the chair at the end of the walkway (away from the viewing device) and the piece of paper on the floor at the other end of walkway (near the viewing device), and (c) leave 2 extra feet to allow a safe turn around the piece of paper.

The total duration (in seconds) during the 20-feet walk (10 feet away from the chair and 10 feet toward the chair), at normal pace, was recorded for both walking conditions. The dual-task costs, measured in percentage, at each time point were calculated as follows: (dual-task gait speed – single-task gait speed) / single-task gait speed x 100). The final dual-task costs on gait speed were estimated by taking the difference between dual-task costs at baseline and at 6 months, with negative values indicating deteriorated performance in dual-task walking speed (i.e., dual-task cost), whereas positive values represent an improvement in dual-task walking speed with respect to single-task (i.e., dual-task benefit).

5. Modifications made to the assessment protocol

Modified assessment procedure. We modified our follow-up assessment protocol (involving both cognitive and physical performance measures) to accommodate the switch from in-person to online assessment conducted via Zoom. Modifications included the following:

1. The study assessor made a phone call or sent an e-mail reminder to the study participant, notifying the participant of the follow-up assessment and requesting that it be scheduled.
2. Prior to the scheduled assessment date, the participant received an e-mail with a secure ORI Zoom link.
3. On the assessment day, the assessor:
    a. admitted the participant into the Zoom session
    b. described the assessment activities
    c. visually checked the home environment
    d. conducted the assessment per the protocol.

Special note: Because there was no in-person assessment, information about each participant's weight, height, and blood pressure was collected via a self-report during the online assessment.

Modified survey completion procedure. We established a secure online site to allow participants to complete their study surveys online via Qualtrics (Qualtrics.com) if they chose to. Participants could still choose to submit their surveys via regular U.S. mail, as planned in the original protocol.

6. Modifications made to data analysis

No major modifications were made from the original SAP. However, in order to examine whether the intervention effects were impacted by shifting from in-person (before COVID-19 restrictions) to virtual delivery, we conducted post hoc sensitivity analyses on the two primary outcomes by excluding those who participated in our COVID-19-induced hybrid protocol.

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