Statistical Plan

Last updated: September 12, 2024

Identifiers:NCT04070703
Unique Protocol ID: AG059546

Published in: Li F, Harmer P, Eckstrom E, Fitzgerald K, Winters-Stone K. Clinical effectiveness of cognitively enhanced tai ji quan training on global cognition and dual-task performance during walking in older adults with mild cognitive impairment or self-reported memory concerns: A randomized controlled trial. Ann Intern Med. 31 October 2023. [Epub ahead of print]. doi:10.7326/M23-1603

Supplement 1: Trial Protocol

Table of Contents

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).

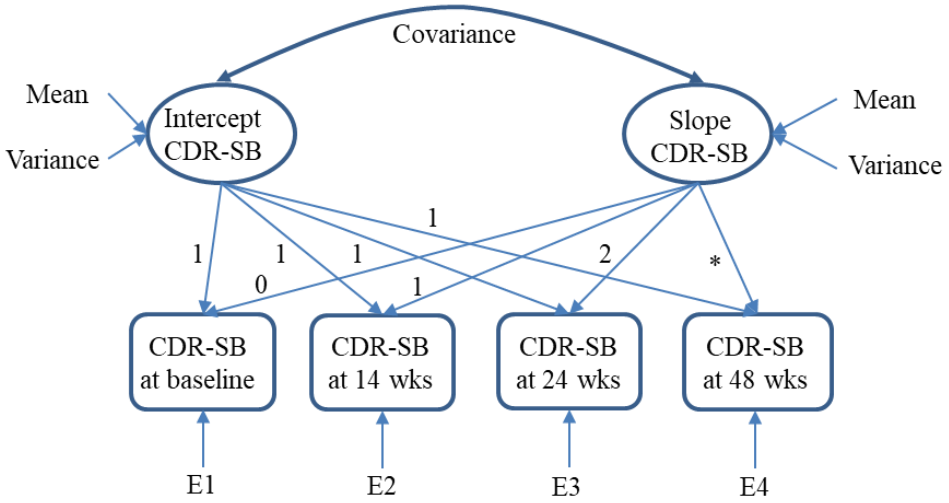
Accordingly, we will operationalize our basic growth curve model with two latent growth factors: Intercept (defining the initial level of CDR-SB – baseline) and Slope (defining the rate of change over the course of the 48-week study period), with each factor being defined by the four time-specific CDR-SB

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.

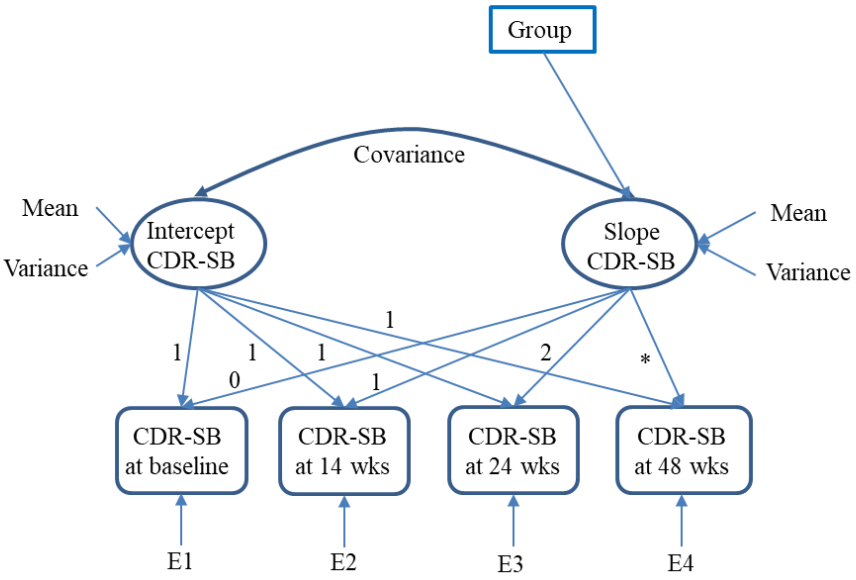
A statistically significant regression coefficient indicates the difference in the rate of CDR-SB progression. All tests and CIs will be 2-sided, and statistical significance will be defined as a P value of <0.05. The planned statistical analyses on change in CDR-SB will be performed in *Mplus* statistical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

***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.

References Cited

1. Alzheimer's Association. 2019 Alzheimer's Disease Facts and Figures. Available at: https://www.alz.org/media/Documents/alzheimers-facts-and-figures-2019-r.pdf. Accessed May 30, 2022.
2. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol* 1999;56:303–8.
3. Roberts R, Knopman DS. Classification and epidemiology of MCI. *Clin Geriatr Med* 2013;29(4):753-72.
4. Mitchell AJ, Shiri-Feshki M. Rate of progression of mild cognitive impairment to dementia: meta-analysis of 41 robust inception cohort studies. *Acta Psychiatr Scand* 2009;119:252-65.
5. Ward A, Tardiff S, Dye C, Arrighi HM. Rate of conversion from prodromal Alzheimer's disease to Alzheimer's dementia: a systematic review of the literature. *Dement Geriatr Cogn Dis Extra* 2013;3:320-32
6. Northey JM, Cherbuin N, Pumpa KL, Smee DJ, Rattray B. Exercise interventions for cognitive function in adults older than 50: a systematic review with meta-analysis. *Br J Sports Med* 2017;0:1–9.
7. Panza GA, Taylor BA, MacDonald HV, et al. Can exercise improve cognitive symptoms of Alzheimer's disease? *J Am Geriatr Soc* 2018;66(3):487-495.
8. Gheysen F, Poppe L, DeSmet A, et al. Physical activity to improve cognition in older adults: can physical activity programs enriched with cognitive challenges enhance the effects? A systematic review and meta-analysis. *Int J Behav Nutr Phy Act* 2018;15:63.
9. Wayne PM, Walsh JN, Taylor-Piliae RE, et al. The impact of Tai Chi on cognitive performance in older adults: A systematic review and meta-analysis. *J Am Geriatr Soc* 2014;62(1):25-39.
10. Li F, Harmer P, Fitzgerald K, et al. Effectiveness of a therapeutic Tai Ji Quan intervention vs a multimodal exercise intervention to prevent falls among older adults at high risk of falling. *JAMA Intern Med* 2018(10):1301-1310.
11. Li F, Harmer P. Liu P. Tai Ji Quan and global cognitive function in older adults with mild cognitive impairment: a pilot study. *Arch Gerontol Geriatr* 2014;58:434–439.
12. Li F, Harmer P, Chou L-S. Dual-task walking capacity mediates Tai Ji impact on physical and cognitive function. *Med Sci Sports Exer* 2019;51(11):2318-2324.
13. Petersen RC. Mild cognitive impairment as a diagnostic entity. *J Int Med* 2004;256:183-194.
14. Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute of Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer Dement* 2011;7(3):270-279.
15. Hues C, Berg L, Danziger W, Coben L, Martin R. A new clinical scale for the staging of dementia. *Br J Psychi* 1982;140:566-572.
16. Folstein MF, Folstein SE, McHugh PR. "Mini-Mental State". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatric Res* 1975:12:189-198.
17. Almeida OP, Almeida SA. Short versions of the geriatric depression scale: a study of their validity for the diagnosis of a major depressive episode according to ICD-10 and DSM-IV. Int J Geriatr Psychiatry 1999;14(10):858-865.
18. National Archives. Code of Federal Regulations. Available at: https://www.ecfr.gov/on/2018-07-19/title-45/subtitle-A/subchapter-A/part-46#46.102. Accessed June 1, 2019.
19. Li F. Transforming traditional Tai Ji Quan techniques into integrative movement therapy – Tai Ji Quan: Moving for Better Balance. *J Sport Health Sci* 2012;3:9-15.
20. Li, F, Harmer P, Fisher KJ, McAuley E, Chaumeton N, Eckstrom E, Wilson NL. Tai Chi and fall reductions in older adults: A randomized controlled trial. *J Gerontol: Med Sci* 2005;60A:66-74.
21. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow H. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*. 2005;53(4):695-9.

22. van Dyck, CH, Swanson CJ, Aisen P, et al. Lecanemab in early Alzheimer's disease. *N Engl J Med* 2023;388;9-21.
23. Corrigan JD, Hinkeldey MS. Relationships between Parts A and B of the Trail Making Test. *J Clin Psychol* 1987;43:402–9.
24. Golden CJ, Freshwater SM. *Stroop Color and Word Test Adult Version: A Manual for Clinical and Experimental Uses*. Wood Dale, Illinois: Skoelting; 2002.
25. Sager MA, Hermann BP, LaRue A, Woodard JL. Screening for Dementia in community-based memory clinics. *Wisconsin Medical Journal* 2006;105(7):25-29.
26. Wechsler D. Wechsler Adult Intelligence Scale – IV. Pearson: Bloomington, MN: Psychological Corporation; 1980.
27. Duncan PW, Weiner DK, Chandler J, Studenski S. Functional reach: a new clinical measure of balance. *J Gerontol* 1990;45(6):M192-M197.
28. Guralnik JM, Simonsick EM, Ferrucci L, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. *J Gerontol*. 1994;49(2):M85-M94.
29. Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc* 1991;39(2):142-148.
30. Farias ST, Mungas D, Harvey DJ, Simmons A, Reed BR, DeCarli C. The measurement of Everyday Cognition (ECog): Development and validation of a short form. *Alzheimers Dement* 2011;7(6):593-601.
31. Buysse DJ, Reynolds CF III, Monk TH, et al. The Pittsburgh Sleep Quality Index: A new instrument for psychiatric practice and research. *Psychiatry Res* 1989;28:193-213.
32. The EuroQol Group: The EuroQol – a new facility for the measurement of health-related quality of life. *Health Policy.* 1990;16:199–208. doi:10.1016/0168-8510(90)90421-9
33. Shaw JW, Johnson JA, Coons SJ. US valuation of the EQ-5D health states: development and testing of the D1 valuation model. *Med Care* 2005;43:203–220.
34. Craig CL, et al. International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc* 2003;35:1381-95.
35. Li F, Duncan TE, McAuley E, Harmer P, Smolkowski K. A didactic example of latent curve analysis applicable to the study of aging. *J Aging Health* 2000;12(3):388-425.
36. Baker LD, Frank LL, Foster-Schubert K, et al. Effects of aerobic exercise on mild cognitive impairment: a controlled trial. *Arch Neurol* 2010;67(1):71-79.
37. Lautenschlager NT, Cox KL, Flicker L, et al. Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: a randomized trial. *JAMA* 2008;300(9):1027-37.
38. Wu CY, Hung SJ, Lin KC, et al. Responsiveness, minimal clinically important difference, and validity of the MoCA in stroke rehabilitation. *Occup Ther Int* 2019;2019:2517658.
39. Orkin AM, Gill PJ, Ghersi D, et al. Guidelines for Reporting Trial Protocols and Completed Trials Modified Due to the COVID-19 Pandemic and Other Extenuating Circumstances: The CONSERVE 2021 Statement. *JAMA* 2021;326(3):257–265.
40. Li F, Harmer P, Voit J, Chou LS. Implementing an online virtual falls prevention intervention during a public health pandemic for older adults with mild cognitive impairment: A feasibility trial. *Clin Interv Aging* 2021;16:973-983.
41. Li F, Harmer P, Fitzgerald K, Winters-Stone K. A cognitively enhanced, virtual exercise intervention for older adults with mild cognitive impairment: A feasibility trial. BMC *Geriatrics* 2022;22:76.