Brain Health Together: A Live-Streaming Group-Based Digital Program

Short title: Boost Your Brain Health

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Study Title

Full: Brain Health Together: A Live-Streaming Group-Based Digital Program

Short: Boost Your Brain Health

Objectives

The primary goal of this Phase II Small Business Innovation Research (SBIR) grant is to develop and test a comprehensive Brain Health Together program for older adults living with cognitive decline. Older adults with cognitive decline (including either mild cognitive impairment [MCI] or subjective cognitive decline [SCD]) represent a large market with important unmet needs. Approximately one in three older adults (18 million Americans) are currently living with cognitive decline, which places them at increased risk of developing Alzheimer's disease and related dementias (ADRD). There are no medications that can prevent development of dementia in people with cognitive decline; however, there is growing evidence that behavioral interventions targeting modifiable dementia risk factors—such as increasing physical activity and reducing social isolation—may help improve cognitive function and could potentially delay dementia onset. Our preliminary results suggest that our Moving Together™ program is associated with significant improvements in cognitive function, physical function, social isolation, and self-regulation as well as increased default mode network connectivity on pre/post resting state functional magnetic resonance imaging scans in people with cognitive decline. We believe that these benefits would be even greater if Moving Together were combined with a comprehensive brain health coaching program.

Design and Outcomes

The **Specific Aims** of this grant are to:

1. Work with our Scientific Advisory Board and use human-centered design to develop evidence-based content for Brain Health Together, a 12-week, group-based, live-streaming, digital program that combines Moving Together with brain health education and coaching to address modifiable dementia risk factors in people with cognitive decline;

2. Perform a randomized, controlled trial to determine whether Brain Health Together improves cognitive function and reduces dementia risk factors over 12 weeks in people with cognitive decline;

3. Determine whether maintenance classes help to sustain the effects of Brain Health Together over 12 weeks after the intervention and explore potential mechanisms of action.

If we can demonstrate that Brain Health Together has immediate and sustained benefits, it will position Together Senior Health as a national leader in evidence-based programs to improve outcomes in older adults with cognitive decline.

Interventions and Duration

- Study participants will be randomly assigned to one of three groups.
    - **Brain Health Academy** will watch expert videos on a wide range of brain health topics and will complete quizzes for 2.5 hours a week for 12 weeks (30 hours total)
    - **Brain Health Together** will participate in online, live-streaming Moving Together classes (1 hour a week) and group brain health classes (1 hour a week) and will work 1-on-1 with a brain health coach to set personalized risk reduction goals (0.5 hours a week) for 12 weeks (30 hours total)
    - **Maintain Brain Health Together** will participate in the full Brain Health Together program for 12 weeks (30 hours) followed by weekly group classes and six 1-on-1 coaching sessions for another 12 weeks (additional 15 hours; 45 hours total)
- Outcome measures will include cognitive tests and validated surveys on dementia risk factors administered at baseline, 3 months and 6 months
- The co-primary outcomes are: 1) change in global cognitive function and 2) change in dementia risk score.
- Secondary outcomes will include specific cognitive domains and individual dementia risk factors.
- Adverse events will be assessed in all participants using monthly check-in surveys.

Sample Size and Population

216 older adults with cognitive decline

STUDY TEAM ROSTER AND STUDY SITES

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STUDY OBJECTIVES

Primary Objective

The primary goal of this Phase II Small Business Innovation Research (SBIR) grant is to determine whether the Brain Health Together™ program improves cognitive function or reduces dementia risk factors in older adults with cognitive decline. Brain Health Together is a live-streaming, group-based, digital program that combines our evidence-based Moving Together™ program—which includes movements to support daily function, mindful body awareness exercises and social engagement—with brain health education and coaching to address modifiable dementia risk factors in people with cognitive decline. We also will determine whether maintenance classes help to sustain effects over time. Brain Health Together is being developed and tested by TOGETHER.

Milestones

AIM 1. Work with our Scientific Advisory Board and use a human-centered design process—in which users are involved in all stages of development and testing—to create Brain Health Together, a 12-week, group-based, live-streaming, digital program that combines Moving Together with evidence-based content and best practice health coaching techniques to address

modifiable dementia risk factors in people with cognitive decline.

> **Milestone 1**: Expand TOGETHER's platform to deliver Brain Health Together content and support.

AIM 2. Determine whether the Brain Health Together program improves cognitive function or reduces dementia risk factors in people with cognitive decline.

> **Milestone 2a**: Perform a randomized, controlled trial (RCT) comparing the effects of Brain Health Together with a Brain Health Academy comparison group in older adults with cognitive decline.
>
> **Milestone 2b**: Test the hypothesis that cognitive function and dementia risk factors improve more over 12 weeks in the Brain Health Together group than the Brain Health Academy comparison group.

AIM 3. Determine whether ongoing classes and support help to sustain the effects of the Brain Health Together program over 12 weeks after the intervention, and to explore potential mechanisms of action such as changes in social isolation or well-being.

> **Milestone 3a.** Test the hypothesis that participants randomized to receive ongoing support will experience sustained cognitive and dementia risk reduction benefits compared to those who only participate in the 12-week program, and that both intervention groups will experience maintenance of cognitive function and dementia risk reduction relative to the Brain Health Academy comparison group.
>
> **Milestone 3b.** Explore whether changes in cognitive function may be mediated by changes in dementia risk factors.

BACKGROUND AND RATIONALE

Background

Approximately 20% of people aged 65 years or older are living with mild cognitive impairment (MCI), and an additional 12% report subjective cognitive decline (SCD), collectively referred to here as cognitive decline. Older adults with cognitive decline have an increased risk of developing Alzheimer's disease and associated dementias (ADRD). There are no medications available to prevent or delay onset of ADRD in people with cognitive decline. However, there is growing evidence that behavioral interventions targeting modifiable dementia risk factors—such as increasing physical activity and reducing social isolation—may help improve cognitive function and could potentially delay dementia onset in people with cognitive decline.

Our pilot study found that our in-person Preventing Loss of Independence through Exercise (PLIÉ) program–a 12-week, mind-body, group movement program for people with cognitive decline–was associated with statistically significant increases in default mode network (DMN)

connectivity on resting state functional magnetic resonance imaging (rs-fMRI) scans that were correlated with significant improvements in cognitive function. Participants also reported significant improvements in validated measures of well-being, social isolation, and the ability to self-regulate emotions. Graduates of this pilot study have been participating in the online version of this program, called Moving Together™, since the beginning of the COVID-19 pandemic and are reporting sustained benefits.

As part of our Aim 1 work for this grant, we invited this group to participate in development and pilot-testing of Brain Health Together–a 12-week, online program that combines Moving Together (1 hour per week) with group brain health education sessions (1 hour per week) and individual brain health coaching sessions (30 minutes per week). We observed high levels of engagement as well as self-reported behavior change, including increased physical activity, reduced social isolation, and more sleep.

The current study will build on our pilot work by testing the efficacy of Brain Health Together compared to a Brain Health Academy control group in older adults with cognitive decline.

Study Rationale

The primary goal of this study is to refine and test the efficacy of the Brain Health Together program. Aim 1 involves using a human-centered design process to refine Brain Health Together through semi-structured interviews and iterative testing of prototypes with up to 20 individuals with cognitive decline. Aim 2 involves testing the hypothesis that cognitive function and dementia risk improve more over 12 weeks in the Brain Health Together group than the Brain Health Academy comparison group. Aim 3 involves testing the hypothesis that participants randomized to receive ongoing classes and support will experience sustained cognitive and dementia risk benefits compared to those who only participate in the 12-week program, and that both intervention groups will experience maintenance of cognitive function and dementia risk reduction relative to the Brain Health Academy comparison group.

STUDY DESIGN

Aim 1. We will convene a Scientific Advisory Board (SAB) that will provide guidance on content and design for our comprehensive, evidence-based Brain Health Together program. Simultaneously, we will use a human-centered design (HCD) process to identify and integrate appropriate best-practices for behavior change support and coaching specifically for older adults with cognitive decline. The HCD process will involve conducting 45 to 60-minute semi-structured interviews with up to 20 people with cognitive decline, creating user profiles, generating ideas for health coaching approaches, and testing prototypes to obtain feedback and refine the program.

Aims 2 and 3. Study participants (216 older adults with cognitive decline) will be randomly assigned to one of three groups: Brain Health Academy, Brain Health Together, Maintaining

Brain Health Together. The **Brain Health Academy** group will review online content about brain health (1 hour, 2 days/week for 12 weeks) and will complete a brief survey after each module to assess compliance (30 hours total). The **Brain Health Together** group will participate in online, live-streaming, group-based Moving Together classes (1 hour/week); Brain Health education group classes (1 hour/week) and individual brain health coaching sessions (0.5 hours/week) for 12 weeks (30 hours total). The **Maintaining Brain Health Together** group will participate in the full Brain Health Together program (30 hours) for 12 weeks followed by weekly group classes and six individual coaching for an additional 12 weeks (additional 15 hours). Outcome measures will include online cognitive tests and surveys administered at baseline, 3 months and 6 months. The primary outcomes are 1) change in global cognitive function, which will be assessed using the validated Maintain Your Brain Online Cognitive Test Battery; and 2) change in dementia risk score, which will be assessed using the validated Australian National University Alzheimer's Disease Risk Index (ANU-ADRI). Secondary outcomes will include specific cognitive domains (e.g., complex attention, executive function, learning and memory) and individual dementia risk factors (e.g., social isolation, depression, physical activity). Adverse events will be assessed in all participants using monthly check-in surveys.

Setting

All study activities will be performed online or over the telephone. Research staff may be in offices on the UCSF campus or working remotely. Together Senior Health staff may be in their offices or working remotely. Research study participants will participate in classes remotely and complete surveys online or by telephone.

The UCSF team will oversee participant enrollment and collection of outcome data using REDCap and/or Qualtrics. Together Senior Health will oversee delivery of the intervention through their secure web-based platform. Some data may be transferred securely and stored in a project-specific, restricted-access UCSF Research folder. All identifiable data will be collected and stored off-site by the prime grant holder -- Together Senior Health -- or using UCSF systems (e.g., REDCap, Qualtrics).

Regulatory Review and Approval

All study procedures have been reviewed and approved by the Institutional Review Board (IRB) at UCSF, the Safety Officer (SO), and the NIA Program Officer (PO). The study will be registered on ClinicalTrials.gov. All study participants will review informed consent materials online and will sign electronically by typing their name into a designated field.

SELECTION AND ENROLLMENT OF PARTICIPANTS

Inclusion Criteria

Participants must meet all inclusion criteria to participate in this study.

- Age 55 to 85 years
- English-language fluency*
- Reside in the U.S.
- Cognitive decline, defined as either
    - Self-report of confusion or memory loss in the past 12 months that is happening more often or getting worse (SCD) OR
    - Physician diagnosis of MCI in the past 12 months;
- Want to make changes to improve brain health
- Have at least 2 brain health risk factors (e.g., low physical activity, low cognitive activity, difficulty sleeping, loneliness, overweight, unhealthy diet, depression, smoking, hypertension, diabetes, vision impairment, hearing impairment)
- Access to a laptop, desktop computer or iPad/tablet with a video camera and broadband internet
- Able to participate in online, live-streaming classes with two-way video

*English language fluency is necessary because we do not have the staffing or resources to offer the intervention or control group activities in other languages. For example, we do not have health coaches or movement instructors available to teach classes in languages other than English. We also are not budgeted to translate all online materials (screener, consent form, background survey, outcome measures, etc) into other languages, and study measures are not necessarily validated in other languages.

Exclusion Criteria

Candidates meeting any of the exclusion criteria will not be eligible to participate.

- Alzheimer's disease or dementia
- Major neurological disorder (e.g., Parkinson's disease, Multiple Sclerosis, Amytrophic Lateral Sclerosis)
- Schizophrenia or other psychotic disorder
- Autism or autism spectrum disorder
- Major mood or anxiety disorder that is not well-controlled (e.g., symptoms of depression or anxiety that made it hard to do daily tasks in past 6 months)
- Fracture of spine ("compression fracture") in the past 12 months
- Vertigo or severe dizziness in the past 12 months
- Severe vision or hearing impairment (e.g., unable to see and hear well enough to watch a movie on TV);
- Stroke or heart attack in the past 12 months

- Physical limitation that would restrict ability to participate (e.g., use wheelchair or walker to get around home, unable to stand up from sitting without assistance)
- Currently in another research study that could confound results of this study (e.g., drug study or other study to improve brain health)
- Previous participation in Moving Together or Brain Health Together
- Limited life expectancy (e.g., enrolled in hospice, undergoing cancer treatment)

Recruitment

As described in more detail in the recruitment section below, we will use a variety of strategies that we have used successfully in our prior studies to recruit study participants. These will include:

- recruiting UCSF patients using the Clinical and Translational Sciences Institute (CTSI) Participant Recruitment Program (PRP)
- listing on websites such as TogetherSeniorHealth.com, ClinicalTrials.gov, and Alzheimer's Association TrialMatch
- posting or advertising in online forums for people concerned about cognitive decline
- posting or advertising on social media platforms such as Facebook and Twitter
- targeted advertising (e.g., based on Google searches);
- direct mailing/emailing to targeted groups (e.g., purchasing distribution lists);
- giving talks to targeted audiences (e.g., assisted living or senior communities);
- word-of-mouth campaigns with current and former clients;
- contacting individuals who have given permission to be contacted for research studies;
- asking clinical colleagues to share recruitment materials with patients who might be interested; and
- asking stakeholders to share recruitment materials with their networks (e.g., Alzheimer's Association, Family Caregiver Alliance).

STUDY PROCEDURES

Schedule of Evaluations

Assessment	Screening	Consent	Background Info	Baseline (V1)	Monthly Check-Ins (C1,2,3)	3-Month Assessment (V2)	Monthly Check-Ins (C4,5,6)	6-Month Assessment (V3)
Eligibility Criteria	X							
Informed Consent		X						
Demographics, Medical History			X					
Cognitive Function				X		X		X
Dementia Risk (ANU-ADRI)				X		X		X

Assessment	Screening	Consent	Background Info	Baseline (V1)	Monthly Check-Ins (C1,2,3)	3-Month Assessment (V2)	Monthly Check-Ins (C4,5,6)	6-Month Assessment (V3)
Lifestyle Behaviors / Mediators				X		X		X
Adverse Events					X		X	
Experience / Satisfaction						X		X

Description of Evaluations

Screening

Individuals who are interested in participating in the study will contact us directly through our website or by email or telephone; we also may directly contact individuals who have previously given permission to be contacted about research studies. Interested participants will complete a questionnaire to assess eligibility. The eligibility questionnaire may be completed online or by phone or email.

Consent

Those who are eligible and interested will review an online consent form and will type their name and date to confirm their consent.

Background Information

After providing consent, participants will be asked to complete a brief background survey that includes questions about demographics (age, gender, sexual orientation, race/ethnicity, education, marital status, living situation), healthcare utilization (falls, hospitalizations, emergency department visits, other major health events), motivators and barriers, and readiness to change. The background survey may be completed online or by phone.

Baseline and Follow-Up Assessments

All participants will complete the assessments listed below at baseline (V1), 3 months (V2) and 6 months (V3).

Monthly Check-Ins

Participants will be asked to complete monthly check-in surveys throughout the 24-week study period. The goals of the check-ins are to: a) assess for adverse events, including hospitalizations, emergency department visits, and falls; b) assess for co-interventions that could impact our study outcomes; and c) maintain contact and interest. Check-ins may be performed by email, telephone, text, or online survey.

Experience and Satisfaction Surveys

All participants will be sent an experience and satisfaction survey after either withdrawal from the study or completion of the 3-month and 6-month assessment visits. The survey will ask participants to provide an overall rating of the program (e.g., poor, fair, good, or excellent) and likelihood of recommending to others (e.g., Net Promoter Score). Participants will be asked to rate program effectiveness for various outcomes (e.g., learning about brain health, behavior change to improve brain health) and what they learned. In addition, open-ended questions will ask about qualitative changes observed; what they liked most; and suggestions for improvement.

Changes in Other Dementia Risk Factors

In addition to the outcome measures described above, we will ask participants to describe any other changes they make during the study period related to dementia risk factors. This will include both structured and open-ended questions about the domains listed above.

Adverse events

We will monitor adverse events in all groups by administering brief, monthly check-in surveys that will ask about falls, hospitalizations, emergency department visits and other major health events.

Fidelity

All intervention-related activities will be automatically video-recorded for quality control and research purposes. In addition, interventionists will track attendance and fidelity to class elements in the research study database.

Outcome Measures

Co-Primary Outcomes

Global cognitive change

We will assess cognitive function at 0, 3 months, and 6 months. To facilitate comparison of results from this study with other similar ongoing studies, cognitive function will be assessed using the Maintain Your Brain (MYB) Online Cognitive Test Battery. This includes the following domains and tests: 1) Complex attention (Cogstate Detection and Cogstate Identification); 2) Executive function (Cogstate One Back, Cambridge Brain Sciences Spatial (Tokens) Search and Cambridge Brain Sciences Grammatical Reasoning); and 3) Learning and memory (Cogstate One Card Learning and Cambridge Brain Sciences Paired Associates). This battery has been successfully used online in MYB participants. Consistent with MYB's methods, individual test scores will be converted to standard scores (z scores) using the means and standard deviations (SDs) of the study population at baseline. Tests within each domain will be averaged to create domain scores, and the three domain scores will then be averaged to create a single

global composite score.

Dementia Risk Score

The Australian National University – Alzheimer's Disease Risk Index – Short Form (ANU-ADRI-SF) is a validated measure that combines validated component measures of individual dementia risk factors and also provides a summary dementia risk score. It includes items related to demographics (age, sex, education), obesity, diabetes, hypercholesterolemia, head injury, depression, physical activity, cognitive activity, social isolation, alcohol consumption, smoking, pesticide exposure, and fish intake.

Secondary Outcomes

Secondary outcomes are designed to enable us to examine the impact of Brain Health Together on specific cognitive and dementia risk factor domains and to explore potential mechanisms of action. We have selected brief, validated measures for each outcome domain.

Physical activity

The ANU-ADRI-SF assesses physical activity using the validated International Physical Activity Questionnaire short form. Participants are asked about time spent (days/week, minutes/day) doing vigorous physical activity, moderate physical activity, walking and sitting in the past 7 days, and responses are converted into metabolic equivalents per week.

Depression

The ANU-ADRI-SF assesses depressive symptoms using the validated 10-item version of the Center for Epidemiologic Studies-Depression Scale (CES-D). Participants are asked about feelings in the past week with response categories of 0 (<1/day), 1 (1-2 days), 2 (3-4 days) or 3 (5-7 days). Scores may range from 0 to 30, with higher scores indicating more depressive symptoms.

Loneliness / social isolation

We will measure loneliness / social isolation using the validated measure 3-item UCLA Loneliness Scale, which consists of 3 items (lack companionship, feel left out, feel isolated) that are rated as 1 (hardly ever), 2 (some of the time), or 3 (often). Scores may range from 3 to 9, with higher scores reflecting greater loneliness.

Diet

We will measure diet using the validated MIND diet score. The MIND diet is a hybrid of the Mediterranean and DASH (Dietary Approaches to Stop Hypertension) diets. It has 15 dietary components including 10 brain healthy foods (e.g., green leafy vegetables, berries) and 5 less healthy foods (e.g., red meat, fried/fast foods). The frequency of consumption for each item is scored as 0, 0.5 or 1, and the total MIND diet score is calculated by summing over the 15 components. Scores may range from 0 to 15, with higher scores reflecting better adherence to the MIND diet.

Obesity/weight

The ANU-ADRI-SF includes questions about self-reported height and weight, which will be used to calculate body mass index (BMI).

Sleep

We will measure sleep disturbance using the validated PROMIS Sleep Disturbance Short Form 4-item measure which asks about sleep quality and disturbance in the past 7 days on a 5-point Likert scale. Scores may range from 4 to 20 which higher scores indicating more sleep disturbance. In addition, we will include a single item from the Pittsburgh Sleep Quality Index on hours of sleep per night in the past month.

Self-efficacy for engaging in brain health activities

We adapted the validated Self-Efficacy for Managing Chronic Disease 6-item scale to measure self-efficacy for engaging in activities to support brain health. Each item is rated on an 11-point Likert scale from 0 (not at all confident) to 10 (totally confident). The score is the mean of the 6 items with higher scores reflecting higher self-efficacy.

Cognitive activity

We will measure engagement in cognitive stimulating activities using a validated measure such as the Cognitive Activity Questionnaire (CAQ). The CAQ includes 11 items that ask how often individuals engage in various cognitive activities such as reading or playing games on a 6-point Likert scale (once a month/never to every day).

Alcohol

We will measure alcohol consumption using 2 items in the ANU-ADRI that ask about frequency and amount of alcohol consumption.

Smoking

We will assess smoking with standard questions about current tobacco use ever and during the past 7 days.

Emotional well-being

We will measure well-being using the validated Neuro-QOL v1.0 Positive Affect and Well-Being Short Form, which includes 9 items (e.g. sense of well-being, feeling hopeful, life was satisfying, etc.) with 5-point responses from never (1) to always (5). Scores may range from 9 to 45, with higher scores reflecting greater feelings of well-being.

Mind-body awareness

We will measure mind-body awareness using the self-regulation subscale of the validated Multidimensional Assessment of Interoceptive Awareness version 2 (MAIA-2). The self-

regulation sub-scale includes 4 items rated on a six-point Likert scale (0/never to 5/always) about the ability to regulate distress by paying attention to bodily sensations (e.g., "When I feel overwhelmed I can find a calm place inside.") Scores reflect the mean of responses (range 0 to 5), with higher scores indicating greater self-regulation.

Global quality of life

We will measure global quality of life using the validated PROMIS Scale v1.2 - Global Health. This scale includes 10 items rated on a 5-point Likert scale from 1 (poor) to 5 (excellent) and includes questions about overall self-rated health, overall quality of life, physical health, mental health, social relationships, fatigue and pain.

RANDOMIZATION AND BLINDING

Randomization

Based on the recommendation of our biostatistician, Dr. Fei Jiang, we will enroll the first cohort in a block of 24 (8 per group) and assess for imbalances in baseline characteristics due to chance. If there are any large imbalances evaluated by examining significance in the mean differences using the student t-test for continuous covariates and the Fisher exact test for categorical covariates, Dr. Jiang will implement an adaptive randomization process to ensure that the groups are balanced at the end of the study. The same assessment and adjustment of enrollment will be conducted after the 2nd and 3rd cohorts. No endpoints will be assessed for these interim looks.

Blinding

Individuals who enroll study participants or collect or analyze outcome data will be unaware of the randomization sequence and blinded to group assignment. Every effort will be made to ensure that blinding is maintained including:

- Maintaining the group assignment list separately from other study documentation.
- Having outcomes assessors remind study participants not to discuss any aspect of the study or ask any questions related to the study prior to scheduling or performing assessments.
- Randomly labeling intervention arms as Group A and Group B for the study statistician.
- Excluding assessors from staff meetings that discuss details of the intervention.
- Restricting access to the intervention section of the database to authorized personnel.

If unblinding occurs, the following will be recorded:

- The ID(s) of the unblinded participant
- The reason for unblinding
- The study staff person responsible for unblinding
- A list of person(s) who have been unblinded

Orientation

After participants have completed baseline assessments and been randomized, an intervention team member will schedule a video-conference call to confirm their ability to participate in online, live-streaming classes with two-way video (final eligibility criteria). If eligibility is confirmed, the intervention team member will let them know what group they have been assigned to, answer questions, and orient them to their assigned activities.

STUDY INTERVENTIONS

Schedule of Intervention Procedures

After randomization and orientation, each group will engage in their assigned intervention activities. Over the first 12 weeks, all three groups will be exposed to 2.5 hours of brain health content each week (30 hours total). In week 13, we will re-administer cognitive tests and risk factor surveys and will collect evaluation data. In weeks 14 to 25, the Maintaining Brain Health Together group will be exposed to an additional 15 hours of brain health content to support maintenance of improvement achieved during the first 12 weeks. In week 26, the cognitive tests and risk factor surveys will be repeated, and a final evaluation survey will be administered.

Intervention	Weeks 1-12 (30 hours)	Weeks 14-25 (15 hours)
Brain Health Academy	Expert videos and surveys, 2/week	
Brain Health Together	Moving Together, 1/week Brain Health education, 1/week Individual coaching, 1/week	
Maintaining Brain Health Together	Moving Together, 1/week Brain Health education, 1/week Individual coaching, 1/week	Moving Together, 1/two weeks Brain Health education, 1/two weeks Individual coaching, 1/two weeks

Description of Intervention Procedures

Brain Health Academy (Control) Group

Materials for the Brain Health Academy control group were developed for another study and include 24 1-hour videos related to aging and brain health. Participants will take a brief survey after each session to assess their compliance (total: 30 hours).

Brain Health Together

Detailed content for Brain Health Together was developed and refined during Aim 1. Content includes Moving Together classes (1 hour/week), Brain Health Education classes (1 hour/week) and Individual Brain Health Coaching sessions (0.5 hours/week) for 12 weeks (total: 30 hours).

Moving Together classes

Each class begins with greetings and a brief check-in, to ensure that everyone feels welcomed and acknowledged. Next participants engage in seated, mindful body awareness exercises that involve massaging or tapping all major body parts (including hands, arms, thighs, calves, ankles/feet, belly, back, neck and head) and breathing exercises. The goal of these movement sequences is to bring participants into awareness of their bodies and breathing in the present moment, and to create a calming ritual that is repeated at the beginning and end of each class. Next participants engage in a series of seated and/or standing exercises that focus on increasing capacity to perform movements that are most needed for daily function such as increasing range of motion, transitioning smoothly between sitting and standing, and balancing while standing and moving. Movement sequences build slowly in complexity over the course of the program, depending on the functional ability levels of each class. Mindful rests are incorporated throughout the program, and personally meaningful music may be included. Each class ends with a repetition of the body awareness and breathing exercises and an invitation for participants to share what makes them feel grateful, appreciative, or happy. The goal of this section of the program is to facilitate positive emotions and feelings of social connection.

Brain Health Education classes

The curriculum includes an overview brain changes that occur with age; differences between "normal" aged-related decline and dementia; the impact of lifestyle behaviors and medical conditions on brain health and dementia risk; information about how to change risky behaviors by setting SMART (specific, measurable, achievable, relevant, time-limited) goals; and detailed information about specific risk factors including physical activity, social connection, sleep, diet/weight, depression, hypertension, diabetes, hearing, and vision. Classes include brief expert videos and a facilitated discussion with a brain health coach.

Individual Brain Health Coaching sessions

Before the first individual coaching session, participants complete a brief survey about lifestyle behaviors and medical conditions linked to brain health that is used to create a personalized brain health report that identifies areas with low, moderate and high opportunities for change. Coaches meet with participants for 30 minutes a week to review their brain health report and help them set SMART goals to address the specific risk factors they are interested in working on. Each week, they discuss their progress, revise the goal if needed, celebrate successes, and troubleshoot set-backs.

Maintaining Brain Health Together

Participants assigned to this group will receive the full Brain Health Together program over the first 12 weeks (30 hours). In addition, they will be offered a maintenance program that will include weekly classes (e.g., alternating Moving Together and Brain Health Education) as well as six additional individual coaching sessions (e.g., weeks 1, 2, 4, 6, 8, 12) for another 12 weeks (additional 15 hours). This design will enable us to determine whether maintenance classes and support help to sustain any benefits observed over the first 12 weeks.

SAFETY ASSESSMENTS

Potential Risks and Benefits for Participants Potential Risks

Potential Risks

- Negative feelings such as anxiety, frustration or sadness related to study procedures such as tests of memory and thinking, questionnaires, or learning about brain health risk factors.
- Physical discomfort, pain or injury from engaging in new physical activities.
- Frustration using technology to access the online classes.
- Concern about loss of privacy related to interacting with research team members or other study participants online or release of research data outside the research team.

Potential Benefits

- Study participants may benefit directly by experiencing improvements in cognitive function, physical function, emotional well-being, or social connection.
- Study activities may help participants reduce their risk of developing dementia.
- Study participants may feel that they are helping others by contributing to knowledge about programs for older adults with cognitive decline.

Adverse Events (AEs) and Serious Adverse Events (SAEs)

Study participants will be monitored for adverse events (AEs) during livestreaming classes and health coaching sessions by Brain Health Together intervention team members. In addition, we will elicit information about AEs including falls, emergency visits and hospitalizations in all study participants as part of monthly check-ins. All AEs will be tracked in a research study database that will include:

- date of occurrence
- date of first awareness
- brief description of AE
- classification of AE severity (mild, moderate, severe)
- determination of whether the event was study-related (definitely, possibly, unrelated)
- determination of whether the event was serious and/or unexpected
- description of actions taken

Definitions are provided below.

Adverse event (AE)
Any untoward or unfavorable medical occurrence in a human study participant, including any abnormal sign (e.g., abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participants' involvement in the research, whether or not considered related to participation in the research.

Serious adverse events (SAEs):

Any AE that:

- Results in death
- Is life-threatening, or places the participant at immediate risk of death from the event as it occurred
- Requires or prolongs hospitalization
- Causes persistent or significant disability or incapacity
- Requires medical or surgical intervention to prevent an outcome listed above
- Changes the risk/benefit ratio

Severity Classification

- **Mild:** Awareness of signs or symptoms, but easily tolerated and are of minor irritant type causing no loss of time from normal activities. Symptoms do not require therapy or a medical evaluation; signs and symptoms are transient.
- **Moderate:** Events introduce a low level of inconvenience or concern to the participant and may interfere with daily activities, but are usually improved by simple therapeutic measures; moderate experiences may cause some interference with functioning
- **Severe:** Events interrupt the participant's normal daily activities and generally require systemic drug therapy or other treatment; they are usually incapacitating

Severity is not synonymous with seriousness. A severe rash is not likely to be an SAE. Likewise, a severe headache is not necessarily an SAE. However, mild chest pain may result in a day's hospitalization and thus is an SAE.

Determination of Relatedness

- **Definitely Related:** A n AE is definitely related to study participation if it is clear that the event was caused by study participation. A definitely related event has a strong temporal relationship, and an alternative cause is unlikely.
- **Possibly Related:** An AE is possibly related when there is a reasonable possibility that the event might have been caused by study participation or there is uncertainty about the relationship. For example, the AE may have a strong temporal relationship, but a potential alternative cause may be present. In other circumstances, there may be significant uncertainty about the cause of the event, or a possible relationship to study participation cannot reasonably be ruled out.
- **Unrelated:** The cause of the AE is known, and the event is in no way related to any aspect of study participation. If there is any uncertainty regarding AE causality, then the event should be assessed as possibly related to research participation. Often, the cause of an unrelated AE is disease progression.

Unanticipated Problems (UPs)

Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected, in terms of nature, severity, or frequency given (a) the

research procedures described in the study protocol and informed consent documents and (b) the characteristics of the study population
- Definitely or possibly related to participation in the research
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized

Expectedness
Because the study population includes older adults with cognitive decline and other underlying health conditions, expected SAEs include:
- Death due to underlying health condition
- Life-threatening event due to underlying health condition
- Hospitalization for underlying health condition or illnesses unrelated to the study (such as infectious diseases)
- Decline in physical or cognitive function consistent with disease progression

Reporting Procedures

All AEs that are both serious (SAE) and unexpected will be reported to the NIA Program Officer (PO), the Safety Officer (SO), and the Institutional Review Board (IRB) at the University of California, San Francisco (UCSF) within 48 hours of PI awareness.

All other AEs will be reported per UCSF IRB policies. In addition, they will be reported to the NIA PO and SO at the frequency requested by NIA and/or by the SO, or annually at a minimum. Given the relatively low risk of this study and the high likelihood that some study participants may die due to causes unrelated to this study, deaths that are definitely not study-related will be reported with other AEs

Data and Safety Monitoring

The multiple PIs (Cynthia Benjamin and Dr. Deborah Barnes) will share responsibility for overseeing participant safety on a daily basis. Dr. Barnes will be responsible for tracking AEs, SAEs and UPs and for preparing reports for the UCSF IRB, NIA PO and SO. The SO will act in an advisory capacity to the NIA PO to monitor participant safety and evaluate the progress of the study.

Protocol Violations and Research-Related Incidents

The University of California, San Francisco (UCSF) Institutional Review Board (IRB) is serving as the IRB of record for this study. Consistent with current UCSF guidelines, we will track all protocol violations and research-related incidents.

Protocol Violations: Any unapproved changes, departures or deviations from the study design or procedures of the research project that are under the investigator's control and have not been reviewed and approved by the IRB.

Major (Reportable) Protocol Violations: Any protocol violations that affect the participant's rights, safety, or well-being, or the completeness, accuracy and reliability of the study data. Criteria for defining major violations include any of the following:

- The violation has harmed, or posed a significant or substantive risk of harm, to the research participant.
- The violation resulted in a change to the participant's clinical or emotional condition or status.
- The violation has damaged the completeness or soundness of the data collected for the study.
- The violation is evidence of willful or knowing misconduct on the part of the investigator(s).
- The violation involves serious or continuing non-compliance with federal, state or local guidelines.

Minor (Non-Reportable) Protocol Deviations: Any protocol violations that do not have a major impact on participant's rights, safety, or well-being or the completeness, accuracy, and reliability of the study data. For example:

- A study participant skips a question on a survey, and the research team fails to check the survey for completeness.

Major (Reportable) Incidents: Any problematic or unanticipated events involving the conduct of the study or study participants that affect the rights, safety, or well-being of participants or others, or the completeness, accuracy and reliability of the study data. Examples include:

- Significant complaint or concern received from a potential or enrolled study participant.
- Inappropriate behavior of study participants and/or research personnel.
- Problems during study recruitment or the informed consent process.
- Problems with the study design in which a majority of participants have difficulty adhering to the study schedule of procedures.
- Potential breach of study participant's privacy or confidentiality (must be reported within 48 hours of PI awareness).
- Withdrawal or significant reduction in resources necessary to safely and adequately conduct study activities.
- Changes to the protocol to eliminate or reduce an apparent immediate hazard to the safety research participants or others.

Minor (Non-Reportable) Incidents: Any events involving the conduct of the study or study participants that are not problematic and do not involve significant potential to harm participants or others. Example:

- Receipt of a minor complaint from a study participant that is resolved by the research team.

Reporting of Protocol Violations and Research-Related Incidents

- All major protocol violations and major incidents will be reported to the UCSF IRB within 10 working days, and a copy of the report will be sent immediately to the NIA PO and SO.
- Any breach of study participant's privacy or confidentiality will be reported to the UCSF IRB within 48 hours, and a copy of the report will be sent immediately to the NIA PO and SO.
- All minor protocol violations and minor incidents will be tracked in the research database and available for review by the NIA PO and SO if requested.

INTERVENTION DISCONTINUATION

Study participants may withdraw voluntarily from participation in the study at any time and for any reason. Participants will continue to be followed, with their permission, even if the study intervention is discontinued. Follow-up assessment visits will continue to be offered if the participant is agreeable.

STATISTICAL CONSIDERATIONS

General Design Issues

The primary goals of this study are to perform a randomized, controlled trial to determine whether 1) Brain Health Together improves cognitive function or reduces dementia risk over 12 weeks in people with cognitive decline (Milestone 2a), and 2) benefits observed are sustained in those who received ongoing support and maintenance for an additional 12 weeks (Milestone 3a).

Sample Size and Power

To be conservative, power estimates were performed based on a repeated measures analysis of variance analysis using STATA/SE V16.1 with two-sided alpha=0.05. For Milestone 2b, we will have two groups (n1=144; n2=72: total N=216) and two time points (0 and 12 weeks), which will provide 80% power to detect a minimum standardized effect size (ES) of 0.19. For Milestone 3a, we will have three groups (n=72/group) and three time points (0, 12, 24), which will provide 80% power to detect a difference between the groups of 0.21.

Data Analyses

We will examine distributions of all variables to assess for missingness, outlier values or skewed distributions using standard techniques (e.g., means, medians, standard deviations, ranges, tables, graphs). We will assess balance between the three intervention groups by comparing baseline characteristics. Our primary analytic approach will be linear mixed models (LMMs) with terms

included for group, time, and group*time interaction with random intercepts and slopes. This approach will enable efficient estimation of change in primary outcomes over time while including all participants randomized (intent-to-treat) and accounting for baseline values and correlations between repeated measures over time.

Milestone 2b will test the hypothesis that cognitive function improves more from 0 to 12 weeks in the Brain Health Together group compared to the Brain Health Academy control group by determining whether there is a significant group*time interaction for our co-primary outcomes of change in global cognitive function and change in dementia risk. The two Brain Health Together intervention groups will be combined to maximize power.

Milestone 3a will test the hypothesis that participants randomized to receive ongoing classes and support will experience sustained cognitive benefits compared to those who only participate in the 12-week program, and that both intervention groups will experience maintenance of cognitive function relative to the comparison group, by testing the significance of the group*time interaction over all assessment visits (0, 12, and 24). Time will be modeled as categorical to allow for nonlinear relationships over time.

Milestone 3b will involve exploratory analyses to assess whether changes in cognitive function may be mediated by behavioral changes in dementia risk factors. These will involve using PROCESS to assess for indirect effects (mediation) and contingent effects (moderation) based on baseline characteristics of our study participants (e.g., age, sex, race/ethnicity) and changes in secondary outcomes (e.g., well-being, isolation, self-regulation). Exploratory analyses also will examine the impact of "dose" (based on class attendance), and sensitivity analyses will be restricted to those with high compliance (≥80% class attendance) or who have higher risk factor levels at baseline (i.e., have more room for improvement). We will use multiple imputation to examine the impact of missing data and will adjust for covariates that may differ between groups by chance.

Interim Analyses and Stopping Rules

No interim data analyses are planned. The SO or NIA PO may request that an interim analysis be performed at their discretion. If interim analyses are requested, criteria for stopping the study will be clearly defined in advance by SO and NIA PO.

DATA COLLECTION AND QUALITY ASSURANCE

Data Collection Forms

Our primary approach to data collection will be online surveys administered through REDCap or Qualtrics, with data stored on the UCSF network (e.g., in REDCap or project-specific RAE folders). If participants prefer, questionnaires may also be completed by telephone or email, or paper forms may be sent through the mail.

Data in the Brain Health Together intervention group will be collected on Together Senior Health's secure, proprietary platform. This will include: information about dementia risk factors (to generate a personalized Brain Health Report); video recordings of group classes (for quality control purposes); and tools for tracking attendance, adherence, and goals. Surveys will be administered using HubSpot, which is hosted in a secure virtual private cloud on Amazon Web Services and protected by a Web Application Firewall.

Data Management

UCSF is responsible for collection and secure storage of all research data. A REDCap database will be created to enable research staff to track enrollment of study participants, collection of outcome data, and delivery of the intervention. Access to the database will be restricted to the research team. In addition, the enrollment and assessment team will not be able to see or access the intervention section of the database, and the intervention team will have read access only to the enrollment and assessment section of the database. The outcomes section of the database will not include any protected health information (PHI) and will identify participants by unique personal identification numbers (PIDNs) only.

Sharing permissions will be configured to ensure files containing PHI can only be accessed by authorized individuals. Two-step verification will be used as an additional safeguard against unauthorized access. Permissions will be updated when personnel roles change and they no longer need access to PHI or when they leave the research team.

Quality Assurance

Training

New research team members will be trained by having them first review current versions of the Study Protocol and Manual of Operating Procedures (MOP). They will observe senior team members engaging with study participants and will then practice with senior team members through role play. Senior team members will then observe them interacting with study participants and provide feedback until they achieve competency. Competency will be reassessed annually or more frequently if needed.

Any documents containing personally identifying information (e.g., names and contact information for potential study participants) will be sent by encrypted email.

All study staff will be trained by the same lead person in the same manner. Dr. Barnes will train staff in administering assessments. Jennifer Lee will train Moving Together instructors. Trish Turo will train Brain Health Together instructors. Each lead will also monitor performance and provide feedback to ensure consistency.

Monitoring

The database manager, supervised by the PIs, will enact and monitor data quality control checks. Data quality control checks will be included to identify potential data anomalies such as:

- Missing data or forms
- Out-of-range or erroneous data
- Inconsistent and illogical dates over time
- Data inconsistency across forms and visits
- Not completing all fields of a "completed form" or no reason for missing data is provided

The data entry forms will include logic and range checks to minimize the possibility of missing or invalid entries. Calculations will be automated whenever possible.

At the end of each outcome assessment, research staff will review all questionnaires to check for incomplete data and logical inconsistencies. Whenever possible, errors will be identified and corrected in the moment. If incomplete data or logical inconsistencies are discovered later, research staff may follow up with study participants to clarify if possible. Otherwise, those items will be entered as missing.

PARTICIPANT RIGHTS AND CONFIDENTIALITY

Institutional Review Board (IRB) Review

The UCSF IRB will serve as the IRB of record for this study. They will review and approve the initial Study Application, on which this Study Protocol is based. In addition, they will review and approve all patient-facing materials and scripts such as recruitment materials, telephone screeners, informed consent documents, and intervention-related scripts. All modifications of these documents will be reviewed and approved by the IRB before being used with study participants.

Informed Consent Forms

All study participants will review an online informed consent document and will indicate their consent by typing their first and last name and the date at the end of the form. The consent form will include all standard elements of consent such as the purpose of the study, the study procedures, and the risks and benefits of participation. Participants may download a copy of the consent form or may request that a copy be sent to them by email or mail.

Participant Confidentiality

All research team members will complete mandatory trainings in human subjects research and confidentiality required by the UCSF IRB, including training to ensure Health Insurance Portability and Accountability Act (HIPAA) compliance. All forms and study procedures are reviewed by UCSF's IRB for compliance with HIPAA and human subjects protections. Any data that will be accessed or disclosed outside the research team will meet HIPAA requirements,

through the use of business associate agreements, data use agreements, de-identification, and/or accounting of disclosures, as applicable.

Research team members will be required to use computers that require passwords and DUO authentication to access the research database and participant PHI.

Study Discontinuation

The study may be discontinued at any time by the IRB, the NIA, the SO, or other government agencies as part of their duties to ensure that research participants are protected.

INTELLECTUAL PROPERTY AND DATA SHARING

Material Transfer Agreement (MTA)

Together Senior Health, Inc., will enter into a Material Transfer Agreement (MTA) with UCSF that will govern sharing of research data between these organizations.

PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by the policies and procedures of UCSF and NIA. Results of this study will be disseminated in a variety of ways. We will present results at major conferences such as the American Geriatrics Society, Gerontological Society of America, American Academy of Neurology, or Alzheimer's Association International Conference. We will publish all key findings in peer-reviewed journals and anticipate multiple publications related to our Specific Aims and Milestones.

We will also provide updates to the public through our website, e-newsletters, and on social media channels such as LinkedIn, Instagram, Facebook, and Twitter. In addition, we will share periodic results-to-date with study participants.

Finally, if Brain Health Together proves to be effective for improving cognitive function or reducing dementia risk factors in people with cognitive decline, then we will seek to disseminate our findings more broadly to media outlets, investors, clinical partners, and clients through targeted marketing and advertising.

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