scientific reports

Check for updates

OPEN

Testing the iMplementation Framework fOr behavioral and LIfestyLe interventions in AlZheimer's DiseasE (MOBILIZE) via the ACT randomized controlled trial

Dereck L. Salisbury[1], F. Vankee Lin[2]✉ & Fang Yu[3]✉

Implementing multi-site behavioral intervention trials to study Alzheimer's disease (AD) has many unique challenges, leading to substantial variations in delivered intervention doses and cognitive findings. These issues can be addressed by the IMplementation Framework fOr Behavioral and LIfestyLe Interventions In AlZheimer's DiseasE (MOBILIZE), which was developed to guide the design and implementation of behavioral interventions in AD. Building on the person-centered principle, MOBILIZE includes three implementation outcomes with corresponding team processes: (1) screening (processes), (2) intervention adherence (processes), and (3) safety (processes). This study systematically evaluated MOBILIZE implementation outcomes of the 3-site *a*erobic exercise and *c*ognitive *t*raining (ACT) Trial (recruitment started on 4/1/2018 and last follow-up on 7/17/2024). Outcomes included time in screening phases, intervention adherence (attendance and intervention dose adherence, and safety [adverse events]). Sample ($n = 146$) was 73.8 ± 5.7 years in age and 23.4 ± 2.1 on Montreal Cognitive Assessment score, with 48.0% female and 91.8% White. The median days of screening-to-enrollment averaged 98 days. Attendance was 76.7 ± 28.6%. Adherence to 100% exercise session dose and 100% cognitive session dose was 71.7 ± 30.8% and 51.5 ± 26.2%, respectively. There were 10 study-related adverse events. MOBILIZE helped the ACT Trial achieve high intervention attendance and safety and may be important for early-stage trials in AD.

Trial registration **The ACT Trial is registered at clinicaltrials.gov (NCT03313895). Registered 15 July 2017, https://clinicaltrials.gov/study/NCT03313895.**

Keywords Exercise training, Cognitive training, Mild cognitive impairment, Clinical trials

In 2024, Alzheimer's disease (AD) dementia affected nearly 7 million Americans and cost $360 billion; these estimates are projected to increase to 13 million Americans and $1 trillion by 2050[1]. Preventative approaches to address AD dementia's substantial impacts remains a public health priority. The prodromal stage of AD dementia is mild cognitive impairment (MCI), which represents a critical opportunity for AD dementia prevention. MCI incidences per 1,000 person-years range from 22.5 to 60.1, and increase per decade of life after the age of 65 years[2].

In recent years, there has been growing interest in behavioral and lifestyle interventions, such as aerobic exercise and cognitive training[3], for preventing AD and cognitive decline. Aerobic exercise can positively affect cognition and brain integrity through enhancing aerobic fitness and peripheral neurotrophic factors, as well as modify AD risk factors[5–7]. Cognitive training is thought to broadly target cognitive processes and enhance brain function[7–10]. As both intervention modalities affect brain integrity and cognition via distinct mechanisms, their

[1]University of Minnesota School of Nursing, Minneapolis, MN, USA. [2]Department of Psychiatry and Behavioral Sciences, Stanford University, Palo Alto, CA, USA. [3]Arizona State University Edson College of Nursing and Health Innovation, 500 N 3rd St, Mail Code 3020, Phoenix, AZ 85004, USA. ✉email: Vankee_Lin@stanford.edu; Fang.Yu.2@asu.edu

use in combination may provide a synergistic effect for preventing AD[11]. But a single intervention or combined interventions had mixed findings for cognitive outcomes, attributable to major implementation challenges, such as recruitment, retention, adherence, and safety[13–16], particularly in early-phase or early-stage clinical trials (i.e., Stage I-III by the NIH Stage Model[16]), limiting trial advancement to later phases or stages.

To overcome the implementation challenges in testing early-stage behavioral and lifestyle intervention trials, we have developed the I**M**plementation Framework f**O**r **B**ehavioral and L**I**festy**L**e Interventions **I**n Al**Z**heimer's Diseas**E** (MOBILIZE) (Fig. 1) over 6 early-stage clinical trials[11,17–21]. Building upon the person-centered care principle, MOBILIZE emphasizes three implementation outcomes: (1) screening, (2) intervention adherence, and (3) safety. For each implementation outcome, MOBILIZE highlights corresponding standardized team processes (Fig. 1). In addition, our framework recognizes the dynamic, interactive, and circular nature among the implementation outcomes and team processes. For example, the team process "set up reminders" can influence both screening and intervention adherence. Intervention adherence and safety can be influenced collectively by the processes "assess safety" and "individualize intervention dose."

Because most known implementation frameworks are used to serve the late-phase or late-stage studies (e.g., RE-AIM or CFIR[22]), MOBILIZE uniquely focuses on early-phase and early-stage (Stage I-III) clinical trials to ensure their internal validity, which is particularly important for complex, time-consuming, multi-modality, and/or multi-site studies of behavioral and lifestyle interventions. The purposes of this paper is to (1) systematically evaluate MOBILIZE implementation outcomes of the *a*erobic exercise and *c*ognitive *t*raining (ACT) trial, (2) examine implementation consistency across sites, and (3) test sex and race influences on implementation consistency.

Methods

Design

The ACT Trial was a Phase II and Stage II, single-blinded randomized controlled trial with three geographically diverse sites (Midwest, Southwest, and East Coast) and used a 2×2 factorial design[11]. Participants were randomized to one of four arms with equal allocation for six months (ACT, cycling only, cognitive training only, or attention control within site) and then followed for 12 months. Randomization was performed by a study statistician and was stratified by site (University of Minnesota [UMN] and University of Rochester [UR]) and age (<75 and ≥ 75 years), using random permuted blocks of 4 and 8 participants. All participants signed an informed consent form to participate in the study[11]. All outcome assessors and study investigators were blinded. Data collectors were not involved in the delivery of the intervention and did not participate in trainings for intervention implementation, while study participants were instructed not to reveal details of their intervention during outcome visits. The study was approved by the Institutional Review Board (IRB) at each site: IRB# STUDY00001135 on 8/23/2017 at UMN, STUDY00001484 on 2/19/2018 at UR, and WCG IRB #1305160 & IRB#STUDY00013092 on 04/21/2021 at, and Arizona State University [ASU]). The ACT Trial was conducted in accordance with the Declaration of Helsinki. This trial was registered at Clinicaltrials.gov (NCT03313895) on 10/18/2017; details of the trial protocol were previously published[11].

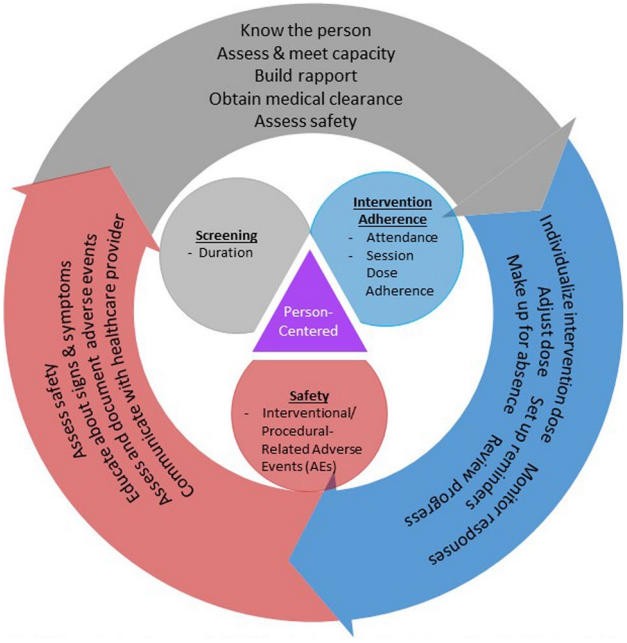

Fig. 1. I**M**plementation Framework f**O**r **B**ehavioral and L**I**festy**L**e Interventions **I**n Al**Z**heimer's Diseas**E** (MOBILIZE).

Setting

All screenings and data collections (4/1/2018-7/17/2024) were performed on each university campus. Prior to the pandemic in March 2020, all intervention sessions were supervised in-person at YMCA gyms or senior community centers. During the pandemic (March 2020-November 2020), interventions were delivered via video, using a synchronous, audiovisual telerehabilitation format (Zoom®). Post-pandemic, intervention sessions continued in-person, over telerehabilitation, or in a hybrid format.

Sample

Older adults 65 + years old who were English-speaking, community-dwelling, and did not have dementia were eligible for the study if they met criteria for a clinical diagnosis of aMCI according to 2011 diagnostic criteria. This criteria includes the following: (1) Montreal Cognitive Assessment (MoCA) scores 18–26, (2) memory deficits on the Rey Auditory Verbal Learning Test (RAVLT) criteria of at least 1 standard deviation below age- and/or education corrected population norms, (3) preserved activities of daily living (Activities of Daily Living-Prevention Instrument [ADL-PI] score < 30), and (4) no dementia[11]. Individuals were excluded who had psychiatric disorders (e.g., major depressive disorder), alcohol or chemical dependency, or neurologic disorders (e.g., Parkinson's disease) that were likely causative of the aMCI. Additional exclusionary criteria included exercise contraindications and abnormal findings from the magnetic resonance imaging (MRI)[11].

Recruitment

The ACT Trial used a comprehensive multi-channel recruitment approach, including presentations to community partners (e.g., YMCAs), fliers and brochures, websites, social media, advertisement, exhibits, registries, listservs, referrals, and other online tools. Fliers and brochures were placed in community centers, clinics, libraries, and fitness and rehabilitation facilities. Online tools included the use of eLetters that were sent to persons with a clinical aMCI diagnosis who had opted in to research contact within their electronic health record.

Implementation overview

Based on the team processes of MOBILIZE, we developed a study protocol and its accompanying standard operating procedure (SOP) for screening, intervention delivery, safety, and data collection for use by all sites. Staff were trained using these materials through the initial onboard training, semi-annual training, and quarterly booster training. In addition, weekly interventionist meetings and monthly cross-site team meetings focused on impromptu training to ensure compliance. For this paper, team processes that function in multiple outcomes of MOBILIZE are discussed according to the logical sequence of the study procedure for simplicity. For example, two team processes for safety that started during screening (obtain medical clearance and assess safety) were discussed under "Screening."

Screening (minimize time in screening phase)

A thorough but efficient and timely screening process is important to attenuate change in interest regarding study participation. Five team processes for screening were implemented (Fig. 1) to balance a thorough but efficient process.

Know the person (screening 1–4 [S1-S4])

Participants were screened for eligibility and exercise safety using a four-step procedure: a phone interview (screening 1 [S1]), an in-person interview with consenting (screening 2 [S2]), primary-care provider clearance, and cardiopulmonary exercise test (CPET) (screening 3 [S3]) and MRI (screening 4 [S4]). During the 20–30 min S1, participants provided answers to questions directed at health history related to exercise and MRI risk and history of cognitive impairment.

Assess and meet capacity (S2-S3)

During the S2 phase (1.5–2 h), informed consent was obtained. Additionally, study staff administered instruments to (a) assess clinical diagnosis of aMCI, (b) conduct a focused physical assessment, and (c) complete MRI safety checklist. Staff interacted with potential participants based on a capacity assessment in the previous step(s) and identified capacity barriers to address. Staff communicated at a person's communication level and arranged transportation for study activities as needed. During the S2 phase, study staff ensured participants understood the time demands of the study, addressed any questions or concerns the participant had regarding the study and aMCI, and inquired about previous experiences with research and lifestyle interventions. Participants gave verbal consent at the beginning of each encounter and formal written consent at 12 and 18 months.

Build rapport

Rapport was built from the first encounter and solidified over the screening steps as staff got to know the potential participants over time. Flexibility was given to accommodate participant's preference for intervention sessions and locations, and staff worked with participants' schedules and needs for vacations and time off.

Obtain medical clearance

Following the S2 and prior to scheduling the CPET, clearance for study participation from each participants' primary-care provider was sought. Faxes were sent, which contained a study synopsis and a brief checklist regarding ability to participate in a supervised exercise program and a 3T MRI. Follow-up calls were made to ensure receipt of faxes and on a weekly basis for status update as needed.

Assess safety

During the S2 and S3 phases, study staff administered a comprehensive health-history questionnaire that focused on diagnoses and symptoms pertaining to cardiovascular, renal, metabolic, and pulmonary health. Summaries from the questionnaire were subsequently generated for the exercise physiologist to evaluate for potential contraindications to exercise prior to scheduling the CPET. The medically supervised S3 CPETs with 12-lead ECG were conducted as previously discussed[23], with the first goal of excluding participants with latent cardiac ischemia, serious arrhythmia, or other exercise contraindications. Stage measurements of heart rate and blood pressure allowed for comprehensive monitoring of hemodynamic response to exercise stimuli. Results from the CPET also provided information (symptoms to watch for) for the study interventionists when later creating the individualized exercise prescriptions. For instance, the study staff informed the study exercise physiologist orthopedic concerns in S2 and/or joint discomfort in S3 to receive instructions on how to modify the exercise prescription and delivery to minimize adverse symptoms during intervention sessions. The CPET allowed for study investigators ability to analyze baseline aerobic fitness and limitations to cycling performance, providing information about the participants' abilities to successfully participate in the intervention phase. Screening MRIs (S4) were implemented to search for any clinically significant brain abnormalities that would interfere with a research definition of aMCI, including normal pressure hydrocephalus, brain tumor, subdural hematoma, significant post-traumatic encephalomalacia, or one or more large hemispheric infarctions.

Intervention adherence (maximize attendance and session dose adherence)

Following randomization, participants completed 1 of 4 assigned activities (ACT, cycling only, speed of processing [SOP] training only, or attention control). Each participant was encouraged to attend three supervised sessions weekly for 6 months (72 total sessions). Because poor adherence to intervention can affect efficacy-related outcomes, team processes for exercise delivery (Fig. 1) were implemented and operationalized as follows.

Individualized intervention dose

Briefly, cycling only was performed on recumbent cycle ergometers at moderate intensity (heart rate reserve [HRR] 50–60% or rating of perceived exertion [RPE] 11–12) with a session length of 30 min. Exercise was gradually progressed to achieve moderate-vigorous intensity (HRR 65–75% or RPE 13–15) for 50 min by week 8. Session lengths did not include the 5-minute warm-up and 5-minute cool-down. SOP training was conducted with computerized BrainHQ, which adjusts based on a participant's performance. The session duration of SOP training started at 50 min per session and was progressively reduced to 30 min by week 8. ACT sessions were 80 min in duration, excluding the 5-minute warm-up and 5-minute cool-down. Cycling was completed first, followed by the SOP activity, with intensity and duration progressions mimicking the cycling and SOP training groups. Attention control followed a similar format to ACT but included low intensity (HRR < 30% or RPE ≤ 9) range of motion and stretching exercise followed by mental leisure activities (e.g., Sudoku).

Monitor responses

Interventionists monitored heart rates, RPE talk ability, blood pressure, and signs and symptoms continuously during each session. De-identified session reports and summarized session duration, HRR and RPE achieved (the latter two for ACT, cycling, and stretching control groups only) were reviewed weekly by the study exercise physiologist during weekly intervention meetings.

Adjust dose (as needed)

When participants were unable to achieve minimally prescribed heart rate or RPEs, discussions ensued to promote greater dose adherence. Factors that may have been limiting these adherence indicators could have included beta-blocker use (heart rate) or inadequate understanding of the RPE scale. In the former, advice included how to use the RPE and talk test as the primary indicators of intensity. For the latter, advice included using markers 11, 13, and 15 only (ACT or cycling) so that the participant could gain better understanding of light, moderate, and hard on the scale for simplicity and training purposes. For individuals who did not have medication or subjective reasons for reduced dose (intensity) adherence, other strategies were implemented on a case-by-case basis.

Set up reminders

Day and time of the next intervention session was confirmed prior to adjourning the current session. Staff provided participants a reminder text the night before for morning sessions or in the morning for afternoon sessions.

Make up for absences

When a session was cancelled, interventionists attempted to schedule the make-up session within the same week if possible or in the subsequent week. Only one make up session could be scheduled per week in an attempt to not exceed four sessions/week.

Review progress

Intervention protocol adherence was monitored during weekly Zoom meetings held by the study exercise physiologist and each of the study interventionists from the three sites. Meetings focused on review of attendance, adherence to intervention prescription, tolerance to intervention dose and adverse symptoms. Attendance to interventions were reviewed for each participant and individual factors that were limiting attendance were discussed. Strategies for overcoming participant barriers to attending sessions were discussed for implementation thereafter.

Safety (minimize interventional/procedural-related AEs)

Team processes for preventing AEs to increase minimize occurrence of interventional/procedural-related AEs (Fig. 1) were operationalized as follows:

Educate about signs and symptoms

Prior to the CPET and prior to the first intervention session (ACT, cycling, and attention control groups), participants were educated on adverse symptoms of exercise pertaining to cardiovascular, pulmonary, and musculoskeletal systems. Participants were educated through the reading of a brief standardized script and were offered time for questions. In addition, prior to each intervention session, study interventionist interviewed participants regarding residual symptoms from the previous session, evaluating tolerability to the intervention and making any necessary adjustments.

Assess and document adverse events

In the event of an AE, protocols were set for when to defer sessions, adjust the prescription of sessions, terminate sessions, or refer the participant to their primary care provider for further evaluation. When needed, interventionists contacted the study investigators for further guidance in evaluation. Following any AE, summaries were written by the interventionist and shared with the study investigators for grading and evaluation.

Communicate with healthcare provider

In the event that the AE warranted further evaluation from a participant's primary care provider, summaries of the AE were shared with the participant and faxed to the primary care provider. Participants were then required to obtain "re-clearance" from their primary care provider prior to continuing interventions or physical assessments in the study. Efforts were made by study staff to help facilitate the process.

Measures for implementation outcomes

Screening

Screening outcomes were operationalized to capture the team processes: (1) durations in days between each screening step (S1-S4), (2) duration in days from enrollment to the first intervention session, and (3) duration in days from S1 to the first intervention session.

Intervention adherence

Intervention adherence outcomes were operationalized as (1) session attendance defined as the total number of sessions attended out of 72 possible sessions and (2) Session dose adherence was calculated by dividing the number of sessions that achieved prescribed session dose/total number of sessions completed. For exercise sessions, adherence to 100% exercise dose means that participants exercised above the minimum target HR or RPE for the prescribed duration for attended sessions when cycling or exercised below the maximum target HR or PRE for the prescribed duration when stretching for attended sessions. For SOP/MLA, adherence to 100% cognitive session dose means that all attended sessions met the prescribed durations for attended sessions.

Safety

Safety outcomes were operationalized as the type, number, and severity of AEs. Type of AEs were dichotomized as (1) non-study-related: either "clearly not related to the study" or "doubtfully related to the study" and (2) study-related (intervention or procedure-related): "possibly," "likely," or "clearly" related to the study. In the ACT Trial[11], each study-related AE was rated for severity and classification. The severity was rated with a 4-point Likert scale: 1 = minor (no treatment required), 2 = moderate (resolved with treatment), 3 = serious (resulted in inability to carry on normal activities or ongoing medical treatment was still required), and 4 = life threatening or fatal. Classifications of study-related AEs included (1) fall, (2) cardiac, (3) musculoskeletal, (4) gastrointestinal, and (5) other. All AEs were assessed and graded by the interventionist, the exercise physiologist, and a principal investigator with consensus.

Statistical analysis

Continuous variables were quantified with means (standard deviation) and median (interquartile range) and categorical variables with frequency (percent). Normality and homogeneity of variance were assessed by the Shapiro Wilk test and Levene's test, respectively. Implementation consistency across sites was assessed by analysis of variance (ANOVA) or Kruskal Wallis test to satisfy test assumptions. Collective sex and race-based differences in outcomes were assessed using independent samples t-test or Mann Whitney U test. Specifically, days spent in screening phases and intervention length were non-normally distributed. Site-based differences were assessed by the Kruskal Wallis test, while Mann Whitney U test was used for assessing collective sex and race-based differences. Chi Squared test and Fisher's exact tests were used to analyze AEs and sex and racial effects on AEs for the entire sample. Alpha was set at $p = 0.05$. All data were analyzed using SPSS version 28.0 (IBM Corp.; Armonk, NY).

Results

Recruitment and screening occurred between 4/1/2018–8/31/2023. Together, 1,020 people responded to our recruitment, 911 were reached and screened over the phone, 337 were interviewed in person, 325 signed informed consent, and 146 were enrolled and randomized. This represented 16.0% who were phone screened, 43.3% who were interviewed in person, and 44.9% who signed consent. The enrolled sample ($n = 146$) was 73.7 ± 5.7 years in

age and 23.4 ± 2.2 on Montreal Cognitive Assessment (MoCA) score, with 48% female, 91.8% White Caucasian, and 16.9 ± 2.9 years of education (Table 1).

Screening

The median duration from S1 to S2 was 10.5 (7.0–20.0) days, S2 to S3 (CPET) was 31.0 (20.0–38.0) days, S3 to S4 (MRI) was 14.0 (8.0–35.0) days, S4 to enrollment was 16.0 (10.0–26.0) days, and the duration from enrollment to intervention session 1 was 11.0 (6.0–18.0) days. Site based differences were seen in days between S4 (MRI) to enrollment ($H(2) = 37.1$, $p < 0.01$) and enrollment to intervention session 1 ($H(2) = 16.8$, $p < 0.01$). The median duration from initial screening to study enrollment was 98 (78.0-143.3) days ($H(2) = 17.7$, $p < 0.01$). Collectively across sites, there were no significant sex or race-based differences for days in between screening stages, but there was a significant racial-based difference for days between S3 (CPET) and S4 (MRI) ($z = -2.08$, $p = 0.04$). The breakdown of days between screening phases are broken down by site, sex, and race in Table 2.

Intervention adherence

Twenty-one participants dropped out of the study during the 6-month intervention phase, and number of dropouts was significantly different across sites ($p = 0.03$). For the entire sample, the mean average attendance was 76.7 ± 28.6% (UMN: 79.7 ± 32.3%; UR: 79.5 ± 22.5%; ASU: 65.7 ± 32.1%) ($F = 2.79$, $p = 0.07$). Adherence to 100% exercise session dose and 100% cognitive session dose was 71.7 ± 30.8% (UMN: 76.6 ± 30.6%; UR: 70.5 ± 30.5%; ASU: 60.1 ± 30.1%) ($F = 1.98$, $p = 0.07$) and 51.5 ± 26.2% (UMN: 73.3 ± 21.6%; UR: 39.6 ± 32.8%; ASU: 35.7 ± 20.3%) ($F = 21.24$, $p < 0.01$) respectively. The median length of the 6-month intervention period was 188.0 (173.5-197.3) days (UMN: 185.0 [170.0-196.0] days; UR: 190.0 [182.0-199.0] days; ASU: 184.0 [127.5-207.5] days) ($H(2) = 4.50$, $p = 0.11$). Results pertaining to intervention adherence for individuals who completed the 6-month intervention are presented in Table 2. When excluding participants who dropped out of the study during the intervention period, adherence to cognitive session dose (53.8 ± 30.7%) and attendance (83.0 ± 22.1%) were significantly different among sites ($F = 17.82$, $p < 0.01$ and $F = 3.48$, $p = 0.03$), while adherence to exercise session dose (73.7 ± 29.0%) and length of intervention (190 [180–200] days) were not ($F = 2.37$, $p = 0.10$ and $H(2) = 3.32$, $p = 0.19$). Attendance (24.0 ± 20.1%), adherence to exercise session dose (49.8 ± 36.8%) and cognitive session dose (35.3 ± 32.1%), and length of intervention (39.5 [7.0-102.7] days) were not significantly different among sites for dropouts ($p > 0.05$).

Number of dropouts was not significantly different between sex ($p = 0.25$) or race ($p = 0.46$). For the entire sample, women had lower attendance ($t = 2.23$, $p = 0.03$) and adherence to cognitive session dose ($t = 3.21$, $p < 0.01$). No other significant sex-based differences were present. Non-White participants took fewer days to complete the intervention ($z = -2.03$, $p = 0.05$). Intervention adherence data for those who completed the intervention by sex and race are presented in Table 2. Women had significantly lower adherence to cognitive session dose ($t = 3.31$, $p < 0.01$). There were no significant sex or race-based differences for intervention adherence metrics for dropouts ($p > 0.05$).

Safety

There were 10 study-related AEs. One occurred during screening for an individual who did not disclose having seen a cardiologist for cardiac symptoms and being advised for stent placement, screening exercise test showed ST depression on ECG. Nine study-related AEs occurred during the intervention period: cardiac symptoms (mild–resolved without treatment, $n = 3$]), cardiac procedure for progression of incomplete trifasicular block (moderate, $n = 1$), musculoskeletal (wrist/hand pain [mild, $n = 1$]), phlebitis (mild, $n = 1$), fall with leg injury (moderate–resolved with treatment, $n = 1$), fall without injury (mild, $n = 1$), and hypertensive response (moderate, $n = 1$). The 9 study-related AEs occurred over 8,136 intervention sessions, which equates to an AE rate of 0.001 AEs/session. Five AEs occurred at UR (3 cardiac symptoms, 1 wrist/hand pain, 1 phlebitis), 3 at UMN (1 fall, 1 hypertension, 1 cardiac procedure), and 1 fall at ASU. Number of study-related AEs did not differ

Variable	Total sample ($N = 146$)	By site				By sex			By race		
		UMN ($n = 55$)	UR ($n = 58$)	ASU ($n = 33$)	*P*-value	Male ($n = 76$)	Female ($n = 70$)	*P*-value	Non-Hispanic White ($n = 134$)	Other Race ($n = 12$)	*P*-value
Age	73.8 (5.7)	73.4 (5.5)	74.0 (5.7)	74.4 (6.1)	0.71	74.9 (5.5)	72.7 (5.8)	0.02	74.0 (5.8)	71.9 (5.0)	0.22
Sex (male/%)	76 (52.0)	32 (58.2)	28 (48.3)	16 (48.4)	0.53	-	-	-	70 (92.1)	64 (91.4)	0.99
Race (NHW/%)	134 (91.8)	54 (98.1)	49 (84.5)	31 (93.9)	0.03	70 (92.1)	64 (91.4)	0.99	-	-	-
Education (yrs)	16.9 (2.9)	16.5 (2.8)	17.1 (2.7)	17.1 (3.2)	0.46	17.4 (3.2)	16.3 (2.5)	0.02	16.9 (2.9)	16.1 (2.2)	0.35
MoCA	23.4 (2.1)	23.1 (2.0)	23.8 (2.1)	23.1 (2.4)	0.12	23.2 (2.2)	23.6 (2.1)	0.33	23.5 (2.1)	22.5 (3.0)	0.14
ADL-PI	18.1 (2.9)	18.5 (3.3)	17.9 (2.6)	17.7 (3.1)	0.43	18.2 (2.8)	17.9 (3.2)	0.58	18.1 (3.1)	17.3 (2.1)	0.38
WHOQOL	16.9 (2.8)	17.6 (12.9)	17.8 (14.4)	14.2 (9.4)	0.40	16.7 (12.1)	17.1 (13.7)	0.86	17.1 (13.2)	14.3 (7.3)	0.46
GDS	1.9 (1.9)	2.0 (1.7)	1.7 (2.2)	2.1 (1.7)	0.53	1.9 (1.8)	1.9 (2.0)	0.91	2.0 (1.9)	1.0 (1.5)	0.08

Table 1. Participant characteristics. UMN: University of Minnesota; UR: University of Rochester; ASU: Arizona State University; NHW; non-Hispanic White: MoCA; Montreal Cognitive Assessment: ADL-PI; Activities of Daily Living-Prevention Instrument: WHOQOL; World Health Organization Quality of Life: GDS; Geriatric Depression Scale.

Screening (days)*											
		By site				By sex			By race		
Variable	Total sample (*N* = 141)	UMN (*n* = 50)	UR (*n* = 58)	ASU (*n* = 33)	p-value	Male (*n* = 75)	Female (*n* = 66)	p-value	Non-Hispanic White (*n* = 129)	Other Race (*n* = 12)	p-value
S1-S2	10.5 (7–20)	8.5 (6–18)	13.0 (8–22)	10.0 (8–17)	0.08	10.0 (6–18)	11.0 (7–20)	0.36	10.0 (7–20)	14.0 (6–34)	0.29
S2-CPET	31.0 (20–38)	28.0 (16–49)	32.0 (20–47)	36.0 (26–49)	0.13	34.0 (20–52)	30.0 (18–44)	0.19	31.0 (20–47)	35.0 (27–52)	0.36
CPET-MRI	14.0 (8–35)	16.0 (6–43)	14.0 (8–22)	14.0 (8–46)	0.60	18.0 (8–37)	13.0 (7–28)	0.11	15.0 (8–37)	10 (6–13)	0.04
MRI-enrollment	16.0 (10–26)	10.0 (7–15)[a]	20.0 (14–33)[b]	20 (14–27)[b]	< 0.01	15.0 (8–27)	16.0 (13–26)	0.37	16.0 (10–26)	15.5 (12–22)	0.97
Enrollment-session 1	11.0 (6–18)	8.0 (5–22)[a]	9.0 (6–14)[a]	14.0 (12–35)[b]	< 0.01	10.0 (5–15)	12.0 (7–21)	0.06	11.0 (6–18)	10.0 (7–15)	0.95
Adherence (%)†											
		By site				By sex			By race		
Variable	Total sample (*N* = 125)	UMN (*n* = 47)	UR (*n* = 54)	ASU (*n* = 24)	p-value	Male (*n* = 67)	Female (*n* = 58)	p-value	Non-Hispanic White (*n* = 114)	Other Race (*n* = 11)	p-value
Attendance	83.1 (22.1)	87.6 (22.1)	83.6 (16.9)	73.2 (28.6)	0.03	86.6 (18.4)	79.0 (25.3)	0.06	84.2 (22.4)	71.8 (14.7)	0.08
Exercise Session Dose	73.7 (29.0)	80.9 (24.9)	71.7 (30.8)	63.3 (30.5)	0.10	73.6 (30.1)	73.8 (28.0)	0.98	74.7 (28.8)	66.3 (31.8)	0.37
Cognitive Session Dose	53.9 (30.7)	75.0 (18.6)	41.6 (33.0)	39.8 (20.8)	< 0.01	63.4 (26.3)	43.0 (32.1)	< 0.01	53.5 (31.3)	59.0 (25.2)	0.65
Days on Intervention‡	190 (180–200)	188 (177–196)	192 (185–199)	196 (177–211)	0.19	190 (180–200)	189 (180–200)	0.84	190 (180–200)	198 (188–204)	0.19
Safety (frequency)											
		By site				By sex			By race		
Variable	Total sample (*N* = 146)	UMN (*n* = 55)	UR (*n* = 58)	ASU (*n* = 33)	p-value	Male (*n* = 76)	Female (*n* = 70)	p-value	Non-Hispanic White (*n* = 134)	Other Race (*n* = 12)	p-value
Study-related	9 (6.2)	3 (2.7)	5 (2.7)	1 (0.8)	0.82	6 (4.1)	3 (2.1)	0.50	6 (4.1)	3 (2.1)	0.03

Table 2. Implementation outcomes. Days in screening phase and days on intervention reported as median (IQR). Other adherence reported as means (SD). Safety reported as frequency (%). UMN; University of Minnesota: UR; University of Rochester: ASU; Arizona State University: S1; Screening 1: S2; Screening 2: CPET; Cardiopulmonary exercise test: MRI; Magnetic resonance imaging, *Participants who initiated S1 screening prior to COVID-19 government shutdown and resumed screening after the shutdown were excluded ($n = 5$) from analysis, sample sizes. †All adherence data exclude participants from analysis who dropped out from the 6-month intervention phase ($n = 19$). ‡Expressed in days (not %). Adherence data reported collectively and not by group assignment, some participants received aerobic exercise or stretching activities and not cognitive/mental leisure activities, while others received cognitive or mental leisure activities but no aerobic or stretching activities

significantly among sites ($p = 0.76$). There were no significant sex differences ($p = 0.50$) but significant racial-differences ($p = 0.03$) pertaining to number of study-related AEs during the intervention period.

Discussion

The results of our study showed that when we followed the MOBILIZE standardized team process, it promoted the achievement of implementation outcomes against benchmarks and similar implementation outcomes across sites. The duration from S1 to the first intervention averaged 98 days. When looking at the entire sample, MOBILIZE promoted high attendance (76.7%), high adherence to 100% exercise session dose (71.7%) and 100% cognitive session dose (51.5%) among attended sessions, and safe conduction of the RCT with minimal study-related AEs over the course of 7,616 sessions (< 0.001 AEs/session). Additionally, there were some site differences related to adherence to 100% cognitive session dose and sex differences in attendance.

We believe that this is the first study that has investigated the use of a framework to guide implementation of an early-stage randomized controlled trial investigating the efficacy of behavioral intervention in persons with cognitive impairment. The implementation outcomes were comparable to the anticipated benchmarks or other studies. Our anticipated screening benchmark from S1 to the first intervention session was 2–3 months, and our accrual time was 98 days (median). However, comparisons to other studies regarding screening length is impractical given the heterogeneity of screening steps required in many studies.

Although not universally defined, previous studies looking at the therapeutic effects of behavioral interventions in older adults[24] and adults with neurological diseases[25] have suggested that an adequate and optimal session attendance is 60% and 80% respectively. In our study, our attendance was 76.7%. However, comparisons to adherence measures of behavioral interventions utilized in other studies can be challenging given heterogeneity of interventions and the thresholds implemented to evaluate adherence. The large, multi-center DAPA study[26] that investigated the effects of a multimodal exercise program in persons with dementia defined attendance a priori as attending 75% or more sessions. 65% of DAPA participants (usual care group excluded from their analysis) achieved threshold. In the ACT Trial, 91 (62.3%) participants attended 75% or more sessions among

all enrollees ($n = 146$), 65.9% among the 138 participants who attended at least one session, and 72.8% when removing the dropouts ($n = 21$).

Two important differences between these studies should be mentioned. First, the DAPA trial was an 8 week intervention (30 possible sessions), while the ACT Trial was a 26-week intervention (72 possible sessions). Second, the ACT Trial used a sham control group, while the DAPA study utilized a usual care control group and subsequently would not affect attendance metrics. Finally, a recent meta-analysis or randomized controlled trials of supervised exercise interventions (34 studies, $n = 2,830$ participants, total sessions 12–132, intervention length 4–52 weeks) in older adults without AD and an acute disease [e.g., stroke], reported that an average attendance of 81%[27].

Reporting of intervention dose adherence, including exercise, is sparse in the literature. In the meta-analysis by Gómez-Redondo, only two of the studies reported intervention dose adherence[27]. For instance, one study in older adults with intermittent claudication reported that 24% of the participants were classified as fully adherent when full adherence was defined as ≥ 80% of the exercise sessions meeting the prescribed intensity[28]. In the ACT Trial, we used the most restrictive definition and defined full adherence as meeting both the exercise intensity and duration prescription for the session at 100% or as meeting the cognitive duration prescription at 100% among attended sessions. Using this definition, 71.7% and 51.5% of sessions achieved 100% exercise dose adherence and 100% cognitive dose adherence, respectively. While it is beyond the scope of this manuscript, this finding has important implications for the ACT Trial and future studies of ACT that analyzing dose-response relationships is critical to understand intervention efficacy and identify the minimally effective intervention dose.

Safety is often a common concern for persons participating in behavioral and lifestyle interventions, such as exercise. In the DAPA study, there were a reported 25 AEs (7% of participants), 4 of which were categorized as severe[26]. In comparison, the ACT Trial had 10 study-related AEs during the intervention phase among enrolled participants 6.2% of participants), with no severe AEs. Furthermore, this study adds to data from a recent meta-analysis of randomized controlled trials ($n = 93$ studies; 28,523 participants) that behavioral interventions, such as those with an exercise component, are safe for older adults (including those with cognitive impairments) and are not associated with AE-related dropout compared to control groups[29].

Overall, male participants had significantly better attendance compared to females. Data investigating the influence of sex on adherence to behavioral interventions are mixed. For instance, some studies with older adult samples have shown that males have better attendance to behavioral interventions, such as exercise-focused interventions, compared to females[30,31]. However, a study from Tullo and colleagues ($n = 4775$) tested predictive validity of several individual difference factors (including sex), found no predictability of sex on adherence to cognitive training, measured by the number of sessions completed[32]. Lastly, non-White participants took longer to complete the 6-month intervention than non-Hispanic White participants. This may have been attributed to the higher percentage of study-related AEs seen in this group, which often are associated with missing time during the intervention, with the need to make-up the missed sessions on the back end of the program.

Person-centeredness was the operating context of MOBILIZE. The person-centered concept is often seen in community-based research, where participants often have input regarding study design. However, in the context of early-stage clinical trials where statistical design in rigor is paramount, we devised the MOBILIZE framework (guided by the Generic Implementation Framework[33]), but allowed participants to have the opportunity to have their thoughts heard and incorporated (when in alignment of the study protocol). The goal of the person-centered approach that guides MOBILIZE was from a study-team viewpoint to allow for successful, efficient, and safe screening and intervention delivery. From the participant vantage point, it is important for participants to find fulfillment and minimize study burden. Specifically, the MOBILIZE person-centered approach included allowing participants to participate in decisions regarding screening and intervention schedules and timelines, tailoring interventions to their capacities, improving interactions between participants and their healthcare providers, and making intervention sessions and screening visits feel empathetic and compassionate, not merely transactional. However, it should be stated that a limitation of this study was the inability to measure person-centeredness as an outcome in assessing the implementation of MOBILIZE.

Several lessons learned can inform future studies. First, implementation outcomes should be evaluated regularly during trial implementation. While we reviewed screening during weekly staff meetings, we did not quantify durations among screening steps. Knowing the exact durations may have prompted us to improve. Second, this study revealed a large degree of variability in time spent in screening stages and may have caused loss of interest. It is important for research staff to keep participants engaged and informed during times of delay. Third, medical clearance is a bottleneck, requiring multiple methods (contacting provider after sending fax, having participant reach out to provider, and resending faxes) to obtain clearance timely. Fourth, two major influencers on intervention adherence are illnesses that require medical re-clearance and vacations; makeup sessions should be started prior to vacation absence. Lastly, weekly meetings to review intervention logs and progress are vital to ensure proper intervention dose is being received across intervention arms according to protocol. Future research is needed to further test MOBILIZE and examine sex and racial differences in implementation outcomes.

Conclusions

The MOBILIZE framework, which promoted a person-centered approach to behavioral and lifestyle intervention studies and which guided the design of the ACT Trial Protocol, was effective at ensuring the comprehensiveness of screening, attendance, and safety of the ACT Trial. The outcomes are relevant and provide quantitative targets for evaluating trial implementation success and implementation consistency for multi-site trials, such as the ACT Trial.

Data availability

Implementation data related to the ACT Trial are available upon reasonable request to Dr. Fang Yu.

Glossary

AD	Alzheimer's disease
NIH	National Institutes of Health
MOBILIZE	I**M**plementation Framework f**O**r **B**ehavioral and LI**f**esty**L**e Interventions **I**n Al**Z**heimer's Dis-eas**E**
AEs	Adverse events
RE-AIM	Reach, Effectiveness, Adoption, Implementation, Maintenance (Framework)
CFIR	Consolidated Framework for Implementation Research
ACT	*A*erobic Exercise and *C*ognitive *T*raining
aMCI	Amnestic mild cognitive impairment
IRB	Institutional Review Board
MoCA	Montreal Cognitive Assessment
RAVLT	Rey Auditory Verbal Learning Test
ADL-PI	Activities of Daily Living-Prevention Instrument
MRI	Magnetic resonance imaging
SOP	Standard Operating Procedure
S1	Screening 1
S2	Screening 2
S3	Screening 3
CPET	Cardiopulmonary exercise test
S4	Screening 4
HRR	Heart rate reserve
RPE	Rating of perceived exertion
ANOVA	Analysis of variance
SPSS	Statistical Package for Social Sciences

Received: 6 April 2024; Accepted: 31 January 2025
Published online: 13 February 2025

References

1. Association Association. Alzheimer's DiseaseFacts and Figures. Accessed 6-29-2023 (2023). https://www.alz.org/media/documents/alzheimers-facts-and-figures.pdf
2. Gillis, C., Mirzaei, F., Potashman, M., Ikram, M. A. & Maserejian, N. The incidence of mild cognitive impairment a systematic review and data synthesis. *Alzheimers Dement.* **11**, 248–256. https://doi.org/10.1016/j.dadm.2019.01.004 (2019).
3. National Academies of Sciences EaM, Health and, Medicine, D. & Board on Health Sciences, P. Committee on Preventing Dementia and Cognitive I. In Downey A, Stroud C, Landis S, Leshner AI, editors. *Preventing Cognitive Decline and Dementia: A Way Forward*. Washington (DC): National Academies Press (US) (2017).
4. Burns, J. M. et al. Cardiorespiratory fitness and brain atrophy in early Alzheimer disease. *Neurology* **7**, 210–216. https://doi.org/10.1212/01.wnl.0000317094.86209.cb (2008).
5. Honea, R. A. et al. Cardiorespiratory fitness and preserved medial temporal lobe volume in Alzheimer disease. *Alzheimer Dis. Assoc. Disord.* **23**, 188–197. https://doi.org/10.1097/WAD.0b013e31819cb8a2 (2009).
6. Huuha, A. M. et al. Can exercise training teach us how to treat Alzheimer's disease? *Ageing Res. Rev.* **75**, 101159. https://doi.org/10.1016/j.arr.2022.101559 (2022).
7. Lovden, M., Backman, L., Lindenberger, U., Schaefer, S. & Schmiedek, F. A theoretical framework for the study of adult cognitive plasticity. *Psychol. Bull.* **136**, 659–676. https://doi.org/10.1037/a0020080 (2010).
8. Turnbull, A., Seitz, A., Tadin, D. & Lin, F. V. Unifying framework for cognitive training interventions in brain aging. *Ageing Res. Rev.* **8**, 101724. https://doi.org/10.1016/j.arr.2022.101724 (2022).
9. Martin, M., Clare, L., Altgassen, A. M., Cameron, M. H. & Zehnder, F. Cognition-based interventions for healthy older people and people with mild cognitive impairment. *Cochrane Database Syst. Rev.* **1**, CD006220. https://doi.org/10.1002/14651858.CD006220.pub2 (2011).
10. Takeuchi, H. et al. Effects of training of processing speed on neural systems. *J. Neurosci.* **31**, 12139–12148. https://doi.org/10.1523/JNEUROSCI.2948-11.2011 (2011).
11. Yu, F. et al. Efficacy and mechanisms of combined aerobic exercise and cognitive training in mild cognitive impairment: study protocol of the ACT trial. *Trials* **19**, 700. https://doi.org/10.1186/s13063-018-3054-0 (2018).
12. Li, H. et al. Exercise training for mild cognitive impairment adults older than 60: a systematic review and meta-analysis. *J. Alzheimers Dis.* **88**, 1263–1278 (2022).
13. Xue, D., Li, P., Yu, D. & Lin, R. Combined exercise and cognitive interventions for adults with mild cognitive impairment and dementia: a systematic review and network meta-analysis. *Int. J. Nurs. Stud.* **147**, 104592. https://doi.org/10.1016/j.ijnurstu.2023.104592 (2023).
14. Lin, M. et al. Effects of exercise interventions on executive function in old adults with mild cognitive impairment: a systematic review and meta-analysis of randomized controlled trials. *Ageing Res. Rev.* **82**, 101776. https://doi.org/10.1016/j.arr.2022.101776 (2022).
15. Gavelin, H. M. et al. Combined physical and cognitive training for older adults with and without cognitive impairment: a systematic review and network meta-analysis of randomized controlled trials. *Ageing Res. Rev.* **66**, 101232. https://doi.org/10.1016/j.arr.2020.101232 (2021).
16. Nielsen, L. et al. The NIH Science of Behavior Change Program: transforming the science through a focus on mechanisms of change. *Behav. Res. Ther.* **101**, 3–11. https://doi.org/10.1016/j.brat.2017.07.002 (2018).
17. Yu, F. et al. Effects of aerobic exercise on cognition and hippocampal volume in Alzheimer's disease: study protocol of a randomized controlled trial (the FIT-AD trial). *Trials* **15**, 394–6215. https://doi.org/10.1186/1745-6215-15-394 (2014). [doi].
18. Salisbury, D., Plocher, T. & Yu, F. Efficacy of simultaneous aerobic exercise and cognitive training in subjective cognitive decline: study protocol for randomized controlled trial of the Exergames Study. *Trials* **22**, 14. https://doi.org/10.1186/s13063-020-04950-7 (2021).

19. Yu, F. & Kolanowski, A. Facilitating aerobic exercise training in older adults with Alzheimer's disease. *Geriatr. Nurs.* **30**, 250–259. https://doi.org/10.1016/j.gerinurse.2008.11.001 (2009).
20. Yu, F., Savik, K., Wyman, J. F. & Bronas, U. G. Maintaining physical fitness and function in Alzheimer's disease: a pilot study. *Am. J. Alzheimers Dis. Other Demen.* **26**, 406–412. https://doi.org/10.1177/1533317511414861 (2011).
21. Yu, F. et al. Affecting cognition and quality of life via aerobic exercise in Alzheimer's disease. *West. J. Nurs. Res.* **35**, 24–38. https://doi.org/10.1177/0193945911420174 (2013). [doi].
22. Glasgow, R. E. et al. RE-AIM planning and evaluation framework: adapting to new science and practice with a 20-year review. *Front. Public. Health.* **7**, 64 (2019).
23. Salisbury, D. & Yu, F. Establishing reference cardiorespiratory fitness parameters in Alzheimer's disease. *Sports Med. Int. Open.* **4**, E1–E7. https://doi.org/10.1055/a-1089-4957 (2020).
24. Salisbury, D., Olafinoboba, O. & Yu, F. Implementation of exergame telehealth in subjective cognitive decline. *J. Clin. Exerc. Physiol.* **12**, 1–10 (2023).
25. Bianchini, E. et al. Feasibility, safety, and effectiveness of telerehabilitation in mild-to-moderate Parkinson's disease. *Front. Neurol.* **13**, 909197. https://doi.org/10.3389/fneur.2022.909197 (2022).
26. Lamb, S. E. et al. Dementia and physical activity (DAPA) trial of moderate to high intensity exercise training for people with dementia: randomised controlled trial. *BMJ* **361**, 1675 (2018).
27. Gómez-Redondo, P., Valenzuela, P. L., Morales, J. S., Ara, I. & Mañas, A. Supervised versus unsupervised exercise for the improvement of physical function and well-being outcomes in older adults: a systematic review and meta-analysis of randomized controlled trials. *Sports Med.* **54**, 1877–1906 (2024).
28. Sandberg, A. et al. Effectiveness of supervised exercise, home-based exercise, or walk advice strategies on walking performance and muscle endurance in patients with intermittent claudication (SUNFIT trial): a randomized clinical trial. *Eur. J. Cardiovasc. Nurs.* **22**, 400–411 (2023).
29. García-Hermoso, A. et al. Safety and effectiveness of long-term exercise interventions in older adults: a systematic review and meta-analysis of randomized controlled trials. *Sports Med.* **50**, 1095–1106 (2020).
30. Oosenbrug, E. et al. Sex differences in cardiac rehabilitation adherence: a meta-analysis. *Can. J. Cardiol.* **32**, 1316–1324. https://doi.org/10.1016/j.cjca.2016.01.036 (2016).
31. Ruano-Ravina, A. et al. Participation and adherence to cardiac rehabilitation programs. A systematic review. *Int. J. Cardiol.* **223**, 436–443. https://doi.org/10.1016/j.ijcard.2016.08.120 (2016).
32. Tullo, D. et al. Investigating the role of individual differences in adherence to cognitive training. *J. Cogn.* **6**, 48. https://doi.org/10.5334/joc.315 (2023).
33. Moullin, J. C., Sabater-Hernández, D., Fernandez-Llimos, F. & Benrimoj, S. A systematic review of implementation frameworks of innovations in healthcare and resulting generic implementation framework. *Health Res. Policy Syst.* **13**, 1–11. https://doi.org/10.1186/s12961-015-0005-z (2015).

Acknowledgements

We wish to acknowledge the support of Nick Verhoef and Hector Cervantes for their work in coordinating and facilitating the data auditing of the ACT trial.

Author contributions

All authors led the conceptual development and structure of the manuscript. All authors contributed to initial drafts of the recommendations and participated in decisions about what information to prioritize and how to tailor the information with implementation research examples. DS drafted the manuscript and FL and FY reviewed and edited manuscript sections. All authors reviewed and revised several iterations of the manuscript and approved the final version.

Funding

The ACT Trial was supported by the National Institute on Aging of the National Institutes of Health under Award Number R01AG055469-01A1. The content is solely the responsibilty of the authors and does not necessarily represent the official views of the National Institutes of Health.

Declarations

Competing interests

The authors declare no competing interests.

Ethics approval and consent to participate

The study was approved by the Institutional Review Board (IRB) at each site: IRB# STUDY00001135 on 8/23/2017 at UMN, STUDY00001484 on 2/19/2018 at UR, and WCG IRB #1305160 & IRB#STUDY00013092 on 04/21/2021 at ASU. Informed, written consent was obtained from all study participants. Capacity to provide informed consent was evaluated for all participants with the University of California, San Diego Brief Assessment of Capacity to Consent (UBACC).

Consent for publication

Not applicable.

Additional information

Correspondence and requests for materials should be addressed to F.V.L. or F.Y.