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COMbined Exercise Trial (COMET) to improve cognition in older adults: Rationale and Methods

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Abstract

Substantial evidence suggests physical exercise may sustain cognitive function and perhaps prevent Alzheimer's Disease(1, 2). Current public health recommendations call for older adults to do at least 150 minutes a week of aerobic exercise (e.g. walking) and twice a week resistance exercise (e.g. weight lifting) for physical health. Yet, much remains unknown about how these exercise modalities support brain health independently or in combination. The COMbined Exercise Trial (COMET) is designed to test the combined and independent effects of aerobic and resistance training specifically focusing on exercise-related changes in 1) cognitive performance, 2) regional brain volume, 3) physical function, and 4) blood-based factors. To explore these questions, we will enroll 280 cognitively normal older adults, age 65–80 years, into a 52-week community-based exercise program. Participants will be randomized into one of four arms: 1) flexibility/toning- control 2) 150 minutes of aerobic exercise only, 3) progressive resistance training only, or 4) combined aerobic and progressive resistance training. Outcomes assessed include a comprehensive cognitive battery, blood biomarkers, brain magnetic resonance imaging, physiological biomarkers, cardiorespiratory fitness, physical function, and battery of psychosocial questionnaires is assessed at baseline, 6 and 12-months. COMET will provide rigorous randomized controlled trial data to understand the effects of the most common exercise modalities, and their combination (i.e., the standard public health recommendation), on brain health.

NCT Registration: NCT02913664

Keywords

Alzheimer's Disease; Exercise; Cognition; Brain Structure; Resistance Training; Aerobic Activity; Fitness

1.0. Introduction

The societal and economic burden of aging-related cognitive and functional decline underscores the need to develop interventions to maximize successful aging, independence, and health(3–7). Physical activity has a biologically plausible and temporal relationship with coronary heart disease, atherosclerosis, stroke, type 2 diabetes, some cancers, and all-cause mortality(3, 4). Regular aerobic and resistance training decreases age-related morbidity and mortality, improves risk factors for chronic disease, and helps maintain independent functioning(3, 4, 7). Accumulating data suggest exercise may attenuate age-related cognitive and functional decline(1, 2, 8, 9). Expert consensus panels (NIH, CDC, ACSM) have concluded, however, that the available clinical trial evidence is insufficient to demonstrate that exercise prevents cognitive decline or dementia(5–7). Ongoing research designed to definitively determine the effect of aerobic exercise on brain health in cognitively normal older adults will provide key insights (i.e., IGNITE, NCT02875301 (10)). Yet, trials exploring cognitive and brain effect of other exercise modalities and the potential interactions of modalities, key to sustaining function, are still lacking.

We have designed the COMbined Exercise Trial (COMET; R01 AG070036, NCT04848038) to provide rigorous randomized controlled trial data to understand the effects of the most common exercise modalities (aerobic and resistance exercise) independently, and their combination (i.e., the standard public health recommendation), on brain health and cognition. When completed, COMET will provide key information for: 1) patients who need guidance on how much and what types of exercise are necessary to impact brain health, 2) healthcare providers who provide front-line advice and exercise prescription to their patients, 3) healthcare systems in need of definitive proof before major efforts are undertaken to invest in preventative health programs and infrastructure. Moreover, if aerobic and resistance training are both necessary to promote optimal brain health or delay dementia, realizing the benefits would require additional public health efforts to support adoption by older adults. A more precise understanding of the role and impact of current exercise recommendations on cognitive function is essential knowledge for our healthcare force and for convincing the millions of older adults in the United States who do not currently meet all aspects of the recommendations.

1.2 Exercise and Brain Health

1.2.1 Exercise and Brain Health

Aerobic exercise consists of prolonged physical exertion with energy requirements supplied primarily by aerobic metabolism. Public health recommendations from the World Health Organization (WHO), Centers for Disease Control (CDC), American College of Sports Medicine (ACSM), and others, recommend that older adults do at least 150 minutes of

moderate intensity aerobic exercise per week, like walking or swimming, as part of a regular exercise regimen to maintain health and fitness(7). Though results of prior trials have been mixed, the overall evidence suggests that aerobic exercise in healthy, older adults may have a beneficial impact on cognitive performance(2, 11), brain plasticity(11), and hippocampal atrophy while improving visual attention and memory(11). One meta-analysis(8) examined 18 aerobic intervention studies of varying quality and found a moderate effect for combined exercise programs across all cognitive outcome measures (effect size=0.6).

Resistance training is also considered an important component of a complete exercise program for older adults(12). It uses muscular contraction against resistance to mitigate the effects of aging on neuromuscular function and functional capacity(13). It also has the potential to improve muscle strength, mass and output(14). Older adults retain the ability to benefit from resistance exercise to a similar extent as younger adults(7). In addition to aerobic exercise, public health recommendations suggest that older adults perform resistance training at least two days per week to maintain function, health, and fitness(15). Few large, well-designed randomized controlled trials assessing resistance training on brain health outcomes have been conducted, although the available literature has proved promising(12, 16, 17).

1.2.2 Brain Health Mechanisms of Exercise

A wealth of animal research suggests that exercise positively impacts brain health(18–27). Exercise appears to stimulate neurogenesis(18) as evidenced by increased counts of new neurons in adult animals on an exercise regimen. Exercise is associated with enhanced neuronal survival(21), resistance to brain insults(19), and increased synaptic development and plasticity(22). Exercise promotes brain vascularization(23), increases learning(18), mobilizes gene expression profiles predicted to benefit brain plasticity(24), and maintains cognitive function(25). Additionally, exercise in cognitively normal older adults is associated with evidence of lower cerebral amyloid-beta, Aβ, deposition(26, 27). Exercise modulates vascular risk factors for dementia, decreases systemic inflammatory markers, increases levels of endogenously-produced, neuroprotective proteins such as brain derived neurotrophic factor (BDNF) that support neuronal growth and survival(28). Exercise also positively affects energy balance and glucose metabolism via actions on AMP kinase and insulin signaling, processes that have been suggested to increase Aβ trafficking and clearance(29).

Randomized clinical trials have examined the effects of resistance training on cognitive function and have found that participation results in improvements in executive function(30), memory(31), verbal fluency(31), and global cognition(31, 32). However, results have been inconsistent in showing that resistance training can prevent cognitive decline and AD(8).

The field has not directly assessed whether public health recommendations provide independent or combined effects on cognition in older adults. Conclusions from prior work are limited by design:

- 10 studies comparing resistance or combined exercise to a non-exercise control (16, 30, 33–36);

- Variability in aerobic exercise: walking, circuit training, running(37), swimming/aqua aerobics(38), etc.(8, 11);
- Variability in resistance training parameters including modality, weekly sessions, and progression(16, 30, 33–36).

1.2.3 Rationale for Studying Combined Exercise

Despite widespread recommendation for combined exercise, no studies have directly compared the effects of aerobic vs. resistance or combined training on cognition, although studies have assessed the differential impact of these exercise modalities on body weight and composition(39), insulin resistance(39–41), inflammation(42), and functional limitations(40, 41, 43). The results of these studies suggest that combining aerobic and resistance training is optimal for effects on insulin resistance(41) and physical function(41) but does not offer advantages for altering adiposity(44).

Resistance and aerobic training elicit different physiologic adaptations to cardiovascular, muscular, bioenergetic, and neuroendocrine systems(17, 36). Resistance training relies preferentially on anaerobic metabolism during the short but intense bouts of training. This improves muscle strength and quality while increasing high energy phosphate (ATP and creatine phosphate) availability, mitochondrial density, and oxidative capacity(7), effects that are generally not observed with aerobic exercise. In contrast, aerobic exercise training increases the capacity of muscle to generate energy though increased myoglobin content in muscle and increased efficiency of oxygen extraction and carbohydrate oxidation. Despite some concern that combined aerobic and resistance training will result in an “interference effect” where the development of strength during the same period might influence the development of aerobic capacity, and vice versa, several studies have found no evidence of this possible effect(42).

1.3 Hypotheses

Our guiding scientific premise is that standard public health recommendations will have benefits for brain health specific to the type of exercise performed. Specifically, we hypothesize that combined aerobic and resistance exercise will be associated with cognitive benefits, our primary outcome, and combining modalities will have additional benefits over either one alone. We hypothesize similar combined benefits for our secondary and ancillary outcomes of hippocampal volume, maximal oxygen consumption, maximal strength, and functional fitness.

2.0 Methods

This is a randomized controlled trial testing the effects of 52 weeks of aerobic, weight training or combined aerobic and weight training on cognition and brain structure in 280 cognitively normal older adults aged 65 to 80 years. Participants are equally randomized into one of four treatment groups:

1. Core and Fusion Training (CFT)
2. Resistance training (RT)

3. Aerobic training (AT)
4. Combined weight and aerobic training (COMBO)

Figure 1 provides an overview of the screening and study events. In addition, the ongoing IGNITE trial (NCT02875301 (10)) a 12-month, randomized dose-response exercise trial in 639 cognitively normal adults between 65 and 80 years of age to definitively addressing whether aerobic exercise influences cognitive and brain health in cognitively normal older adults helped to inform the methods of the COMET trials. During the IGNITE study, participants are randomized to (1) a moderate intensity aerobic exercise (3–6 METs) condition of 150 min/week (N = 213), (2) a moderate intensity aerobic exercise condition at 225 min/week (N = 213), or (3) a light intensity core and fusion control condition for 150 min/week (N = 213). Participants are engaged in 3 days/week of supervised exercise and two more days per week of unsupervised exercise for 12 months. A comprehensive cognitive battery, blood biomarkers and battery of psychosocial questionnaires is assessed at baseline, 6 and 12-months. In addition, brain magnetic resonance imaging, physiological biomarkers, cardiorespiratory fitness, physical function, and positron emission tomography of amyloid deposition are assessed at baseline and at the 12-month follow-up. While this trial does not explore the influence of resistance training or combination (COMBO) on cognitive and brain health, it does provide infrastructure that was leveraged to investigate the present studies aims.

2.1 Screening

2.1.1 Participant Recruitment

The KU ADRC is a national leader in developing and testing recruitment strategies for brain aging studies. COMET leverages the research recruitment infrastructure of the KU ADRC, reducing study staff load. Research inquiries are returned in a timely manner and all contacts are recorded to create continuity and track timely interactions managed with an in-house “participant relationship management” system we developed using REDCap (45) and Shiny (shiny.rstudio.com) (46). This system allows the team to manage interactions with potential participants, improve communication among staff and across teams, and reliably manage handoffs of participants from staff to staff. Referral source, enrollment progress, and recruitment strategy success are monitored in near real time.

2.1.2 Initial Eligibility

After initial interest screening by KU ADRC recruitment staff, the COMET study team phone screens potential participants prior to scheduling an in-person baseline evaluation. Screening occurs in two parts, basic study explanation, and medical history. We collect demographic information on those who express interest after hearing a basic explanation of the study. The medical history portion of the phone screen assesses inclusion and exclusion criteria (Table 1). Screening questions are asked in reverse order of likelihood(47) to capture the maximum amount of information from each screener. Source of referral is also captured for recruitment return-on-investment analyses.

2.2 Baseline Evaluation

Baseline evaluation consists of approximately 3 visits to the KU ADC within a time window of 35 days between consent initiation of exercise, for those who do not screen fail on the phone.

2.2.1 Cognitive testing

In consultation with the IGNITE study team, we have constructed a comparable battery, emphasizing key domains while reducing the overall time required for testing (Table 2). The battery captures global cognitive function while focusing on executive, attentive and visuospatial aspects of cognition specifically, as they appear to be most responsive to exercise(10). The same battery is administered at baseline, 6- and 12-month visits, with changes in form versions of tests as available. Cognitive testing is performed by a trained psychometrists after standardized training, who undergo annual fidelity checks. Testing takes approximately 2 hours to complete during 1 visit. Participants have the right to refuse to complete any test, however doing so may result in ineligibility.

2.2.1.2 Study Adjudication—A clinician interprets the baseline neuropsychological data and determines exclusion based on possible/probable cognitive impairment in the context of age, sex, race, ethnicity, reported schooling, and any other factors the medical monitor may consider important. A potential participant must be successfully adjudicated to be randomized.

2.2.2 Health and Activity Surveys

Health surveys focus on quality of life, psychological state, and self-reported activity (Table 3). The questionnaires are completed either during a study visit or done at home by the participants on paper or on computer via REDCap Survey. The battery takes about 1 hour to complete. The surveys are administered at baseline and 52 weeks.

2.2.3 Physical Assessment and Blood Collection

If a participant passes medical monitor adjudication of cognitive testing, they are scheduled for the fasting blood collection, anthropometry, and physical function assessment. Height, mass, and dual x-ray absorptiometry are performed to estimate body composition, wearing a standardized hospital gown. The Senior Fitness Test(48) is performed. One-repetition maximum leg press and chest press are used to index strength, following ACSM guidelines for administration(49). Finally, a graded maximal exercise test is performed, holding speed constant, and increasing grade by 2% each 2-minute stage, like a Modified Balke protocol(49, 50). Initial speed finding is performed by a blinded exercise test leader based on heart rate response and rating of perceived exertion after the Senior Fitness test. Blood collection is performed prior to the Senior Fitness Test and approximately 20 minutes after the end of the exercise test. The visit lasts approximately 2 hours and is performed at baseline and 52 weeks (Supplemental Material 1).

2.2.4 Brain MRI

Participants undergo an MRI at baseline and 52 weeks. While willingness to attempt MRI is required, if a participant is consented and cannot complete the MRI due to discomfort, they are not excluded from the study. Standard structural, functional, and cerebral blood flow protocols are followed to maximize comparison with IGNITE(10). Data collected consist of images of brain structure, cerebral blood flow, and function. To assess brain function, the n-Back task is used to index working memory(10). Before entering the MRI machine, participants the n-Back task that they will be performing. MRI Sequences include:

- **i.** T1-weighted magnetization prepared rapid acquisition gradient echo structural: sagittal, 0.8 mm isotropic resolution, TE/TI/TR = 2.31/1060/2400 ms, field of view 256 mm, 224 slices
- **ii.** High-resolution Hippocampus: 0.4×0.4×2 mm, TE/TR = 78/8830 ms, aligned perpendicular to hippocampus
- **iii.** Resting fMRI with eyes open (2.5×2.5×2.5 mm, TE/TR = 40/1000 ms, multiband factor = 8 (CMRR EPI sequence60–63), 64 slices, 480 measurements)
- **iv.** fMRI n-back task Resolution: 2.5×2.5×2.5 mm, TE/TR = 40/2000 ms, Multiband factor = 4, 64 slices, 183 measurements
- **v.** Pseudo-continuous arterial spin labeling: 3D gradient spin echo, sequence 64,65, 3.1×3.1×2.5 mm, TE/TR = 22.08/4300 ms, 48 slices, post-label delay 2s, Background Suppression, 10 measurements for labeling and control, 4 segment readout

The visit lasts approximately 75 minutes to complete.

2.3 Week 3 Assessments

The activity-specific questionnaires of the home survey battery are completed again during the third week of the intervention.

2.4 Week 26 Evaluation

At 26 weeks after intervention start (+/− 2 week), participants return for an in-person evaluation to repeat the cognitive testing (Table 2). Health surveys and self-efficacy assessments are administered (Table 3).

2.5 Week 52 Evaluation

At 52 weeks after intervention start (+/− 2 weeks), participants return for an in-person evaluation to repeat the cognitive testing (Table 2), physical function testing, MRI, and health surveys (Table 3) are administered.

2.6 Telephone Checks

Participants are contacted by phone for formal review of medication changes, medical history, and adverse events in the first week of initiating the exercise intervention and again

at Weeks 6, 13, 19, 32, 39, and 45 during the active intervention. Additionally, the telephone checks facilitate communication between the study team and the participants and encourage compliance with the intervention, supplementing regular supervised training session.

2.7 Randomization and Blinding

2.7.1 Randomization

Upon successful completion of baseline screening and testing, participants are randomized to 1 of 4 study arms. Intervention arms include:

- **a.** core and fusion training (CF) condition,
- **b.** 150 minutes of aerobic training (AT) only,
- **c.** 2 days a week of progressive weight training (RT) only,
- **d.** 150 minutes of AT and RT.

We use the REDCap randomization module including a block randomization strategy to balance two factors: (1) age at study entry (=<72, >72), and (2) gender. We allow co-randomization for a limited number of couples (married, domestic partner etc.) with the intent of increasing male enrollment in the study(51). If a couple passes screening, they are randomized as one to the same group. A limited number of unblinded study staff can reveal the group assignment and none have access to the randomization table created by the study statistician prior to study start. Also, at the time of randomization, a staff member organizes date, day, time, and location of the participant's first exercise session.

2.7.2 Blinding

Raters (psychometrician, exercise physiologist) who perform outcome assessments are blinded to the participant's intervention group. The study medical monitor is unblinded to assist with safety assessments and address safety concerns or adverse events.

The MPIs are blinded to primary and secondary outcomes identified in ClinicalTrials.gov. The MPI team may have access to group assignments. This may be needed in the event exercise modification is needed by a physical therapist (i.e., PI Vidoni). However, any interventionist interactions or exercise prescription changes by the MPI team must be recorded.

2.8 Exercise Intervention Arms

This study tests aerobic and resistance exercise as they form the core of the current consensus recommendations for general health benefits(52, 53). Our intervention plans follow current public health recommendations. All participants, regardless of intervention assignment complete both supervised and unsupervised exercise during the study. Table 4 provides planned number of exercise visits.

1. **Aerobic training (AT):** moderate-intensity aerobic training (150 minutes/week over 3–5 days). Exercise duration is increased from 60 minutes in the first week to 150 minutes in the seventh week. Intensity is dosed by heart rate reserve

(HRR) using the resting maximum heart rate achieved during the Physical Assessment visit. Target intensity is 40–50% HRR in Weeks 1–12, 45–55% HRR in Weeks 13–39, and 50–60% HRR in Weeks 40–52.

2. **Progressive weight training (RT):** 2 days/week, non-consecutive, of 2 sets (10 – 15 repetitions) of 10 exercises (~75 minutes/week). Resistance progression is based on repetition completion, and increases from 60–75% of estimated 1-repetition maximum of each exercise. In addition, 3 days of core and fusion control exercise is also recommended for a total of about 150 minutes a week of exercise.
3. **Combined training (COMBO):** 150 minutes/week of aerobic training and 2 days/week of resistance exercise for a total training duration of ~225 minutes/week).
4. **Core and Fusion (CFT):** ~150 minutes/week of core and fusion exercise as implemented in IGNITE, previously(10).

Additional details regarding these conditions can be found in Supplemental Material 2.

2.9 Exercise Compliance

Participants in the study complete part of the exercise under supervised conditions and part of the exercise under unsupervised conditions. Monitoring compliance during the supervised exercise is assisted by trainers monitoring attendance, duration of exercise, perceived exertion, mode of activity, and heart rate intensity. However, compliance during the unsupervised sessions is inherently more challenging. COMET takes a two-faceted approach for monitoring compliance during the unsupervised periods. First, participants summarize their weekly exercise via a REDCap survey or paper log. These summaries are a natural component of training since training involves the identification of barriers and approaches to overcoming non-compliance while keeping individuals engaged and continuing to return for the sessions. We provide feedback to participants to assist with compliance by helping them see exercise activity increases.

In addition to the self-reported exercise summaries, participants are encouraged to wear their Fitbits' daily throughout the 52-week exercise period. Fitbit data are gathered nightly through the Fitbit application programming interface. Compliance with the exercise prescription is based on the information gathered from the weekly summary, the supervised exercise sessions, and the accelerometer recording.

Participants are provided with email correspondence about their weekly performance and upcoming exercise prescription. Emails include name, historical information on their exercise and performance, and their upcoming prescription. Participants who do not have email receive paper correspondence with the same information via their personal trainer.

2.10 Outcomes and Analysis plan

The primary outcome is Global Cognition, a composite score of cognition test scores. Global Cognition will be calculated as a latent variable of the results across the cognitive test

battery. We will use a second order confirmatory factor analysis (CFA) to estimate the factor loadings between the observed indicators and the first order factors and between the first and second order factors. The CFA will use baseline data to avoid any potential intervention related biases. The primary outcome will be constructed by summing the weighted average (by the estimated first and second order loadings) of the standardized observed scores across the fourteen tests. Global Cognition will be analyzed with a linear mixed model (LMM) with intent-to-treat using baseline, 26- and 52-week measures while adjusting for measurements obtained at baseline (i.e., demographics). Since there is only one primary outcome, we will test with $\alpha = 0.05$. Secondary outcomes including whole brain volume, fitness and strength will be analyzed using similar strategies. Post-hoc analyses will include linear contrasts for resistance training vs control and endurance exercise vs control. With 280 patients and 15% attrition we expect to be able to detect a significant benefit of combined training for an effect size of 0.60 with >80% power.

We will employ an intent-to-treat analysis where all participants, regardless of whether they complete all sessions, are invited to return for follow-up assessments. However, there will likely be some participants who refuse to return for follow-up assessments or miss a mid-point assessment (cognitive and questionnaires are collected at the 6-month period). We will assess the missingness of data consistent with the assumptions of the modeling approach described above. We will determine if the proportion of participants lost to follow-up differs by treatment and demographic characteristics between completers and non-completers. If missing data are related to treatment and/or demographic characteristics (e.g., sex, baseline weight, etc. with $p< 0.05$) then we will assume the data is missing at random (MAR) and we will use model-based imputation since multiple imputation will only provide unbiased estimates if enough variables predictive of missingness are included in the model(54). If missingness is not related to these variables we will not use multiple imputation since linear mixed models do not require complete cases to provide unbiased estimates assuming the data is missing completely at random (MCAR) and neither mixed models nor imputation models are guaranteed to provide unbiased estimated if the data is not missing at random. Additional information can be found in supplemental material 3.

2.11 Community-Based Exercise

2.11.1 Intervention Supervision

Participants can exercise at any study approved exercise facilities for which we have established relationships. We have previously reported on our community exercise protocols(50) which predominantly use the YMCA network. Each YMCA employs certified personal trainers who conduct the exercise session. Direct supervision of participants by personal trainers occurs throughout the 52-week intervention. We introduce more flexibility in scheduling exercise after Week 26 if the participant is consistently and safely exercising by allowing unsupervised exercise sessions at the YMCA at times when personal trainers may not be available (i.e. early morning, nights, and weekends). Participants are required to have at least one directly supervised exercise session per week to maintain contact with program staff and encourage adherence to the program. This titration procedure has been successful in several completed (R01AG033673, R01AG034614) and ongoing studies

(R01AG052954, R01AG49749, R01AG043962). YMCA trainers are asked to report anyone who has missed two weeks or more of supervised exercise to study staff. Study staff will then follow-up with the participant. Additional information on study safety can be found in Supplemental Material 4.

Trainers are oriented to the COMET protocol and are monitored during an annual fidelity check-off with study staff. Additionally, all participants are observed by study staff quarterly, providing additional opportunities to assess protocol fidelity and remediate deviations.

2.12 Data Management

Behavioral data are stored and linked on a HIPAA secure server (REDcap)(45). Imaging data are archived and stored using XNAT. Both REDcap and XNAT allow investigators to access data and coordinate analyses. Fitbit activity monitor data are harvested nightly from the Fitbit server and stored on protected university servers, but these data also exist on the Fitbit company server. To provide additional security, no protected health information is entered as part of Fitbit account creation. Additional information on quality control and data curation is available in Supplemental Methods 5.

3.0 Conclusion

Regular aerobic and resistance training decreases age-related morbidity and mortality, improves risk factors for chronic disease, and helps maintain independent functioning(3, 4, 7). Yet, trials exploring cognitive and brain effect of other exercise modalities and the potential interactions of modalities, key to sustaining function, are still lacking. Thus, a more precise understanding of the role and impact of current exercise recommendations on cognitive function is essential knowledge for our healthcare force and for convincing the millions of older adults in the US who do not currently meet all aspects of the recommendations. The COMET Study is vital to providing clinicians, researchers, public health organizations, and policy makers information of the independent and combined importance of aerobic and resistance exercise treatments on cognitive and physiological health of older adults. This study is among the first and likely the largest, exercise-specific randomized controlled trial to assess the independent and combined effect of aerobic training and resistance training on cognition in older adults withing the context of the public health recommendations(5–7, 15). The COMET study will provide rigorous randomized controlled trial data to understand the effects of the most common exercise modalities (AT and RT) more precisely, and their combination (i.e., public health recommendation), on brain health. In addition, the design selected, is potentially deployable as is uses community partners (i.e., YMCA and other local exercise facilities) to deliver the exercise prescription.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding:

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Abbreviations:

NIH	National Institutes of Health
CDC	Centers for Disease Control and Prevention
ACSM	American College of Sports Medicine
AD	Alzheimer's Disease
Aβ	Amyloid Beta
BDNF	Brain Derived Neurotrophic Factor
WHO	World Health Organization
ATP	Adenosine triphosphate
COMET	Combined Exercise Trial
KU ADRC	University of Kansas Alzheimer's Disease Research Center
fMRI	functional Magnetic Resonance Imaging
DXA	Dual-energy x-ray absorptiometry
SFT	Senior Fitness Test
1RM	1-Repetition Maximum
CPET	Cardiopulmonary Exercise Test
RPE	Rating of Perceived Exertion
PCASL	Pseudo-Continuous Arterial Spin Labeling
fMRI	Functional Magnetic Resonance Imaging
CF	Core and Fusion
RT	Resistance Training
AT	Aerobic Training
MCAR	Missing completely at random
MAR	Missing at random
QC	Quality Control
LMM	Linear Mixed Model
OLS	Ordinary least squares
IGF-1	Insulin Growth Factor-1
DSMC	Data and Safety Monitoring Committee

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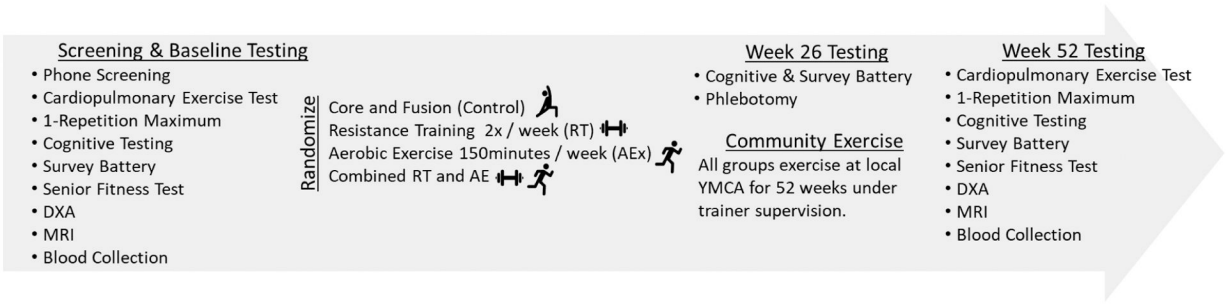

Figure 1.
Study Flow and Schedule of Testing

Table 1.

Inclusion and Exclusion Criteria

Inclusion criteria	Exclusion criteria
• Age 65–80 yrs (inclusive at time of consent). • Able to speak and read English conversantly. • Medical clearance by a healthcare provider. • Reliable means of transportation. • Telephone Interview of Cognitive Status score > 25(55, 56) and adjudication of normal cognition based on cognitive test data by a study medical monitor.	• Intention to move out of the area or travel for more than 4 weeks in the next year. • Use of an assistive device for ambulation. • Joint pain severe enough to prevent taking walks in community, lifting objects over your head due to pain or restriction of movement, or that is worsened by increasing physical activity. • Any MRI contraindications or refusal to attempt MRI. • Treatment for alcohol or substance abuse in the last 2 years. • Treatment for cancer (other than non-metastatic, localized cancer) in the last 2 years. • Currently taking insulin. • Diagnosis of heart disease, heart failure, heart attack, heart surgery, chest pain with effort, atrial fibrillation, valve replacements, angioplasty or stent placement unless cleared by primary cardiac provider. (If in cardiac rehabilitation, must be in independent maintenance phase). • History of major psychiatric illness including schizophrenia (not including general anxiety disorder or depression), MS, Parkinson's, Dementia, MCI, brain injury (traumatic or clinically evident Stroke), or similar, likely to negatively impact cognitive testing. • Head injury with loss of consciousness for more than a few minutes. • Change in blood pressure medication in the last 2 months. • Considered "Active" or engaging in a progressive resistance training 2 or more times a week per TAPA(57)

Table 2.

Cognitive Testing Battery

Task	Time	Description
WECHSLER TEST OF ADULT READING(58)	3 min	This test asks participants to pronounce a list of words that are recorded. It is a proxy of IQ. This will be administered only at baseline.
HOPKINS VERBAL LEARNING TEST-REVISED(59)	10 min	This is a word list learning and memory task that measures immediate and short-term and longer-term retention. It consists of three presentations with recall of a 12-word list, a delayed recall trial (20 minutes after Trial 3), and a delayed recognition trial. It is recorded for review.
DIMENSIONAL CARD SORT- NIH TOOLBOX(60)	4 min	Two target pictures are presented that vary along two dimensions (e.g. shape and color). Participants are asked to match a series of test pictures (e.g. yellow balls and blue trucks) to the target pictures, first according to one dimension (e.g. color) and then, after several trials, according to the other dimension (e.g. shape).
ORAL SYMBOL DIGIT TEST-NIH TOOLBOX(61)	3 min	Symbols on the screen are associated with a number, then presented with symbols without numbers.
FLANKER-NIH TOOLBOX(60)	3 min	The task requires the participant to focus on a particular stimulus while inhibiting attention to the stimuli flanking.
LOGICAL MEMORY-VCAP(62)	10 min	Participants are read stories and asked to recite as much as they remember at two different time points during testing.
SPATIAL RELATIONS-VCAP(63)	15 min	Participants are asked to determine the correspondence between a 3-D figure and alternative 2-D figures.
MATRIX REASONING-VCAP(64)	15 min	Participant determines which pattern best completes the missing cell in a matrix.
TASK SWITCHING(10)	15 min	This task asks participants to alternate between attention to stimuli presented on a computer display. Participants are asked to response to whether the number is greater than or less than 5 (task 1) or to respond to whether the number is odd or even (task 2).
LETTER COMPARISON-VCAP(65)	5 min	In this task participants are asked to determine whether a series of letters is the same as another series of letters. They are asked to do this as quickly as they can.
SPATIAL WORKING MEMORY(11)	15 min	This Task measures spatial memory functions. It requires that participants attend to and retain the location of several dots presented simultaneously on a computer display. They are requested to press buttons on a keyboard that correspond to whether a probe dot appeared in one of the same locations as the previous dots.
STROOP TASK(10)	10 min	This task measures selective attention, cognitive flexibility and processing speed and is used as a tool in the evaluation of executive function. This task is administered on a computer and the participants are asked to respond to the colors of the ink for printed words on the display as quickly as they can while ignoring the meaning of the word.

Table 3.

Health and Activity Surveys

CONSTRUCT	SURVEY
DEMOGRAPHICS AND HEALTH HISTORY	Cumulative Illness Rating Scale (CIRS), at in-person screening) (66)
	Medication List
	MacArthur Scale of Subjective Social Status(67)
ACTIVITY	Florida Cognitive Activities Scale(68)
	Godin Exercise Leisure-time Questionnaire(69)
SUBJECTIVE COGNITION AND PSYCHOLOGICAL DISTRESS	Cognitive Function Index(70)
	PROMIS Applied Cognition: General Concern(71)
	PROMIS Anxiety(72)
	PROMIS Depression(72)
	Perceived Stress Scale (PSS-10)(73)
DIET AND NUTRITION	NHANES DSQ(74)
QUALITY OF LIFE	PROMIS: Life Satisfaction(75)
	EQ-5D-5L(76)
PHYSICAL AND SOCIAL ROLES	PROMIS Physical Function(77)
	PROMIS Ability to Participate in Social Roles and Activities(78)
SELF-EFFICACY AND SELF-REGULATION (AT BASELINE, 3, 26, AND 52 WEEKS)	Barriers Self-Efficacy Scale (BARSE)(79)
	Exercise Self-Efficacy (EXSE)(80)
	Lifestyle Self-Efficacy Scale (LSE)(81)
	Physical Activity Self-Regulation (PASR-12)(82)
SLEEP/CIRCADIAN	Pittsburgh Sleep Quality Index (PSQI)(83)

Table 4

Planned exercise visits per week by intervention group

Design Overview	Intervention groups											
	CFT			RT			AT			COMBO		
	Weeks			Weeks			Weeks			Weeks		
Supervised Exercise	1–26	27–36	37–52	1–26	27–36	37–52	1–26	27–36	37–52	1–26	27–36	37–52
RT w/Trainer				2	1	1				2	1	1
Core and Fusion Exercise w/Trainer	3	2	1	1	1	0						
AT w/Trainer							3	2	1	1	1	0
Independent Exercise												
RT						1					1	1
Core and Fusion	2	3	4	2	2	3						
AT							2	3	4	2	3	4
Total Exercise Sessions	5	5	5	5	5	5	5	5	5	5	5	5

CFT= Core and Fusion Training; RT= Weight Training; AT= Aerobic Training; COMBO= RT+AT