FLADEX Project

Understanding cerebral blood Flow dynamics for Alzheimer's Disease prevention through EXercise

Study protocol

University of Granada, Spain
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2. Trial Summary

Official Title: Understanding cerebral blood flow dynamics for Alzheimer's Disease prevention through acute exercise. Protocol for a randomized controlled trial with crossover design

Brief title: flADex project

ClinicalTrials.gov ID: **NCT06584656**

Study ID: PID2022-137399OB-I00

Brief summary: flADex is a counterbalanced crossover trial in 20 older adults designed to examine the acute effects of different types of exercise (resistance vs. aerobic vs. control) on cerebral blood flow (CBF) and blood biomarkers for Alzheimer's Disease (AD), and their cognitive implications.

Keywords: dementia, magnetic resonance imaging, cerebral blood flow, blood biomarkers, physical exercise.

Detailed summary:

Introduction:

Dementia is a leading cause of disability worldwide. Underlying biological mechanisms are crucial in preclinical stages of Alzheimer's disease (AD). For instance, alterations in cerebral blood flow (CBF) and AD blood biomarkers may be fundamental at early stages of the pathology. Notably, physical exercise is one of the most promising non-pharmacological interventions to delay the onset of dementia and slow down the progression of cognitive decline. Yet, the specific mechanistic pathways by which exercise modulates brain health in late adulthood remain largely understudied. FlADex aims to examine the acute effects of different types of exercise on CBF, blood biomarkers for AD pathology, neurodegeneration and growth factors, and their cognitive implications in older adults. This protocol provides the description and rationale of the flADex trial.

Methods:

FlADex is a counterbalanced crossover trial that will include 20 adults aged 68 to 83 with negative brain amyloid status (<12 centiloid) and APOE e4 noncarriers. All participants will complete one 30-minute session of each study condition in a randomized order: (i) moderate-intensity aerobic exercise (maximal heart rate (HRmax): 60-70%); (ii); moderate-intensity resistance exercise (rating of perceived exertion: 4-6/10 points) and (iii) control resting condition. CBF– primary outcome– will be assessed by magnetic resonance imaging using pseudo-continuous arterial spin labeling at pre- and at 3 timepoints post-condition (at 20, 27, 34 min). Blood biomarkers for AD and neurodegeneration (e.g., Aβ42, Aβ40, p-tau217, p-tau181, BD-tau, GFAP, NfL) and growth factors (e.g., BDNF, IGF-1) will

be measured pre- and post-condition (at 3, 50, 70 min). Cognitive outcomes (i.e., Flanker test and Picture sequence memory test) and mood status (i.e., POMS questionnaire and feeling scale) will be measured pre- and post-condition.

Expected conclusions:

The flADex trial will shed light on the acute effects of different types of exercise on CBF and blood biomarkers in older adults before beta-amyloid accumulation begins. We expect that aerobic and resistance exercise will have different effects on CBF dynamics and blood biomarker levels over time in older adults.

3. Scientific background and rationale

Dementia encompasses a range of neurodegenerative disorders characterized by progressive cognitive decline and impaired functional abilities. Alzheimer's Disease (AD) is the most prevalent form of dementia, accounting for 60-70% of cases, and is marked by a gradual deterioration in memory, thinking, and behaviour (3,4). The cognitive impairment associated with aging can range from mild symptoms to more severe cases, with pathophysiological signs of AD appearing 10-20 years before the onset of cognitive losses (5).

AD progresses often from preclinical stages to dementia, involving gradual memory loss and cognitive impairment. Notably, physical exercise is one of the most promising non-pharmacological interventions to delay the onset of dementia and slow down the progression of cognitive decline. Studies have explored the effects of physical exercise on CBF, highlighting improvements associated with both aerobic and strength exercise
(11,12). While most research on interventions to improve CBF focuses on chronic exercise programs, there is increasing interest in understanding the acute benefits of physical exercise (13). Therefore, flADex aims to examine the acute effects of different types of exercise on CBF, blood biomarkers, and its cognitive implications in older adults.

4. Objectives

The <u>overall objective</u> of the flADex trial is to investigate the acute effects of a single bout of different types of exercise on brain health in older adults.

The <u>primary objective</u> of the flADex trial is to examine the acute effects of different types of exercise (resistance exercise vs. aerobic exercise vs. resting condition) on global and regional CBF, blood biomarkers for AD and neurodegeneration (Aβ42, Aβ40, p-tau217, p-tau231, brain-derived tau [BD-

tau], Anti-Glial Fibrillary Acidic Protein [GFAP] and NfL) and growth factors (BDNF, IGF-1), and their cognitive implications in older adults.

The secondary objectives of the flADex trial are to examine:

(i) the acute effect of a single bout of resistance exercise vs. aerobic exercise vs. resting condition on blood biomarkers in older adults;

(ii) the acute effect of a single bout of resistance exercise vs. aerobic exercise vs. resting condition on cognitive and mood outcomes in older adults;

(iii) whether exercise-induced changes in CBF mediate changes in blood biomarkers (or vice versa) in older adults; and,

(iv) whether exercise-induced changes in CBF or blood biomarkers mediate changes in cognitive and mood outcomes in older adults.

5. Trial Design

FlADex will follow a repeated measures within-subject crossover design in 20 individuals (10 males and 10 females) aged 68-83. Figure 1 shows the study design and participant flow of the flADex trial. The study will be performed at two research institutes from the University of Granada (Granada, Spain): (i) Instituto Mixto Universitario Deporte y Salud (iMUDS); and (ii) Centro de Investigación Mente, Cerebro Y Comportamiento (CiMCYC).

The study is already registered in the clinicaltrial.gov database (NCT06584656; approval date: 04-09-24). The trial will be conducted in accordance with the principles of the Declaration of Helsinki and has been approved by the Research Ethics Board of the Andalusian Health Service (CEIM/CEI Provincial de Granada; #SICEIA-2024-000602, 30/04/2024). All participants will provide written informed consent once all study details have been explained. Manuals of the trial procedures will be made available to ensure transparency and credibility of the study findings, as well as to allow other researchers to replicate the results if necessary (https://github.com/fladexprojectugr). The study has been designed following the Standard Protocol Items for Randomized Interventional Trials (SPIRIT) (1,2), the SPIRIT-Outcomes 2022 Extension (3) (Supplementary Table S1), and the Consolidated Standards of Reporting Trials (CONSORT) 2020 statement for extension to randomized crossover trials (4). Any significant changes to the protocol will be reported to the trial registry and the Research Ethics Board. Moreover, participants in the flADex trial are insured under a social responsibility policy from the University of Granada, which covers ancillary services, care or compensation, if necessary.

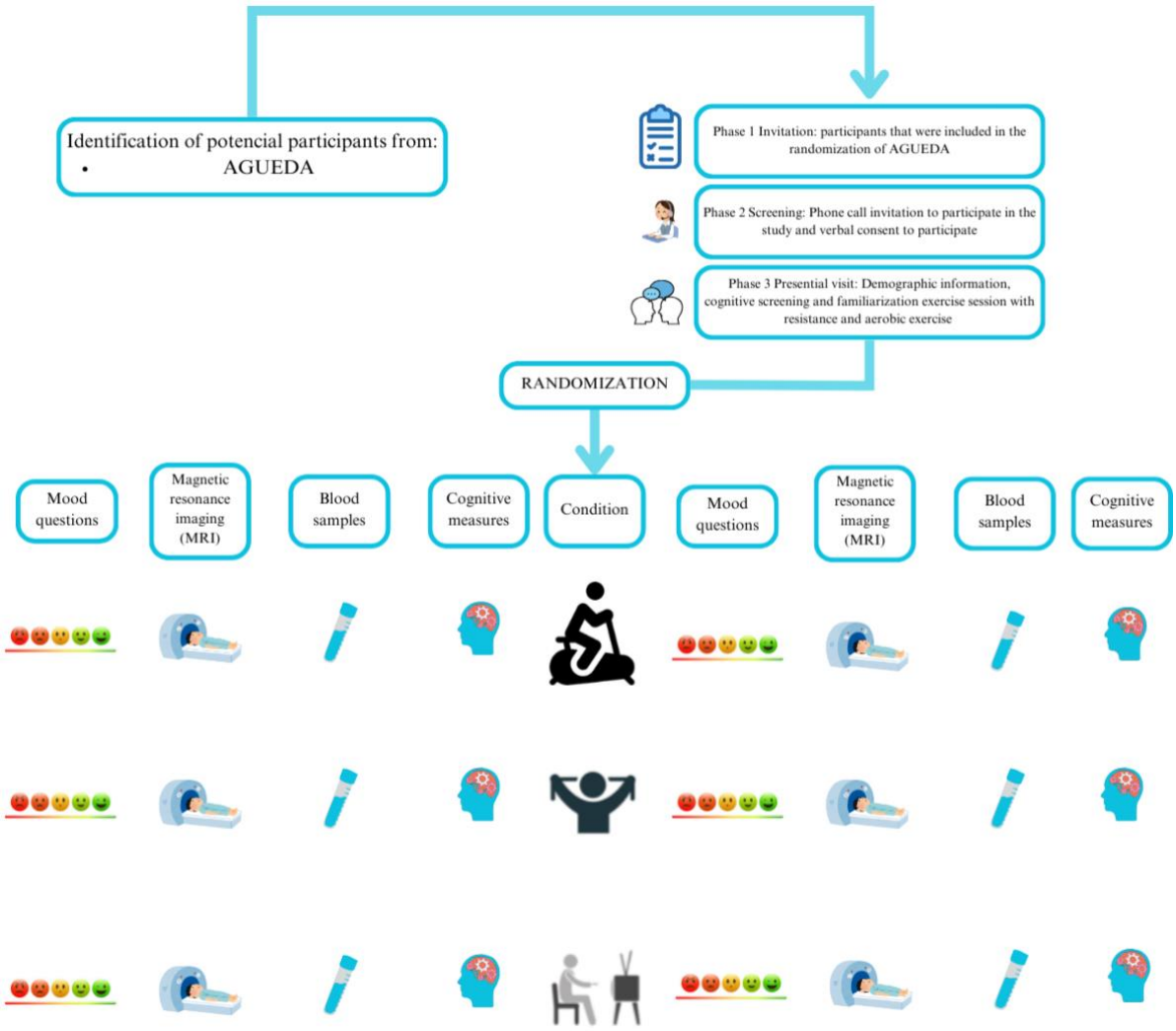

Fig 1. Study design and participant flow.

6. Screening and recruitment

Participant selection follows the process illustrated in Fig. 2, including individuals who were previously enrolled in the AGUEDA trial. All participants from AGUEDA between 68 and 83 years, who meet the negative brain amyloid criteria and APOE negative status will receive a phone call invitation to participate in flADex trial. Figure 2 shows the flowchart for participants initially eligible for the flADex trial. From the 90 participants randomized in the pre-assessment of the AGUEDA project, 80 completed the trial. Among those, 26 participants were excluded for amyloid beta positivity (n=17) or APOE e4 carriers (n=26). Thus, 53 participants (n=31 females) met the initial eligibility criteria for flADex. Participants will be called to perform a phone screening with some eligibility questions regarding health, medications, and MRI. Then, participants will receive a detailed explanation of the flADex trial, benefits and potential risk, as well as the complete schedule and organization of assessments. Recruitment was set to begin in September 2024.

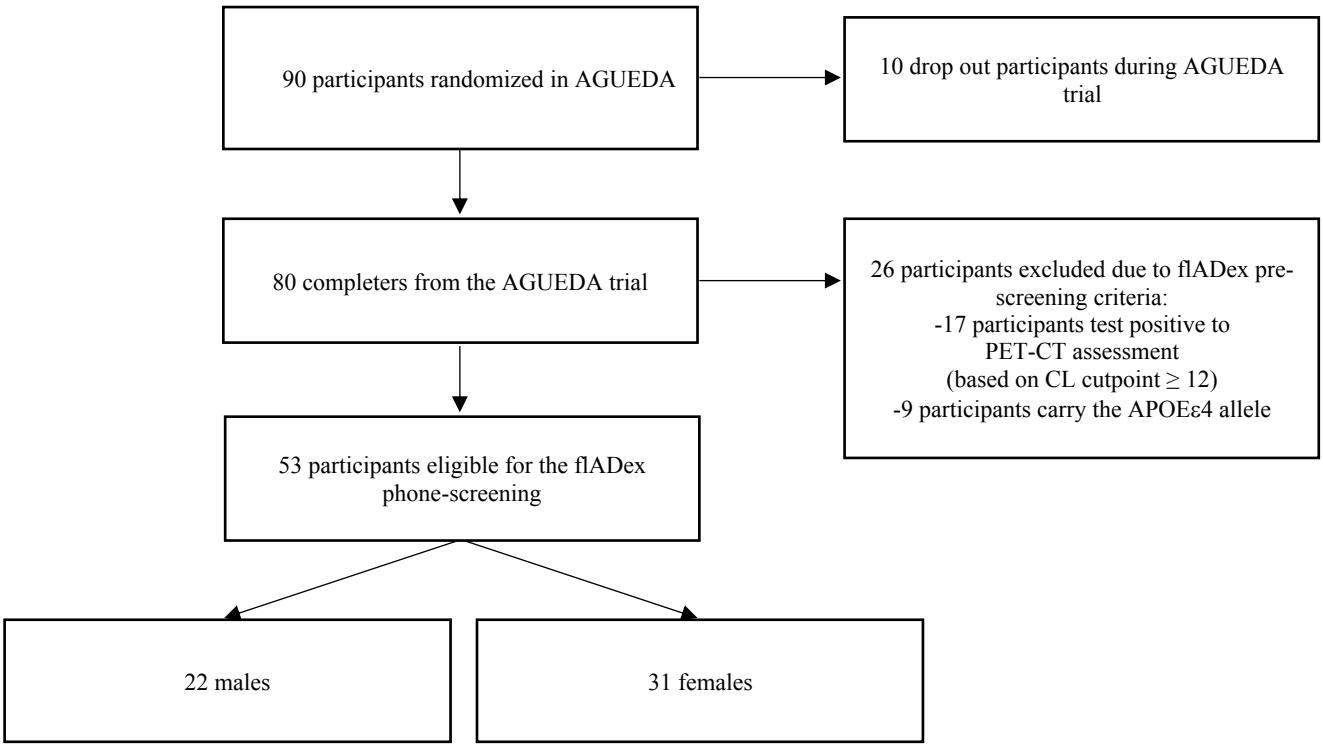

Fig 2. Recruitment and screening of participants.

7. Eligibility criteria

We plan to enroll 20 older adults (balanced sex distribution). Eligibility criteria will be checked in two phases, pre-screening phase and phone-screening phase. In the pre-screening phase, participants will be checked for the following inclusion criteria: (i) non-pathological cerebral beta-amyloid status (based on Centiloid cut-point <12 measured by PET), and (ii) APOEe4 non-carriers. Then, additional exclusion criteria will be screened during the phone-screening phase: (i) ambulatory with pain or regular use of an assisted walking device; (ii) not living in community settings during the study; (iii) pathological diagnosis related to physical or mental condition; and (iv) MRI incompatibility. The eligibility criteria for the flADex study are shown in Table 1.

Table 1. Inclusion and exclusion criteria of the flADex trial

Inclusion Criteria	Exclusion Criteria
Older adults aged between 68 and 83 years	Ambulatory with pain or regular use of an assisted walking device
Non-pathological cerebral beta-amyloid status (based on a Centiloid cut-point <12, measured by PET-CT)	Not living in community settings during the study
APOEe4 negative status	Pathological diagnosis related to any physical or mental condition
	MRI incompatibility
	Only participants who meet two main inclusion criteria will be initially eligible for the flADex study

8. Outcome measures

Primary outcome measures:

1. Change in Cerebral Blood Flow (CBF). Specific acquisition parameters for Pseudo continuous Arterial Spin Labeling (pCASL) sequence will be used to determine global and regional CBF in resting condition. Structural T1 sequence (only pre-condition) will be used to coregister the pCASL and delineate regions of interest for CBF. Time-of-flight angiography (TOF) (before pCASL pre-condition and before first pCASL post-condition) sequence will be used to identify the carotid arteries. Unit of measurement of CBF: milliliters per 100 grams of brain tissue per minute (mL/100 g/min).
Time frame: 30 minutes before the experimental condition; and 20, 27 and 34 minutes after the experimental condition.

Secondary outcome measures:

1. Change in AD blood biomarkers (Aβ42/40 ratio). The following biomarkers will be assessed: Amyloid-beta 42 (Aβ42), Amyloid-beta 40 (Aβ40). Aβ42 and Aβ40 will be combined to report Aβ42/40 ratio. Unit of measurement: Aβ42/40 is a ratio (no units) and represents the relative concentration of Aβ42 to Aβ40.
Time frame: 5 minutes before the experimental condition; and 3, 50 and 70 minutes after the experimental condition.

2. Change in AD and neurodegeneration blood biomarkers (p-tau217, p-tau181, BD-tau, NfL and GFAP). The following biomarkers will be assessed: phosphorylated tau protein at positions 217 and 181 (p-tau217, p-tau181), brain-derived tau (BD-tau), Glial Fibrillary Acidic Protein (GFAP) and

Neurofilament Light Chain (NfL). Unit of measurement: p-tau217, p-tau181, BD-tau, NfL and GFAP are commonly measured in picograms per milliliter (pg/mL).
Time frame: 5 minutes before the experimental condition; and 0 minutes, 50 minutes and 70 minutes after the experimental condition.

3. Change in growth factors (BDNF). Brain-Derived Neurotrophic Factor (BDNF) will be measured. Unit of measurement: BDNF is commonly measured in picograms per milliliter (pg/mL).
Time frame: 5 minutes before the experimental condition; and 0 minutes, 50 minutes and 70 minutes after the experimental condition.

4. Change in growth factors (IGF-1). Insulin-Like Growth Factor 1 (IGF-1) will be measured. Unit of measurement: IGF-1 is commonly measured in nanograms per milliliter (ng/mL).
Time frame: 5 minutes before the experimental condition; and 0 minutes, 50 minutes and 70 minutes after the experimental condition.

5. Change in episodic memory assessed using the Picture Sequence Memory Test from the Cognitive NIH Toolbox. The Cognitive NIH Toolbox is a computer-based battery which is available in Spanish. The Picture Sequence Memory Test measures episodic memory. The raw score from the cumulative number of adjacent pairs of pictures remembered correctly over two learning trials will be used as outcome.
Time frame: 15 minutes before the experimental condition and 60 minutes after the experimental condition.

6. Change in inhibition/attention. The Flanker task measures inhibitory control and attention. The outcome will be the inverse efficiency score of incongruent trials calculated as reaction time/accuracy (RT/ACC).
Time frame: 15 minutes before the experimental condition; and 60 minutes after the experimental condition.
7. Mood status. The Profile of Mood States (POMS) scale is a psychological assessment tool used to measure and evaluate a person's mood states. It consists of a questionnaire with a list of 15 adjectives or mood descriptors, where individuals rate how they have been feeling on a scale typically ranging from "Not at all" to "Extremely". We use an abbreviated version of the scale with 15 items divided into 5 dimensions: depression, vigour, anger, tension and fatigue. The final score is: ([depression]+[anger]+[tension]+[fatigue]) - [vigour]).

Time frame: POMS will be measured 60 minutes before the experimental condition; and 70 minutes after the experimental condition.

8. Emotional response. The feeling scale (FS) is an 11-point scale ranging from -5 (very bad) to +5 (very good) used to measure an individual's emotional feeling in terms of pleasure or displeasure at a specific moment.
Time frame: Feeling scale will be measured 1 minute before the experimental condition; and 1 minute after the experimental condition.

Exercise-related variables

1. *Rate of perceived exertion* (in aerobic condition and resistance condition).
Measure description: Rating of perceived exertion (RPE) will be assessed during the exercise conditions using the OMNI-Resistance Exercise Scale (OMNI-RES) of perceived exertion from 0-10 points.
Time frame: During the experimental condition at minutes 12, 20, and 30.

2. *Cognitive engagement.*
Measure description: Cognitive engagement will be assessed by the Cognitive Load Measurement scale. The Cognitive Load Scale is a 9-item scale used to assess the mental effort or cognitive load experienced by individuals when engaging in a task, particularly in educational or learning contexts. It involves a self-reported measure where participants rate their perceived mental effort on a scale, ranging from 1 very low mental effort; to 9 very high mental effort.
Time frame: During the experimental condition at minutes 12, 20, and 30.

3. *Heart rate (HR).*
Measure description: HR will be continuously monitored second-by-second during all three conditions using a Polar H10 monitor, which includes a chest strap and wristwatch.
Timeframe: During all conditions.

4. *Repetitions in reserve (in resistance condition).*
Measure description: The Repetitions in Reserve (RIR) will be assessed after each exercise in the resistance condition. The RIR method is a self-regulation technique used in strength training to gauge

exercise intensity. It involves estimating how many more repetitions you could perform before reaching failure after completing a set.
Time frame: During the resistance condition after each exercise at minutes 5, 6, 7, 8, 9, 10, 11, 12 / 14, 15, 16, 17, 18, 19, 20, 21 / 23, 24, 25, 26, 27, 28, 29, 30.

5. *Enjoyment.*
Enjoyment of Physical activity will be assessed using the Physical activity Enjoyment scale (PACES): The PACES is an 18-item scale, but we will use the reduced and validated version of 8 items, assessing in a range of 1 to 7 a series of sensations or moods with respect to its opposite.
Time frame: 5 minutes after the experimental condition.

6. *Blood pressure (BP).*
Measure description: BP will be measured using a validated automated monitor (Omron M3, Intellisense, OMRON Healthcare Europe, Spain) with participants seated and their left arm at heart level. After 5 minutes of rest, two readings will be taken at 1-minute intervals, and the average of the readings will be used for analysis.
Timeframe: 60 minutes before the experimental condition and one minute after the experimental condition.

7. *Temperature.*
Measure description: Body temperature will be measured using a digital infrared forehead thermometer (iPiccoli, AET-R1B1), with participants standing, ensuring their forehead is clean and free from sweat.
Timeframe: 50 minutes before the experimental condition and 20 minutes after the experimental condition.

9. Sample size calculations and statistical analysis
Previous studies on acute exercise have shown that a single session of exercise changed CBF by 15% (5) and 9% (6). Specifically, the sample size is based on the mean changes (M) in CBF of 6 mL/100 g/min (M1=40.5 and M2=34.2) with a standard deviation (SD) of 6.46 mL/100 g/min. Considering the calculation of Cohen's d based on previous studies (d=M1-M2/combined SD), we expect a large effect size (Cohen's d = 0.9) (7). Therefore, using an alpha of 0.05 and a standard power of 80%, a sample size of 20 is needed. Participants who withdraw will be replaced. Thus, the experiment will be completed when at least 20 participants have completed all three experimental conditions.

The flADex trial will analyze primary and secondary outcomes using a per-protocol approach with linear mixed models. The model will include fixed effects for time (four or two levels depending on the outcome), condition (three levels), time*condition interaction, as well as the unique participant identifier as a random effect, while handling missing data and assessing model assumptions. Condition effects will be assessed using time-by-treatment interactions, estimated marginal means with 95% confidence intervals, and a significance level of $p < 0.05$ for two-tailed tests.
Mediation analyses will follow AGReMA guidelines, exploring CBF and blood biomarkers as mediators for cognitive, mood, and biomarker outcomes, complemented by correlation analyses. Exercise parameters (e.g., RPE, HR, enjoyment) will be descriptively reported to confirm target intensities, and exploratory moderation analyses will investigate sex differences in CBF responses across conditions, acknowledging limited statistical power.

10. Treatments / Interventions

The duration of the project per participant will be three weeks. All participants will carry out the 3 experimental conditions (Figure 3), with a separation of one week between them. A familiarization session will be performed one week before the experimental conditions.

Aerobic exercise condition

The aerobic exercise session will last 30 minutes. The intensity will be matched with the average intensity of the resistance exercise session. Participants will perform a continuous, moderate-intensity aerobic exercise on a cycle ergometer at 60%-70% of their maximal heart rate (HRmax).

Resistance exercise condition

The resistance exercise session will last 30 minutes at a moderate intensity based on 4-6 RPE (OMNI-Resistance Exercise Scale of Perceived Exertion from 0-10). The session model will be similar to one of the exercise sessions performed in the previous AGUEDA project. The bout of resistance exercise will include a combination of upper- and lower-body exercises using elastic bands with different resistance levels and the participants' body weight as the primary resistance. Eight different exercises will be performed with a duration of 40 sec per exercise, for a total of 3 sets, and 1 minute rest between sets. The exercises will be based on basic movement patterns and include glute bridge, front plank, standing face pull, incline push-up, squat, pallof press, walking lunge and seated shoulder press.

Control resting condition

Participants will remain seated while watching a neutral documentary in a tablet during 30 minutes. The documentary will be standardized for all participants without cognitive engagement.

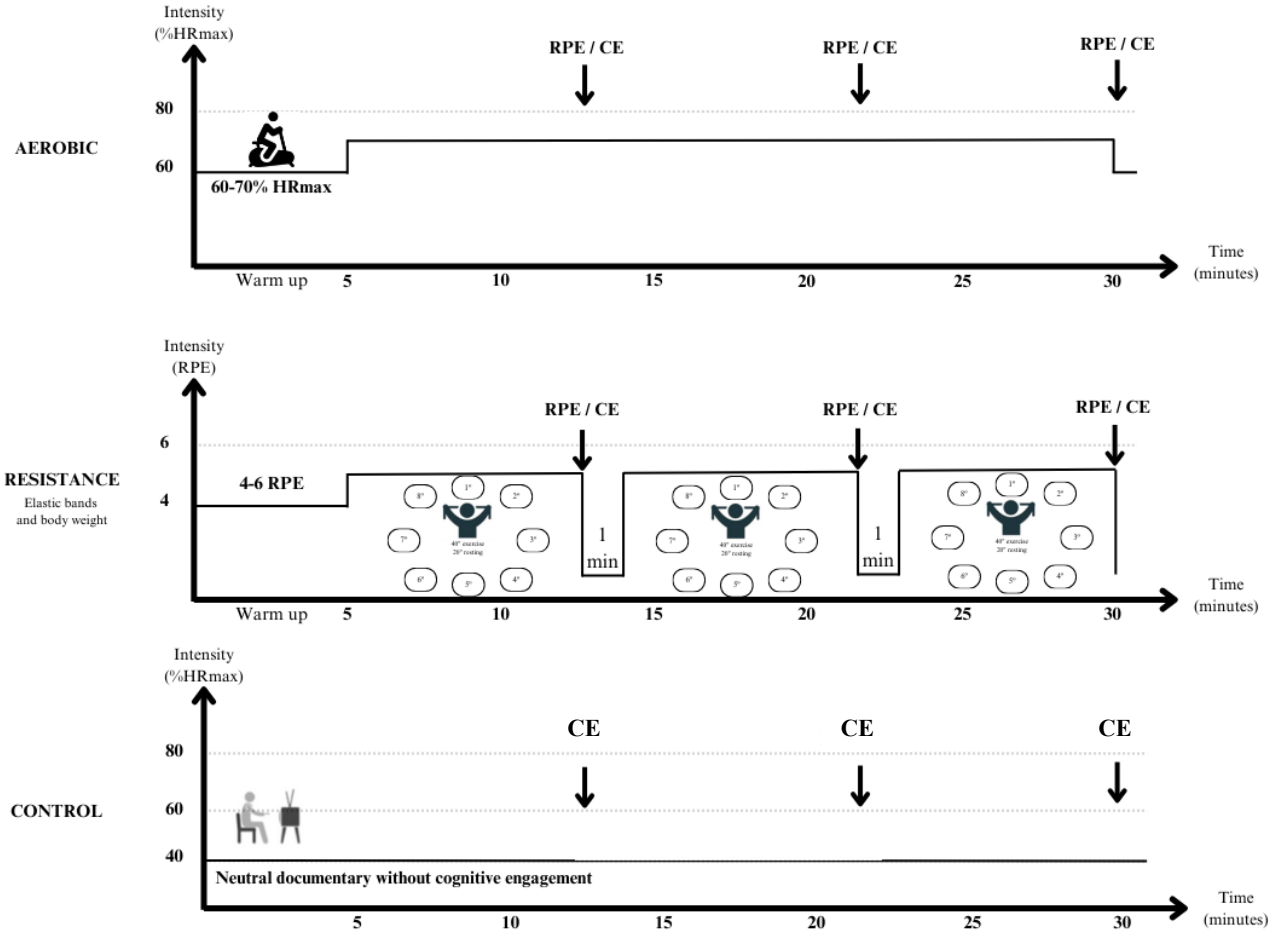

Fig 3. Experimental conditions of the flADex trial. HR: Heart Rate; RPE: rate of perceived exertion; CE: Cognitive Engagement.

11. Safety and adverse events

During the conditions participants may experience very mild symptoms/sensations:

- Expected physiological symptoms/sensations during physical activity: These include fatigue, muscle soreness, shortness of breath, and rapid heart rate. Especially for those not accustomed to riding a bicycle, muscle soreness may be felt after a session of exercise.
- Unexpected adverse symptoms/events that could be triggered by physical activity: These include irregular heart rate, chest pain, headache, nausea, dizziness, muscle cramps, musculoskeletal injuries, vomiting, intense chest pain, malignant arrhythmia, or cardiac arrest. However, the training program

and tests will be conducted in a medically supervised environment equipped to handle emergencies, with a team prepared to address any adverse event.

During the assessments:

The assessments conducted during the study pose no significant risk to participants' health. Minor symptoms/sensations include:

- MRI: Participants may experience a slight degree of claustrophobia, but technical and study staff will be present to provide assistance.
- Blood Draws: Participants may experience bruising, dizziness, skin irritation, swelling, or pain. However, the healthcare staff are trained to assist and minimize these effects.

Participants can choose to stop the assessments at any time if they wish.

12. Ethics and legal issues

The trial protocol is in accordance with the principles of the Declaration of Helsinki and was approved by the Research Ethics Board of the Andalusian Health Service (CEIM/CEI Provincial de Granada; #SICEIA-2024-000602 on April 30th 2024).

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13. References

1. Rudnicka E, Napierała P, Podfigurna A, Męczekalski B, Smolarczyk R, Grymowicz M. The World Health Organization (WHO) approach to healthy ageing. Maturitas. 2020 Sep 1;139:6–11.
2. Muir T. Measuring social protection for long-term care. 2017 [cited 2024 Aug 18]; Available from: http://dx.doi.org/10.1787/a411500a-en
3. Prince M, Wimo A, Guerchet M, Ali GC, Wu YT, Prina M, et al. World Alzheimer Report 2015. The Global Impact of Dementia: An analysis of prevalence, incidence, cost and trends. World Alzheimer Report 2015 The Global Impact of Dementia An Analysis of prevalence, Incidence, cost And Trends. [cited 2024 Aug 18]; Available from: www.alz.co.uk/worldreport2015corrections
4. International D. World Alzheimer Report 2018 - The state of the art of dementia research: New frontiers; World Alzheimer Report 2018 - The state of the art of dementia research: New frontiers.
5. Vermunt L, Sikkes SAM, van den Hout A, Handels R, Bos I, van der Flier WM, et al. Duration of preclinical, prodromal, and dementia stages of Alzheimer's disease in relation to age, sex, and APOE genotype. Alzheimer's & Dementia. 2019 Jul 1;15(7):888–98.
6. Hardy JA, Higgins GA. Alzheimer's disease: The amyloid cascade hypothesis. Science (1979) [Internet]. 1992 [cited 2024 Aug 18];256(5054):184–5. Available from: https://www.science.org/doi/10.1126/science.1566067
7. Selkoe DJ, Hardy J. The amyloid hypothesis of Alzheimer's disease at 25 years. EMBO Mol Med [Internet]. 2016 Jun [cited 2024 Aug 18];8(6):595–608. Available from: https://www.embopress.org
8. Braak H, Braak E. TECHNICAL NOTE Demonstration of Amyloid Deposits and Neurofibrillary Changes in Whole Brain Sections. Brain Pathology [Internet]. 1991;1:213–6. Available from: https://onlinelibrary.wiley.com/doi/10.1111/j.1750-3639.1991.tb00661.x
9. Wang Y, Mandelkow E. Tau in physiology and pathology. 2015 [cited 2024 Aug 18]; Available from: www.nature.com/nrn
10. Zlokovic B V. Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders. 2011; Available from: www.nature.com/reviews/neuro
11. Iadecola C. The Pathobiology of Vascular Dementia. 2013 [cited 2024 Aug 18]; Available from: http://dx.doi.org/10.1016/j.neuron.2013.10.008
12. Iadecola C. Neurovascular regulation in the normal brain and in Alzheimer's disease. Nature Reviews Neuroscience 2004 5:5 [Internet]. 2004 [cited 2024 Aug 19];5(5):347–60. Available from: https://www.nature.com/articles/nrn1387

13. Ruitenberg A, Den Heijer T, Bakker SLM, Van Swieten JC, Koudstaal PJ, Hofman A, et al. Cerebral Hypoperfusion and Clinical Onset of Dementia: The Rotterdam Study. 2005; Available from: https://onlinelibrary.wiley.com/doi/10.1002/ana.20493
14. Smith CD, Andersen AH, Kryscio RJ, Schmitt FA, Kindy MS, Blonder LX, et al. Altered brain activation in cognitively intact individuals at high risk for Alzheimer's disease. Neurology. 1999 Oct 22;53(7):1391–6.
15. Palmer JA, Morris JK, Billinger SA, Lepping RJ, Martin L, Green Z, et al. Hippocampal blood flow rapidly and preferentially increases after a bout of moderate-intensity exercise in older adults with poor cerebrovascular health. Cerebral Cortex [Internet]. 2023 Apr 25 [cited 2024 Aug 18];33(9):5297–306. Available from: https://dx.doi.org/10.1093/cercor/bhac418
16. Mulser L, Moreau D. Effect of acute cardiovascular exercise on cerebral blood flow: A systematic review. Brain Res. 2023 Jun 15;1809:148355.
17. Milà-Alomà M, Ashton NJ, Shekari M, Salvadó G, Ortiz-Romero P, Montoliu-Gaya L, et al. Plasma p-tau231 and p-tau217 as state markers of amyloid-β pathology in preclinical Alzheimer's disease. 1925; Available from: https://doi.org/10.1038/s41591-022-01925-w
18. Ashton NJ, Janelidze S, Mattsson-Carlgren N, Pichet Binette A, Strandberg O, Brum WS, et al. Differential roles of Aβ42/40, p-tau231 and p-tau217 for Alzheimer's trial selection and disease monitoring. 2074; Available from: https://doi.org/10.1038/s41591-022-02074-w
19. Janelidze S, Teunissen CE, Zetterberg H, José ;, Allué A, Sarasa L, et al. Head-to-Head Comparison of 8 Plasma Amyloid-β 42/40 Assays in Alzheimer Disease.
20. Pascual-Lucas M, Allué JA, Sarasa L, Fandos N, Castillo S, Terencio J, et al. (No Title). Available from: http://creativecommons.org/licenses/by/4.0/.TheCreativeCommonsPublicDomainDedicationwaiver
21. Rodriguez-Ayllon M, Solis-Urra P, Arroyo-Avila C, Alvarez-Ortega M, Molina-García P, Molina-Hidalgo C, et al. Physical activity and amyloid beta in middle-aged and older adults: A systematic review and meta-analysis. J Sport Health Sci [Internet]. 2024 [cited 2024 Aug 31];13:133–44. Available from: https://doi.org/10.1016/j.jshs.2023.08.001
22. Chatterjee P, Zetterberg H, Goozee K, Lim CK, Jacobs KR, Ashton NJ, et al. Plasma neurofilament light chain and amyloid-β are associated with the kynurenine pathway metabolites in preclinical Alzheimer's disease. [cited 2024 Sep 1]; Available from: https://doi.org/10.1186/s12974-019-1567-4
23. Joisten N, Rademacher A, Warnke C, Proschinger S, Schenk A, Walzik D, et al. Exercise Diminishes Plasma Neurofilament Light Chain and Reroutes the Kynurenine Pathway in Multiple Sclerosis. Neurol Neuroimmunol Neuroinflamm. 2021 May 29;8(3).