Supplementary Table 1. Trial registration data

Category	Information
Protocol version	Version 1
Primary registry and trial identifying number	anzctr.org.au: ACTRN12617001440314
Date of registration in primary registry	11 October 2017
Secondary identifying numbers	National Health and Medical Research Council (NHMRC) grant: APP1121409
Source of support	National Health and Medical Research Council (NHMRC) grant: APP1121409
Primary sponsor	University of Sydney Susan Wakil Health Building D18, Western Avenue, Camperdown NSW 2006, Australia
Contact for public and scientific queries	Professor Maria Fiatarone Singh, maria.fiataronesingh@sydney.edu.au Susan Wakil Health Building D18, Western Avenue, Camperdown NSW 2006, Australia
Public title	BRAIN Training Trial: Balance, Resistance, And INterval Training Trial: A Randomised Controlled Trial of Three Exercise Modalities in Mild Cognitive Impairment
Scientific title	BRAIN Training Trial: A randomised controlled trial of Balance, Resistance, And INterval training on cognitive function in older adults with Mild Cognitive Impairment
Countries of recruitment	Australia, Canada
Health problem studied	Mild cognitive impairment
Intervention(s)	Interventions: high intensity power training (POWER); high-intensity interval training (HIIT) Comparator: Sham exercise control group: Balance, toning and mobility (SHAM)
Key inclusion and exclusion criteria	Ages eligible for the study: ≥60 years; gender eligible: male and female. Inclusion criteria: Mild Cognitive Impairment (MCI) defined as the presence of all four generally accepted criteria including: (1) *absence of dementia:* Clinical Dementia Rating scale (CDR) score <1; *no or minimal functional impairment due to cognition:* Amsterdam Independent Activities of Daily Living Questionnaire (Amsterdam IADL) score ≥40, rated by informant or participant if no informant available; (3) *subjective memory/cognitive complaint:* Cognitive Change Index (CCI) scale: participant or informant responds to 3 or more statements with a rating of 3, 4 or 5 ('mild to severe problem'); OR Subjective memory complaint questionnaire: participant or informant responds 'yes' to question 1 and 'yes' to questions 2 OR 3 (Q1 'Have you noticed difficulties with your memory?', Q2 'Have you been concerned about your memory?, (Q3) Have you mentioned any concerns about memory to anyone? as per recommendations for the assessment of subjective memory complaint; (4) *objective cognitive impairment:* Score between 19 and 25 on the Montreal Cognitive Assessment (MoCA); ambulatory without the assistance of a person; if from non-English speaking background, must have completed some education in English; residing in the community, including retirement villages and other senior housing or activity sites (independent level of care); willing to participate in a study which involves attending supervised exercise sessions 3 days per week for 12 months Exclusion criteria: Diagnosis of dementia; high level residential care; non-ambulatory or requiring person to assist when walking; 1 stroke in the past 12 months or ≥2 strokes in a lifetime; cardiovascular event/surgery in the past 6 months; progressive neurological disease;

	inability to read and identify objects on a computer screen and draw on a piece of paper due to vision impairment; current major depressive episode (Patient Health Questionnaire-9 (PHQ-9) score of ≤9); psychosis; alcohol abuse (responded 'Yes' to questions 3 and 4 of the CAGE Questionnaire for alcohol use, and reported risky drinking behaviour using the National Health and Medical Research Council (NHMRC) standard criteria); from a non-English speaking background (NESB) without any education in English; already practicing ≥150 minutes of moderate intensity exercise, progressive resistance training or high-intensity interval training regularly; medical contraindications to the planned exercise due to chronic or unstable or terminal diseases; planned move, or planning to be away for ≥4 consecutive weeks during the study period
Study type	Interventional Allocation: randomised; intervention model: parallel; masking: double blinded Primary purpose: treatment Type of endpoint: efficacy
First and last enrolment date	29 January 2018; 02 March 2020
Target sample size	210
Recruitment status	Closed. Recruitment ended early with 160 participants enrolled due to the inability to carry out participant assessments and interventions due to COVID-19 restrictions.
Anticipated date of last data collection	02 March 2026
Primary outcome	Change in overall executive domain of cognitive function score (composite measure) at 26 and 52 weeks after randomisation
Key secondary outcomes	Change in individual tests scores of secondary domains of cognitive function (memory, attention/working memory, visual-spatial, language, information processing speed, motor skills), global cognition, clinical cognitive status, subjective cognitive complaint, and functional impairment due to cognition. Time frame: 26- and 52-weeks post intervention, and long-term follow-up at 24-, 36-, 48- and 72-months post randomisation. Other secondary outcomes: Nutritional status and body composition, cardiovascular and vascular parameters, physiological function (muscle strength and power, maximal aerobic capacity, functional mobility, balance), disability, functional limitations, frailty status, sleep quality, habitual physical activity, biomarkers of brain pathology and cognitive function, psychosocial measures, quality of life, brain morphology and cerebral perfusion, health status. Time frame: 52 weeks post intervention, and long-term follow-up at 24-, 36-, 48- and 72-months post randomisation. Adherence to the training protocol and adverse events (time frame: weekly until 52-weeks post randomisation), attitudes towards the intervention (time frame: 52-weeks post randomisation).

Supplementary Table 2. Cinical trial support structure

Support structure	Composition, roles and responsabilities
Coordinating Centre	The University of Sydney is the coordinating centre of the BRAIN multi-national clinical trial. A clinical trial co-ordinator/ project manager was appointed prior to comencement of the trial (TV). Roles of the clinical trial coordinator include: preparation of ethics application and trial governance documentation, maintenance of trial documentation and master database, reporting of all adverse events, serious adverse events and suspected unexpected serious adverse reactions to the Ethics Committee (in accordance with HREC requirements), development of quality assurance protocols, development of manual of procedures, responsible for assessment of intra and inter reliability, assistance in the development of screening, intervention and assessment protocols, oversight of recruitment and screening of participants, performance of site initiation visits and training of staff across sites in all study related procedures, data analysis and interpretation, preparation of manuscripts.
Principal Investigator and Study Physician	Professor Maria Fiatarone Singh, MD, FRACP (Geriatrician) is the principal investigator and study physician. She is the acting study physician for the USYD study site. She is responsible for confirming eligibility of subjects across sites in relation to their past and current medical history, medications, outcome of physician assessments and signs and symptoms presented during any baseline physical assessments. She is also responsible for providing case-by-case tailoring of the exercise intervention when required for participants who are unable to complete an exercise due to pain or limitation in their range of motion, or due to a change in their medical status during the study intervention period.
Trial Management Committee (TMC)	The trial management committee is composed of the principal investigator at each study site (MFS, JC, TLA). The TMC is responsible for providing the annual S/AE report to HREC and clinical trial governance, responsible for trial master file, budget administration and contractual issues with individual centres, overall data verification and randomisation. The TMC work with the clinical trial co-ordinator and oversee the study site coordinators. The TMC is responsible for organising Steering Committee meetings. All members of the TMC will have access to the final trial dataset.
Study Site Co-ordinator	In each study site a site co-ordinator is nominated to be responsible for recruitment, participant identification, management of data collection, follow-up of study participants and adherence to study protocol and study manual of procedures. The study site co-ordinators report to the PI of the respective study sites. The study site co-ordinators are responsible for providing site specific updates as required to the clinical trial co-ordinator. Weekly meetings (virtual) are held between the TMC, the clinical trial co-ordinator and the study site coordinators.
Steering Committee	The steering committee (SC) is composed of all the lead investigators. The steering committee provided input in the development of the study protocol, and agreed to the final study protocol. The SC is responsible for reviewing the progress of study and if necessary agreeing changes to the protocol to facilitate the smooth running of the study.
Data Safety Monitoring Committee	A data safety monitoring committee composed of Professor Maria Fiatarone Singh, MD, FRACP (Geriatrician) and Professor Jaqueline Close (Geriatrician) from UNSW was established prior to commencement of the study. This committee meets virtually biannually and as needed to triage study events. After each review, the DSMC makes recommendations regarding the conduct of the study. Weekly conference calls are held with all principal investigators, clinical trial co-ordinator and site-specific study coordinators to discuss information related to the study participants, adverse events, and exercise interventions across sites.

Trial data management plan	Data is collected over the phone (telephone screening) and in person (assessments), using researcher-administered questionnaires, and physical testing at each participating site. Data gathered from the screening process, assessment, and training sessions is entered by the research staff into a central database created in REDCap web application hosted by The University of Sydney. Data is entered in a re-identifiable form using unique identifying numbers. All data entered into the database is stored on a secure server of the University of Sydney. Access to the database is provided only to research staff working on the study. User privileges and data access groups are used to limit the viewing and/or editing access that research members have within the database. The REDCap database, including management of access rights are managed by the clinical trial co-ordinator at the University of Sydney. Efforts will be made to gather all outcome measures for study participants who discontinue the intervention. All data will be de-identified prior to depositing in a repository at the end of the study, as required by the National Health and Medical Research Council.
Adverse event managment plan	The standard USYD HREC process for reporting adverse events are followed throughout the conduct of the trial: ▪ The PI and/or sub-investigators review all AE information which may be gathered via any of the following means: - Spontaneous reports by participants at their study visits or via phone or email - Observations by clinical research staff - Reports to research staff by family or medical care providers - Reports collected in participant diaries - Possible AEs documented in medical records, progress notes, hospitalisations etc. - Reports of a participant death within four weeks after stopping treatment or during the protocol-defined follow-up period, whichever is longer, whether considered treatment-related or not ▪ All subjects enrolled in the study are required to complete a weekly health status report to indicate whether there have been changes to their health status, medical conditions, or adverse events. In addition, participants are asked to classify the cause of the event to different diseases/incidents. ▪ Adverse events categorised as serious adverse event (SAE) occurring in research participants at the University of Sydney are reported to the Principal Investigator immediately and to HREC within 72 hours of study staff becoming aware of the SAE by completing the study specific SAE form using IRMA. ▪ All SAE's at sites other than the University of Sydney and where the event materially impacts the continued ethical acceptability of the trial or indicates the need for a change to the trial protocol including changes to safety monitoring in the view of the investigator or sponsor will be reported to HREC as soon as practical study staff at USYD become aware of the SAE using IRMA, and also to Clinical Trial Governance. ▪ AE information is immediately recorded in the participant's medical records and reported to HREC annually using IRMA. A SAE follow up report is provided to the HREC and Governance as required. ▪ The PI and/or sub-investigators provide further information if requested to the University of Sydney as sponsor of the clinical trial for related adverse events that could result in an insurance claim. ▪ All S/AEs are recorded and reported within the established period for safety. The study PI Prof Maria Fiatarone Singh, MD, will follow-up on participants suffering from harm related to participation in the study to ensure that adequate medical

	care is provided to a subject for any adverse events related to the trial. This encompasses the time from baseline assessment prior to intervention commencement, until follow-up is completed for each participant. ▪ The study physician in conjunction with the PI at each intervention site will inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed. ▪ The study physician will inform subjects when medical care is needed for intercurrent illness(es). ▪ Although subjects are not obliged to give reason(s) for withdrawing prematurely from a trial, the investigators will make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights. Reasons for withdrawal will be reviewed and rates of drop out compared between groups at each biannual virtual board meeting.

Supplementary Table 3. Baseline assessment schedule

DAY 1 (4hrs)		
MORNING	**AFTERNOON**	**Morning (8:30am-12:30pm) or Afternoon (1:00-5:00)**
8:30 9:30	13:00 14:00	Gait under usual and dual task conditions Habitual and Maximal Gait Speed Test Six-Minute Walk Test (Trial 1)
9:30-10:30	14:00-15:00	Physician Screening
10:30-11:30	15:00-16:00	ECG Stress Test
11:30 12:30	16:00 17:00	Provide home-based questionnaire package and 7 day Axivity monitor and log
DAY 2 (4hrs)		
MORNING ONLY		**Morning only: FASTING (8:30 to 12:30)**
8:30-10:30		Collect Axivity monitor and log Weight and height; waist, mid-arm, and mid-cuff circumference Preparation for haemodynamic measures: 10 minutes resting in supine Heart rate variability, Pulse Wave Analysis Pulse Wave Velocity Orthostatic Blood Pressure Dual-energy X-ray absorptiometry scan Peripheral quantitative computed tomography (UQ study site only) Blood collection (USYD and UQ study sites only)
10:30 11:00		*Breakfast*
11:00 11:30		Clinic-based questionnaires
11:30 12:00		Static and dynamic balance assessment Five Times Sit-to-stand
12:00 12:30		Maximal muscle strength test (Trial 1)
DAY 3 (4hrs)		
MORNING	**AFTERNOON**	**Morning (8:30am-12:30pm) or Afternoon (1:00-5:00)**
8:30 9:30	13:00 14:00	Hand grip strength and isometric muscle strength test
9:30 9:45	14:00 14:15	Six-Minute Walk Test (Trial 2)
9:45 11:45	14:15 16:15	Maximal muscle strength test (Trial 2)
11:45 12:30	16:15 17:00	Provide 24h ambulatory blood pressure monitor and log
DAY 4 (4hrs)		
MORNING ONLY		**Morning only (8:30 to 12:30)**
8:30-10:30		Cognitive Assessment (Neurotrax battery) *15-minute break* Paper-based cognitive assessment
10:30 11:30		Muscle power test
11:30 12:00		Randomization
DAY 5 (2 hrs)		
MORNING ONLY		**Morning only (8:30 to 10:30)**
8:30 10:30		Brain MRI (USYD study site only) or cerebral blood flow and brachial flow mediated dilation (UQ study site only)

Supplementary Table 4. Description of tests used to calculate secondary domains of cognitive function

Cognitive test	Description
Memory domain	
NeuroTrax Verbal Memory test [1, 2]	Ten pairs of words are presented, followed by a recognition test in which one member (the target) of a previously presented pair appears together with a list of four candidates for the other member of the pair. Participants must indicate which word of the four alternatives was paired with the target when presented previously. Four consecutive repetitions of the recognition test are administered during the 'learning' phase. An additional recognition test is administered following a delay of approximately 10 minutes.
NeuroTrax Non-Verbal Memory test[1, 2]	Eight pictures of simple geometric objects are presented, followed by a recognition test in which four versions of each object are presented, each oriented in a different direction. Participants are required to remember the orientations of the originally presented objects. Four consecutive repetitions of the recognition test are administered during the 'learning' phase of the test. An additional recognition test is administered following a delay of approximately 10 minutes.
Hopkins Verbal Learning Test Revised [3, 4]	Repeat a verbally-presented list of 12 words from three semantic categories over three learning trials; delayed recall after 20-25 minutes.
Attention/working memory domain	
NeuroTrax Go-No Go test[1, 2]	A series of large coloured stimuli are presented at pseudo-random intervals. Participants are instructed to respond as quickly as possible by pressing a mouse button if the colour of the stimulus is any colour except red, for which no response is to be made.
NeuroTrax Stroop Interference test[1, 2]	The Stroop is a well-established test of response inhibition. The NeuroTrax Stroop test consists of three levels. Participants are presented with a pair of large coloured squares, one on the left and the other on the right side of the screen. In each level, participants are instructed to choose as quickly as possible which of the two squares is a particular colour by pressing either the left or right mouse button. First, participants are presented with a general word in coloured letters. In the next level, participants are presented with a word that names a colour in white letters. In the final level (the Stroop interference level), participants are presented with a word that names a colour, but the letters of the word are in a colour other than that named by the word. The instructions for the final level are to choose the colour of the letters, and not the colour named by the word.
NeuroTrax Staged Information Processing test[1, 2]	This test comprises three levels of information processing load: single digits, two-digit arithmetic problems (e.g., 5-1), and three-digit arithmetic problems (e.g., 3+2-1). For each of the three levels, stimuli are presented at three different fixed rates, incrementally increasing as testing continues. Participants are instructed to respond as quickly as possible by pressing the left mouse button if the digit or result is less than or equal to 4 and the right mouse button if it is greater than 4.
WAIS-IV Digit Span Test[5]	Two subtests are administered. In the first part (digits forward) the individual is read a series of numbers and is required to repeat the sequence in order to the examiner. In the second part (digits reversed) he/she is again read a series of numbers but this time she/he is required to repeat the sequence in reverse order.
Visual-spatial domain	
NeuroTrax Visual Spatial Processing test[1, 2]	Computer-generated scenes containing a red pillar are presented. Participants are instructed to imagine viewing the scene from the vantage point of the red pillar. Four alternative views of the scene are presented as choices.
Language/ verbal function domain	
NeuroTrax Verbal Function test[1, 2]	Pictures of common objects are presented. Participants are instructed to select the word that best rhymes with the name of the picture from among four choices. In

	another test level, participants are instructed to match the picture with its name by choosing the name from among four choices.
Information processing speed domain	
NeuroTrax Staged Information Processing test[1, 2]	Test described earlier within attention/ working memory domain.
WAIS-IV Coding test[5]	In this subtest individuals are asked to quickly write symbols paired with numbers according to a key, within a 120 second time limit.
Trails Making Test form A[6]	Individuals are asked to draw lines connecting consecutive numbers (TMT-A) as quickly as possible.
Motor skills domain	
NeuroTrax Finger Tapping test[1, 2]	Participants are instructed to tap on a single mouse button for 12 seconds with their dominant hand. This task is repeated twice.
NeuroTrax Catch Game test[1, 2]	The Catch game is a novel screen that assesses psychomotor function. Participants must "catch" a rectangular white object falling vertically from the top of the screen before it reaches the bottom of the screen. Mouse button presses move a rectangular green "paddle" horizontally so that it can be positioned directly in the path of the falling object. The test requires hand-eye coordination, scanning and rapid responses.

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Supplementary Table 5. Secondary outcome measures: Physical health and functional status

Outcome measure	Name of scale	Description
Nutritional Status/ Body composition	Mini Nutritional Assessment Short form (MNA-SF)	Validated nutritional screening that can identify geriatric patients age 65 and above who are malnourished or at risk of malnutrition.[1]
	Mediterranean Diet and Culinary Index (MediCul)	Short survey index tool developed to assess adherence to a 'traditional' Mediterranean dietary pattern and certain aspects of cuisine, within a Western population. It includes a blend of frequency and serve questions spanning seventeen main elements and assesses their exposure over the past 6 months.[2]
	CAGE Questionnaire	Widely used screening test for problem drinking and potential alcohol problems.[3]
	Anthropometrics	Measures include standing height, body weight and waist, cuff, and arm circumferences. Body mass index (BMI) is calculated as fasting body weight kg/ height m^2.
	Dual-energy X-ray absorptiometry (DXA) and Peripheral quantitative computed tomography (pQCT)	Measures include whole body and regional lean and adipose tissue; and bone density in the lumbar spine and hip.
Cardiovascular profile	Arterial stiffness	Measures include carotid-femoral pulse wave velocity (PWV), pulse wave analysis (PWA), central aortic systolic blood pressure, central pulse pressure, and augmentation index (AIx) assessed using SphygmoCor Xcel.
	Heart rate variability	Changes in Heart Rate Variability (HRV) assessed using SphygmoCor CvMS.
	Blood Pressure (BP)	Orthostatic blood pressure and orthostatic hypotension assessed in a fasted state and after rising from a five-minute rest in supine position using SunTech automatic blood pressure monitor. Twenty-four-hour ambulatory BP monitoring, awake and nocturnal means and circadian rhythm also obtained using Oscar 2 with Sphygmocor inside.
Vascular profile	Cerebral blood flow	Cerebral blood flow assessed using Transcranial Doppler Ultrasound.
	Braquial Flow Mediated Dilation (FMD)	Flow Mediated Dilation assessed using reactivity of the brachial artery via 2D Ultrasound.
Physiological function	Muscle strength	Maximal dynamic muscle strength assessed using 1 repetition maximum (1RM) on pneumatic resistance machines: bilateral leg press, unilateral knee extension, bilateral chest press, bilateral triceps extension.
		Maximal isometric muscle strength assessed using stand-held dynamometer: unilateral hip abduction, unilateral knee extension, unilateral triceps extension, unilateral ankle dorsiflexion. Maximal isometric handgrip strength of the non-dominant hand assessed using a JAMAR handgrip dynamometer (Sammons Preston, Bolingbrook, IL).
	Muscle power	Maximal muscle power assessed using pneumatic resistance machines: bilateral leg press, unilateral knee extension, bilateral chest press, bilateral triceps extension.

	Aerobic Capacity	Maximal exercise capacity assessed by indirect calorimetry during a maximal walking treadmill exercise test to fatigue.
	Short Physical Performance Battery (SPPB)	Objective measurement instrument of balance, lower extremity strength, and functional capacity in older adults. It is a powerful predictor of disability, institutionalization, and mortality.[4]
	Static Balance	Assessed while standing without the use of assistive devices and with feet in different positions for 20 seconds (eyes open: feet apart in parallel stance, feet together in parallel stance, half tandem stance, tandem stance, and single leg stance; eyes closed: tandem stance and single leg stance). Two trials performed at each stance. Total static balance calculated by summing the time recorded for the best trial at each stance.
	Tandem walk	Assessed with a 3 meter forward tandem walk along a marked course. Dynamic balance score calculated based on time to complete and number of errors recorded.
Disability	KATZ Index of Independence in Activities of Daily Living	Instrument used to assess functional status as a measurement of the person's ability to perform activities of daily living independently.[5]
	Use of Community & Health Services	Instrument used to measure a person's use of community and health care services during the year preceding the assessment.
	Use of assistive devices	Instrument used to measure a person's use of assistive devices during the week preceding the assessment.
	Amsterdam Instrumental Activity of Daily Living Questionnaire	Adaptive and computerized questionnaire designed to assess impairments in instrumental activities of daily living (IADL) in early dementia. The questionnaire is completed by an informant if available. Scores are attained for IADL related to cognitive deficit as well as non-cognitive deficits.[6]
	Life space assessment	Instrument used to evaluate mobility by measuring a person's usual pattern of mobility during the month preceding the assessment.[7]
Functional limitations	Gait speed	Habitual gait speedand maximal gait velocities assessed over a 4-metre distance.
	Gait under usual and dual task condition	Distance covered at habitual walking speed over 1 minute under the following conditions in random order: 1) Gait at usual speed without cognitive task; 2) gait at usual speed with a subtraction task; 3) gait at usual speed with a verbal fluency task. A seated letter fluency task is administered either prior or after the three gait trials (determined at random).
	Five Times Sit-to-Stand Test	Used as a proxy for lower extremity power and has a predictive value of subsequent disability.[8]
	6-minute walk distance (6MWD)	Walking endurance was assessed using the six-minute walk test which is a proxy for overall cardiovascular endurance capacity (aerobic capacity) and in the elderly subject it may be determined by muscle strength and endurance, balance, orthopaedic or neurologic abnormalities, and other problems.[9]
Frailty	FRAIL Scale	Simple tool for the identification of frailty in older people comprising 5 yes-or-no questions—Fatigue, Resistance, Ambulation, Illnesses, and Loss of weight. It has predictive value for disability[10] and mortality.[11]

	Fried phenotype	Tool for the assessment of frailty in older adults based on the presence of five components: weakness, slowness, exhaustion, low physical activity, and unintentional weight loss. [12]
Sleep quality	Motion Watch 8 actigraphy	Objective sleep quality measurement assessed over 7 days using a Motion Watch 8 actigraphy system (MW8; Comtech) together with a 7-day Consensus Sleep Diary (CSD)
	Pittsburgh Sleep Quality Index (PSQI)	Subjective measure of sleep quality and patterns. The tool looks at seven areas: The tool looks at seven areas including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, the use of sleep-promoting medication, and daytime dysfunction.[13]
Habitual physical activity level	Axivity MEMS 3-axis accelerometer	Objective measure of physical activity participation assessed over 7-days using an Axivity MEMS 3-axis accelerometer positioned on the person's lower back.
	Paffenbarger Physical Activity Questionnaire	Self-report measure of physical activity. Activities assessed include number of flights of stairs climbed and blocks walked in a typical day as well as duration of weekly sports and recreational activities.[14]
	Physical Activity Scale for the Elderly (PASE)	Brief survey designed to assess physical activity in older adults during the week preceding the assessment. It includes a section on leisure time activities, household activities and work-related activities.[15]
	Australian National Health Questionnaire (physical activity module)	Brief survey which is part of the Australian Bureau of Statistics 2017-18 National Health Survey. The survey is designed to assess physical activity which consists of four domains, walking for transport, walking for fitness, sport or recreation, moderate exercise and vigorous exercise, which was undertaken in the last week.[16]
Biomarkers of brain pathology and cognitive function	Serum samples for nutritional, biochemical and hormonal factors, pro- and anti-inflammatory Cytokines	BDNF, IGF-1, IGF-1 Binding protein 3, HOMA (insulin and glucose), APOE, Serum Cortisol, Epigenetic analysis, GWAS, Nitric Oxide, Vitamin D, Vitamin B12

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Supplementary Table 6. Secondary outcome measures: psycho-social and quality of life

Outcome measure	Name of scale	Description
Psycho-social	Geriatric Depression Scale (GDS) 30-item	The GDS is used to assess an older person's level of depression with simple yes/no response set and the fifteen-item screening test has been reported to be satisfactory.[1]
	Duke Social Support (DSS)	The DSS is used to assess perceived adequacy and size of social support network on a 3-point scale with higher total scores reflecting higher levels of social support.[2]
	Oxford Happiness Questionnaire (OHQ)	The OHQ is a compact scale for the measurement of psychosocial well-being derived from the Oxford Happiness Inventory (OHI). It includes 29 items each presented as a single statement which are answered on a uniform six-point Likert scale (1=''strongly disagree'' to 6=''strongly agree'').[3]
	Attitudes to Ageing Questionnaire (AAQ)	The AAQ is a self-administered questionnaire consisting of 24 items scored on a 5-point Likert scale which capture general attitudes towards the ageing process and personal experience of ageing. [4]
	Toronto Empathy Questionnaire (TEQ)	The TEQ is a short scale for the measurement of empathy. It contains 16 items that represent a wide variety of empathy-related behaviors. Items are presented as a single statement which are answered on a uniform five-point Likert scale (1=''Never'' to 5=''Always"). Scores are summed to derive total for the Toronto Empathy Questionnaire.[5]
	Core self evaluations scale (CSES)	The 12-item CSES is a direct and relatively brief measure of the core-self-evaluations personality trait which has been described as a basic, fundamental appraisal of one's worthiness, effectiveness, and capability as a person, and has shown to be significantly correlated to life satisfaction. This is the only current CSE scale and is known to have sound psychometric properties. The CSE scale measures a single factor that is the intersection of self-esteem, locus of control, generalized self-efficacy, and emotional stability. Responses for each item are recorded on a 5-point Likert type scale ranging from 1 (disagree strongly) to 5 (agree strongly). Sample items from this scale are "Sometimes I feel depressed," "I am capable of coping with most of my problems," and "I determine what will happen in my life."[6]
	Ewart's Self-efficacy Scale	The Ewart's Self-efficacy scale is a measure of self-perceived ability to perform a variety of exercise related activities. Each activity is scaled by presenting the subject with a list of increasingly difficult behavioural tasks. For example, the walking scale includes: walk 1/2 mile (approximately 10 minutes); walk 1 mile (20 min); walk 1.5 miles (30 min),…walk 6 miles (2 h). Altogether there are 12 levels of task difficulty for each scale. Subjects indicate how certain they are that they can perform each of the levels on a scale ranging from 0 (completely uncertain) to 100 (completely certain).[7]
	Iconographical Falls Efficacy Scale (Icon-FES)	The 30-item Icon-FES questionnaire is used to assess concern about falling in older people during a wide range of daily activities and situations using pictures and brief text.[8]
	Outcome expectancy training questionnaire	Older adults are asked to indicate how confident they are that three different types of exercise (namely resistance exercise, aerobic exercise, and balance, toning and mobility exercises) will result in improved memory and thinking rated using a 10-item Likert scale.
Quality of life	Physical and Mental Health Summary Scales (SF-36)	The Physical & Mental Health Summary Scales include eight generic health concepts, selected from 40 included in the Medical Outcomes Study (MOS), and MOS researchers selected and adapted questionnaire items and developed new measures for a 149-item Functioning and Well-Being Profile the source for SF-36® items.[9]

Perception of the intervention	Semi-structured interview	Attitudes towards the intervention assessed using semi-structured interviews with participants allocated to HIIT and POWER intervention groups.

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Supplementary Table 7. Summary of MRI scanning parameters

	Acquisition duration (min:sec)	Acquisition matrix size (mm^3)	Voxel size (mm^3)	TR (ms)	TE (ms)	TI (ms)	FA (degree)
3D MPRAGE	4:32	198×256×256	1×1×1	8.388	3.168	900	8
3D FLAIR	5:55	198×256×256	1×1×1 (interpolated to 1×0.5×0.5)	6502	91.481	1753	90
Blipped DWI	0:43	240×240×132	2×2×2	5430	107.1	-	90
2D DWI	11:51	240×240×132	2×2×2	4772	107.1	-	90
3D SWAN	3:35	240×240×150	0.4688×0.4688×3	53.2	8 readouts (5, 8.756, 12.512, 16.268, 20.024, 23.78, 27.536, 31.292 ms)	-	15
3D ASL	4:35	240×240×144	1.875×1.875×4	4854	10.7	2025	111
2D resting-state BOLD	7:20	240×240×165	3.243 × 3.243 × 3	1100	30	-	70
Field map	1:53	256×256×140	1×1×4	860	Dual echo (8 and 20 ms)	-	15

TR, repetition time; TE, echo time; TI, inversion time; FA, flip angle; MPRAGE, magnetization-prepared rapid acquisition gradient echo; FLAIR, T2-weighted fluid-attenuated inversion recovery; DWI, diffusion-weighted imaging; SWAN, susceptibility-weighted angiography; ASL, resting-state arterial spin labelling imaging; BOLD, resting-state blood oxygenation level dependent imaging.

Supplementary Table 8. Detailed MRI scanning parameters

Imaging modality	Description
T1-weighted images	T1-weighted scans were acquired with a Magnetization-prepared Rapid Acquisition Gradient Echo (MPRAGE) pulse sequence with prospective motion correction (PROMO). The following scanning parameters have been used: repetition time (TR) = 8.388 ms, echo time (TE) = 3.168 ms, inversion time (TI) = 900 ms, flip angle (FA) = 8°, pixel bandwidth = 244.141 Hz, acquisition matrix = 256 × 256, 198 slices, yielding 1 mm isotropic voxels. Autocalibrating Reconstruction for Cartesian imaging (ARC) was applied for parallel imaging (acceleration factor = 3 in the phase encoding direction).
T2-weighted fluid-attenuated inversion recovery (FLAIR)	T2-FLAIR was acquired with a 3D fast spin echo sequence (sagittal slices) and variable flip-angle readouts (CUBE). TR/TE = 6,502/92 ms, TI = 1,745 ms, FA = 90°, acquisition matrix = 256 × 256 (being interpolated to 512 × 512), 198 sagittal slices, 1 mm isotropic voxels (being interpolated to 1.0 × 0.5 × 0.5 mm3).
Diffusion-weighted imaging (DWI)	Diffusion data were acquired with a multiband, multishell pulse sequence. A phase offset was applied to each multiband component. The following scanning parameters were used: TR = 4,671 ms, TE = 108.7 ms, acquisition matrix 120 × 120, 66 slices, 2 mm isotropic voxels, FA=90°, multiband factor = 3, phase encoding direction=AP. The acquisition includes 8 non-diffusion weighted volumes (b=0 s/mm2; one b0 each 20 volumes), as well as 25 (b=700 s/mm2), 38 (b=1000 s/mm2), and 77 (b=2800 s/mm2) unique directions. A separate diffusion-weighted acquisition with 1 non-diffusion weighted volume (b=0 s/mm2) and 6 diffusion directions (b=700 s/mm2) was achieved with PA phase encoding direction to correct for distortion.
Susceptibility-weighted angiography (SWAN)	3D gradient-echo T2*-weighted enhanced SWAN was acquired with TR = 53.2 ms, multi-TE readout technique (8 readouts at TE = 5, 8.756, 12.512, 16.268, 20.024, 23.78, 27.536, 31.292 ms), FA=15°, acquisition matrix = 256 × 256 (interpolated to 512 × 512), 50 slices, voxel size=0.4688 × 0.4688 × 3 mm3 (after interpolation).
Resting-state Arterial spin labelling (ASL) imaging	Pseudo-continuous ASL images were acquired with 3D multi-shot spiral sequence. Sixteen TRs were acquired to construct 1 tag-control pair (8 TRs for tag and 8 TRs for control image) (number of excitations (NEX) = 1, spiral arms = 8). TR/TE = 4,854/10.7 ms, FA = 111°, acquisition matrix = 128 × 128, 36 slices with slice thickness of 4 mm and no gap between slices, 1.875 × 1.875 × 4.0 mm3 voxel size, label duration = 1,450 ms, post-label delay = 2,025 ms. A proton density weighted image was also acquired with the same TR/TE and spatial resolution as control-tag pairs as a reference for cerebral blood flow quantification.
Resting-state blood oxygenation level dependent (BOLD) imaging	To acquire resting-state BOLD maps, T2*-weighted gradient-echo echo-plan sequence was applied with TR = 1,100 ms, TE = 30 ms, FA = 70°, acquisition matrix = 74 × 74, 54 slices, 400 timepoints, voxel size = 3.2432 × 3.2432 × 3 mm3, 2 × in-plane acceleration, multiband factor = 3, and acquisition direction = AP. Dual-echo field maps with phase maps were also acquired to assess any field drift for distortion correction (TR = 860 ms, TE = 8 and 20 ms (dual echo), FA = 15°, acquisition matrix = 256 × 256, 35 slices, 1 × 1 × 4 mm3 voxel size).