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RESEARCH ARTICLE

The AUstralian multidomain Approach to Reduce dementia Risk by prOtecting brain health With lifestyle intervention study (AU-ARROW): A study protocol for a single-blind, multi-site, randomized controlled trial

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Abstract

INTRODUCTION: The Finnish Geriatric Intervention Study (FINGER) led to the global dementia risk reduction initiative: World-Wide FINGERS (WW-FINGERS). As part of WW-FINGERS, the Australian AU-ARROW study mirrors aspects of FINGER, as well as US-POINTER.

METHOD: AU-ARROW is a randomized, single-blind, multisite, 2-year clinical trial (n = 600; aged 55–79). The multimodal lifestyle intervention group will engage in aerobic exercise, resistance training and stretching, dietary advice to encourage MIND diet adherence, BrainHQ cognitive training, and medical monitoring and health education. The Health Education and Coaching group will receive occasional health education sessions. The primary outcome measure is the change in a global composite cognitive score. Extra value will emanate from blood biomarker analysis, positron emission tomography (PET) imaging, brain magnetic resonance imaging (MRI), and retinal biomarker tests.

DISCUSSION: The finalized AU-ARROW protocol is expected to allow development of an evidence-based innovative treatment plan to reduce cognitive decline and dementia risk, and effective transfer of research outcomes into Australian health policy.

KEYWORDS
Alzheimer's disease, Australia, brain health, dementia, multidomain lifestyle intervention, randomized controlled trial, study protocol

Highlights

- Study protocol for a single-blind, randomized controlled trial, the AU-ARROW Study.
- The AU-ARROW Study is a member of the World-Wide FINGERS (WW-FINGERS) initiative.
- AU-ARROW's primary outcome measure is change in a global composite cognitive score.
- Extra significance from amyloid PET imaging, brain MRI, and retinal biomarker tests.
- Leading to development of an innovative treatment plan to reduce cognitive decline.

1 | BACKGROUND

Dementia is one of the biggest global health issues of the 21st century and Alzheimer's disease (AD) is the leading cause of dementia, representing 50%–70% of all cases. Worldwide in 2015, nearly 46.8 million people had AD or a related dementia. This number has been projected to double every 20 years to reach 74.7 million by 2030, and 131.5 million by 2050.[1] The economic impact of dementia on the health care system and community is considerable; in fact, the annual global societal costs of dementia were estimated at US $1313.4 billion for 55.2 million people with dementia in 2019,[2] and as the number of people with dementia is increasing at an alarming rate, the cost of dementia has the potential to cripple economies worldwide.[1]

There is widespread and increasing interest in the maintenance of brain function well into late life. The multifactorial etiology of dementia has led to the concept that simultaneous changes in several risk factors over a long period of time will have a protective effect on cognition. This approach is particularly important given that individuals with similar overall dementia risk may have quite different contributions from various risk factors. Thus, it is unlikely that a single-component treatment plan targeting a single risk factor will be effective in a public health context. The rationale for combining multiple intervention components is supported by evidence suggesting synergistic effects result from combined treatments.[3]

One proof-of-concept study involving healthy community-dwelling older Australians (n = 224) showed that a multidomain plan comprising physical exercise (walking, resistance training) and BrainHQ (formerly Posit Science, United States) exercises can improve episodic memory,[4] whereas a recent pilot clinical trial that tested an interactive physical and cognitive exercise program (iPACESTMv2.0) reported significant improvements in executive function.[5] The ENCORE (Exercise and Nutritional Interventions for Cardiovascular Health) study

investigated the effect of aerobic exercise, following the Dietary Approaches to Stop Hypertension (DASH) diet and the combination of the two on blood pressure (BP) and metabolic outcomes in an overweight middle-aged cohort. The DASH diet resulted in lower BP, and the addition of exercise and weight loss resulted in even greater BP reductions.[6] The combined treatment also improved the secondary outcome measures of executive functioning, learning, and memory.[7] The Australian Body Brain Life program which included interventions in physical activity, diet, and cognitive training resulted in dementia risk reduction in obese middle-aged adults,[8] and reduction in cognitive decline in older adults with Mild Cognitive Impairment and Subjective Cognitive Decline.[9]

The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) trial combined regular aerobic exercise, aspects of the Mediterranean diet (MeDi) and DASH diets, a computerized brain training program, and regular health monitoring.[10–13] In their cohort of adults aged 60–77, with cardiovascular risk factors and some evidence of neurocognitive weakness based on the Consortium to Establish a Registry for Alzheimer's Disease neuropsychological battery (CERAD-NB), this study provided evidence of neurocognition improvements resulting from the 2-year intervention. Cardiorespiratory fitness was assessed as peak oxygen uptake (VO2peak, L/min) measured directly in a symptom-limited maximal exercise test on a cycle ergometer at baseline and at 24 months. Cardiorespiratory fitness was found to be associated most strongly with the observed neurocognitive improvements in executive function and processing speed.[14]

Findings from the FINGER study led to the global initiative for dementia risk reduction known as World-Wide FINGERS (WW-FINGERS).[15] As part of the WW-FINGERS collaboration, the Australian AU-ARROW trial will follow the general protocol of the FINGER trial and will be aligned with the US study, US POINTER, though will have minor cultural and dietary modifications, to determine the validity of the intervention in an Australian setting.

The results of this clinical trial could be used to develop evidence-based programs which are cost-effective, broadly applicable preventative approaches specifically aimed at enhancing cognitive health and decreasing AD incidence, conferring substantial social and economic impact.

The primary study hypothesis is that, in a population of older Australian adults at an increased risk of cognitive decline and dementia, a structured program comprising health education, regular physical and cognitive activity, increased social engagement, diet improvements, and medical counseling over 24 months will have a protective effect on cognition, compared with health education (only) intervention.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature using traditional (e.g., PubMed) sources and meeting abstracts and presentations for protocols or methodology of multidomain lifestyle interventions, particularly members of the World-Wide Finnish Geriatric Interventions Study (WW-FINGERS) initiative.
2. **Interpretation**: Our methodology provides details on the recruitment, and procedures for a single-blind, multisite, randomized controlled trial, namely The AUstralian multidomain Approach to Reduce dementia Risk by prOtecting brain health With lifestyle intervention study (AU-ARROW). The population-based AU-ARROW study addresses whether a multidomain intervention (nutritional guidance; exercise, cognitive and social activities, and medical monitoring and health education) can prevent or delay cognitive impairment in older adults at increased risk of cognitive decline.
3. **Future directions**: Valuable insights can be gathered from this protocol for conducting large-scale, multidomain lifestyle interventions. The finalized AU-ARROW protocol is expected to allow (a) development of an evidence-based innovative treatment plan to reduce cognitive decline and dementia risk, (b) effective transfer of research outcomes into Australian health policy, and (c) validation of emerging blood and retinal diagnostic biomarkers in preclinical screening.

2 | METHODS

2.1 | Intervention design

The AU-ARROW study is registered on the Australian New Zealand Clinical Trials Registry (ANZCTR) (ACTRN12621001760864).

The design is a phase III, single-blind randomized trial to study the effects of a 24 month structured multidomain lifestyle intervention on cognition, in participants deemed to be at risk of cognitive decline. Participants will be randomized equally into one of two groups:

1. **M**ultimodal **L**ifestyle Intervention Plan (ML).
2. **H**ealth Education and **C**oaching (HC).

Figure 1 shows the timeline for the two arms of the clinical trial.

2.1.1 | Multidomain Lifestyle Intervention

Physical exercise: The exercise component of the Multidomain Lifestyle Intervention (ML) includes a gym-based regimen of aerobic exercise, resistance training, and stretching, balance, and range of motion activities. Aerobic exercise is performed at moderate/high levels of cardiorespiratory intensity, at approximately 70%–80% of heart rate reserve (HRR: 220-age-resting HR) for 30–40 min, not including warm-up and cool-down time, four times per week.[16] Fitbit devices will be supplied to participants and provide continuous heart

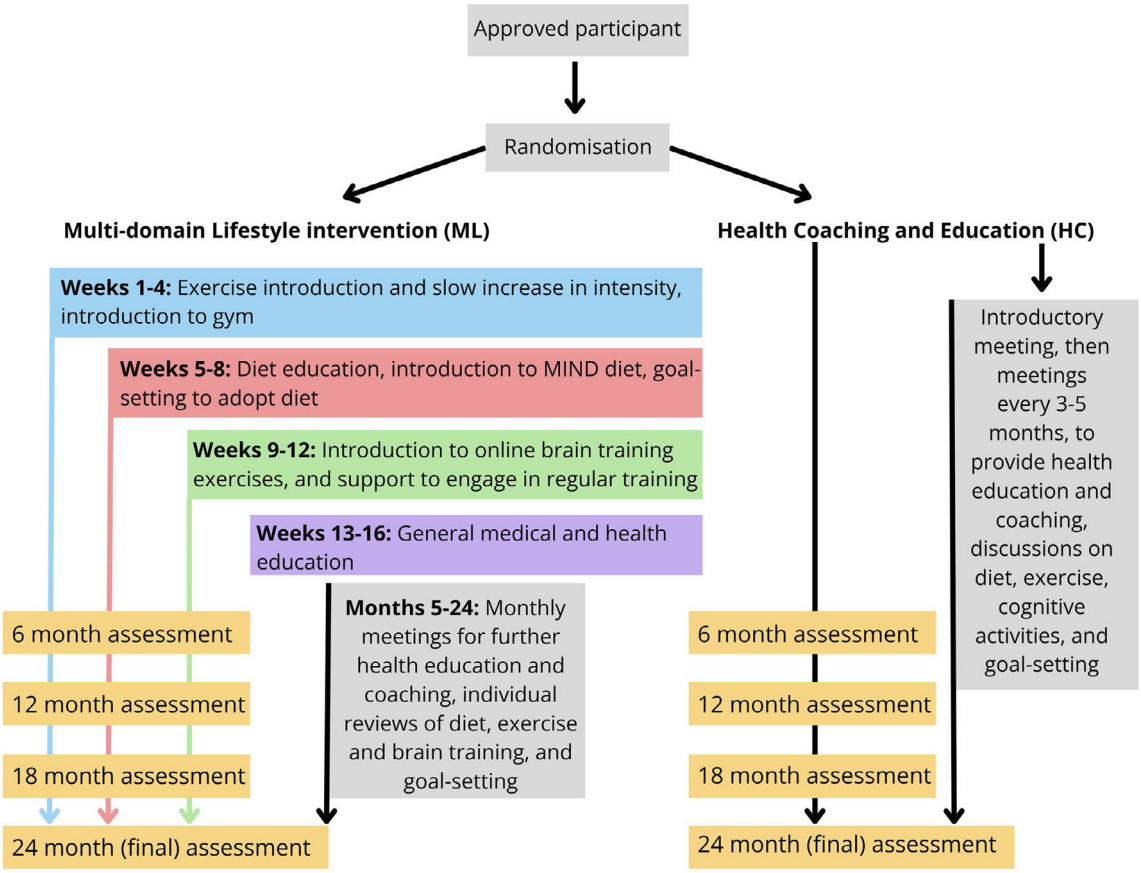

FIGURE 1 Summary of timeline for the two arms of the clinical trial.

rate readings. Resistance training is performed using weight machines, free weights, and/or resistance bands for 20 min 2 days per week. Upper and lower body exercises are performed at an intensity of 4–6 on the modified Ratings of Perceived Exertion (RPE) scale that ranges in value from 0 (minimal to no effort) to 10 (maximal effort possible). A variety of stretching, balance, and range of motion exercises are performed for 15 min 2 days per week, at an RPE of 2–3. Individual handouts of stretches and balancing exercises will be provided to all ML participants.

ML participants are provided with flexibility in the design of their exercise programs. Participants are required to attend 1 of 10 study-designated gyms (5 in Sydney and 5 in Perth) to use the facility's aerobic and resistance training equipment (e.g., elliptical trainer, treadmill, weight machines, hand-held weights, elastic tubing with handles, and exercise balls), and will also be encouraged to attend up to two group classes per week at their study-designated gyms. Once a participant is comfortable with their particular exercise program, the exercise physiologist may approve home exercise once per week; however, resistance training must be performed at the study-designated gyms. Group exercises will be performed in approved group exercise classes designed for older adults. Approved classes at the participating study-designated gyms will include a combination of aerobic training, resistance exercises, and stretching/balance activities, thus meeting some of the study's physical activity requirements. The exercise physiologist will assist participants in identifying appropriate classes to attend, provide strategies to meet the AU-ARROW exercise goals, address participant questions and concerns, and provide ongoing encouragement and accountability. Guidelines and resources are provided from an exercise physiologist to assist participants in completing these activities. Onboarding of the exercise program is gradual to build self-efficacy and stamina, and to reduce risk of injury. The duration and intensity of the aerobic exercise is implemented in a ramped fashion such that intensity begins at a low level and gradually increases over time until the target intensity and duration are achieved.

The physical and mental activities questionnaire (modified CHAMPS) will be completed every 3 months to collect data on physical activity performed outside of the study-designated gyms. Physical function tests every 6 months will assess physical fitness improvements, including a Short Physical Performance Battery (SPPB), a 400 m walk test, and the grip strength test.

Diet: Dietary counselling (including education) via group education and individual synchronous telehealth to support dietary behavior change in adopting the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet. The MIND diet recommendations (increased berry, green leafy vegetable, fish and olive oil consumption, while reducing intake of fried/fast foods, red and processed meats,

TABLE 1 MIND diet food components.

Food groups to include in the MIND diet	
Whole grains	3 or more servings per day
Green leafy vegetables	1 or more servings per day (1 serve = ½ cup cooked, or 1 cup raw)
Other vegetables	1 or more servings per day (1 serve = ½ cup cooked)
Nuts	5 servings per week (1 serve = 30 g)
Berries	4 or more servings per week (1 serve = ½ cup)
Beans or legumes	4 or more servings per week (1 serve = ½ cup cooked)
Fish (not fried)	1 or more servings per week (1 serve = 100 g cooked)
Poultry (white meat, skinless; not fried)	2 or more servings per week (1 serve = 80 g cooked)
Olive oil	2 tablespoons of extra virgin olive oil per day, and also use as the main cooking oil
Food groups that should be reduced or minimized in the MIND diet	
Pastries and sweets	No more than 4 serves per week
Red meat and processed meat	No more than 3 serves per week
Cheese	Less than 1 serves per week
Fried and fast food	No more than 1 meal per week
Butter	No more than 1 tablespoon per day

saturated fats, and high sugar foods and drinks) will be presented in the context of the National Health and Medical Research Council (NHMRC) Australian Dietary Guidelines[17] and food group and serving size recommendations.

The dietitian will provide nutrition counseling and work with participants on how to incorporate these MIND diet food components (listed in Table 1) into their diet in an individualized and tailored manner. At each monthly review, progress with the specific goals negotiated and barriers and enablers to achieving the goals will be discussed. New goals will be set for improving dietary behaviors and adherence to the MIND diet and Australian Dietary Guidelines. Individualized tips and strategies or additional recipe ideas based on taste preferences and cooking skills, will be provided by the dietitian to support participants in achieving MIND diet goals. These follow-up consultations will also enable the dietitian trained in medical nutrition therapy to provide nutrition education regarding any other chronic disease conditions the participant has and to implement dietary counselling and behavioral strategies to support behavior change and encourage adherence to dietary recommendations. Total fat for the MIND diet is ad libitum as long as most of it comes from fatty fish, olive oil, and nuts. For safety, there is no diet recommendation for wine (or alcohol) consumption in AU-ARROW.

A cookbook (Maggie Beer's "Recipe for Life") with recipes containing ingredients and nutrients, for which there is evidence they are protective against AD risk factors, will be provided to ML participants after 12 months. Recipes from this book may be integrated into the individualized dietary counselling and education.

Completion of the Cancer Council of Victoria Food Frequency Questionnaire every 6 months will assess improvements in MIND diet adherence.

Cognitive Activity: 30-min sessions of computer-based cognitive training exercises from BrainHQ, four times a week independently at home. Each session has 12 levels. Participants should complete 48 levels per week to be considered compliant. Over the course of the intervention, participants will be expected to complete 29 unique visual and auditory exercises that engage low- to high-level perceptual and cognitive processes. Each exercise implements an adaptive procedure to ensure learning, stimulus sets, and stimulus emphasis to ensure its generalization to real-world function.[18] Specifically, all exercises adapt to ~80% criterion accuracy on an ongoing trial-by-trial basis using an n-up/m-down algorithm to participant responses to estimate threshold. Thus, as a user gets trials correct, task difficulty increases by decreasing exposure duration and driving the brain to process information more quickly; conversely, as the user gets trials incorrect, task difficulty decreases by increasing exposure duration. This adaptive framework drives improvements in the control of flexible changes between cognitive operations as well as in the rapid registration of motor responses. The BrainHQ program designed is web-based (can be accessed from any computer or tablet) and targets four cognitive functions affected by aging and AD: speed of processing, working memory, other executive functions, and episodic memory.[19] The program includes an extensive set of engaging tasks that are (i) easy to complete, (ii) adaptive in difficulty to maintain high levels of accuracy, and (iii) presented in a rotating sequence across training sessions to provide varied experiences and minimize boredom. Facilitated monthly group meetings to support increased cognitive and social engagement. These meetings will provide information about the importance of intellectual and social stimulation, and study staff will work with participants at each meeting to set personal goals to increase intellectual and social stimulation in the coming weeks. During the subsequent group meetings, participants report back to the group about their experiences.

Medical Monitoring: Consultations with a study clinician every 6 months to provide Australian medical guideline-based health education[20] to help them understand the major health risk factors facing middle-aged-older individuals. Topics covered include cardiovascular disease, diabetes type II, and hypertension, and how lifestyle modifications can reduce the risk of all three. The links between these conditions and cognitive decline and dementia will also be described, thus underscoring the advantages of reducing the risk of these conditions. These consultations aim to promote improved self-management of cardiometabolic risk factors through regular blood laboratory testing (fasting glucose, lipids, Hemoglobin A1c), weight monitoring, blood pressure measurement, and goal setting.

Monthly Meetings: Facilitated group meetings to provide further health education and support relevant to the four points above.

2.1.2 | Healthy lifestyle education and coaching group

Lifestyle Education: The exercise physiologists, dietitians, or research assistants on the trial will provide talks and educational material from online Australian Government websites at in-person group meetings 2–3 times a year (range of 2–15 participants per group), lasting approximately 90 min each. The topics covered will include the value of healthy eating patterns, physical exercise and cardiovascular health, social engagement, cognitive activities, as well as strategies for taking up lifestyle changes. The meetings will be semi-structured, allowing some one-to-one interaction, as well as group interactions.

Australian Guideline-based[20] health monitoring and clinical advice: Annual consultation with a clinician to discuss 6-monthly blood test results (fasting glucose, lipids, Hemoglobin A1c), blood pressure, body weight measurement, medication changes, any adverse events, and to reinforce the health advantages of adopting a healthier lifestyle.

Tables 2 and 3 show the schedule of contact with Multidomain Lifestyle Intervention participants and Health Education and Coaching participants, respectively.

2.2 | Eligibility criteria

2.2.1 | Inclusion criteria

- Males or females, Age 55–79 years.
- Insufficiently active (undertaking less than 150 min per week of moderate/vigorous exercise [with vigorous exercise minutes scoring double] calculated via self-report).
- Lives independently.
- Not allergic to seafood.
- Poor diet (as per the MIND Diet Screener, with a score ≤9).
- Must have Internet access, mobile phone, and computer, laptop, or tablet such as an iPad (minimum 12-inch screen) at home.
- Lives in a region where the interventions will be delivered (i.e., within easy travel distance of one of the gym locations).
- Participants must be willing to complete all study-related activities for the 24 months of the trial.
- Participants must be able to provide written consent in English. All study procedures will be conducted in English only.
- Participants must not have any physical disabilities that would preclude them from being able to complete any of the lifestyle intervention domains.
- Does not plan to travel outside of the home geographic area for more than 1 month at a time, or for more than 3 months over the course of the study.
- Not currently engaging in accredited online brain training programs for more than 30 min per week (e.g., BrainHQ, Luminosity, CogniFit, Elevate, or Peak).
- Absence of cognitive impairment as per the Telephone Montreal Cognitive Assessment test (tMoCA) with a score required to be ≥18, and the Clinical Dementia Rating Scale[21] (CDR ≤0.5), and CDR-Sum of Boxes (CDR-SB ≤1).
- Needs to satisfy at least 1/4 of the following four criteria:
  - Increased vascular and/or metabolic risk factors, as indicated by
    - Systolic blood pressure ≥125 mm Hg at screening, or on treatment for hypertension
    - Low density lipoprotein (LDL) cholesterol at ≥3.0 mmol/L at screening, TG/HDL ratio >1.0 at screening, or on treatment for dyslipidemia, or
    - Glycated hemoglobin at 6% (42 mmol/L) or higher at screening, or on treatment for diabetes (except insulin)
  - Aged ≥ 70
  - First or second-degree family history of significant cognitive decline/memory problems/dementia (including parent, siblings, aunts/uncles, grandparents, and/or half-siblings)
  - Body mass index (BMI) 30–40
- Must be willing to be randomized to either of the lifestyle intervention groups.

2.2.2 | Exclusion criteria

- BMI ≥40
- Regular use of prescribed or over the counter medication with cognitive adverse effects, including opiates, anticholinergics, antiepileptics, or benzodiazepines. Rare pro re nata use is permitted, provided that these medications are not taken within five half-lives of cognitive testing, and they are, in the opinion of the investigator, unlikely to interfere with participation in the trial including the exercise and cognitive training interventions.
- Use of mood-stabilizing psychotropics, psychostimulants, or antipsychotics within the past 3 months.
- If on an antidepressant, must be on a stable dose for 4 weeks prior to screening.
- Current regular use of systemic corticosteroids.
- Any significant neurologic disease, including any form of dementia, mild cognitive impairment, Parkinson's disease, Huntington's disease, normal pressure hydrocephalus, brain tumor, progressive supranuclear palsy, seizure disorder, subdural hematoma, multiple sclerosis, or history of significant head trauma with persistent neurologic sequelae or known structural brain abnormalities (significant identified by any ongoing physical or cognitive deficits, usually having had a magnetic resonance imaging (MRI) or computed tomography (CT) brain scan, or prolonged hospitalization at the time).
- Current or past use of medications for memory impairment or AD (e.g., cholinesterase inhibitors, memantine).
- History of major depression within the past 6 months (based on a diagnosis from their general practitioner (GP); self-harm risk assessment can be utilized if the clinician feels mental health is poor).

TABLE 2 Schedule of contact with multidomain lifestyle intervention participants.

Multidomain lifestyle intervention																									
Parameter	**Introductory months**				**Maintenance**																				
Month	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	
Physical activity introduction	xxxx																								
Nutrition meetings		xxxx																							
Brain training sessions			xxxx																						
Health education meetings				xxxx																					
Phone calls to review diet and adherence (o)		o	o	oo	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	
Exercise review at gym (g) or by phone call (e)	g	e	g	e	g		e		g						g						g				
Group meetings (x)						x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Clinic visit, blood tests, memory and brain function tests, questionnaires, physical assessment (c)						c						c						c						c	
Health coaching and medical review by clinician (t)						t												t							
Health coaching by clinician, extra memory test (need study partner) (h)												h												h	
																									Total visits
Group meetings (x + g)	5	4	5	4	1	1	1	1	2	1	1	1	1	1	2	1	1	1	1	1	2	1	1	1	41
Phone calls (o + e)		2	1	3	1	1	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	27
Clinic visits (c)						1						1						1							4
Health coaching (t)						1												1							2
Extra clinic visit/clinician health coaching (h)												1												1	2
																									76

Note: x = team meeting; o = phone call to review diet; e = phone call to review physical exercise, c = study site visit; h = health coaching and CDR (partner required), visits occur several days after (c) visits, so that a clinician can review and discuss blood test results; g = group gym visit; t = clinician consultation.

TABLE 3 Schedule of contact with the health education and coaching participants.

Health education and coaching intervention																									
Month	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	
Group meetings for lifestyle and health education, and goal setting (x)	X		X						X						X						x				
Clinic visit, blood tests, memory and brain function tests, questionnaires, physical assessment (c)						c						c						c						c	
Health coaching by clinician, extra memory test (need study partner) (h)												h												h	
																									Total visits
Group meetings (x)	1		1						1						1						1				5
Clinic visits (c)						1						1						1						1	4
Clinician health coaching (h)												1												1	2
																									11

Note: x = team meeting; h = study site visit, health coaching by clinician and CDR (partner required); c = study site visit for blood tests, neurocognitive tests, physical assessments, and the filling out of questionnaires. In months 12 and 24, clinician (h) appointments occur after study site (c) visits, to enable discussion of blood test results, as well as general health advice and coaching.

- History of bipolar disorder or schizophrenia as per DSM-5 criteria.
- History of alcohol or substance abuse or dependence within the past 2 years, as per DSM-5 criteria, or pattern of alcohol use over the past 3 months averaging in excess of 21 standard drinks per week or 4 standard drinks in any given day.
- Significant cardiovascular disease (including NYHA Class III or IV congestive heart failure, clinically significant aortic stenosis, history of cardiac arrest, or uncontrolled angina).
- Serious conduction disorder (e.g., third degree heart block), uncontrolled arrhythmia, or new Q waves or ST-segment depressions (>3 mm) on electrocardiogram (ECG; treated atrial fibrillation for more than 1 year or occasional premature ventricular contractions on ECG are not exclusions).
- Myocardial infarction, major heart surgery (i.e., valve replacement, bypass surgery, stent placement, angioplasty), deep vein thrombosis, or pulmonary embolus in the past 6 months.
- Large vessel stroke in the past 2 years.
- History of transient ischemic attack (TIA) or small vessel stroke in the past 6 months; TIA occurring more than 6 months ago with residual effects.
- Lung disease requiring either regular use of oral corticosteroids or the use of supplemental oxygen (inhaled steroids for asthma are permissible).
- Clinically significant abnormalities in laboratory blood tests, as judged by the site study clinician.
- Renal disease (estimated glomerular filtration rate [eGFR] <30 mL/min).
- Past or current use of insulin to treat type 2 diabetes.
- Past or current history of gallbladder stones (cholecystectomy accepted).
- History within the past 2 years of treatment for primary or recurrent malignant disease, excluding non-melanoma skin cancers, resected cutaneous squamous cell carcinoma in situ, basal cell carcinoma, cervical carcinoma in situ, or in situ prostate cancer with normal prostate-specific antigen post-treatment.
- History of hip fracture, joint replacement, or spinal surgery in the past 6 months.
- Currently receiving physical therapy or cardiopulmonary rehabilitation.
- Currently receiving dietitian advice.
- History of a malabsorptive bariatric procedure (gastric bypass, biliopancreatic diversion); or other bariatric procedures involving restriction (i.e., sleeve, band).
- Site Principal Investigator/Study Clinician discretion regarding medical status, appropriateness of participation, or concern about intervention adherence.
- Enrolment in another clinical trial, either currently, or in the 30 days prior to randomization.
- Failure to adhere to relevant state regulations regarding coronavirus disease 2019 (COVID-19) vaccinations required for attendance at clinic and gym settings.

2.3 | Recruitment

Cognitively normal, community-dwelling older adults aged 55–79 years, both males and females (50/50 split), who are at higher risk of developing cognitive decline and dementia (i.e., with increased vascular and/or metabolic risk factors, family history of dementia, insufficiently active lifestyle, or poor diet) will be recruited from the community (retirement complexes, community centers, medical centers, golf and bowling clubs, social clubs) and through mass-media and social media advertisements, including paid targeted online advertising, television advertising, newspaper print, and radio advertising on stations commonly listened to by our target audience.

A total of 600 participants will be recruited, with 300 in Sydney, New South Wales (NSW), and 300 in Perth, Western Australia (WA). The two study sites for the AU-ARROW study are Macquarie University (NSW), and Alzheimer's Research Australia (WA). While Sydney has a population approximately 2.5 times that of Perth, the research team in Perth has over 25 years of experience recruiting and conducting Alzheimer's disease research studies, therefore, recruiting an equal number of participants as the Sydney site is feasible. There are existing community resources in place in Perth to support recruitment including a large database of contacts from previous research studies and Alzheimer's Research Australia.

As the physical exercise component for the ML group is gym-based, participant recruitment needs to be targeted to specific suburbs, so that participants live in close proximity to the gyms chosen for the intervention. If in the active intervention program, participants will be asked to carry out physical exercise at their allocated gym on a regular basis and adherence is likely to be much greater if the gyms are close to participants' homes.

2.4 | Ethics and informed consent

This study will be conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects are approved by the institutional ethics committees of Ramsay Health Care Western Australia | South Australia, Edith Cowan University, and Macquarie University. Written informed consent will be obtained from all participants.

Consent forms will be in English, and participants must be able to provide written consent in English. The AU-ARROW study investigators will provide ample time (7–10 days) to the potential participants to read the participant information and consent form (PICF), discuss the study requirements with family and friends, and ask questions of study staff if needed. At the start of the Screening Visit, following a 30-min discussion of the trial PICF and its requirements with one of the study clinicians, consent will be given in both oral and written form in the presence of the clinician.

The informed consent will not only cover consent for the trial itself, but also for the genetic research, biomarker studies, and biological

sample storage. Consent forms will specify that deoxyribonucleic acid (DNA) and biomarker samples are for research purposes only; the tests on the DNA are not diagnostic in nature and participants will not receive results. The consent for storage will include consent to access stored data, and blood and urine samples for biomarker analyses related to dementia and AD research.

2.5 | Randomization

Eligible participants will be randomized to either ML or HC study arms on a 1:1 basis. The "allocationTable" function within the "redcapAPI" R library will be used to generate an allocation table which will be uploaded for use via the REDCap Randomization Module. Randomizations in the allocation table will be stratified using the REDCap entries for by sex (male or female), age group at screening (<70 and ≥70), and study site (Perth or Sydney). Allocations will also be based on blocked randomization, with block sizes known only to the study statistician and data manager.

2.6 | Study procedures

2.6.1 | Candidate screening steps

The Initial Phone Survey begins with a short description of the trial requirements and commitments. Candidates who confirm their continued interest in the trial following this short description of the trial requirements and commitments will then undergo the Initial Phone Survey. The Initial Phone Survey takes approximately 15 min and asks brief questions on the most common exclusion criteria, including radius to gym location, whether they have a computer, laptop, or tablet such as an iPad at home with internet access, whether they have someone willing to be a study partner, basic questions about general health, a brief question on whether they currently do moderate/vigorous exercises and how many minutes per week, if they are currently receiving dietitian advice, if they do computer brain training games, and a "spare time" calculator. If these questions do not immediately exclude a candidate, they will be asked to complete the Online Pre-Screen Survey. Candidates will be asked to read the main study PICF and ask questions about the study, prior to completing the Online Pre-Screen Survey. The Online Pre-Screen Survey includes a computer and phone use survey, a MIND diet survey, a medical survey, and a physical activity survey, and takes approximately 40 min to complete.

The Online Pre-Screen Survey answers will be assessed by study staff to determine eligibility for the trial, and if trial criteria are satisfied, a telephone Montreal Cognitive Assessment (T-MoCA) is performed. If the T-MoCA test is passed (pass score ≥18), then candidates will have the PICF emailed to them again, to review for a few days. Candidates will be asked if they are still interested in the trial and will again be given the opportunity to ask questions, following which an appointment for the Screening Visit will be made. They will be asked if they can provide a medical history summary from their GP (GP history (optional)) to be brought to the clinic for the Screening Visit.

Screening visit assessments (which require two separate visits lasting approximately 5 hours in total) include:

1. Written consent taken by a study clinician, following a discussion of trial protocol and requirements
2. Brief health assessment (weight, height, BMI calculated, waist and hip measurement, pulse, blood pressure, completion of SOZO body composition measures)
3. ECG
4. Fasting blood collection for clinical pathology for electrolyte/urea/creatinine test (EUC), liver function test (LFT), full blood count (FBC), hemoglobin A1c, glucose, and lipid panel
5. Questionnaires—Medications and dietary supplement list filled (must bring medications and supplements to the clinic), demographic data questionnaire, and the Alcohol Use Disorder Identification Test (AUDIT)
6. Medical history, medication review, and general physical and neurological examination by study clinician
7. The study partner will first be asked to provide written consent by signing the Study Partner Acknowledgment Form. They will then be asked to complete surveys: Instrumental Activities of Daily Living (IADL), Everyday Cognition (ECog), and McCusker Subjective Cognition Impairment Inventory (McSCI) partner forms. The participant also completes the ECog and McSCI
8. Perform CDR
9. Physical function test
    I. Short Physical Performance Battery (SPPB)
    II. 400 m Walk Test
    III. Grip Strength Test

If the candidate passes the CDR assessment (result (≤0.5), or CDR-Sum of Boxes (≤1)), the blood test results are not exclusionary, and the candidate is assessed to be physically capable of engaging in the ML physical exercises of the trial, they are informed that they are eligible.

2.6.2 | Schedule of participant assessment visits from baseline visit to end of study

Table 4 provides outcome tests, medical tests, assessments, and questionnaires completed at each assessment time point.

2.7 | Optional ancillary studies

2.7.1 | MRI

MRI of the brain is optional and will be conducted at baseline and 24 months (post-intervention) on approximately 150 of the participants at each site on a 3T scanner. MRI scans to be conducted include T1 fast spoiled gradient-echo (FSPGR), diffusion tensor imaging (DTI), resting state functional MRI (rs-fMRI), diffusion-weighted imaging (DWI), susceptibility-weighted angiography (SWAN), and T2-FLAIR

TABLE 4 Procedures performed at each assessment time-point.

Appointments/procedures/tests/questionnaires	Baseline[f] or screening	Month 3[h]	Month 6[g,i]	Month 9[h]	Month 12[g,f]	Month 15[h]	Month 18[g,i]	Month 21[h]	Month 24[g,f]
Initial data collection[a]	X								
ECG	X								
Vital signs and anthropometric measurements, including SOZO machine scan (height measured at 0 and 24 months only)	X		X		X		X		X
Brief physical and neurological exam	X								
Medical assessment and review (ML)	X		X		X		X		X
Medical assessment and review (HC)	X				X				X
Adverse Event Monitoring and review of medication use			X		X		X		X
Cognitive assessment (FCSRT, SR, VPA, Number Span, Verbal fluency, DSST, Trail-making test, MMSE, Clock Drawing Test, Cogstate[b],	X		X		X		X		X
Clinical Dementia Rating	X				X				X
Cambridge Contextual Reading Test	X								
BrainHQ assessment	X		X		X		X		X
Questionnaires									
Health status (SF-36)	X				X				X
Brief Medical Review Survey	X	X	X	X	X	X	X	X	X
Everyday Cognition	X				X				X
McCusker Subjective Cognitive Impairment Inventory	X				X				X
Depression, Anxiety, Stress Scale	X		X		X		X		X
Sleep questionnaires (Pittsburgh Sleep Quality Index, Insomnia Severity Index), STOP Bang questionnaire)	X		X		X		X		X
Quality of life (EuroQol-5D)	X				X				X
Speech, Spatial and Qualities of Hearing scale	X		X		X		X		X
Brief Pain Inventory	X		X		X		X		X
De Jong Gierveld Loneliness Scale	X		X		X		X		X
Lubben Social Network Scale	X		X		X		X		X
Diet questionnaire (CCVFFQ)	X		X		X		X		X
Alcohol Use Disorder Identification Test	X								
MIND diet survey	X	X	X	X	X	X	X	X	X
Physical and mental activities questionnaire (modified CHAMPS)	X	X	X	X	X	X	X	X	X
Five Facet Mindfulness Questionnaire	X				X				X
Sleep diary	X		X		X		X		X
Physical monitoring									
Short Physical Performance Battery	X		X		X		X		X
Grip Strength test	X		X		X		X		X
400 m walks	X		X		X		X		X
Diagnostic tests									
Blood collection for clinical lab tests (glucose, HbA1c, lipids)	X		X		X		X		X
Screening EUC, LFT blood tests	X								

(Continues)

TABLE 4 (Continued)

Diagnostic tests				
Blood and urine collection for biomarker analysis	X	X[c]	X	X
MRI imaging[d]	X			X
Amyloid PET imaging[d]	X			X
Retinal imaging[d]	X			X
Objective sleep assessment (WatchPAT)[e]	X		X	X
Study partner activities				
Clinical Dementia Rating (partner)	X		X	X
Instrumental activities of daily living	X		X	X
Everyday cognition (partner)	X		X	X
McCusker Subjective Cognition Impairment Inventory (partner)	X		X	X
Other				
Participant end of study Feedback Survey				X
Motivation to change lifestyle and health behaviors for dementia risk reduction	X			X
Study close-out discussion (clinician)				X

Abbreviations: ECG, electrocardiogram; CCVFFQ, Cancer Council of Victoria Food Frequency Questionnaire; DSST, Digit Symbol Substitution Test; EUC, Electrolyte/Urea/Creatinine test; FCSRT, Free and Cued Selective Reminding Test; HC, healthy lifestyle education and coaching group; LFT, Liver Function Test; ML, multidomain lifestyle intervention; MMSE, Mini Mental State Examination; SR, Story Recall; VPA, Visual Paired Associates.

[a]Comprises signing of informed consent, collection of a fasting blood sample, collecting of demographic data, medical history and medication list, exercise and diet history, family history of cognitive impairment, and clinical dementia rating test by certified trained nurse.

[b]Cogstate only at baseline and 12 and 24 months.

[c]Urine only.

[d]Optional assessments that require separate visits to be completed, and only a subset of 50% (300) of total participants will undergo these tests.

[e]Optional sleep study assessment undertaken in a subset of approximately 400 study participants.

[f]Assessment at baseline, 12 months, and end-of-intervention assessment at 24 months require two visits each, lasting up to 7 h.

[g]All 6-monthly visits will occur at 6-month intervals following the start of intervention with a 2-week leeway either side resulting in a 4-week window of possible visit scheduling, allowing for greater flexibility around participant's personal commitments.

[h]Survey completion by participants at 3, 9, 15, and 21 months will be completed within 2 weeks of their due date (1 week either side).

[i]Assessment at 6 and 18 months last approximately 4.5 h.

(fluid attenuated inversion recovery). Scans will assess brain structural abnormalities and atrophy, white matter (WM) hyperintensities and microstructure, and cerebral blood flow. MRI provides quantitative and qualitative data. MRI scans will be briefly reviewed by the local radiologist for any obvious pathology that may have a serious impact on the participant's health. Any abnormalities will be reported to the investigator for follow-up with a participant's treating doctor. Clinically significant abnormalities will also be reported as adverse events.

2.7.2 | Positron emission tomography (PET) Aβ amyloid imaging

Together with the MRI, this imaging is optional and will be conducted at baseline and 24 months (post-intervention) on approximately 150 of the participants at each site (the same participants who undergo MRI). Aggregated Aβ amyloid is one of the neuropathological hallmarks of AD, and brain Aβ amyloid burden will be imaged and quantified via positron emission tomography (PET) using one of the following tracers: ^{18}F-Florbetaben (NeuraCeq), or ^{18}F-NAV4694 (Navidea), or ^{18}F-Florbetapir (AMYVid), or ^{18}F-Flutemetamol (VizAmyl). Due to tracer availability at both sites, a range of tracers will be used. The same tracer will be used at baseline and 24 months. The procedure for the PET scans will be outlined in an imaging manual. Briefly, PET images will be analyzed using CapAIBL[22] and brain Aβ burden will expressed in the Centiloid (CL) scale, to normalize values from different radiotracers, the methodology of which has been shown to be valid and reliable.[22,23] The CL scale provides a single continuous scale across the different Aβ-amyloid imaging tracers, where a value of '0' represents the typical brain Aβ load in young controls, and "100" the typical brain Aβ load seen in mild AD patients.[24]

2.7.3 | Retinal scans

The retinal imaging is optional and will be conducted at baseline and 24 months (post-intervention) on the same subset of participants as those undergoing MRI and Aβ amyloid imaging. A NASA-derived

technology in the form of a metabolic hyperspectral retinal camera (Optina diagnostics, Canada) device will be used to test the proposition that a single-visit eye scan can show detectable changes in the retina that can correctly reflect brain Aβ burden.[25,26] A successful outcome will facilitate an accurate and quick eye screening test device for mass population screening.

2.7.4 | Sleep ancillary study

The Sleep Ancillary Study will test whether intensive lifestyle modification (diet, exercise, and cardiovascular risk reduction) can improve sleep disordered breathing, sleep fragmentation, duration, and other objective measures of sleep quality in older adults at-risk for cognitive decline and dementia. It will also examine whether intervention-related improvements in cardiometabolic health and sleep can predict 2-year improvements in cognitive function. Although there is some evidence to suggest diet, exercise, and cardiovascular risk reduction can improve sleep, and that improved sleep positively impacts cognitive function in older adults,[27] these effects have not been confirmed in a large-scale rigorous clinical trial. The Sleep Ancillary Study to AU-ARROW will allow this critical knowledge gap to be addressed.

As part of the Sleep Ancillary Study, optional objective sleep assessments will be undertaken at baseline, 12 and 24 months in a subset of approximately 400 study participants using wrist-worn clinically validated WatchPAT devices (Itamar Medical, Atlanta, Georgia, USA) for continuous overnight measurement of oxygen desaturation, pulse tonometry, and heart rate using finger pulse oximetry, and 2 day/night measurements of total rest-wake activity using actigraphy. The devices measure peripheral arterial signal, heart rate, oximetry, actigraphy, body position, snoring, and chest motion via three points of contact. WatchPAT derived data provides Apnoea–Hypopnoea Index (AHI; indicates severity of sleep apnea), central AHI (AHIc), Respiratory Disturbance Index (RDI; reports on respiratory events during sleep, including respiratory-effort related arousals), and Oxygen Desaturation Index (ODI; the number of times per hour of sleep that the blood's oxygen level drops by a certain degree from baseline) based upon True Sleep Time and Sleep Staging.

Individual WatchPAT participant accounts are set up prior to use of the devices, using AU-ARROW participant ID numbers for identification (therefore deidentified), through Itamar Medical Ltd's software "zzzPAT." Following data download and analysis through this software on a local computer, results are reviewed by trial staff. An ODI > 10, and/or an AHI > 15 will result in AU-ARROW trial assistants notifying a study clinician. Participants will be informed by a trial staff member that their sleep analysis has returned an abnormal reading, and that their GP will be notified. These participants will also be given the option to discuss their abnormal sleep results with a study clinician. Depending on diagnosis and recommended treatment in such cases, decisions may need to be made concerning study continuation.

WatchPAT data will also be supplemented with the continuous measurements for the 24 months of the trial of total sleep-wake activity collected using actigraphy via the Fitbit. This additionally provides measures of sleep fragmentation, duration, heart rate, and other activity-based metrics. In addition to these devices, an optional sleep diary will be offered to all participants at baseline, 6, 12, 18, and 24 months. The sleep diary will assess participants' perceptions of their sleep quality over a 7 day/night period as well as provide additional information on factors that may impact sleep, such as diet and physical activity on a particular day. The data obtained from the sleep diary will complement data obtained from the Fitbit (and WatchPAT, if used) over the same week.

2.8 | Strategies to improve adherence to intervention

Behavioral management strategies will be utilized by trial staff to help maintain a positive environment and high adherence to the various components of the intervention.

Participants will receive several phone calls during the study from the exercise physiologist who will discuss with participants whether their individualized prescribed exercises can be upgraded to a higher intensity: this will occur more frequently at the start of the intervention, as participants adjust to engaging in regular physical exercise. The dietitian will apply motivational interviewing to discuss with the individual participant any dietary issues and determine solutions for any challenges with adhering to the MIND diet. There may also be phone calls by a (non-blinded) member of the clinical trial team to discuss any problems with Fitbits, BrainHQ exercises, computer problems, program adherence, to record any time of non-adherence due to illness or holidays, and in general to discuss how the participant is coping with each aspect of the intervention.

2.8.1 | Physical exercise

Study-designated gym attendance records

Information provided by the participant's gym entry scanning card will be monitored for tracking gym attendance.

Wristband-style Fitbits

Fitbits will be provided to all participants. For the ML participants, these will serve as a reminder of exercise levels and will be employed to assess steps and heart rate, and METs (metabolic equivalent of task; no intervention goals based on Fitbit data), and to determine completion of at least 75% physical exercise sessions (three sessions per week). Fitbits are expected to be worn continuously (although optional at night) for 24 months, and as such are very useful as a form of ever-present encouragement to be more active. Although we are also providing Fitbits to the HC participants, apart from the initial explanatory session and support if devices are not working as expected, the HC participants will not be provided with any specific encouragement to monitor their physical activity; any use of the devices will be of their own volition. Fitbits worn by HC participants will provide physical activity, heart rate, and sleep data, for comparison to ML participants.

Physical complaints such as aches and pains, tiredness, and sore muscles will be expected particularly in the first few weeks of the exercise program. These will be discussed at the meetings, or via the

regular phone conversations between meetings, to reduce the risk of over-exertion and injury, but also to provide encouragement and to reduce the risk of lowering the intensity of the exercise program, or of dropping out of the intervention altogether.

Fitbit data collection, storage, download, and security. When Fitbits are provided to the participants, a participant Fitbit account will be set up manually. Participants will each use a study-specific account that does not require any personally identifiable information. Participants will be required to download the Fitbit app onto their phones. The device will synchronize with the Fitbit application on their phones, and data will be transferred to Fitbit servers. Participants must agree to the same Fitbit privacy policy as a commercial Fitbit user, in addition they will be asked to authorize third party access to their data in order for it to be accessed by approved study staff. When participant devices sync with Fitbit applications or software, data recorded on the devices will be transferred to secure Fitbit servers that are based in the United States. With an account appropriately authorized by Fitbit, the data on the servers can be accessed and downloaded using Application Programming Interfaces (API). We will be utilizing this option to download device data from the Fitbit servers to a secure study location on a daily basis, and there will be monitoring of this data to ensure all participant watches are active and functional to ensure continuous data flow.

2.8.2 | Diet

A multi-pronged strategy to maintain dietary compliance will be used that includes: (i) group motivation strategies; (ii) self-monitoring of diet using the diet app, Easy Diet Diary (Xyris Pty Ltd.), for 1 week every month; (iii) monthly telehealth dietary consultation with one of the study dietitians, following the dietician's review of the diet app data to discuss diet progress, and to provide individualized goal setting to improve adherence to recommendations and guidelines.

Easy diet diary app for dietary logs

Participants will be asked to use the Easy Diet Diary app to record and self-monitor their dietary intake for the week prior to their follow-up telehealth consultation with the dietitian. The Easy Diet Diary app is a diet app designed specifically for the Australian context, allowing users to log Australian branded and generic food items which link in with the AUSNUT food composition database to allow for calculations of energy, specific nutrients, and food group intake. Additional technology-enhanced features of the app to improve usability include the ability to take photos of foods or meals, a barcode scanner, and recipe creation functions.

The app has been determined to be a reliable electronic food record tool for use in younger adults, as well as for use in middle-aged and older adults, provided dietitian support is present.[28–30] It is feasible for use in epidemiological studies and provides a valid measure of energy and nutrient intakes, with the exception of alcohol.[29]

The app also integrates into the Easy Diet Diary Connect platform and the nutrient analysis program, FoodWorks. This integration will allow the study dietitian to conveniently link in and access participant diet records in real-time, to enable more tailored nutrition care, goal setting, and dietary counseling to take place.[31]

2.8.3 | Cognitive activity

BrainHQ online tracking will be used to determine the number of completed cognitive training sessions and to determine completion of at least 70% cognitive exercise sessions (an average of three times per week). Participants also complete an online version of the AU-ARROW Physical and Mental Activities Questionnaire—This questionnaire is a modified version of the Community Healthy Models Program for Seniors II (CHAMPS II): Program Manual. (2003) (University of California, San Francisco, Institute for Health and Aging, San Francisco, CA, USA) administered to gain information concerning the usual physical activity and mentally stimulating activities participants engage in, in their everyday life.

2.8.4 | Strategies to maintain the cohort

There are several established retention strategies within longitudinal cohort studies[32] which AU-ARROW will employ to maximize cohort retention. These strategies include (i) barrier-reduction strategies, such as offering assistance with parking and transport, incorporating online group meetings and online surveys where possible to reduce participant burden having to attend the site for face-to-face visits; (ii) community-building strategies, such as creating a recognizable study brand via logos and color schemes, create a sense of project community through group meetings, promoting the future sharing of study results (at the end of the study), and sharing of news and events with participants via newsletters and social media; (iii) strategies to improve follow-up rates within each assessment time-point, including the use of phone calls, electronic (text messages and email) reminders to participants to complete assessments; and (iv) tracing strategies, such as collecting the details of an alternative contact person (a study partner) for each participant at baseline.

3 | RESULTS

3.1 | Primary outcome

The primary aim is to investigate whether a 24 month intensive ML intervention provides greater benefits than a health education (only) intervention on a global composite score derived from subset scores from the AU-ARROW modified neuropsychological test battery.

3.2 | Secondary outcomes

These will assess further the effects of a structured multidomain lifestyle intervention versus a healthy lifestyle education intervention

on specific cognitive domains, assessed as episodic memory composite, executive function composite, and processing speed composite, comparing 24 months to baseline measurement.

We will also investigate the effects of a structured multidomain lifestyle intervention versus a healthy lifestyle education group on risk of cardiovascular disease, type 2 diabetes/metabolic syndrome and/or hypertension, as assessed by measuring weight, blood pressure, blood lipid profile, and blood glucose, comparing 24 months to baseline measurement.

The safety and feasibility of a structured multidomain lifestyle intervention versus healthy lifestyle education intervention throughout the study will be determined, via reporting of adverse events, vital signs, blood lipid profile, blood glucose, medical monitoring, adherence, and compliance.

We will also investigate the effects of a structured multidomain lifestyle intervention versus a healthy lifestyle education intervention on physical function, dietary changes, mood, pain levels, social isolation, loneliness, mindfulness, levels of physical and cognitive activities, hearing, overall quality of life and measures of healthcare utilization, as assessed by questionnaires and physical assessments, at 6- or 12-month intervals after baseline.

We will also examine whether differences between intervention groups with respect to the primary and secondary composite cognitive outcomes vary among subgroups defined by baseline cognitive status and genetic risk (Apolipoprotein E (APOE)).

Process evaluation will be conducted to assess the perceptions and engagement with this multidomain lifestyle intervention to understand the intervention effects. Data collected for process evaluation will include the frequency of use of the intervention components (dose), engagement with the program components, and perceptions of the intervention components. The cost of delivery will also be estimated.

3.3 | Exploratory outcomes

A range of other data is being collected to:

- Investigate the effects of the study interventions on hippocampal volume and brain Aβ amyloid load, with imaging completed at 24 months compared to baseline.
- Validate hyperspectral retinal imaging for the early detection of cognitive decline.
- Identify novel blood and urine biomarkers for early AD diagnosis. Potential AD blood biomarkers, including but not limited to Aβ 40/42 peptides, glial fibrillary acidic protein, and various phosphorylated forms of tau, will be measured in the processed blood samples using the Quanterix SIMOA sensitive immunoassay technology. Urine samples will be investigated using liquid-chromatography mass spectrometry (LCMS), immunoassay, and/or nuclear magnetic resonance spectroscopy. The measurements may include, but are not limited to, inflammatory markers, biogenic amines, short chain fatty acids, cytokines, and small molecules such as organic acids, sugars and phenolics. See Supplementary Material for Blood and Urine Processing Standard Operating procedures.
- Determine intervention effects on oxygen desaturation index and markers of sleep apnea and sleep quality, as assessed by the WatchPAT device, and sleep quality.
- Investigate how body composition, as measured by SOZO bioimpedance spectroscopy (BIS) technology, may be linked to cognitive function, as well as cognitive outcomes and general well-being, following the interventions.
- Collaborate with other international investigators conducting similar lifestyle intervention trials to promote harmonization of intervention protocols, outcomes, data management, and data analytics to facilitate data sharing and inter-study comparisons.

3.4 | Blinding

All personnel responsible for data collection and entry concerning neuropsychological assessments, exercise physiology 6-monthly assessments, and questionnaires, will be masked to the intervention. The Easy App Diary data will only be obtained from ML participants and this data will be documented and stored by the study dietitians. All Fitbit data, including ML data which will be reviewed by the exercise physiologists to monitor intervention adherence and progress, will also only be accessible to staff who are not blinded. The dietitians, exercise physiologists, clinicians, staff members providing education on BrainHQ and medical monitoring as well as those staff implementing the intervention phone calls, introductory information meetings, and monthly meetings for all groups will not be blinded.

3.5 | Sample size estimates

Sample size calculations were derived from the US POINTER study, which has a sample size of 2000 participants. The US POINTER sample size was chosen to provide a minimum of 85% power at the (two-sided) 0.05 significance level to detect a mean difference 0.03 SD/year in the primary outcome—a composite score of global cognition that is comparable across cohorts. The target sample size of 600 participants was chosen to obtain 80% power to detect a 0.05 SD/year change in the primary outcome variable. As AU-ARROW is being conducted in the context of several other similar trials, it is not a stand-alone assessment and will also contribute to the power of the overarching international initiative.

3.6 | Safety monitoring and the data safety management board

An independent data and safety management board (DSMB) will be established for the purpose of reviewing blinded participant safety and efficacy data. The board will be made up of three independent experts (clinician, a statistician, and a researcher with considerable clinical

trial experience). The board will meet at regular intervals to review any adverse events/serious adverse events and monitor the reporting and follow-up of abnormal blood pressure and blood test measures during the study. Safety will be assessed by summarizing and analyzing targeted adverse events in line with ethics approval. The regular monitoring by the DSMB will enable for early detection of risks and problematic behaviors.

3.6.1 | Participant safety

All participants will be monitored routinely for safety issues during group meetings and study site assessment visits, as well as via the study's online 3-monthly brief medical review survey. Assessment visit monitoring will include assessments of vital signs, changes in medications, physical examinations and follow-up of any issues that may have occurred during the physical exercise sessions. Safety assessments include incidence of adverse events/serious adverse events, as all participants will be encouraged to report adverse events (AEs) as soon as possible. An AE can be any unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom or disease, whether or not considered related to the clinical trial. In the event of an injury, unexpected pain, or other form of adverse event (whether related to the study activities or not), the details of the event will be collected and reported at every point of participant contact. A serious AE (SAE) is an untoward medical occurrence that at any time (i) results in death; (ii) is life threatening (i.e., the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe); (iii) requires hospitalization or prolongation of existing hospitalization; (iv) results in persistent or significant disability or incapacity; or (v) other medically important events that in the opinion of the investigator may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above. All ML participants will receive telephone calls and be in contact with study staff at weekly group meetings for the first 16 weeks to follow-up study progress, to confirm study compliance and to ensure they follow safety steps provided by study interventionists, with the aim of avoiding adverse events. Exercise levels in the ML group will be tailored to the physical limitations of each individual, partly in order to prevent over-exertion, but also to help with compliance.

Commercially obtained blood pathology test results that are outside the normal ranges for fasting glucose, HbA1c, and lipids will be referred to the study clinicians for review. The study clinicians will assess the results on an individual basis, taking into account a participant's current conditions and medications. Unless there is a specific condition/medication that would contribute to abnormal readings that indicate the abnormal results do not require follow-up, the participant's GP will be informed, and the participant will be referred to their GP for further investigation. Regardless of abnormal readings, all screening blood pathology results are forwarded to participant GPs, along with a brief explanation of the clinical trial.

Any participant with a systolic BP reading of 160 or over, or less than 100 with symptoms (dizziness, light-headedness, unsteadiness, fainting, blurred vision, weakness, fatigue, rapid shallow breathing), a diastolic BP of over 110, or below 50 will be reviewed by a study clinician and referred to their GP for investigation.

3.7 | Statistical methods

A comprehensive statistical analysis plan (SAP) will be finalized in close collaboration with the US POINTER statistical team and approved prior to the study database lock and before the study blind is broken. The analyses will incorporate the intention-to-treat (ITT) principle, in which data from all participants will be analyzed according to their original intervention assignment. All results will be reported as point estimates (mean differences across groups) and interval estimates (95% confidence intervals).

To construct the composite, (1) scores for each constituent test will be converted to *z*-scores by dividing the differences between individual scores from the cohort-wide mean at baseline by the cohort-wide standard deviation at baseline; (2) *z*-scores will be transformed so that positive scores reflect better performance; (3) *z*-scores will be averaged by cognitive domain provided that ≥50% of the scores per domain are available (otherwise, domain score is missing); and (4) the mean *z*-score across cognitive domains will be re-normalized by subtracting it from the cohort wide mean at baseline and dividing this difference by the cohort-wide SD at baseline. Secondary domain-specific composite outcomes will be analyzed using a similar approach.

For all outcomes of interest, up to five repeated measures will be available for each participant (baseline, 6 months, 12 months, 18 months, 24 months). Linear mixed models or random effects models will be used to analyze continuous outcomes, with the primary dependent variable being the global composite score. Covariates that will be included in each model are sex, age, site (WA vs. NSW), study arm (ML vs. HC), interaction between visit and age (to control for potentially nonlinear factors, e.g., learning effects; different outcomes assessors) that may systematically affect both intervention groups and vary by age), and interaction between study arm and time since entry into the study. Each individual will be included in the model as a random effect to account for the longitudinal correlation due to repeated measures. Random effects models will be fitted using restricted maximum likelihood, and a Wald test will be used to test for the significance of the interaction between the study arm and time since the study entry. A two-sided *p*-value of 0.05 will be considered statistically significant and provide evidence of a difference between the two arms. For secondary outcomes, false discovery rate (FDR)-adjusted *p*-values will be used. Additional covariates may be considered to be included in the secondary or exploratory analyses models, for example, if a participant has an AHI >15 and commences continuous positive airway pressure (CPAP) therapy during the study, it may be important to include this information in longitudinal analysis.

Differences in intervention response by APOE genotype and other AD and related dementias risk factors (e.g., family history of memory impairment) will be assessed.

Attrition rates will be monitored and taken into consideration if they become substantial, however the linear mixed model framework allows data from all participants to be utilized in the analysis, regardless of how many follow-up visits they complete. Additional sensitivity analyses may need to be considered if there is a large attrition rate but we envisage that our engagement plan will mitigate the need.

An overview of AEs, including the number and percentage of participants who died, had SAEs, and discontinued due to AEs, will be provided. A comparison between intervention arms will be performed using Fisher's exact tests. Summaries of AEs by system organ class will be provided for (1) pre-existing conditions, (2) possibly or probably related AEs, and (3) SAEs.

3.8 | Harmonization of the study protocol

One key element of the AU-ARROW study design was harmonizing eligibility criteria, aims, intervention, and assessments to make them comparable and consistent with other WW-Fingers studies, in particular US POINTER. AU-ARROW added ancillary studies to maximize overall scientific impact, including select blood and urine biomarkers, a mindfulness questionnaire, and a retinal scan optional sub-study.

The FINGER inclusion criteria were used to include those with cognitive performance at the mean level or slightly lower than expected for age according to Finnish population norms.[12] US POINTER inclusion criteria were designed to identify at-risk individuals who may benefit most from a multimodal lifestyle intervention,[33] and AU-ARROW followed their design. Table 5 provides a comparison between the main inclusion criteria from US POINTER and AU-ARROW.

Our outcome selection aimed to reproduce the results from US POINTER in the Australian population and harmonize our data. Hence, we aligned with the outcomes from US POINTER to permit a cross-study comparison. Outcome assessments are completed at baseline and months 6, 12, 18, and 24, and the primary outcome is a global cognition composite score that will allow harmonization with US POINTER, FINGER, and other trials. Furthermore, our full neuropsychological battery is identical to that being conducted in US POINTER.

Diet is associated with local factors, such as the availability of ingredients, cost, and cooking habits in a region. The nutrition intervention of AU-ARROW is based on the MIND diet, which is a hybrid between the Mediterranean and the DASH diets that have shown beneficial effects on dementia risk.[34] The original FINGER trial[12] included a Mediterranean-like diet (Healthy Nordic diet) and the US POINTER study[33] included the MIND diet, thus we again, aligned with US POINTER. Australia is a highly multicultural society, with more than one-third of the population born overseas, as opposed to one in six in the United States being born overseas.[35] As a result, the culture includes food and traditions from a wide variety of cultures including Chinese, French, Greek, Indian, Italian, Japanese, Mexican, Thai, and Vietnamese.

Data harmonization was a priority in the design of the study protocol. The aims of the data harmonization process were to make data sharing feasible across the WW-FINGERS network. For this, we coordinated with US POINTER on the REDCap system[36,37] to create the trial dataset and the data dictionary.

In 2020, the COVID-19 pandemic presented a number of challenges for the US POINTER study that affected recruitment, assessment schedules, and intervention delivery. In response to the multiple pandemic-related challenges, study protocols and procedures were adapted to facilitate and encourage participant adherence to intervention activities. When designing the AU-ARROW protocol, lessens learned from the US POINTER study were able to be incorporated. Notably, the ability to conduct team meetings via web conferencing for the ML group. We also planned to maintain regular contact with participants to encourage continued participation in intervention activities and to provide support as needed if we faced another lockdown period.

3.9 | Dissemination

The findings from analysis of the AU-ARROW randomized controlled trial data will be published promptly in peer-reviewed journals. This will be accessible to people through paid subscriptions and through tertiary institutions. Data will be submitted as abstracts to be presented at international conferences. Data will additionally be disseminated through higher degree research theses utilizing AU-ARROW study data and made available on the Alzheimer's Research Australia website and the Cognitive, Molecular Biomarkers and Preventative Treatments for Alzheimer's Disease (COMBAT-AD) Facebook page where participants can review this information. The dissemination of these findings will be completely anonymous, no identifiable information will be published.

Findings will also be reported to local, state, and federal governments to inform policy and new and revised national guidelines. Reports made to funding bodies and institutes that supported the AU-ARROW randomized controlled trial will also be made from these study findings. Members of the research team will have publishing and authorship rights in accordance with National Health and Medical Research Council Australian Code for the Responsible Conduct of Research and as described in research agreements.

4 | DISCUSSION

The primary aim of the AUstralian multidomain Approach to Reduce dementia Risk by prOtecting brain health With lifestyle intervention study is to assess whether a structured program comprising health education, regular physical and cognitive activity, increased social engagement, diet improvements and medical counselling over 24 months will have a protective effect on cognition, compared with a health education (only) intervention in a population of older Australian adults. A key goal of AU-ARROW is to confirm and expand WW-FINGER study findings in a representative cohort of older

TABLE 5 Comparison between the main inclusion criteria from US POINTER and AU-ARROW.

US POINTER	AU-ARROW
Age: 60–79 years	Age: 55–79 years
Sedentary lifestyle	Insufficiently active lifestyle
Suboptimal diet (MIND diet screener score ≤9.5)	Poor diet (MIND diet screener score ≤9)
Absence of cognitive impairment—TICSm ≥32	Absence of cognitive impairment—tMoCA ≥18
CDR ≤ 0.5, and CDR-Sum of Boxes ≤1	CDR ≤0.5, and CDR-Sum of Boxes ≤1
Lives in US POINTER intervention region	Lives in a region where the interventions will be delivered
No travel plans for more than 3 months	Does not plan to travel outside of the home geographic area for more than 1 month at a time, or for more than 3 months over the course of the study
No significant disabilities that would interfere with intervention participation.	No physical disabilities that would preclude them being able to complete any of the lifestyle intervention domains
Willing to complete all study-related activities for 24 months	Willing to complete all study-related activities for the 24 months of the trial
Willing to be randomized to either lifestyle intervention group	Willing to be randomized to either of the lifestyle intervention groups
Two or more of the following: • first-degree family history of memory impairment, • African American/Black or Native American race, Hispanic ethnicity, • older age (≥70 years), and at least mild elevation in systolic blood pressure, low-density lipoprotein cholesterol, or glycated hemoglobin.	Needs to satisfy at least one-fourth of the following four criteria: • Increased vascular and /or metabolic risk factors, as indicated by - Elevated systolic blood pressure - Elevated LDL cholesterol • Aged ≥70 • First or second-degree family history of significant cognitive decline/memory problems/dementia • BMI 30–39.9 Participants must be able to provide written consent in English Must have internet access, mobile phone, and computer, laptop, or iPad (minimum 12-inch screen) at home
Exclusion criteria—residence in an assisted living facility or nursing home	Lives independently Not allergic to seafood Not currently engaging in accredited online brain training programs for more than 30 min per week

Abbreviations: AU-ARROW, the Australian multidomain approach to reduce dementia risk by protecting brain health with lifestyle intervention study; BMI, body mass index; CDR, Clinical Dementia rating; LDL, low-density lipoprotein; MIND, Mediterranean-DASH Intervention for Neurodegenerative Delay; TICSm, modified Telephone Interview for Cognitive Status; tMoCA, Telephone Montreal Cognitive Assessment; US POINTER, US Study to Protect Brain Health through Lifestyle Intervention to Reduce Risk.

Australian adults who differ in their lifestyle, and culture relative to the other cohorts involved in the WW-FINGERS collaboration including Finland, United States, China, and Singapore.

Individuals may experience an improvement in their general health, both in the healthy lifestyle education and coaching group and the multidomain lifestyle intervention. However, the major aim of this research is to enhance knowledge concerning treatment options that may reduce disease incidence and prevalence. The project will also benefit society by enhancing knowledge related to AD early diagnosis. We anticipate that the findings from AU-ARROW and other WW-FINGERS studies could have an immense impact for millions of at-risk individuals worldwide.

An economic evaluation will be conducted alongside the intervention to identify the cost-effectiveness of the intervention as understanding these costs are key to identifying aspects of the intervention that may require further refinement before being taken large scale in communities. This will be evaluated in terms of improved quality of life, and also the validated items from the Acceptability of Intervention Measure (AIM), the Intervention Appropriateness Measure (IAM), and the Feasibility of Intervention Measure (FIM).[38] The findings will contribute to the development of cost-effective care models that can improve the well-being of Australians and reduce aged care costs to the government.

The AU-ARROW study commenced recruitment in February 2022, and despite having some delay due to the COVID-19 pandemic, we have been able to recruit individuals from the community, with several participants already enrolled into each of the study arms. The study will remain in the recruitment and data collection phase until at least mid-2026 before data cleaning, coding, and analyses will commence.

We have aligned with the US arm of the WW-FINGERS collaboration with only minor cultural and dietary modifications to determine the validity of the intervention in an Australian setting. Data-sharing will allow researchers to test the generalizability, adaptability, and sustainability of findings in diverse and global populations as a large-scale, single clinical trial, and will also allow for sufficiently powered sub-group analyses in key sub-populations of interest. Australian involvement through the AU-ARROW trial is essential to validate the effectiveness of a multimodal treatment plan in an *Australian*

setting. AU-ARROW has been able to leverage lessons learned from US POINTER and other similar studies to strengthen the design, and ancillary studies have been included to maximize overall scientific impact. Data collection tools employed in this study have been validated in Australian populations.

AU-ARROW eligibility criteria were designed to enrich the cohort for risk of cognitive decline, including cardiovascular disease, as indicated, for example, by mild elevations in systolic BP, LDL cholesterol, or HbA1c. The large, well-characterized AU-ARROW cohort will provide an unprecedented data resource of outcomes spanning cognition, physical function, blood and brain imaging AD biomarkers, sleep quality, peripheral and neurovascular function, and the gut microbiome.

Developing effective, translatable, and scalable strategies to promote and sustain participant adherence and intervention delivery is integral to the study's concept and design. Behavioral changes required to ensure adherence to the study interventions are fostered through motivation, belief that change is possible, means to implement behavioral changes, and ongoing support and reinforcement.

To conclude, given the strengths and the significance of this study's potential findings, analysis of the data arising from this study will be used to develop evidence-based programs which are cost effective and broadly applicable. These preventative approaches will be specifically aimed at enhancing cognitive health and decreasing AD incidence, conferring substantial social and economic impact.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to report. Author disclosures are available in the supporting information.

CONSENT STATEMENT

Ethical clearance from all participating institutions and signed informed consent from participants will be obtained before their recruitment into the study.

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REFERENCES

1. Prince M, Wimo A, Guerchet M, Ali GC, Wu YT, Prina M. World Alzheimer Report 2015. The Global Impact of Dementia: An analysis of prevalence, incidence, cost and trends (Doctoral dissertation, Alzheimer's Disease International). 2015.
2. Wimo A, Seeher K, Cataldi R, et al. The worldwide costs of dementia in 2019. *Alzheimers Dement*. 2023;19:2865-2873.
3. Noach S, Witteman B, Boss HM, Janse A. Effects of multidomain lifestyle interventions on cognitive decline and Alzheimer's disease prevention: a literature review and future recommendations. *Cereb Circ Cogn Behav*. 2023;4:100166.
4. Shah T, Verdile G, Sohrabi H, et al. A combination of physical activity and computerized brain training improves verbal memory and increases cerebral glucose metabolism in the elderly. *Transl Psychiatry*. 2014;4:e487.
5. Wall K, Stark J, Schillaci A, et al. The enhanced interactive physical and cognitive exercise system (iPACES(TM) v2.0): pilot clinical trial of an in-home iPad-based neuro-exergame for mild cognitive impairment (MCI). *J Clin Med*. 2018;7:249.
6. Blumenthal JA, Babyak MA, Hinderliter A, et al. Effects of the DASH diet alone and in combination with exercise and weight loss on blood pressure and cardiovascular biomarkers in men and women with high blood pressure: the ENCORE study. *Arch Intern Med*. 2010;170:126-135.
7. Smith PJ, Blumenthal JA, Babyak MA, et al. Effects of the dietary approaches to stop hypertension diet, exercise, and caloric restriction on neurocognition in overweight adults with high blood pressure. *Hypertension*. 2010;55:1331-1338.
8. Anstey KJ, Cherbuin N, Kim S, et al. An internet-based intervention augmented with a diet and physical activity consultation to decrease the risk of dementia in at-risk adults in a primary care setting: pragmatic randomized controlled trial. *J Med Internet Res*. 2020;22:e19431.
9. McMaster M, Kim S, Clare L, et al. Lifestyle risk factors and cognitive outcomes from the multidomain dementia risk reduction randomized controlled trial, body brain life for cognitive decline (BBL-CD). *J Am Geriatr Soc*. 2020;68:2629-2637.
10. Kivipelto M, Mangialasche F, Ngandu T, World Wide Fingers Network. World Wide Fingers will advance dementia prevention. *Lancet Neurol*. 2018;17:27.
11. Ngandu T, Lehtisalo J, Solomon A, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. *Lancet*. 2015;385:2255-2263.
12. Kivipelto M, Solomon A, Ahtiluoto S, et al. The Finnish geriatric intervention study to prevent cognitive impairment and disability (FINGER): study design and progress. *Alzheimers Dement*. 2013;9:657-665.
13. Wimo A, Handels R, Antikainen R, et al. Dementia prevention: the potential long-term cost-effectiveness of the FINGER prevention program. *Alzheimers Dement*. 2023;19(3):999-1008.
14. Pentikainen H, Savonen K, Ngandu T, et al. Cardiorespiratory fitness and cognition: longitudinal associations in the FINGER study. *JAD*. 2019;68:961-968.
15. Coon DW, Gomez-Morales A. Modifiable risk factors for brain health and dementia and opportunities for intervention: a brief review. *Clin Gerontol*. 2023;46:143-154.
16. Norton K, Norton L, Sadgrove D. Position statement on physical activity and exercise intensity terminology. *J Sci Med Sport*. 2010;13:496-502.
17. Brownie S, Muggleston H, Oliver C. The 2013 Australian dietary guidelines and recommendations for older Australians. *Aust Fam Physician*. 2015;44(5):311-315.
18. Merzenich M. BrainHQ. 2023. https://www.brainhq.com/
19. Arokiaraj AS, Khairudin R, Sulaiman WW. The impact of a computerized cognitive training on healthy older adults: a systematic review focused on processing speed and attention. *Int J Acad Res Bus Soc Sci*. 2020;10:645-685.

20. Royal Australian College of General Practitioners (RACGP) TRACoGP. https://www.racgp.org.au/. 2023
21. Cahn DA, Salmon DP, Monsch AU, et al. Screening for dementia of the Alzheimer type in the community: the utility of the Clock Drawing Test. *Arch Clin Neuropsychol*. 1996;11:529-539.
22. Dore V, Bullich S, Rowe CC, et al. Comparison of (18)F-florbetaben quantification results using the standard Centiloid, MR-based, and MR-less CapAIBL((R)) approaches: validation against histopathology. *Alzheimers Dement*. 2019;15:807-816.
23. Bourgeat P, Dore V, Fripp J, et al. Implementing the centiloid transformation for (11)C-PiB and beta-amyloid (18)F-PET tracers using CapAIBL. *Neuroimage*. 2018;183:387-393.
24. Klunk WE, Koeppe RA, Price JC, et al. The Centiloid Project: standardizing quantitative amyloid plaque estimation by PET. *Alzheimers Dement*. 2015;11:1-15.e1-4.
25. Hadoux X, Hui F, Lim JKH, et al. Non-invasive in vivo hyperspectral imaging of the retina for potential biomarker use in Alzheimer's disease. *Nat Commun*. 2019;10:4227.
26. Sharafi SM, Sylvestre JP, Chevrefils C, et al. Vascular retinal biomarkers improves the detection of the likely cerebral amyloid status from hyperspectral retinal images. *Alzheimers Dement (N Y)*. 2019;5:610-617.
27. Gildner TE, Liebert MA, Kowal P, Chatterji S, Josh Snodgrass J. Sleep duration, sleep quality, and obesity risk among older adults from six middle-income countries: findings from the study on global AGEing and adult health (SAGE). *Am J Hum Biol*. 2014;26:803-812.
28. Chen J, Allman-Farinelli M. Impact of training and integration of apps into dietetic practice on dietitians' self-efficacy with using mobile health apps and patient satisfaction. *JMIR Mhealth Uhealth*. 2019;7:e12349.
29. Ambrosini GL, Hurworth M, Giglia R, Trapp G, Strauss P. Feasibility of a commercial smartphone application for dietary assessment in epidemiological research and comparison with 24-h dietary recalls. *Nutr J*. 2018;17:5.
30. Lancaster R, Radd-Vagenas S, Fiatarone Singh M, et al. Electronic food records among middle-aged and older people: a comparison of self-reported and dietitian-assisted information. *Nutr Diet*. 2021;78:145-153.
31. Chen J, Gemming L, Hanning R, Allman-Farinelli M. Smartphone apps and the nutrition care process: current perspectives and future considerations. *Patient Educ Couns*. 2018;101:750-757.
32. Teague S, Youssef GJ, Macdonald JA, et al. Retention strategies in longitudinal cohort studies: a systematic review and meta-analysis. *BMC Med Res Methodol*. 2018;18:151.
33. Baker LD, Snyder HM, Espeland MA, et al. Study design and methods: US study to protect brain health through lifestyle intervention to reduce risk (US POINTER). *Alzheimers Dement*. 2024;20(2):769-782.
34. Kheirouri S, Alizadeh M. MIND diet and cognitive performance in older adults: a systematic review. *Crit Rev Food Sci Nutr*. 2022;62:8059-8077.
35. Bryant S. 14 Cultural Differences between the USA and Australia. 2021. https://www.countrynavigator.com/blog/usa-and-australia/
36. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: building an international community of software platform partners. *J Biomed Inform*. 2019;95:103208.
37. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)–a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42:377-381.
38. Weiner BJ, Lewis CC, Stanick C, et al. Psychometric assessment of three newly developed implementation outcome measures. *Implement Sci*. 2017;12:108.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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