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An Online, Person-Centered, Risk Factor Management Program to Prevent Cognitive Decline: Protocol for A Prospective Behavior-Modification Blinded Endpoint Randomized Controlled Trial

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Abstract.
Background: Several modifiable risk factors for dementia have been identified, although the extent to which their modification leads to improved cognitive outcomes remains unclear.

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Objective: The primary aim is to test the hypothesis that a behavior modification intervention program targeting personalized risk factors prevents cognitive decline in community-dwelling, middle-aged adults with a family history of dementia.

Methods: This is a prospective, risk factor management, blinded endpoint, randomized, controlled trial, where 1510 cognitively normal, community-dwelling adults aged 40–70 years old will be recruited. Participants will be screened for risk factors related to vascular health (including physical inactivity), mental health, sleep, and cognitive/social engagement. The intervention is an online person-centered risk factor management program: BetterBrains. Participants randomized to intervention will receive telehealth-based person-centered goal setting, motivational interviewing, and follow-up support, health care provider communication and community linkage for management of known modifiable risk factors of dementia. Psychoeducational health information will be provided to both control and intervention groups.

Results: The primary outcome is favorable cognitive performance at 24-months post-baseline, defined as the absence of decline on one or more of the following cognitive tests: (a) Cogstate Detection, (b) Cogstate One Card Learning, (c) Cogstate One Back, and (d) Cognitive Function Instrument total score.

Conclusion: We will test the hypothesis that the BetterBrains intervention program can prevent cognitive decline. By leveraging existing community services and using a risk factor management pathway that tailors the intervention to each participant, we maximize likelihood for engagement, long-term adherence, and for preserving cognitive function in at-risk individuals.

Trial Registration: ACTRN 12621000458831. Registered on the Australian New Zealand Clinical Trials Registry (http://www.anzctr.org.au)

Keywords: Alzheimer's disease, clinical trial, cognitive decline, dementia, lifestyle intervention, non-pharmacological, randomized control trial

INTRODUCTION

Dementia is the second largest cause of death in Australia, of which Alzheimer's disease (AD) is the most common form. No disease modifying therapy is currently available. However, it is estimated that approximately 35% of all dementias can be attributed to risk factors that are potentially modifiable [1, 2]. Risk factors for late-life cognitive decline are well established and include hypertension, low physical activity, poor diet quality, anxiety and depressive symptoms, low cognitive engagement, and poor sleep [2–7]. Several major challenges in reducing disease burden with behavior modification exist, including the implementation of innovative solutions that are effective in changing behaviors and changing behaviors that favorably modify disease onset in a timeframe that allows for the prevention of cognitive decline.

Clinicopathological studies of AD suggest that pathophysiological changes can begin up to 30 years before the onset of clinical symptoms [8, 9], with the accumulation of AD proteinopathies (e.g., amyloid-β (Aβ), tau) likely beginning in midlife (e.g., 40–70 years) [10–12]. This has given rise to the prevention strategy of identifying cognitively normal at-risk individuals for early intervention to slow cognitive decline and the clinical onset of AD [13, 14]. Modifiable risk factors have been shown to have the strongest association with dementia risk in the decades before clinical diagnosis of dementia. As such, behavioral interventions targeting personalized risk factors for cognitive decline may have maximal efficacy when implemented in midlife [4, 15–17].

While mood, vascular risk (including nutrition and physical inactivity), cognitive engagement, and sleep are modifiable risk factors for dementia, some barriers limit their successful management. Participation rates in behavior modification trials are low. Only 13–47% of trial participants seek to improve diet or increase physical activity [18, 19]. Additionally, risk factors for dementia vary between individuals and therefore effective solutions need to be specific to an individual's risk factor profile, providing a targeted, relevant, and person-centered approach. Person-centered approaches are advantageous as they may encourage individuals to adopt and enact risk mitigation strategies that will be effective in their daily lives and leverage existing community services around the individual to promote long-term adherence [20].

There are several multi-domain behavior modification trials to prevent cognitive decline (e.g., the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) and Maintain Your Brain (MYB)) [21, 22], yet few have utilized a person-centered approach using a risk factor management pathway to prevent cognitive decline.

There is evidence that such programs are successful in other conditions, such as falls prevention. The RESPOND program was a telephone-based, patient-centered falls prevention program that was demonstrated to reduce falls, but not fall injuries, in older people presenting to the emergency department with a fall [20]. Program evaluation of RESPOND showed high acceptability among participants, and that the participant-centered approach, use of goal setting and motivational interviewing, positive health messaging, and leveraging technologies (e.g., telehealth), increased participant engagement [20].

Based on the same guiding principles as RESPOND, we have designed a program (BetterBrains) to prevent cognitive decline in middle-aged adults (40–70 years) through the delivery of a person-centered intervention that targets individual risk factors known to increase risk of cognitive decline and dementia (see Box 1 for an overview of the intervention). These risk factors relate to vascular health, low mood, poor sleep, and low social and cognitive engagement. BetterBrains adopts a risk factor management strategy where each targeted risk factor is dependent on individual goal prioritization and the presenting modifiable risk factor(s) for dementia (Box 1). This flexibility has been shown to increase participation, adherence and engagement [23].

Through these guiding principles, BetterBrains, an online, person-centered, risk factor management program aims to delay cognitive decline in Australian middle-aged adults with a family history of dementia. This program will incorporate five unique components: 1) remote assessment of outcomes via an online web platform (betterbrains.org.au), 2) screening to identify personalized risk factor profiles; 3) targeted risk factor management driven by participant preference and supported by motivational interviewing and goal-setting, 4) telehealth support (via phone or video call) by trained coaches to review and support behavior change, and 5) smartphone-app support to assist participants in undertaking their recommended strategies (e.g., notifications, weekly check-ins, assessment of barriers to engagement, alerts to coaches if participants' indicate repeated disengagement).

Box 1. Intervention (BetterBrains) Overview

- Delivered by BetterBrains Coaches trained in motivational interviewing, behavior change strategies and risk factor management via telehealth
- Active intervention will last for 12 months from randomization
- Suggested strategies for intervention are dependent on risk factor management pathway, and driven by participant preference
- Risk factor management will target one or more of the following:
  - Medical management facilitation
  - Psychology or counselling service referral (health literacy, education, and GP referral)
  - Behavioral activation
  - eTherapy (e.g., web and/or app-based programs)
  - Smoking cessation
  - Physical activity
  - Dietary modification
  - Responsible consumption of alcohol and/or caffeine
  - Social engagement
  - Continuing education/skill development
  - Participation in cognitively stimulating activities
  - Sleep psychoeducation
  - Advanced sleep phase (light) therapy
- Risk factor management strategies map onto one or more of the common categories of modifiable risk factors for dementia (i.e., vascular risk, poor mood, low social and cognitive engagement, and poor sleep).

TRIAL DESIGN

This is a prospective blinded endpoint 24-month randomized controlled trial (RCT) to test the effectiveness of BetterBrains, an online, person-centered, risk factor management intervention to prevent cognitive decline. We will compare the outcomes in the BetterBrains intervention group with those in a control group receiving standard health education.

Aims and hypotheses

Primary aim

The primary aim is to test the hypothesis that the BetterBrains intervention program can prevent cognitive decline in middle-aged adults. We hypothesize that a higher proportion of participants randomized to the BetterBrains program will show a favorable cognitive outcome at 24-months than those randomized to the control group.

Secondary aims

Secondary aims are to determine whether participants randomized to the BetterBrains intervention program show changes in 1) cognitive function (complex attention, executive function, memory and learning), 2) subjective ratings of health and quality of life, and 3) dementia risk as measured by the Australian National University Alzheimer's Disease Risk Index (ANU-ADRI) and the Cardiovascular Risk Factors, Aging and Incidence of Dementia (CAIDE) risk scores, compared to the control group.

Tertiary aims

Tertiary aims are to determine whether participants randomized to the BetterBrains intervention program show changes in 1) health literacy, 2) motivation to change health behavior, and 3) work productivity, compared to the control group.

Exploratory aims

Exploratory analyses will aim to identify variables that may moderate the efficacy of the intervention to prevent cognitive decline. Variables of interest include 1) the apolipoprotein E (*APOE*) ε4 allele (strongest genetic risk factor for sporadic AD), 2) the nature and number of dementia risk factors, 3) individuals' readiness to change behavior, and 4) level of engagement with the intervention. A full program evaluation of this RCT will also be conducted. The program evaluation protocol will be published separately.

Participants and setting

Community-dwelling adults aged 40–70 years old (inclusive), living in Australia, who have a first- or second-degree family history of AD or dementia and meet the below defined 7 inclusion criteria will be eligible for recruitment. Exclusion and inclusion criteria for this study are detailed below. The BetterBrains intervention program and corresponding RCT will be conducted virtually via a website, smartphone application, and telephone coaching sessions.

Inclusion criteria

- Aged between 40–70 years;
- Plans to reside in Australia for at least 2 years (irrespective of citizenship);
- First- or second-degree family history of dementia (AD, Parkinson's disease, Lewy body dementia, or other known diagnosis of dementia);
- Fluent in the English language;
- Access to a tablet, desktop, or laptop computer with internet connectivity (to complete computerized cognitive tests via our online platform and engage in telehealth sessions with the BetterBrains coaches);
- Willing and able to provide informed consent;
- Willing and able to commit to undertaking a series of online assessments over 2 years;
- At least one modifiable dementia risk factor identified during the online screening process;
- Willing and able to provide a saliva sample for genotyping.

Exclusion criteria

- Diagnosis of mild cognitive impairment (MCI), AD, Parkinson's disease, Lewy body dementia, or other known diagnosis of dementia;
- Current use of any Therapeutic Goods Administration (TGA) approved medication for the treatment of AD (e.g., donepezil, galantamine, rivastigmine, memantine, or other newly approved medication);
- Current use of any TGA approved medication for the treatment of Parkinson's disease (e.g., Sinemet, amantadine, bromocriptine, pergolide, selegiline, or other newly approved medication)
- History of severe traumatic brain injury or other significant neurological disease or insult (e.g., multiple sclerosis, stroke, epilepsy);
- Uncontrolled major depressive disorder or another Axis I psychiatric disorder as described in DSM-IV-TR within the past year, psychotic features, agitation, or behavioral problems;
- History of alcohol or substance abuse or dependence within the past 2 years;
- Regular (daily) use of narcotics or antipsychotic medications;
- History of myocardial infarction in the past year or unstable severe cardiovascular disease including angina or congestive heart failure with symptoms at rest;
- Respond "no, and I have no intention to make changes" in response to the question "have you made any changes to your lifestyle during the past year to actively reduce your risk of dementia (e.g., increasing physical activity, engaging in cognitively stimulating activities, lowering stress)?";
- No modifiable dementia risk factors identified during the online screening process;

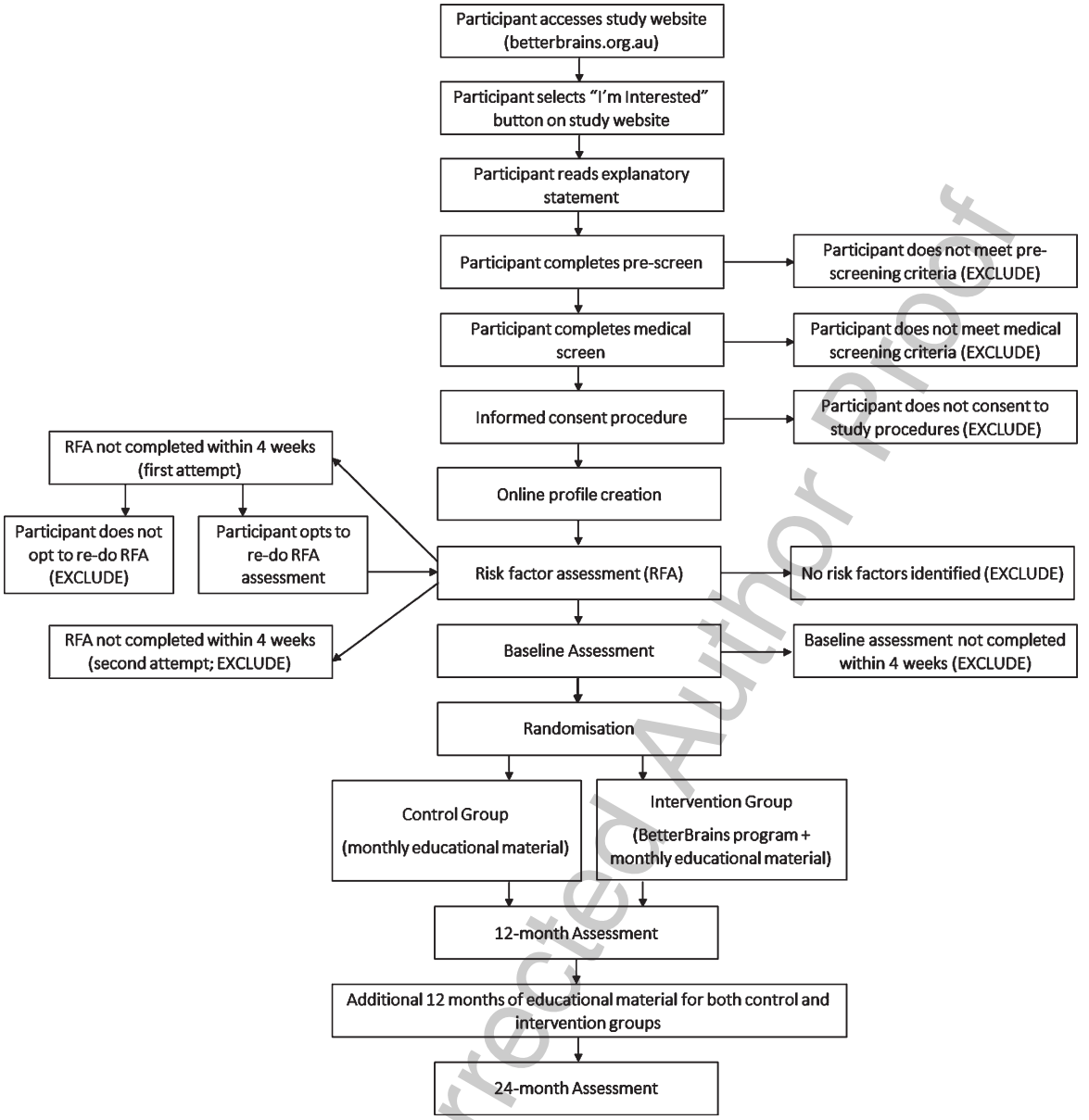

Fig. 1. Study procedure flowchart.

– Participant does not complete their risk factor assessment within a 4-week period (2 attempts will be provided, see Fig. 1).

Outcomes

The primary outcome is favorable cognitive performance at 24-months, defined as the absence of decline (rate of change over 24-months that is less than 0.5SD) on one or more of the following cognitive tests: (a) Cogstate Detection test (speed), (b) Cogstate One Card Learning test (accuracy), (c) Cogstate One Back test (speed), and (d) total score on the Cognitive Function Instrument.

Secondary outcomes are as follows:

1. Change in cognitive function (complex attention, executive function, memory, and learning) assessed by the Cogstate Brief Battery, Cogstate IDSST-Medicines, and the Online Repeatable Cognitive Assessment (ORCA) battery;

2. Change in subjective ratings of general health and quality of life, as measured by the RAND
3. Change in health literacy, assessed by the Health Literacy Questionnaire (HLQ);
4. Change in motivation to change health behavior, assessed using the Motivation to Change Health Behaviour for Dementia Risk Reduction questionnaire;
5. Change in work productivity (absenteeism and presenteeism), assessed using the Valuation of Lost Productivity questionnaire.

All measures will be collected at baseline, 12- and 24-months.

Primary estimand

1. **Population:** All included participants.
2. **Individual level measure:** presence or absence of cognitive decline.
3. **Population level measure:** the proportion of participants with cognitive decline in each group (intervention and control).
4. **Intercurrent events:** An intercurrent event is one that occurs after randomization and either precludes observation of the outcome or affects its interpretation, e.g., by impacting on the primary outcome or on intervention participation. We have adopted a composite strategy of handling intercurrent events. We have classified potential intercurrent events into those that may potentially modify cognitive outcomes, and those that will not.

For intercurrent events that may potentially modify cognitive outcomes (e.g., stroke, traumatic brain injury) and for events relating to the prescription of concomitant medications which are listed in the exclusion criteria and/or likely to impact on trial outcomes (e.g., donepezil, memantine), a team of medical monitors (Yassi, Brodtmann, Bush) will assess in a fully-blinded manner, the nature of the event, and determine whether the event is likely to have sufficiently modified cognitive outcomes. If the team identify an intercurrent event that is cognitively modifying, the participant in question will still be included in the primary outcome analysis, but the classification of the primary cognitive outcome for that participant will be automatically classified as negative (i.e., presence of cognitive decline), irrespective of their actual cognitive performance. For intercurrent events that influence intervention participation (e.g., motor vehicle accident with no head injury), intervention discontinuation, prescription of rescue medications/alternative therapies not listed in the exclusion criteria, or death, no a priori amendments will be made to any outcomes.

Sample size

Sample size calculations were based on unpublished data from 800 participants enrolled in the Healthy Brain Project, an observational study on individuals with similar characteristics as the BetterBrains trial (i.e., participants are aged 40–70 years, have a family history of dementia, have undergone cognitive testing using the same outcome measures and the same remote, unsupervised, web-based mode of assessment) [24]. Of this group, 680 participants were classified as having at least one modifiable risk factor for dementia (120 participants had no modifiable risk factors for dementia). Participants were classified as having an "unfavorable" cognitive outcome (slope estimate of >0.5 SD decline) or a "favorable" cognitive outcome (slope estimate of <0.5 SD decline). Change over time for each participant was estimated using linear mixed models, with random slopes and intercept. We found that over 24 months, ~78% of individuals with at least one modifiable risk factor presented with no cognitive decline, defined using the cognitive tests that make up our primary outcome. Conversely, ~88% of individuals with no modifiable risk factors presented with no cognitive decline.

We have conservatively estimated that the BetterBrains intervention program will result in a 7% absolute increase in the proportion of participants with a favorable cognitive outcome in the intervention compared to the control group. Recruiting 1,510 participants (755 per group) would yield 90% power to detect at least a 7% increase in the proportion of participants achieving a favorable cognitive outcome in the intervention group compared to the control group (78% in control, 85% in intervention, total $n = 1{,}290$ (645 per group), two-sided $p = 0.05$), allowing for potential 10% loss-to-follow-up.

To allow for a trial run-in period in which operational and procedural difficulties can be identified and rectified as needed, the first 10 participants enrolled in the trial will be excluded from the primary outcome analyses. The number of participants to be included in primary outcome analyses is therefore 1500. Sample size estimates were obtained using G*Power 3.1.9.2, using z-tests to determine the difference between two independent proportions.

Recruitment

Recruitment will consist of two approaches. First, a small number of invitations (e.g., $n = 15$) will be sent to a randomly selected group of participants from the Healthy Brain Project (healthybrainproject.org.au) via email, from which we anticipate enrolling 10 participants. The first 10 participants will complete consent, registration, risk factor assessment, baseline and randomization before a broader invitation is extended to the rest of the Healthy Brain Project cohort. This will be done via email, study newsletters and social media announcements. The Healthy Brain Project is an online observational cohort study that has enrolled 7,000 participants aged 40–70 years at study entry [24]. Participants from the Healthy Brain Project have been recruited through the community. Should existing Healthy Brain Project participants consent to be a part of this trial, their participation in the Healthy Brain Project will be suspended for the duration of their participation in the trial. They will have the opportunity to re-engage with the Healthy Brain Project at the conclusion of this trial. Second, community dwelling middle-aged adults will be invited to take part in this trial via a variety of sources, including newspaper and radio advertisements, through social media, consumer organizations and public lectures.

Study procedure

Figure 1 provides an overview of the study procedure.

Pre-screen

Interested individuals will be directed to access the study website at betterbrains.org.au. Participants will be able to access an explanatory statement on this website. This statement forms part of the Participant Information and Consent form and will provide participants with a summary of the trial, its aims, the requirements of participation and a participant's rights as a volunteer in the BetterBrains trial. Participants will also be able to download and save a PDF copy of the explanatory statement for their reference. After indicating that they have read the explanatory statement, prospective participants will then be directed to complete pre-screening, by confirming that they meet the criteria outlined in Supplementary Table 1. They will do this by answering a series of questions. Prospective participants will be required to select "yes" to each of these questions in order to proceed to the medical screen.

Medical screen & readiness for change

Participants will be required to tick a box to indicate their consent for the study team to collect information pertaining to their medical history. Once participants have indicated their consent, they will be required to respond "Yes" or "No" to a series of prompts based on the inclusion and exclusion criteria for the study (Supplementary Table 1) to determine further eligibility. Participants will also be presented with a single Likert-scale question to determine their readiness for change (Supplementary Table 1).

Informed consent

Upon completion of the pre-screen and medical screen sections, participants will proceed to undergo the informed consent process. Given the online nature of this trial, we have presented the consent form in an interactive manner, whereby participants will be presented with selected key components of the study that they will be required to consent to by selecting "Yes" or "No". Once the participant has completed this, they will be asked to provide their full name in lieu of an electronic signature.

Online profile creation

After providing informed consent, participants will create an online profile by entering the following information: first name, last name, email address, contact phone number, handedness, date of birth, sex, residential address, postcode, and state. Participants will also be asked to indicate whether they are enrolled in the Healthy Brain Project, whether they have a smartphone (iPhone or Android), and to provide details of their general practitioner (GP).

Risk factor screening

Participants will then be directed to complete a risk factor screening assessment. This comprises of 10 questionnaires (~30 min) which map onto 4 risk domains: (a) Hearts (vascular risk), (b) Mood (depressive, anxiety or stress symptoms), (c) Sleep (extent of sleep disruption), and (d) Minds (level of social and cognitive engagement) (Table 1). Participants will be encouraged to complete these risk factor surveys within four weeks. If a participant does not complete the risk factor assessment within 4 weeks, they will be provided with an opportunity to re-take the assessment in its entirety. This is to ensure that the most accurate information regarding participants' lifestyle risk factors for dementia are collected. If the participant does not complete their risk factor assessment within 4 weeks on their

Table 1
Schedule for Pre-Baseline Risk Factor Screen (RFS), and Baseline Assessment

Risk Category	Questionnaire/Assessment	RFS	Baseline Assessment							Reference
			Block 1	Block 2	Block 3	Block 4	Block 5	Block 6	Block 7	
Mood	Depression, Anxiety and Stress Scale (DASS) (21-item)	X (3 m)								[27]
	Centre for Epidemiological Studies, Depression Scale	X (2 m)								[28]
	Hospital Anxiety and Depression Scale (HADS)	X (3 m)								[29]
Mind	Relationships Questionnaire	X (1 m)								–
	Educational and Occupational History	X (1 m)								–
Sleep	Epworth Sleepiness Scale (ESS)	X (1 m)								[30]
	Insomnia Severity Index (ISI)	X (1 m)								[31]
	Berlin Sleep Apnoea Questionnaire (BQ)	X (2 m)								[32]
	Advanced Sleep Phase Questionnaire	X (3 m)								–
Heart	International Physical Activity Questionnaire (IPAQ)	X (10 m)								[33]
	Medical history and health (smoking, alcohol intake)	X (3 m)								–
Outcome										
Primary	Cogstate Brief Battery (CBB)		X (18 m)							[34]
Secondary	Cogstate IDSST-Medicines		X (2 m)							
Primary	Cognitive Function Instrument (CFI)		X (2 m)							[35]
Secondary	Online Repeatable Cognitive Assessment Battery			X (15 m)	X (15 m)	X (15 m)	X (15 m)	X (15 m)	X (15 m)	[36]
–	Demographics		X (1 m)							–
–	Family Demographics		X (1 m)							–
–	Family Health History		X (1 m)							–
Secondary	Health Literacy Questionnaire (HLQ)			X (4 m)						[37]
–	Health and Surgical History				X (7 m)					–
–	Medications Questionnaire				X (2 m)					–
Secondary	Motivation to Change Health Behaviour					X (3 m)				[38]
Secondary	General Health (RAND)					X (3 m)				[39]
–	Greene Climacteric Scale					X (2 m)				[40]
–	Perceived Stress Scale (PSS)					X (1 m)				[41]
–	Connor-Davidson Resilience						X (1 m)			[42]
–	Pittsburgh Sleep Quality Index (PSQI)						X (4 m)			[43]
Exploratory	Valuation of Lost Productivity (VOLP)						X (4 m)			[44]
Exploratory	Cognitive beliefs and perceived risk of AD							X (2 m)		[45]
–	Cognitive Reserve Index Questionnaire (CRI-q)							X (4 m)		[46]
Exploratory	Saliva sampling								X (5 m)	–
–	COVID-19 Questionnaire								X (2 m)	–
–	Additional Information								X (1 m)	–
	Total Time Per Block	30 m	25 m	19 m	24 m	24 m	24 m	21 m	23 m	

second attempt, no further opportunities to re-take the assessments will be offered, and the participant will be excluded from the trial. Participants will be sent several notifications and reminders. If no risk factors across the four domains are identified during the risk assessment, the participant will be notified of their ineligibility to take part in the trial via the BetterBrains website and offered participation in the Heathy Brain Project instead. If one or more risk factors are identified, participants will be informed via the BetterBrains website that at least one lifestyle risk factor has been identified, which makes them eligible for enrolment in the trial. In participants for whom elevated depressive and/or anxiety symptoms have been identified, a letter to their nominated GP will be sent, irrespective of whether the participant is randomized to the intervention or control group. Upon completion of the risk factor screen, participants will be directed to complete the baseline assessment.

Baseline assessment

Participants have 4 weeks (28 days) from the completion of their risk factor assessment to complete their baseline assessment. As part of the baseline assessment, participants will be asked to complete approximately 110 min of cognitive testing, with the Cogstate Brief Battery, the Cogstate iDSST-Medicines test, and the ORCA battery that has recently been shown to be sensitive to subtle cognitive dysfunction in preclinical AD [25, 26]. Participants will also be required to complete several detailed questionnaires evaluating several medical, lifestyle, health, and work productivity factors (33 min total). Participants will also be asked if they are currently taking medications. Participants who respond 'yes' will be instructed to take a photo of their medication packaging and label and to upload this to their BetterBrains profile. An RA will then be responsible for data entry and coding of the medications uploaded. If the reason for the prescription is not ascertainable from the photo provided by the participant, then a study RA will contact the participant via phone call or internal message to clarify reasons for taking each medication provided. Given the comprehensive testing, we have organized the baseline assessment into seven 20 min blocks of testing (Table 1). Participants have the option of completing all 7 blocks consecutively in one day or across 4-weeks. This design is similar to what has been implemented in the Healthy Brain Project [24], and has been designed to reduce assessment fatigue and to provide maximum flexibility for participants, while collecting a comprehensive set of key outcome variables.

A maximum of five reminder notifications will be sent to participants when each assessment is due, provided it is yet to be undertaken. If the participant fails to complete all baseline surveys and tests in the specified time interval (i.e., 4 weeks), they will not progress in the trial (i.e., no further participation).

Randomization

Upon the completion of all baseline assessments, participants will be asked to upload a photo of their ID (e.g., driver's license, Medicare card). This ID will then be verified by a research assistant. After ID verification, participants will be randomly assigned into the intervention (BetterBrains) or control groups in a 1:1 ratio based on the following stratification variables: (a) age (< 55 years versus ≥ 55 years), and (b) rurality (i.e., urban versus rural/regional based on classifications from the Australian Bureau of Statistics). Age and rurality were selected as stratification variables as they were considered to have a substantial impact on the primary outcome and community/health resources available to participants in the intervention group. Computer-generated allocation as a part of the electronic Case Report Form (eCRF) will be conducted using permuted blocks of variable sizes (not disclosed in the protocol due to its public availability) after the baseline assessment. Participants will be notified of group allocation automatically via the BetterBrains platform. Depending on their allocation, participants will receive the relevant procedures outlined below.

Blinding

Outcome assessments will be conducted entirely online and will be assessor blinded. A research assistant will monitor completion of all primary, secondary, and exploratory outcomes, and follow-up with participants if necessary. As genetic analyses will only be conducted at the end of the trial, participants, investigators, coaches, and research assistants will remain blinded to participants' *APOE* status for the entire trial duration.

Intervention (BetterBrains)

The intervention (BetterBrains) will be delivered by trained psychologists, physiotherapists, dieticians, nurses, or occupational therapists with expertise in motivational interviewing, behavior change strategies, and risk factor management (henceforth referred to as 'BetterBrains Coaches'). The 12-month

Table 2
Summary of BetterBrains risk factor management strategies

		Categorization of common dementia risk factors			
		BetterHearts	BetterMood	BetterMind	BetterSleep
Risk Management Strategies	Medical Management Facilitation				
	Attend Psychology or Counselling Service				
	Behavioral Activation				
	eTherapy (web and app-based programs)				
	Smoking Cessation				
	Physical Activity				
	Dietary modification				
	Responsible consumption of alcohol and/or caffeine				
	Social Engagement				
	Continuing education/ skill development				
	Cognitively stimulating activities				
	Sleep Psychoeducation				
	Advanced Sleep Phase (Light) Therapy				

intervention will commence from the completion of the participant's baseline assessment. Key risk factors and associated evidence-based management strategies will form the basis of the intervention. Intervention group participants will nominate which risk factor they intend to address, in consultation with their BetterBrains coach. During the first call, the BetterBrains coach will engage the participant in a discussion about their risk factor(s) and explore barriers and enablers to addressing them. Suggested strategies are dependent on the risk factor management pathway, which have been developed to map onto four common risk factor categories of dementia (Table 2):

1. BetterHearts, which targets cardiovascular risk factors, including physical inactivity;
2. BetterMind, which targets social and cognitive engagement;
3. BetterMood, which targets depressive, anxiety or stress symptoms; and
4. BetterSleep, which targets symptoms of insomnia, advanced sleep phase disorder, sleep apnea, and overuse of sleep medications.

Suggested strategies within each risk factor pathway are dependent on participant access to healthcare services and their financial position (e.g., Medicare or Private Health Insurance). Coaches will encourage participants to address multiple risk factors across the 12-month intervention. BetterBrains Coaches will provide education and coaching to participants in the intervention group via telehealth during the active intervention phase (Table 3). Intervention group participants will receive a minimum of 6 scheduled calls from their coach (Fig. 2). Coaching in these telephone calls will focus on person-centered care to optimize participant engagement. Motivational interviewing will be used to support the participant to understand the findings of their risk assessment and to facilitate goal-setting based on the participant's identified risk factors for cognitive decline. Anticipated barriers to engagement (e.g., work and/or family commitments) will also be identified, and coaches will assist participants to find solutions to barriers identified. Further, coaches will also assist intervention group participants by recommending action strategies to meet goals and assist with finding appropriate support services and resources local to the participant's residential area (community linkages). Should intervention group participants require additional support, they will be able to schedule a phone call (as needed) with their BetterBrains coach. Based on the evaluation of the RESPOND program [23], we estimate that intervention group participants will receive an average of 8 hours of intervention delivery (4 hours every 6 months). Participants assigned to the intervention group will also receive monthly updates on general news about dementia and general psychoeducational health material about dementia risk reduction for as long as the trial is active (i.e., at least 24 months).

By leveraging existing community services and tailoring the intervention to each participant, we ensure that we maximize the likelihood for engagement, that lifestyle modifications undertaken have the highest chance of long-term adherence, and that ultimately, cognitive function will be preserved for at-risk individuals.

Control

Participants assigned to the control group will receive monthly updates on general news about

Table 3
Intervention description as per TIDieR [47]

TIDieR item no		Item
1.	Brief name	BetterBrains: An online, person-centered, risk factor management lifestyle intervention program to delay cognitive decline
2.	Why	Mood, vascular risk, cognitive engagement, and sleep are modifiable risk factors for dementia. This trial will test the effectiveness of an online, person-centered, risk factor management program to prevent cognitive decline.
3.	What (materials)	The BetterBrains program targets risk factors for dementia that are broadly categorized as: (a) vascular risk (including physical inactivity), (b) low mood, (c) disrupted sleep, and (d) low cognitive engagement. A monthly blog will provide educational material about current dementia research, and risk factor reduction.
4.	What (procedures)	BetterBrains incorporates: (1) online risk factor screening; (2) telehealth-based goal setting, coaching, and follow-up support, health care provider communication and community linkage for management of identified risk factors; and (3) provision of health education regarding dementia risk reduction; and (4) smartphone-app support to assist participants in undertaking their recommended intervention.
5.	Who provided	BetterBrains Coaches employed by the BetterBrains team. A health professional trained in motivational interviewing and behavior change strategies.
6.	How delivered	Intervention is personalized and provided on a one-to-one basis via telehealth (phone or video call). Intervention will be supplemented by weekly check-ins on the BetterBrains website or smartphone app.
7.	Where delivered	One-to-one intervention delivered via telehealth.
8.	When and how much	BetterBrains Coaches will provide an initial 30 min telehealth consult within 2 weeks of the baseline assessment. The second coaching phone call will be made within 2 weeks of the first, and the third within 6 weeks. BetterBrains Coaches will conduct the first booster call 6 months (24 weeks) after the baseline assessment, the second at 26 weeks, and the third at 30 weeks. We anticipate an average of 5 scheduled follow-up phone calls with each call lasting approx. 15 min. Participants will have the option of scheduling additional phone calls as needed to allow progress towards goals.
9.	Tailoring	Participants may choose to address one or more risk factors throughout the active intervention period (i.e., 12 -months).
10.	Modifications	Modifications made to the intervention during the study will be reported in the outcome paper.
11.	Assessment of intervention fidelity	A detailed program evaluation will be conducted concurrently to the RCT to assess if the intervention was implemented as planned. This evaluation will be reported in a separate protocol paper.

dementia, and general psychoeducational health material about dementia risk reduction for as long as the trial is active. Material will simultaneously be available on the BetterBrains website and smartphone app. Control group participants will not receive personalized information about their risk profile or personalized intervention recommendations including phone calls with the BetterBrains coaches. After completing their risk assessment at baseline, they will only receive mention of the number of risk factors for dementia that apply to them, based on their responses.

Follow-up assessments

Twelve and 24 months after baseline, all participants, irrespective of group allocation, will be notified to complete follow-up assessments (surveys and cognitive testing). The assessment schedule for the follow-up visits is outlined in Table 4. At each follow up visit (i.e., 12 and 24 months), participants will repeat the risk assessment completed at screening and the baseline questionnaires and cognitive testing undertaken at sign up (i.e., all questionnaires, apart from the inclusion/exclusion screening specific questions, presented to the participant up until the point of randomization). A total of 5 reminder notifications will be sent to participants when each assessment is due, provided it is yet to be undertaken.

BetterBrains smartphone application

All participants with a smartphone will also be asked to download the BetterBrains smartphone application. This is an optional study component that will provide a smoother experience. Participants without a smartphone will still be able to participate, and all notifications and assessments sent through the app will be made available through the website. The BetterBrains app will be used to provide psychoeducational material about dementia risk reduction, supplement intervention participants' contact with their BetterBrains Coach, and to enhance the overall trial experience. For both groups, participants will have access to psychoeducational material about

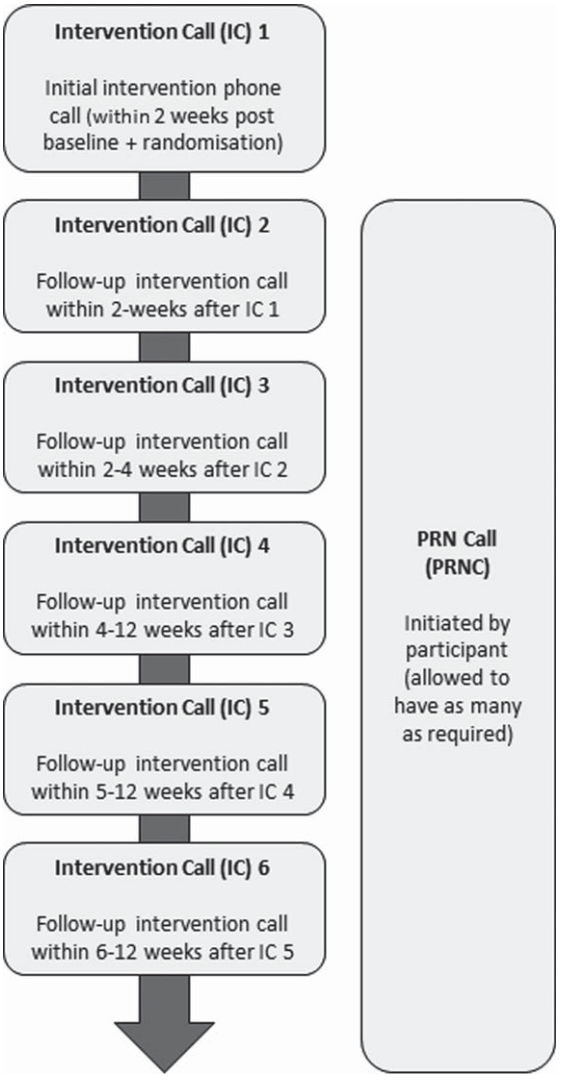

Fig. 2. Call schedule for intervention participants.

dementia risk reduction. In the intervention group, participants will also be sent regular notifications and reminders to check-in on their recommended intervention, whether they have experienced any barriers to engaging in their recommended intervention, and whether they would like to schedule a call with their BetterBrains Coach. Participants will receive these notifications weekly from their first intervention phone call up until week 52 of the intervention. From Months 12–24, these notifications will be sent monthly (option to speak with a coach will no longer be available from Month 12 onwards).

Adverse and serious adverse event reporting

Any unexpected, untoward event that occurs during the trial will be recorded in an SQL database and reported in line with the National Health and Medical Research Council (NHMRC) guidelines on safety monitoring and reporting. An adverse event is defined as any untoward medical occurrence. A serious adverse event is defined as any untoward medical occurrence that 1) results in death, 2) is life-threatening, 3) requires inpatient hospitalization or prolongation of existing hospitalization, 4) results in persistent or significant disability/incapacity, or 5) is a congenital anomaly/birth defect.

When a participant reports an event to a BetterBrains coach or research assistant, the reporting process begins (see Fig. 3 for a flow-chart of the adverse/serious adverse event reporting process). A rostered doctor within the medical management team (Yassi, Brodtmann, or Bush) will review the event, including 1) the date of the report, 2) details of the event, 3) a description of the adverse event, and 4) relevant medical history and medications. The medical management team are blinded to participant group and will be notified of the event by a research assistant, rather than a BetterBrains coach. Finally, an emergency protocol is in place should a participant report an urgent medical or mental health crisis, advising them to attend their GP or local emergency department, or, if not possible, to ring 000 (emergency services) immediately.

Data collection

Questionnaires and self-report surveys

The assessment schedule for this study is outlined in Tables 1 and 3 and consists of a set of validated questionnaires which assess participants' motivation to change, depression, anxiety, and stress levels, subjective ratings of cognitive function, social engagement, general health, sleep quality, engagement in physical activity, work productivity, health literacy, menopausal symptoms (for women), resilience and perceived risk of dementia. The questionnaires will be presented to participants in their published and validated forms.

Self-report data will also be collected from participants in the form of demographic and health and family history surveys. The following **demographic** variables will be collected from participants at their baseline visit: sex, ethnicity, date of birth, employment status, primary occupation, marital status. At the 12- and 24-month visits, we will ask participants to indicate whether they have experienced any change in employment status and if yes, to please detail this change. **Educational history**,

Table 4
Assessment Schedule for 12- and 24-month Follow-Up Assessments

Test/Questionnaire	12- and 24-month Assessment						
	Block 1	Block 2	Block 3	Block 4	Block 5	Block 6	Block 7
Cogstate Brief Battery	X (18 m)						
Cogstate IDSST-Medicines	X (2 m)						
Cognitive Function Index (CFI)	X (2 m)						
Demographics	X (1 m)						
Health questions (smoking, alcohol intake)	X (1 m)						
Family Demographics	X (1 m)						
Family Health History	X (1 m)						
Online Repeatable Cognitive Assessment Battery		X (15 m)	X (15 m)	X (15 m)	X (15 m)	X (15 m)	X (15 m)
Health History		X (5 m)					
Surgical History		X (2 m)					
Relationships Questionnaire		X (1 m)					
Medications Questionnaire		X (2 m)					
Valuation of Lost Productivity (VOLP) + Educational History			X (5 m)				
Depression, Anxiety and Stress Scale (DASS) (21-item)			X (3 m)				
Centre for Epidemiological Studies, Depression Scale (CES-D)			X (2 m)				
Hospital Anxiety and Depression Scale (HADS)				X (3 m)			
Health Literacy Questionnaire (HLQ)				X (4 m)			
Motivation to Change Health Behaviour				X (3 m)			
General Health (RAND)					X (3 m)		
Perceived Stress Scale (PSS)					X (1 m)		
Connor-Davidson Resilience					X (1 m)		
Epworth Sleepiness Scale (ESS)					X (1 m)		
Berlin Sleep Apnoea Questionnaire					X (3 m)		
Cognitive Reserve Index Questionnaire (CRI-q)					X (4 m)		
Insomnia Severity Index (ISI)						X (1 m)	
Pittsburgh Sleep Quality Index (PSQI)						X (4 m)	
Advanced Sleep Phase Questionnaire						X (3 m)	
Greene Climacteric Scale for Menopausal Symptoms						X (2 m)	
Cognitive beliefs and perceived risk of AD						X (2 m)	
International Physical Activity Questionnaire (IPAQ)							X (10 m)
Covid-19 Questionnaire							X (2 m)
Additional Information							X (2 m)
Total Time Per Block	26 m	25 m	25 m	25 m	28 m	28 m	29 m

family demographics, and **family health history** will also be self-reported and collected at baseline, 12- and 24-months. Participant's own **surgical and health history** including medical or psychiatric diagnoses, current medications, drug and/or alcohol use, first- and second-degree family history of dementia, cardiovascular disease and/or psychiatric illness will also be self-reported and collected at baseline, 12- and 24-months. Data obtained from these surveys will be used to compute the ANU-ADRI and CAIDE dementia risk scores [48, 49].

Cognitive testing

Unsupervised cognitive testing will be carried out using the Cogstate Brief Battery (CBB), the Cogstate iDSST Medicines, and the Online Repeatable Cognitive Assessment (ORCA) battery. Instructions and delivery of these tests have been designed and optimized for unsupervised, online assessment [36, 50, 51], and have demonstrated sensitivity to AD-related cognitive change [25, 52].

The CBB has a game-like interface which uses playing card stimuli and requires participants to provide "Yes" or "No" responses. The CBB consists of four tests: Detection (DET), Identification (IDN), One Card Learning (OCL), and One-Back (OBK). These tests have been described in detail previously [34, 52]. Briefly, DET assesses psychomotor function, and IDN assesses visual attention. The primary outcome for both DET and IDN was reaction time in milliseconds (speed). OCL assesses visual learning, and OBK assesses working memory and attention. The primary outcome measures for OCL and OBK was proportion of correct answers (accuracy).

The Cogstate International Daily Symbol Substitution Test (IDSST) Medicines is a measure of complex attention (processing speed) and simple executive function. In this test, a key is provided at the top of the screen. This key shows nine pairs, each consisting of

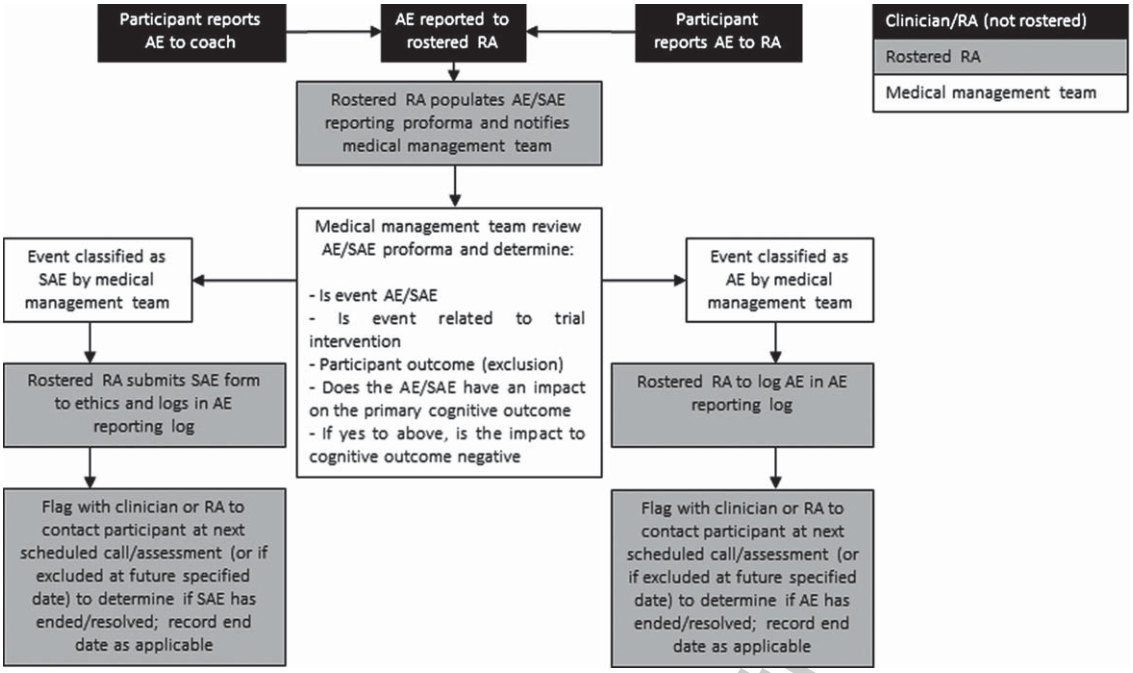

Fig. 3. Adverse and Serious Adverse Event Reporting Process.

a single medicine (capsule, tablet, pill) and calendar date and month (e.g., FEB 1, FEB 2, FEB 3, FEB 4, FEB 5, FEB 6, FEB 7, FEB 8, and FEB 9). Each medicine has a unique shape and color, and each corresponds to a different date (e.g., a round red tablet may be allocated to FEB 3). In the middle of the screen, an empty pill box is presented, and a date is shown at the top of the pill box. At the bottom of the screen, the same medicines as those shown in the key are presented. The participant/subject is asked to select the medicine form the set at the bottom of the screen that corresponds to the date highlighted on the pill box in the center of the screen based on the correct pairing between medicine and date shown in the key (e.g., if FEB 3 is the label on the empty box in the middle of the screen, the subject should select the red tablet). At any decision, the four previous and four upcoming trials are also displayed, on either side of the current date. The software records each selection as correct or incorrect, and once a response is made it cannot be changed. The medicines are selected randomly from a repository of 100 stimuli. Their position in the key showing pairings of medicine and date is also randomized. After the practice, the subject is allowed 120 s to make as many correct responses as possible. The primary outcome for the IDSST-medicines is the total number of correct responses made in 120 s.

ORCA is a paired associate learning task that involves learning the correct pairing of a visually presented Chinese character (e.g., 莓) and the audio English translation of the word (i.e., berry) [25, 36]. The presentation of "correct" pairings will occur over the course of 6 training blocks (one per day) ten times more often than "incorrect" pairings (e.g., chair and 莓). Each trial will consist of a visually presented Chinese character, presented for 1000 ms after the onset of the auditory presentation of the English word. After the characters are presented, participants will have to press one of two keys on a laptop to indicate whether the pairing was correct or not. The instruction will be to "decide if the English word and Chinese characters match or not". Through this process, participants will have the opportunity to learn a range of commonly used Chinese characters. This task will take a maximum of 15 min to complete. Participants will be required to complete 6 blocks of testing (90 min in total). In order to do this test, participants should not be proficient in Chinese (i.e., intermediate level onwards). In order to account for this, we will ask "How proficient are you with Chinese characters?" The responses will be multiple choice: "Not at all", "Beginner level", "Intermediate level", "Advanced level", or "I am fluent/It is my first language". If the participant selects "Intermediate level", "Advanced level", or "I am fluent/It is my first language", the

participant will not complete the ORCA task. Based on HBP estimations [24], we anticipate that ∼90% of participants will be eligible to undertake this task. In addition to the five reminder emails sent as part of the baseline, 12- and 24-month assessment protocol, participants with low adherence rates on the ORCA task (e.g., < 80%) will also be sent an additional reminder email and SMS at 21 days. This will allow participants an additional 7 days to complete the task prior to the 28-day cut-off.

Saliva sampling

All participants that proceed to randomization will also be asked to provide a sample of saliva for genetic testing. After randomization, participants will receive via post at their residential address a Genotek Oragene (OG-500) 2 mL saliva kit in a pre-paid envelope. The DNA tubes will be coded (deidentified) at the Turner Institute before being sent to the participant in the post. Participants will be instructed to return the saliva sample via pre-paid Registered Post to our research team at the Turner Institute for Brain and Mental Health. Samples will be temporarily stored at the Turner Institute. At the end of the trial, a commercial vendor will be identified to conduct genotyping. All samples will be deidentified before being sent for analysis. SNPs for *APOE* (rs429358, rs7412) and those identified to be associated with risk of AD or dementia will be analyzed [53, 54].

Clinical information

Information about intervention group participants' engagement in behavior change strategies related to their goals will be collected from two sources: 1) coach phone calls and 2) the BetterBrains smartphone app. Coaches will complete an eCRF during their scheduled phone calls with intervention participants which will capture relevant behavior change information including: whether the participant has made progress in meeting their goal, barriers and facilitators related to goal progress, and strategies used to affect behavior change. The BetterBrains smartphone app will send participants 'prompts' in the form of notifications weekly (first 12-months of the trial) and monthly (second 12-months of the trial) with questions asking about goal progress, barriers and facilitators.

Participant's engagement in behavior change will also be captured through their responses to questionnaires and surveys administered at the outcome assessments.

Statistical analysis

Outcome analyses will be conducted following intention-to-treat principles. All outcomes and analyses are prospectively categorized as primary, secondary, or exploratory. Differences in all endpoints between the two study groups will be tested independently at the two-tailed 0.05 level of significance. All estimates of treatment effects will be presented with 95% confidence intervals (CIs). No formal adjustments will be undertaken to constrain the overall Type I error associated with the secondary, tertiary, and exploratory analyses. Their purpose is to supplement evidence from the primary analysis to more fully characterize the treatment effect. Results from the secondary, tertiary, and exploratory analyses will be interpreted in this context. Descriptive statistics will be generated for each of the measures used in the study.

The primary outcome will be analyzed using an adjusted logistic regression model with the achievement of a favorable cognitive outcome at 24 months (yes/no) as the dependent variable and the treatment group as the independent variable.

Secondary, tertiary, and exploratory endpoints will be analyzed using appropriate regression models. Exploratory longitudinal analyses will be conducted using linear mixed models (LMM) with random slopes and random intercepts to determine any between-group differences in rates of change in objective and subjective cognitive function, subjective ratings of general health and quality of life, health literacy, motivation to change behavior for dementia risk reduction, and perceived risk of dementia. We will also explore the moderating effects of *APOE* ε4, the nature and number of risk factors, and participants' readiness to change on cognitive outcomes. The details of the statistical analysis will be summarized in a separate Statistical Analysis Plan prior to the lock of the trial data.

COVID-19 related considerations

To ensure the safety and wellbeing of our research participants and to preserve trial integrity in the context of the COVID-19 pandemic, consideration has been given to intercurrent events related to COVID-19 as well as any adequate provisions that may be required to mitigate the potential impact of COVID-19 on trial outcomes (Table 5 details these considerations).

Table 5
COVID-19 Impact

Factor	BetterBrains Trial Impact
COVID-19 Testing	Due to the nature of the intervention (remotely administered via telephone calls and self-directed by the participant in their own community), and the nature and timing of the outcome assessments (remotely administered via a web-based platform at baseline, 12- and 24-months), we do not anticipate a significant impact of participant COVID-19 testing on our trial. Regarding outcome assessments, participants who are tested for COVID-19 and are required to self-isolate will still be able to complete their required outcome assessments. Participants also have 4 weeks within which they can complete outcome assessments, so may choose to complete their assessment after completion of the self-isolation period if it coincides with the start of their study visit.
COVID-19 Infection	A series of questions which collects information regarding COVID-19 testing, treatment, and hospitalization have been included in the outcome assessments and monthly participant check-ins. Participants will have the opportunity to advise the study team if they have tested positive for COVID-19 infection during their outcome assessments and/or monthly check-ins (delivered remotely via the web and smartphone app platforms). For those randomized to the intervention groups, participants may also communicate this information to their coach. Should a participant test positive for COVID-19, they may require treatment, and this may result in potentially relevant complications or medication needs. If the participant is unable to proceed with their chosen intervention plan as a result of this (e.g., the participant exhibits respiratory symptoms and is engaged in a vigorous physical activity program), then they may consult with a member of the study team to revise their intervention strategy or plan. Further, if the participant becomes too unwell to continue in the trial in its entirety, they can withdraw from the study, and this withdrawal will be treated in the same way as any other departure due to medical illness. However, we expect that risk of discontinuation of the intervention due to COVID-19 infection overall will be low.
Quarantine and Travel Limitations	Given that BetterBrains is a remote trial, requirements to quarantine and travel limitations will not impact the participant's assessments and interactions with their coach (if applicable). However, we anticipate some impacts on the intervention aspect of the trial, particularly the participant's ability to access services (e.g., GP, psychologist) that may be required as part of their intervention plan. We have made provisions for this by outlining comparable, but alternative, strategies for intervention (e.g., utilizing telehealth consultations to access appointments with GP or allied health services). Please see Supplementary Table 2 for details.
Site Closures	Given that BetterBrains is a remote trial, there will be no impact of research site closures on participants' assessments and interactions with their coach. Loss to follow-up due to site closure is therefore expected to be minimal. However, we anticipate some impacts to intervention engagement due to contact point closures (e.g., GP, psychologist). As above (see: 'quarantine and travel limitations'), we have made provisions for this by outlining comparable, but alternative, strategies for intervention (e.g., utilizing telehealth consultations to access appointments with GP or allied health services). Please see Supplementary Table 2 for details.
Interruption to supply chain of participant's medications	In the unlikely event that supply chain of medications is interrupted as a result of the COVID-19 outbreak, and the participant has no access to the medication, the participant will be classified as not taking the relevant medication. Coaches will enquire as to whether any changes in medications have occurred.
Stopped enrolment	COVID-19 infection surges and restrictions may lead to geographic region-specific recruitment reductions, delays, and suspension of recruitment. Due to the distributed nature of this study, where individual participants are enrolled centrally online, and is not related to specific enrolling centers, there are no relevant restrictions identified other than those based on geographic region. The need for unplanned interim analysis for futility due to COVID-19 is expected to be unlikely.
Delayed assessment	Outcome assessments in this trial are administered remotely via the internet on three occasions: baseline, 12- and 24-months. Further, assessments are participant-driven, which means that participants can complete their assessments over multiple sittings and at a time that is convenient for them. Participants also have a window of 4 weeks within which they can complete each outcome assessment. Thus, we do not anticipate a delay in assessment completion beyond what would be normally expected in a clinical trial.
Missed visit assessment	As above (see 'delayed assessment').
Stopped intervention due to COVID-related safety concerns	If the participant is unable to proceed with their chosen intervention plan as a result of COVID-related safety concerns, then they may consult with a member of the study team to revise their intervention strategy or plan. However, we expect that risk of stopped intervention due to COVID-19-related safety concerns overall will be low.
Discontinuing participants due to infection	We expect that risk of discontinuation of the intervention due to COVID-19 overall will be low. However, if a participant becomes too unwell to continue in the trial in its entirety, they can withdraw from the study, and this withdrawal will be treated in the same way as any other departure due to medical illness.

(Continued)

Table 5
(Continued)

Factor	BetterBrains Trial Impact
Alternative administration of intervention	See Supplementary Table 2 for details.
Alternative collection of specimens	As part of the trial, we will be collecting saliva samples for genotyping. We will defer collection of saliva samples until indicated that it is safe to proceed with this as advised by government restrictions and the analyzing laboratory. All saliva samples will be securely stored in a locked cabinet at the Turner Institute, Monash University, until they are able to be shipped to the analyzing laboratory. We have planned for samples to be analyzed only at the end of the trial. At this stage, we will communicate with the analyzing laboratory to determine whether they are still operational and accepting biosamples.
Alternative data collection	This study has approval to collect participant Medicare Benefits Schedule (MBS) and Pharmaceutical Benefits Scheme (PBS) data. This is an optional component of the study, and for those participants who opt-in for collection of this information, this data will be used to identify whether participants have attended their GP or other health professionals as a result of COVID-19.
Concomitant Medications due to COVID-19	Participants will advise the study team of their current medications via outcome assessments and monthly check-ins. If a participant starts a new medication or treatment as a result of COVID-19 that is known to impact physical or mental health or cognitive function in a way that may influence the results of outcome assessments, this will be reviewed by the team of medical monitors (Yassi, Brodtmann, Bush) who will determine whether the event is likely to have sufficiently modified cognitive outcomes.

DISCUSSION

This RCT is, in its entirety, a remote clinical trial through its use of web-, smartphone-, and telephone-based platforms to assess, monitor, and deliver the intervention to participants. The aim is to test the hypothesis that the BetterBrains intervention program will prevent cognitive decline in community-dwelling, middle-aged adults with a family history of dementia. The BetterBrains program targets known modifiable risk factors for cognitive decline and dementia through a person-centered, risk factor management online intervention. As modifiable risk factors rarely present in isolation, our multi-risk factor approach has the potential to maximize the anticipated benefits of modifying lifestyle variables on reducing risk of cognitive decline.

The online nature of the trial reduces the burden on participants as attendance at a clinical research facility is not required and completion of cognitive tests and surveys can be completed at a time of convenience over several days. It also facilitates the recruitment and participation of regional and rural participants who are often underrepresented in clinical research due to geographic barriers. As a substantial proportion of Australians aged 40–70 years have access to the Internet via a computer, tablet or phone, this mode of assessment will allow us to reach a wide demographic of individuals. We have successfully utilized this method of recruitment and assessment in the Healthy Brain Project [24]. If successful, there will be an opportunity to apply the testing and intervention methods more broadly as part of clinical care for other patient groups such as chronic disease.

TRIAL STATUS

The trial plans to recruit from June 2021 to June 2022.

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SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/JAD-210589.

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