

Maintain Your Brain: Protocol of a 3-Year Randomized Controlled Trial of a Personalized Multi-Modal Digital Health Intervention to Prevent Cognitive Decline Among Community Dwelling 55 to 77 Year Olds

Megan Heffernan^{a,*}, Gavin Andrews^b, Maria A. Fiatarone Singh^{c,d,t}, Michael Valenzuela^{c,e}, Kaarin J. Anstey^f, Anthony J. Maeder^g, John McNeil^h, Louisa Jormⁱ, Nicola T. Lautenschlager^{j,q}, Perminder S. Sachdev^a, Jeewani A. Ginige^k, Megan J. Hobbs^b, Christos Boulamatsis^k, Tiffany Chau^a, Lynne Cobiac^l, Kay L. Cox^m, Kenneth Daniel^d, Victoria M. Flood^{n,o}, Yareni Guerrero^d, Jane Gunn^r, Nidhi Jain^d, Nicole A. Kochan^a, Amit Lampit^{e,j}, Yorgi Mavros^d, Jacinda Meiklejohn^d, Yian Noble^d, Fiona O'Leary^p, Sue Radd-Vagenas^d, Courtney C. Walton^{e,s}, *Maintain Your Brain* Collaborative Team and Henry Brodaty^a

^aCentre for Healthy Brain Ageing, University of New South Wales, Australia

^bClinical Research Unit for Anxiety and Depression, School of Psychiatry, University of New South Wales, Australia

^cSydney Medical School, University of Sydney, Australia

^dPhysical Activity, Lifestyle, Ageing and Wellbeing Faculty Research Group, Faculty of Health Sciences, University of Sydney, Australia

^eBrain and Mind Centre, University of Sydney, Australia

^fSchool of Psychology, University of New South Wales, Australia

^gCollege of Nursing & Health Sciences, Flinders University, Australia

^hMonash University, Australia

ⁱCentre for Big Data Research in Health, University of New South Wales, Australia

^jUniversity of Melbourne, Australia

^kWestern Sydney University, Australia

^lCSIRO Health and Biosecurity

^mMedical School, University of Western Australia, Perth, Australia

ⁿFaculty of Health Sciences, University of Sydney, Australia

^oWestern Sydney Local Health District, Westmead Hospital, Australia

^pNutrition and Dietetics Group, School of Life and Environmental Science, Faculty of Science & The Charles Perkins Centre, University of Sydney, Australia

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*Correspondence to: Megan Heffernan, Dementia Centre for Research Collaboration, AGSM Building, The University of New

South Wales, Sydney, NSW, 2052, Australia. Tel.: +612 9385 3098; Fax: +612 9385 2200; E-mail: meganh@unsw.edu.au.

^q*North Western Mental Health, Melbourne Health, Melbourne, Australia*

^r*Department of General Practice, University of Melbourne, Melbourne, Australia*

^s*School of Psychology, University of Queensland, Melbourne, Australia*

^t*Hebrew SeniorLife and Jean Meyer USDA Human Nutrition Research Center on Aging at Tufts University, Boston, MA USA*

Abstract:

Background: *Maintain Your Brain* (MYB) is a randomized controlled trial of an online multi-modal lifestyle intervention targeting modifiable dementia risk factors with its primary aim being to reduce cognitive decline in an older age cohort.

Methods: MYB aims to recruit 8,500 non-demented community dwelling 55 to 77 year olds from the Sax Institute's 45 and Up Study in New South Wales, Australia. Participants will be screened for risk factors related to four modules that comprise the MYB intervention: physical activity, nutrition, mental health, and cognitive training. Targeting risk factors will enable interventions to be personalized so that participants receive the most appropriate modules. MYB will run for three years and up to four modules will be delivered sequentially each quarter during year one. Upon completing a module, participants will continue to receive less frequent booster activities for their eligible modules (except for the mental health module) until the end of the trial.

Discussion: MYB will be the largest internet-based trial to attempt to prevent cognitive decline and potentially dementia. If successful, MYB will provide a model for not just effective intervention among older adults, but an intervention that is scalable for broad use.

Keywords: Alzheimer's disease, clinical trial, cognitive decline, cognitive training, dementia, depression, non-pharmacological, physical activity, nutrition, randomized controlled trial

Trial registration: ACTRN 12618000851268. Registered on the Australian New Zealand Clinical Trials Registry (<http://www.anzctr.org.au>).

INTRODUCTION

Dementia affects approximately 44 million people worldwide [1] and assuming the *status quo* is projected to expand to over 136 million by 2050 [1, 2]. Globally, it is a leading cause of disability with costs estimated to exceed 800 billion dollars [1]. In the next 40 years, these costs are projected to exceed those of all other chronic diseases [3]. In light of the modest efficacy of symptomatic drugs for Alzheimer's disease and the lack of success in trials of disease-modifying medications, interventions to delay onset and possibly prevent dementia have gained momentum [4]. Given that dementia has a multifactorial etiology, multi-domain interventions are arguably more likely to be effective in delaying onset [5, 6]. However, evidence for the benefits of multiple combined interventions such as physical activity and cognitive training is limited [7, 8].

In the FINGER (Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability) trial a multi-modal intervention (physical activity, diet, and cognitive training) was effective at reducing cognitive decline in a group of 60 to 77 year olds at risk of dementia and with average or below cognitive scores [9]. Two other trials, the

Multidomain Alzheimer Preventive Trial (MAPT) and the Prevention of Dementia by Intensive Vascular care (PreDIVA), reported encouraging results in *post-hoc* or subgroup analyses [10, 11]. Importantly, a limitation of both FINGER and PreDIVA was their requirement for clinic attendance that would restrict large scale deployment should positive results on clinically meaningful outcomes be found. Internet delivered interventions have the potential to overcome some of the limitations of traditional face-to-face interventions, in that the former are scalable, can reach geographically isolated individuals, are convenient (e.g., can be undertaken at home), and are cost effective.

We therefore designed an internet-delivered multi-domain preventative intervention—*Maintain Your Brain* (MYB)—to target multiple risk factors for dementia in general and AD in particular. Targeted risk factors are physical inactivity, sub-optimal dietary patterns, cognitive inactivity, depression, anxiety, and health-related issues implicated in dementia risk such as overweight, obesity, excess alcohol consumption, smoking, and chronic health conditions. The MYB program is organized into four different modules—Physical Activity, Nutrition, Peace of Mind, and Brain Training—each of which is cus-

tomized to a person's individual risks. MYB builds upon previous trials but introduces novel elements and state-of-the-art concepts in mode of delivery and behavioral change theory to make it unique. Other advantages of MYB are that it is comprehensive in addressing risk factors and it will be one of the first prevention trials to address depression. Modules are also responsive to individual participant progress rather than a one-size-fits-all approach. The program will initially deploy interventions sequentially and then build up booster sessions over time, minimizing the possibility of interference or over-dose effects [12, 13]; it introduces innovations in computer-based cognitive training including insights from gaming, remote supervision, social support, and coaching when required. Finally, the randomized controlled trial (RCT) will be larger than previous studies allowing for sub-analyses of subsidiary questions

MYB aims to: 1) in the short term, develop a new MYB digital platform that delivers multi-modal, personalized, and sequential modules that target dementia risk factors via the Internet; 2) in the medium term, evaluate the efficacy of the MYB digital platform to reduce the rate of cognitive decline in non-demented community dwelling persons aged 55 to 77 years; 3) to examine the impact on reduction in risk factors, improvement in specific module targets (physical activity, nutrition, depression, individual cognitive domains); and 4) evaluate the relative cost effectiveness of the platform.

The primary hypothesis of MYB is that over three years of intervention participants engaging with coaching (intervention) modules on the MYB digital health platform will have less cognitive decline than the information only control group. Secondary hypotheses are that there will be less incident all-cause dementia than the control group; a relationship between intervention fidelity (compliance and adherence) and cognitive outcomes; there will be less categorical cognitive impairment in the intervention group compared to the control; dementia risk profile will improve significantly more in the intervention group; and such a risk profile improvement will correlate with better cognitive outcomes.

METHODS

Design

MYB is an online single-blind randomized controlled trial (Australian New Zealand Clinical Trials

Registry ACTRN 12618000851268) of a personalized, multi-modal intervention designed to target modifiable risk factors for Alzheimer's disease and dementia. Risk factors to be addressed include physical inactivity, poor diet, cognitive inactivity, depression/anxiety, and chronic diseases and habits (alcohol, smoking) linked to dementia risk. Up to four intervention modules (physical activity, nutrition, peace of mind, and brain training) will be administered based on individual risk profiles. Each module will be initially delivered using the MYB digital platform over 10 weeks. In the first year of the RCT, participants will complete their assigned modules sequentially, noting that the total number of modules varies depending on the respective individual's risk factors. In practice, this will translate to a minimum of two modules and a maximum of four modules. Upon completing a module, booster sessions (specific to each module) and ongoing monitoring will then continue for up to three years. Follow-up assessments measuring these risk factors and cognition will be completed annually for three years. The control group ("information" group) will receive basic psychoeducation about dementia risk factors accessed through the MYB digital platform. Set activities will be organized by corresponding module eligibility and also themed into the same modules of physical activity, nutrition, peace of mind, and brain training. Control participants will not be receiving any module-related tailored advice (i.e., the "coaching" component in intervention). They will otherwise undertake the same enrolment, baseline and annual follow-up assessments. An overview of participant flow through the trial is provided in Fig. 1.

Owing to the nature of the intervention, participants and research staff involved in delivering modules will not be blind to allocation. However, the MYB digital platform is an automated system with all activities and assessments delivered electronically without researcher intervention (unless a participant has requested to be withdrawn or for safety). Researchers responsible for analyses will be blinded to group allocation and analyses will be completed (as much as possible) without the use of data that may incidentally unblind the analysis (e.g., module allocation, types of completed activities).

Setting

MYB is online and all study procedures will be delivered and managed via the MYB digital platform. Participants will access all trial materials and associ-

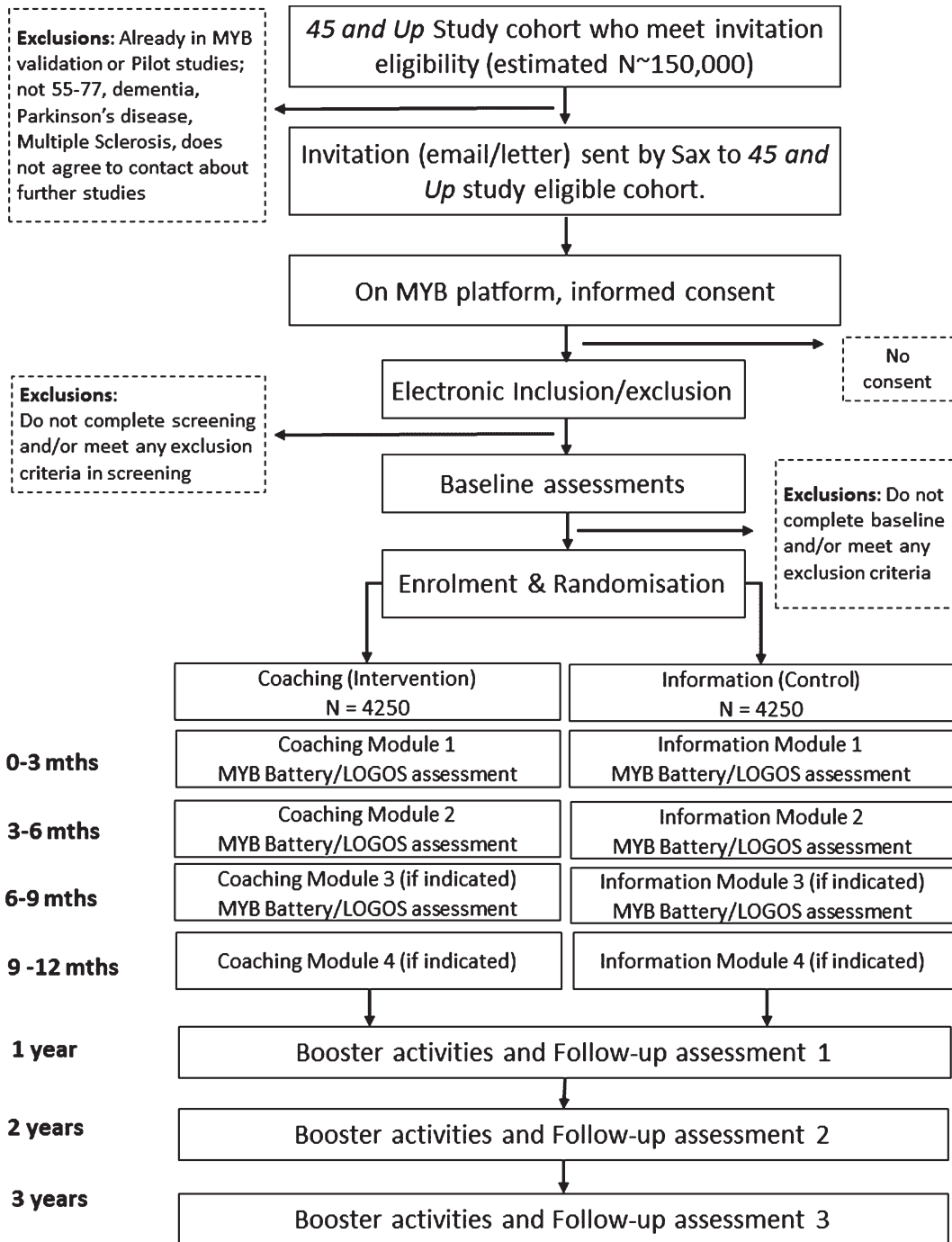


Fig. 1. MYB trial flowchart.

ated help by logging into the MYB digital platform. Personalized activities, with due dates, reminders, and progress will be available through this online platform. MYB will be supported by a team of researchers

who will provide technical assistance to participants. Each module is led and supported by experienced researchers with relevant expertise in delivering their respective interventions.

Recruitment and selection of participants

Participants will be recruited from the Sax Institute's 45 and Up Study [14]. From January 2006 to December 2009, men and women from the general population of New South Wales (NSW), Australia were sampled through the Department of Human Services (formerly Medicare Australia) database and joined the study by completing a postal questionnaire. Participants provided written informed consent for follow-up through repeated contact and linkage to population health databases. A total of 267,153 people, about 1 in every 10 NSW men and women aged over 45, are participating in the 45 and Up Study, making it the largest ongoing study of healthy aging in the Southern Hemisphere. Now 8–11 years after recruitment, participants are aged 53 years and up. The 45 and Up Study is among the most heterogeneous large-scale cohort studies internationally, with participants from diverse socio-demographic, geographic, and cultural backgrounds, which will increase the likelihood that any cognitive effects or risk reduction observed in the trial are generalizable to other populations.

Invitations will be sent by the 45 and Up Study electronically and by mail to potential MYB participants. Participants will not receive both types of invitations. As MYB, being fully online, requires participants to have an email address to be able to login and receive notifications; electronic invitations will be prioritized over physical mail. Invitations sent by email or mail will be identical, except that a unique registration link cannot be sent with the physical mail. Participants receiving mailed invitations will need to enter an email address to be able to receive the unique registration link. All subsequent registration procedures will be identical.

Participants will be eligible to receive invitations if they are enrolled in the 45 and Up Study, have agreed to be contacted about further studies, are aged 55 to 77 years on the first day of the year recruitment commences, do not have dementia, Parkinson's disease, or multiple sclerosis (based on available 45 and Up records) and did not participate in any previous MYB validation or pilot studies.

Participants who provide consent and register on the MYB digital platform will complete a brief screening tool developed for the MYB trial. Participants will be excluded if they: do not respond to the invitation (one reminder may be sent); are unwilling or unable to access trial tasks on the MYB digital platform; are involved in another inter-

vention trial involving exercise, brain training, diet, depression/anxiety treatment, or any drug/nutritional supplement trial; do not have home internet or computer access (desktop or laptop); have vision problems which prevent them from reading a computer screen or are otherwise unable to use a mouse/keyboard without assistance; have a life threatening condition; have any dementia, Parkinson's disease, or multiple sclerosis; have ever been prescribed a medication used to treat Alzheimer's disease; have been hospitalized overnight (≥ 24 h) more than 6 times in the past 12 months; report having had a stroke or heart attack in the previous 3 months; have been diagnosed with brain cancer; have any form of current malignancy other than cancer that has been in remission for at least 5 years (and does not currently require continuing chemotherapy), or non-metastatic prostate or skin cancer; have ever been diagnosed with bipolar disorder or schizophrenia; have severe depression (Patient Health Questionnaire [15], PHQ9 total score >19); report having suicidal intent (PHQ-9 item 9 >1 and Beck Depression Inventory [16] item 9 >1); are unable to write/converse in English; do not have at least two unique risk factors and are not eligible for at least two modules (risk factors determined after baseline assessment).

Participants who are eligible for the trial will then complete baseline assessments used to assess their risk factors and module eligibility. Participants will be enrolled if they complete all baseline assessments (by the MYB start date) and have at least two unique risk factors and are eligible for at least two modules.

Randomization

Participants who provide informed consent, meet trial inclusion criteria and none of the exclusion criteria, and complete all baseline assessments will be enrolled in the trial. Participants agreeing to be in MYB will be randomized (1:1 allocation ratio) using the minimization technique [17] based on the following stratification variables:

- Age (55–65 years; 66–77 years) as of 01/01/2018
- Gender (male, female)
- Dementia risk as measured by Australian National University Alzheimer's Disease Risk Index Short Form [18] (tertiles total risk score)
- Module eligibility (1 module; 2 modules; 3 modules; 4 modules)

Per the minimization technique, a weighted-coefficient variable is used to assign the participants within each profile into intervention and control groups (1:1 allocation ratio). Randomization will occur after baseline assessments have been completed and therefore after module eligibility has been determined. We will conceal allocation with randomization performed centrally by a computerized process and activities are then automatically delivered to participants through the MYB digital platform.

Module eligibility

Participants who are otherwise eligible for the trial will be assessed for module eligibility using baseline assessments (i.e., prior to randomization). Each module is designed to address a known dementia risk and therefore criteria are unique to each of the modules (see below). Module rules are built into the MYB platform and applied automatically. Researchers cannot override this pre-set decision algorithm except in cases of safety where participants may be removed from a module should they reveal, as the trial progresses, a new health issue not disclosed or present at baseline, or they withdraw consent.

Participants with only one unique risk factor and hence eligible for less than two modules will be allowed to enter in MYB, however, only participants with at least two unique risk factors and eligible for at least two modules will be included in the planned primary MYB analyses. This means if a participant has only one risk factor, such as high blood pressure, which makes them eligible for two modules (such as physical activity and nutrition) they will not be included in the primary analysis.

Individual module eligibility

Physical activity (PA)

Participants will be eligible for the PA module based on health conditions identified in the Australian National University Alzheimer's Disease Risk Index Short Form (ANU-ADRI-SF [18, 19], medical history (MYB Medical History), and MYB Physical Assessment battery (includes measures of body composition, Harvard Alumni Questionnaire [20], International Physical Activity Questionnaire [21] sitting, and Virtual Short Physical Performance Battery Protocol [22]). Risks identified include low levels of physical activity (aerobic and/or resistance training), high levels of sitting, high blood pressure,

dyslipidemia, diabetes, heart related issues, stroke, transient ischemic attack (TIA), high body mass index (BMI), high waist circumference, and active smoking status. Participants will be excluded from the PA module (but not the trial) if they report any health concerns that would make continuing in this module unsafe. This includes being advised not to exercise by a health professional, worsening angina in the previous three months, angina at times other than moderate to vigorous activity, unrepaired aneurysms and 12 or more seizures in the previous 12 months.

Nutrition

Participants will be eligible for the Nutrition module based on health conditions identified in the MYB Medical History or a dietary assessment using the Mediterranean Diet and Culinary Index (MediCul). MedCul is a newly created diet assessment for the Mediterranean diet [23] from which a score for the Mediterranean Diet Adherence Screener (MEDAS) [24] is also derived. MEDAS was selected as it is used in PREDIMED (Prevención con Dieta Mediterránea), the largest clinical trial on the Mediterranean diet, and has been associated with cognitive outcomes [25, 26]. A MEDAS score of nine or less indicates low adherence with a Mediterranean dietary pattern. Other risks identified include high blood pressure, high cholesterol, diabetes, heart related issues, stroke, TIAs, peripheral vascular disease, BMI, waist circumference, and excessive alcohol consumption.

Peace of mind

Participants who currently meet probable criteria for unipolar depression and/or an anxiety disorder as assessed by their total Patient Health Questionnaire (PHQ-9) [15] and/or Generalized Anxiety Disorder-7 (GAD-7) [27] scores; and/or report having been diagnosed and/or treated for unipolar depression or their anxiety during their lives (MYB Medical History) will be eligible for the "ThisWayUp Mixed Depression and Anxiety" course (e.g., see <https://thiswayup.org.au>).

Brain training

Participants will be eligible for Brain Training based on years of education (ANU-ADRI-SF), or lower than average late life mental activity (Life Experiences Questionnaire, LEQ late life subscale subthreshold [28]) or mental activity during mid-life (LEQ midlife sub scores subthreshold).

Sequencing of modules

The order that participants will receive modules is determined by a pseudo-random process (Supplementary Material 1). This process is carried out automatically by the MYB digital platform once a participant has completed all baseline assessments, module eligibility has been determined and prior to randomization.

Interventions

Coaching (intervention)

The MYB intervention comprises up to four 10-week modules delivered quarterly in the first 12 months of the trial, with monthly boosters for modules where appropriate thereafter. These modules are Physical Activity, Nutrition, Peace of Mind, and Brain Training. All procedures described will be accessed through the MYB digital platform. All modules will begin with a brief module expectations questionnaire and end with a brief questionnaire measuring participants' appraisal of the module.

Physical activity (PA)

The basic PA prescription is designed to increase aerobic and resistance training to levels with a demonstrated positive impact on cognition and other health outcomes [29, 30]. Where feasible, the module will support progression to higher exercise intensities as this is linked to improved risk reduction, fitness outcomes and cognition in observational and experimental studies [31, 32]. In addition, daily balance training exercises and information on smoking cessation will be included. A behavioral change program [33] is integrated within the PA module by providing personalized goals and feedback, and by encouraging activity logging.

The PA module is fully online and provided through the PA portal on the MYB digital platform. All goals, feedback, and materials (e.g., videos, factsheets) are arranged around three exercise modalities: aerobic exercise, resistance training, and balance training. Information is provided to support achievement of the long-term goal of 300 min/week of moderate to vigorous intensity aerobic activity, three days/week of vigorous intensity progressive resistance training, and challenging balance training every day. Behavioral change is integrated within the module through updating feedback and goals. These are personalized based on activity logged by the participant (weekly self-report via Short Physical Activity

Assessment). Feedback is responsive to both participants who are improving (for example, providing updated goals) and participants who are not progressing or are regressing. If a lack of progression is detected, the module will direct participants to information on barriers and how to overcome them, as well as how exercise can be modified for pain or injury. Participants are also encouraged to use the online Action Plan to write how their goals will be achieved. Feedback on progress is displayed to participants visually (via a virtual "staircase") for each of the three exercise modalities. Short term goals and feedback will follow the general approach of starting exercise at low frequencies and intensities for those not currently exercising and then reaching the target volume within the first month. Once the desired volume is reached, intensity goals will be addressed aiming to reach these by the end of the 10-week module. Progression from moderate to vigorous aerobic and resistance training activities will be encouraged as feasible based on their logged behavior which includes modality, volume, frequency, and perceived intensity (Borg Scale of Perceived Exertion). Participants will be encouraged to add dual tasking to their balance exercises once they have achieved daily balance practice and reached the most challenging level of each exercise. Balance intensity is advanced by gradual reduction of hand support and visual input during static and dynamic exercises. After the initial 10 weeks of the intervention, booster or "refresher" sessions will be added. Booster sessions are identical to module activities but occur less frequently (every four weeks for up to three years follow-up) to allow internalization of monitoring and progression.

All materials are developed by qualified exercise physiologists and/or physiotherapists and provided on the MYB digital platform. Content can be accessed as many times as the participant wishes and will also cover topics related to behavioral change, chronic diseases, relapse prevention, progression, variety, and long-term adherence. All materials can be updated, removed, and new materials added. The PA module is designed to be self-administered, with participants able to engage with materials in their own time. During the module and follow-up, participants will also be able to contact "module trainers" (qualified exercise physiologists or physiotherapist) with questions or issues related to the module. This contact will initially be via the online interface, with follow-up contact as appropriate (e.g., email and phone). Module trainers will also update "Frequently asked questions" factsheets for triaging common problems

and questions arising during exercise adoption, refer participants to their GP for suspected exercise-related or other injury, recurrent falls, potential medication-related side effects, or instability /progression of underlying chronic diseases such as osteoarthritis, angina, etc.

The PA module will be adjusted if a participant reports being diagnosed with osteoporosis, or a high number of falls in the past 12 months, or scores poorly in the virtual Short Physical Performance Battery (vSPPB) [22] by removing any goals and feedback related to aerobic exercise as walking may increase risk of falls until strength and balance are improved [34, 35]. During annual assessments, participants could be reallocated to the main PA module if appropriate. Initially, baseline assessments will be used to exclude any participant from PA owing to safety concerns (for example, being advised by a medical professional not to exercise). Participants who are eligible for PA at baseline may subsequently report a health concern that requires adjustment to their PA module. The aerobic component of the module can be removed based on pre-set rules applied automatically by the MYB digital platform (for example too many reported falls). Their PA module can also be temporarily blocked (or 'unblocked' if recovered) on a case-by-case basis by qualified PA module staff (e.g., clinicians and exercise physiologists). For any health-related concern that is not planned or reported via the MYB platform, researchers may inform the MYB administrator to remove participants from the module entirely.

Physical activity logged via the Short Physical Activity Assessment (weekly in the first 10 weeks, then monthly) will be used to measure PA/sedentary behavior levels during the module. These weekly logging tasks, email notifications about new tasks as well as intermittent newsletters will be used to support adherence to the module. Whether a participant completes activity logs and action plans, and how many times they visit the PA module can be used to assess engagement with the module.

Nutrition

The Nutrition module is designed to encourage adoption of a Mediterranean diet acknowledged in dietary guidelines as a healthy eating pattern for chronic disease [36, 37]. The rationale for this diet is based on its relevance to risk factors for cognitive decline and RCT and prospective cohort data for a Mediterranean diet [38–41]. At this time, the Mediterranean diet appears to be the most strongly supported

dietary pattern for cognitive benefits in clinical trials [41].

The Nutrition module is fully online and provided through the Nutrition portal on the MYB digital platform. All dietary messages, feedback, and materials (such as cooking videos, meal plans, recipes, shopping lists, health tips, factsheets, and behavioral change resources) are arranged around 10 food groups (discretionary foods, animal protein, extra virgin olive oil, nuts, vegetables, fruit, legumes, wholegrains, fish and seafood, and water) within the Mediterranean diet to provide smaller manageable targets for change. The Nutrition portal provides a visual display of the Mediterranean diet that participants are aiming to achieve (via an ideal "Mediterranean diet food pyramid") based on their self-reported food intake. Food intake will be via the MiniCul, a screener form of the MediCul [23] that is used to prompt behavior change within the module. The components of the Mediterranean diet food pyramid will be completed in sections, with personalized messages and feedback provided for food groups that require improvement. Although personalized, the overall approach of dietary messages and feedback is to target the most poorly scored and crucial changes first. Additionally, participants will only receive a manageable number of changes each week (maximum four messages). If a participant does not make any changes for two weeks (as measured by weekly online food intake logging), messages will move onto other poorly scored food groups and cycle back to the unchanged groups if time is available. Therefore, even a participant who needs to make changes across all 10 food groups but shows no change in their weekly log, will receive advice and recommendations for all food groups. If a participant reaches the 'ideal' Mediterranean diet food pyramid they will be encouraged to maintain their Mediterranean diet.

The initial Nutrition module is delivered over 10 weeks during the first 12 months of MYB. During the first 10 weeks participants are encouraged to log their adherence to the Mediterranean diet weekly (self-report via MiniCul). Participants are also encouraged to fill out a weekly action plan for how they will improve their Mediterranean diet score for each of the suggested food changes. After the initial 10 weeks of intervention, booster sessions will be added. Procedures and materials for booster sessions are identical to the initial Nutrition module. However, booster sessions and therefore diet logging will occur less frequently (every 4 weeks).

All materials are designed by qualified dietitians and can be accessed as many times as the participant wishes. Materials include recipes, videos, shopping lists, and factsheets. Topics covered by these materials will be related to the recommended diet as well as areas such as behavioral change, scientific literature, special dietary considerations and food allergies, intolerances and drug interactions. All materials can be updated, removed, and new materials can be uploaded by the Nutrition module staff (i.e., qualified dietitians).

The Nutrition module is designed to be self-administered with participants able to engage with the materials in their own time. During the module and follow-up, participants will also be able to contact “module trainers” (qualified dietitians) with questions or issues related to the module. This contact will initially be via the online interface, with follow-up contact as appropriate (e.g., email and phone). Module trainers will also provide updates to “Frequently asked questions” and refer participants to a GP if necessary.

There are two planned modifications to the Nutrition module based on alcohol consumption and being underweight. If participants report a high rate of alcohol consumption, diet messages related to alcohol will be prioritized and remain until participants report a reduced alcohol intake. Participants reporting low body weight will receive modified advice that encourages adapted serving sizes compared to the main Nutrition module. After the 10-week intervention, such participants could be reallocated to the main Nutrition module if goals are achieved. Likewise, participants receiving the main Nutrition module could be reallocated to the modified alcohol or underweight Nutrition module after the 10-week intervention if appropriate. These modifications are pre-set and the rules are applied automatically by the MYB digital platform. For any other diet-related concerns, such as medical advice not to alter their diet, researchers may remove participants from the module entirely if it becomes unsafe for them to continue. However, there is flexibility to allow for food preferences, financial circumstances, special dietary requirements, food allergies, intolerances, and ethnic backgrounds.

The MiniCul is used weekly in the first 10 weeks, then monthly, to track progress with adopting a Mediterranean diet during the intervention. In addition, self-reported body measurements (waist circumference, weight) are also checked during this module. Weekly email reminders to complete

MiniCul and intermittent newsletters to support adherence to the module are also provided. Engagement with the Nutrition module is tracked by the number of completed MiniCuls, action plans to achieve Mediterranean goals and the number of times participants login.

Peace of mind

Participants who are currently depressed and/or anxious; and/or have ever been diagnosed/treated for depression and/or anxiety will have access to the “ThisWayUp Mixed Depression and Anxiety” course. This course has been developed by the Clinical Research Unit for Anxiety and Depression (CRUFAD) at UNSW/St Vincent’s Hospital and the efficacy and effectiveness of the program reported previously [42–44]. During the module, participants will be able to contact CRUFAD staff with clinical and technical questions.

The Mixed Depression and Anxiety course includes six lessons delivered over 10 weeks. These lessons include: 1) Psychoeducation about anxiety and depression, identifying symptoms, the fight or flight response, controlled breathing and physical activity/exercise; 2) Cognitive therapy components: education about the cognitive model, cognitive distortions, and introduction to thought monitoring; activity planning; 3) Thought challenging/cognitive restructuring; challenging positive & negative meta-cognitive beliefs about repetitive thinking; shifting attention, hunt for positives; 4) Education about avoidance and safety behaviors; graded exposure and structured problem solving; 5) Advanced graded exposure (imaginal exposure, interoceptive exposure); troubleshooting difficulties with graded exposure; and 6) Relapse prevention. There are no boosters associated with the Peace of Mind module.

Participants’ completion of each lesson will be used to assess adherence to the module. During the module, participants will complete measures of: psychological distress at the start of each lesson (Kessler Psychological Distress Scale, K10) [45]; and depression (PHQ-9) [15] and anxiety symptom severity (GAD-7) [27] prior to lessons 1, 4, and 6.

Brain training

Participants with an at-risk cognitive profile will be eligible for the Brain Training module. Participants will complete a personalized cognitive training program that is vertically and horizontally adaptive called the “Brain Training System” (BTS). That

is, the training regimen is defined on participant's baseline cognitive profile and continues to evolve in response to within-training task performance. Individual cognitive exercises are run as Flash files as provided by our commercial partner (Synaptikon, trading as NeuroNation, Germany); more than 30 are available at the outset and will be supplemented throughout the trial. BTS has otherwise been originally designed, including the approach to exercise selection, streaming, feedback, coaching, and social support.

A participant's cognitive profile is generated based on cognitive tests completed at baseline. These profiles will rank performance across cognitive domains (i.e., verbal executive, speed, verbal memory, visual executive, visual memory, visual attention) in descending order. The initial exercise selection and streaming order will reflect this profile, preferentially targeting areas of weakness in the middle of the session. Exercise selection and streaming will be recalibrated during training several times, in this case based on degree of improvement on exercises at the domain-level.

Exercises will be presented as three sessions per week, translating to 30 sessions over 10 weeks. Each session will last 45 minutes and comprise 17 exercises. If participants miss sessions, they will remain available until completed. During follow-up, booster exercises will be offered once a month (up to three years follow-up). Cognitive training materials (e.g., factsheets) will also be provided and can be accessed as many times as the participant wishes.

After completing the first five sessions, participants will receive a feedback performance graph that summarizes their cognitive performance on each cognitive domain trained thus far. This performance graph will also indicate the range of scores for the top 25% performers in the module based on previous sessions. Participants' individual performance will be updated after completing each session and the top 25% range will be updated weekly.

In order to maximize adherence and motivation, BTS will deploy several socialization and gaming strategies. This includes access to an online Trainer, prioritized for participants 'red-flagged' as struggling with engagement or performance. Video chat will be preferred for these interactions, but participants will also be able to contact module trainers via MYB's online interface. Participants can also nominate friends or family members who will be advised via email when the participant reaches certain adherence milestones, with the aim of providing social

support and encouragement and establishing a community of practice.

The Brain Training module is therefore designed to be automatically adaptive to a participant's baseline score and progress during training. Safety issues are not foreseen for this module.

Participants will receive email notifications when a new activity is available as well as when performance problems are noted to support adherence. The Brain Training module will measure within-exercise improvement, domain-level performance changes, program adherence (completed sessions) and social platform engagement.

Information (Control)

Participants in the control group will receive basic health information organized in the same module topics as the intervention (Physical Activity, Nutrition, Peace of Mind, and Brain Training). Participants will have access to these information-based modules based on their module eligibility and in a pseudo-random order as described in the previous section. Although control participants receive modules based on their individual risk profile they will not be provided with any tailored advice (i.e., the 'coaching' intervention component) about how to improve their risk factors. The control group will receive information monthly for up to four 10-week modules in the first 12 months. All procedures described will be delivered online and accessed through the MYB digital platform. All modules will begin with a brief module expectations questionnaire and end with a brief questionnaire measuring participants' appraisal of the module.

For the Physical Activity, Nutrition, and Peace of Mind control modules, the information provided will be focused on existing health guidelines and general advice for achieving these targets. For example, providing the Australian Dietary Guidelines from the Australian Government Department of Health and Ageing without specifying how participants can achieve these guidelines. The Brain Training control module will involve a brief task (such as showing videos with a brief quiz). These tasks have been used in previous trials and have been shown to be enjoyable with minimal impact on cognition [46]. Participants will access the 10-week modules via the MYB digital platform with new module information or tasks provided once a month. Upon completing the Physical Activity, Nutrition, and Brain Training modules, these activities are then reduced to quarterly (i.e.,

boosters) for up to three years follow-up. As with intervention, there will be no boosters for the Peace of Mind module.

The control group will receive periodic emails reminding them to login to the MYB digital platform to access module information. All participants in a control module will receive the same basic health information or task (with no tailored advice). However, they may be removed from a module for safety reasons (e.g., a previously undisclosed/undiagnosed health issue that might prevent safe exercise). Engagement with the module can be measured by the amount of times a participant logs into the MYB eHealth platform and the amount of times they visit the module information webpage.

Outcome measures

Primary outcome

The primary outcome is *change in cognition from baseline to three years*. We will test whether the groups show differential change over the trial as indicated by the group by time interaction. In addition, we will test the group difference at three years as a planned comparison. The outcome variables are the global cognition composite domain scores, at baseline and three years, as measured by the MYB online cognitive test battery (“MYB Battery”). Domains and tests in MYB are defined as: 1) Complex attention (Cogstate Detection and Cogstate Identification); 2) Executive Function (Cogstate One Back, Cambridge Brain Sciences Spatial (Tokens) Search and Cambridge Brain Sciences Grammatical Reasoning); and 3) Learning and Memory (Cogstate One Card Learning and Cambridge Brain Sciences Paired Associates). Two valid test scores per domain are required to generate a participant’s domain score at each time point. Individual test scores will be converted to standard scores (z-scores) using the means and standard deviations (SD) of the MYB baseline sample. Domain scores will be calculated by first averaging the z-scores of the component tests, and then transforming the composite scores using the means and SDs of the MYB baseline sample. A global cognition score will be calculated by averaging across the three standardized domain scores, and then the score will be similarly transformed to z-scores using the means and SDs of the MYB baseline sample.

Secondary outcomes

Secondary outcomes related to cognitive impairment and dementia are: 1) incident dementia at three

years; 2) change in dementia risk (ANU-ADRI-SF total score); and 3) using the method described for the primary outcome, change in cognitive domain scores and individual cognitive tests that form the MYB Battery as well as LOGOS.

Dementia in MYB will be determined according to the following:

- Participants are screened for dementia at baseline via self-report questions. However, if baseline dementia is subsequently identified during baseline assessment via any of the processes below, participants will be retrospectively censored as they cannot meet the definition of incident dementia.
- Dementia is assumed if there is any self-reported dementia to MYB via the medical history questionnaire (diagnosis or dementia medications), stated as a reason to withdraw from the trial, or it is otherwise reported to MYB that dementia has been confirmed by a medical professional.
- If there is no self-report, dementia will be assumed if linked data contain any of the following:
 - Pharmaceutical Benefits Scheme (PBS) claims for dispensing of Alzheimer’s disease medications (donepezil, galantamine, or rivastigmine or memantine).
 - Dementia listed as a diagnosis in hospital records.
 - Dementia listed as a cause of death in mortality records.
- If none of the above indicates dementia, DSM-5 criteria [47] requiring cognitive impairment *and* functional impairment will be applied.
 - Cognitive impairment is measured by the MYB Battery and an additional automated telephone-based verbal memory test (LOGOS), developed and validated for MYB.
 - Cognitive impairment is defined as ≥ 2 SD below the mean of the baseline sample on any individual test (stratified for age, sex, education) OR ≥ 1.5 SD below the mean of the baseline sample in ≥ 1 domain. (stratified for age, sex, education).
 - Functional impairment is defined by the Amsterdam-Instrumental Activity of Daily Living-Short Form (A-IADL-SF; cut-off is less than 51.4 [48]).
- If there are no cognitive data, dementia will be “undetermined”.

- If there is evidence for cognitive impairment (defined above) but no data on function, participants will be classified as “impaired cognition, function undetermined”.

Secondary outcomes related to the overall impact of the intervention and participant experience are: 1) service utilization identified through routinely collected linked data: hospital admissions, emergency department presentations, medical and social care services, and prescribed medications; 2) costs of program as determined by quality adjusted life years (QALYs) based on MYB used resources (e.g., staff time) and intervention effect; 3) change in module expectations as measured by the Module Expectations questionnaire (total; adapted from Rabipour & Davidson [49]); 4) compliance with the intervention and for each module undertaken (percentage activities complete and accessed per module; MYB digital platform login data); and 5) number of adverse events reported to MYB via the medical history and medical events forms. Events include hospitalizations, muscle soreness and food allergies.

Secondary outcomes related to risk factors targeted by the four module interventions are: 1) change in waist circumference and BMI if overweight/obese (self-report in MYB Physical Activity questionnaire); 2) change in level of physical activity (HAQ energy expenditure, stair climbing, walking, IPAQ sitting time and volume and intensity of aerobic exercise, resistance training, and balance exercise/week); 3) new chronic conditions (count based on medical history and medical events forms); 4) change in physical functional performance during the PA module as measured by the virtual Short Physical Performance Battery Score; 5) change in adherence to the Mediterranean diet (MediCul score and derived MEDAS score); 6) change in exposure to foods/culinary practices assessed via MediCul; 7) change in alcohol (self-report in ADRI-SF and MediCul) and smoking status (self-report in ADRI-SF); 8) change in within task cognitive training performance in the Brain Training module (percentage correct per session); 9) change in mental activity levels (LEQ late-life subscale); 10) engagement during Brain Training module (count use of social platform); and 11) change from baseline to three years in psychological distress (K10).

Data management

Electronic files collected by MYB that are not linked data will be stored on a secure server. The des-

ignated MYB data custodian (MYB Data Manager) will be responsible for maintaining data security and assigning access controls. MYB has implemented a role-based access mechanism that controls the access to research data. The MYB platform can allow authorized researchers, responsible for the day-to-day running of the trial, to access information needed for tasks such as responding to participant enquiries, while ensuring trial-wide clinical data are not accessible through the same pathway.

Assessments and linked data

MYB assessments to be completed by all participants (self-report), module specific assessments and data sources for linked health data are summarized in Table 1. Medicare Benefits Schedule (MBS) and Pharmaceutical Benefits Scheme (PBS) data will be accessed from the Department of Human Services (DHS) and linkage completed by the Sax Institute using a unique identifier that was provided by DHS. Other linkage data (Table 1) will be performed by the Centre for Health Record Linkage (CHeReL, www.cherel.org.au) using probabilistic record linkage techniques and ChoiceMaker software.

Statistics

Sample size

We will have 80% power to detect significant group by time interaction in the MYB Battery primary outcome, assuming linear change and a final difference of 0.1 SD if we have 1,714 people in each group (total $N = 3,428$) with type 1 error rate of 0.05. This assumes a within-subjects correlation of 0.6 and a Lear deterioration rate of 0.1. If we assume a 20% drop out rate over the trial, we will need to recruit at least 2,143 people in each arm. With 2,143 participants per arm (4,285 in total), we will also have 80% power to detect differences of at least 0.1 SD for continuous secondary outcomes.

Sample size estimates were obtained using GLIMPSE 2.0.0 [50] and G*Power 3.1 [51]. MYB has the capacity to enroll up to 16,000 persons if it is oversubscribed.

Analysis

Participants with at least two unique risk factors and eligibility for two modules or more will be included in the MYB analysis. The trial will be reported in accordance with the CONSORT guidelines. We will analyze all outcomes by the arm to

Table 1
MYB assessments and timing of administration

Assessment/data source	Measures	Timing
MYB Eligibility 1 ^a	Trial eligibility	Screening only
ANU-ADRLSF	Dementia risk	Baseline and annual follow-up
MYB Battery ^b	Cognitive ability	Baseline, every 3 months in the first 12 months and then annually
LOGOS ^c	Verbal memory	Baseline, every 3 months in the first 12 months and then annually
Medical History Baseline	Medical history	Baseline only
Medical History Follow-up	Medical history	Annual follow-up
Physical Assessment battery ^d	Body composition, physical activity, sitting time and functional mobility performance	Baseline and annual follow-up
MediCul and derived MEDAS ^e	Dietary pattern	Baseline and annual follow-up
Wellbeing ^f	Psychological distress, depression and anxiety	Baseline and annual follow-up
LEQ	Cognitive lifestyle	Baseline only
LEQ– Late life	Late life subscale of LEQ	Annual follow-up
A-IADL-SF ^g	Daily function	Baseline and annual follow-up
Module Expectations	Module expectations	Pre/post modules only
Medical Events form	Adverse events	Every 3 months
Short Physical Activity measure (HAQ)	Weekly physical activity	Intervention Physical Activity module only - module baseline and weekly during the module; monthly during follow-up
MiniCul, weight and waist circumference	Weekly nutrition	Intervention Nutrition module only - module baseline and weekly during the module; monthly during follow-up
K10	Psychological distress	Intervention Peace of Mind module only - start of each lesson (6 over 10 weeks)
PHQ-9	Depression	Intervention Peace of Mind module only - start of lessons 1, 4 and 6
GAD-7	Anxiety	Intervention Peace of Mind module only - start of lessons 1, 4 and 6
Medicare Benefits Schedule (MBS) ^h	Primary health care service use	Available data at baseline to follow-up
Pharmaceutical Benefits Scheme (PBS) ^h	Prescribed medicines	Available data at baseline to follow-up
NSW Admitted Patient Data Collection (APDC) ^h	Hospital use	Available data at baseline to follow-up
NSW Emergency Department Data Collection (EDDC) ^h	Emergency department admissions	Available data at baseline to follow-up
NSW RBDM Death Registrations ^h	Deaths	Available data at baseline to follow-up
Cause of Death Unit Record File (COD URF) ^h	Deaths	Available data at baseline to follow-up
NSW Mental Health Ambulatory Data Collection ^h	Service utilization	Available data at baseline to follow-up

ANU-ADRLSF, ANU Alzheimer's Disease Risk Index Short Form [18]; A-IADL-SF, Amsterdam IADL Questionnaire Short Form [48]; LEQ, Lifetime of Experiences Questionnaire [28]; K10, Kessler Psychological Distress Scale [45]; GAD-7, Generalized Anxiety Disorder 7-item [27]; PHQ9, Patient Health Questionnaire [15]. ^aMYB Eligibility 1 includes baseline Patient Health Questionnaire (PHQ-9). ^bThe MYB Battery comprises tasks from the Cogstate Brief Battery (Detection, Identification, One Card and One Back) and Cambridge Brain Sciences (Spatial (Tokens) Search, Grammatical Reasoning and Paired Associates). ^cLOGOS: an automated telephone-based test of episodic verbal memory developed and validated for MYB. ^dThe Physical Assessment battery includes measures of body composition (self-reported standing height, body mass, waist circumference); physical activity (the Harvard Alumni Questionnaire, HAQ [20]); sitting time (item from the International Physical Activity Questionnaire, IPAQ [21]); and a measure of functional mobility and performance (the Virtual Short Physical Performance Battery Protocol, vSPPB [22]). ^eAdherence to the Mediterranean dietary patterns include MediCul (Mediterranean Diet and Culinary Index) [23] and MEDAS (Mediterranean Diet Adherence Screener [24]). ^fWellbeing assessment includes the Generalized Anxiety Disorder 7-item (GAD-7), PHQ-9^a, and Kessler Psychological Distress Scale (K10). ^gA-IADL-SF to be completed by an informant for all participants (non-compulsory assessment). ^hLinked data.

which participants were allocated (i.e., intention to treat analyses). We will analyze the primary outcome, change in cognition, using linear mixed models to examine the treatment group by time interaction and will obtain a test of the difference between the groups at the end of the trial. We will also conduct anal-

yses adjusting for baseline demographic variables; additional adjustment for differential expectations between arms or modules will be applied as necessary. In addition, we will conduct subgroup analyses on the primary outcome to determine if there is effect modification by the number of risk factors at baseline

(3 or 4 risk factors versus 2 risk factors). We expect change in cognition to show a normal distribution. However, if there are violations of the assumptions of linear mixed models, appropriate transformations or a generalized linear mixed model with an appropriate distribution will be used.

Secondary outcomes will be analyzed using linear mixed models for continuous normally distributed outcomes or chi-squared tests for categorical outcomes. We will use nonparametric tests for analyzing continuous outcomes if the assumption of normality is violated.

Safety

Data safety and monitoring board (DSMB)

A DSMB will be convened for this trial. It is an independent group of experts that advises MYB investigators. No member of the DSMB will have direct involvement in the conduct of the study; financial, proprietary, professional, or other interests that may affect independent decision-making by the DSMB.

Adverse event and serious adverse events

All MYB participants will be routinely logging into the MYB platform (both control and intervention group) for trial procedures. During these, they will be prompted every 3 months by an on-screen ‘pop-up’ to report any adverse event(s) in both a check box and text box format, which will be followed by specific advice to continue/start exercises or dietary changes or not, or to see their health care provider if indicated. All participants can also report adverse events at any time of the trial (ad hoc reporting). Adverse events during the Physical Activity and/or Nutrition modules that are potentially related to the interventions (e.g., muscles soreness, bloating) will be proactively defined via factsheets and instructions within each module, and recorded by the participants on the web interface as they occur. These logged events will be triaged by the Physical Activity and/or Nutrition module leader and trainers as appropriate for follow-up, referral to GP or study physicians, or reporting to ethics.

A serious adverse event (SAE) is death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions. All SAEs will be reported to the relevant ethics committees for this trial.

Ethics

All trial procedures have been approved by the University of New South Wales Human Research Ethics Committee (#16252) and NSW Population and Health Services Ethics Committee (#2016/03/636). The conduct of the 45 and Up Study was approved by the University of New South Wales Human Research Ethics Committee (HREC).

DISCUSSION

Maintain Your Brain targets known modifiable cognitive decline and dementia risk factors through a personalized, multimodal online intervention. The expected benefits of this approach are that MYB has the capacity to target a number of risks in a large number of participants. A range of modifiable risk factors for Alzheimer’s disease and vascular dementia including vascular, cognitive, lifestyle, and psychosocial factors, account for up to one third of the population attributable risk for Alzheimer’s disease [52] and are major risk factors for vascular dementia. In Australia, there is an even higher estimated population attributable risk for dementia of 48% owing to the distribution of these risk factors in the Australian population [53]. Should Maintain Your Brain be successful in addressing cognitive decline by targeting multiple risk factors, it could provide a model for interventions suitable for use in the broader community.

TRIAL STATUS

The MYB trial (Protocol v1.29, 03/05/18) plans to recruit from June to October 2018.

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SUPPLEMENTARY MATERIAL

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REFERENCES

- [1] Wortmann M (2014) World Alzheimer report 2014: Dementia and risk reduction. <https://www.alz.co.uk/research/world-report-2014>
- [2] Ferri CP, Prince M, Brayne C, Brodaty H, Fratiglioni L, Ganguli M, Hall K, Hasegawa K, Hendrie H, Huang Y, Jorm A, Mathers C, Menezes PR, Rimmer E, Sczufca M (2005) Global prevalence of dementia: A Delphi consensus study. *Lancet* **366**, 2112-2117.
- [3] Access Economics (2009) *Keeping dementia front of mind: Incidence and prevalence 2009-2050*, Report by Access Economics Pty Limited for Alzheimer's Australia. https://www.dementia.org.au/sites/default/files/20090800_Nat_AE_FullKeepDemFrontMind.pdf
- [4] Barnes DE, Yaffe K (2011) The projected effect of risk factor reduction on Alzheimer's disease prevalence. *Lancet Neurol* **10**, 819-828.
- [5] Intiaz B, Tolppanen AM, Kivipelto M, Soininen H (2014) Future directions in Alzheimer's disease from risk factors to prevention. *Biochem Pharmacol* **88**, 661-670.
- [6] Richard E, Andrieu S, Solomon A, Mangialasche F, Ahtiluoto S, Moll van Charante EP, Coley N, Fratiglioni L, Neely AS, Vellas B, van Gool WA, Kivipelto M (2012) Methodological challenges in designing dementia prevention trials - the European Dementia Prevention Initiative (EDPI). *J Neurol Sci* **322**, 64-70.
- [7] Law LLF, Barnett F, Yau MK, Gray MA (2014) Effects of combined cognitive and exercise interventions on cognition in older adults with and without cognitive impairment: A systematic review. *Ageing Res Rev* **15**, 61-75.
- [8] Karssemeijer EGA, Aaronson JA, Bossers WJ, Smits T, Olde Rikkert MGM, Kessels RPC (2017) Positive effects of combined cognitive and physical exercise training on cognitive function in older adults with mild cognitive impairment or dementia: A meta-analysis. *Ageing Res Rev* **40**, 75-83.
- [9] Ngandu T, Lehtisalo J, Solomon A, Levälähti E, Ahtiluoto S, Antikainen R, Bäckman L, Hänninen T, Jula A, Laatikainen T, Lindström J, Mangialasche F, Paajanen T, Pajala S, Peltonen M, Rauramaa R, Stigsdotter-Neely A, Strandberg T, Tuomilehto J, Soininen H, Kivipelto M (2015) 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* **385**, 2255-2263.
- [10] Andrieu S, Guyonnet S, Coley N, Cantet C, Bonnefoy M, Bordes S, Bories L, Cufi M-N, Dantoine T, Dartigues J-F, Desclaux F, Gabelle A, Gasnier Y, Pesce A, Sudres K, Touchon J, Robert P, Rouaud O, Legrand P, Payoux P, Caubere J-P, Weiner M, Carrié I, Ousset P-J, Vellas B (2017) Effect of long-term omega 3 polyunsaturated fatty acid supplementation with or without multidomain intervention on cognitive function in elderly adults with memory complaints (MAPT): A randomised, placebo-controlled trial. *Lancet Neurol* **16**, 377-389.
- [11] van Charante EPM, Richard E, Eurelings LS, van Dalen J-W, Ligthart SA, van Bussel EF, Hoevenaar-Blom MP, Vermeulen M, van Gool WA (2016) Effectiveness of a 6-year multidomain vascular care intervention to prevent dementia (preDIVA): A cluster-randomised controlled trial. *Lancet* **388**, 797-805.
- [12] Lampit A, Hallock H, Valenzuela M (2014) Computerized cognitive training in cognitively healthy older adults: A systematic review and meta-analysis of effect modifiers. *PLoS Med* **11**, e1001756.
- [13] Lampit A, Valenzuela M (2015) Pointing the FINGER at multimodal dementia prevention. *Lancet* **386**, 1625-1626.
- [14] 45 and Up Study Collaborators (2008) Cohort profile: The 45 and Up Study. *Int J Epidemiol* **37**, 941-947.
- [15] Kroenke K, Spitzer RL, Williams JBW (2001) The PHQ-9: Validity of a brief depression severity measure. *J Gen Intern Med* **16**, 606-613.
- [16] Beck AT, Ward CH, Mendelson MM, Mock JJ, Erbaugh JJ (1961) An inventory for measuring depression. *Arch Gen Psychiatry* **4**, 561-571.
- [17] Altman DG, Bland JM (2005) Treatment allocation by minimisation. *BMJ* **330**, 843.
- [18] Kim S, Cherbuin N, Anstey KJ (2016) Assessing reliability of short and tick box forms of the ANU-ADRI: Convenient alternatives of a self-report Alzheimer's disease risk assessment. *Alzheimers Dement (N Y)* **2**, 93-98.
- [19] Anstey KJ, Cherbuin N, Herath PM (2013) Development of a new method for assessing global risk of Alzheimer's disease for use in population health approaches to prevention. *Prev Sci* **14**, 411-421.
- [20] Pereira MA, FitzerGerald SJ, Gregg EW, Joswiak ML, Ryan WJ, Suminski RR, Utter AC, Zmuda JM (1997) A collection of Physical Activity Questionnaires for health-related research. *Med Sci Sports Exerc* **29**, S1-205.
- [21] Hagströmer M, Oja P, Sjöström M (2007) The International Physical Activity Questionnaire (IPAQ): A study of concurrent and construct validity. *Public Health Nutr* **9**, 755-762.

- [22] Marsh AP, Wrights AP, Haakonssen EH, Dobrosielski MA, Chmelo EA, Barnard RT, Pecorella A, Ip EH, Rejeski WJ (2015) The Virtual Short Physical Performance Battery. *J Gerontol A Biol Sci Med Sci* **70**, 1233-1241.
- [23] Radd-Vagenas S, Fiatarone Singh MA, Inskip M, Mavros Y, Gates N, Wilson GC, Jain N, Meiklejohn J, Brodaty H, Wen W, Singh N, Baune BT, Suo C, Baker MK, Foroughi N, Sachdev PS, Valenzuela M, Flood VM (2018) Reliability and validity of a Mediterranean diet and culinary index (MediCul) tool in an older population with mild cognitive impairment. *Br J Nutr* **120**, 1189-1200.
- [24] Schroder H, Fito M, Estruch R, Martinez-Gonzalez MA, Corella D, Salas-Salvado J, Lamuela-Raventos R, Ros E, Salaverria I, Fiol M, Lapetra J, Vinyoles E, Gomez-Gracia E, Lahoz C, Serra-Majem L, Pinto X, Ruiz-Gutierrez V, Covas MI (2011) A short screener is valid for assessing Mediterranean diet adherence among older Spanish men and women. *J Nutr* **141**, 1140-1145.
- [25] Estruch R, Ros E, Salas-Salvado J, Covas MI, Corella D, Aros F, Gomez-Gracia E, Ruiz-Gutierrez V, Fiol M, Lapetra J, Lamuela-Raventos RM, Serra-Majem L, Pinto X, Basora J, Munoz MA, Sorli JV, Martinez JA, Martinez-Gonzalez MA (2013) Primary prevention of cardiovascular disease with a Mediterranean diet. *N Engl J Med* **368**, 1279-1290.
- [26] Valls-Pedret C, Sala-Vila A, Serra-Mir M, Corella D, de la Torre R, Martinez-Gonzalez MA, Martinez-Lapiscina EH, Fito M, Perez-Heras A, Salas-Salvado J, Estruch R, Ros E (2015) Mediterranean diet and age-related cognitive decline: A randomized clinical trial. *JAMA Intern Med* **175**, 1094-1103.
- [27] Spitzer RL, Kroenke K, Williams JB, Lowe B (2006) A brief measure for assessing generalized anxiety disorder: The GAD-7. *Arch Intern Med* **166**, 1092-1097.
- [28] Valenzuela MJ, Sachdev P (2007) Assessment of complex mental activity across the lifespan: Development of the Lifetime of Experiences Questionnaire (LEQ). *Psychol Med* **37**, 1015-1025.
- [29] Chodzko-Zajko WJ, Proctor DN, Fiatarone Singh MA, Minsion CT, Nigg CR, Salem GJ, Skinner JS (2009) American College of Sports Medicine position stand. Exercise and physical activity for older adults. *Med Sci Sports Exerc* **41**, 1510-1530.
- [30] Livingston G, Sommerlad A, Orgeta V, Costafreda SG, Huntley J, Ames D, Ballard C, Banerjee S, Burns A, Cohen-Mansfield J, Cooper C, Fox N, Gitlin LN, Howard R, Kales HC, Larson EB, Ritchie K, Rockwood K, Sampson EL, Samus Q, Schneider LS, Selbaek G, Teri L, Mukadam N (2017) Dementia prevention, intervention, and care. *Lancet* **390**, 2673-2734.
- [31] Brown BM, Peiffer JJ, Sohrabi HR, Mondal A, Gupta VB, Rainey-Smith SR, Taddei K, Burnham S, Ellis KA, Szoek C, Masters CL, Ames D, Rowe CC, Martins RN; AIBL research group (2012) Intense physical activity is associated with cognitive performance in the elderly. *Transl Psychiatry* **2**, e191.
- [32] Mavros Y, Gates N, Wilson GC, Jain N, Meiklejohn J, Brodaty H, Wen W, Singh N, Baune BT, Suo C, Baker MK, Foroughi N, Wang Y, Sachdev PS, Valenzuela M, Fiatarone SMA (2017) Mediation of cognitive function improvements by strength gains after resistance training in older adults with mild cognitive impairment: Outcomes of the study of mental and resistance training. *J Am Geriatr Soc* **65**, 550-559.
- [33] Geidl W, Semrau J, Pfeifer K (2014) Health behaviour change theories: Contributions to an ICF-based behavioural exercise therapy for individuals with chronic diseases. *Disabil Rehabil* **36**, 2091-2100.
- [34] Ebrahim S, Thompson PW, Baskaran V, Evans K (1997) Randomized placebo-controlled trial of brisk walking in the prevention of postmenopausal osteoporosis. *Age Ageing* **26**, 253-260.
- [35] Preisinger E, Alacamlıoglu Y, Pils K, Bosina E, Metka M, Schneider B, Ernst E (1996) Exercise therapy for osteoporosis: Results of a randomised controlled trial. *Br J Sports Med* **30**, 209-212.
- [36] National Health and Medical Research Council (2013) *Australian Dietary Guidelines*, Canberra. <https://www.nhmrc.gov.au/guidelines-publications/n55>
- [37] US Department of Health and Human Services *Dietary Guidelines for Americans, 2015-2020*, U.S. Department of Health and Human Services.
- [38] Sofi F, Macchi C, Abbate R, Gensini GF, Casini A (2013) Mediterranean diet and health status: An updated meta-analysis and a proposal for a literature-based adherence score. *Public Health Nutr* **17**, 2769-2782.
- [39] Psaltopoulou T, Sergentanis TN, Panagiotakos DB, Sergentanis IN, Kosti R, Scarmeas N (2013) Mediterranean diet, stroke, cognitive impairment, and depression: A meta-analysis. *Ann Neurol* **74**, 580-591.
- [40] Opie RS, Ralston RA, Walker KZ (2013) Adherence to a Mediterranean-style diet can slow the rate of cognitive decline and decrease the risk of dementia: A systematic review. *Nutr Diet* **70**, 206-217.
- [41] Radd-Vagenas S, Duffy SL, Naismith SL, Brew BJ, Flood VM, Fiatarone Singh MA (2018) Effect of the Mediterranean diet on cognition and brain morphology and function: A systematic review of randomized controlled trials. *Am J Clin Nutr* **107**, 389-404.
- [42] Newby JM, Mackenzie A, Williams AD, McIntyre K, Watts S, Wong N, Andrews G (2013) Internet cognitive behavioural therapy for mixed anxiety and depression: A randomized controlled trial and evidence of effectiveness in primary care. *Psychol Med* **43**, 2635-2648.
- [43] Newby JM, Mewton L, Andrews G (2017) Transdiagnostic versus disorder-specific internet-delivered cognitive behaviour therapy for anxiety and depression in primary care. *J Anxiety Disord* **46**, 25-34.
- [44] Newby JM, Mewton L, Williams AD, Andrews G (2014) Effectiveness of transdiagnostic internet cognitive behavioural treatment for mixed anxiety and depression in primary care. *J Affect Disord* **165**, 45-52.
- [45] Kessler RC, Andrews G, Colpe LJ, Hiripi E, Mroczek DK, Normand SL, Walters EE, Zaslavsky AM (2002) Short screening scales to monitor population prevalences and trends in non-specific psychological distress. *Psychol Med* **32**, 959-976.
- [46] Fiatarone Singh MA, Gates N, Saigal N, Wilson GC, Meiklejohn J, Brodaty H, Wen W, Singh N, Baune BT, Suo C, Baker MK, Foroughi N, Wang Y, Sachdev PS, Valenzuela M (2014) The Study of Mental and Resistance Training (SMART) Study—Resistance training and/or cognitive training in mild cognitive impairment: A randomized, double-blind, double-sham controlled trial. *J Am Med Dir Assoc* **15**, 873-880.
- [47] American Psychiatric Association (2013) *Diagnostic and statistical manual of mental disorders : DSM-5*. American Psychiatric Association, Arlington, VA.

- [48] Sikkes SA, Pijnenburg YA, Knol DL, de Lange-de Klerk ES, Scheltens P, Uitdehaag BM (2013) Assessment of instrumental activities of daily living in dementia: Diagnostic value of the Amsterdam Instrumental Activities of Daily Living Questionnaire. *J Geriatr Psychiatry Neurol* **26**, 244-250.
- [49] Rabipour S, Davidson PSR (2015) Do you believe in brain training? A questionnaire about expectations of computerised cognitive training. *Behav Brain Res* **295**, 64-70.
- [50] Kreidler SM, Muller KE, Grunwald GK, Ringham BM, Coker-Dukowitz ZT, Sakhadeo UR, Barón AE, Glueck DH (2013) GLIMPSE: Online power computation for linear models with and without a baseline covariate. *J Stat Softw* **54**, i10.
- [51] Faul F, Erdfelder E, Lang AG, Buchner A (2007) G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods* **39**, 175-191.
- [52] Norton S, Matthews FE, Barnes DE, Yaffe K, Brayne C (2014) Potential for primary prevention of Alzheimer's disease: An analysis of population-based data. *Lancet Neurol* **13**, 788-794.
- [53] Ashby-Mitchell K, Burns R, Shaw J, Anstey KJ (2017) Proportion of dementia in Australia explained by common modifiable risk factors. *Alzheimers Res Ther* **9**, 11.